PHM330Y

PATHOPHYSIOLOGY AND CLINICAL BIOCHEMISTRY

2007-2008

LECTURE NOTES PACKAGE

OCTOBER MIDTERM – DECEMBER EXAM

Adrenal Diseases and Adrenal Function Tests

PHM 330Y (Pathophysiology and Clinical Biochemistry)

Sharon Yamashita Pharm.D.
Assistant Professor, Faculty of Pharmacy, University of Toronto
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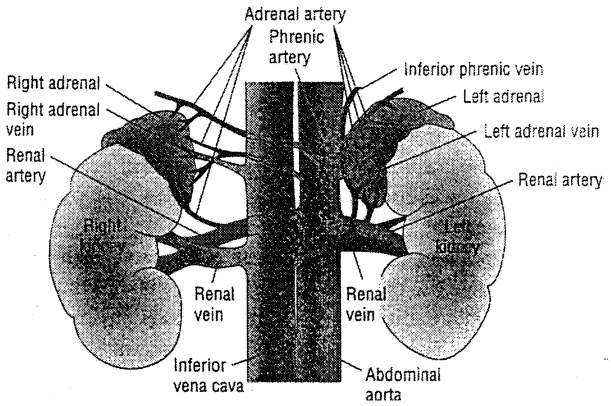
Adrenal Diseases and Adrenal Function Tests

Teaching Objectives:

- briefly review adreno-cortical physiology
- briefly review clinical causes and features of the common adreno-cortical diseases
- discuss the biochemical tests involved with the diagnosis of these disorders

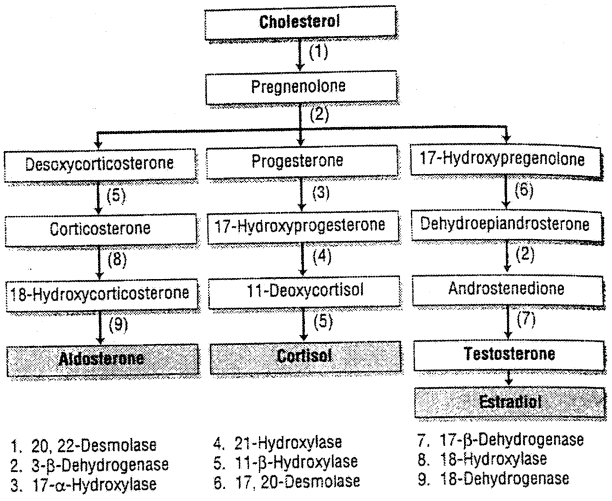
Adrenal Glands



Adrenal Gland

- Located on upper poles of kidneys
- Adrenal Medulla (10% of gland)
  - secretion of catecholamines
- Adrenal Cortex
  - Zona Glomerulosa (15% of cortex)
    - mineralocorticoid production
  - Zona Reticularis (60% of cortex)
    - glucocorticoid production
  - Zona Fasiculata (25% of cortex)
    - adrogen production

Adrenal Hormones



Adrenal Gland

- Catecholamines:
  - hemodynamic stability
- Mineralocorticoids (aldosterone):
  - electrolyte and volume status
- Glucocorticoid (cortisol):
  - regulation of fat, carbohydrate and protein metabolism
- Androgens (testosterone, estrogen):
  - reproductive system

Importance of the Adrenal Gland

- Gluco-corticoids are required for the normal maintenance of several important cardiovascular and metabolic functions
- De-rangement of normal adreno-cortical function can lead to significant morbidity and mortality if un-recognized (immediately)

HPA Axis

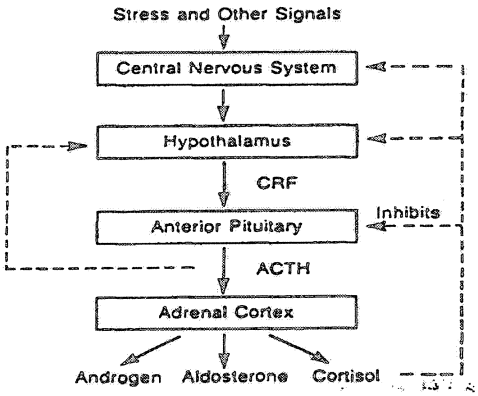


Fig. 13-5 Mechanism for regulation of glucocorticoid secretion. Solid arrows indicate stimulation; dashed arrows indicate inhibition. Glucocorticoids are known to inhibit both pituitary ACTH and hypothalamic corticotropin-releasing factor (CRF) secretion. ACTH also exerts a short negative feedback effect on CRF release.

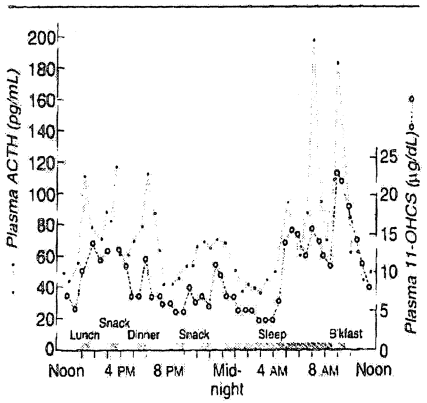


Figure 9–7. Fluctuations in plasma ACTH and glucocorticoids (11-OHCS) throughout the day. Note the greater ACTH and glucocorticoid rises in the morning before awakening. (Reproduced, with permission, from Krieger DT et al: Characterization of the normal temporal pattern of corticosteroid levels. J Clin Endocrinol Metab 1971;32:266.)

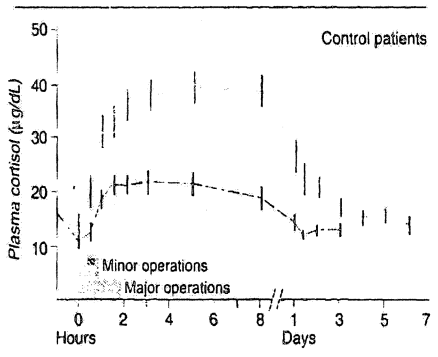


Figure 9–8. Plasma cortisol responses to major surgery (continuous line) and minor surgery (broken line) in normal subjects. Mean values and standard errors for 20 patients are shown in each case. (Reproduced, with permission, from Plumpton FS, Besser GM, Cole PV: Anaesthesia 1969;24:3.)

Adrenal Disorders

- Overactivity:
  - Cushing's Syndrome
  - Hyperaldosteronism
  - Pheochromocytoma
- Underactivity:
  - Addison's Disease

Common Causes of Cushing's Syndrome

- ACTH-dependent (80%)
  - pituitary adenoma
  - ectopic ACTH syndrome
- ACTH-independent (20%)
  - exogenous: prednisone, megestrol (Megace)
  - adrenal carcinoma (20%)/adenoma (80%)

Signs/Symptoms of Cushing's Syndrome

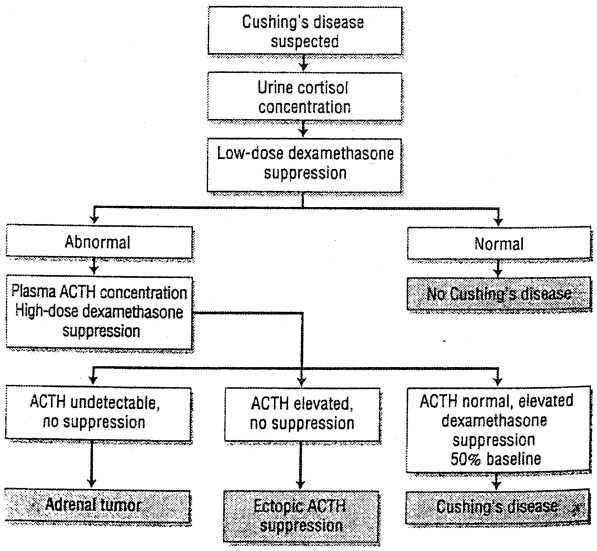
- GENERAL

  Central obesity, "moon face", "Buffalo hump", weakness, hypertension, psychiatric changes
- SKIN

  striae, acne, hirsutism, bruising
- ENDOCRINE/METABOLIC

  Hypokalemia, DM, osteopenia, menstrual dysfunction

Diagnosis of Cushing's Disease



Screening Tests for Cushing's Syndrome

- Dexamethasone Suppression Test:
  - 1mg @ 11pm, 0800h cortisol
  - many false positives, but normal test rules out inappropriate ACTH secretion syndromes
- 24hr Urinary Free Cortisol
  - most sensitive/specific for Cushing's

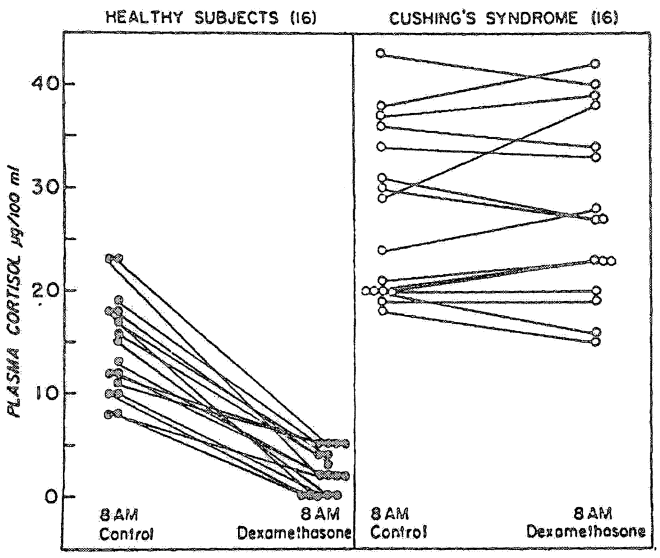
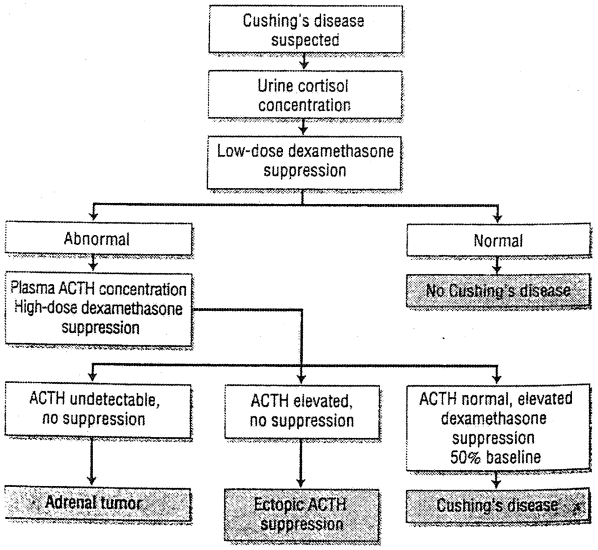


Figure 3. Plasma Cortisol Levels at 8 a.m. on Two Subsequent Days before and after 1 Mg of Dexamethasone Given by Mouth at 11 p.m. in Healthy Subjects and Patients with Cushing's Syndrome.

Confirmatory Tests for Cushing's Syndrome

- plasma ACTH level
- Low/High dose Dex Supp Test
  - 1, 2mg vs. 8mg
- Imaging(CT, MRI)

Diagnosis of Cushing's Disease



THE ADRENAL GLANDS

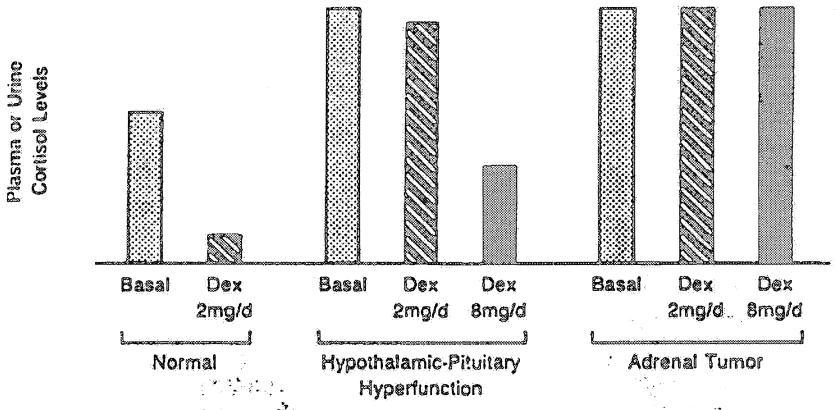


Fig. 13-9 Expected changes in plasma or urine cortisol values after 2 days of low (2 mg/day) and high (8 mg/day) dexamethasone in divided doses in normals and patients with Cushing's syndrome caused by hypothalamic–pituitary hyperfunction or an adrenal tumor.

Cushing's Syndrome: Management

- Nonpharmacologic
  - Surgery
  - radiation
- Pharmacologic
  - steroidogenic inhibitors
  - adrenolytic agents
  - neuromodulators of ACTH release
  - glucocorticoid receptor blocking agents

Cushing's Syndrome: Pharmacologic Management

- Steroidogenic Inhibition
  - metyrapone, aminoglutethimide, ketoconazole
- Adrenolytic Agents
  - mitotane
- Neuromodulators of ACTH release
  - cyproheptadine, bromocriptine, valproic acid, octreotide
- glucocorticoid receptor blocking agents
  - mifepristone, spironolactone

Hyperaldosteronism

- Primary
  - aldosterone-producing adenoma (65%), bilateral adrenal hyperplasia
- Secondary
  - Hypertensive
    - renal vascular hypertension, renin-secreting tumours, estrogen therapy
  - Non-hypertensive
    - edema, pregnancy, sodium depletion, diuretic therapy, CHF, cirrhosis, Bartter's syndrome

Hyperaldosteronism

- Signs and Symptoms:
  - hypertension, weakness, nocturnal polyuria, polydipsia, reduced glucose tolerance, hypokalemia (90%), hypernatremia, metabolic alkalosis
- Diagnosis:
  - serum/urine K^+
  - plasma aldosterone/plasma renin
  - CT scan
- Management:
  - aldosterone antagonist (spironolactone)
  - surgical resection (adenoma)

Pheochromocytoma

- A chromaffin tumour of the adrenal medulla which secretes catecholamines
- characterized by hypertension, palpitations, sweating, headache
  - < 1% of HT is secondary to pheo
- usually benign

Pheochromocytoma

- Diagnosis:
  - urinary catecholamines
    - VMA (vanillylmandelic acid)
    - metanephrines
    - free catecholamines
  - CT scan
- Management:
  - α- and β-receptor blockade
  - Surgical resection

Common Causes of Adrenal Insufficiency (Addison's)

- Slow Onset
  - Primary- Autoimmune, TB, AIDS
  - Secondary- Pit.tumour, sarcoid, fast withdrawal of steroids
- Abrupt Onset
  - adrenal hemorrhage (sepsis, coagulaopathies, warfarin, HIT), head trauma, pit/adrenal surg
- "Relative Adrenal Insufficiency"
  - critically ill

Common Signs/Symptoms of Adrenal Insufficiency

- Weakness, depression, anorexia, weight loss, hypotension (shock)
- Hyponatremia, hypoglycemia
- Hyperpigmentation

Laboratory Evaluation of Adrenal Function

- Basal Cortisol level:
  - <83 nmol/L- Addison's
  - >525 nmol/L- normal
- Basal ACTH level:
  - Primary Addison's- >100 pg/ml (see figure)

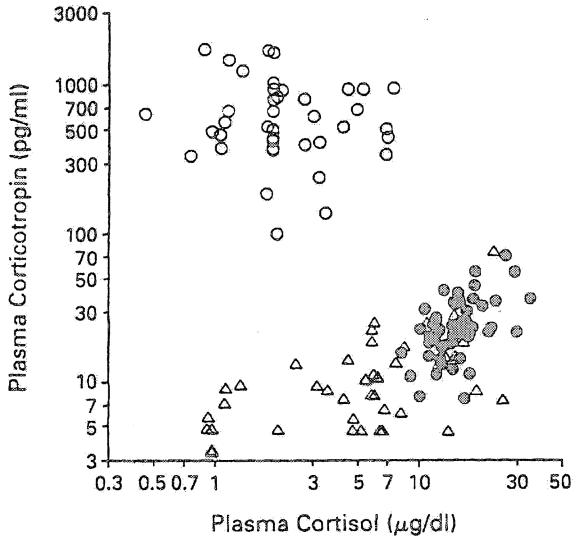


Figure 1. Logarithmic Plot of Plasma Cortisol Concentrations as a Function of Plasma Corticotropin Concentrations in Patients with Primary Adrenal Insufficiency, either Untreated or 24 Hours after a Dose of Hydrocortisone (○), Normal Subjects (●), and Patients with Pituitary Disease with or without Adrenal Insufficiency (△).

Lab. Evaluation of Adrenal Function (con't)

- Plasma adrenal autoantibody tests
- Cosyntropin (~ACTH, Cortrosyn®) test
  - 250μg IV/IM in a.m.
  - Plasma for cortisol before and @30' and 60'
  - any result >20 μg/dl (550 nmoL/L)
  - 1 μg IV: for detecting mild secondary adrenal insuff (head injury), steroids

Other diagnostic tests

- Insulin Tolerance Test
  - 0.1 - 0.15 unit/kg of regular insulin (BS < 2.2 mmol/L)
  - ↑ cortisol > 550 nmol/L
- Metyrapone test
  - inhibits 11-hydroxylation of 11-deoxycortisol to cortisol
  - midnight dose (30mg/kg)
  - measure 11-deoxycortisol in am (↑ > 200 nmol/L)
- Prolonged ACTH stimulation test (over 6h)
  - replaced by short stimulation test

Suppression and recovery of adrenal response after short-term, high-dose 'prednisone' Henzen C et al. Lancet 2000; 355:542-45.

- 75 pts on 25mg prednisone daily or greater for 5-30 days
- 1 μg of cosyntropin (~ACTH) given within 24-72 hr after withdrawal of steroid
- adrenal response normal in 41 and suppressed in 34
- no correlation between dose/duration and cortisol response to cosyntropin

Recovery of Adrenal Gland after Prednisone(cont'd)

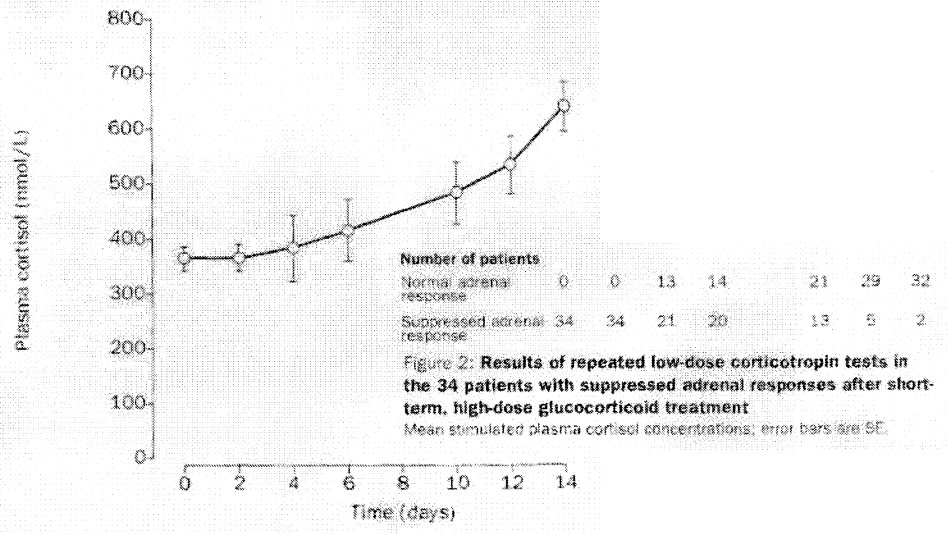


Figure 2: **Results of repeated low-dose corticotropin tests in the 34 patients with suppressed adrenal responses after short-term, high-dose glucocorticoid treatment**
Mean stimulated plasma cortisol concentrations; error bars are SE.

Addison's Disease: Management

- Corticosteroid replacement
  - prednisone, hydrocortisone, cortisone
  - bid dosing to simulate circadian rhythm
- Mineralocorticoid replacement
  - fludrocortisone

Steroid Equivalents

Duration	Steroid	Equivalent Dose	Relative Anti-Inflammatory Potency	Sodium Retaining Potency	Physiologic Replacement Dose
Short-Acting (8-12h)	Cortisone	25 mg	0.8	++	37.5 mg
	Hydrocortisone	20 mg	1.0	++	30 mg
Intermediate Acting (18-36h)	Methylprednisolone	4 mg	5	0	6 mg
	Prednisone	5 mg	4	+	7.5 mg
	Triamcinolone	4 mg	5	0	6 mg
Long-Acting (36-54h)	Betamethasone	0.6mg	25-30	0	0.75 - 1 mg
	Dexamethasone	0.75mg	25-30	0	0.75 – 1 mg

Recovery of HPA axis following discontinuation of steroids

Graber AL et al. J Clin Endocr 1965;25:11-16

- @ 1 month: "complete suppression"
  - ↓ cortisol, ↓ ACTH, ↓ adrenal response
- @ 2-5 months: "ACTH recovery"
  - N/ ↑ ACTH , ↓ cortisol, ↓ adrenal response
- @ 6-9 months: "cortisol recovery"
  - N cortisol, ↓ adrenal response
- @ > 9 mos: "complete recovery"
  - N ACTH, N cortisol, N adrenal response

Peri-operative Steroid Supplementation

Salem M et al. Ann Surg 1994;219:416-25

Surgical Stress	Surgical Procedure	Supplementation
Minor	Inguinal Hernia	HC 25mg preop, then resume
Moderate	Colon resection, joint replacement, hysterectomy	HC 50-75mg/day x 2 days, then resume
Severe	Cardiac bypass	HC 100-150mg/day x 2-3 days, then resume

Withdrawal of Chronic Steroids

- Taper over several months to restore normal HPA axis
  - ↓ by 2.5 - 5mg prednisone q 3-7 days until 5mg then ↓ by 1mg/month
  - monitor for S&S of adrenal insufficiency and disease flare
- MEDIC Alert Bracelets
- Counsel patients to increase steroid dose if illness/injury

Summary

- Adrenal disease, although rare, can lead to significant morbidity and mortality
- Initial screening and definitive testing for adrenal disease requires the use of drugs in a diagnostic role
- Final diagnostic evaluation may require imaging studies

Case 1

- C.S. is a 63 year old female who complains of weakness and weight gain (especially in her face)
- On examination, she is found to be hypertensive
- Lab tests are normal except for hyperglycemia

- *Overactivity or underactivity of adrenals?*
- *Glucocorticoid, mineralocorticoid or catecholamine problem?*
- *Which diagnostic tests?*

Case 2

- A 70 year old female with Rheumatoid Arthritis is admitted to hospital for an elective hip replacement
- MOA: diclofenac, methotrexate, omeprazole, (chronic steroids tapered off 6 months ago)
- Meds in hospital:cefazolin, dalteparin
- Her post-operative course is complicated by hypotension (refractory to intravenous fluids) and hypoglycemia

Case 2 cont'd

- *Overactivity or underactivity of adrenals?*
- *Glucocorticoid, mineralocorticoid or catecholamine problem?*
- *Which diagnostic tests?*

THYROID FUNCTION TESTS & THYROID DISEASE

Wm.R.Bartle,BScPhm, Pharm.D.,FCSHP
Sunnybrook & Women's College
Health Sciences Centre
University of Toronto
2005

Teaching Objectives

- Review briefly thyroid physiology
- Discuss basics of thyroid function testing
- Discuss use of tests in diagnosis, screening and management of thyroid disease

Importance of thyroid function tests

- Symptoms of thyroid disease are generally non-specific
- Canadian data suggests over-use of certain thyroid function tests(TFTs)
- Screening for thyroid disease with TFTs in certain patients is recommended
- Thyroid function tests used to adjust thyroxin doses

Biologic Effects of Thyroid Hormone

- Stimulate neural/skeletal development
- Stimulate O_2 consumption at rest
- Stimulate bone turnover
- Control chronotropic and inotropic cardiac effects
- Increase RBC production
- Alter metabolism of CHO, fats and protein

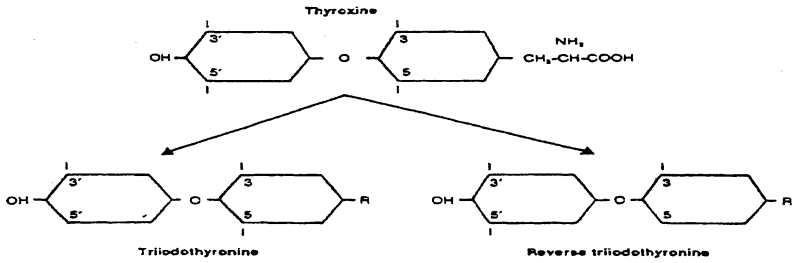


Figure 1. Chemical structures of thyroxine (T_4), triiodothyronine (T_3), and reverse T_3 (rT_3). T_3 is produced by peripheral monodeiodination of T_4 by enzyme that removes iodine from 5' position on outer ring. Monodeiodination at 5 position on inner ring results in rT_3.

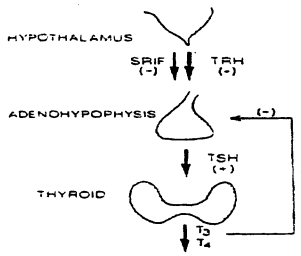
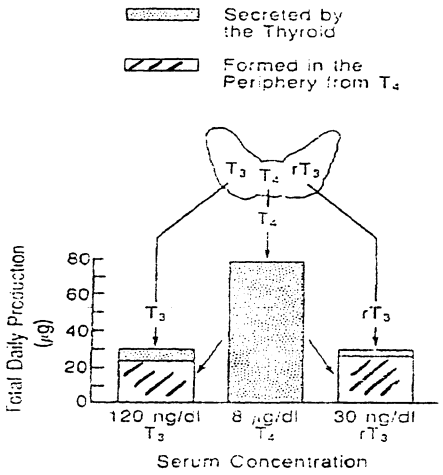


Fig. 2. Hypothalamic-pituitary-thyroid axis.

g. 12-4 Dynamics of thyroid hormone production and mean serum concentrations. he total daily production and distribution into the components of directed secretion by e thyroid and peripheral conversation of secreted thyroxine are shown. T_4, thyroxine; 3,5,3'-triiodothyronine; rT_3, reverse triiodothyronine or 3,3',5'-triiodothyronine. Adapted with permission from Schimmel M, and Utiger RD: Thyroidal and peripheral roduction of thyroid hormones. Review of recent findings and their clinical implications. n Intern Med 87:760, 1977.)



Thyroid Function Tests

- Blood tests the most commonly performed
- Serum TSH now considered the most useful screening test for thyroid dysfunction
- >99% of T4 and T3 bound to serum proteins; measurement of free(unbound) T4/T3 eliminates incorrect interpretation due to drugs,disease,pregnancy

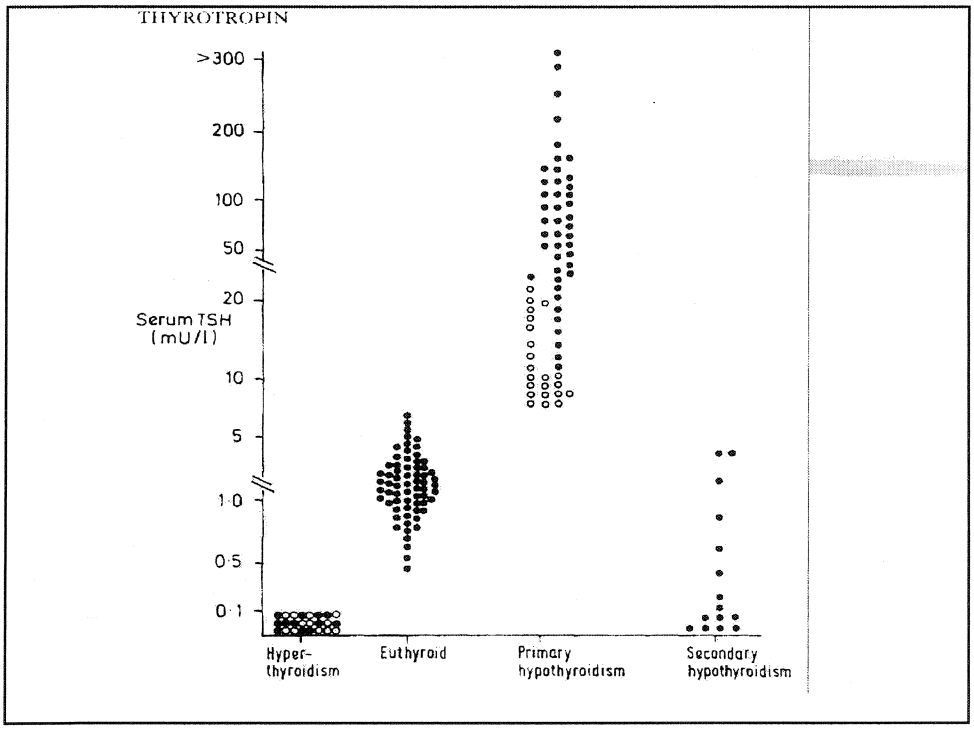
THYROID FUNCTION TESTS

- Direct measurement of T_4 and T_3
- Pituitary test: TSH
- Thyroid Uptake of Radioactive Iodine(RAIU)
- Thyroid Scan(anatomic)
- Thyroid auto-antibodies(anti-microsomal,anti-thyroid peroxidase)

Thyroid Tests: Drug Effects

⌘Drug 'interference' with thyroid function test interpretation(eg. BCP*,phenytoin salicylates) no longer a problem because we use TSH and/or free T_4

*woman on thyroxin supplement who becomes pregnant/begins BCP will probably require a bigger thyroxin dose to remain euthyroid



Use of Serum TSH in Diagnosis of Thyroid Disease

- Most thyroid disorders are due to a primary problem with the thyroid gland
- Negative feedback between thyroid and pituitary important in analyzing results

Dayan CM. Interpretation of thyroid function tests.Lancet 2001;357: 619-24

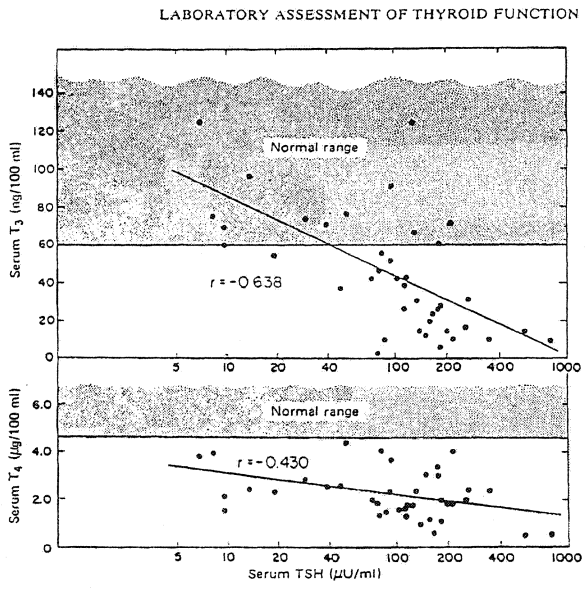


Figure 19-4. Serum T_3, T_4, and TSH concentrations in 39 patients with untreated primary hypothyroidism. The samples represent all those with an elevated serum TSH (>5 μU/ml) received in the laboratory over a 9-month period. The T_3 and T_4 concentrations for each sample are plotted directly above the corresponding TSH concentration on the abscissa. The correlation coefficients are both significant at $p < 0.01$.

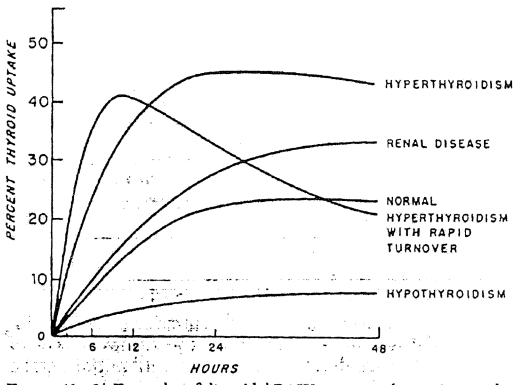
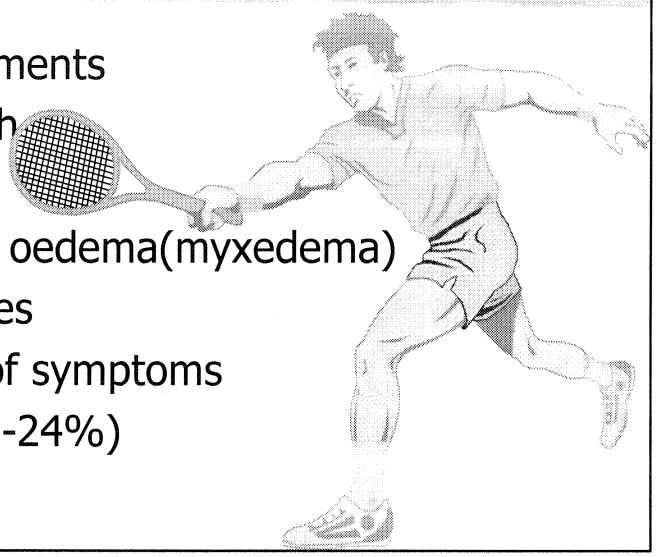


FIGURE 41–2. Examples of thyroidal RAIU curves under various pathological conditions. Note the prolonged uptake in renal disease due to decreased urinary excretion of the isotope and the early decline in thy-

Common Signs and Symptoms of Hypothyroidism

- Fatigue, lethargy, sleepiness
- Mental impairment, depression
- Cold intolerance
- Weight gain
- Constipation
- Dry skin

Cont'd



⌘Slow movements
⌘Slow speech
⌘Hoarseness
⌘Non-pitting oedema(myxedema)
⌘Slow reflexes
- sensitivity of symptoms very poor(2-24%)

Common Causes of Hypothyroidism

⌘Post thyroidectomy or I^{131}
⌘Hashimoto's thyroiditis
⌘Drugs(amiodarone, lithium, interferon)
⌘Pituitary failure(tumour,Sx, thrombosis)
⌘Withdrawal of thyroxine

Epidemiology of Hypothyroidism

⌘Reported Prevalences in Adult Pop'n.(%)*

- Overt Hypothyroidism 2
- Subclinical Hypothyroidism 5-17

* depends on age/gender

2450 Subjects (9.5%)

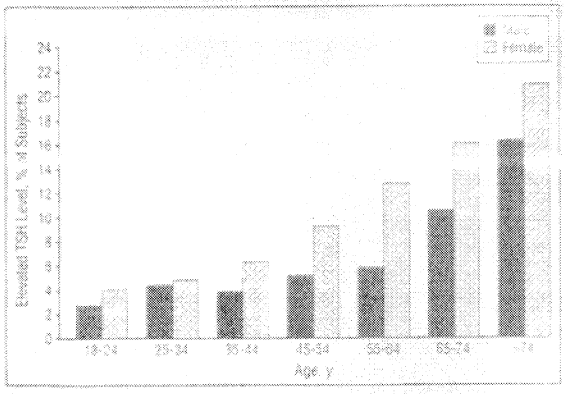


Figure 1. *The percentage of subjects with an elevated thyrotropin (thyroid-stimulating hormone [TSH]) level by sex and decade of age. Percentages of hypothyroidism ranged from 4% to 21% in women and from 3% to 16% in men.*

Subclinical Hypothyroidism

- No symptoms, Normal T_4, sl.↑ TSH(5-10IU/ml)
- 5-20% adult women
- treat or monitor?
- Treating would generate 400,000 new Rx in 1st yr and add'n 60,000-100,000 q 5yr

Cooper DS. Subclinical Hypothyroidism. NEnglJMed 2001;345: 260-65

Recommendations for Screening of Asymptomatic Adults for Thyroid Dysfunction

- Amer Thy Assoc: female/male >35 yr q5yr
- Aassoc Clin Endo: older patients,espec. Females
- Coll Amer Pathol: females >50 if they seek medical care or are hospitalized
- AAcadFamPhys: >60
- US Preventive Services TaskForce/RoyColl Phys → unjustified

Drug-induced Hypothyroidism

⌘Amiodarone

- ~35% iodine: ↓T4 secretion
- inhibits T4 to T3 conversion
- -increased if pt has thyroid auto-antibodies

Lithium- inhibits secretion of T4

Ann.Intern.Med 1997;126:63-73

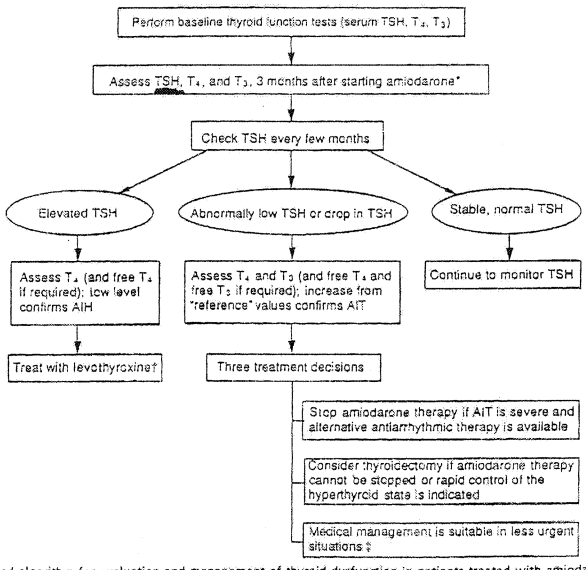


Figure 3. Suggested algorithm for evaluation and management of thyroid dysfunction in patients treated with amiodarone. *Test should be done to serve as a reference for comparison with future test results. †Goal is to increase serum levels of thyroxine (T_4) to high normal or slightly above normal (normalization of levels of thyroid-stimulating hormone [TSH] should not be attempted). ‡Combination of thionamides (methimazole, 40 mg/d, or propylthiouracil, 400 to 800 mg/d) with potassium perchlorate (800 to 1000 mg/d for 15 to 45 days) or prednisone (0.5 to 1.25 mg/kg of body weight per day for 40 days) is beneficial; β-blockers may be added. AIH = amiodarone-induced hypothyroidism; AIT = amiodarone-induced thyrotoxicosis; T_3 = triiodothyronine.

Thyroid Function Tests and Thyroxin Replacement

- Thyroid supplement requirement not affected by many factors ,unlike diabetes and adrenal insufficiency
- Once appropriate thyroid supplement dose attained, TSH once a year(approx) unless symptoms of hypo- or hyperthyroidism appear
- ~25% of pts on thyroxine have a high normal or elevated T4 to normalize the TSH
- *Some pts do better if TSH is slightly ↓ and T4 is slightly ↑*

Brit Med J 2003;326:295-6

Epidemiology of Hyperthyroidism

- Hyperthyroidism
  - Reported prevalence in adult pop. 0.2%
- Subclinical Hyperthyroidism
  - Reported prevalence in adult pop. 0.1-6.0%

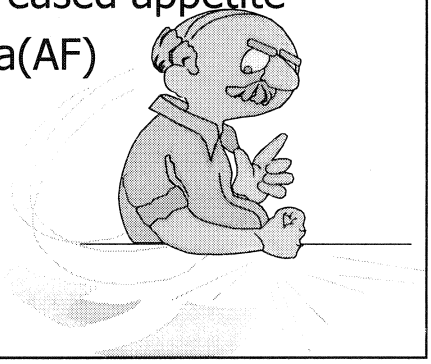
Cooper DS. Hyperthyroidism. Lancet 2003;362:459-68

Common Causes of Hyperthyroidism

- Graves' disease
- toxic multi-nodular goitre
- toxic adenoma
- thyroxin treatment(therapeutic,factitious)
- Drugs(amiodarone)
- Subacute thyroiditis

Common Signs and Symptoms of Hyperthyroidism

- Sweating
- Heat intolerance
- Weight loss despite increased appetite
- Palpitations, tachycardia(AF)
- Muscle weakness
- Diarrhea
- Eye changes,insomnia



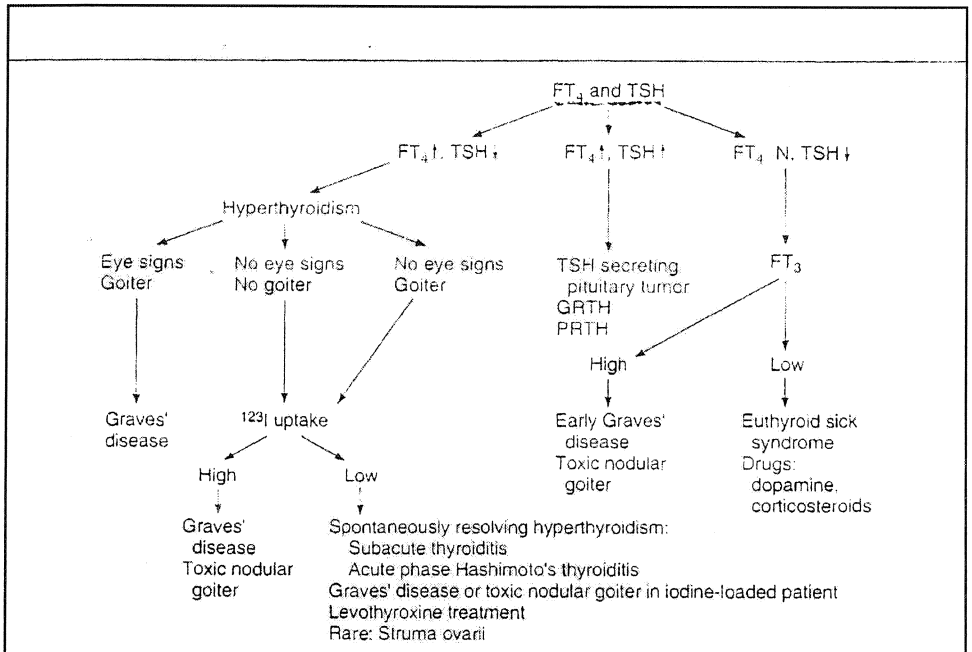
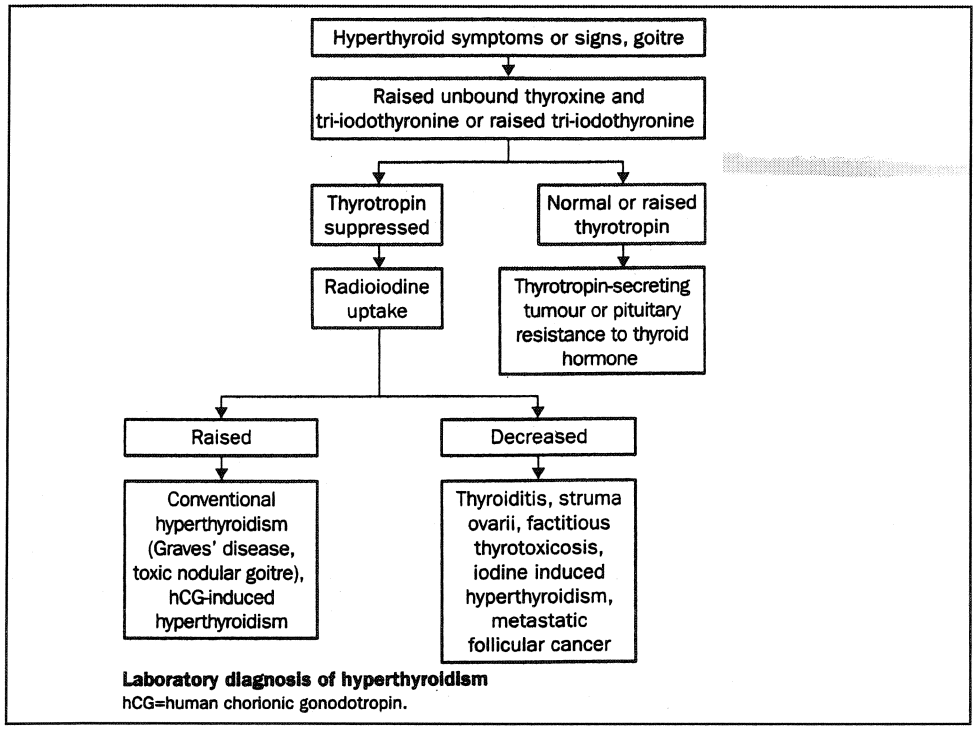


Figure 7–49. Laboratory tests useful in the differential diagnosis of hyperthyroidism. (See text for details.)



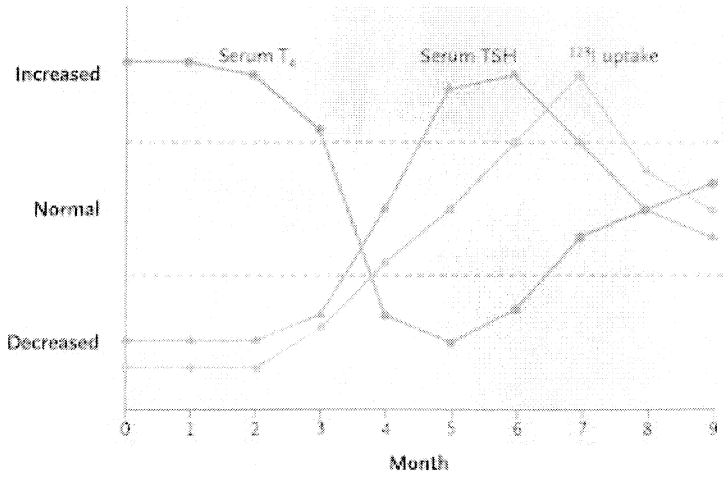
Laboratory diagnosis of hyperthyroidism
hCG=human chorionic gonodotropin.

OTHER TYPES OF THYROID DISEASE

- Painless postpartum thyroiditis, painless sporadic thyroiditis, painful subacute thyroiditis
- Etiology-autoimmune/unknown?
- More common in women
- Thyroid antibodies commonly present
- Thyroid function tests fluctuate
- Symptomatic treatment only

N Engl J Med 2003;348:2646-55

Clinical Course of Thyroiditis



Summary

- Appropriate diagnosis of thyroid disease requires biochemical thyroid function tests and occasionally imaging of the gland
- Serum TSH is the best biochemical marker of the common thyroid diseases
- T4 and T3 are useful in hyperthyroidism to estimate severity of the disease
- Drug 'interference' with thyroid function test interpretation is now avoidable
- Serum TSH should be done once yearly in pts on thyroxin supplement who are asymptomatic

JERALD BAIN BScPhm,MD,MSc,FRCPC,CertEndo,BA

MOUNT SINAI HOSPITAL
600 UNIVERSITY AVENUE, SUITE 1501
TORONTO, ONTARIO M5G 1X5
TELEPHONE (416)586-4436, FAX (416)586-3134

ENDOCRINOLOGY-ANDROLOGY
REPRODUCTIVE AND SEXUAL MEDICINE

PROFESSOR OF MEDICINE - UNIVERSITY OF TORONTO

LECTURE OUTLINE

Faculty of Pharmacy
Pathophysiology and Clinical Biochemistry Course
- Year 3
Selected Topics in Reproductive Endocrinology
Jerald Bain, M.D.

This lecture will cover a broad spectrum of reproductive medicine. Selected areas of clinical interest and importance both to the physician and pharmacist will be presented according to the following general outline using actual cases:

I Male and Female Development After Conception.
- A. What is expected to happen according to the genetic background.
- B. Errors that can occur in
  - genetic predetermination.
  - hormone receptor action.
  - hormone synthesis.
- C. Treatment strategies.

II Abnormalities in Puberty.
- A. What is normal?
- B. Causes of delayed puberty.
  - primary vs. secondary hypogonadism.
- C. Treatment strategies.

III Male Hypogonadism.
- A. Testicular causes.
- B. Hypothalamic pituitary causes.
- C. Treatment strategies.

IV Female Hypogonadism.
- A. Ovarian causes.
- B. Hypothalamic pituitary causes.
- C. Treatment strategies.

V Infertility.
- A. Female factors.
- B. Male factors.
- C. Principles of treatment.

VI Menopause.
- A. What is it?
- B. Principles of hormone replacement therapy.

VII Andropause.
- A. What is it?
- B. Sexual Dysfunction.
- C. Are we on the verge of hormone replacement therapy for men?

Pathology, Pathophysiology and Clinical Biochemistry Course (PAT 331H / PHM 330Y) - Faculty of Pharmacy

Jerald Bain M.D.

Lecture: Disorders of Sex Hormones
November 25, 1998

You will have received an outline for this lecture. Students in the past have asked for handouts that expand upon the outline. As you can see from the number and nature of the topics in the lecture, the only appropriate handout would be a book on reproductive and sexual medicine. What follows below will hopefully be an acceptable alternative. A search of the medical literature will usually bring up review articles of any specific topic which captures your interest.

I Male and Female Development After Conception.

All human beings are destined to become females unless there is active intervention to cause male differentiation which occurs after the undifferentiated gonads are transformed into testes when exposed to testicular determining gene found on the Y chromosome. Even after that happens, mistakes occur in testosterone and dihydrotestosterone production, in androgen receptor action, in mullerian inhibiting substance availability.

Errors occur anywhere along this sequence of events. Some examples will be discussed both clinically and therapeutically.

II Abnormalities in Puberty.

If puberty does not take place, an adolescent boy or girl does not develop secondary sexual characteristics. This occurs when there is a failure of sex hormone production (testosterone induces virilization in boys, and estrogens induce feminization in girls). This will be due to either primary hypogonadism (the problem lies in the gonads - ovaries or testes) or to secondary hypogonadism (the problem lies in the hypothalamus or pituitary gland). How we make a diagnosis and what treatment strategies we use will be discussed.

III Male Hypogonadism.

Inefficient or absent testicular function is due either to primary or secondary hypogonadism. Examples of primary hypogonadism are: inflammation (e.g. mumps orchitis), cyptorchidism (undescended testes), trauma, effects of chemotherapy or radiation, Klinefelter's syndrome. Examples of secondary hypogonadism are: hyperprolactinemia, pituitary tumour, gonadotropin releasing hormone insufficiency. Cases will be shown and treatment discussed.

IV Female Hypogonadism.

Inefficient or absent ovarian function is due either to primary or secondary hypogonadism. Examples of primary hypogonadism are: oophoritis (permanent or transient), streak ovaries (as seen in Turner's syndrome), premature menopause (as seen in autoimmune ovarian failure), ovarian agenesis, gonadal dysgensis. Examples of secondary hypogonadism are the same as for the male.

V Infertility.

Infertility affects approximately 15% of couples, with male and female factors having about equal causation.

Female factors can be due to: primary or secondary hypogonadism, androgen disorders, inefficient ovulation, endometriosis, obstructed or diseased fallopian tubes. Male factors can be due to: primary or secondary hypogonadism, substance abuse (cigarettes, alcohol, drugs), obstruction or absence of the vas deferens bilaterally, sexual dysfunction, unexplained.

For most female factors there is effective therapy. For the majority of male factor infertility, however, there are few treatment options to improve sperm count or quality. Many couples often turn to donor sperm insemination or in vitro fertilization (IVF) particularly intracytoplasmic sperm injection (ICSI).

Some medical treatments will be discussed.

VI Menopause.

Somewhere around 50 years of age, the ovaries cease to function and estrogen production is lost. In many women this induces overt symptoms such as hot flashes and vaginal dryness. Loss of estrogen secretion is also a major risk factor for the subsequent development of osteoporosis and cardiac disease.

Hormone replacement therapy will be discussed.

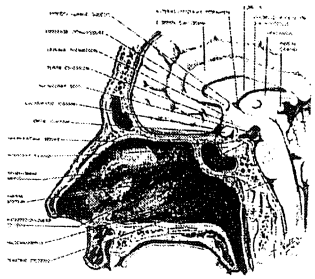
VII Andropause.

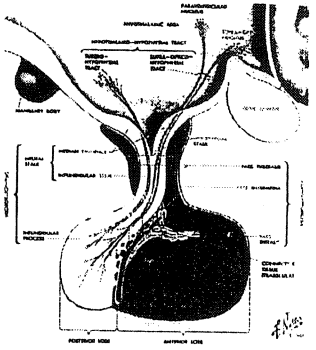
Somewhere after the age of 40, there is a gradual decline in testosterone production in the male. Also somewhere around this time there is the onset of a variety of symptoms including: decreased libido, erectile dysfunction, weakness, fatigue, loss of drive and motivation, mood disturbances. Some men who have a combination of reduced testosterone production plus some of the above symptoms are said to have the andropause.

Treatment strategies for erectile dysfunction and the andropause will be discussed.

PITUITARY

Dr. Ivy Fettes





OBJECTIVES

1. To discuss the function and dysfunction of the posterior and anterior pituitary.
2. To discuss the current approach to evaluation of the pituitary.
3. To discuss treatment options for pituitary disease.

POSTERIOR PITUITARY
=
NEUROPHYOPHYSIS

1. Terminal axons of the vasopressin and oxytocin neurons.
2. Store vasopressin and oxytocin for release as required.

STIMULUS FOR RELEASE

1. Increase in plasma osmolality for vespressin (ADH).
2. Delivery and suckling for oxytocin.

VASOPRESSIN STIMULATION

1. V_2 receptors (in collecting ducts).
2. Cyclic AMP.
3. Aquaporin 2 (water channel).
4. Water conserved.

CENTRAL NEUROGENIC DIABETES INSIPIDUS (D1)

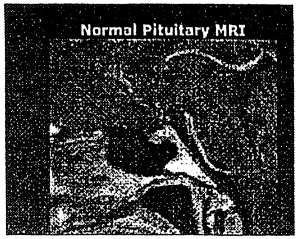
1. Represents destruction of more than 90% at vasopressin cells in hypothalamus.
2. Polyuria (4 to 18 litres/day).
3. Polydipsia (cold liquids).

CAUSES OF CENTRAL DI

1. Idiopathic.
2. Hypothalamic tumors.
3. Trauma (head injury or neurosurgery)
4. Infiltrative diseases.
5. Heriditary.

MRI OF POSTERIOR PITUITARY

- High intensity signal on T_1.
- Bright spot related to stored vasopressin.
- Bright signal lost in DI.



THERAPY OF CENTRAL DI

1. Monitor serum sodium, urine osmolality and fluid balance.
2. Hydrate with water orally or IV D5W.
3. DDAVP (desmopressin) (acts on antidiuretic V_2 receptors).
   * use sc for acute post-op/post-trauma
   * use intranasal spray or solution or tablets for chronic DI.
   * Bid use for complete DI and qhs for partial DI.

ILLUSTRATIVE CASE

- 25 year old man in MVA.
- Semi-conscious with basal skull fracture.
- Polyuria with dilute urine 8 l/day elevated serum sodium (147) and osmolality 301.

NO STANDING ORDERS FOR ACUTE DI

- Hydrate.
- DDAVP 1 microgram sc as required.
- Monitor for triphasic response.
- Majority only need transient therapy.

ANTERIOR PITUITARY

1. Secretes growth hormone (GH), LH, FSH, TSH, ACTH and prolactin (PRL).
2. Regulated by hypothalamic hormones and by feedback from target glands/organs.

PITUITARY ADENOMAS

1. Arise from the anterior pituitary.
2. Most common sellar mass (MRI).
3. Secretory (70-75%) or nonsecretory
4. May result in decreased secretion of hormones due to compression.

HYPERSECRETORY SYNDROMES

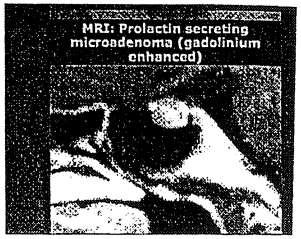
1. PRL excess causes hypogonadism.
2. GH excess causes acromegaly.
3. ACTH excess causes Cushing's disease.
4. TSH excess may cause hyperthyroidism or may present as large sellar mass.
5. FSH/LH excess usually presents as large sellar mass.

PROLACTIN

1. Regulated by tonic inhibition from dopamine
2. Deficiency results in inability to lactate.
3. Excess results in hypogonadism.
4. Excess may cause decreased libido (male).
5. Excess may cause galactorrhea (female).

CAUSES OF HYPERPROLACTINEMIA

1. Pregnancy.
2. Primary hypothyroidism.
3. Drugs e.g., phenothiazines, resperidol, antipsychotics that block dopamine.
4. PRL secretory tumors (50% of pituitary tumors).
5. Other sellar or parasellar tumors by cosecretion or stalk compression.



PROLACTINOMAS

1. Micro (<1 cm) or macroadenomas (>1 cm).
2. Medical therapy with dopamine agonists (bromocryptine and cabergoline).
3. Surgery for macroadenomas if unresponsive or intolerant of medical therapy or increasing tumor size.

BROMOCRYPTINE VS. CABERGOLINE

1. Dosing once or twice daily with bromocryptine and once or twice weekly with cabergoline.
2. Fewer side effects e.g., nausea, dizziness with cabergoline.
3. Should be started at a low dose with snack in evening and gradually increased.

PREGNANCY/LACTATION AND PROLACTINOMAS

1. Bromocryptine can be used to induce pregnancy.
2. Complications <5% with micros and 15% with macros.
3. Complications can be reversed with bromocryptine.
4. No contraindication to nursing.

PROLACTIN AND TESTOSTERONE IN MEN

1. As PRL levels fall with medical therapy testosterone levels rise as does libido.
2. May take 3 to 6 months for normal sexual function.
3. If gonadotropes destroyed then testosterone replacement will be required.

GROWTH HORMONE

1. Dual regulation by the hypothalamus.
2. Stimulation by GRH.
3. Inhibition by somatostatin.
4. Somotomedin (IGF-1) mediates many GH effects.

GROWTH HORMONE DEFICIENCY

1. Present in about 50% of patients before pituitary surgery and 80% after surgery and 100% five years after radiotherapy.
2. Results in growth retardation in children.
3. Newly recognized syndrome in adults.

ADULT GH DEFICIENCY

1. Increased abdominal obesity.
2. Reduced exercise performance.
3. Depression or reduced vitality.
4. Reduced bone mineral density.

LABS IN ADULT GH DEFICIENCY

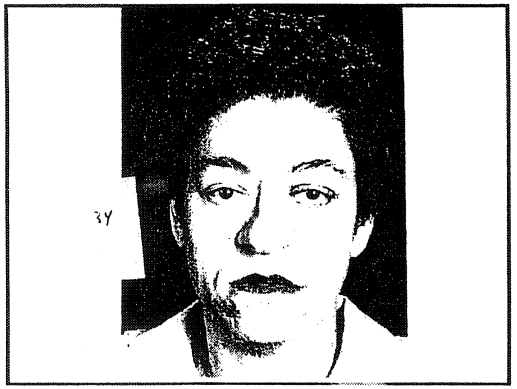
1. Low IGF-1 (in 60%).
2. Reduced GH response to hypoglycemia.
3. Hyperlipidemia (↑LDL-C,↓HDL-C).
4. Elevated fasting insulin.

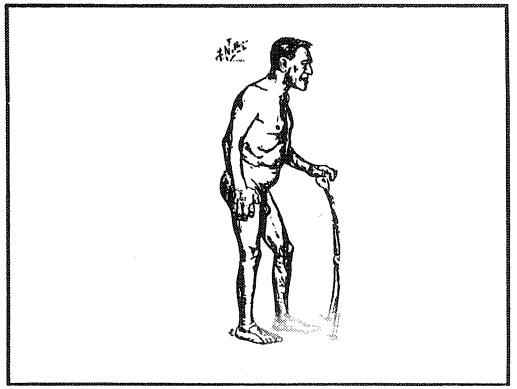
GH REPLACEMENT IN ADULTS

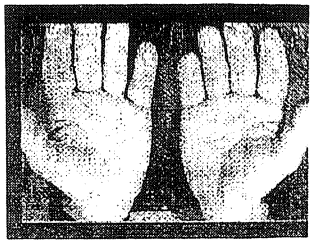
1. Start with 0.5 IU (0.15 mg)/day and titrate up to normalize IGF-1. Usually requires 3 IU or 1 mg/day.
2. Side effects include fluid retention (edema, arthralgia, carpal tunnel).
3. Contraindicated in active malignancy, benign intracranial hypertension and proliferative retinopathy.

GH EXCESS ACROMEGALY

1. Coarsening of facial features.
2. Enlargement of hands and feet.
3. Headache, fatigue.
4. Parasthesise, arthralgia, OA.
5. Increased perspiration.
6. Diabetes mellitus.
7. Hypertension, heart disease.
8. Colon cancer.

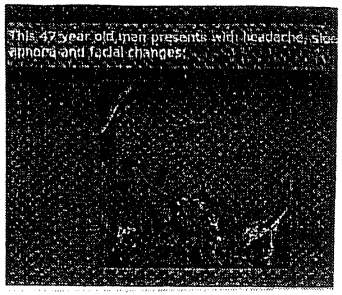


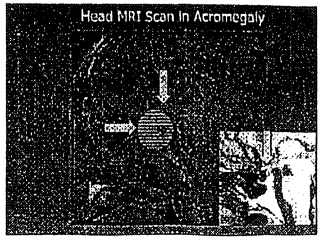




ACROMEGALY

1. 70% macroadenomas.
2. Elevated GH that does not suppress with glucose (GTT).
3. Elevated IGF-1 (somatomedin).





TREATMENT OF ACROMEGALY

1. First line - surgery (transphenoidal adenomectomy).
2. Second line - radiotherapy or medical therapy.
3. Cure is GH <2.5 ug/l and normal IGF-1.

RESPONSE TO TREATMENT

1. Surgery - 85% cure with micros and
   - 50% cure with macros.
2. Radiotherapy (external beam irradiation)
   - 30 to 50% cure in five years.
   - 70% cure in 10 to 15 years.
3. Medical therapy - treatment, not a cure.

SOMATOSTATIN ANALOGUES FOR ACROMEGALY

1. Octreotide treatment results in clinical/biochemical improvement in 60-70% of patients.
2. Long acting preps injected monthly.
3. Side effects include gallbladder sludge, abdominal pain, flatulence and diarrhea or constipation.

ACTH

- Processed from same high molecular weight precursor propiomelanocortin (POMC) as beta endorphin and alpha, beta and gamma MSH.
- Induced by hypothalamic CRF
- Vasopressin enhances CRF mediated ACTH release.

ACTH REGULATES

- Glucocorticoid synthesis.
- Adrenal sex steroid synthesis
- Mineralocorticoid synthesis (lesser extent)

ACTH/CORTISOL

- ACTH pulses lead to diurnal variation in cortisol (peak ACTH at 4 to 5 am and peak cortisol 8 am).
- Major stresses (trauma, major surgery, depression) can increase ACTH and cortisol secretion.

ACTH-CORTISOL FEEDBACK

- ACTH increases cortisol.
- Cortisol decreases CRH and ACTH

ADRENAL ANDROGENS

- DHEA and androstenedione follow the circadian secretion of cortisol.
- DHEA-S has a long half-life and exhibits little diurnal variation.
- Adrenarche occurs prior to puberty.

CORTISOL/FREE CORTISOL

- Cortisol circulates as a free (biologically active) form or bound to cortisol binding globulin (CBG).
- Pregnancy and oral contraceptives increase CBG and thus total cortisol levels, but not free cortisol.

EXCESS GLUCOCORTICOIDS AND WBC

- Increase neutrophils.
- Decrease lymphocytes and eosinophils

EXCESS GLUCOCORTICOIDS AND BONE

- Decreased calcium absorption in gut.
- Increased urinary loss of calcium.
- Increased bone resorption.
- Decreased bone formation.
- Osteoporosis (GIO)

EXCESS GLUCOCORTICOIDS AND BRAIN

- Spontaneous - depression.
- Exogenous therapy - well being, mania.

Excess glucocorticoid use is most common cause of Cushing's Syndrome

CUSHING'S SYNDROME (ENDOGENOUS)

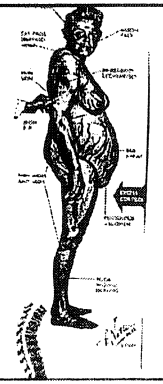
- Manifestations of glucocorticoid excess.
- ACTH dependent (Cushing's Disease (80%) or Ectopic ACTH syndrome) or
- ACTH independent (Adrenal adenoma or carcinoma.

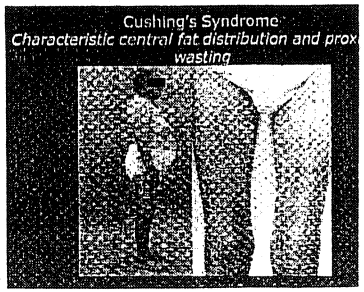
CUSHING'S DISEASE

- Pituitary microadenomas in 80 to 90%.
- Bilateral adrenal hyperplasia.
- Hypersecretion of ACTH and cortisol.

10 MOST COMMON S/S OF CUSHING'S SYNDROME

- Central weight gain.
- Plethora, round (moon) face.
- Decreased libido (men and women).
- Menstrual irregularities, hirsutism.
- Hypertension.
- Bruising, striae (wide, purple).
- Depression





SCREENING TESTS FOR CUSHING'S SYNDROME

- Urinary free cortisol (24 hr. urine).
- 1 mg. overnight dexamethasone suppression test (1 mg. at midnight, cortisol at 0800 next morning should be <140 mmol/l).

Note: phenytoin, alcohol, rifampin, phenobarbital increase dexamethasone clearance.

PITUITARY VS. ECTOPIC ACTH

- Pituitary MRI with gadolinium enhancement.
- ACTH modest elevation from pituitary, marked with ectopic.
- ACTH responds to CRH/AVP in Cushing's disease, but not ectopic.
- Overnight 8 mg (high dose) dexamethasone suppression test shows cortisol levels 50% below baseline with pituitary origin, but no suppression with ectopic ACTH.

INFERIOR PETROSAL SINUS SAMPLING (IPSS)

- With CRH/AVP stimulation.
- Measure side to side and central to peripheral gradients of ACTH.
- To distinguish between pituitary and ectopic.
- To lateralize pituitary adenoma.

TREATMENT OF CUSHING'S DISEASE

- Selective pituitary adenonectomy by transphenoidal surgery.
- Parallel treatment of compliations (hyperension, osteoporosis and diabets mellitus).
- May require glucocorticoid replacement for 6 to 12 months post-op.

Cortisone is essential for life.

ADRENAL INSUFFICIENCY

- Low ACTH with secondary causes and high ACTH in primary adrenal failure (Addison's Disease).
- Glucocorticoid therapy is most common secondary cause and idiopathic/autoimmune for primary.

SECONDARY VS. PRIMARY ADRENAL INSUFFICIENCY

- Weakness, fatigue, weight loss, anorexia, hypotension in both.
- Salt craving and hyperpigmentation only in primary failure.

TREATMENT OF ACTH/ CORTISOL DEFICIENCY

- Cortisol replacement in form of cortisone, hydrocortisone or prednisone.
- Education and medic-alert bracelet.
- Unlike primary adrenal insufficiency mineralcorticoid replacement not needed.

TSH

- α subunit shared with hCG, LH, FSH.
- β subunit unique.
- Synthesis stimulated by thyrotropin releasing hormone (TRH).
- Feedback inhibition by thyroid hormones T3 and T4.

HIGH TSH LEVELS

- Usually seen in primary hypothyroidism.
- Rarely a cause of hyperthyroidism.

TSH SECRETING PITUITARY TUMORS

- <3% of pituitary tumors.
- Unlike Graves' disease, no gender predilection.
- Hyperthyroidism, goitre.
- Headaches, visual field defects if macroadenomas.

TSH SECRETING PITUITARY TUMORS

- High ratio of α subunit to TSH.
- No response of TSH to TRH.
- May cosecrete other pituitary hormones.

TREATMENT OF TSH SECRETING TUMORS

- Prepare for surgery.
- Transphenoidal surgery initial therapy.
- Somatostatin analogues following surgery.
- Other - radiotherapy, dopamine agonists.
- Monitor and replace deficiencies post op.

THYROID HORMONE DEFICIENCY

- Replacement with Lthyroxine.
- Monitor free T4 for secondary deficiency vs. TSH for primary thyroid failure.

LH, FSH

- Glycoproterns with a common α subunit and a unique β subunit.
- Stimulated by gonadotropin releasing hormone (GnRH).
- Pulsatile secretion of LH is dependent on the pulsatile secretion of GnRH.
- Feedback inhibition by gonadal steroids and peptides.

LH, FSH

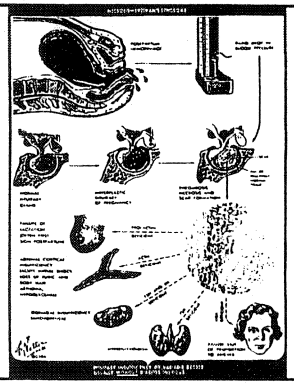
- Male: LH regulates testosterone synthesis and FSH regulates spermatogenesis.
- Female: Biphasic feedback (mostly negative with positive feedback at midcycle to induce ovulation).

KALLMAN'S SYNDROME

- Isolated GnRH deficiency with low LH, FSH, sex steroids.
- KAL gene defects in X chromosome.
- Failure of GnRH neurons to migrate from nasal mucosa to hypothalamus.
- Decreased sense of smell.
- Lack secondary sex characteristics.

SHEEHAN'S SYNDROME

- Acute necrosis of the anterior pituitary due to post partum hemorrhage and shock.
- Varying degrees of hypopituitarism.



PITUITARY APOPLEXY

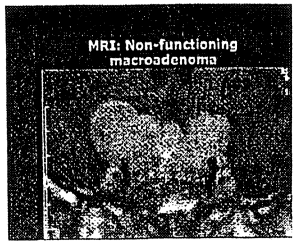
- Acute massive infarction of the pituitary.
- More common with non-secretoary tumors.
- SEVERE headache.
- Cranial nerve defects.
- Hypopituitarism of varying degrees.
- Glucocorticoids are life saving.
- Decompressive **surgery** may be required.

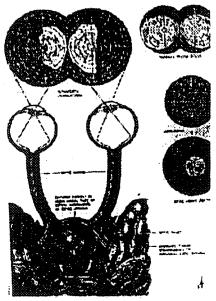
LYMPHOCYTIC HYPOPHSITIS

- Lymphocytic infiltration of anterior pituitary.
- Usually pregnant or post-partum.
- Modest increase in prolactin and varying degrees of hypopituitarism.
- Pituitary enlargement.
- Responds to surgical decompression.

GONADOTROPH ADENOMAS

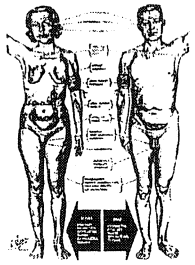
- Secrete FSH, α or β subunits.
- Follistatin used as tumor marker.
- Usually in **men** over 50 years of age.
- Hypogonadism.
- Headaches, visual field defects.
- Usually macroadenomas.





TREATMENT OF GONADOTROPH ADENOMAS

- Surgery
- Radiotherapy
- Adjunctive medical therapy (e.g. GnRH antagonists).
- Replace deficiencies.



FSH LEVELS IN POSTMENOPAUSAL WOMEN

- Should be high.
- If low suspect hypopituitarism.

REPLACEMENT OF SEX STEROIDS

- Usually oral, cutaneous or IM routes.
- Males: Testosterone
- Females: Estrogen and progesterone (uterus intact).

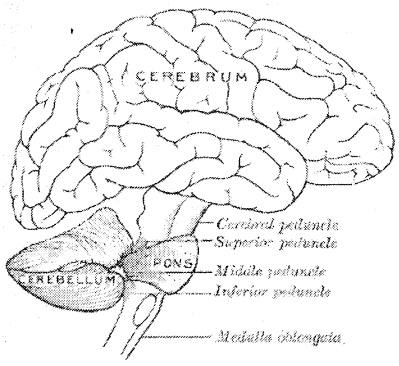
AXIS OF REGULATION OF ANTERIOR PITUITARY

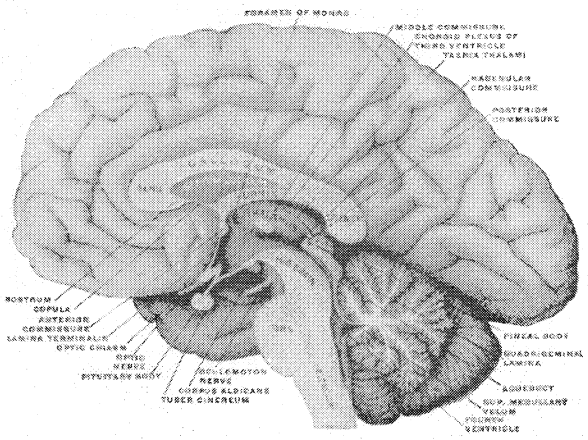
1. Higher CNS.
2. Hypothalamus (releasing and inhibiting).
3. Pituitary (trophic).
4. Peripheral glands/targets (Hormones) (feedback).
5. Physiologic actions (feedback).

PITUITARY HORMONE LEVELS

- Low in hypopituitarism.
- High in primary gland failure.
- Peripheral gland hormones low in both cases.

Evaluating Nervous System Function



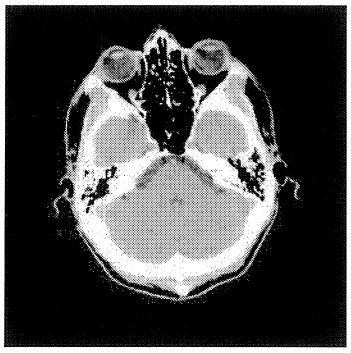


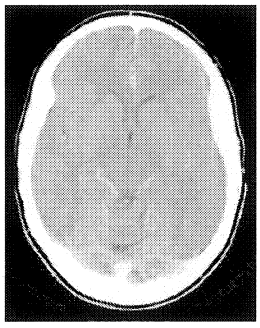
Neurological Investigations

STRUCTURE	FUNCTION
• CT scan	• EEG
• MRI scan	• Evoked Potentials
• Duplex scanning	• EMG
• Angiography	• PET scan
	• SPECT scan

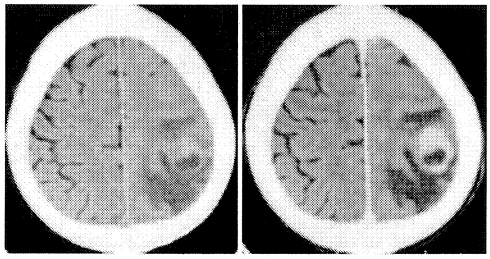
Tests to assess structure

Normal CT Scan Brain



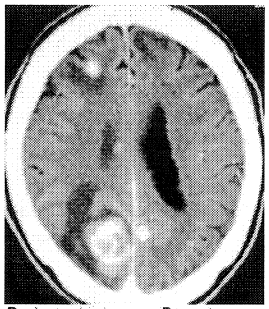


Brain Tumor



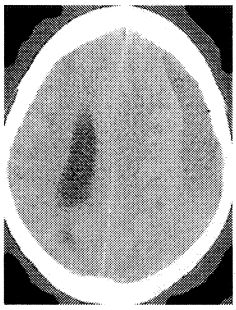
Non-contrast Contrast
Esophageal cancer - solitary metastasis

Multiple Metastases

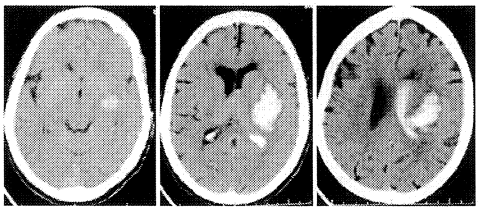


Brain metastases - Breast ca.

Subdural Hematoma



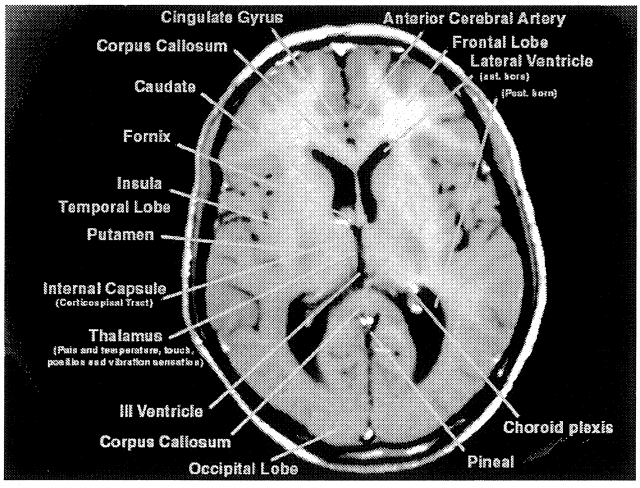
Intracerebral hematoma



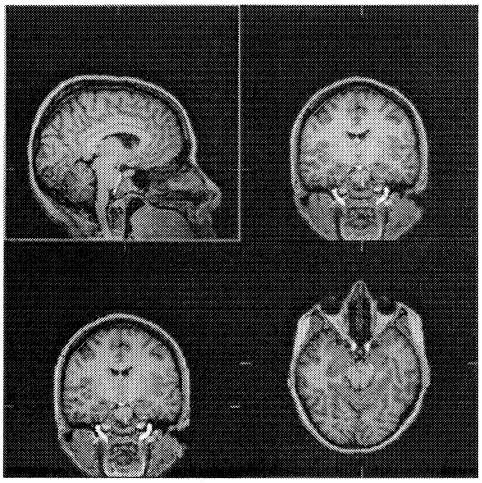
MRI Scan

- Most sensitive imaging technique
- Uses magnetic field rather than radiation to produce image
- Images in any plane can be constructed

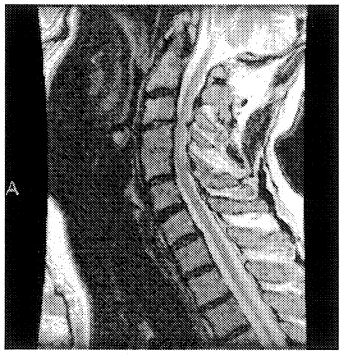
MRI Brain



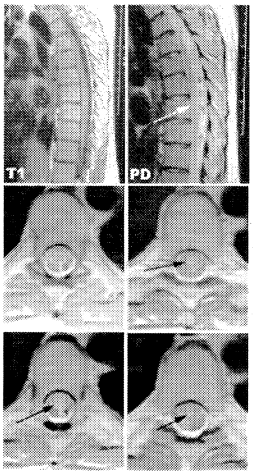
MRI Brain



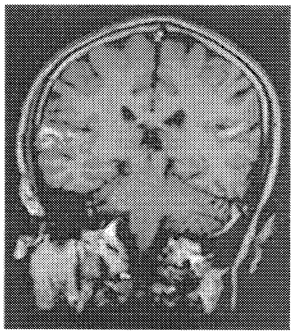
MRI Spine



MRI spine/transverse myelitis



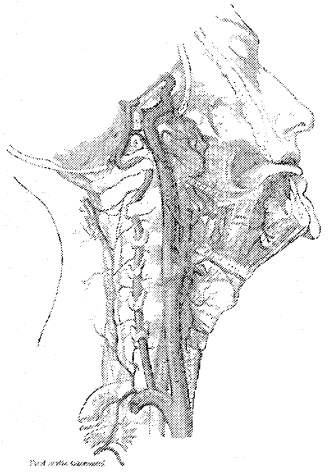
Functional MRI



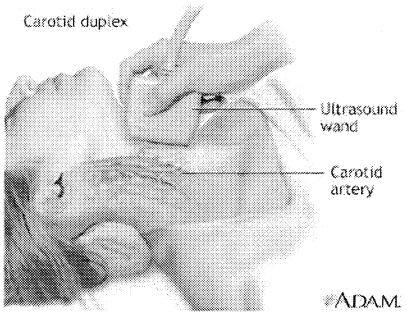
Duplex Scan

- Combined ultrasound (to visualize anatomy) + doppler (to assess blood flow)
- Main use is assessing internal carotid artery

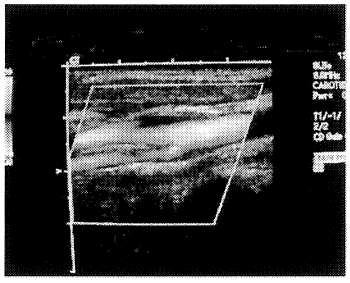
Internal Carotid Artery



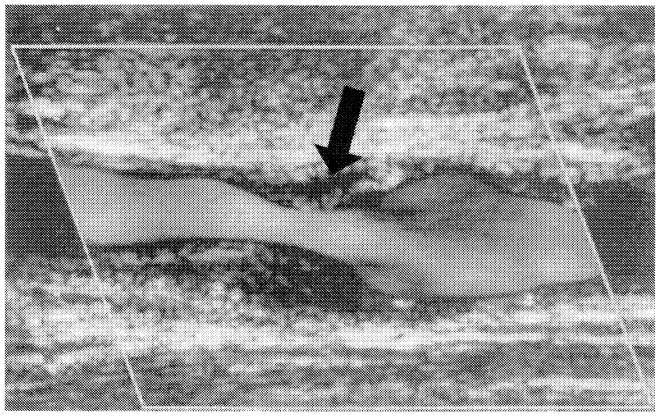
Carotid Duplex Scan



Carotid Duplex Scan



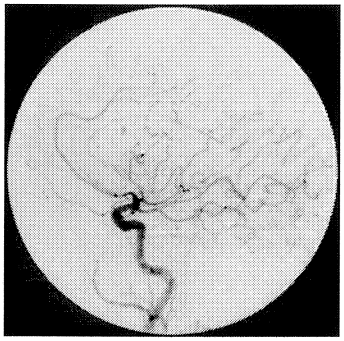
Carotid Duplex Scan



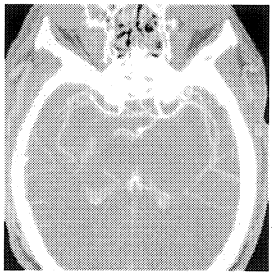
Cerebral Angiography

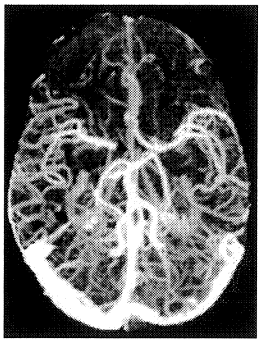
- Images cerebral blood vessels
- CT angiogram
- MR angiogram
- Conventional angiogram (invasive)

Cerebral Angiogram

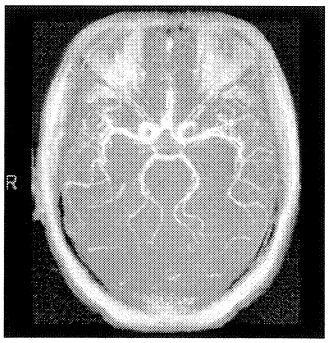


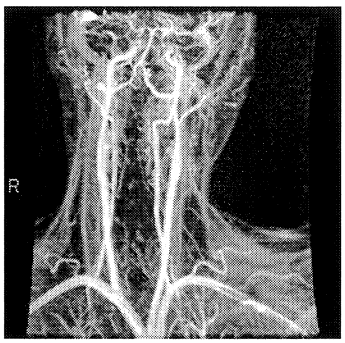
CT angiogram





MR angiogram



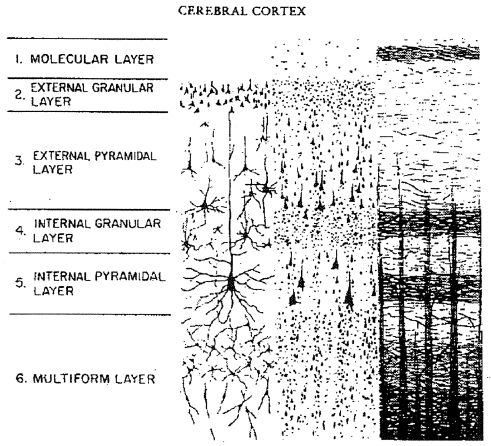


Tests to Assess Function

Electroencephalogram

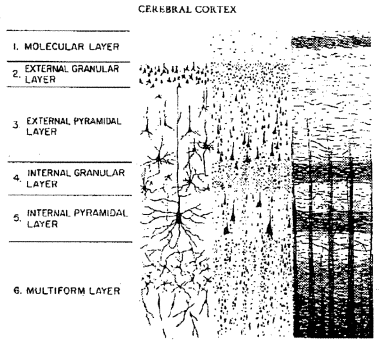
- Spontaneous electrical activity arising from brain detected with scalp electrodes
- Records summated excitatory and inhibitory postsynaptic potentials arising from pyramidal cells from cerebral cortex

Cerebral Cortex

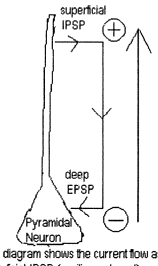


Cerebral Cortex

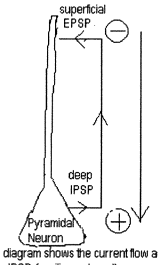
- 1:dendrites
- 2:input from cortex
- 3:output to cortex
- 4:input from extracortical sites
- 5:output to extracortical sites
- 6:output to thalamus



EEG: summated pyramidal cell post synaptic potentials

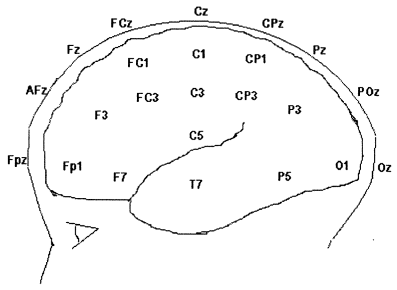


This diagram shows the current flow associated with a superficial IPSP (positive outward) or deep EPSP (negative inward) and the vertical upward equivalent dipole source .



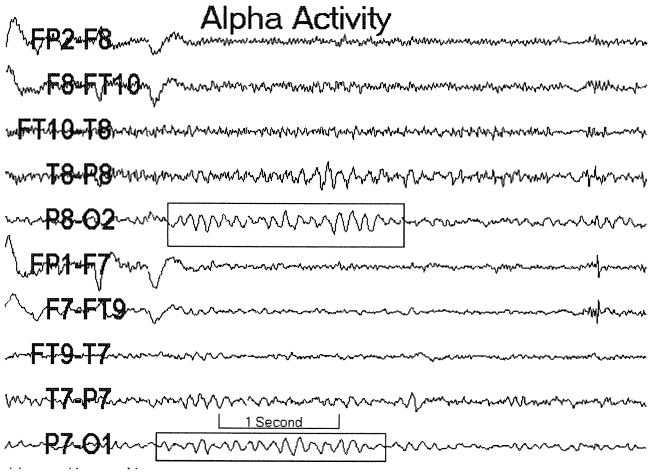
This diagram shows the current flow associated with a deep IPSP (positive outward) or superficial EPSP (negative inward) and the vertical downward equivalent dipole source .

10-20 system

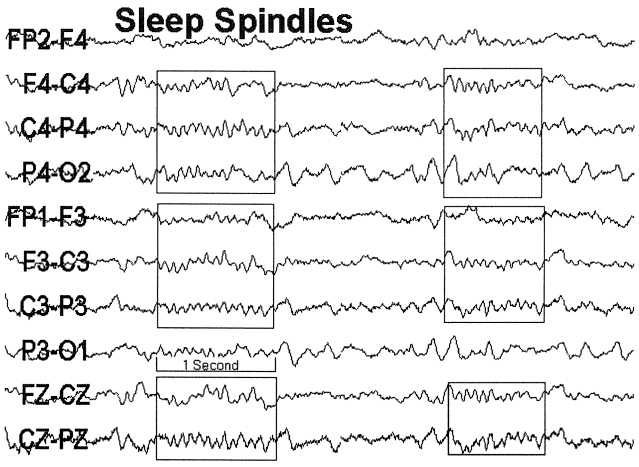


This illustration shows some of the standard electrode positions

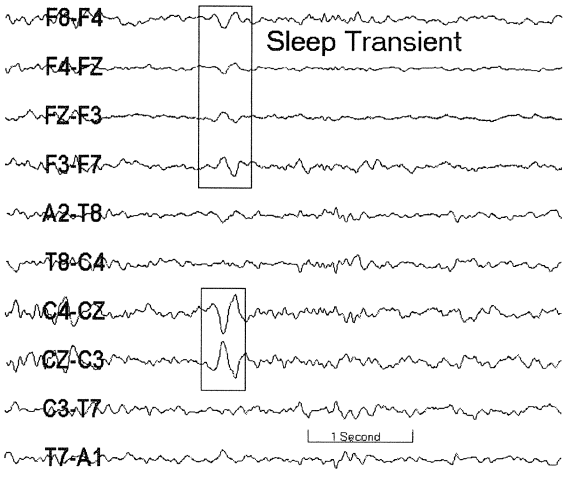
EEG



Sleep Spindles



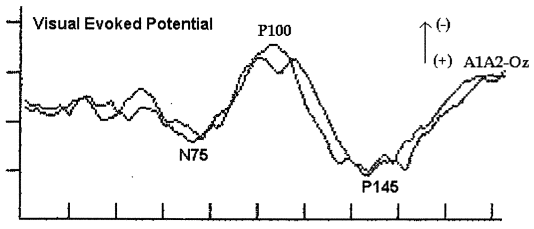
Sharp wave transients of sleep



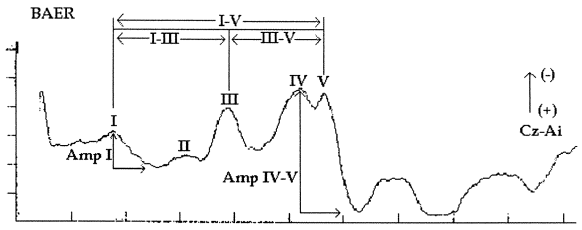
Evoked Potentials

- Electrical activity evoked by a particular sensory stimulus
- Visual, auditory, somatosensory
- Main use is assessing multiple sclerosis
- Subset of event-related potentials

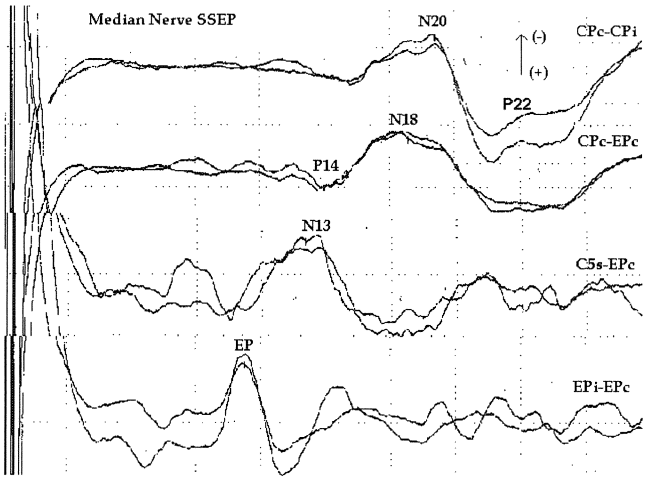
Visual Evoked Response



Brainstem Auditory Evoked Response



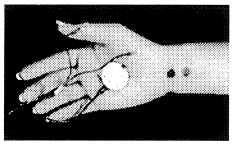
Somatosensory Evoked Response

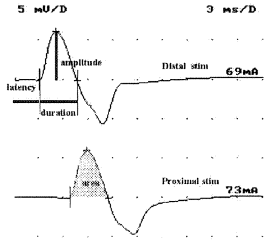


Nerve conduction studies and electromyography

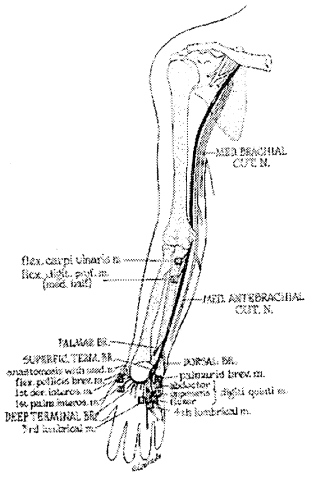
- Assesses peripheral nervous system function (nerve and muscle)

Nerve Conduction Studies

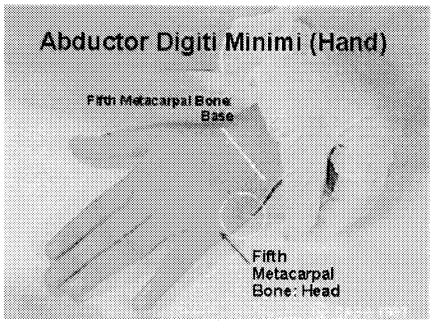




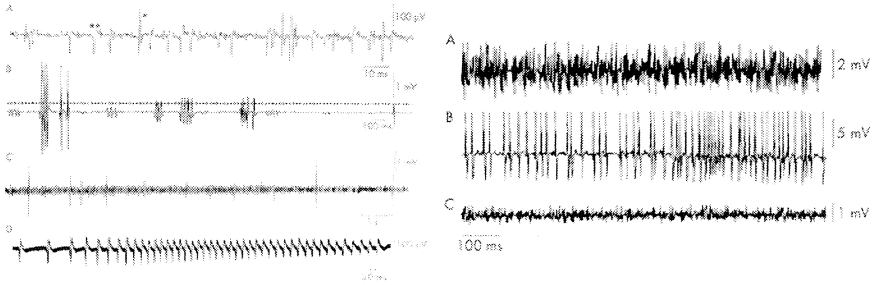
Peripheral Nerve



EMG



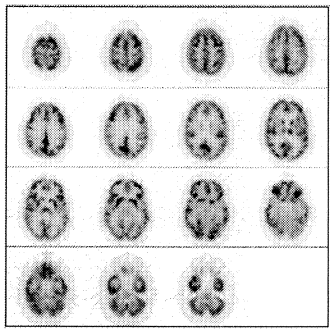
EMG (spontaneous(L) and voluntary activity(R))



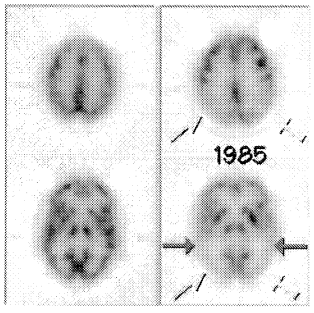
Positron Emission Tomography

- Uses positron emitting isotopes
- Fluorodeoxyglucose scan images areas that have decreased (or increased) metabolic rates

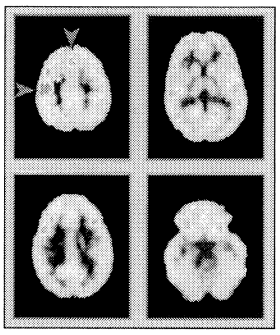
Normal PET



PET in Alzheimer's Disease



PET Move right foot

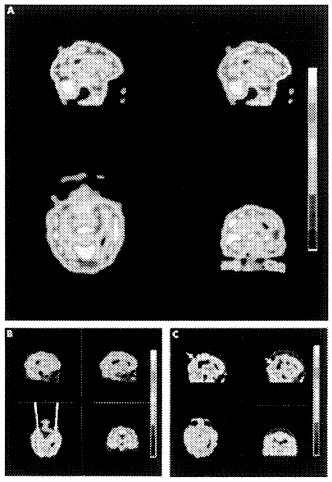


SPECT scan

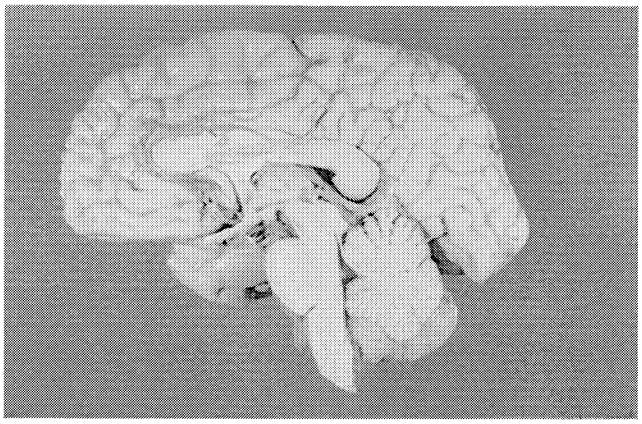
- Uses photon emitting isotopes (Tc-HMPAO)
- Perfusion scan reflecting metabolic activity

SPECT Scan

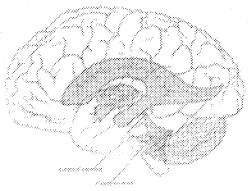
- A: normal brain (L and R parasagittal, transverse temporal and coronal)
- B: late onset Alzheimer's (decrease temporal perfusion)
- C: early onset Alzheimer's (decrease parietal perfusion)

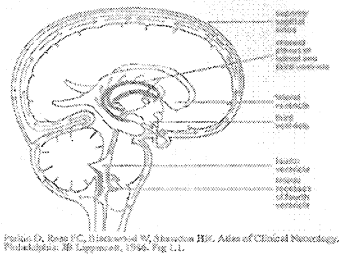


Analysis of CSF

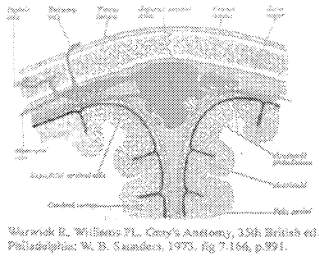


CSF production and flow





CSF absorption

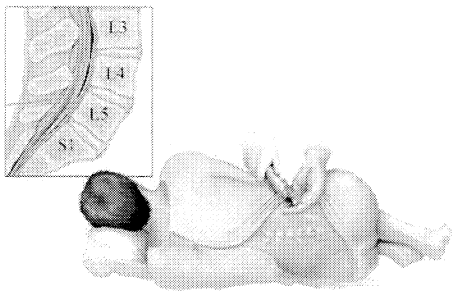


Warwick R., Williams P.L. Gray's Anatomy, 35th British ed. Philadelphia: W. B. Saunders, 1973. Fig 7.164, p.891.

Cerebrospinal Fluid

- There is about 150 cc CSF produced at a rate of 500 cc/day
- CELLS: less than 5*10^6 WBC/liter
- PROTEIN: less than 0.45 gm/liter
- GLUCOSE: less than 2/3 blood glucose

Lumbar Puncture



Lumbar Puncture

- Opening pressure: less than 180 mm H2O
- CSF: clear and colourless
- CSF analysis: cell count
  microbiology
  protein, glucose
  +/- cytology
  +/- special studies

CSF pleocytosis

- Polymorphonuclear pleocytosis = bacterial meningitis
- Mononuclear pleocytosis = viral meningitis, TB meningitis, fungal meningitis

CSF biochemistry

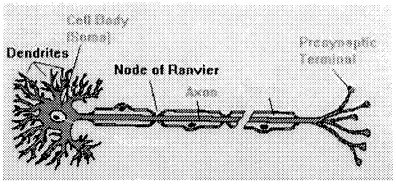
- increased protein: non-specific
- Decreased glucose = bacterial meningitis

CSF special studies

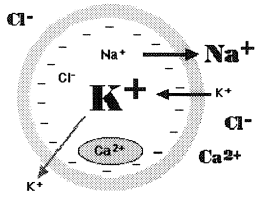
- Oligoclonal banding
- Bacterial and viral antigens (PCR)
- 14-3-3 protein (JC disease)
- Tau, beta-amyloid (Alzheimer's)

Neurophysiology Review

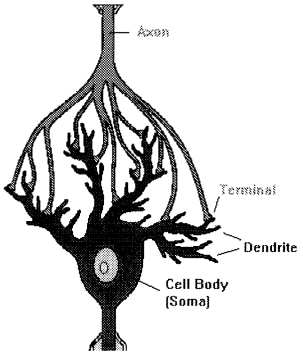
The Neuron

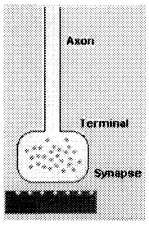


Membrane Potential

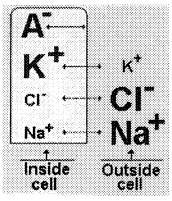


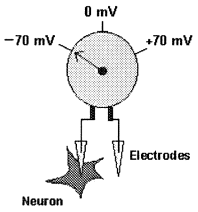
Synaptic Terminal

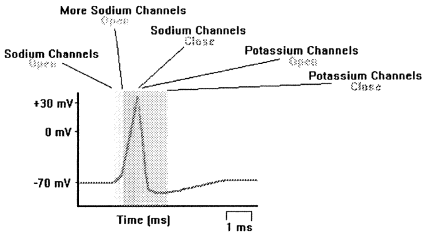




Membrane Potential







Neurophysiology Review

- Transmission of information in nervous system is electrical and chemical
- Post-synaptic potentials -> action potential

Neurotransmitters

- Excitatory-ionotropic
  -metabotropic
- Inhibitory-ionotropic
  -metabotropic

Glutamate

Main excitatory neurotransmitter

1) Ionotropic receptors: non-NMDA and NMDA
2) Metabotropic receptors

Glutamate(ionotropic receptors)

- AMPA: main non-NMDA receptor
  opens Na channels

- NMDA: opens Ca channels

Acetylcholine
excitatory neurotransmitter

- Ionotropic receptor: nicotinic
- Metabotropic receptor: muscarinic

GABA

- Main inhibitory neurotransmitter
- GABA-A receptor: Ionotropic
  opens Cl channels
- GABA-B receptor: Metabotropic
  presynaptic action

Neuromodulators

- Neurotransmitter that has only metabotropic effects
- Examples include dopamine, norepinephrine, serotonin, enkephalins, other peptides including substance P and cholecystokinin.

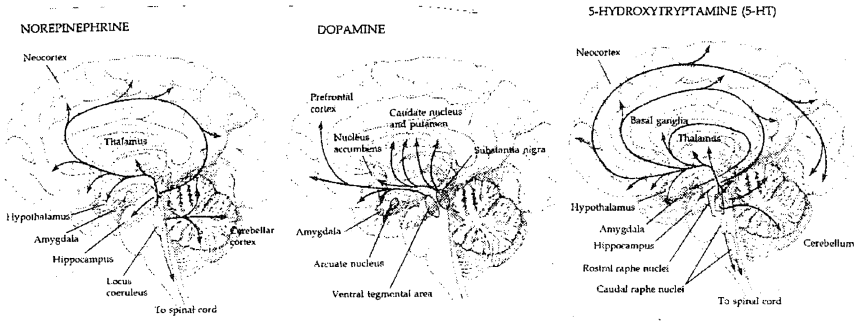
Diffuse neuromodulators

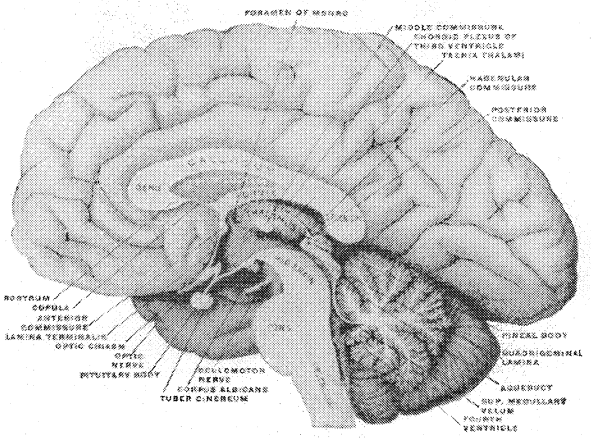
- Dopamine, norepinephrine, serotonin and acetylcholine
- Found diffusely in CNS
- Cell bodies of neurons that produce these neurotransmitters are localized.
- Produce diffuse facilitation or inhibition
- Implicated in anxiety, depression etc.

Origin of the cell bodies of diffuse neuromodulators

- Dopamine: midbrain-substantia nigra
- Norepinephrine: pons-locus coeruleus
- Serotonin: whole brainstem-dorsal raphe nuclei
- Acetylcholine: basal forebrain-nucleus basalis of Meynert

Neuromodulator pathways




FORAMEN OF MONRO
MIDDLE COMMISSURE
CHOROID PLEXUS OF THIRD VENTRICLE
TAENIA THALAMI
HABENULAR COMMISSURE
POSTERIOR COMMISSURE
ROSTRUM
CORPUS CALLOSUM
ANTERIOR COMMISSURE
LAMINA TERMINALIS
OPTIC CHIASM
OPTIC NERVE
PITUITARY BODY
OCULOMOTOR NERVE
CORPUS ALBICANS
TUBER CINEREUM
PINEAL BODY
QUADRIGEMINAL LAMINA
AQUEDUCT
SUP. MEDULLARY VELUM
FOURTH VENTRICLE

EPILEPSY

Epilepsy

- Common: 1% population epileptic
- Life-time chance of non-febrile seizure: 2-5%.
- Risk of febrile seizure before age 5 : 5%
- ++pharmacology

Epilepsy

- Epilepsy: chronic disorder characterized by recurrent seizures
- Seizure: hypersynchronous discharge among large populations of neurons

Seizure Etiology

- Provoked: alcohol withdrawl and syncope
- Unprovoked: etiology is dependent on age at initial onset.
  - before 30: idiopathic
  - 30-55: neoplasm
  - over 55: cerebrovascular disease
  - geriatric: cerebrovascular and Alzheimer's

Seizure Classification

Partial: 1) Simple (No alteration in consciousness)

2)Complex (Alteration in consciousness)

Generalized

Partial (focal, local) seizures:
Simple - motor, somatosensory, autonomic, psychic

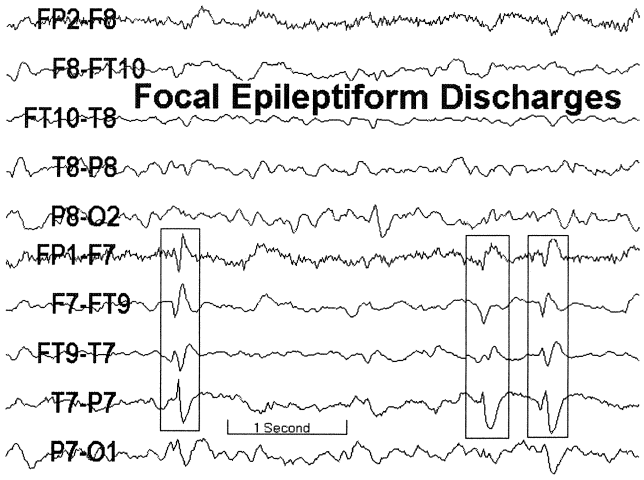
Complex
Impaired consciousness at outset
Simple partial followed by impaired consciousness

Partial seizures evolving to generalized tonic-clonic (GTC)
Simple to GTC
Complex to GTC

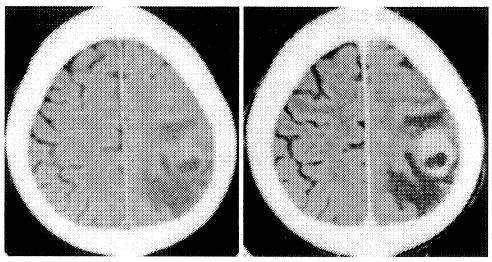
Generalized seizures (convulsive or non-convulsive)
Absence seizures
Atypical absences
Myoclonic
Clonic
Tonic
Tonic-clonic
Atonic
Combinations

Unclassified epileptic seizures

Focal Seizure



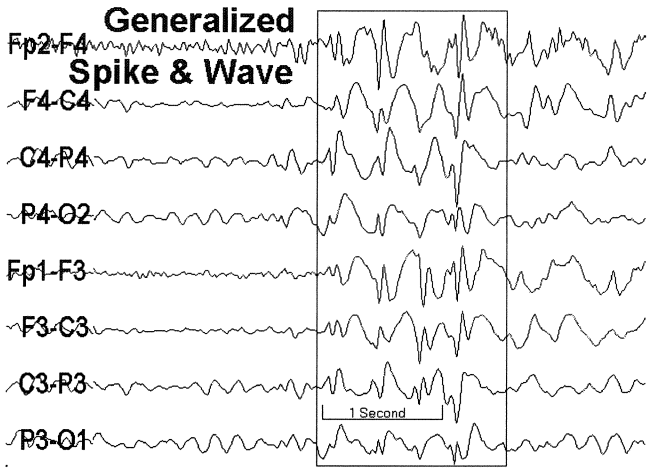
Brain Tumor



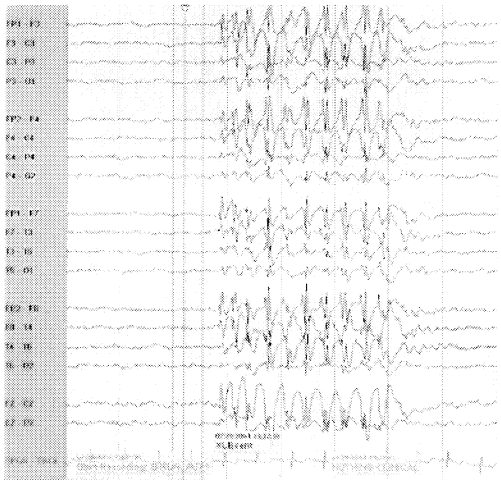
Non-contrast Contrast

Esophageal cancer - solitary metastasis

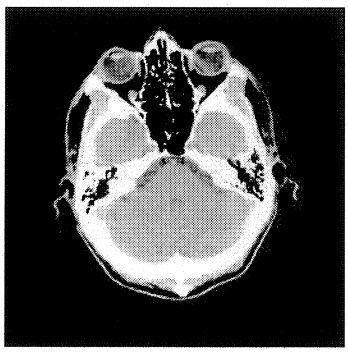
Generalized Seizure

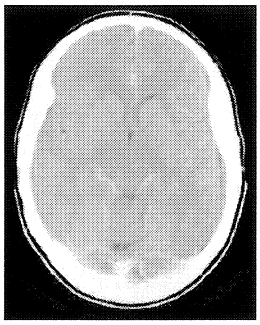


3/second spike and wave



Normal CT Scan Brain





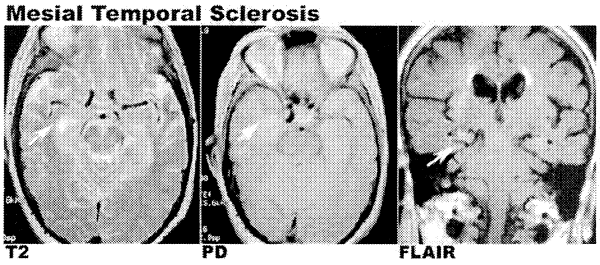
Epilepsy Classification

- Syndromes classified according to seizure type, EEG, age of onset, hereditary factors

- Two groups of epilepsy syndromes:
  1) localization related
  2) generalized

  commonest epileptic syndrome is complex partial seizures+/- secondary generalization due to mesial temporal sclerosis.

Mesial Temporal Sclerosis



Syndromes

EPILEPSY SYNDROMES AND RELATED CONDITIONS

- **Benign familial neonatal seizures**
- **Early myoclonic encephalopathy**
- **Ohtahara syndrome**
- *** Migrating partial seizures of infancy**
- **West syndrome**
- **Benign myoclonic epilepsy in infancy**
- **Benign familial and non-familial infantile seizures**
- **Dravet's syndrome**
- HH syndrome
- *** Myoclonic status in nonprogressive encephalopathies**
- **Benign childhood epilepsy with centrotemporal spikes**
- **Early onset benign childhood occipital epilepsy (Panayiotopoulos type)**
- **Late onset childhood occipital epilepsy (Gastaut type)**
- **Epilepsy with myoclonic absences**
- **Epilepsy with myoclonic-astatic seizures**
- **Lennox-Gastaut syndrome**
- **Landau-Kleffner syndrome**
- **Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)**
- **Childhood absence epilepsy**
- Progressive myoclonus epilepsies
- Idiopathic generalized epilepsies with variable phenotypes
  - **Juvenile absence epilepsy**
  - **Juvenile myoclonic epilepsy**
  - Epilepsy with generalized tonic-clonic seizures only
- Reflex epilepsies
  - **Idiopathic photosensitive occipital lobe epilepsy**
  - **Visual sensitive epilepsies**
  - **Primary reading epilepsy**
  - **Startle epilepsy**
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial temporal lobe epilepsies
- * Generalized epilepsies with febrile seizures plus
- * Familial focal epilepsy with variable foci
- Symptomatic (or probably symptomatic) focal epilepsies
  - Limbic epilepsies
    - Mesial temporal lobe epilepsy with hippocampal sclerosis
    - Mesial temporal lobe epilepsy defined by specific etiologies
    - Other types defined by location and etiology
  - Neocortical epilepsies
    - **Rasmussen syndrome**
    - Other types defined by location and etiology

* Syndromes in development

Conceptualizing seizures

- Normal behavior -> sudden, unprovoked change in behavior
- Normal EEG -> sudden, unprovoked change in EEG
- How to conceptualize?

Linear Systems

- Intuitive
- $F(a+b)=F(a) + F(b)$

Non-linear Systems

- Many examples: dripping faucet, turbulence
- In chemistry, non-linear systems often demonstrate auto-catalysis where the product of a chemical reaction facilitates its own synthesis (the product may activate the enzyme responsible for the product's synthesis=positive feedback).

Non-linear Systems

- The dynamics of a non-linear system remains fixed over a range of parametric values but at a critical value, a sudden change in dynamics occurs (bifurcation)
- The brain is an immense non-linear dynamical system (action potentials are non-linear)
- Neuronal excitability is the relevant parameter

Non-linear systems and seizures

- Under normal conditions, over the range of general neuronal excitability experienced, the brain dynamics does not change.
- Under certain conditions (alcohol withdrawl etc.) brain excitability can increase enough so that even normal brain dynamics can bifurcate-> seizure
- In seizure disorders, even in the range of normal excitability fluctuations, a change in dynamics can occur spontaneously -> seizure.

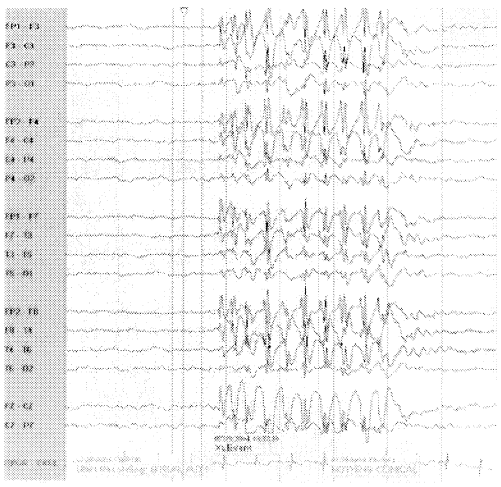
HOW? -> nonlinear system

WHY?

Primary Generalized Seizures

- Usually start in childhood
- Often genetic (channelopathies)
- Brain is often structurally normal
- EEG: paroxysmal discharges over both hemispheres
- Prototype primary generalized seizure is absence seizure
- Absence :brief LOC (staring spell)
  EEG is 3/sec spike and wave

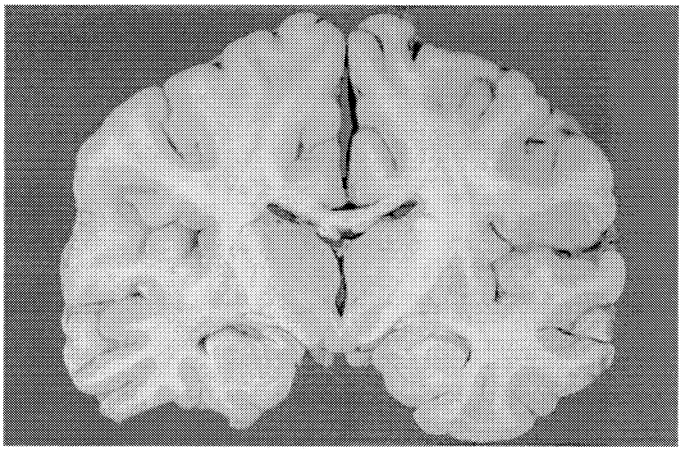
3/second spike and wave



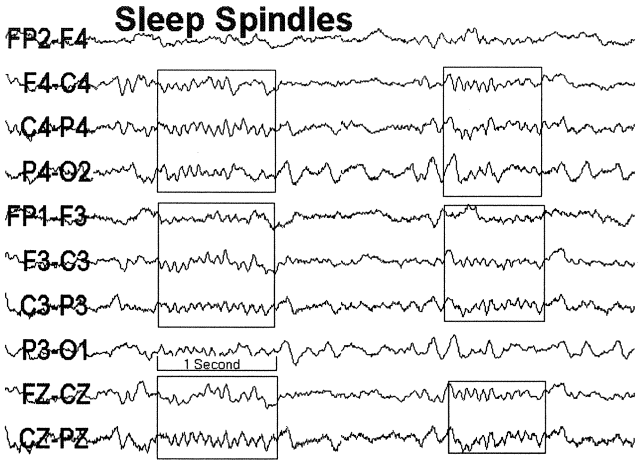
3/sec spike and wave

- Generation of 3/sec spike and wave related to same system that generates sleep spindles
- System involves reticular nucleus of thalamus, thalamic neurons and cortex

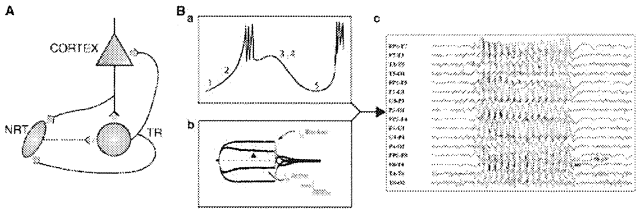
Reticular Nucleus of Thalamus



Sleep Spindles



Absence Seizure



Absence Seizure

- Normally, reticular nucleus and thalamic neurons are tonically active
- During sleep, these cells become hyperpolarized
- Hyperpolarization may cause these cells to burst fire which is the basis of sleep spindles

Absence Seizures

- In absence seizures, neurons of reticular nucleus and thalamus burst fire spontaneously (even when awake)
- Burst firing with spindles or 3/sec SW is associated with opening of Ca channels (NMDA receptors) followed by opening of Ca dependent K channels which causes hyperpolariztion of the neurons after the burst.
- Ethosuximide blocks this Ca dependent K conductance.

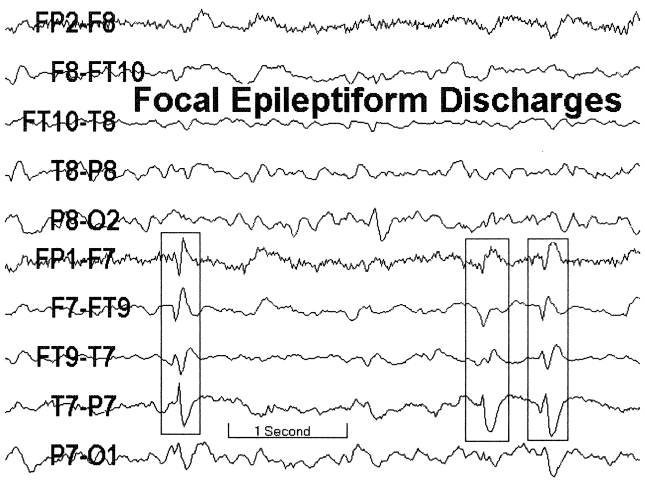
Primary Tonic Clonic Seizure

- Pathophysiology not as well defined as with absence seizure
- Neurons in thalamocortical loops suddenly change dynamics resulting in whole brain electrical discharge

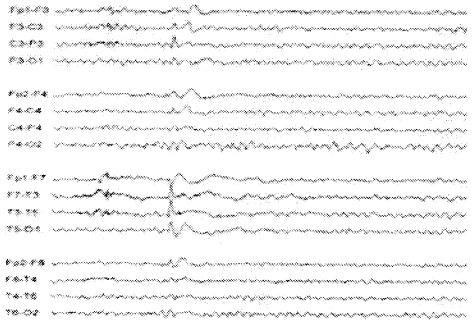
Partial Seizures

- Often acquired
- Brain has a focal structural abnormality
- EEG :focal discharges localized to area of involvement
- EEG hallmark: interictal spike

Focal Seizure



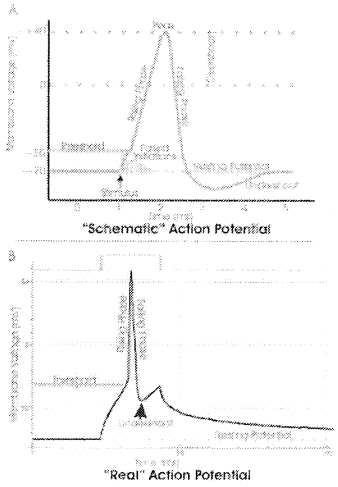
Focal Seizure (interictal)



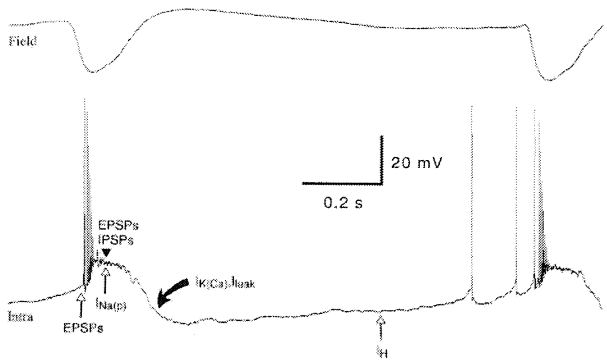
Interictal spike

- Cellular basis of interictal spike is the paroxysmal depolarization shift (PDS)
- PDS is a large, prolonged EPSP on which is superimposed a burst of action potentials (burst firing)
- Burst firing requires opening of Ca channels through NMDA receptors

Normal action potential



Paroxysmal depolarization shift



Paroxysmal depolarization shift

- There are cells in the cortex that normally burst fire; these cells are particularly common in hippocampus in temporal lobes and may be a reason temporal lobe seizures are common
- These cells initiate the interictal spike (PDS)

Paroxysmal depolarization shift

- In normal brain, if these cells discharge-> no seizure
- Lesion in CNS induces changes that amplify the effect of these burst firing cells leading to PDS

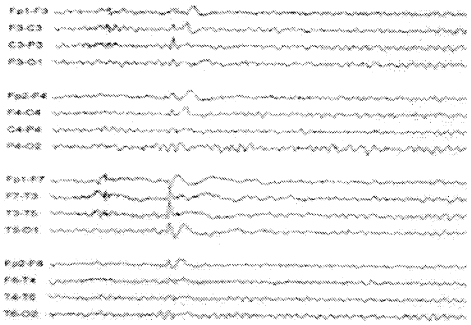
Paroxysmal depolarization shift

- Axon sprouting in lesions produces recurrent loops that result in re-excitation; this is probably most important structural basis for partial seizures
- Inhibitory neurons more sensitive to injury
- Neuronal membrane properties change in lesions

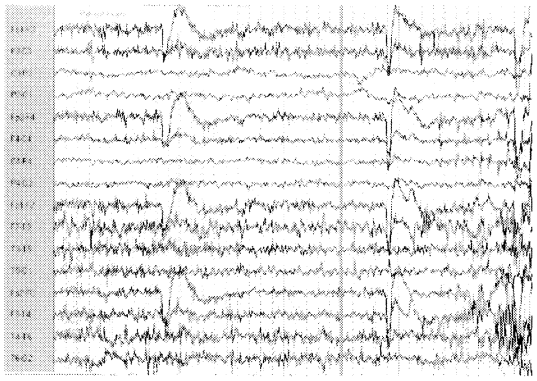
Paroxysmal depolarization shift

- Interictal spike (PDS) is not seizure
- Seizure occurs when there is spread of discharge into normal surrounding cortex leading to self sustained persistent discharge

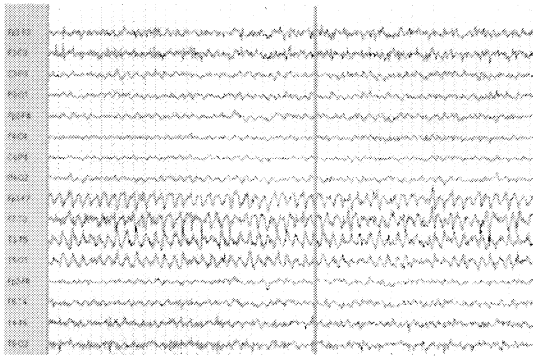
Focal Seizure (interictal)



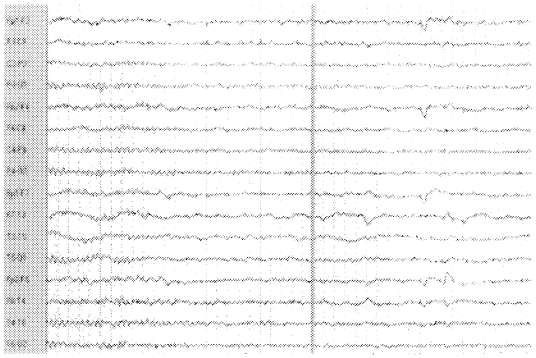
Focal Seizure
(clinical onset; EEG normal)



Focal Seizure
(rhythmic temporal theta activity)



Focal Seizure
(post-ictal slowing)



PDS to Seizure

- Normally PDS followed by a local hyperpolarization (spike and wave); in addition PDS usually surrounded by area of hyperpolarization (surround inhibition)
- These hyperpolarizations are replaced by persistent electrical activity as normal brain is entrained in the seizure

Synaptic mechanisms for interictal to ictal transformation

- Repetitive neuron firing leads to increase in strength of excitatory synapses (due to increased intracellular Ca in presynaptic terminal)
- Repetitive neuron firing leads to decrease in strength of inhibitory synapses (due to increased intracellular Cl)

Goldman Equation

-
- E=K*(Pna[Na]o + Pk[K]o + Pcl[Cl]i) /
- (Pna[Na]i + Pk[K]i + Pcl[Cl]o).

- P =permeability

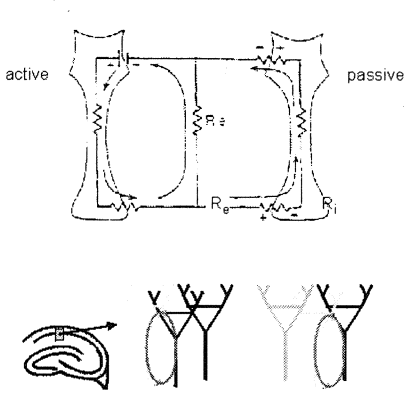
Ion Concentrations

	Extracellular (mmol/L)	Intracellular (mmol/L)	Equilibrium pot (mV)
• Na	145	12	66
• K	4	155	-97
• Cl	120	4	-90

Non-synaptic mechanisms for interictal to ictal transformation

- Increase in extracellular K with neuronal firing leads to diffuse depolarization
- Ephaptic interaction; synchrounous discharge from many neurons causes large extracellular current flows that can depolarize surrounding neurons

Ephaptic Interaction



Generalized seizure

- After partial seizure starts, there can be spread of abnormal discharge to thalamus and subsequent spread to all areas of cerebral hemispheres

Seizure prevention

- Decrease neuronal excitability pharmacologically
- Prevent PDS (Benzodiazepines, Pb)
- Prevent neurons from discharging rapidly (phenytoin, carbamazepine, valproate)

Alzheimer's Disease and Parkinson's Disease

Degenerative Diseases

- Chronic neurological conditions associated with progressive loss of neurons (without evidence of cell necrosis or inflammation)
- Alzheimer's disease, Parkinson's disease, motor neuron disease (ALS).
- Pathogenesis not definite in any degenerative condition but theories similar in all conditions

Pathogenesis of degenerative conditions

- Excitatory amino acid toxicity (glutamate)
- Free radical formation
- Neural apoptosis (programmed cell death)
- Accumulation of misfolded intracellular proteins

Intracellular protein

- Tau=microtubule associated protein
- Hyperphosphorylated tau -> insoluble fibrils -> neurofibrillary tangles (Alzheimer's disease)
- Synuclein=intracellular protein->can polymerize to form Lewy body (Parkinson's disease)

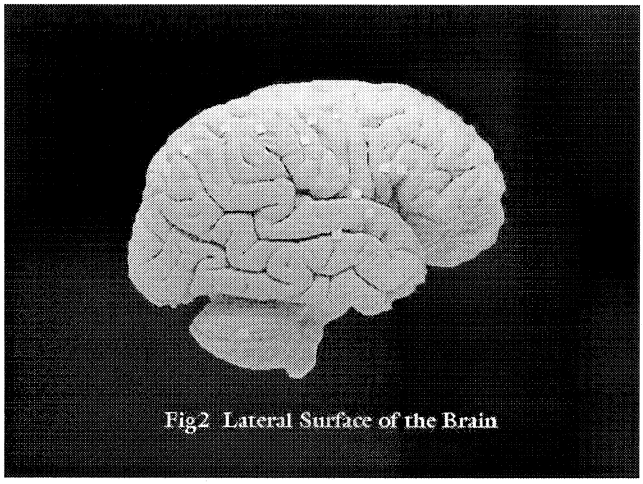
Alzheimer's disease

- Common
- Progressive memory loss and cognitive dysfunction
- Familial and sporadic

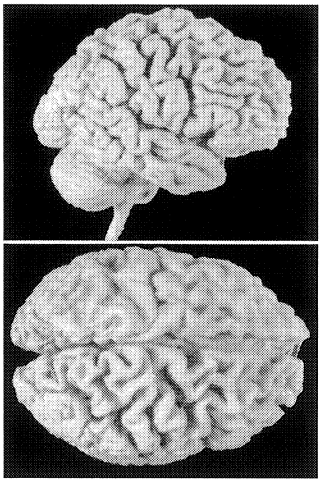
Alzheimer's Disease Pathology

- Neuronal loss (temporal/parietal)
- Neurofibrillary tangles
- Amyloid plaques

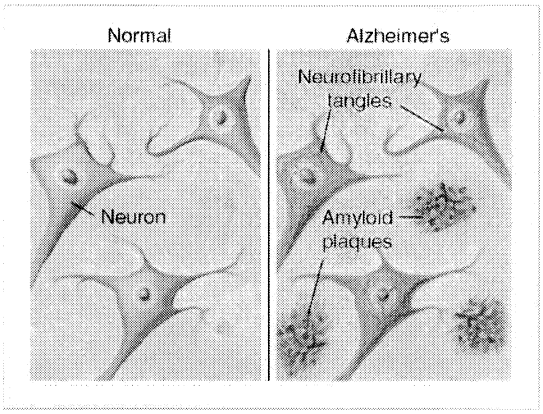
Normal Brain



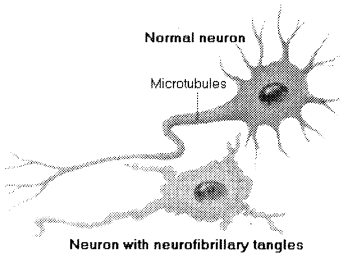
Cerebral Atrophy

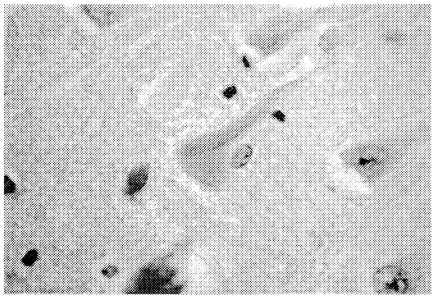


Alzheimer's Disease

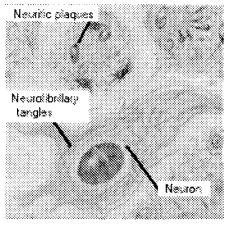


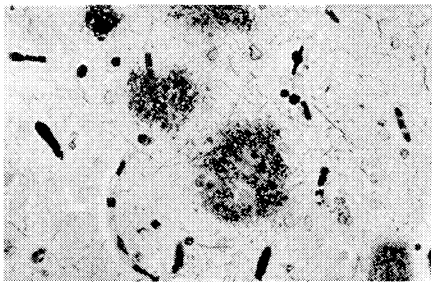
Neurofibrillary Tangle





Amyloid Plaque

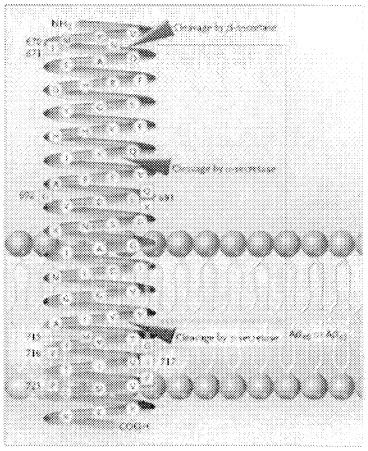




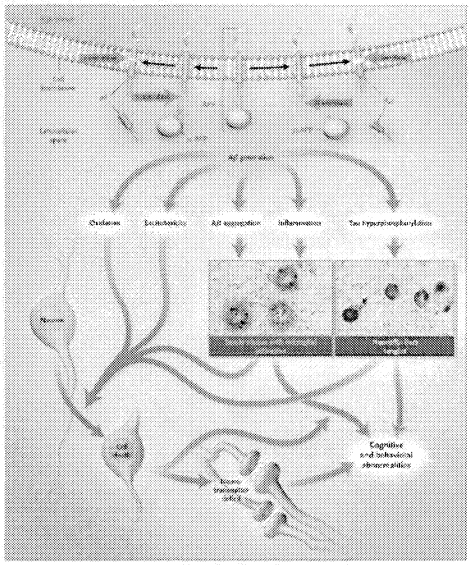
Pathogenesis

- Tauists believe AD is a primary neuronal disturbance and amyloid deposition is secondary
- Baptists believe amyloid deposition is primary and results in neuronal death

Amyloid Precursor Protein



Amyloid Toxicity



Familial Alzheimer's disease

- Early onset, autosomal dominant familial AD due to mutations in gene that codes for amyloid precursor protein (chr 21)
- Subsequently, two other genes responsible for early onset, autososmal dominant AD found (code for presenilin 1 and presenilin 2)

Familial Alzheimer's disease

- Late onset, autosomal recessive AD due to gene that codes for apolipoprotein E4 (chr 19).

Sporadic Alzheimer's disease

- Risk factors include age, apolipoprotein E status (E4 bad, E2 good), history head trauma, limited education
- Protective factors include NSAIDs (?), physical exercise (?), mental exercise, antioxidants(vit E)?

Prevention of Alzheimer's disease

- Prevent beta amyloid deposition by blocking breakdown of amyloid precursor protein to beta amyloid peptide (block the secretases)

Symptomatic treatment of AD

- Early changes of AD seen in nucleus basalis of Meynert -> acetylcholine deficiency cause of early symptoms such as memory loss
- Cholinesterase inhibitors improve symptoms
- Mementine (NMDA antagonist) beneficial in moderate to severe AD

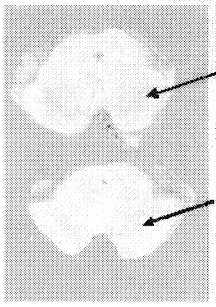
Parkinson's disease

- Common
- Classic triad of tremor, rigidity and bradykinesia (slowness of movement)
- Familial and sporadic

Parkinson's Disease pathology

- Loss of neurons in substantia nigra of midbrain -> dopamine deficiency
- Lewy bodies in substantia nigra neurons

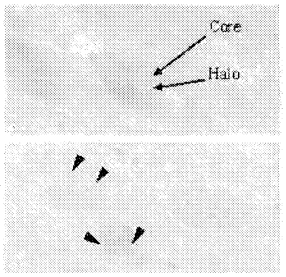
Parkinson's Disease



The substantia nigra in a normal individual appears as a black line on post-mortem examination due to the presence of large pigmented neurons that produce dopamine

The substantia nigra becomes pale (loss of pigmented neurons) in PD with the loss of neurons

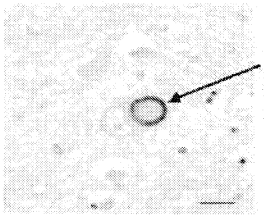
Lewy Body (H&E)



Lewy Bodies in the substantia nigra have a round appearance with a dense "core" surrounded by a clear "halo".

A single neuron may contain multiple Lewy bodies

Lewy Body (immunoperoxidase)



Lewy bodies can be more easily detected using special antibodies against the alpha-synuclein protein

Parkinson's disease

- Initial treatment with l-dopa very effective
- 5 years later -> wearing off
- 10 years later -> dyskinesia

PD pathogenesis

- Familial PD: first mutation discovered was in gene that coded for synuclein; several further gene loci discovered.
- Sporadic PD: no significant gene association as opposed to AD with the apolipoprotein E association
- Sporadic PD risk factors: exposure to insecticides and herbicides; smoking is protective for PD!

Parkinson's Disease Genes

Table 1. **Mutations in Single Genes That Lead to Parkinson's Disease.**

Locus	Gene	Location	Mode of Inheritance	Where Found
PARK1	α-Synuclein	4q21	Autosomal dominant	Greece, Italy, and Germany
PARK2	Parkin	6q25–27	Autosomal recessive; may also be autosomal dominant	Ubiquitous
PARK3	Unknown	2p13	Autosomal dominant	Germany
PARK4	Unknown	4p15	Autosomal dominant	United States
PARK5	Ubiquitin C-terminal hydrolase	4p14	May be autosomal dominant	Germany
PARK6	Unknown	1p35	Autosomal recessive	Italy
PARK7	DJ-1	1p36	Autosomal recessive	Netherlands
PARK8	Unknown	12p11.2–q13.1	Autosomal dominant	Japan

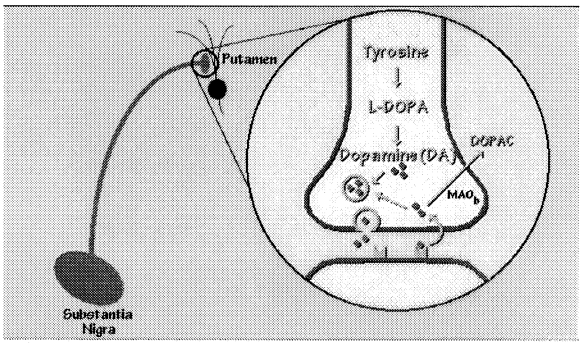
Oxidative stress and PD

- Dopamine metabolism results in reactive oxygen species (oxidative deamination of dopamine by MAO -> H2O2)
- Glutathione (an antioxidant) levels depressed in PD
- Coenzyme Q10 study: 1200 mg/day may slow progression

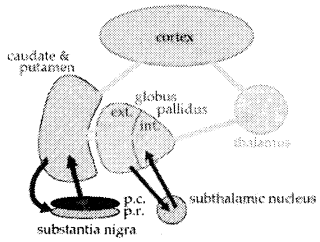
Animal model of PD

- The MPTP story and MAO-B inhibitors

Origin of signs and symptoms of dopamine deficiency



Cortical basal ganglia loop



Physiological consequence of dopamine deficiency

- Increased tonic output of inhibitory neurons from globus pallidus to thalamus
- Treatment with l-dopa reverses this change
- Lesion in subthalamic nucleus reverses this change

Dyskinesia

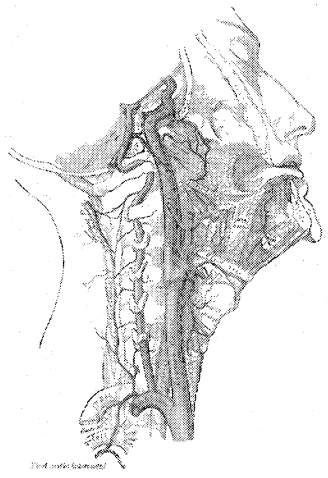
- Occurrence related to fluctuations in dopamine levels from oral l-dopa treatment
- Amantadine (a NMDA antagonist) improves dyskinesia

Surgery

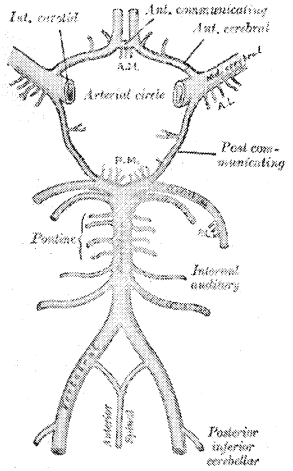
- Pallidotomy
- Stimulator into globus pallidus, subthalamic nucleus or thalamus
- Brain transplants
- Stem cells

STROKE/MIGRAINE

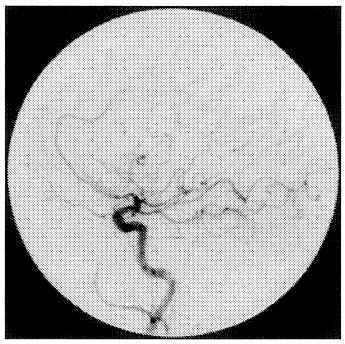
Internal Carotid Artery

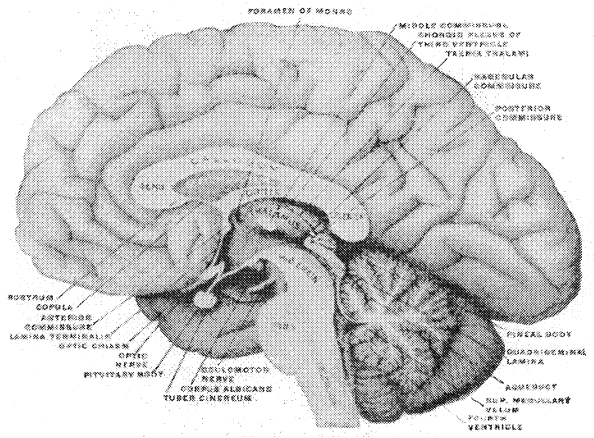


Arteries at Base of Brain

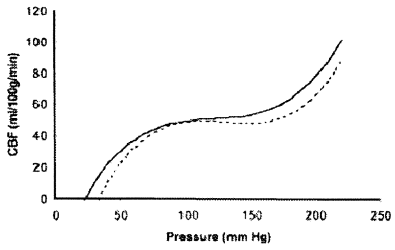


Cerebral Angiogram





Cerebral Autoregulation



Stroke

- Stroke=acute neurological deficit (on vascular basis)

- Classify according to temporal evolution:
  1) TIA: less than 30 minutes
  2) RIND: less than 24 hours
  3) Stroke: permanent deficit
  4) Stroke-in-evolution: progressive deficit

Stroke classification based on pathogenesis

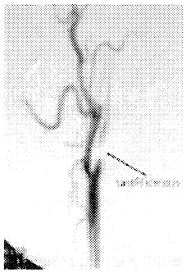
Infarcts: 1) large vessel disease
(thromboembolic infarct)
2) small vessel disease
(lacunar infarct)
3) cardiac emboli

Bleeds: 1) intraparenchymal
2) subarachnoid

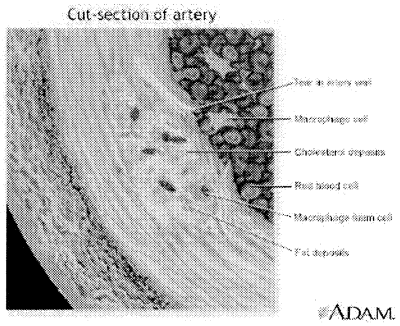
Thromboembolic Infarct

- 30-40% of strokes
- In case of carotid distribution stroke, almost always due to atheroma at origin of internal carotid artery
- In case of vertebrobasilar distribution stroke, atheroma more evenly distributed

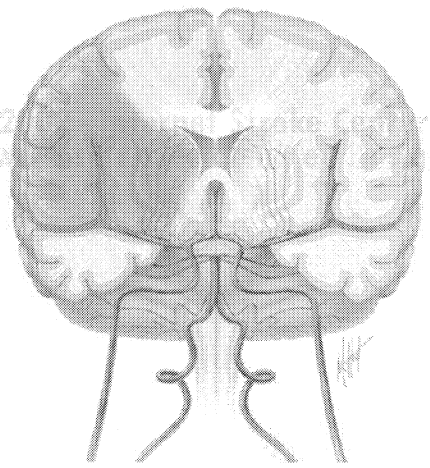
Carotid Stenosis



Large vessel atherosclerosis



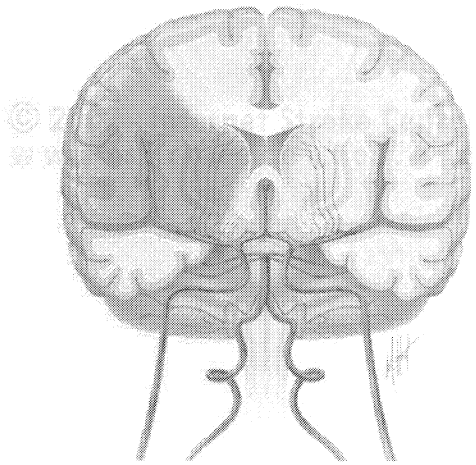
Ischemic Infarct



Lacunar Infarct

- 15-20% of strokes
- Hypertension most important risk factor
- Lipohyalinosis of perforating vessels
- Typical syndromes produced

Ischemic Infarct



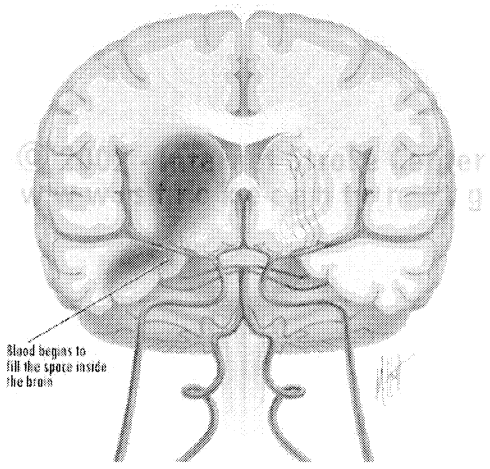
Cardiac emboli

- 20% of strokes
- Causes include valve disease (mitral stenosis), recent myocardial infarction and isolated atrial fibrillation

Intraparenchymal Hemorrhage

- 10-15% strokes
- Hypertensive hematomas are deep and due to rupture of Charcot- Bouchard aneurysms on deep perforating arteries
- Lobar hematomas are more superficial and often secondary to amyloid angiopathy

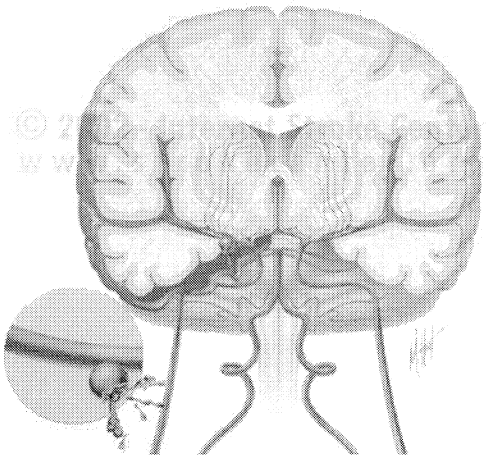
Cerebral Hemorrhage



Subarachnoid hemorrhage

- 5% of strokes
- Rupture of berry aneurysm

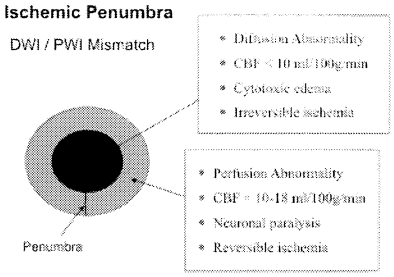
Subarachnoid Hemorrhage



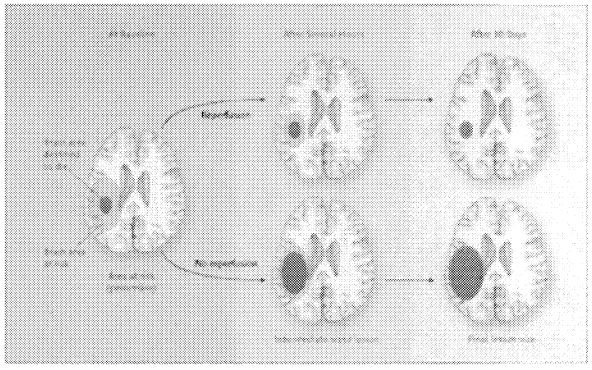
Pathogenesis of ischemic damage in cerebral infarct

- Ischemia due to vascular occlusion not the same as anoxia
- In infarct, surrounding a core of deep tissue, is an ischemic penumbra

Ischemic Penumbra



Ischemic Penumbra



Mechanism of conversion of penumbra to infarct

- Endothelial swelling
- Glutamate release -> excess NMDA activation. (spreading depression in penumbra)
- PMN inflammatory factors

Preserve penumbra

- Re-establish blood flow (t-PA)
- Keep blood pressure elevated because of loss of autoregulation
- Treat fever
- Treat hyperglycemia
- Neuroprotection (nothing yet)

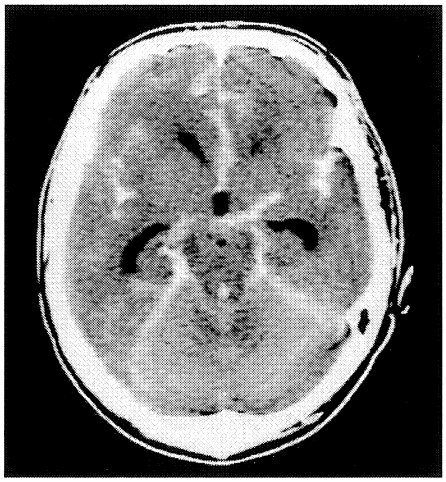
Pathogenesis of damage in hemorrhage

- Immediate tissue damage
- mass effect of hematoma
- ?penumbra around hematoma

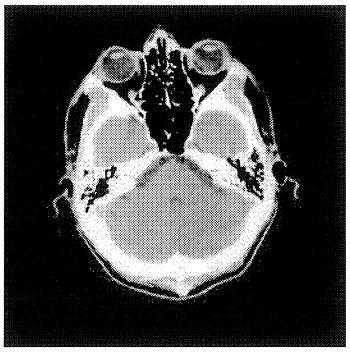
Delayed deterioration in stroke

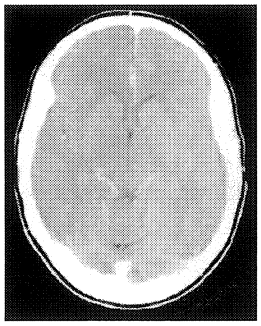
- Cerebral edema maximal 3-5 days after infarct or hemorrhage

Subarachnoid Hemorrhage



Normal CT Scan Brain

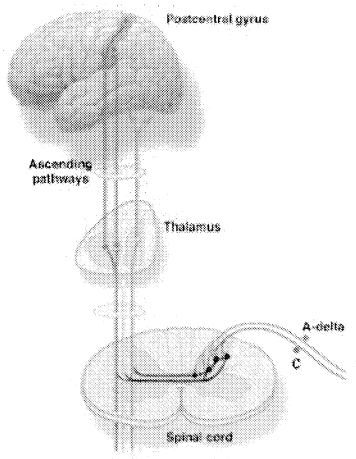




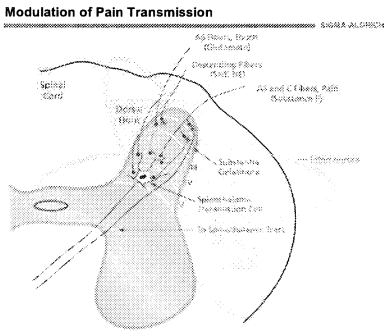
Migraine

- Pain of migraine arises from cerebral vasculature
- Therefore, to understand pathophysiology of migraine, need to review pain transmission, innervation of cerebral vessels and mechanisms of neurogenic inflammation.

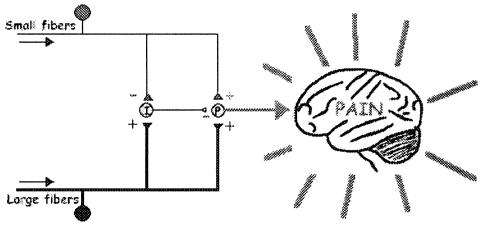
Pain Pathways



Spinal Pain Modulation



Gate Theory of Pain



NEUROCHEMISTRY

- Substance P is neurotransmitter of primary afferent neurons
- Descending serotonergic input from dorsal raphe nuclei in medulla suppresses ascending activity
- Descending enkephalinergic input from midbrain activates dorsal raphe nuclei

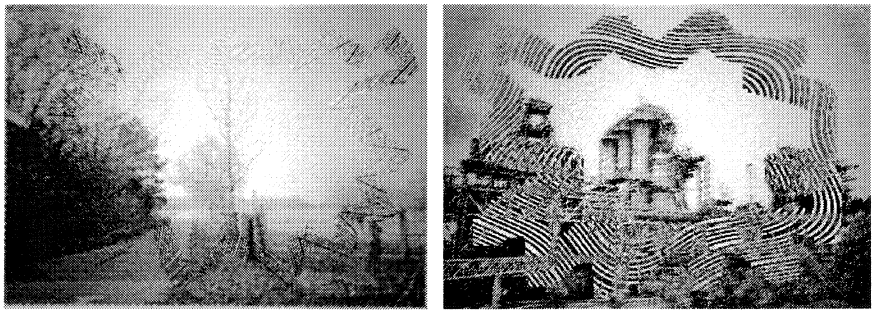
Pain sensitive structures of the skull

- The skull, much of the dura and piaarachnoid and brain parenchyma itself is pain insenstitive
- All tissue external to skull is pain sensitive
- Intracranially, dura at base of brain and the main arteries including the anterior, middle and posterior cerebral arteries are pain sensitive

HEADACHE

- Migraine (with or without aura)
- Tension type
- Cluster

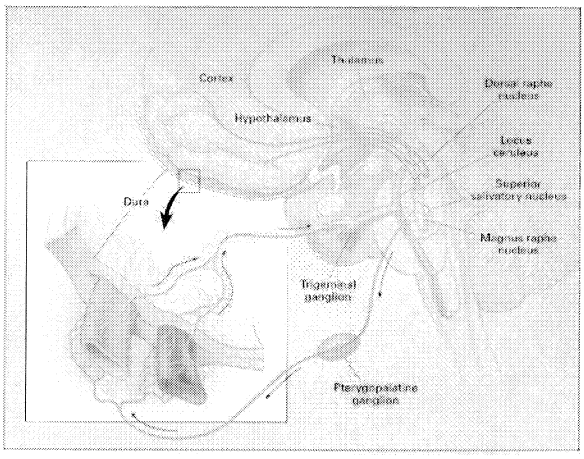
Migraine Aura



Spreading Depression of Leao

- Wave of electrical depression that spreads in all directions from a particular starting point; the advancing edge has electrical activity resembling seizure activity (spikes and sharp waves from surface EEG)
- Release of K or glutamate that then diffuses circumferentially in extracellular space activating surrounding neurons?

Trigeminal Vascular System



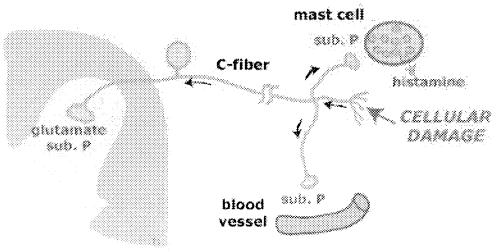
Trigeminovascular system

- Orthodromic transmission=normal periphery to CNS action potentials
- Antidromic transmission=action potential procede towards the periphery

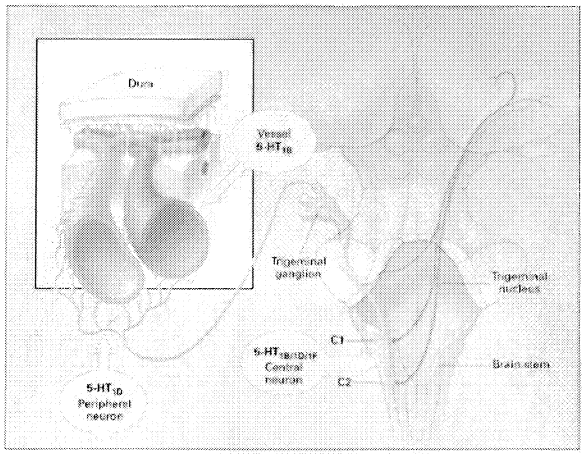
Neurogenic theory of migraine

- A spreading depression is initiated (mechanisms include usual triggers for migraine)
- Release of neurotransmitters into the extracellular space by the spreading depression activates pain terminals on blood vessels
- Axon reflex causes antidromic transmission along pain fibers and neurogenic inflammation

Axon Reflex

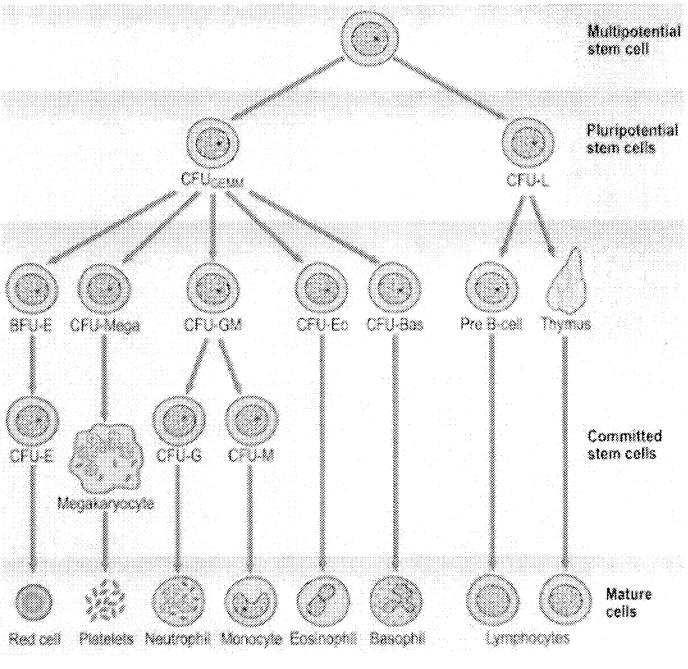


5-HT agonist actions



Hematopoietic System

Hong Chang MD, FRCPC
University Health Network, University of Toronto

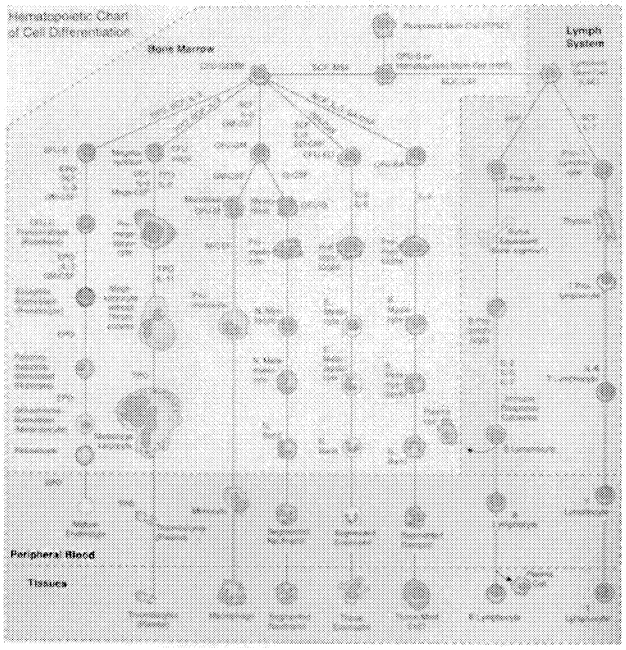


Erythropoietin(Epo)

- The principal factor regulating RBC production
- Normally produced by kidney cells
- Promote proliferation and maturation of erythroid precursor cells
- Recombinant product available, therapeutic use for anemia of chronic renal disease, of ADIS, of cancer etc.

Hemopoietic Growth Factors

Name	Principal Site of Production	Principal Action
Erythropoietin	Renal peritubular cells	CFU-E differentiation
	Hepatocytes	BFU-E proliferation
G-CSF	Macrophages	CFU-G proliferation and differentiation
	Endothelial cells	Granulocyte function
Thrombopoietin (Tpo)	Liver, muscle, spleen	Megakaryocytes proliferation and differentiation
GM-CSF	T lymphocytes	CFU-GM proliferation and differentiation
	Endothelial cells	General progenitor cell proliferation
		Granulocyte function
M-CSF (CSF-1)	Macrophages	CFU-M proliferation and differentiation
	Endothelial cells	
IL-1	Monocytes and macrophages	Mediates inflammation
	Endothelial cells	
IL-2	Activated T cells	T and B cell proliferation
IL-3 (Multi CSF)	Activated T and B cells	General progenitor cell proliferation
IL-4	Activated T cells	T and B cell activation
		IgE synthesis



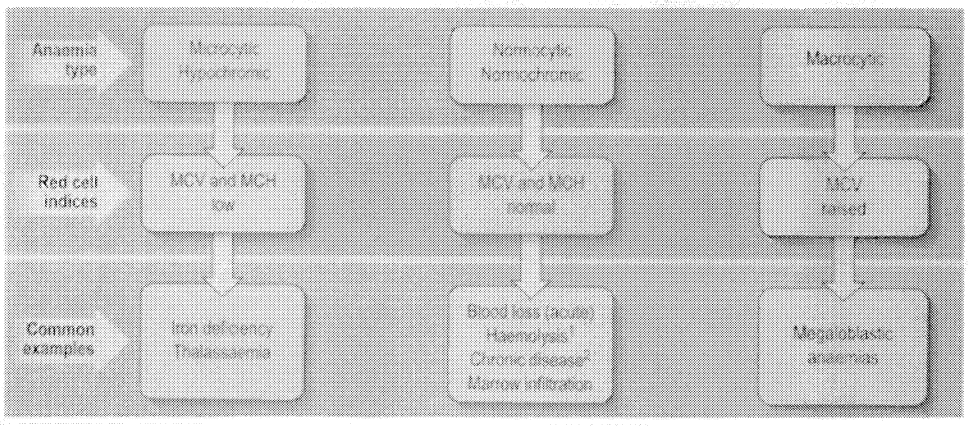
Pathogenic Mechanisms of Anemias

- Impaired RBC production
  - Aplastic anemia
  - Marrow infiltration by malignant cells
  - Thalassemia
  - Nutritional deficiency: iron, B12/folate
- Increase destruction
  - Immune-hemolytic anemia
  - Disorders of RBC membranes
  - Hypersplenism
  - Hemoglobinopathies, sickle cell disease, etc.

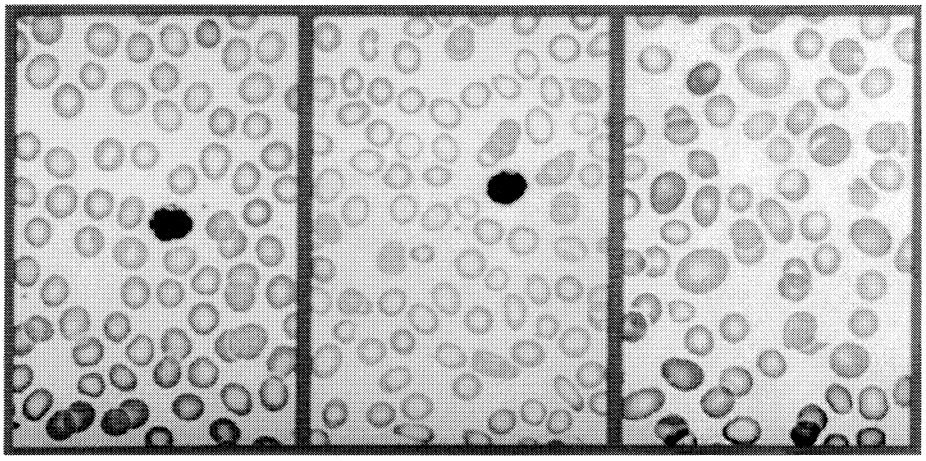
Clinical and Laboratory Approach to Anemia

- What type
- What is the mechanism
- What is the etiology
- Treatment
  - Treat anemia
  - Treat the cause

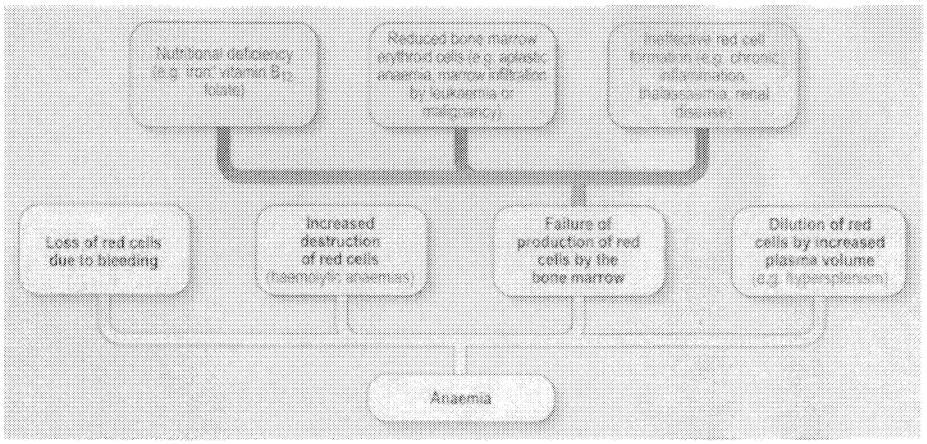
Classification of Anaemia Based on Red Cell Measurement

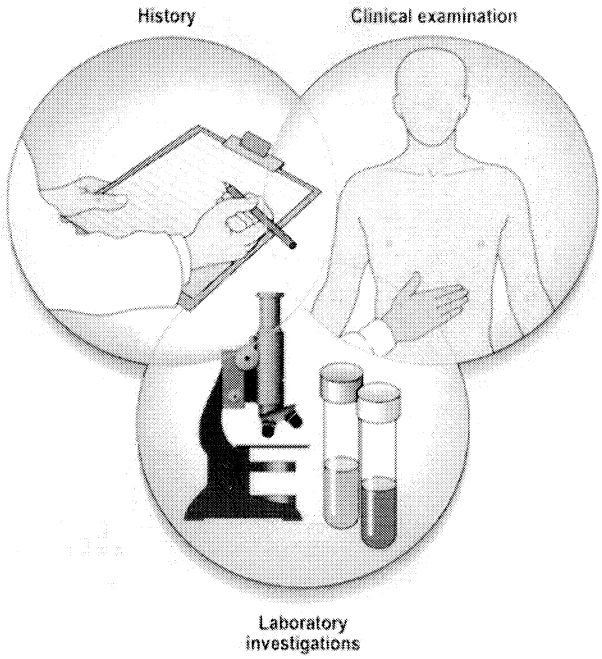


[1] Occasionally macrocytic [2] Occasionally microcytic hypochromic



Classification of Anaemia Based on Cause





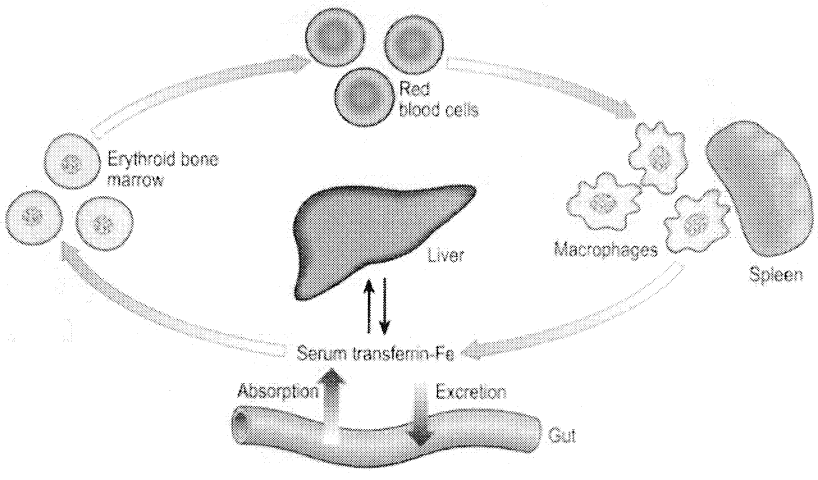
Case #1

- 60 YO male, presenting with gradual onset of fatigue, poor concentration, dyspnea, and palpitation
- Physical exams: vitals were normal, pale, no lymphadenopathy; right lower quadrant of the abdomen mass and tender.
- Lab tests: CBC: Hb 73 g/l, MCV 72, RDW 18; normal WBC and platelets
- Serum ferritin: 2 ng/ml (range: 20-250)

Case #1. Cont'd.

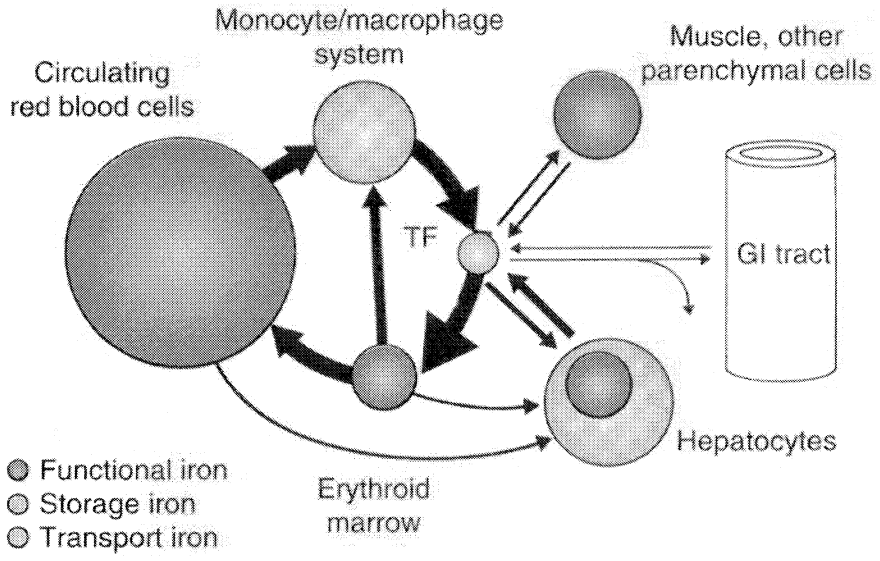
- Stool occult blood positive (GI bleed, chronic)
- Colonoscopy and biopsy: Carcinoma at right ascending colon

The Normal Iron Cycle



Distribution of Iron in the Adult

Type of Iron	Concentration (mg/kg) Men	Women
Functional iron		
Hemoglobin	31	28
Myoglobin	5	4
Heme enzymes	1	1
Nonheme enzymes	1	1
Transport iron		
Transferrin	<1 (0.2)	<1 (0.2)
Storage iron		
Ferritin	8	4
Hemosiderin	4	2
Total	50	40

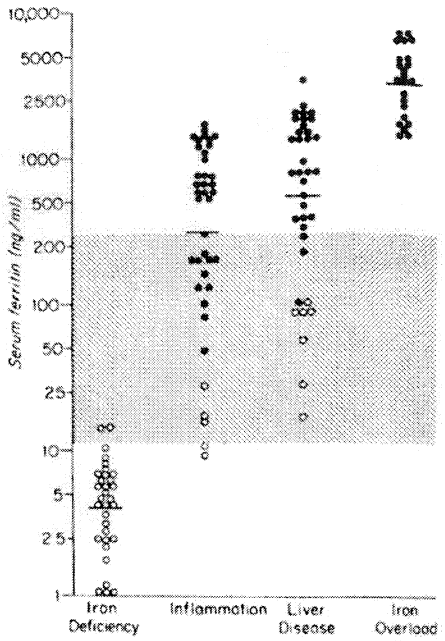


Causes of Iron Deficiency

- Increased iron requirements
  - Blood loss
    - Gastrointestinal tract
    - Genitourinary tract
    - Respiratory tract
    - Blood donation
  - Growth
  - Pregnancy and lactation
- Inadequate iron supply
  - Diets with insufficient amounts of bioavailable iron
  - Impaired absorption of iron
    - Intestinal malabsorption
    - Gastric surgery
- Impaired iron transport

Tests for Iron

- Serum iron
- Total iron binding capacity (TIBC)-measuring total transferrin
- Transferrin saturation
- Serum ferritin- the test of choice for iron deficiency



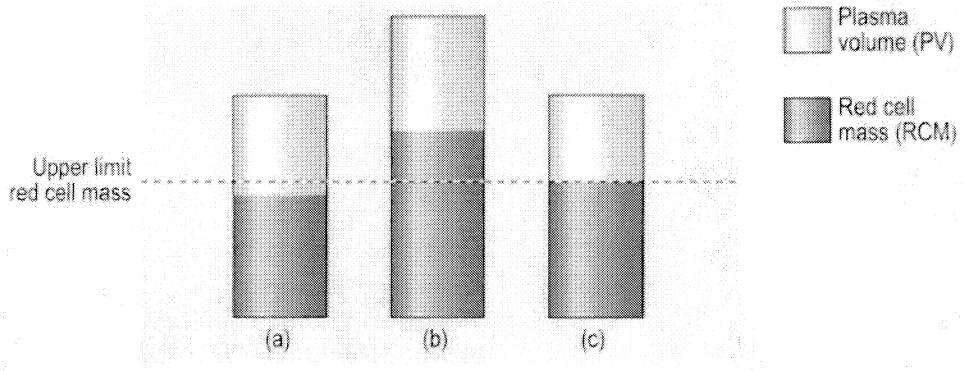
Treatment of iron deficiency anemia

- Underlying cause
- Oral iron therapy
  - Daily total 150-200 mg elementary iron, (65mg iron in 325mg ferrous sulfate)
  - Reticulocytosis at 1-2 weeks
  - Normal Hb level at 2-4 weeks
  - Continue for 12 months to replenish iron stores
- Parental iron therapy rarely justified

Polycythemia (erythrocytosis)

- RBC, hemoglobin and hematocrit are above the upper limit of normal
- Relative, due to decreased plasma volume (dehydration)
- Secondary, due to high altitude, cardiopulmonary diseases, Hb variants, etc.
- Polycythemia vera, a primary myeloproliferative disorder, also often presented with leukocytosis, thrombocytosis and splenomegaly.

Red Cell Mass and Plasma Volume in Normality, True Polycythaemia and Apparent Polycythaemia



Prognosis of P.Vera

- Median survival 10-15 years
- Causes of death:
  - Thrombosis
  - Hemorrhage
  - Acute leukemia
  - Marrow fibrosis
  - Other neoplasms

Thrombocytopenia

- A reduction of platelet count below normal (<150 $x10^9$/L)
  - — due to decreased production
  - — and/or increased destruction
- Spontaneous bleeding can occur with a platelet count <20 $x10^9$/L and more likely if the count is below 10 $x10^9$/L

Pathologic classification

- Decreased platelet production
  - Congenital hypoplasia of megakaryocytes
  - Marrow infiltrate by malignancy
- Increased platelet destruction
  - ITP(idiopathic, auto-immune thrombocytopenia purpura)
  - Allo-immune neonatal thrombocytopenia and post transfusion thrombocytopenia
  - Non-immune mechanisms of platelet consumption of destruction. DIC (disseminated intravascular coagulation), infection
  - Microangiopathies: thrombotic thrombocytopenic purpura(TTP), HUS(hemolytic uremic syndrome), etc.

Case 2

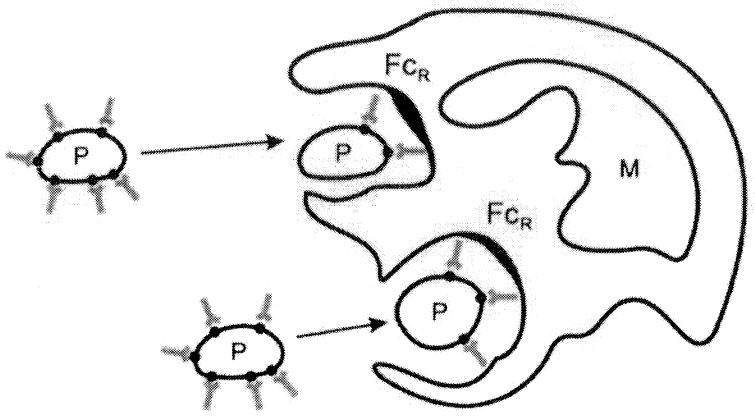
- 32 y.o. female
- Hx: Well until a week ago, noticed spontaneous appearance of red-purple rash, non-blanch on pressure, (petechiae) mainly at lower legs, belt, and stocking areas; gingival bleeding when brushing teeth.
- No past history or family history of bleeding
- No medication except birth control pills

Case 2. Cont'd

- Physical exam: petechiae around ankle area, otherwise unremarkable
- Laboratory features:
  - Coagulation tests: normal PTT, PT, TT and fibrogen
  - CBC: Hb 125g/L, WBC 5.8×10^9/L, Platelet 8×10^9/L
- Bone marrow: normal cellularity, normal erythropoiesis and granulopoiesis, increased megakaryocytes
- Diagnosis: ITP

Idiopathic Immune Thrombocytopenia Purpura

- Platelet destruction caused by autoantibodies directly against platelet and megakaryocytes
- Childhood ITP, usually acute form and self-limited, often following viral infection
- Acute ITP, F>M, usually chronic, usually associated with a collagen vascular disease
- Diagnosis: Clinical features and exclusion of other causes.

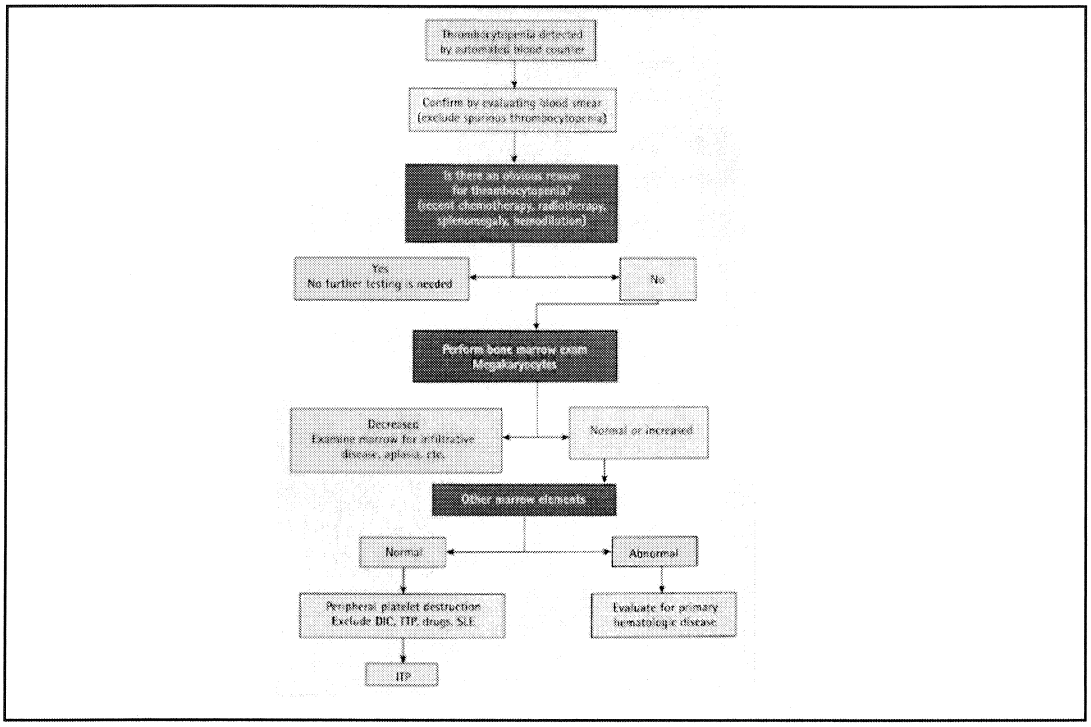


- Platelet membrane antigen
- Platelet auto antibody

P Platelet
M monocyte/macrophage
Fc_R - Fc receptor

Laboratory Features

- Thrombocytopenia is the essential abnormality. The blood film should be reviewed to rule out pseudothrombocytopenia. The platelets present are usually of normal size buy may be enlarged.
- White blood cell count and hemoglobin levels are usually normal unless significant hemorrhage has occurred.
- Coagulation studies are normal.
- Marrow megakaryocytes may be increased in number, with a shift to younger, less polyploid forms.



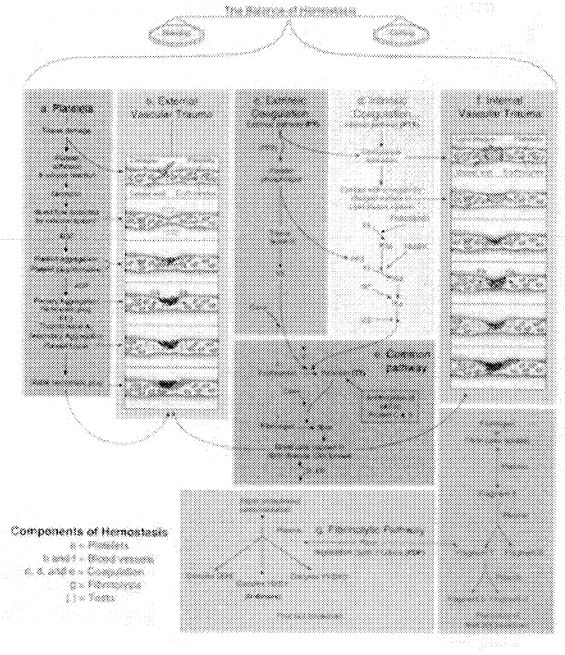
Treatment of ITP

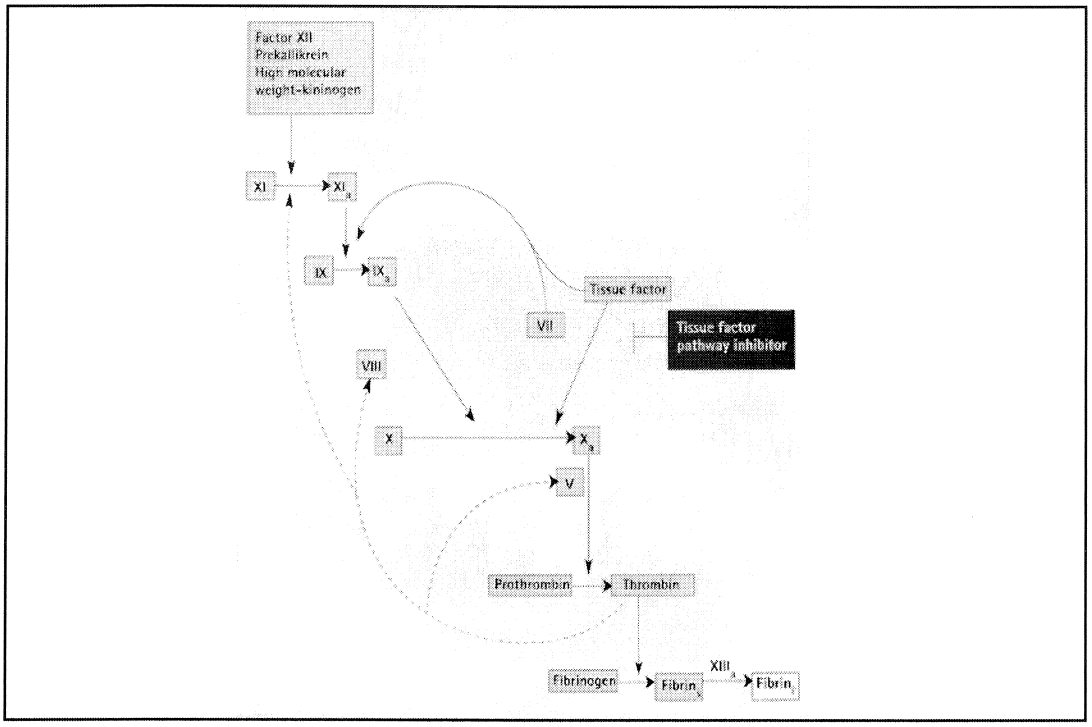
- Glucocorticoid
- Intravenous immunoglobulin (IV IG)/RhD, antisera
- Immunosuppressive agents
- Dannazol
- Other modality: splenectomy

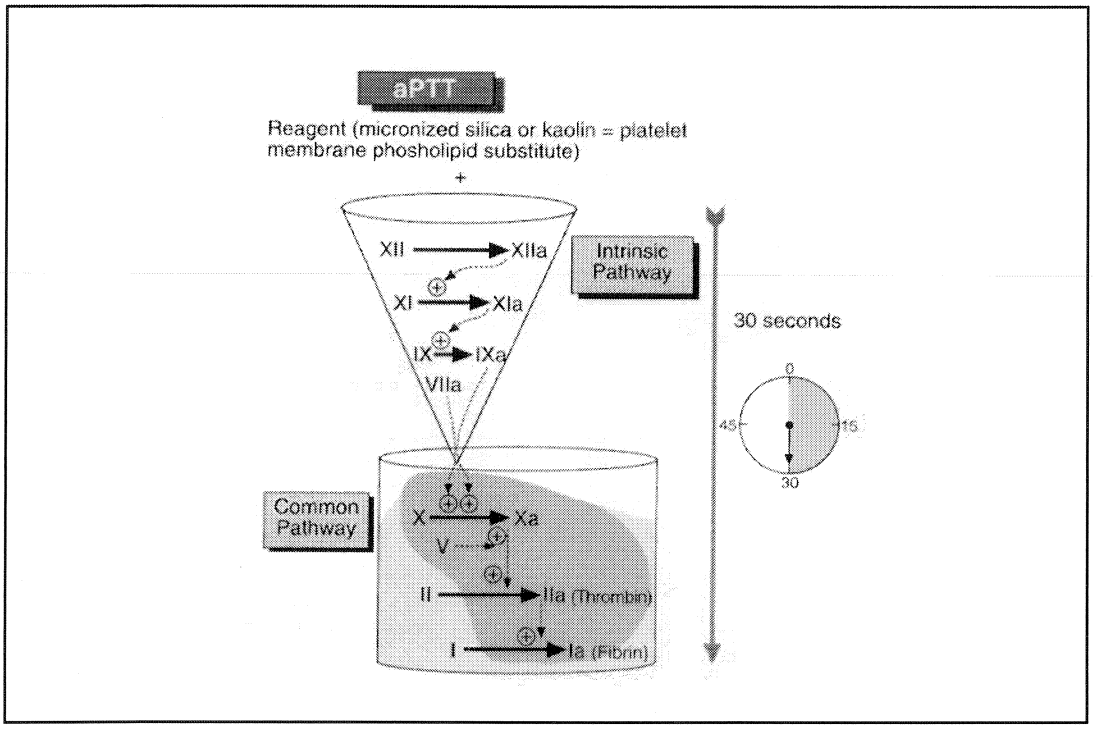
Hemostasis and Coagulation

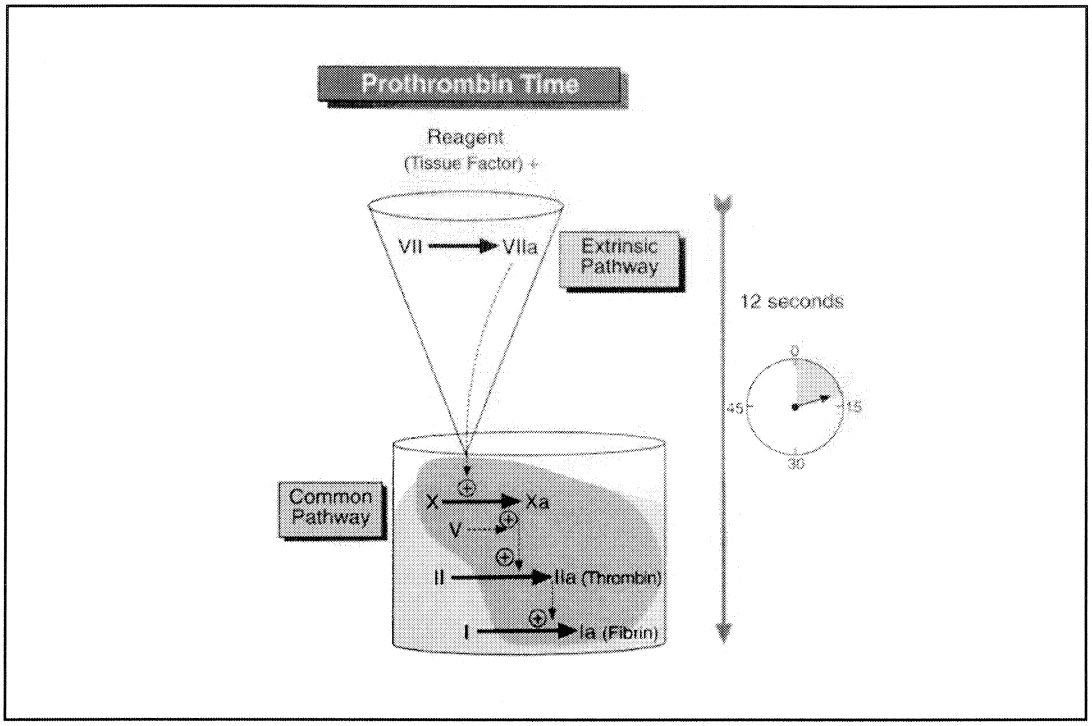
(balance between clotting and anticoagulation systems)

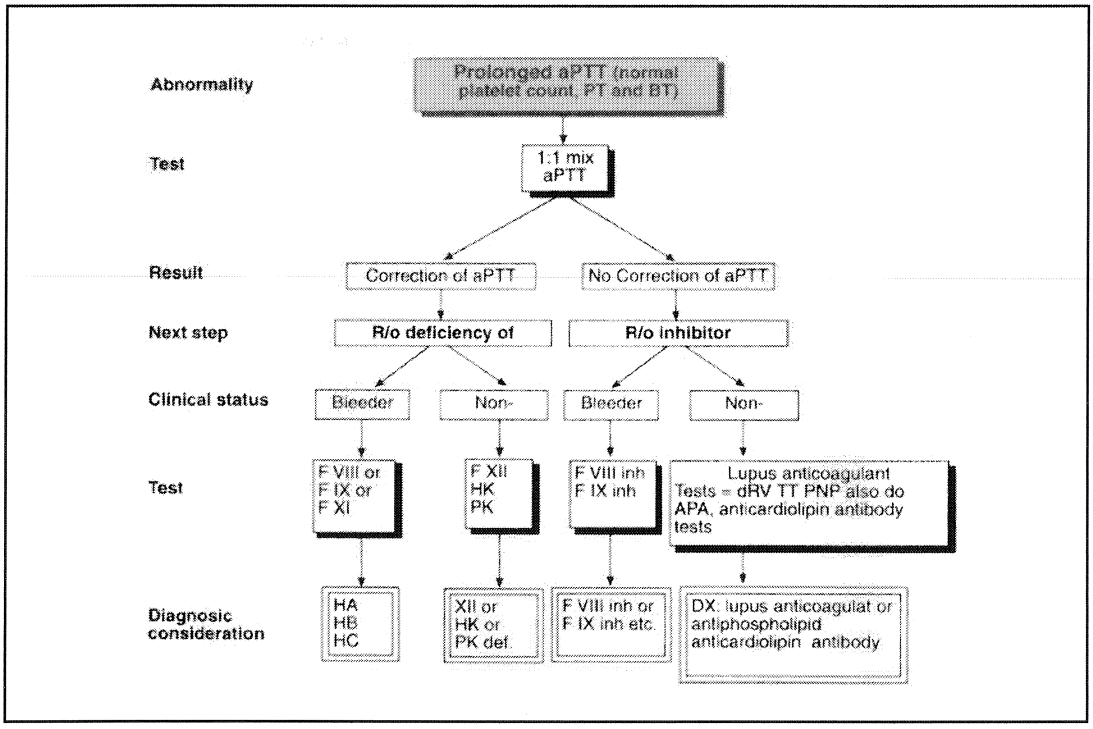
- Blood vessels: endothelial cells form a continuous monolayer lining all blood vessels
- Platelets: aggregation to form plug and procoagulant activity
- Coagulation factors: a catalytic system to convert soluble fibrinogen to stable fibrin clots.




Factor XII
Prekallikrein
High molecular weight-kininogen
XI
XI_a
IX
IX_a
Tissue factor
VII
Tissue factor pathway inhibitor
VIII
X
X_a
V
Prothrombin
Thrombin
Fibrinogen
Fibrin
$XIII_a$
$Fibrin_s$

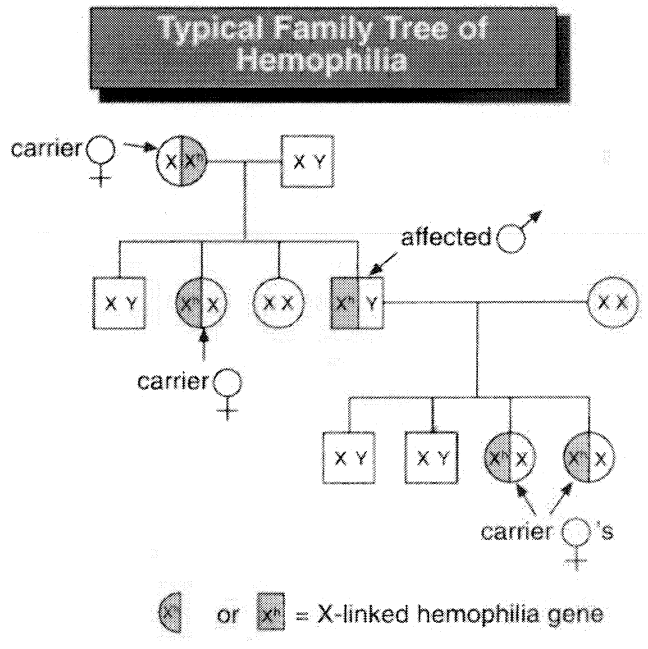

aPTT
Reagent (micronized silica or kaolin = platelet membrane phosholipid substitute)
+
XII
XIIa
Intrinsic Pathway
XI
XIa
IX
IXa
VIIa
30 seconds
0
45
15
30
Common Pathway
X
Xa
V
II
IIa (Thrombin)
I
Ia (Fibrin)


Prothrombin Time
Reagent
(Tissue Factor) +
VII
VIIa
Extrinsic Pathway
12 seconds
0
45
15
30
Common Pathway
X
Xa
V
II
IIa (Thrombin)
I
Ia (Fibrin)


Abnormality
Prolonged aPTT (normal platelet count, PT and BT)
Test
1:1 mix aPTT
Result
Correction of aPTT
No Correction of aPTT
Next step
R/o deficiency of
R/o inhibitor
Clinical status
Bleeder
Non-
Bleeder
Non-
Test
F VIII or F IX or F XI
F XII HK PK
F VIII inh F IX inh
Lupus anticoagulant Tests = dRV TT PNP also do APA, anticardiolipin antibody tests
Diagnosic consideration
HA HB HC
XII or HK or PK def.
F VIII inh or F IX inh etc.
DX: lupus anticoagulat or antiphospholipid anticardiolipin antibody

Hemophilias

- Hemophilia A: Factor VIII deficiency, 1/10000 male
- Hemophilia B: Factor IX deficiency, 1/25000 male
- Both X-linked recessive disorder
- Severe forms with a factor level of <1%
- Usually delayed, deep soft tissue bleed after minor trauma
- Tx. factor replacement



LABORATORY CHARACTERISTICS AND CLINICAL MANIFESTATIONS OF HEMOPHILIAS

LABORATORY DEFECTS (%)	CLINICAL MANIFESTATIONS	BLEEDING SYMPTOMS
<1	Severe	Early childhood, spontaneous
1–5	Moderate	After minor trauma or surgery May be spontaneous
5–20	Mild	Only after trauma or surgery

Case 3.

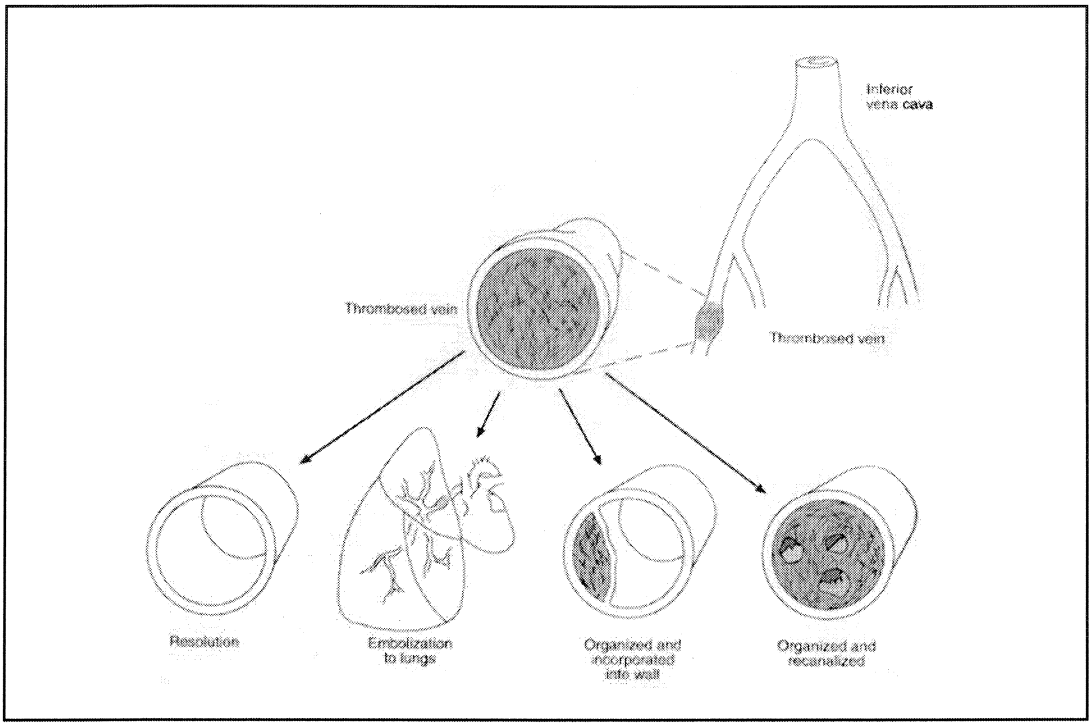
- 65 y.o. male
- A sudden onset of chest pain, worsening with breathing dyspnea and tachycardia
- History of osteoarthritis, surgery for hip replacement 2 weeks ago
- No history of coronary heart disease
- physical examination: chest: unremarkable; swollen and tender of left leg

Case 3. Cont'd

- ECG: no evidence of cardiac ischemia
- CXR: Non-specific changes (slight pleural effusion)
- Doppler ultrasound: suggestive of DVT(deep venous thrombosis) of left leg
- Clinical diagnosis: pulmonary embolism(PE), secondary to DVT

Case 3. Cont'd

- V/Q scan (ventilation/perfusion): defect in perfusion Q, normal in V, C/W PE
- Treatments: IV heparin, followed by oral coumadin, monitored by PTT and PT tests.



Acquired Hypercoagulable State

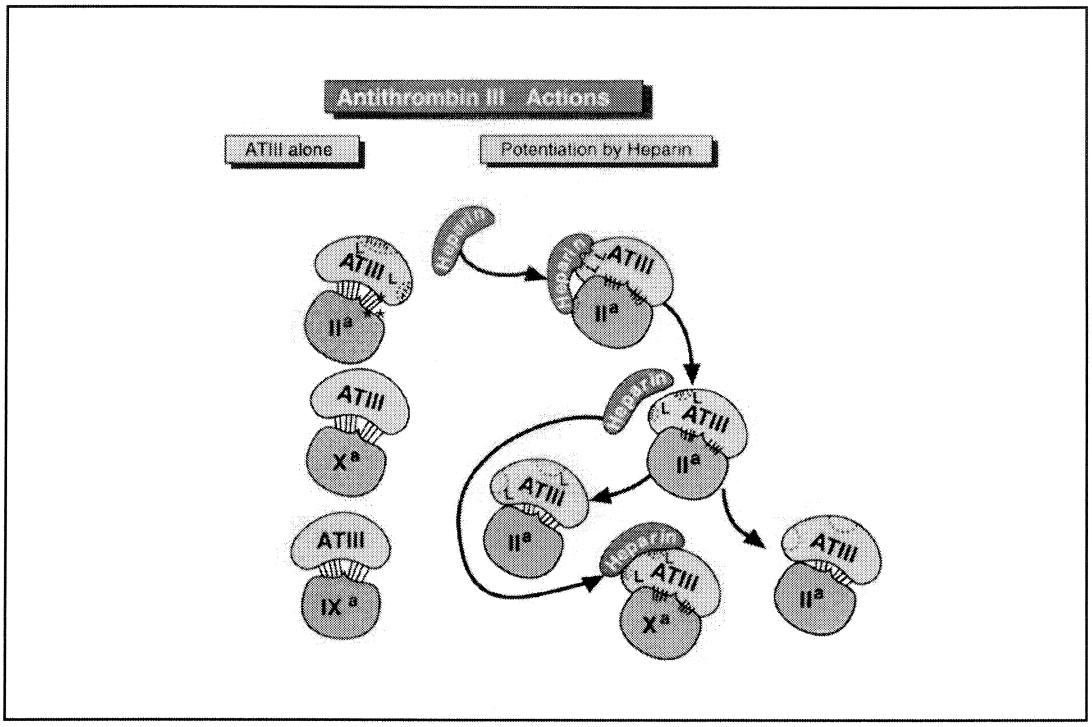
- Venous stasis, immobilization, congestive heart failure
- Obesity
- Pregnancy
- Malignancy (Trousseau syndrome)
- Paroxysmal nocturnal hemoglobinuria

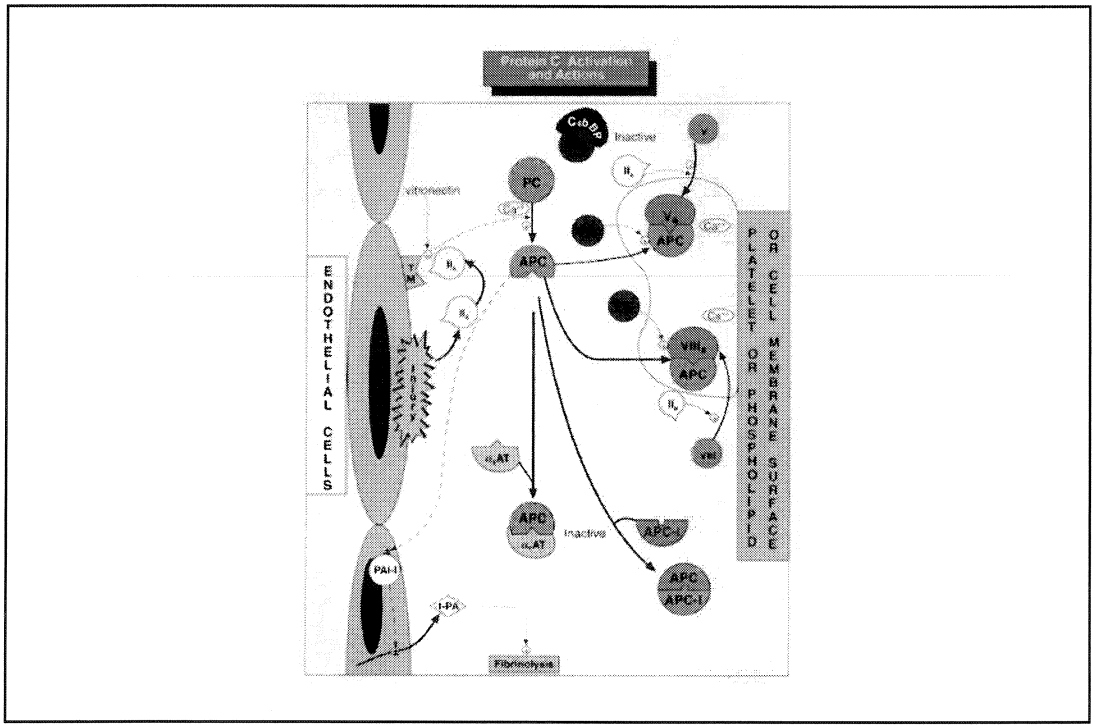
Thrombophilia(Hypercoagulability)

- Thrombosis at an early age
- Family history of thrombosis
- Unusual sites of thrombosis , hepatic mesenteric veins
- Recurrent thrombosis
- Warfarin induced skin necrosis

HEREDITARY CAUSES OF THROMBOPHILIA: (PRIMARY HYPERCOAGULABLE STATES)

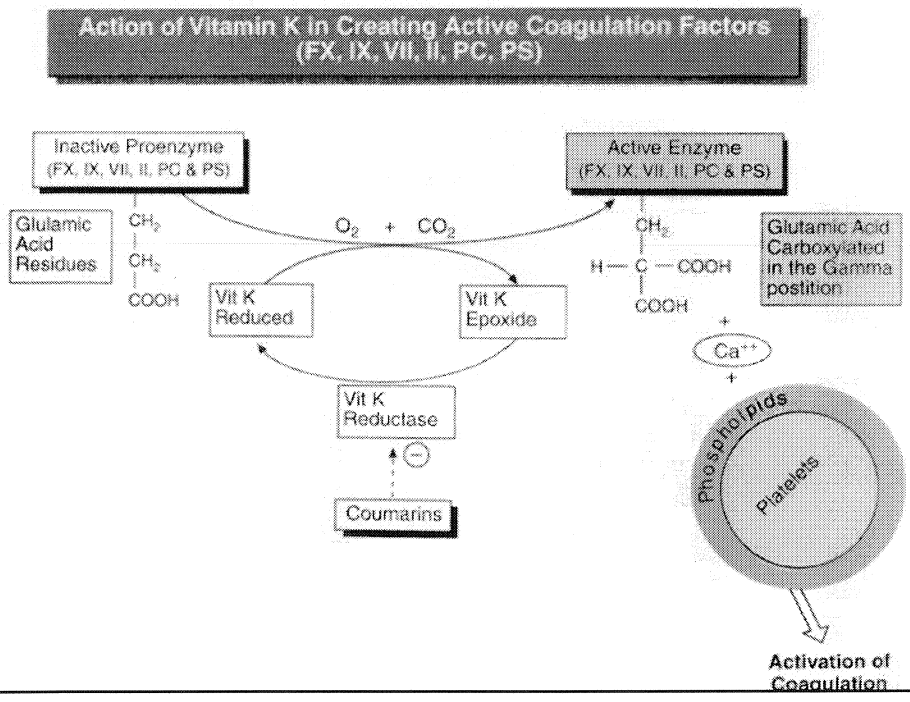
COMMON CAUSES	FREQUENCY IN VENOUS THROMBOSIS (%)	RARE CAUSES	FREQUENCY IN VENOUS THROMBOSIS (%)
ATIII deficiency	1–5	Dysfibrinogenemia	?
PC deficiency	1–9	Hypo- or dysplasminogenemia	?
PS deficiency	1–8	Heparin cofactor deficiency	?
APC resistance (FV mutation)	20–60	High plasminogen activator Inhibitor (PAI-1)	?
Hyperhomocysteinemia	19	Histidine-rich glycoprotein (1)	?
		Abnormal thrombomodulin	?


Antithrombin III Actions
ATIII alone
Potentiation by Heparin
ATIII
II^a
X^a
IX^a
Heparin


Protein C Activation and Actions
C4b BP
Inactive
PC
APC
thrombin
ENDOTHELIAL CELLS
PLATELET OR PHOSPHOLIPID OR CELL MEMBRANE SURFACE
PAI-1
t-PA
Fibrinolysis
Inactive

Vitamin K and Oral Anticoagulants

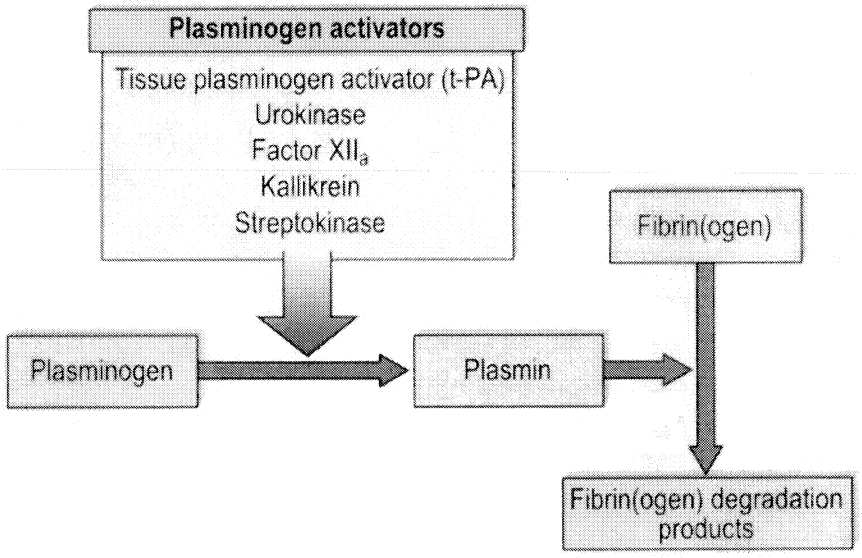
- Vitamin K:
  - Necessary to convert glutamate to carboxyglutamate residuals
  - Required for clotting factors (II, VII, IX, X) and anticoagulants protein C and protein S.
- Warfarin (Coumadin). Vitamin K antagonist
  - Inhibits the two enzymes(cycle-apoxide reductase and V-K reductase) in the V-K cycle and reduce the availability of V-K.
  - Leads to incomplete and non-functional coagulation proteins, including II, VII, IX, X, PC, PS.



Low Molecular Weight Heparins(LMWH)

- Fragmented, average molecular mass 6,000
- Preferentially inhibit Xa over IIa
- Do not prolong APTT, monitored by Xa assay
- Longer half life and higher bio availability
- Once daily dosage, self administration possible

The Fibrinolytic System



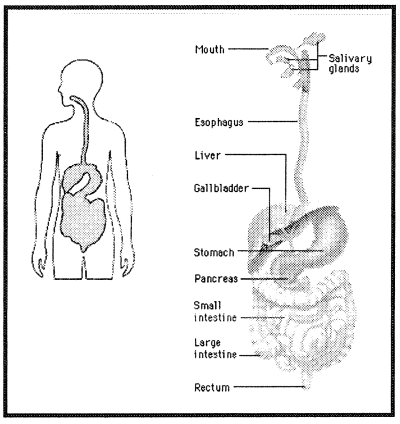
Pathophysiology of the Gastrointestinal Tract

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

November 15, 2006

Lecture Outline

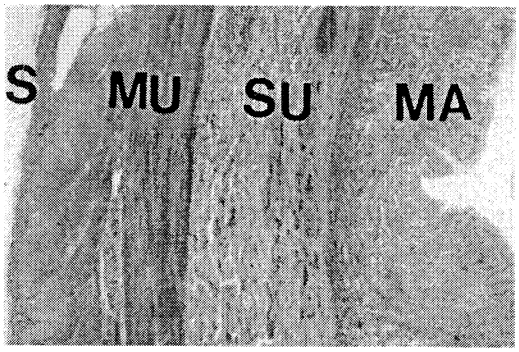
- Overview of GI Histology
- Upper GI Disorders
  - GERD
  - PUD
- Lower GI Disorders
  - Ulcerative Colitis
  - Crohn's Disease



Structure of the GI Tract

4 Cellular Layers:

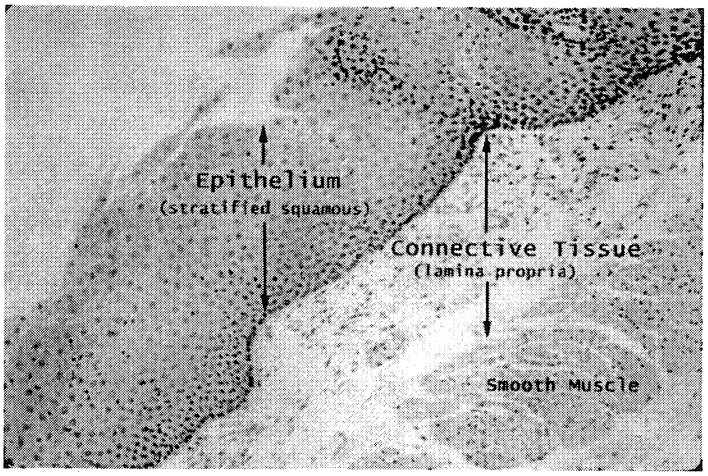
MA = Mucosa.
SU = Submucosa.
MU = Muscularis Externa.
S = Serosa.



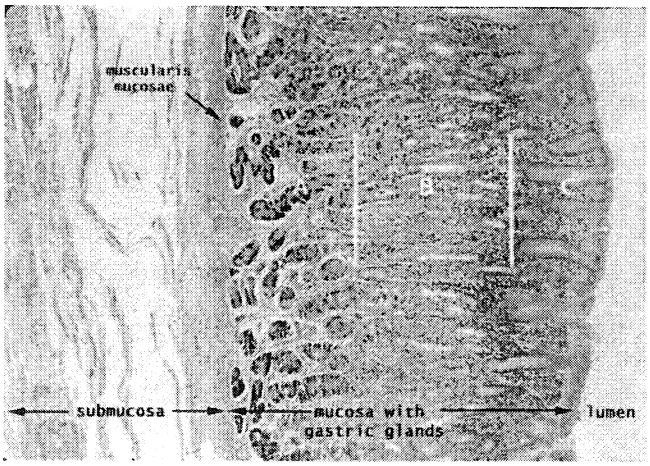
GI Epithelium

- Type of epithelium, presence and nature of mucosal and other glands depends upon the particular functions of each part of the GI tract.
  - Esophagus = stratified, squamous, non-keratinizing epithelium.
  - Stomach = simple columnar epithelium.
  - Intestines = simple columnar epithelium containing mixture of absorptive and goblet cells.

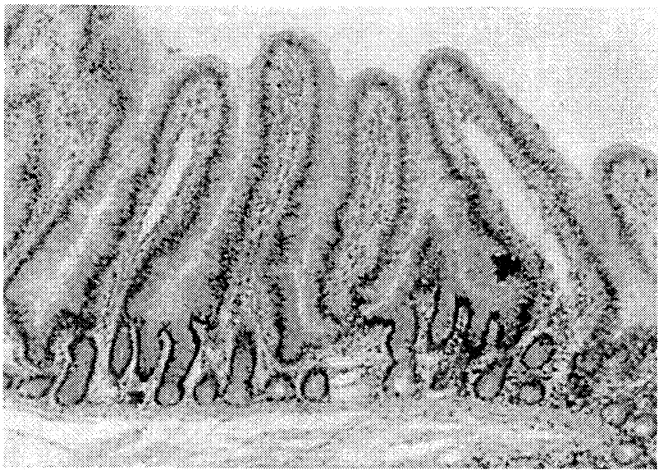
Esophagus



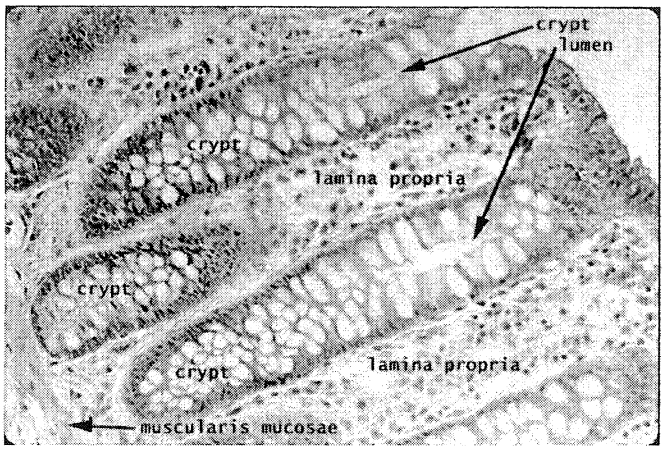
Stomach



Small Intestine



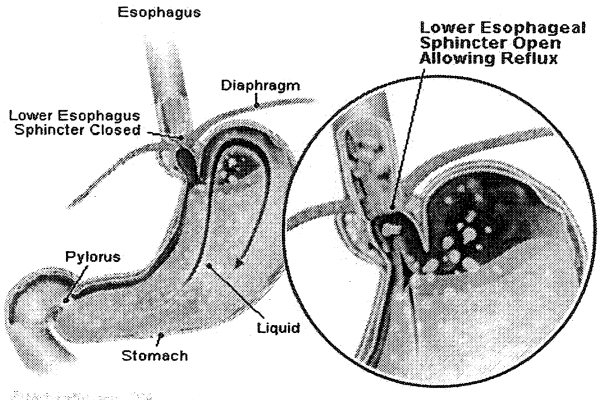
Large Intestine



Gastroesophageal Reflux Disease (GERD)

- GERD is a condition in which the liquid content of the stomach regurgitates (i.e., refluxes) into the esophagus.
- Results in inflammation and potential damage to the esophageal epithelium.
- GERD is a chronic condition.

GERD



Gastroesophageal Reflux

GERD - Etiology

- Impaired function of the Cardiac Sphincter (Lower Esophageal Sphincter).
  - Abnormally weak.
  - Abnormal relaxation.
- Decreased rate of gastric emptying.
  - 20% of patients with GERD have abnormally slow gastric emptying after a meal.
- Abnormal Peristalsis.
  - Smokers – reduces acid clearance from the esophagus.
- Laxity due to distending pressures.
  - Pregnancy.
- Hiatus Hernia.
  - Small portion of upper stomach (i.e., fundus) passes through the diaphragm.

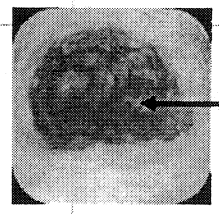
GERD – Symptoms.

- Heartburn.
  - Due to acid and pepsin stimulation of exposed nerve fibers in the esophagus.
- Regurgitation.
  - Appearance of refluxed liquid in mouth.
- Nausea.
  - Uncommon in patients with mild GERD.
  - When it occurs, it is usually severe and leads to vomiting.

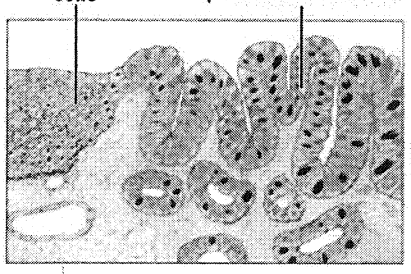
GERD - Complications

- Ulcers.
- Strictures.
- Cough and Asthma.
- Inflammation of throat and larynx.
- Inflammation/infection of lungs.
- Fluid in sinuses and inner ears.

Barrett's Esophagus



Lower esophagus lined by red-coloured tissue, not the usual white-pink colour.



- Demarcated by histological changes in cells lining the esophagus.
- Occurs in 10% of GERD patients.
- Associated with adenocarcinoma of the esophagus.

GERD – Diagnosis

- GERD usually suspected based upon its classical symptom: Heartburn.
- Esophageal Acid Testing
  - Gold-standard for diagnosing GERD.
  - Catheter inserted through the nose and positioned in the esophagus.
- Esophageal Motility Testing and Gastric Emptying Studies.
- Acid Perfusion (Bernstein) Test
  - Used to determine if chest pain is due to acid reflux.
  - Acid perfused into esophagus via a catheter intermittently with a salt solution.
  - Patient does NOT know when acid is being perfused.
  - If pain is induced by acid, the most likely diagnosis is GERD.

GERD - Treatment

- Antacids.
  - Rapidly neutralize acid in the stomach.
  - Duration of action is brief.
  - May be calcium, magnesium or aluminum based.
  - Calcium-based antacids stimulate secretion of gastrin by the stomach.
    - Gastrin stimulates HCl secretion by parietal cells.
    - Acid secretion increases once antacid effect is exhausted = Acid rebound.
  - Magnesium-based antacids may cause diarrhea.
  - Aluminum-based antacids may cause constipation.

GERD - Treatment

- Histamine Antagonists.
  - Histamine stimulates gastric acid production by binding to receptors on the parietal cell surface (H2 receptors).
  - Blockade of H2 receptors leads to longer term suppression of gastric acid production.
  - Effective at relieving symptoms of GERD only.

  Examples:
  - Cimetidine (Tagamet®)
  - Ranitidine (Zantac®)
  - Famotidine (Pepcid®)
  - Nizatidine (Axid®)

GERD - Treatment

- Proton-pump Inhibitors
  - Blocks secretion of acid into the stomach by parietal cells.
  - Blocks acid secretion more effectively and for longer duration than histamine antagonists.
  - Effective at treating both heartburn and protecting the esophagus from acid so that inflammation can heal.

  Examples:
  - Omeprazole (Prilosec®)
  - Lansoprazole (Prevacid®)
  - Rabeprazole (Aciphex®)
  - Pantoprazole (Protonix®)
  - Esomeprazole (Nexium®)

GERD - Treatment

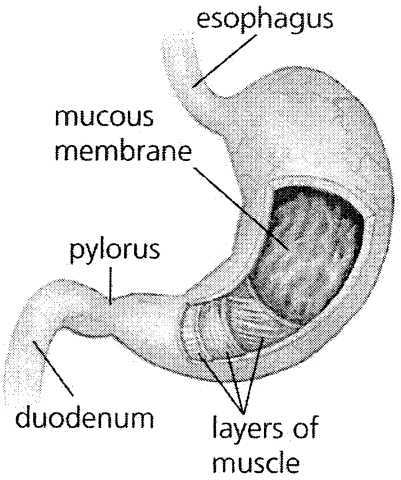
- Pro-motility Drugs
  - Enhance gastric emptying by stimulating smooth muscle of the GI tract (i.e., strengthening of peristalsis).
  - Example: Metoclopromide (Reglan®).
- Foam Barriers
  - Tablets consisting of an antacid and a foaming agent.
  - Foam forms on top of gastric contents thereby forming an artificial barrier to reflux.
  - Antacid neutralizes acid that comes into contact with the foam.
  - Only one such preparation is currently available.
    - Gaviscon® – consists of aluminum hydroxide gel, magnesium trisilicate or magnesium carbonate, and alginate.

Peptic Ulcer Disease (PUD)

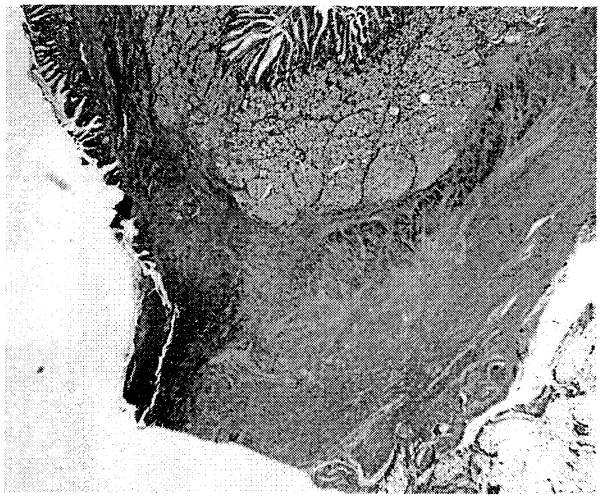
Peptic Ulcer:

Region of the stomach or duodenal lining that becomes eroded by gastric acid.

Affects 1 in 10 North Americans



PUD - Histology



PUD – Risk Factors

- Family History.
- Smoking.
- Heavy Alcohol Intake.
- *H. Pylori* Infection.
- Chronic NSAID use.

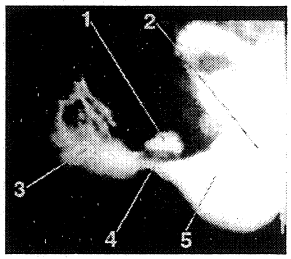
PUD - Symptoms

- Common symptoms include indigestion and upper abdominal/lower chest pain.
- If ulcer is bleeding:
  - Vomiting of Blood.
  - Melaena – passage of black stools.
- Patients with PUD may have suppressed appetite.

PUD Diagnosis

- Upper Gastrointestinal Endoscopy.

- Barium X-ray.
  - Barium acts as a contrast media.
  - Coats GI tract and reveals regions of tissue ulceration.



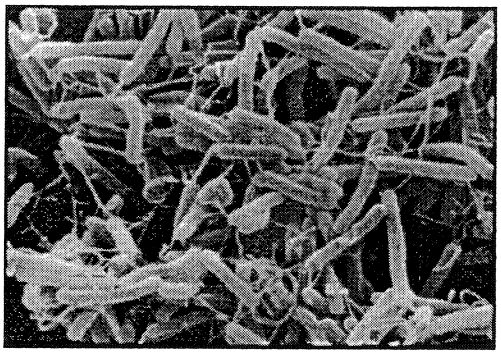
PUD - Treatment

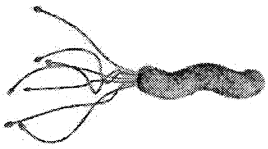
- Educate the patient.
  - Smoking cessation.
  - Reduce alcohol consumption.
  - Eat small meals regularly.
  - Avoid foods that may cause exacerbation of symptoms (i.e., milk, suicide wings).
- Antacid Therapy.
  - Several varieties available in Canada.
  - Offer short-term relief of symptoms.
- Histamine Antagonists/Proton Pump Inhibitors
  - Moderate to severe cases.
- Cytoprotective Agents
  - Misoprostol (Cytotec®)
  - Sucralfate (Carafate®)

Helicobacter Pylori (*H. pylori*).

- Bacterium that may cause chronic inflammation of the stomach's inner lining (i.e., Gastritis).
- Most common cause of ulcers worldwide.
- 1 in 6 people infected with *H. pylori* will develop ulcers of the stomach and/or duodenum.
- Strongly associated with the development of stomach cancer.

Helicobacter Pylori (*H. pylori*).





H. Pylori Infection - Diagnosis.

- Blood-Antigen Tests.
  - Rapid method to detect *H. Pylori* antibodies in the blood.
- Urea Breath Test (UBT).
  - Based on ability of *H. Pylori* to metabolize urea to carbon dioxide.
  - Patient administered capsule containing radiolabelled urea.
  - Breath analyzed for radiolabelled CO_2 approximately 10-20 min after ingestion of tablet.
  - Presence of radiolabelled CO_2 suggests presence of active *H. Pylori* infection.
  - Test becomes negative shortly after antibiotic therapy has eradicated the infection.
- *H. Pylori* Stool Antigen Assay.
- Endoscopic Biopsy.

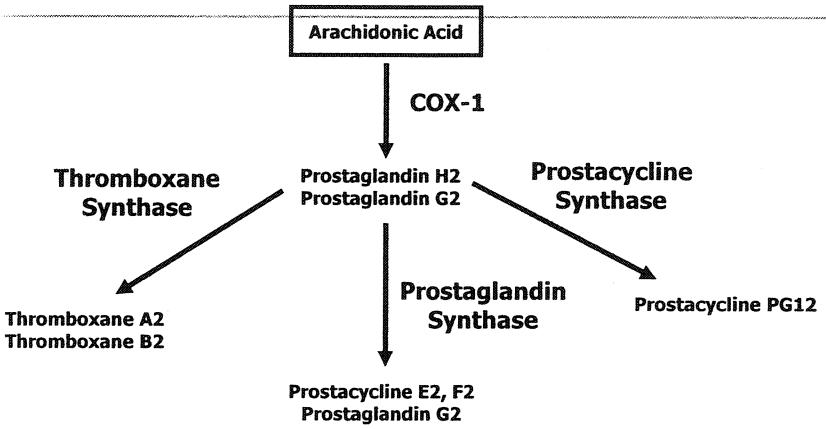
H. Pylori - Treatment

- Treatment is challenging due to ability of *H. Pylori* to develop antibiotic resistance.
- To avoid development of resistance, two antibiotics are commonly used in the presence or absence of a bismuth compound.
- 2 commonly used regimens:
  - 1) PPI, amoxicillin, clarithromycin.
  - 2) PPI, metronidazole, tetracycline, bismuth subsalicylate.
- These combinations have been clinically shown to cure 70-90% of *H. Pylori* infections.

NSAIDs and PUD.

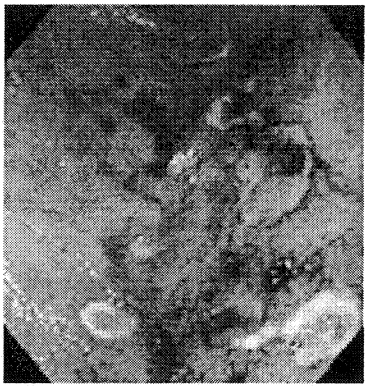
- Many drugs interfere with mucus production and the regulation of acid secretion in the stomach and duodenum.
  - Mechanism: inhibition of cyclooxygenase activity (i.e., COX-1).
- Morbidity may be due to irreversible COX-1 inhibition (i.e., ASA) or reversible COX-1 inhibition (i.e., NSAIDs).

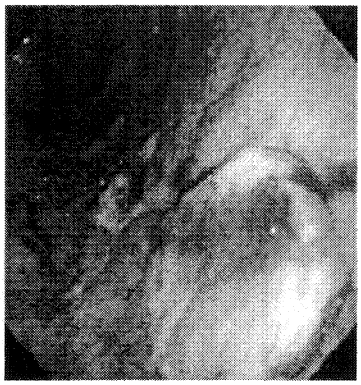
Cyclooxygenase Pathway



RESULT = DECREASED ACID SECRETION & INCREASED MUCUS PRODUCTION

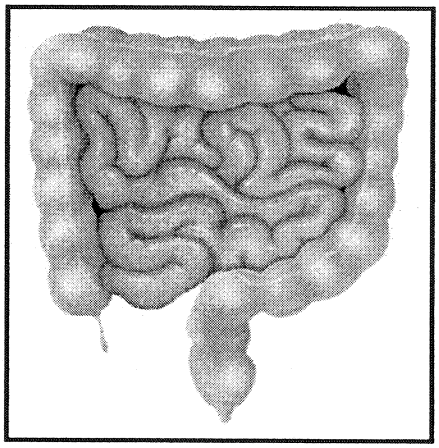
NSAID Induced Ulcers





Inflammatory Bowel Disease (IBD)

- Ulcerative Colitis.
- Crohn's Disease.



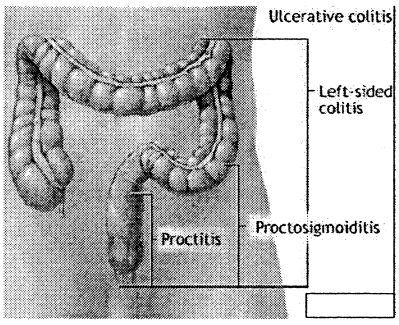
IBD - Definition

IBD is a chronic, relapsing, idiopathic inflammation of the gastrointestinal tract.

Epidemiology of IBD

- Prevalence range of 10-200 cases per 100,000 individuals.
  - Applies for North America and Western Europe.
- Initial diagnosis usually occurs between 15 and 30 years of age.
- Disease incidence is highest in developed, urbanized countries.

Ulcerative Colitis



- Ulceration and inflammation initiates in the rectum.
  - Ulcerative Proctitis
- Extends proximally in a continuous fashion.
- Entire large bowel may be affected
  - Pancolitis.
- Ulcerative colitis occurs in the large bowel only.

Ulcerative Colitis – Risk Factors.

- Family History.
- Jewish Heritage.
- Diet that is high in sugar, cholesterol, and fat (particularly from meat and dairy products).
- Stress.
- Antibiotic Therapy.
- Affects 30% more females than males.

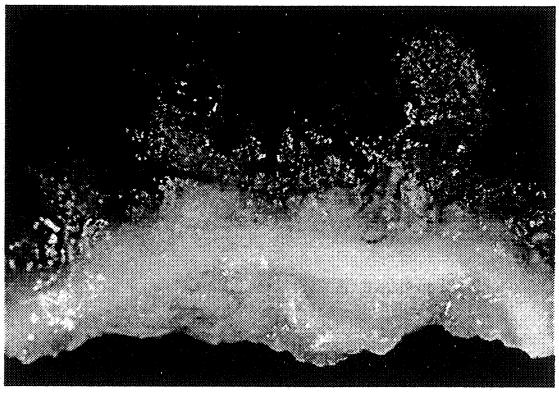
Ulcerative Colitis – Environmental Influences.

- Smoking.
  - Cigarette smoking protects against development of ulcerative colitis.
  - Ex-smokers more likely to develop moderate to severe colitis.
  - WHY?
    - Nicotine increases mucus production in the large intestine.
    - Nicotine may also regulate the inflammatory response within the GI tract.

Ulcerative Colitis – Environmental Influences.

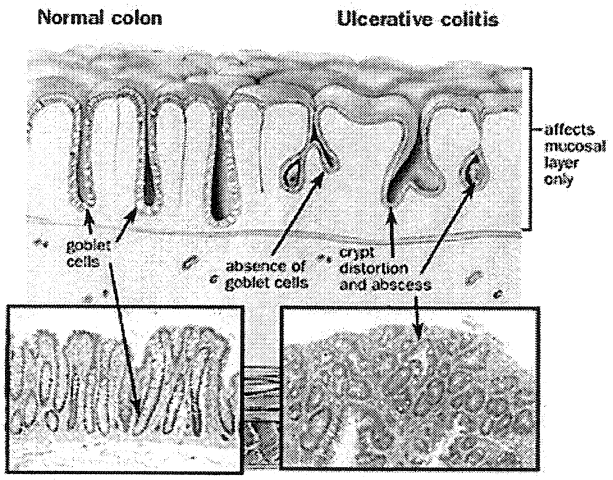
- Appendectomy
  - Reduces likelihood of developing ulcerative colitis.
  - Underlying mechanism is unknown.
- Bacterial Infection
  - Increased numbers of mucosa-associated bacterial strains in ulcerative colitis patients.

Ulcerative Colitis – Gross Morphology



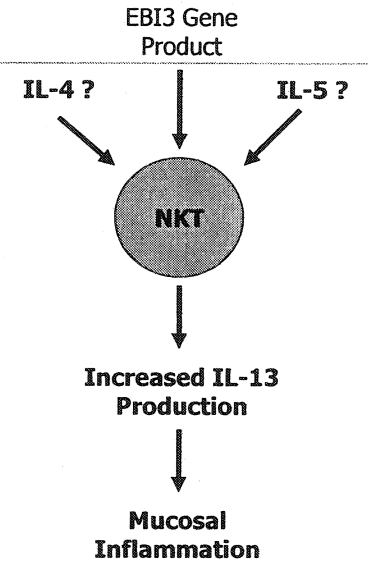
Key Feature: Extensive inflammation and tissue damage in the mucosal layer of GI wall.

Histology of Ulcerative Colitis

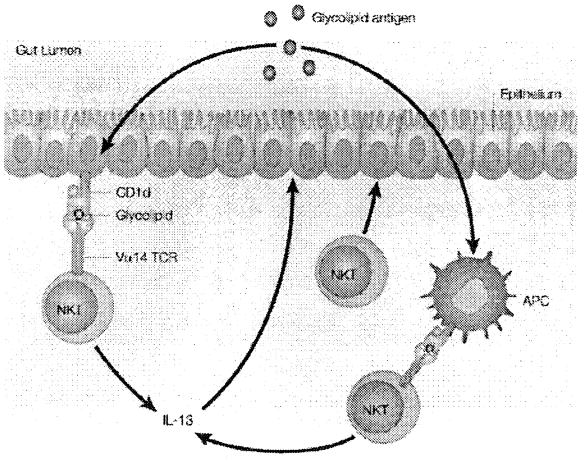


Mechanism of Mucosal Damage

- Involves increased production of T_H2 cytokines from CD4+ T-cells.
- T_H2 cytokines activate Natural Killer T-cells (NKT).
- Result is superficial inflammation and crypt abscesses.



Mechanism of Mucosal Damage



From: Bouma and Strober (2003). *Nature Rev Immunol.* **3**: 521-533.

Autoimmunity

- T_H2 cytokine production is strongly associated with B-cell activation.
- Increased concentrations of IgG1 and IgG4 in ulcerative colitis patients.
  - Anti-neutrophil cytoplasmic antibody (pANCA).
  - Anti-*Saccharomyces cerevisiae* (ASCA).
  - Anti-*Pseudomonas fluorescens* (I2 peptide).
  - Antibodies against *Eschericia coli* cell wall antigens (OMP-C).
- Immuno-inflammatory responses mediated by IgG may lead to GI mucosal damage.
  - Activation of complement system.
  - Production of inflammatory mediators.

Ulcerative Colitis - Symptoms

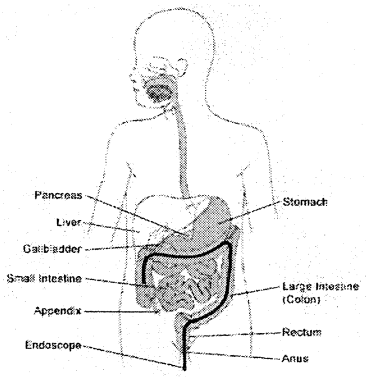
- Diarrhea (blood, mucus may be present).
- Abdominal Pain.
- Borborygmus – gurgling or splashing sound heard over the intestine.
- Tenesmus – pain upon passing of stools.
- Fever.
- Weight Loss.
- Dehydration.

Ulcerative Colitis – Extracolonic Manifestations

- Synovitis.
- Ankylosing spondylitis.
- Iritis.
- Episcleritis.
- Primary sclerosing cholangitis.
- Erythema nodosum.
- Aphthous stomatitis.

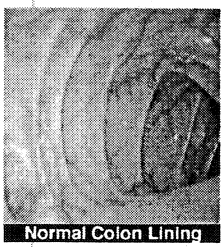
Ulcerative Colitis - Diagnosis

- Visual Examination
  - Colonoscopy = entire colon.
  - Sigmoidoscopy = rectum and lower colon.
  - Reveals inflammation, bleeding, or ulcers on the colonic wall.



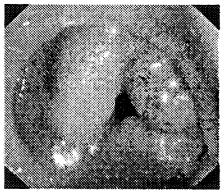
Ulcerative Colitis - Diagnosis

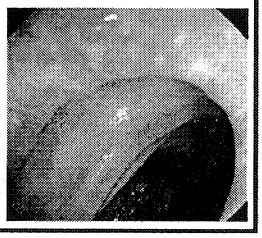
NORMAL COLON



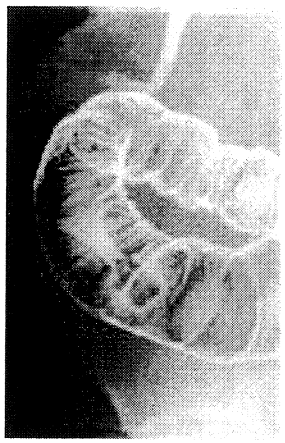
Normal Colon Lining

ULCERATIVE COLITIS





Ulcerative Colitis - Diagnosis



- Barium Enema
  - Radiographic examination of the colon using Barium Sulfate.
  - Barium coats colonic wall and reveals sites of lesions and ulcerations.

Ulcerative Colitis - Diagnosis

- Fecal Occult Blood Test (FOBT)
  - Used to detect presence of hidden blood in the stool.
  - 2 types:
    - Guaiac Smear Test
    - Flushable Reagent Pads
- Lactoferrin.
  - Neutrophil granulocyte derived protein.
  - Presence in stool is an indicator of ulcerative colitis.
  - Quantity in stool is related to disease activity.

Ulcerative Colitis - Diagnosis

- Complete Blood Count
  - Increased WBCs may indicate inflammation.
  - Decreased RBCs may indicate anemia, a sign of GI bleeding.
- Serum Immunological Markers.
  - pANCA, ASCA.
- Serum markers cannot diagnose ulcerative colitis alone.
  - Useful adjunct to help determine disease prognosis or to discriminate between other digestive diseases.

Ulcerative Colitis and Colon Cancer

- Approximately 5% of patients with ulcerative colitis will develop colon cancer.
- Risk of cancer increases with duration of disease and extent of involvement of the colon.
- Routine colonoscopy (every 1-2 years) recommended for ulcerative colitis patients.
  - Dysplasia = abnormal development or growth of tissues.
  - Ulcerative colitis patients that develop dysplasia are more likely to develop colon cancer.

Ulcerative Colitis - Management

- Pharmacologically
  - Aminosalicylates (mesalamine, olsalazine, sulfasalazine).
  - Corticosteroids (prednisone, methylprednisolone).
  - Immunomodulatory drugs.
    - Cyclosporine A – high dose (4 mg/kg) may prevent surgery in 65-70% of patients with severe colitis.
    - Visilizumab – induces apoptosis in activated T-cells without affecting resting T-cells.
  - Nicotine Patches

Ulcerative Colitis - Management

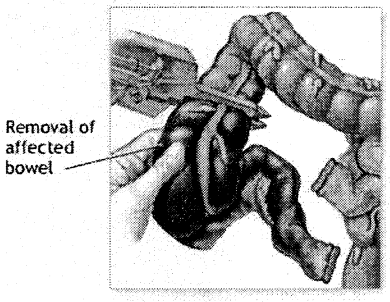
- Natural Therapies
  - Fish Oil – omega-3 fatty acids have been shown to reduce inflammation.
- Lifestyle Modification
  - Regular exercise.
  - Relaxation techniques (e.g.: yoga, meditation).
  - Diet

Ulcerative Colitis – Dietary Management

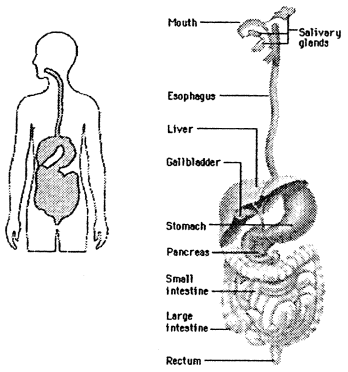
- Certain foods tend to aggravate symptoms of ulcerative colitis.
- Limit:
  - Dairy Products
    - Milk.
    - Soft Cheeses.
    - Alternatives are available.
  - "Gas Producers"
    - Cabbage family.
    - Spicy foods.
    - Apples, Bananas.
- Drink plenty of liquids.
- Multivitamins may be recommended with meals.

Ulcerative Colitis - Management

- Surgery
  - If signs/symptoms not relieved by diet, lifestyle changes, or drugs.
- Colectomy
  - Removal of colitic bowel and/or rectum.
  - Usually includes an ileoanal anastomosis or colostomy.



Crohn's Disease



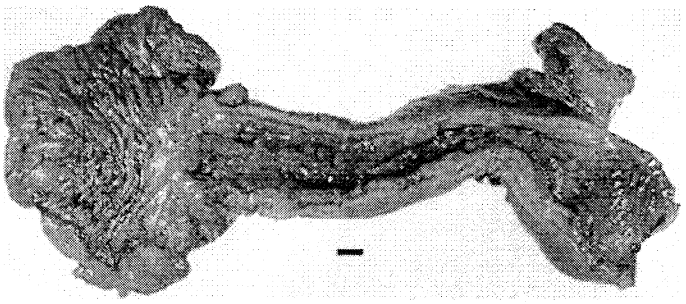
- Chronic, relapsing inflammatory condition affecting ANY part of the GI tract.
- Usually affects both the ileum and the colon.

Crohn's Disease – Risk Factors.

- Ethnicity
  - People of Jewish and European descent are 4-5 times more likely to develop Crohn's disease.
- Family History
- Residence within an Urbanized Area.
- Genotypic expression of an *NOD2* mutant allele.
  - Heterozygotes = 3X greater risk.
  - Homozygotes = 38X greater risk.
- Slightly more common in men than women
  - 1.1-1.8:1 male:female frequency ratio.

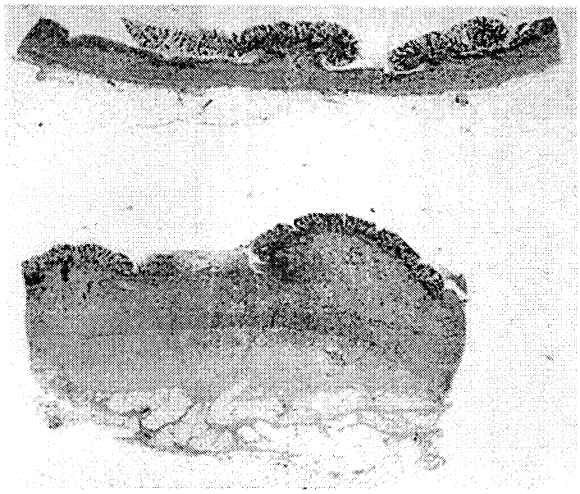
Crohn's Disease – Gross Morphology.

Section of Ileum from a Patient with Crohn's Disease



Key Features: **1) Thickening of intestinal wall.**
2) Narrowing of GI lumen.

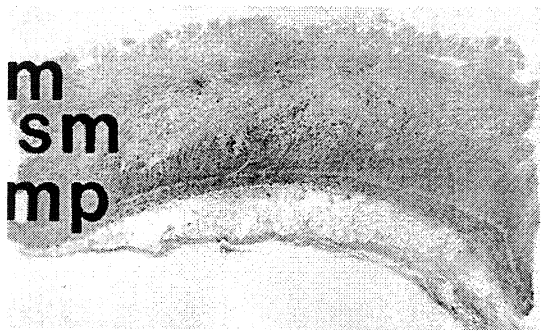
Crohn's Disease - Histology



← **Ulcerative Colitis**

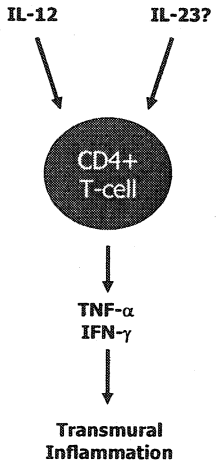
← **Crohn's Disease**

Crohn's Disease - Histology



Extensive fibrosis in the Submucosa, a hallmark of chronic Inflammation.

Crohn's Disease - Mechanism



- Involves production of T_H1 cytokines from CD4+ T-cells.
- T_H1 cytokines activate CD4+ T-cells.
- Result is transmural inflammation of the intestinal wall.

Crohn's Disease – Genetic Basis

- Identified by Hugot *et al.* (1996) using technique of Microsatellite Markers.
  - Principle – marker located close to a disease locus is less likely to be separated during meiosis.
  - Result – marker is co-inherited with disease gene.
- Susceptibility locus identified at the pericentromeric region of chromosome 16.
  - Locus now known as *IBD1.*

Genetic Analysis of *IBD1*

- Analysis of *IBD1* identified a strong association with a single gene known as *NOD2.*
- Sequencing of *NOD2* from Crohn's patients indicated a cytosine insertion at position 3020 in exon 11.
  - Most common frameshift mutation in Crohn's Disease.
  - Result = premature stop codon and truncated *NOD2* protein.
- Other polymorphisms were also identified, leading to missense mutations.
  - 2722G → C [Gly908Arg]
  - 2104C → T [Arg702Trp]

NOD2 and Crohn's Disease.

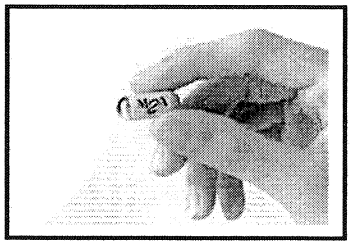
- *NOD2* is highly expressed in epithelial cells of the GI tract.
- *NOD2* is believed to function as an intracellular sensor of bacterial infection.
  - Regulates cellular responsiveness.
- Defective *NOD2* activity leads to defective macrophage activation and spontaneous T_H1 response pathway activation.

Crohn's Disease - Symptoms

- Diarrhea.
  - Frequent, watery, bloody.
- Abdominal Pain.
- Bowel Obstruction.
  - Due to narrowing of gut lumen.
- Fever.
- Significant weight loss.
  - Malabsorption syndrome.
- Gastrointestinal Fissures and/or fistulae.

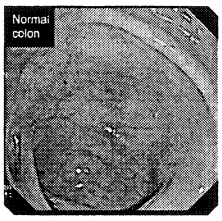
Crohn's Disease - Diagnosis

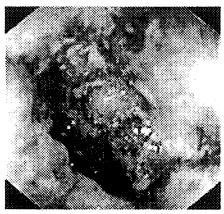
- Colonoscopy.
  - For large intestine only.
- Capsule Endoscopy.
  - Enables imaging of small intestine.
- Barium Enema.
- GI Tissue Biopsy.



Crohn's Disease - Diagnosis

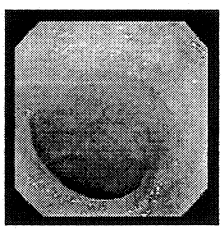
Normal Colon

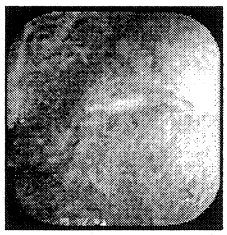




Crohn's Disease Ascending Colon

Normal Ileum





Crohn's Disease Terminal Ileum

Crohn's Disease - Diagnosis

- Complete Blood Count
  - Anemia due to bleeding.
  - Leukocytosis due to inflammation.
- Serum Antibody Levels
  - *Saccharomyces cerevisiae* – 60%
  - *Mycobacterium avium subspecies paratuberculosis* – 86%
- Fecal Occult Blood.
- Stool Culture.
  - Used to rule out infection due to pathogens.

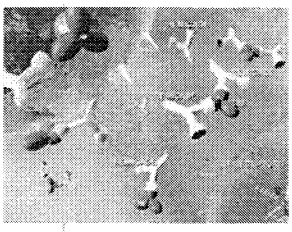
Malabsorption and Crohn's Disease.

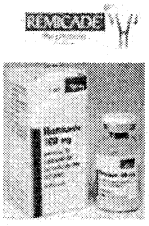
- Damage to small intestine often leads to poor absorption of nutrients.
- Absorptive deficiencies may be diagnosed using D-xylose.
  - D-xylose is a sugar that does not need to be digested but must be absorbed to appear in urine.
  - Low urinary excretion after D-xylose ingestion infers small intestinal absorptive deficiencies.
- Anemia may result due to lack of vitamin B12 absorption (i.e., decreased erythropoiesis).
  - Schilling's Test – if less than 10% of vitamin B12 is excreted in the urine (over 24 h), malabsorption is indicated.
- Steatorrhea = increased lipid excretion resulting from impaired absorption in the small intestine.
  - Fecal Fat Content – elimination of > 6 g/24 h of fat in the stool is considered a positive diagnosis of steatorrhea.

Crohn's Disease - Management

- 5-ASA Compounds.
  - Mesalamine
  - Olsalazine
  - Sulfasalazine
- Corticosteroids.
  - Prednisone
  - Methylprednisolone
- Immunosuppressive Agents.
  - 6-mercaptopurine
  - Azathioprine
- Antibiotics.
  - Metronidazole
  - Ampicillin
  - Cephalosporin
  - Sulfonamide

Remicade® (Infliximab)





- TNF-α neutralizing antibody.
  - Binds with high affinity to both soluble and transmembrane forms of TNF-α and neutralizes its biological activity.
- TNF-α is highly expressed in the stools of patients with Crohn's disease
  - T_H1 response system.
- Clinically shown to decrease expression of inflammatory cytokines and other inflammatory markers [i.e., C-reactive protein (CRP)] in Crohn's patients.
  - Recent study showed clinical improvement in 81% of patients receiving 5 mg/kg Remicade vs. placebo.

Crohn's Disease – Management of Additional Symptoms.

- Antidiarrheals
  - Loperamide (Imodium®)
  - Diphenoxylate
  - Codeine
- Fluid and electrolyte replacement may be required in cases of severe dehydration.
  - Gatorade

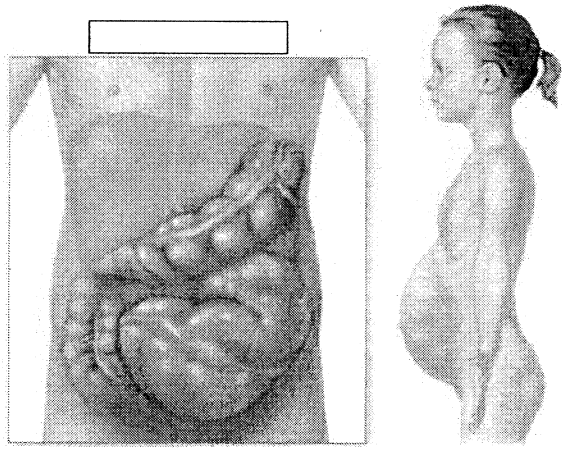
Crohn's Disease – Management

- Nutritional Supplementation.
  - No special diet has proven to be effective in the management of Crohn's disease.
  - Special high-calorie liquid formulas are often used.
  - Severe cases may require intravenous feeding.
- Surgery
  - Colectomy
  - Used to relieve symptoms that do not respond to medical therapy.
    - Blockage
    - Abscess
    - Perforation
    - Intestinal Bleeding

Toxic Megacolon

- Life-threatening condition that may occur in patients with IBD (i.e., ulcerative colitis, Crohn's disease).
- Characterized by significant inflation of the colon and abdominal pain and distention.
  - Loss of bowel sounds, leukocytosis, fever, and tachycardia also occur.
- Significant impairment of colonic function, which may lead to sepsis, shock, and colonic perforation.
- Treatment involves immediate decompression of the bowel.
  - Colectomy required if patient does not respond.
  - Fluid and electrolyte supplementation also used to prevent shock and dehydration.
  - Corticosteroids indicated if ulcerative colitis/Crohn's shows significant inflammatory activity.

Toxic Megacolon



VASCULAR DISEASE
Atherosclerosis

Jagdish Butany ,MBBS,MS,FRCPC,
Prof. Dept Lab Med & Pathobiol.,
Pathologist , UHN-Toronto Gen/Hosp
416 340 3003
jagdish.butany@uhn.on.ca
October 31 2005.

Vascular disease

1.Atherosclerosis
2.Degenerative disease
3.Collagen vascular diseases
4.Tobacco related disease-
T.A.O./Buergers

Butany

ATHEROSCLEROSIS

Atheros: Soft gruel-like

Scleros: Hardening

Atherosclerosis

A chronic disease of elastic and large and medium sized arteries.

Arterial Wall

- Intima - lined by endothelial cell layer
- Media - muscle and elastic tissue
- Adventitia - collagen, elastic fibers
  small vessels (Vasa Vasorum)

Atherosclerosis

- "Disease" of the intima
- Secondary damage to media
- Adventitia - generally uninvolved

Atherosclerosis

The root of **ALL** (almost) Cardiovascular Evil!!

Ischemic Heart Disease

- The SCOURGE of Affluent Societies
- 50% of Deaths
- Significant MORBIDITY

Atherosclerosis

Risk Factors:

- Age
- Gender
- Genetics
- Lipids-hyperlipidemia*
- Hypertension*
- Cigarette Smoking*
- Elevated homocysteine (plasma)
- Other Factors
  - Lack of Exercise
  - Stress
  - Weight gain
  - [Alcohol- Beneficial effect
  - High intake of cholesterol/ Saturated fats

N.B. * Increase risk x4.

Endothelial Cells - Functions

- Lining of Cardiovascular System
- Homeostasis
- Nonthrombogenic Surface
- Multifunctional Tissue
  - "Mechanical" function
    - Regulate vascular tone
    - Regulate Immune/Inflammatory Reactions.
  - "Synthetic" Function
  - "Metabolic" Function
- Semipermeable membrane
- Thrombosis/Thrombolysis
- **Initiate atherosclerosis**

Endothelial Cells

Molecular/Gene Changes

- Adhesion molecules
- Cytokines/Chemokines
- Growth factors
- Vasoactive peptides
- MHC molecules
- Coagulation factors
- Others

[Nuclear factor |< B (NF - |<B)

Vascular Smooth Muscle

Functions:

- Tone - constrict
  - dilate
- Stimuli - normal
  - pharmacologic
- Secrete - Collagen
  - Proteoglycans
  - Growth factors
- Migrate - Intima
- Proliferate
- Repairs

Atherosclerosis

- Pathogenesis: Response to Injury
- Basis:
  - Focal, chronic endothelial injury
  - Endothelial Dysfunction
- Insudation of Lipoprotein
- Adhesion of Blood Cells
  - Platelets
  - Macrophages
  - Migration of Smooth Muscle
  - Accumulation of Lipid
  - Role of Hemodynamics

ATHEROSCLEROSIS

Lesion: 1. Raised intimal "plaque"
- Lipid core
- Fibrous cap
- On the IEL/Media

2. Fatty, fibrous, Fibrofatty Lipid, Fibrolipid Complex

Atherosclerosis

Plaque:
- Yellow white - surface
- Pale white cap - section

  Golden yellow core
- Size: 0.5 - 1.5 cm or more

Atherosclerosis Lesions

Incidence: Aorta
Coronaries
Popliteal
Internal carotid
Circle of Willis

Atherosclerosis Lesions

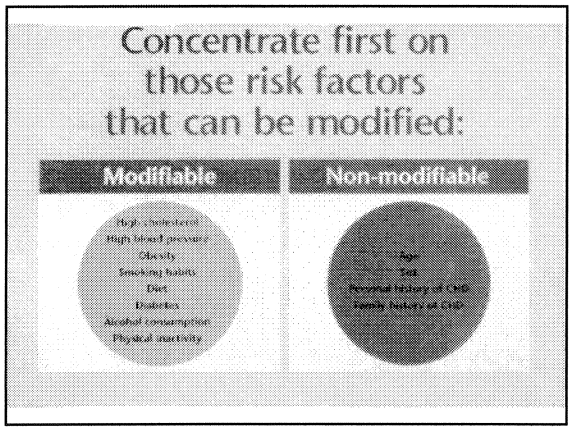
Site: Abdominal > Thoracic
Bifurcation > Rest of Aorta
Branch points > Straight segments

Atherosclerotic Plaque

Composition:
- Varies with age
- Mature plaque
- Cells
- Connective tissue
- Lipid-intra/extra cellular [cholesterol/esters]

Atherosclerotic Plaque

Complications:
- Rupture and/or ulceration
- Plaque Hemorrhage
- Thrombosis
- Calcification



Atherosclerosis

Endothelial injury:

1. Repetitive denuding injury - thrombus - repair
   - atheroma
2. "Non-denuding" injury - E. dysfunction

Atherosclerosis

Endothelial Dysfunction:

- Endotoxin
- Hypoxia
- Tobacco (cigarrette) smoke by products
- Specific Toxins
  - Homocysteine
  - ? Viruses
- Shear Stresses
- Hyperlipidemia

Hypertension

- Common problem
- Easily diagnosed
- Easily treated (not cured) - 90%
- Asymptomatic - Long periods

  BP High: Diastolic > 90 mmHg

  Systolic > 140 mmHg
- Incidence: 25%

  Black people 2x > Caucasians

Hypertension

- Malignant hypertension
- Secondary hypertension

Atherosclerosis

Pathogenesis:

Old - 1. Intimal cellular proliferation

2. Thrombi - repeated

Contemporary: 1 + 2 + More

"Chronic inflammatory response to injury!"

Myocardial Infarction

Jagdish Butany MBBS,MS,FRCPC.
Prof Dept Lab Med &Pathobiol.
Pathologist UHN/TGH
416 340 3003
jagdish.butany@uhn.on.ca
October 31,2005

Myocardial Infarction

- Normal Myocardium
- CAD-Ischemia
- Myocardial Infarction
- Complications of M.I.
- Treatment of M.I.

Acute Coronary Syndromes

- Angina pectoris

Stable

Unstable

Other

- Acute myocardial infarction
- Sudden Cardiac Death

Myocardial Infarction

- Normal Myocardium
- CAD-Ischemia
- Myocardial Infarction
- Complications of M.I.
- Treatment of M.I.

Ischemic Heart Disease

Epidemiology: 80% of cardiac mortality

5 million Americans/year

Atherosclerosis

Multifactorial Disease:

Risk Factors:

Hypertension	Age
Hyperlipidemia	Family history
Diet	Stress
Cigarette smoking	Genetics

Complications of Atherosclerosis

1. Ischemic heart disease
2. Cerebral vascular disease
3. Peripheral vascular disease
4. Aortic aneurysm

Epicardial Coronary Artery

Pathology:

1. Atherosclerosis
2. Plaque changes
3. Thrombosis
4. Non-atherosclerotic disease

Myocardial Infarction

- Normal Myocardium
- CAD-Ischemia
- Myocardial Infarction
- Complications of M.I.
- Treatment of M.I.

ACUTE MYOCARDIAL INFARCTION

- Death of heart muscle due to a prolonged reduction in the supply of oxygenated blood, relative to demand (i.e. ischemia), in the region served by an occluded coronary artery.

ACUTE MYOCARDIAL INFACTION

Causes: Disrupted atherosclerotic plaque with hemorrhage/thrombosis.

MORPHOLOGY OF ACUTE MYOCARDIAL INFARCTION(1)

1. **Microscopy:**
   Early:
   - **Cytoplasmic homogenisation**
   - **Hypereosinophilia**
   - **Nuclear changes**
   - **Wavy fibers**
   - **Infiltration by WBCs (12-18 hours)**
2. **Gross (12-24 hrs):**
   - **Discoloration**
   - **Edema, softening**

MORPHOLOGY OF ACUTE MYOCARDIAL INFARCTION
(2)

- Marked acute inflammation
- Granulation tissue
- Fibrosis

CORONARY ARTERY DISEASE

- Severe stenosis
  - Occlusion
  - Few clinical M.I.
- Mild stenosis
  - 1/3 less occlusion
  - More acute M.I. infarcts

Webster JACC; 15:218A; 1990

Coronary Artery Disease

Plaque disruption

- Primary plaque fissure
- Primary plaque ulceration
- Rupture and hemorrhage

Myocardial Infarction

- Normal Myocardium
- CAD-Ischemia
- Myocardial Infarction
- Complications of M.I.
- Treatment of M.I.

COMPLICATIONS OF ISCHEMIC HEART DISEASE

Myocardial Infarction

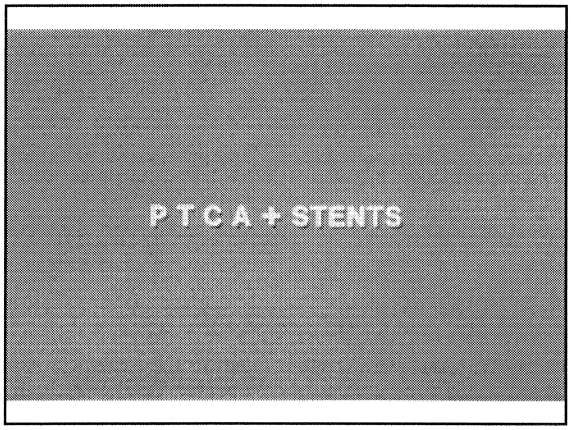
- Normal Myocardium
- CAD-Ischemia
- Myocardial Infarction
- Complications of M.I.
- Treatment of M.I.

Treatment of coronary artery disease

1. Angioplasty
2. Angioplasty + stent
3. Angioplasty + stent + local therapy

Treatment of myocardial infarction

1. Thrombolytic therapy
2. Angioplasty



Complications of thrombolytic therapy

1. Contraindications for therapy
   - Bleeding
   - Previous CVA
   - Recent surgery/trauma
   - Hypotension
   - Active peptic ulcer

Possible complications

1. Stroke
2. Myocardial rupture

Is there a PANACEA

in Medicine, today?

Nearest "thing" to Panacea

"Acetyl Salicylic Acid"

Ms. D.L.C

- 34 year old Caucasian Female
- Admitted by Air Ambulance
- 4/7 Chest pain
- 14/30 General Malaise

Ms. D.L.C. - 2

- Past history:
  - Depression,
  - Schizophrenia disorder
- ER:
- 2/52 - Flu-Rx Home
  2/7 - Gastroenteritis-Rx Home

Ms. D.L.C. - 3

- ICU:
  - Hypotensive
  - Unresponsive
  - RX: Inotropes
    Intubated
    Ventilated

•Investigations:
Electrolytes
Blood Gases
ECG
Echo cardiogram
?Holter Monitor
?MRI/CT Scan

Ms. D.L.C

- Air Ambulance
- In ICU: Neck - no JVP
  - Trachea - Mid
  - Skin - Cool
- Rx (24 hours):
  Levoquin 500 mg
  Dilantin 400 mg
  Cal. Gluc 20 mpg
  Penn / Clinda

Ms. D.L.C. - 5

- AV Dissociation
- Shock - no change
- Rx: Amiodarone
  IABP - Size 40
- Asystole
- Max. Inotropes

Ms. D.L.C.

- [Chaplain - 2 hours}
- Cardiogenic shock
- Anoxic Brain Injury
- Asystole

Congestive Heart Failure
-??Cause

Autopsy - Major Findings

- **Heart**, 330 grams
- Soft, "Baglike"
- Dilated RV and LV
- Thrombus in RAA, LAA and RV
- **Liver:** Thrombus in hepatic artery branches
- **Lungs**: Congestion, bilateral

Differential Dx

- ?Myocardial Infarction
- ?CAD
- Coronary artery dissection
- ?Cardiomyopathy
- ?Conduction Abnormality?
- ??

FINAL DIAGNOSIS

- Myocarditis

Heart Failure

Pathophysiology

Heart Failure

- Definition: Heart failure exists when the heart is unable to pump sufficient blood to meet the metabolic needs of the body at normal filling pressure, provided the venous return is normal.

Congestive Heart Failure

- Syndrome: Complex / variable signs including dyspnea, increased fatigability, peripheral edema

Heart Failure

- Acute
  - Acute MI
  - Tachycardia
  - Rupture Cardiac Valve
- Chronic
  - Myocarditis
  - Cardiomyopathy

Heart Failure

- Primary:
  - Cardiomyopathy, idiopathic
  - Cardiomyopathy - neuromuscular disease
  - Myocarditis
  - Metabolic
  - Diabetes mellitus, Beriberi
  - Hyper/Hypo Thyroidism
  - Toxic e.g. radiation, alcohol, cobalt

Heart Failure

- **Secondary:**
  - **Dysdynamic e.g. increased preload or afterload**
  - **Myocardial Ischemia**
    - **Acute**
    - **Chronic**
  - **Metabolic**
    - **Acromegaly**
    - **Hypoparathyroid**
    - **Pheochromocytoma**
    - **Thyroid disease**
    - **Toxins**

Compensatory Mechanisms

- Autonomic - Heart
  Peripheral
  Circulation
- Kidney - Renin - Angiotensin
- Endothelin I
- Atria Natriuretic Peptides
- Hypertrophy
- Prostaglandins
- Anaerobic Metabolism

C.H.F - Mechanisms

- Dilated Cardiomyopathy
  - ? Decreased level of gene expression for Phospholamban
  - ? Decrease expression for human sarcoplasmic Ca2+-AT Pase gene

Valvular Heart Disease

Jagdish Butany MBBS,MS,FRCPC.
Prof.,Dept Lab Med & Pathobiol.
Pathologist,UHN/TGH.
Nov 2006.

Valvular Disease-Objectives

Understanding of:

- Normal Heart Valve Structure
- Normal Heart valve Function
- Diseases of Heart Valves
- Complications of Heart Valve Dysfunction
- Treatment

Valvular Disease-Objectives

Understanding of:

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- Treatment

Valvular Disease

- A.V. Valves:
  - –Tricuspid
  - –Mitral
- Semilunar:
  - –Pulmonic
  - –Aortic

Valvular Disease-Objectives

Understanding of:

- Normal Heart Valve Structure
- Normal Heart valve Function
- Diseases of Heart Valves
- Complications of Heart Valve Dysfunction
- Treatment

Valvular Disease - Dysfunction

- Etiology:
  - – Congenital
- Acquired:
  - – Inflammatory
  - – Degenerative
  - – Neoplastic
  - – Iatrogenic

Valvular Disease

- Dysfunction:
  - –Stenosis
  - –Incompetence
  - –Combination

Valve Disease

- Rheumatic Heart Disease
  - –Myocardial
  - –Valvular

Valve Disease - Rheumatic Fever (1)

- Acute immune mediated inflammatory disease
- Involves multiple organs
- Follows Group A Hemolytic Streptococcal Pharyngitis (Approximately 3%)
- Acute: Rheumatic Carditis

Valve Disease - Rheumatic Fever (2)

- Clinical Symptoms
  - Multiorgan
  - See Jones Criteria for Diagnosis
- Sequelae: Chronic Rheumatic Valvular Disease

Valve Disease - Rheumatic

- Acute:
  - Pericarditis with Aaschoff bodies
- Valves:
  - Verrucae - Rough Zone
  - Fibrin deposits

Valve Disease - Rheumatic

- Chronic:
  - Myocardium: Focal scars
  - Valves
    - Leaflet fibrosis
    - Leaflet retraction
    - Commissural fusion
    - Calcification
    - Chordal fusion/calcification
  - Orifice

Mitral Valve - Incompetence

- Rheumatic (with "fixed" stenosis)
- Myxomatous change ("floppy")
- Annular dilatation
- Annular calcification
- Infective endocarditis

Aortic Valve - Stenosis

- Acquired: Rheumatic
- Congenital:
  - Bicuspid Valve
  - Unicommissural Valve
  - Unicuspid - "Dome" valve
  - Subvalvular (HOCM)
  - Supravalvular (Atresia)
  - Subaortic Ring

  Degenerative

Aortic Valve - Incompetence

- Fixed stenosis
- Myxomatous change
- Myxomatous change
- "Annular" dilatation
- Sinotubular dilatation
- [Ascending aortic dilatation]

Valvular Disease-Objectives

Understanding of:

- Normal Heart Valve Structure
- Normal Heart valve Function
- Diseases of Heart Valves
- Complications of Heart Valve Dysfunction
- Treatment

Valve Lesions

- Sequelae:
  - Turbulent Blood Flow
- Effects ?

Valve Disease: Infective Endocarditis

- Microbial colonization or infection (also endocardium)
- "Vegetations" on valve tissue:
  - Thrombus
  - Dead Cells
  - Inflammatory cells
  - Bacteria
- Tissue destruction

Pathology of SBE

- Early:
  - Vegetation, friable, bulky
  - Tissue damage +/-
- Pathogenesis:
  - Bacterial colonies in blood
  - Site of entry ?
  - Endothelial damage
  - Thrombi
  - Infection

Valve Disease - Infective Endocarditis

- Virulent Bug:
  - Rapid or acute infective endocarditis
  - Death: days to weeks
- Low Virulence Bug:
  - Subacute bacterial endocarditis

Valve Disease - Infective Endocarditis

- Treatment:
  - General/supportive
  - Antibiotics
  - Valve replacement

Valve Disease - SBE

- Infection:
  - Previously Normal Valve
  - Previously Abnormal Valve
  - Rheumatic
  - Congenital
  - Myxomatous
  - Calcified / Degenerative
  - Prosthetic Valves

Valvular Disease-Objectives

Understanding of:

- Normal Heart Valve Structure
- Normal Heart valve Function
- Diseases of Heart Valves
- Complications of Heart Valve Dysfunction
- Treatment

Valve Disease - Infective Endocarditis

- Treatment:
  - General /supportive
  - Antibiotics
  - Valve replacement

Valve Disease - Surgery

A Valve Repair

B Valve Replacement
- Mechanical
- Biological
- Porcine
- Pericardial

Valve Replacement

- Bioprostheses or Tissue Valves
- Porcine
- Homograft
- Pericardial
- [Duramater]
- Autografts

Valve Replacement

- Mechanical valves
  - Ball in cage
  - Disc (single leaflet)
  - Bileaflet
- N.B. All need lifelong anticoagulation

Valvular Disease-Objectives

Understanding of:

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