Hopkins General Surgery Review Manual

Introduction

This "manual" is a compilation of study notes I have made over the past 5 years based on a number of sources, including those listed here:

- Text books (see reference list)
- Review books (see reference list)
- Didactic lectures and conferences at both Johns Hopkins and the NCI Surgery Branch
- Presentations I gave during weekly conferences at NCI
- Primary and review articles
- Points made by attendings and other residents on rounds or in the OR
- Intern Sunday morning lecture with Dr. Cameron (2001 – 2002)
- Halsted quizzes
- SESAP questions
- UpToDate®

Disclaimer: Individual illustrations and material may belong to a third party.
Unless otherwise stated all figures and tables by Peter Attia

When I began putting my notes together on random pieces of paper and my Palm Pilot, I did not intend to do much else with them. However, in time, they became so numerous that I needed to organize them in a better way. A resident from the Brigham whom I worked with in the lab at NIH encouraged me to put them together in what he jokingly referred to as an "Attia Bible" of surgical wisdom, something he had done with his own notes. The intent of these notes was not as much to be a review for a specific test per se, as it was an "all-purpose" compilation of salient points to consider as I go through residency.

Of course, these notes come with the standard disclaimer that they are not meant to replace reading from primary sources, rather to supplement it. In addition, while I have tried to be as accurate as possible, during my readings I encountered several "facts" that were either contradictory to "facts" I had been taught as a resident or read in other sources. For this reason I can make no guarantees about the validity of each statement made here. I have tried my best to amalgamate each set of facts into a somewhat concise, yet accurate document.

Hopefully, these notes will provide you with some benefit as well. I welcome all criticism and correction and look forward to supplementing and augmenting this first edition many times over.

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Reference List

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Editors

The following individuals have been generous with their time and thoughts, and have made several changes and additions to my original "manual".

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Breast Disease

Surgical Anatomy:

- Intercostobrachial nerve (off 2nd intercostal nerve) sensation to medial arm → can sacrifice
- Long thoracic nerve: to serratus anterior → winged scapula
- Thoracodorsal nerve: to latissimus dorsi → weak arm adduction
- Medial pectoral nerve to pec minor and major; lateral pectoral nerve to pec minor only

Batson's plexus: valveless vertebral veins → allow direct metastases to spine
Poland syndrome: amastia, hypoplastic shoulder, no pecs
Mastodynia: Rx with danazol, OCP
Mondor's disease: thrombophlebitis of superficial vein of breast → Rx with NSAID

DCIS

- Highly curable with survival of 94 – 100%
- 50% of recurrences are invasive
- Excision and radiotherapy OR mastectomy; axillary lymph node dissection (ALND) not required (only 1% have positive nodes). NSABP-17 showed that lumpectomy alone had 13.4% recurrent DCIS and 13.4% recurrent invasive cancer vs. 8.2% and 3.9%, respectively for lumpectomy + radiation.
- Tamoxifen decreases rate of ipsilateral and contralateral breast cancer in ER positive women, role in ER negative women, if any, unknown; but must be balanced against risk factors (1 – 2% DVT, PE; Endometrial cancer). **Tamoxifen has NOT been shown to increase survival, only to decrease rate of recurrence (DCIS and ipsilateral/contralateral invasive breast cancer)**. Several large studies have been done (NSABP-24, 1800 patients, [Fisher B, et al. Lancet 1999;353:1993]) and failed to identify a survival advantage, despite adequate power.
- Ongoing research to identify subset of patients who could be treated without radiation
- Role of Sentinel Lymph is undefined. NO evidence to support use as of 2004.
- Van Nuys classification MAY identify patients who can benefit from lumpectomy alone (low-grade, without necrosis; margin > 1 cm; lesion < 1.5 cm)

LCIS

1. Aka Lobular Neoplasia, encompasses LCIS (> 50% lobular involvement) and Atypical Lobular Hyperplasia (ALH, < 50% lobular involvement)
2. Not clinically, radiographically, grossly detectable
3. 7 – 10 x increased risk of invasive cancer in either breast (especially in young women with a family history)
4. 17% risk at 15 years, 5.6% at 5 years; 20% lifetime risk (70% of which will be ductal invasive, 30% will be lobular invasive); ≈ 1% per year
5. Margins are irrelevant, disease is diffuse (unlike DCIS)
6. LCIS is not itself pre-cancerous, it is simply a marker of a susceptible field

Phyllodes tumor: 10% malignant; large; rare nodes (spread, if any, hematogenous): Rx → WLE, mastectomy not necessary; NO ALND

Intraductal papilloma: No risk of cancer; #1 cause of bloody nipple discharge

Comedo breast cancer: Likely multicentric; do mastectomy; poor prognosis

Paget's disease of the breast: Eczematous lesion on nipple → underlying DCIS or ductal CA

Most recent screening recommendations: First at 40; q 1 – 2 years until 50; yearly thereafter

Radial Scar: associated with carcinoma anywhere in the scar; do not stereotactically biopsy (↑ chance of sampling error), instead → excisional biopsy

Staging:
T1: < 2 cm T2: 2.1 – 5 cm T3: > 5 cm T4: skin involvement (inflammatory → *dermal lymphatic invasion*)

N1: + ax nodes N2: matted/fixed N3: internal mammary nodes

Stage I: T1 Stage II: up to T2N1 or T3N0 Stage III: T4 or N3 Stage IV: any M

Survival by stage (5 years):
I: 90 – 95% II: 50 – 80% III: 30 – 50% IV: 15 – 20%

Note: FNA cannot distinguish between DCIS and invasive

Who gets chemotherapy?
1. Pre-menopausal:
   - ER/PR-
   - T > 1 cm
   - Any N, including micro (SN+)
2. Post-menopausal (up to 90% are ER/PR+ → get tamoxifen):
   - ER/PR- & T > 2 cm
   - ≥ 4 nodes OR matted nodes (regardless of ER/PR)
     (Hence, ER/PR+, ≤ 3 unmatted nodes → no chemo)

Who gets axillary radiation? (In general, want to avoid axillary radiation following dissection)
- + supraclavicular node
- matted nodes (extracapsular extension)
- ≥ 4 nodes

Who gets breast irradiation?
- any segmental resection for invasive or DCIS
- inflammatory disease (T4/skin involvement); some T3

Major studies evaluating role of adjuvant radiation* therapy:

1. The addition of post-op irradiation to chemotherapy (CMF) for women with stage II or III breast cancer following mastectomy increased overall survival and reduced locoregional recurrence. [Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. Overgaard M, et al. NEJM 1997;337:949].
2. Radiotherapy combined with chemotherapy (CMF) after modified radical mastectomy decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer. [Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. Ragaz J, et al. NEJM 1997;337:956].

*Trental is very effective in treating radiation mastitis

Locally Advanced Breast Cancer

- Locally Advanced Breast Cancer (LABC) & Inflammatory Breast Cancer (IBC) sometimes (incorrectly) used interchangeably
- Strictly speaking, LABC includes: T3+N1 – 3 *or* T4+N0 – 3 *or* any T+N2 – 3 (i.e. Stage III A/B disease)
- Term IBC first used in 1924 by Lee and Tannenbaum at Memorial Hospital to describe clinical presentation of 28 patients with: "…breast of affected side usually increased in size…skin becomes deep red or reddish purple…to the touch brawny and infiltrated…after the fashion of erysipelas…"
- Accounts for 1 – 6% of all breast carcinomas (IBC)
- 50 – 75% axillary involvement at diagnosis

Overall prognosis median survival: 2 years

- Diagnosis based on histology of invasive carcinoma *PLUS*
    1. Erythema
    2. Edema, or peau d'orange
    3. Wheals, or ridging of the skin secondary to dermal lymphatic invasion (although tumor invasion only seen in 30%)
- Neoadjuvant treatment and early diagnosis crucial for successful treatment
- Approximately 75% undergo CR or PR to induction therapy → response predicts outcome

Effectiveness of mastectomy by response to induction chemotherapy for control of Inflammatory Breast Cancer [Fleming R, et al. Ann Surg Onc 1997 4:452]

Initial Response to Induction therapy:

- CR → median survival: 120 months (12%)
- PR → median survival: 48 months (62%)
- NR → median survival: < 24 months (26%)

Further Breakdown:

- If > 1 cm^3 residual tumor → median survival: 36 months
- If < 1 cm^3 residual tumor → 70% alive at 5 years

Role of Mastectomy:

- If CR or PR → Chemo + RT + Mastectomy increased median survival from 48 to 120 months (vs. Chemo + RT)
- If **NR** → Chemo + RT + Mastectomy **did not influence median survival** (< 24 months), or **disease-free interval**

Summary for Treatment for Inflammatory breast cancer:

1. Neoadjuvant chemo (cytoxan/adriamycin); response to this predicts survival (10% CR, 80%PR)
2. MRM (if PR or CR)
3. Adjuvant chemo (taxane based)
4. Radiation to chest wall

Chemotherapy/Hormonal* Treatment:

Premenopausal	Postmenopausal
▪ chemo for almost any tumor > 1 cm (regardless of nodal status) ▪ cytoxan & adriamycin ▪ add taxane if node positive ▪ tamoxifen if ER/PR positive ▪ arimidex and aromatase inhibitors not effective in premenopausal since can't compete with estrogen produced	▪ tamoxifen or arimidex if node negative and ER/PR+ ▪ Chemo if poorly differentiated and > 1 cm (even if node negative) ▪ cytoxan & adriamycin ± taxane if node positive ▪ tamoxifen or adriamycin if elderly, node positive, and ER/PR+

*Responses to hormonal therapy by marker:

ER/PR+	80%
ER-/PR+	45%
ER+/PR-	35%
ER/PR-	10%

Inherited Breast Cancer Syndromes: 4 appear to be important

1. Li-Fraumeni Syndrome → mutation of p53
2. Mutation of bcl-2 (18q21) → ↑ expression of bcl-2, which is anti-apoptotic
3. BRCA-1 → on long arm of 17
4. BRCA-2 → on short region of 13q12-13

BRCA 1

- Ch 17q21; reported 1990, positionally cloned 1994
- ↑ Risk of breast cancer (85%) and ovarian cancer (40 – 50%)

BRCA 2

- Ch 13q12-13; reported 1994; positionally cloned 1995
- ↑ Risk of breast cancer (85%) and ovarian cancer (10%)
- ↑ Risk of male breast cancer (6%)

Risks of Tamoxifen use

- ↑Uterine adenocarcinoma, sarcoma
- ↑Cataracts
- ↑DVT, PE
- ↓osteoporosis
- No change in incidence of heart disease

Head & Neck Disease

Parotiditis: Usually caused *staph spp*; seen in elderly, dehydrated; Rx: antibiotics → drainage of abscess if not improving

"Ludwig's angina": Sublingual space infection (severe deep soft tissue infection of neck involving the floor of the mouth); if airway compromise → perform awake tracheostomy under local anesthetic → operative debridement

Leukoplakia can be premalignant; erythroplakia is premalignant (and of much more concern)

Head & Neck SCC: Stage I, II (up to 4 cm, no nodes) → single modality treatment (surgery or RT)
Stage III, IV → combined modality
Perform FNA, **not excisional biopsy** for suspicious masses

Nasopharyngeal SCC: associated with EBV; 50% present late as neck mass; drainage to posterior neck nodes; most common nasopharyngeal cancer in adults (lymphoma is most common in kids). Often see in Asian population

Glottic Cancer: if cords not fixed → RT; if fixed → surgery + RT. Chemo + RT used more often for organ preservation

Lip Cancer (99% epidermoid [i.e. squamous] carcinoma): Lower > upper lip (because of sun exposure) → resect with primary closure if < ½ lip; otherwise flap

Tongue Cancer: usually surgery + RT; seen ↑ in Plummer Vinson (dysphagia, spoon fingers, anemia). More commonly seen in smokers/drinkers

As salivary gland size ↑ [sublingual (60%), submandibular (50%), parotid (20%)] → incidence of malignant disease ↓

Pharyngeal cancers have worse prognosis than oral cancers

Mucoepidermoid carcinoma: #1 **malignant** salivary tumor overall

Adenoid cystic carcinoma: #1 malignant salivary tumor of submandibular/minor glands. Overall: poor prognosis

Pleomorphic adenoma ≡ mixed parotid tumor = #1 **benign** tumor (40 – 70% of all salivary gland tumors)
Do NOT enucleate (or will recur) → needs superficial parotidectomy (spare CN VII).
If malignant → take whole gland + CN VII;
If high grade (anaplastic) → need neck dissection

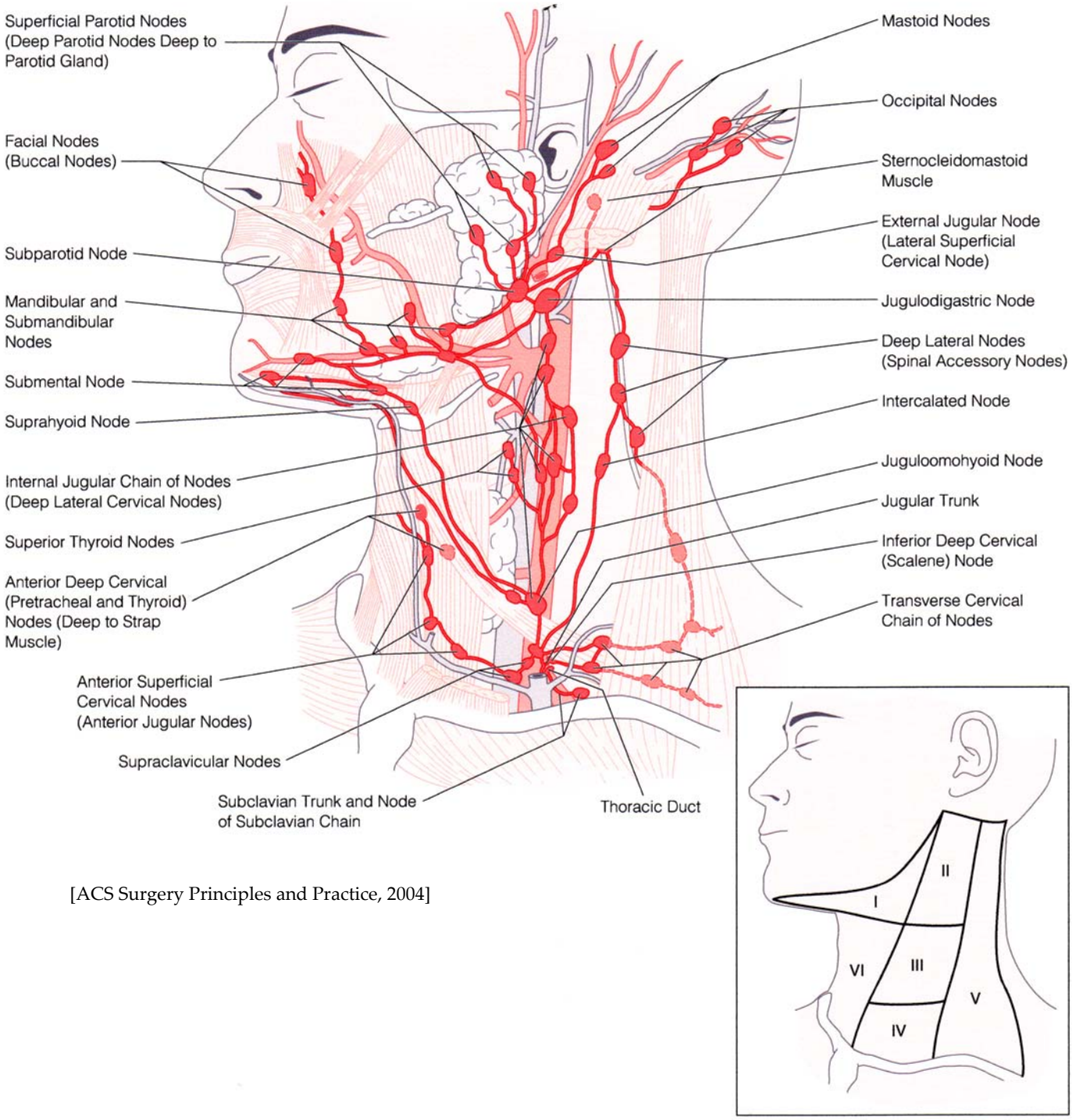
Warthin's tumor (adenolymphoma) #2 benign salivary tumor; male predominance; 10% bilateral; 70% of bilateral parotid tumors are Warthin's tumor; Rx → superficial parotidectomy

Frey's Syndrome: late complication of parotidectomy (occurs ≈ 50% when facial nerve is preserved); perfuse perspiration over cheek following salivary stimulation. Intracutaneous injection of Botox A ≈ 100% effective in treatment, but responses may be short-lived (can be repeated). Usually self-limiting.

Ipsilateral drooling following submandibular gland resection: likely injury to marginal mandibular nerve

Radical neck dissection: takes CN XI, SCM, IJ, submandibular gland; **most morbid is CN XI**

Classification of Cervical Lymph Nodes



[ACS Surgery Principles and Practice, 2004]

Level	Nodes
I	Submental, submandibular nodes
II	Upper IJ nodes
III	Middle IJ nodes
IV	Lower IJ nodes
V	Spinal accessory nodes, Transverse cervical nodes
VI	Treacheoesophageal grove nodes

Cancers of the oral cavity usually metastasize to the nodes in levels I – III.
Laryngeal cancers typically metastasize to the nodes in levels II – IV.

Presence of **Horner Syndrome** (paralysis of the vagus nerve, phrenic nerve, invasion of brachial plexus, and/or paravertebral musculature) generally indicates tumor unresectability

Tracheo-innominate fistula

- Massive bleeding from trachea is innominate artery until proven otherwise; avoid by making tracheostomy no lower than 3rd ring
- Usually occurs 2 – 3 weeks post tracheostomy; poor nutrition and steroids use may contribute
- Mortality ≈ 80%
- Sentinel bleed → to OR for bronchoscopy
- Temporary control (on route to OR) via cuff hyperinflation or finger compression of innominate artery (anterior pressure)
- Treatment is ligation of innominate artery

Most common locations for mandibular fractures: **angle (25%)** and **subcondyl (30%)**; the most common long-term complication of mandibular fracture is **malocclusion**

Carotid body: **chemoreceptor** within the adventitia of the CCA (posteromedial side); responds to ↓O_2 tension, ↑CO_2 tension, ↑blood acidity, and ↑blood temperature by ↑HR, ↑BP, and ↑rate & depth of respiration in an attempt to overcome the above stimuli

Carotid sinus: **pressure sensor** within wall of proximal ICA; responds to ↑BP by ↓HR and ↓BP

Thyroid Gland and Disease

- from the Greek work "Theros" (shield) and "eidos" (form)
- secretes hormones (T4, T3, calcitonin) from **basal** membrane side (into bloodstream)
- antithyroid agents impair (i) iodination and (ii) coupling of DIT/MIT
- T4 → T3 peripherally (kidney, liver) (T3; 10 x more active than T4). Propothiouracil (PTU) blocks peripheral conversion of T4 → T3

Note: Suppression of iodine uptake in patients with increased T3 and T4 levels is pathognomonic for subacute thyroiditis

Usual Causes of Hyperthyroidism:

1. Toxic nodule
2. Toxic multinodular goiter
3. Graves' disease
4. *Early* subacute thyroiditis

Ways to Treat Hyperthyroidism:

1. Medical (PTU, methimazole): interfere with iodine conversion; up to 60% recur
2. Radioiodine Ablation (I^{131}): weeks to months; 1st choice by many except in pregnancy
3. Surgery: risks of surgery

Thyroid Storm: untreated hyperthyroidism + stress (trauma, infection, pregnancy, DKA, etc)
Rx: fluids, O_2, glucose, anti-thyroid drugs, but first → treat underlying cause;
NB: do not use ASA, as it displaces T4 from thyroglobulin

(Differentiated) Thyroid Cancer

- 15,000 – 20,000 cases/yr US
- 15,000,000 nodules/yr (5 – 10% harbor cancer)
- mortality < 1%

Risks

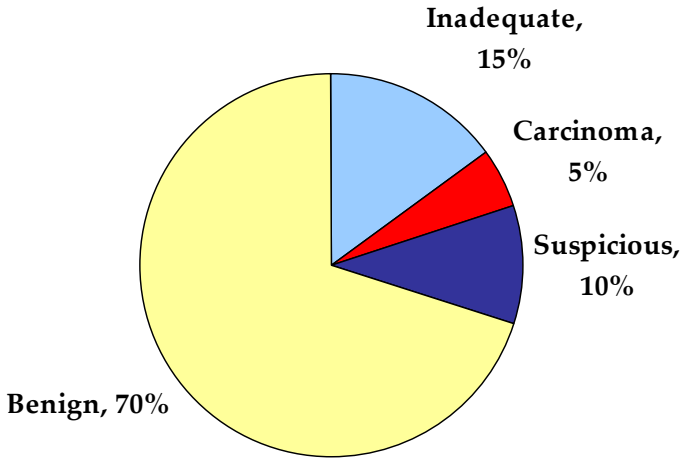
- age < 14, > 65
- previous thyroid cancer
- family history
- enlarging nodule on thyroid hormone suppression
- exposure to low-dose radiation
- Graves' disease or thyroiditis
- syndromes (MEN II, Carney's)

Cancer Histology

- **Papillary** (60%)
- Follicular variant of papillary (20%)
- Follicular (< 5%)*
- Hürthle cell carcinoma (< 5%)
- Medullary (5%)
- Anaplastic (1%)
- Other (1%)

*difficult on FNA to differentiate follicular adenoma from carcinoma

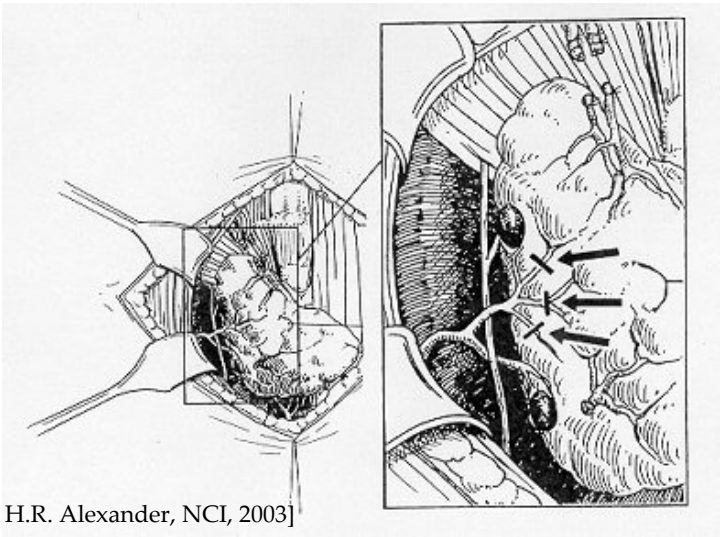
Of FNA'ed lesions in adults*



*Children have higher incidence of carcinoma: 20 – 50%

One option for lesions deemed benign on FNA is hormone suppression: if regresses → follow; If grows→ remove; if same→ repeat FNA

<u>Surgical management</u>
Lobectomy: unclear path (go back for completion, if necessary)
Lobectomy + isthmusectomy: **papillary** < 1 cm, benign unilateral lesions or suspicious lesions
Total thyroidectomy (followed by RAI): **papillary** ≥ 1 cm, **follicular**, **Hürthle, medullary**
IF planning post-op RAI → must do total thyroidectomy, regardless of size (RAI only useful in well-differentiated cancers-**not MTC**)
Medullary is the only histology where you **do central dissection** (level VI and VII) prophylactically (in addition to total thyroidectomy) and modified radical neck dissection (levels II – V) on affected side
***Performing a total thyroidectomy allows use of thyroglobulin for recurrence monitoring and use of RAI for microscopic disease**



[Figure taken from talk given by H.R. Alexander, NCI, 2003]

Medullary Thyroid Cancer: 20% of those with MTC have MEN II (100% of those with MEN II have MTC). MEN II associated MTC tends to be bilateral, younger, worse prognosis, RET-proto-oncogene; aggressiveness as follows: **MEN IIB** [perform thyroidectomy by 6-months-old] > **MEN IIA** [perform thyroidectomy by 5-years-old] > **FMTC**

- May see amyloid on pathology
- ↑ serum calcitonin (can use serum calcitonin levels to monitor for recurrence)
- Originates from parafollicular C cells, which produce calcitonin and hence **do not concentrate iodine**.

Anaplastic: Only operation that should be considered is tracheostomy. Minimal role for palliative resection

Medical management
Thyroid hormone suppression
Radioactive iodine ablation (RIA)
Cytomel (T3) [half-life 3 – 4 days] vs. Synthroid (T4) [half-life 4 weeks]
*Hence use T3 replacement post-op before RIA

Thyroglobulin can only serve as a tumor marker when the following 2 conditions are met:

1. The tumor is well *differentiated* (since it's produced by follicular cells)
2. The patient has had a *total* thyroidectomy

Lymph nodes
For differentiated cancer: no role for prophylactic LND – only for palpable or FNA+ nodes → "regional dissection" (Radical takes levels I – VI + jugular + CNXI; Modified takes levels II – VII, spares IJV, SCM, spinal accessory nerve XI). Levels most at risk are II – VI

Prognosis (for well differentiated thyroid cancer):
AGES/AMES: age, grade/mets, extent, size; TNM;
However, age, grade (histology), size most important
Age (> 45, or < 14) is single greatest factor

Superior laryngeal nerve (both sensory and motor), External branch: motor to cricothyroid; injury → lose projection, high pitch tone; provides sensory to supraglottis
Recurrent laryngeal nerve: innervates all of larynx except cricothyroid; bilateral injury → airway occlusion
Note: Always assess cord function before any operation on thyroid to document RLN function

Parathyroid Gland and Disease

Superior parathyroid glands from 4th pharyngeal pouch; Inferior (and thymus) from 3rd pharyngeal pouch → more variable position (since longer distance traveled)
All parathyroid glands generally receive blood supply from the *inferior thyroid artery*

If only 3 glands found at surgery, fourth may be in:

- Thymus, anterior mediastinum
- Thyroid
- Carotid sheath
- Tracheoesophageal groove*, posterior mediastinum
- Behind esophagus

*Most common ectopic site

PTH produced by Chief cells → increases Ca^{++} via bone breakdown, GI absorption, increased kidney re-absorption, excretion of phosphate by kidney

Hyperparathyroidism

1. **Primary**: ↑ PTH secretion by parathyroid (high Ca^{++}, low PO_4; look for **$Cl^-/PO_4 > 33$**, even with normal Ca^{++})
2. Secondary: ↑ PTH secretion due to renal failure *or* decreased GI Ca^{++} abs (Ca^{++} low or normal)
3. Tertiary: ↑ PTH after correction of 2° hyperparathyroidism (high Ca^{++})
4. Familial Hypercalcemia Hypocaluria (FHH): see ↑ serum Ca^{++}, PTH, but ↓ urine Ca^{++} (defect in set-point for "normal" Ca^{++} levels; patients do not experience the sequelae of elevated Ca^{++}); No surgery

Parathyroid Imagining:

- Sestamibi scan
- U/S
- ^{201}Technetium-thallium subtraction scan
- CT/MRI

Primary Hyperparathyroidism
Incidence: 1/4000
Risks: MEN I, IIa, irradiation, family history (autosomal dominant)
Adenoma > 85% [1], Hyperplasia ≈ 10% [4], Carcinoma ≈ 1% [1], [# glands typically involved]
Typically: $[Cl^-]/[PO_4] > 33$

Initial medical treatment: IV fluids, lasix, NOT thiazides

Treatment

- 1° Adenoma: Surgically remove adenoma (± biopsy all enlarged glands)
- 1° Hyperplasia: Bilateral neck exploration and intraoperative PTH. Subtotal parathyroidectomy (leave ½ lower gland *in situ*) or total parathyroidectomy with autotransplantation
- 1° Carcinoma: WLE with ipsilateral thyroidectomy and lymph node dissection
- 2°: Correct Ca^{++} and PO_4, perform renal transplant (no parathyroid surgery)
- 3°: Correct Ca^{++} and PO_4, perform renal transplant, remove parathyroid glands and re-implant 30 to 40 mg in forearm

Parathyroid Carcinoma

Signs/Sx: HyperCa^{++}, elevated PTH, *palpable* gland (50%), neck pain, recurrent laryngeal nerve paralysis
HCG is a marker

Treatment: En bloc resection including *ipsilateral* thyroid lobe + associated lymph nodes

Post op Complications:

- Recurrent laryngeal nerve injury
- Neck hematoma (open at bedside if breathing compromised)
- HypoCa^{++}

Parathyroid Pearls

- 90% of primary hyperparathyroidism due to a single adenoma → unilateral exposure is ok (with intraop PTH)
- MUST exclude familial/MEN disease (a different entity altogether which requires subtotal parathyroidectomy → leave ½ of a lower gland *in situ*)
- Nuclear medicine expertise is crucial: if possible, subtraction of Tc^{99m} pertechnetate (potassium analog specific for thyroid) from Tc^{99m} Sestamibi (taken up by both thyroid and parathyroid)
- For intra-op PTH to be valid must have >50% drop in baseline PTH within 10 minutes
- Intra-op PTH must be used if doing single gland exploration (MIP), else → must do 4 gland exploration

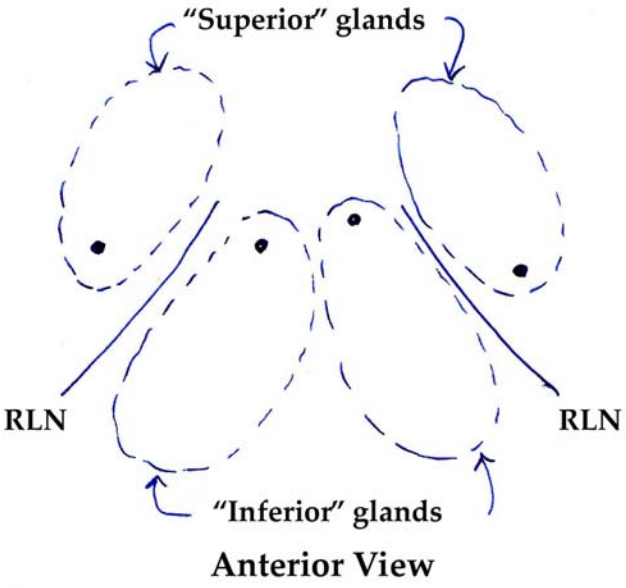
If disease recurs, MUST distinguish between *persistent* and *recurrent:*

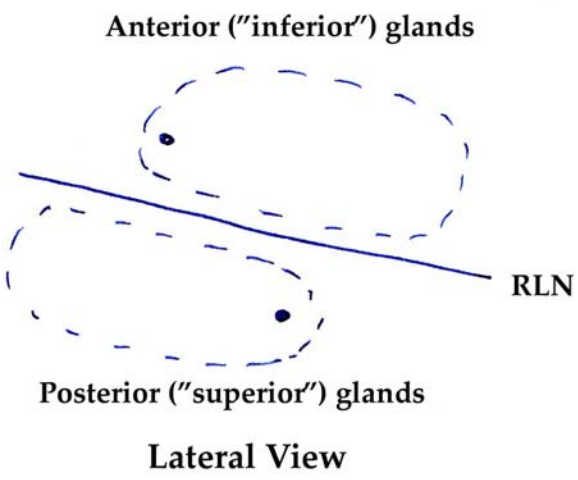
- Persistent: Only transient "cure". Almost always implies missed adenoma. #1 place is TE groove on right side; also consider ectopic glands
- Recurrent (> 6 months normocalcemia): Implies hyperplasia with re-growth (e.g. familial, possibly cancer)
- 10 x increase in RLN injury during re-do surgery. Hence, first step in re-do is confirm diagnosis with 24 hour urinary Ca^{++} (if normal → no disease). Second, check for family history of MEN I manifestations
- Localization with Sestamibi and U/S. Consider CT/MRI (very bright on T2 to differentiate from LNs)

Ultimate pearls:
"Superior glands" is really a misnomer, they should be called "Posterior glands", since they are virtually always posterior and cephalad to the RLN. Ectopic sites are generally *posterior in TE grove*

"Inferior glands" should be called "Anterior glands" since they are virtually always anterior and caudal to the RLN. Ectopic glands are usually *anterior/mediastinal*

The figure below shows in dotted lines the possible locations for the parathyroid glands in relation to the RLN. There is significant vertical overlap, such that superior glands can actually be below inferior glands, and vice versa.





Multiple Endocrine Neoplasia (MEN)

*inherited autosomal dominant (with variable penetrance)

MEN Type I
aka Wermer's Syndrome ("PPP")
•Parathyroid Hyperplasia (≈ 90%)
HyperCa^{++} → usually first
•Pancreatic islet cell tumors (≈ 67%)
Gastrinoma (ZES) (≈ 50%)
Insulinoma (≈ 20%)
•Pituitary Tumor (≈ 67%) most often PL-secreting tumor

MEN Type IIA
aka Sipple's Syndrome ("MPP")
•Medullary Thyroid Carcinoma (100%) → 2nd to 3rd decade
calcitonin secreting
usually quite indolent
•Pheochromocytoma (> 33%)
catechol excess
usually benign, bilateral, adrenal
•Parathyroid Hyperplasia (≈ 50%)
hyperCa^{++}

MEN Type IIB
"MMMP"
•Mucosal Neuromas (100%)
naso, oropharynx, larynx, conjunctiva
•Medullary Thyroid Carcinoma (≈ 85%)
more aggressive than IIA
•Marfanoid body habitus
•Pheochromocytoma (≈ 50%)
often bilateral (70%)

MEN1 Consensus Summary Statements (loss of function)

- **Diverse array of defects (missense, nonsense, frameshift, mRNA splicing); hence difficult to screen because of so many possible mutations**
- **1997: gene Menin found of Ch 11. Exact function unknown, but it is a tumor suppressor gene**
- The MEN1 germline mutation test is recommended for MEN1 carrier identification.
- All kindred with MEN1 are likely to have a mutation in the MEN1 gene.
- However, MEN1 germline mutation tests fail to detect 10 – 20% of mutations. If a family lacks an identifiable MEN1 mutation, 11q13 haplotype testing about the MEN1 locus or genetic linkage analysis can identify MEN1 carriers. Periodic biochemical testing is an alternative when DNA-based tests are not possible.

- The main candidates for MEN1 mutation analysis include index cases with MEN1, their unaffected relatives, and some cases with features atypical for MEN1.
- MEN1 carrier analysis should be used mainly for information. It should rarely determine a major intervention.
- MEN1 tumor patterns in families do not have clear variants or specific correlations with an MEN1 germline mutation pattern. Thus, the MEN1 carriers in a family with either typical or atypical expression of MEN1 should be monitored similarly for typical expressions of MEN1 tumors.
- MEN1 tumors cause morbidity through hormone excess (PTH, gastrin, PRL, etc.) and through malignancies (gastrinoma/islet cell or foregut carcinoid).
- Medications control most features of hormone excess (gastrin, PRL, etc.). Surgery should control features of excess of some other hormones (PTH and insulin). Surgery has not been shown to prevent or cure MEN1-related cancers.
- Hyperparathyroidism develops in over 90% of MEN1 carriers. There is controversy over indications for parathyroid surgery in MEN1 patients.
- The preferred parathyroid operation in the HPT of MEN1 is subtotal parathyroidectomy (without autograft); transcervical near-total thymectomy is also simultaneously. Parathyroid tissue should be cryopreserved.
- Curative surgery for gastrinoma in MEN1 is rare. There is controversy over the indications for surgery for gastrinomas in MEN1.
- Surgery in MEN1 is indicated and is usually successful for insulinoma. For most other pancreatic islet tumors, except gastrinomas, surgery is also indicated; however, there is no consensus over tumor criteria for the latter operations.
- The management of pituitary tumor in MEN1 should be similar to that in sporadic cases.

MEN2 Consensus Summary Statements (gain of function)

- **1995: RET-proto-oncogene (responsible for tyrosine kinase activity) identified on Ch 10**
- **Fewer possible mutations (codons 609, 611, 618, 620, 634; involve replacement of a cystine residue)**
- The main morbidity from MEN2 is MTC. MEN2 variants differ in aggressiveness of MTC, in decreasing order as follows: MEN2B > MEN2A > FMTC.
- MEN2 carrier detection should be the basis for recommending thyroidectomy to prevent or cure MTC. This carrier testing is mandatory in all children at 50% risk.
- Compared with RET mutation testing, immunoassay of basal or stimulated CT results in more frequent false positive diagnoses and delays of the true positive diagnosis of the MEN2 carrier state. However, the CT test still should be used to monitor the tumor status of MTC.
- RET germline mutation (10q11 – 12) testing has replaced CT testing as the basis for carrier diagnosis in MEN2 families. It reveals a RET mutation in over 95% of MEN2 index cases.
- The RET codon mutations can be stratified into three levels of risk from MTC. These three categories predict the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC.

- Thyroidectomy should be performed before age 6 months in MEN2B, perhaps much earlier, and before age 5 yr in MEN2A. Policies about central lymph node dissection at initial thyroidectomy are controversial and may differ among the MEN2 variants.
- MEN2 has distinctive variants. MEN2A and MEN2B are the MEN2 variants with the greatest syndromic consistency.
- FMTC is the mildest variant of MEN2. To avoid missing a diagnosis of MEN2A with its risk of pheochromocytoma, physicians should diagnose FMTC only from rigorous criteria.
- Morbidity from pheochromocytoma in MEN2 has been markedly decreased by improved recognition and management. The preferred treatment for unilateral pheochromocytoma in MEN2 is laparoscopic adrenalectomy.
- HPT is less intense in MEN2 than in MEN1. Parathyroidectomy should be the same as in other disorders with multiple parathyroid tumors.

Gastrinoma

- 50% of patients with MEN I have a gastrinoma
- 33% of patients with **ZES** have MEN I (**Clinical Triad**: 1. PUD 2. gastric acid hypersecretion 3. Islet cell tumor)
- In MEN I associated ZES: Most common site is duodenum (2nd is pancreas)
- ⅔ are **malignant**
- 25% of patients with pheochromocytoma have ZES
- Risk of metastatic behavior from gastrinoma rises sharply at 3 cm (< 3 cm → < 2% chance of mets)

<u>The sporadic disease is a different one from the MEN-associated one</u>

- Sporadic ZES occurs outside of the duodenum 30 – 60% of the time; MEN version is virtually always in the duodenum (with or without pancreatic involvement)
- Sporadic ZES is much more likely to be malignant (the extrapancreatic primaries are less biologically aggressive in both diseases)
- Sporadic ZES is more often solitary and larger at the time of detection, usually > 2 cm
- MEN ZES is a diffuse disease, rarely amenable to true "cure"

"Gastrinoma Triangle" joins:
1. junction of cystic duct & CBD
2. junction of 2nd and 3rd portion duodenum
3. junction of neck & body of pancreas

(90% found in this triangle) [Am J Surg 1984 147:25 Stabile, Morrow, Passaro]

<u>Ddx for increased gastrin</u>:

- Gastrinoma
- Retained excluded antrum (a surgical mistake)
- Gastric outlet obstruction
- Antral G-cell hyperplasia/hyperfunction

} High acid

- Postvagotomy
- Pernicious anemia
- Atrophic gastritis
- Short gut syndrome
- Renal failure
- H2 blocker, proton pump inhibitor*

} Low/minimal acid

*pH < 2 inhibits gastrin secretion in normal patients

<u>Check gastrin levels in patients with</u>:

1. recurrent ulcers
2. ulcers in unusual places (e.g. jejunum),
3. refractory to medical management
4. prior to any elective operation for an ulcer
5. unexplained or persistent diarrhea
6. peptic ulcer and *any* endocrinopathy
7. family history of PUD
8. family history of MEN I

Check: 1. fasting gastrin level
2. post-secretin challenge gastrin level (synthetic secretin – 2 units/kg IV bolus)
3. Ca^{++} (MEN I screen)
4. Chemistry panel

Look for:

- ZES fasting: 200 – 1000 pg/mL (normal < 100 pg/mL)
- Basal acid secretion: ZES > 15 mEq/hr (normal < 10 mEq/hr)

Note: generally will see *failure of feedback*: fasting gastrin ≈ 1000 with gastric pH < 2.5

Secretin Stimulation Test:

- IV secretin administered, gastrin measured
- ZES: *increased* gastrin (by > 200 pg/mL) within 10 to 20 minutes (normal response is *decrease* in gastrin)

Management issues:

- Some believe distal pancreatectomy should be done in any patient with MEN I with either hormonal syndrome or a neuroendocrine tumor regardless of location in pancreas or duodenum. Virtually all patients with MEN I ZES have concomitant neuroendocrine tumors in neck, body, or tail.
- **If patient has gastrinoma *and* hyperparathyroidism → remove parathyroid *first* to normalize Ca^{++} levels** (since hypercalcemia is more dangerous than hypergastrinemia)
- Higher than "normal" doses of PPI are needed for achlorhydria
- Minimal role for CT scan/octreoscan
- Imamura Test: intra-arterial secretin into visceral arteries to measure hepatic vein gastrin levels (look for step up) is good for localization
- No role for debulking functional gastrinoma mets, since patients can be managed medically in this setting with PPIs

Post-Op

Must stay on acid suppression for 3 – 4 months because even after resection acid secretion high for some time

Glucagonoma

The 4D Syndrome: diabetes, diarrhea, dementia, dermatitis (patients look **cachectic**)
Many patients also have normochromic normocytic anemia, hypoalbuminemia, weight loss, beefy red tongue (glossitis), stomatitis, angular chelosis (i.e. signs of malnutrition)

Usually found in tail of pancreas, but can be anywhere. Usually > 3 cm at time of diagnosis; 70% malignant

Diagnosis simple by measuring serum glucagon level, although most patients with elevated glucagons do not have gastrinoma [see review: Wermers RA, et al. Medicine (Baltimore). 1996;75:53]

Sx: **Necrotizing Migratory Erythema**-NME (usually below waist), glossitis, stomatitis, diabetes

- IV Tolbutamide results in elevated glucagon
- Medical treatment for Necrotizing migratory erythema: Somatostatin/octreotide, IV Amino acids (TPN)
- Aggressive surgical resections are indicated, even if metastatic

Insulinoma

Number 1 islet cell neoplasm; associated with MEN I

- 80 – 90% are **benign** solitary adenomas cured by surgical resection
- 30% < 1 cm
- 10% multiple
- 10 – 15% malignant
- 10% hyperplasia or nesidioblastosis

Presents with sympathetic nervous system symptoms due to hypoglycemia (patients look like "Pillsbury Dough Boy")

Whipple's Triad:
1. Hypoglycemia < 50 mg/dl
2. CNS symptoms.
3. Reversal of CNS symptoms. with glucose admin.

Ddx for hyperinsulinemia:

- Reactive hypoglycemia (very common),
- Functional hypoglycemia with gastrectomy,
- Adrenal insufficiency, hypopituitarism, hepatic insufficiency,
- Munchausen's syndrome (self injection)
- Tumors secreting insulin-like molecule (sarcoma, mesothelioma, etc.)

First, check for proinsulin, then:
Get 72 hour fasting levels with q6 hour checks until patient becomes symptomatic

Insulin:Glucose ratio = **insulin** (uU/ml)/**glucose** (mg/dl) > **0.3** found in almost all patients with insulinoma.

Accuracy increased by "Amended ratio" = **insulin** (uU/ml)/ [**glucose** (mg/dl) – **30**] > **0.3**

Localizing Tests:

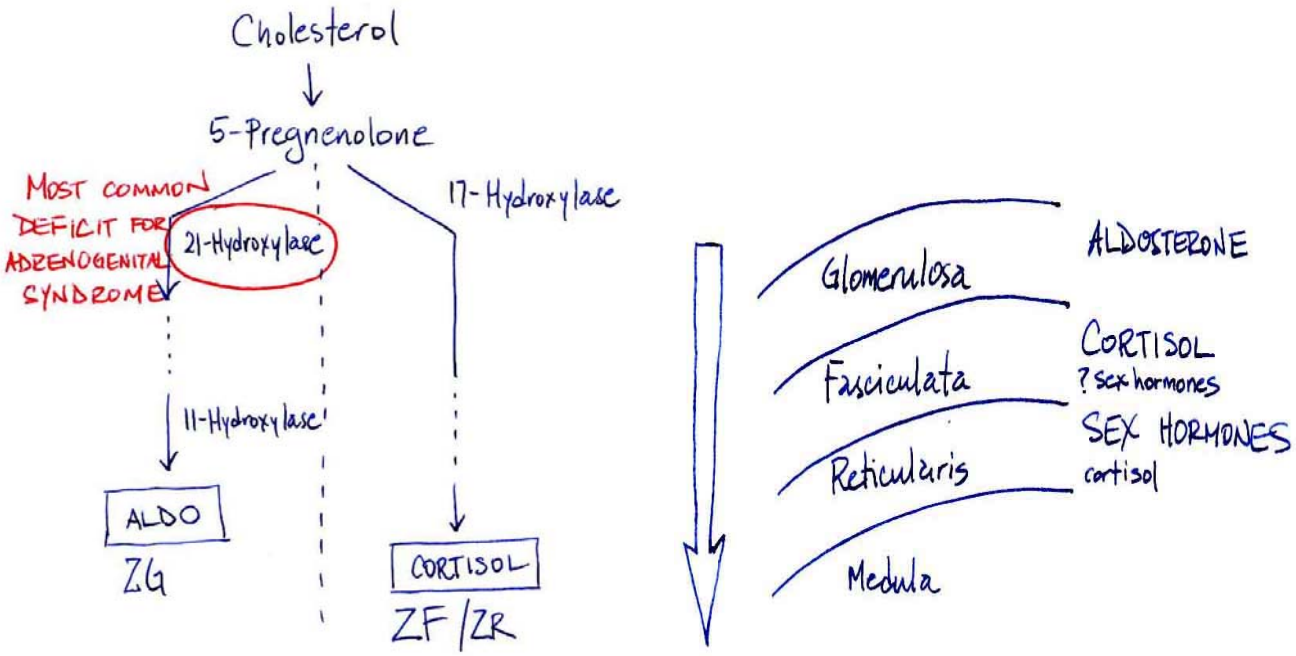
- CT, A-gram, **endoscopic ultrasound**, venous catheterization (sample blood along portal and splenic veins)
- Calcium angiogram: Ca^{++} causes insulin secretion → localize to artery (e.g. splenic for tail) where tumor nearest
- Intraoperative U/S is probably the best test for localization

Medical Treatment:

- Diazoxide to suppress insulin levels (until resection). Diazoxide inhibits the sulfonylurea receptor 1 (SUR1) on the beta cell, which is a component of the K^{+}ATPase responsible for insulin secretion
- Octreotide, IV glucose

Adrenal Gland

Embryology:
Cortex: mesoderm (4th to 6th week)
Medulla: ectoderm/neural crest (sympathetic NS and ganglion); migrates along sympathetic chain
Ectopic location: IMA, Organ of Zuckerkandl
Right gland: drains into IVC; Left gland: drains into renal vein



[Figure adapted from RUSH review manual, 2000]

- **Aldosterone is produced exclusively in the ZG because of the presence of corticosterone methyloxidase ("anatomically specific" enzyme location)**
- **PNMT converts norepinephrine → epinephrine. Found *only* in adrenal medulla.**
- Rate limiting step is Tyrosine → DOPA via Tyrosinase hydroxylase
- 11β-hydroxysteroid dehydrogenase type I is required to convert inactive prednisone to active prednisolone; its activity varies markedly from person to person
- Cortisol is **not** a "storage" hormone; however, it **does** promote gluconeogenesis to preserve hepatic reserve

Regardless of size, an adrenal mass should be removed if it is:
1. Growing,
2. Functioning, or
3. Suspicious on T2 MRI (the brighter it is, the more suspicious it is)

If none of the above, remove lesions greater than 4 – 6 cm (since 15% chance of malignancy if greater than 6 cm → risk increases with size)
Ask: is it Functional? Malignant tumor of adrenal gland? Likely metastatic to adrenal gland?

Syndromes:

I. **Conn's** (↑ aldosterone): 75% unilateral adenoma → Rx: with resection
25% bilateral hyperplasia → Rx: spironolactone + C^{++} channel blocker

II. **Addison's** (↓ aldosterone and cortisol): low Na^{+}, high K^{+}, hypoglycemia; can present in crisis with hypotension

III. **Waterhouse Friedrickson**: adrenal hemorrhage with meningococcal sepsis

IV. **Nelson**: post adrenalectomy (10%) → ↑ ACTH, pigmentation, change in vision from ↑ pituitary response

V. **Cushing's *Disease* (pituitary)**: **80%** of non-iatrogenic causes; pituitary microadenoma → ↑ ACTH (will also see urine 17-OH progesterone)
Adrenal Cushing's Syndrome: (aka ACTH-independent Cushing's) **15%** of non-iatrogenic causes → 10% adrenal adenoma, 5% adrenal carcinoma; bilateral hyperplasia is very rare; will see ↓ ACTH
Ectopic Cushing's Syndrome: **20%** of ACTH-dependent; sources of ectopic ACTH including: Pulmonary (SCLC, bronchial, thymic carcinoids), Neuroendocrine tumors, Pheochromocytoma, MTC

Diagnosis:

1. Start with 24 hour urine free cortisol and plasma ACTH
2. Low dose dexamethasone suppression → will suppress causes of hypercortisolism such as obesity and excess ethanol ingestion, but not others (confirms dx)
3. High dose dexamethasone suppression → will suppress pituitary adenoma, but not ectopic sources (locates cause)
4. MRI, CT, and/or petrosal venous sampling

Treatment:

- "Medical Adrenalectomy" = metyrapone and aminoglutethimide
- Surgical removal of all functional adrenal masses is indicated, including bilateral adrenalectomy for diffuse disease in patients recalcitrant to medical management

Stress Dose Steroids
[Chernow et al. Ann Surg 1994, 219:416]

- Under normal conditions, body produces 30 mg hydrocortisone equivalent (solucortef)/day
- Under extreme stress → up to 300 mg/day
- Prednisone is 4:1 (to solucortef)
- Solu-Medrol is 5:1
- Decadron is 25:1

Normal adrenal secretion is 25 – 30 mg cortisol/24h
Appropriate stress test: 250 mcg cosyntropin →

1. ↑ in plasma cortisol by ≥ 7 mcg/dL, or
2. Absolute level > 20 mcg/dL

For **adrenal crisis**: 200 mg hydrocortisone immediately → 100 mg q8 hours x 48 hours → then taper by 50% reduction q2 days until 25 mg reached

Above 50 mg hydrocortisone/day you are getting enough mineralocorticoid activity (except dexamethasone), BUT below 50 mg/day must replace aldosterone with Florinef Acetate

Proven Adrenal Insufficiency/Chronic Steroids [give following in addition to maintenance doses]:

I. Mild illness/non-febrile
- no replacement

II. Mod illness (fever, minor trauma or surgery)
- 15 mg prednisolone qd until 24 h post resolution

III. Severe illness or major trauma or surgery
- 50 mg hydrocortisone q6h → taper to normal by 50%/day

IV. Septic Shock
- 50 mg hydrocortisone q6h ± 50 mcg florinef qd x 7 days

Pheochromocytoma

Tumor of adrenal medulla and sympathetic ganglion (from chromaffin cell lines) producing catecolamines (NE > Epi)

Incidence: ≈ 0.2% (1/500 hypertensives)

"Rule of 10's"
- 10% malignant
- 10% bilateral
- 10% in kids
- 10% multiple tumors
- 10% extraadrenal

Found in MEN II (A and B) → always rule out MEN with dx of pheochromocytoma

Classic Triad
1. Palpitations
2. Headache
3. Episodic diaphoresis
(also, 50% hypertensive)

Ddx:
Renovascular HTN, menopause, migraines, carcinoid syndrome, pre-eclampsia, neuroblastoma, anxiety disorder, hyperthyroidism, insulinoma

Locations:
- Adrenal (90%)
- Organ of Zuckerkandl (embryonic chromaffin cells around the abdominal aorta near IMA; normally atrophies in childhood)
- Thorax
- Bladder
- Scrotum

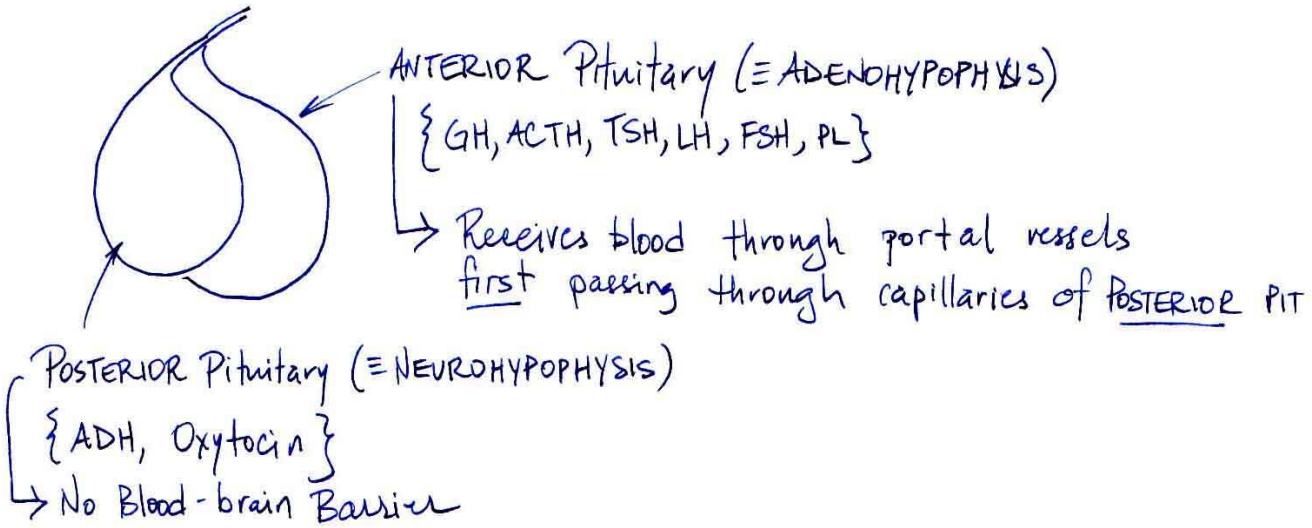
(Note: if epi high, must be at or near adrenals, since nonadrenal sites lack ability to methylate NE to epi)

Locators:
CT, MRI, ^{131}I-MIBG (an NE analog that collects in adrenergic vesicles)

Note: Histology can't determine malignancy; only spread can

Preop Treatment:
- Increase intravascular volume
- Must give α-blockers (phenoxybenzamine or prazosin) for 5 – 7 days prior to surgery to control HTN. If, after BP controlled, still tachycardic → add on β-blocker for 2 to 4 days.
- **Catastrophic error** to begin with β-blocker because this will lead to unopposed vasoconstriction which can cause acute heart failure.

Pituitary Gland



Bitemporal hemianopsia is classic visual change with pituitary mass effect

Prolactinoma: #1 pituitary adenoma

Sheehan syndrome: postpartum lack of lactation, persistent amenorrhea

Thoracic Surgery

Lung Cancer
170,000 cases/yr in US
#1 cancer killer in US
5 year survival < 15%

- **NSCLC** [**80%**; adenocarcinoma seen with increasing frequency (55%); does worse than squamous cell (45%)],
- **SCLC** [**20%**]

Squamous cell associated with PTHrP; Small cell associated with ACTH, ADH

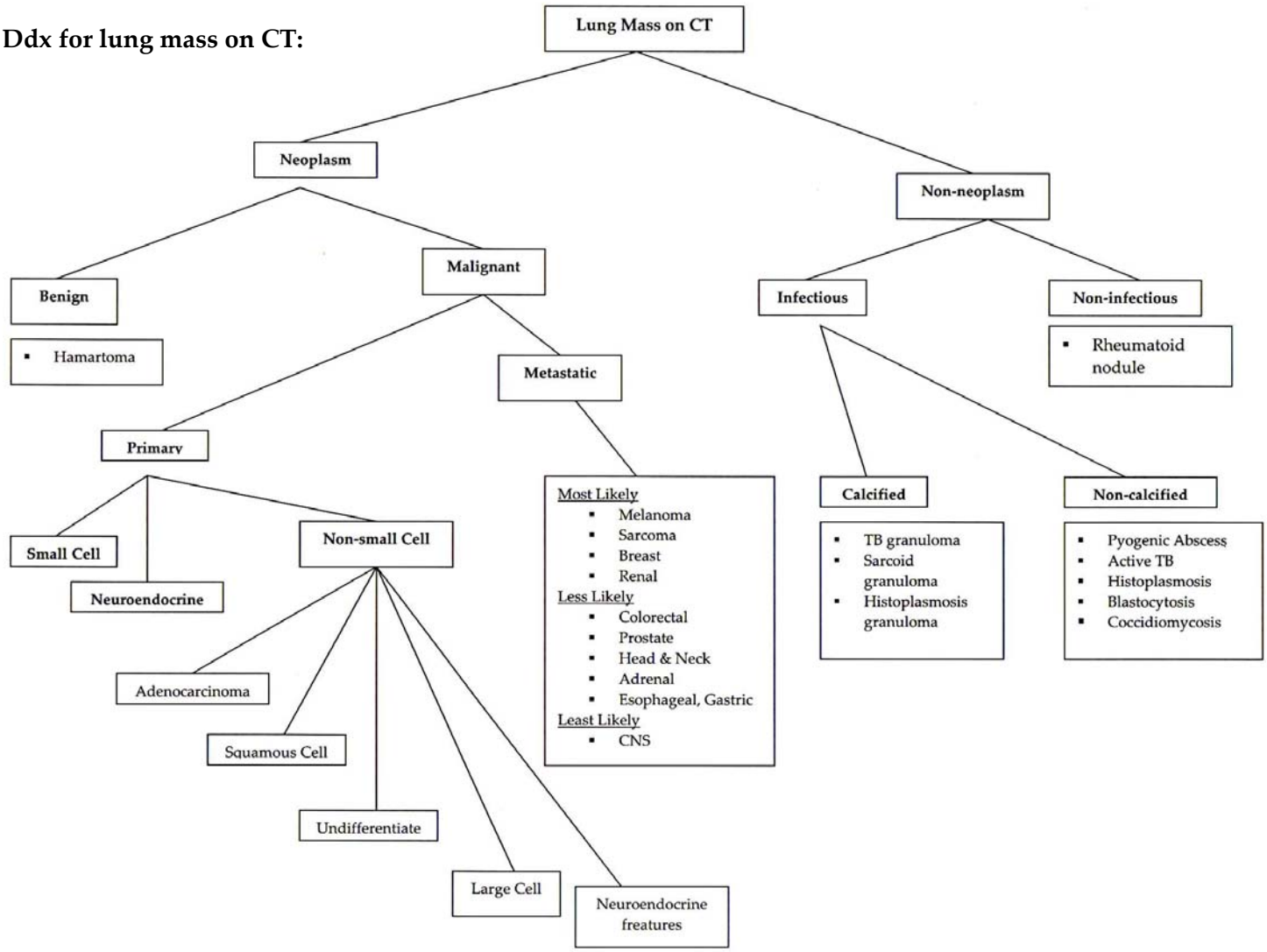
Staging:
T1: ≤ 3 cm T2: > 3 cm T3: invasion of chest wall, pericardium, diaphragm, < 2 cm from carina
T4: unresectable; into mediastinum, heart, great vessels; effusion

N1: ipsi hilar N2: ipsi mediastinal N3: contralateral, scalene, or subclavian

M: 2 separate lesions in same lung → M1 disease under new staging system

Stage I: T1 – 2 Stage II: T2N1, T3N0 Stage IIIa: up to T3 or N2
Stage IIIb: unresectable T4 or N3 Stage IV: any M

Ddx for lung mass on CT:



Association of smoking and lung cancer

- 90% of lung cancer occurs in smokers
- 14 – 20 fold higher risk in smokers; 2 – 5 fold higher (never zero) in former smokers
- Shown to be a multistep process [NEJM 265:253] of "field cancerization"; more smoking → more CIS on autopsy
- 3p14 loss of heterozygosity 88% smokers; 45% formers; 0% nonsmokers

Risk of surgery:

Pre thoracotomy PFT's: need FEV1 > 2L, 1L for pneumonectomy/lobectmy

Want Post-op FEV1 > 800 – 1000 mL (40% predicted)

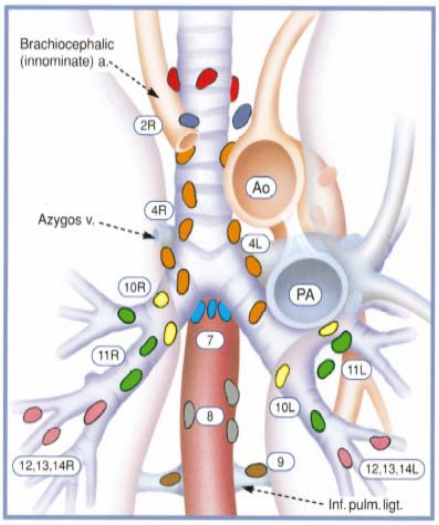
DLCO < 60% → significant risk; MVO_2 < 10 mL/kg/min → significant risk

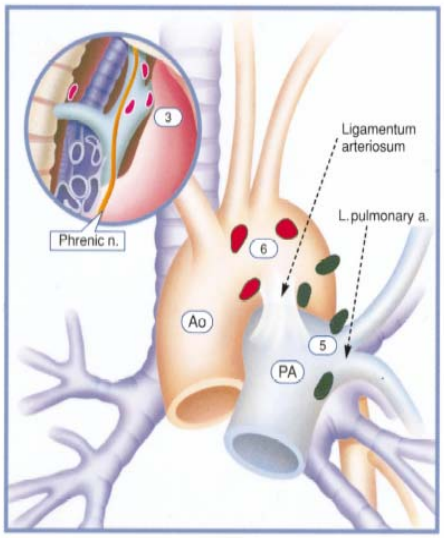
Stage III disease:

1. Confirm N2 status (FNA, mediastinoscopy, VATS)
2. CDDP/Etoposide or Taxol/CDDP + surgery +XRT

Several studies [Rosell NEJM '94, Roth JNCI '94 + follow-ups] could end the role of surgery in IIIA disease. Showed that with induction chemo + XRT ± surgery had equal survival with significantly more deaths in surgery arm, but currently stage IIIA patients undergo surgical resection

Lymph Node Stations [Mountain CF, et al. Chest, 1997]:





Superior Mediastinal Nodes

- **1** Highest Mediastinal
- **2** Upper Paratracheal
- **3** Pre-vascular and Retrotracheal
- **4** Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- **5** Subaortic (A-P window)
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- **7** Subcarinal
- **8** Paraesophageal (below carina)
- **9** Pulmonary Ligament

N_1 Nodes

- **10** Hilar
- **11** Interlobar
- **12** Lobar
- **13** Segmental
- **14** Subsegmental

Mediastinoscopy can sample stations 1,2,4, and 7 (R10 if aggressive)

Pancoast Tumor: involves sympathetic chain (Horner's syndrome); shoulder/medial scapula pain is most common presentation; Mediastinoscopy → induction chemo → radical resection → XRT

Significantly higher incidence of right-sided node involvement with left-sided lung tumors because of lymphatic pathways which travel from left → right; the reverse in not observed

Metastatic tumors (lung, breast) to pleura >> primary pleural tumor (mesothelioma)

In Summary‡:

1. Surgery is still standard of care for I, II, *selected* IIIA, and *selected* IIIB NSCLC (and very rare IV disease, e.g. isolated brain or adrenal N0 disease)
2. XRT improves local control, but not survival
3. Adjuvant RT for > T2, N1 – 2 disease
4. Induction chemo is proven for stage III disease, but is untested for early disease.

‡See excellent review: **Multidisciplinary Management of Lung Cancer** [Spira et al. NEJM 350;379, 2004]

Factors that ↑ air leak after resection:
1. Neoadjuvant chemo/radiation
2. Deep dissection
3. Blebs/emphysema

"Massive" hemoptysis: > 600 mL in 24 hours

Spontaneous pneumothorax: usually result of ruptured small bleb; 15 – 20% of recurrence after initial event (much greater after 2nd event)

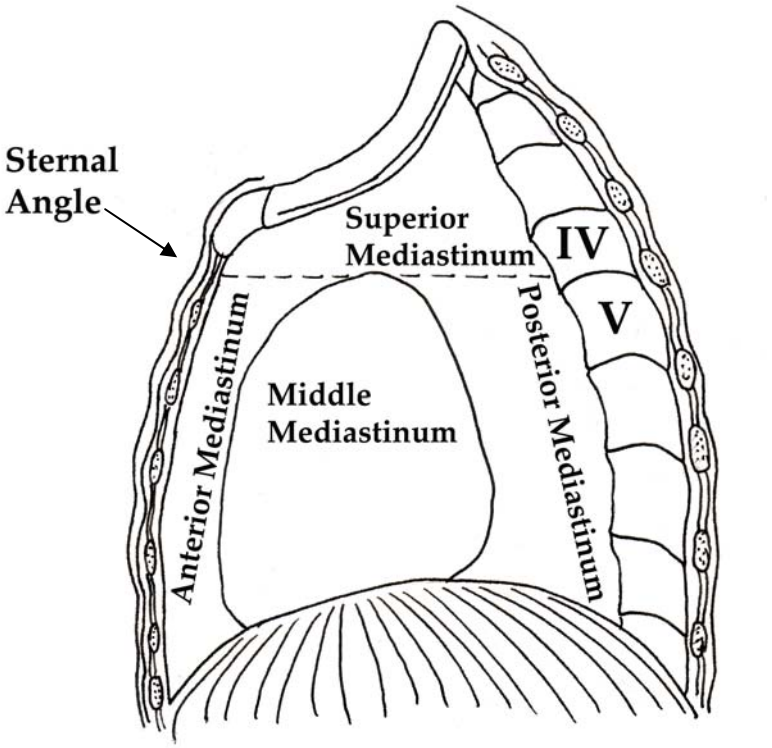
Chyle Leak:

- Thoracic duct enters chest on *right* (with aorta) → crosses to *left* at T4/5 → joins at IJ/subclavian junction on left
- Most often iatrogenic
- Normal chyle flow varies between 1.5 and 2.5 L/day according to diet
- High lymphocytes (making it resistant to infection) and 10 x TG of serum
- Treat with 2 week trial of NPO and drainage (50 – 70% success); if still > 500 mL/day → to OR for duct ligation

Empyema: exudative (thin, free-flowing fluid) → **fibrinopurulent** (fibrin deposition, beginning to loculate) → **organizing** (ingrowth of fibroblasts, "peel")

Exudative Stage: may respond to antibiotics ± drainage	**Fibrinopurulent Stage: requires chest tube ± surgery**
▪ Thin ▪ WBC < 1000/mm^3 ▪ LDH < 500 – 1000 IU (pleural fluid/serum > 0.6) ▪ Pleural fluid/serum protein > 0.5 ▪ pH > 7.30 ▪ Glucose > 60 mg/dL	▪ Turbid, bacterial cellular debris ▪ Glucose < 40 mg/dL ▪ LDU > 1000 IU ▪ WBC >5000/mm^3 ▪ pH < 7.10

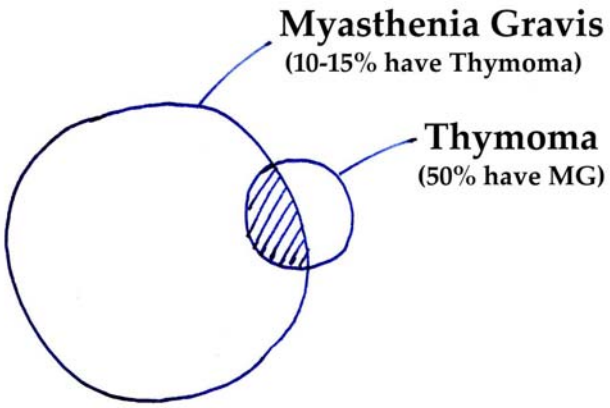
Mediastinal Disease



Division	Contents	Tumors ‡
Anterior (and Superior)	1. Aortic arch and thoracic portions of its branches (brachiocephalic, left common carotid, left subclavian) 2. Brachiocephalic veins, upper half of SVC 3. Vagus nerves, left recurrent laryngeal nerve, phrenic nerves 4. Superior esophagus 5. Upper trachea 6. Thymus 7. Upper portion of thoracic duct 8. Lymph nodes	**Thymoma** **Germ cell tumor** **Lymphoma** Thyroid adenoma Parathyroid adenoma Lipoma Carcinoma Hemangioma
Middle	1. Pericardium 2. Heart 3. Tracheal bifurcation and mainstem bronchi 4. Subcarinal and peribronchial nodes 5. Ascending aorta	**Bronchogenic cysts** Pericardial cysts Lymphoma
Posterior	1. Thoracic portion of descending aorta 2. Azygos, hemiazygos , accessory hemiazygos veins 3. Sympathetic chains 4. Thoracic duct 5. Esophagus	**Neurogenic tumors** Lymphoma Enteric cysts

‡ Most common in bold

Role of thymoma and **Myasthenia Gravis**:



- Resecting thymus in MG, even in absence of thymoma, improves symptoms in 90%, as thymus has been implicated in producing post-synaptic anti-Ach-antibodies
- Complete remission most likely if: age < 60 and operation performed < 8 months from diagnosis
- Radiate thymoma after excision only if margins positive and consider platinum-based chemotherapy.
- Invasiveness at time of resection best predicts outcome

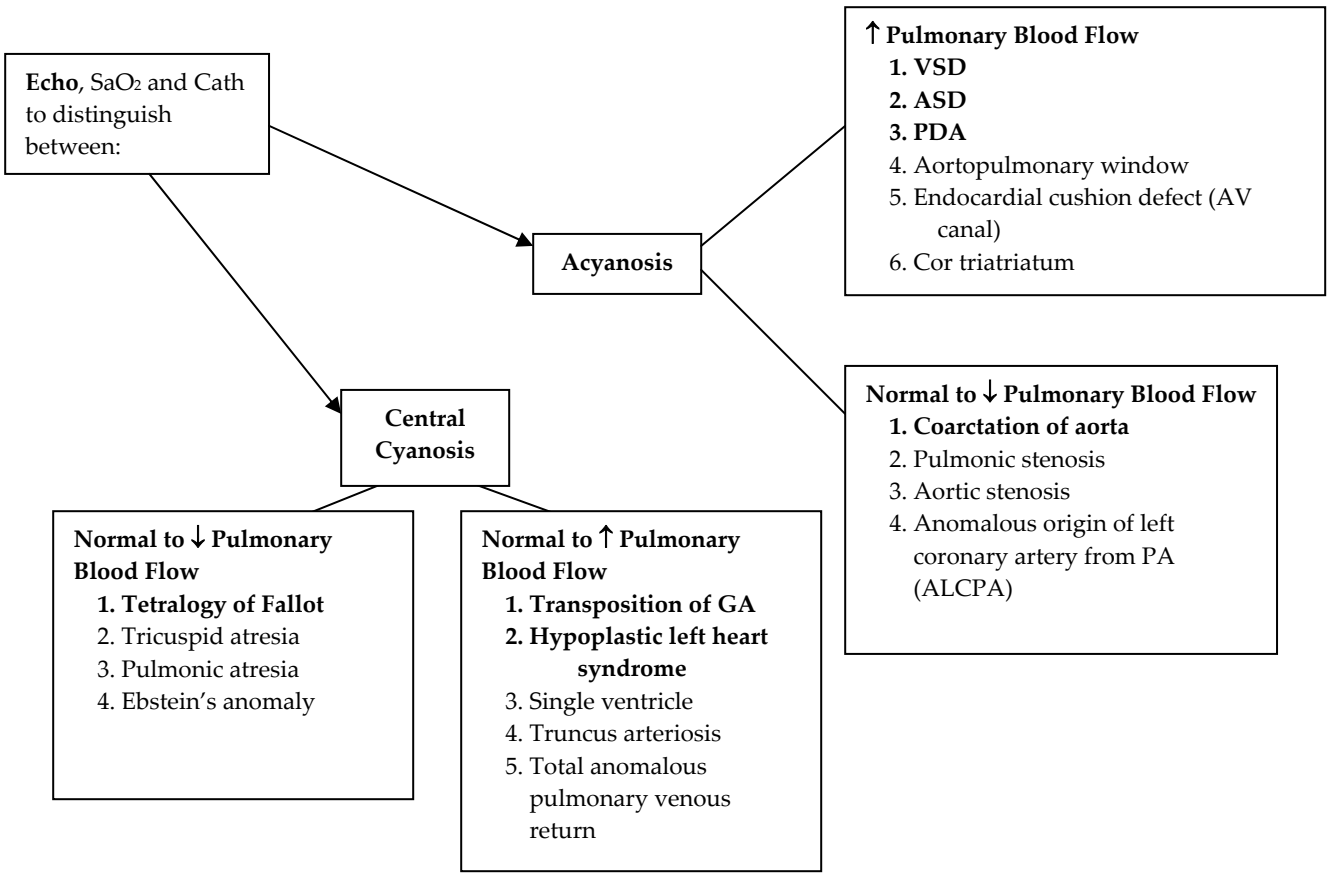
Other diseases associated with thymoma:

- Eaton-Lambert syndrome
- Sjögren's syndrome
- Red cell hypoplasia and aplasia

Diagnostic workup of Mediastinal Masses

Location	**Mass**	**Test**
Superior	Thyroid	Thyroid Scan
Anterior	Thymoma	Resection
	Germ cell	β-HCG, AFT
	Lymphoma	Open biopsy
Posterior	Neurogenic	MRI

Cardiac Surgery: Congenital Defects



[Figure adapted from General Surgery Board Review, Gold et al, 1999]

Ventricular Septal Defect (VSD)

- Most common CHD (25%, 1/1000 live births)
- Multiple types: perimembranous is most common
- Up to 50% have associated anomaly (PDA, coarctation, AS)
- PVR ↑ over time because of pulmonary overcirculation, and my be irreversible at 2 years
- May go on develop Eisenmenger's syndrome with shunt reversal across the VSD
- Fix if shunt fraction (Qp/Qs) > 2 (twice blood flow to lungs)
- Repair unrestrictive VSD prior to 1-year of age (prevent failure to thrive)

Patent Ductus Ateriosis (PDA)

- Communication between upper descending aorta and left/main PA
- Presentation dependant on degree of left → right shunt (pulmonary overcirculation and steal from systemic perfusion)
- Persistent PDA is more common in premature infants
- Medical closure: indomethacin (up to three doses)
- Long term complication of pulmonary overcirculation include: pulmonary HTN, CHF, increased respiratory infections
- Early surgical closure indicated for symptomatic patients who are recalcitrant to medical therapy, or are not suitable candidates for medical therapy
- Use prostaglandin to keep open in cyanotic infants; can also close in cath lab

Coarctation of the Aorta

- Accounts for 6 – 8% of CHD (≈ 2 – 5x more common in males)
- The usual location of the discrete coarctation is juxtaductal (just distal to the left subclavian artery)
- Less often, the coarctation is just proximal to the left subclavian artery; can also be diffuse
- Two theories:
    1. Reduced antegrade intrauterine blood flow, which causes underdevelopment of the aortic arch
    2. Extension of the ductal tissue into the thoracic aorta which, when it constricts, causes coarctation of the aorta
- The most common clinical manifestation is a difference in systolic pressure between the upper and lower extremities (diastolic pressures are usually similar), manifested by:
    1. Upper extremity hypertension
    2. Absent/delayed femoral pulses
    3. Low/unobtainable blood pressure in the lower extremities
- Treatment options include angioplasty ± stenting (if > 25 kg) or surgical repair (resection + end-to-end spatulated anastomosis, bypass if segment too long for primary repair)

Atrial Septal Defect (ASD)

- Strictly speaking, a Patent Foramen Ovale (PFO) only shuts: right → left
- Usually an ASD shunts: left → right
- Accounts for 10 – 15% of CHD (most common one in adults)
- Secundum defect is most common ASD (PFO is more common)
- Spontaneous closure rare > 2-years of age
- Typically asymptomatic with murmur; 50 – 60% have easy fatigability
- Fix almost all persistent ASDs
- Can be closed via catheterization

Tetralogy of Fallot

- Four anatomic features (key is RVOT obstruction):
    1. Stenosis of PA
    2. RV hypertrophy
    3. VSD (usually single, large, and unrestricted; in the perimembranous region of the septum)
    4. Aorta overriding the VSD
- Accounts for 7 – 10% of all congenital heart disease (3.3 per 10,000 live births)
- Approximately 15% of children have extracardiac anomalies (e.g. trisomy 21)
- Physiology and clinical presentation of tetralogy is determined primarily by the extent of RV outflow obstruction. Most children are cyanotic and symptomatic.
    - Severe obstruction with poor pulmonary flow: profound cyanosis during newborn period
    - Moderate obstruction with balanced pulmonary and systemic flow: may be identified during elective workup for a murmur
    - Minimal obstruction: pulmonary overcirculation and late heart failure

Options for repair include:

- Patch repair of the RVOT, possibly rendering the pulmonary valve incompetent, which, if severe, may have significant long term hemodynamic and electrophysiologic consequences.
- An alternate procedure is the insertion of a valved conduit from the RV to the distal main pulmonary artery if there is pulmonary atresia or a coronary anomaly precluding a transanular incision

Cardiac Surgery: Acquired Defects

4 "buzz words" to describe cardiac physiology

- Inotropy: force of contraction (systolic)
- Chronotropy: rate of contraction
- Lusitropy: rate of relaxation (diastolic)
- Dromotropy: conduction

Coronary Artery Bypass is associated with improved survival in patients with

- **triple vessel** disease
- **left main** disease
- patients with **↓EF**
  i.e. the more extensive disease → the greater the benefit

Indications:

- Intractable symptoms, medically refractory
- > 50% left main disease
- Triple vessel disease *with* depressed EF
- Left dominant circulation with high grade LAD stenosis

Dominance: 85% are right dominant, which means RCA supplies:

1. PDA
2. AV node
3. Posterior crux of heart (near IVC)

Branches of main cardiac vessels

1. Left circumflex: obtuse marginals
2. Left anterior descending: diagonals and septals
3. Right coronary: acute marginal branches; if right dominant: PDA, AV nodal; septals

Saphenous vein patency ≈ 50 – 60% at 10 years
IMA patency ≈ 95% at 10 years
Rate of recurrence of angina following CAB is ≈ 5 – 7% per year

IABP

Positioned just distal to left subclavian artery (aortic knob on CXR)
Inflates during diastole (40 msec before T wave; ↓ **afterload**) and deflates with p wave (↑ **coronary perfusion**); AI is a contraindication

Acute MI Complications

1. Arrhythmias: PVC, ventricular ectopy,
   VT/ VF, PEA (pulseless electrical activity) (0 – 48 hours)
   Reperfusion can cause PVCs

2. Recurrence: (0 – 7 days)

3. Pericardial Disease*: pericarditis; Dressler's syndrome (pericarditis + effusion) (6 hours – 14 days); likely autoimmune inflammation of pericardium; pleuritic chest pain, low grade fever, malaise; treat with steroids or NSAIDs;
*key is to differentiate from mediastinitis

4. Mediastinitis: follows ≈ 1 – 3% of cardiac surgery; risks include: DM, age > 60, re-exploration for bleeding, steroids, obesity with bilateral IMA harvest; need re-operative drainage and flap (advancement pec, or transfer)

5. Structural Catastrophes (3 – 5 days)
   a) papillary muscle tear; usually follows posterior MI: acute MR-pulmonary edema
   b) septal rupture: VSD (SOB)
   c) free wall rupture: rapid death

6. Aneurysm formation (weeks); ≈ 10% of patients post-MI; usually after anterolateral infarct caused by proximal LAD occlusion (anterior and apical); can develop progressive LV failure with CHF; nidus for emboli and arrhythmia; surgical intervention if symptomatic

7. CHF + Recurrence: ANYTIME

Mitral stenosis
Symptoms: CHF, pulmonary edema, *right-sided* heart failure, AFib, embolization
Etiology: RF
Normal mitral area = 4 – 5 cm^2; usually symptoms develop when area falls below 1.4 cm^2
Physiology: ↑ LA pressure → ↓ CO → ↑ PVR
Surgery indicated for: Area < **1 cm^2**, CHF, pulmonary HTN, embolization, gradient **> 5 mmHg**

Mitral regurgitation
Symptoms: CHF
Etiology: myocardial ischemia/infarct, endocarditis (acute); MVP, RF, myxomatous degeneration (chronic)
Physiology: abnormality of annulus (dilatation), leaflets (redundancy [prolapse], defect [endocarditis], shrinkage [RF]), chordae tendineae rupture, papillary muscle rupture
Surgery indicated for: acute MR complicated by CHF or shock, endocarditis associated with shock or persistent sepsis/embolization, EF < 55%, E-D dimensions 75 mm, E-S dimensions 45 mm

Mitral Stenosis	Mitral Regurgitation
▪ Almost exclusively caused by RF ▪ Pulm HTN and RH failure seen ▪ Afib and embolization common	▪ RF is common cause, but also endocarditis, MVP, ruptured chordae tendineae, myxomatous degeneration ▪ Pulm HTN and RH failure also seen ▪ Embolization less common; LV failure more common ▪ Operate for ↑LV chamber size (LVESV > 55), heart failure, new Afib. ▪ Earlier operation = ↑ chance for successful repair

Aortic stenosis
Symptoms: Angina, SOB, syncope
Etiology: RF, bicuspid valve, degenerative (in general: < 50 → congenital, 50 – 70 → bicuspid, > 70 → calcific)
- Avoid preload reduction, avoid hypotension and ACE-inhibitors
- Slow carotid upstroke, soft S2
- Critical stenosis < 0.8 cm^2
- Typically CXR shows normal size heart (rule of thumb: stenosis → normal size heart; regurgitation: dilation)

Prognosis depends on symptoms:
1. CHF - worst prognosis (1.5 years*); occurs at approximately 0.7 – 0.8 cm^2
2. Syncope post exertional (3 years*)
3. Angina (5 years*)
*Mean survival from initiation of symptoms

- need antibiotic prophylaxis
- critical AS diagnosed by symptoms, not area
- symptoms → need surgery, good outcome even in 80s
- average progression 0.12 cm^2/year

Surgery indicated for: Area **< 0.8 – 1.0 cm^2**, gradient **> 50 mmHg**, symptoms, evidence of rapid cardiac enlargement

Aortic regurgitation (AR/AI)

3F's: Fast (must be kept tachy), Forward (reduce AL), Full (preload dependent)

Symptoms: Fatigue, angina, progressive dyspnea, palpitations, peripheral vasomotor changes; bounding peripheral pulses (wide pulse pressure)
ESLV diameter greater than 5 cm has increased death rate (19% vs. 5% per year)
Acute Rx: afterload reduction, diuretics for CHF
Surgery: symptoms, evidence of ventricular enlargement

Perioperative MI

Most likely 2 – 3 days post-op
Differentiate Acute MI from Acute Coronary Syndrome

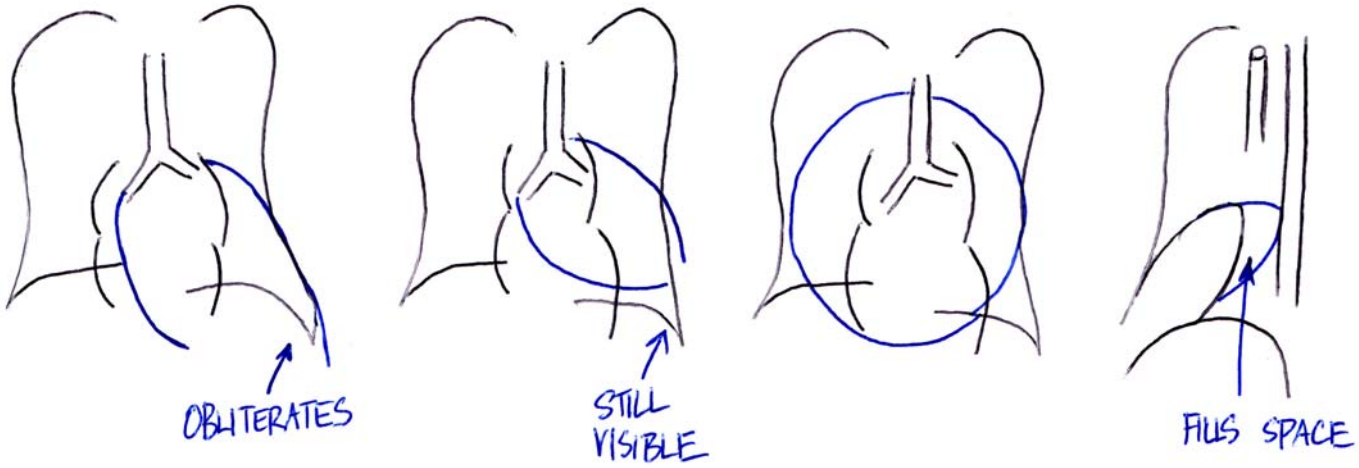
A. **Acute MI**: CP, ST elevations, + enzymes
   Goals are: 1. Reperfusion (fibrinolytic 0 – 6 hours; cath), and 2. Decrease O_2 demand

B. **Acute Coronary Syndrome** is subdivided into Non Q-wave MI and Unstable Angina (CP, with no EKG changes or enzymes)
   Non Q-wave MI: CP, EKG changes *without* ST elevation, **+**enzymes; give MONA (MSO_4, O_2, nitrate, ASA) + β-blocker then IIb/IIIa + heparin

*Note: Inferior infarct → RCA→ 90% chance of AV nodal involvement → 2:1 block more likely to be Mobitz I > II→ give atropine

CXR appearance with cardiac hypertrophy/enlargement

(Black outline is normal cardiac silhouette)



LVH **RV Enlargement** **RA Enlargement** **LA Enlargement**

Arrhythmias

Three Rules of Thumb:

1. If patient is hemodynamically unstable as a result of dysrhythmia → proceed directly to cardioversion (300 J)
2. If patient has a wide complex tachycardia → proceed directly to cardioversion (300 J)
3. If the patient has a narrow complex tachycardia → infuse adenosine (or verapamil) for diagnosis (Amiodarone is becoming drug of choice for treatment)

Adenosine is an endogenous nucleoside with differential antidysrhythmic effects on both supra- and ventricular tissue; also depresses the automaticity of both the SA and AV node.
Two types of adenosine receptors in heart:

A1 (on AV node and myocytes promoting AV block and bradycardic), and
A2 (on vascular endothelial smooth muscle → mediates coronary vasodilation)

Eagle's Criteria: Risk of surgery (More than 2 warrant cardiology work-up prior to surgery)

I. Symptomatic
- -CHF
- -Angina

II. Demographic
- -DM
- -male
- -age >70

III. EKG
- -Q-waves present
- -vent arrhythmia

Pre-op exercise tolerance is the most sensitive indicator of ability to withstand surgery. If patient unable to walk 2 flights of stairs → problems likely

Criteria for use of perioperataive β-blockade	Revised Cardiac Risk Index Criteria (≥ 3 → preop workup)
▪ Age > 65* ▪ Hypertension ▪ Current smoker ▪ Cholesterol > 240 mg/dL ▪ NIDDM	▪ High-risk procedure (intraperitoneal, intrathoracic, suprainguinal vascular) ▪ Ischemic heart disease ▪ History of MI ▪ History of angina ▪ Use of SL nitroglycerin ▪ Positive exercise test ▪ Q waves on EKG ▪ Previous PTCA/CAB with ischemic chest pain ▪ Cerebrovascular disease ▪ History of TIA/CVA ▪ IDDM ▪ CRI (Cr > 2 mg/dL)

*Many would use β-blockade for patients >40

Atrial Fibrillation

Rate Control vs. Rhythm Control: 2 large studies [NEJM 2002, 347:1825 – 1833, 1834 – 1840] evaluated patients with atrial fibrillation for less than 1 year deemed to be at high risk for recurrence. These studies concluded:

1. Rate control was not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes and may be appropriate therapy in patients with recurrence of persistent Afib after electrical cardioversion.
2. Management of Afib with rhythm-control offers no survival advantage over the rate-control strategy. Anticoagulation should be continued in these patients.

Hence, both rate and rhythm controlled patients need anticoagulation as their stroke rate is ≈ 1% per year.

Surgical Approaches:

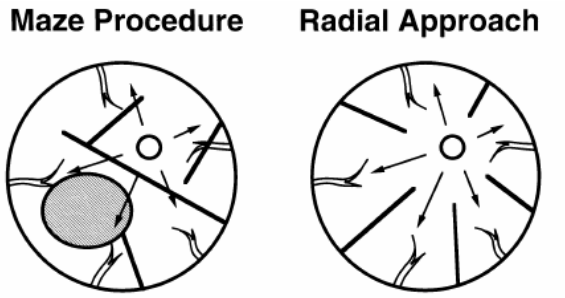


Fig 1. Schema of the concepts of the maze procedure and the radial approach. The large outer circle *denotes the atria, and its outer limit is bounded by the atrioventricular annular margins. The* small circle *indicates the sinoatrial node, and the* shaded area *indicates the isolated portion of the atrium.* Arrows *indicate the activation wavefront from the sinoatrial node, radiating toward the annular margins. The atrial coronary arteries, arising at the atrioventricular groove, are also schematically drawn. Note that the radial approach* (right panel) *preserves a more physiologic activation sequence and preserves blood supply to most atrial segments, whereas the atrial incisions of the maze procedure* (left panel) *desynchronize the activation sequence, and some of the incisions cross the atrial coronary arteries.*

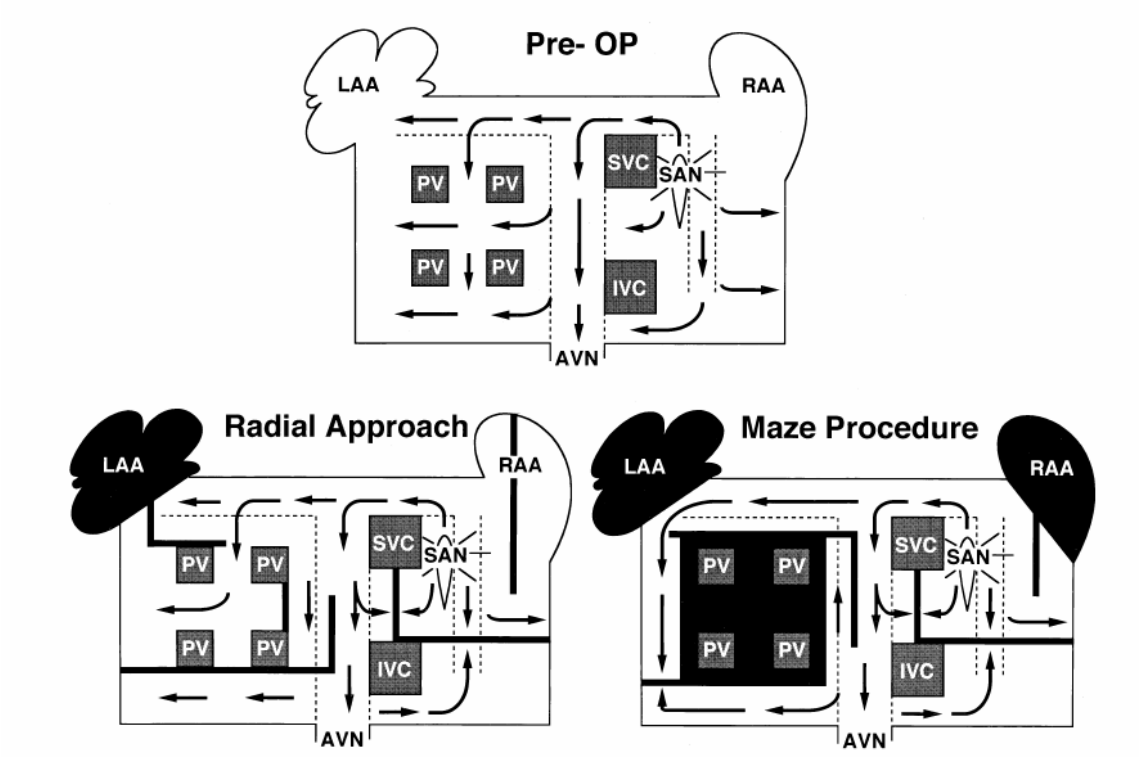


Fig 5. Schematic representation of anatomic correlation between the atrial incisions and the atrial activation pattern during sinus rhythm in normal atria and in the atria after the maze procedure or the radial approach. Thick lines *represent the surgical incisions and the* solid *area represents the part of atria that is surgically isolated or excised.* Dashed lines *represent Bachmann's bundle between the atrial appendages, the interatrial septum, and the crista terminalis.* Arrows *indicate the activation sequence.* (AVN = *atrioventricular node;* SAN = *sinoatrial node; other abbreviations are as in Fig 2.)*

[Nitta T, et al. Ann Thor Surg 1999 67:27]

- Radiofrequency ablation, cryoablation possible interventions for chronic Afib (RFA is becoming popular because of the complexity of the Maze procedure).
- Electrical cardioversion is rarely successful in converting chronic Afib.
- 90% of paroxysmal Afib cured with pulmonary vein isolation alone
- Persistent Afib generally need full Cox Maze III; RFA ≈ 60 – 70% cure; Maze ≈ 90% cure

Vascular Surgery

Nitric Oxide: derived from **L-arginine**; reduces free radicals (by scavenging) and prevents atherosclerosis; cGMP acts as the 2nd messenger

Cerebral ischemia most often caused by atheroembolization (50% of strokes due to HTN, 25% due to carotid disease, 25% due to bleed or other cause).

Clinical Classification

1. Asymptomatic: bruits (**+** bruit → 30 – 50% have significant stenosis; **+** significant stenosis → 20 – 50% bruit; *Bruit are actually a significant predictor of cardiac disease)*
2. TIA: < 24 hour resolution (90% resolve within 2 hours)
3. RIND (Reversible Ischemic Neurologic Deficit): 24 – 48 hour resolution
4. Fixed deficit: stroke

Risks of Stroke:

700,000 per year	**160,000 deaths/year**
1 year post stroke →	2/3 of survivors have disability

TIA: 15% stroke in first year, then about 6% per year thereafter (40% chance of stroke in 5 years without ASA)

Cortical TIA	**Vertebral TIA**
Unilateral	Dizzy
Arm weakness	Bilateral "woozy"
Decreased vision	"Drop attack" (transient loss of motor tone)

Asymptomatic: Stenosis > 50%: about 4% per year
Stenosis > 80%: 35% risk over 2 years
2% per year risk of stroke for patients > 60

Carotid Stenosis

- Low resistance arterial systems (such as ICA): total blood flow does not decrease until stenosis > 50%. Hence, no need to repair stenosis < 50%
- Up to 50% of patients who suffer stroke have had previous TIA

Asymptomatic Carotid Artery Stenosis Trial (ACAS) demonstrated that patients with an **asymptomatic stenosis of 60% or greater** had a 53% relative risk reduction of stroke after undergoing CEA + ASA compared to ASA alone **[11 → 5%]**. The benefit was much greater in men than women.

North American Symptomatic Carotid Endarterectomy Trial (NASCET I) demonstrated that CEA is highly beneficial in patients with recent hemispheric or retinal TIA or nondisabaling stroke and an **ipsilateral high grade stenosis (70 – 99%)**. The benefit of surgery was seen within 3 months of operation. The incidence of stroke was decreased in all subgroups but was largest in patients who experienced major ipsilateral stroke with an 81% risk reduction. Overall, 26% of patients with high-grade (70 – 99%) stenosis sustained a stroke within 18 months with medical management vs. 9% with surgery at 2 years **[26 → 9%]**

NASCET II: looked at symptomatic patients with **50 – 69% stenosis** and found a reduction from **22 → 16%** (p<0.045). More hospitals participated, hence increased morbidity.

Diagnosis: Ask 3 questions (ICA disease? % stenosis? Characteristics of plaque?)
Neck duplex consists of 2 parts: B-mode U/S image and spectral velocity analysis
IC/CC systolic ratio gives % stenosis:

- <2 <50%
- 2 – 3.9 50 – 69%
- >4 70 – 99%

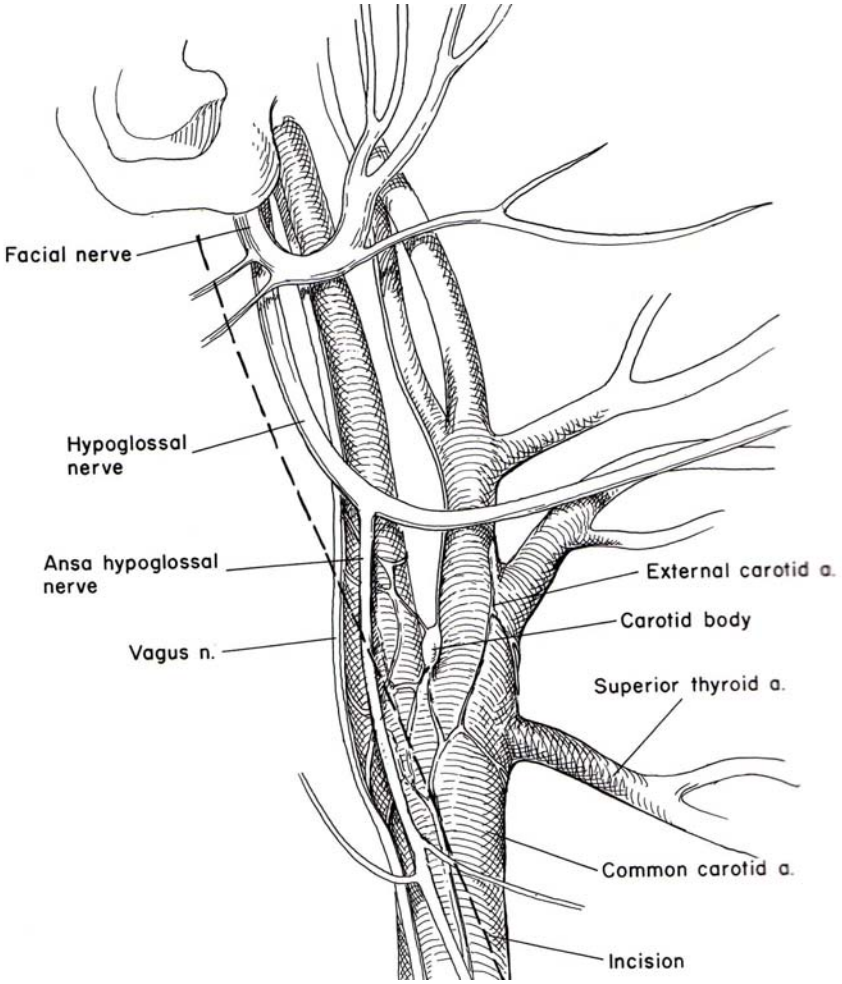
Following CEA:

- If ipsilateral pre-orbital headache → think hyperperfusion (since stenosis removed); usually ≤ 3 – 5 days post surgery.
- Most common CN injury → vagus nerve (clamp) → hoarseness
- CN XII → tongue deviation to side of injury; marginal mandibular → lip droop
- **CAD is main cause of post-op mortality**

Re-stenosis rate ≈ 5 – 10% (>50% stenosis within 2 years: myointimal hyperplasia, not atherosclerosis; F > M)

Upper limit guidelines for acceptable M&M rates for CEA:
Asymptomatic: **3%** Symptomatic: **5%** Symptomatic/CVA: **7%** Recurrent Stenosis: **10%**
To participate in ACAS and NASCET trials centers had to have < 5% overall mortality for CEA

Carotid Anatomy



[Atlas of Surgical Operations, Zollinger & Zollinger, 7th, 1993]

Abdominal Aortic Aneurysm

- 95% infrarenal
- approximately 75% asymptomatic and discovered incidentally
- growth rate ≈ 0.4 cm/year in diameter
- risk of rupture for small (< 5.5 cm) aneurysms: **0.6 – 1% per year** [NEJM 2002, 346: 1437-1444, 1445-1452]
- **Pathology**: ↑ matrix metalloprotease activity (MMP-1,2,3; MMP-9)
- risk of rupture related to size:
    - **< 5 cm**: 20% 5-year risk
    - **5 – 7 cm**: 33%
    - **> 7 cm**: 95%
- 10 – 20% involve iliacs
- when removing distal clamps, remove INTERNAL iliac first, then EXTERNAL iliac to avoid distal embolization to lower extremities
- following rupture with operative repair: cardiac complications are most common cause of early death; renal complications for late death
- **CAD** is most common cause of death for patients with "small" AAA (< 6 cm);
- **Rupture** (75 – 90% mortality) is most common cause of death for patients with "large" AAA (> 6 cm) [unless they have metastatic cancer or debilitating CHF]

Indications for Repair:

Good risk patients: 1. AAA > 5.5 cm + life expectancy > 2 years
2. AAA < 5.5 cm with COPD, expansion > 0.5 cm/6 months

High risk patients: 1. AAA > 6 cm, or symptomatic

The UK Small Aneurysm Trial: [NEJM 346(19):1445, 2002] Randomly assigned over 1000 patients with aneurysms ranging from 4.0 to 5.5 cm to either undergo early elective repair or observation with U/S surveillance. Mean follow-up was 8 years. The mean survival was 6.5 years in the surveillance group vs. 6.7 years in the treatment group (p=0.29). Early mortality was greater in the surgery group, but total mortality was greater in the surveillance group at 8 years.

Indications for Retroperitoneal Approach‡:

- hostile abdomen
- Inflammatory AAA
- juxtarenal AAA
- Right iliac disease is a relative *contraindication*

‡ Benefits (vs. anterior approach) include: ↓respiratory problems, ↓LOS, minimal ileus

Options for occlusive aortoiliac disease:

Procedure	Indications	Contraindications
Thromboendarterectomy	Short stenotic segment of distal aorta on iliac artery	Concomitant aneurysmal disease
Aortofemoral bypass	For the usual aortoiliac involvement To provide inflow or outflow (or both) for concomitant endarterectomy	Short stenosis (relative contraindication)
Axillofemoral, femorofemoral bypass	Infected aortic aneurysm Infected aortic prosthetic graft Poor risk for abdominal operation	Less successful patency, so not appropriate unless conditions at left present
Percutaneous balloon angioplasty with stent placement	Short segment involvement with good distal runoff To provide inflow for a more distal femoropopliteal bypass	Intimal dissection (with occlusion, rupture, distal embolization)

[RUSH Review of Surgery, 2000]

- 40% of aneurysmal infections caused by salmonella
- *Staph aureus* and gram negative bacteria are most common organisms in early graft infection; *staph epidermidis* is more chronic (presents > 4 months; at 2 years on average)

Aortoenteric Fistula (AEF): Primary (no graft) vs. Secondary (graft)

- 80% distal duodenum (aortic pathology > 75%; GI path ≈ 15%)
- causes: **graft infection**, duodenal trauma (→ ischemia) during original operation, inadequate graft coverage

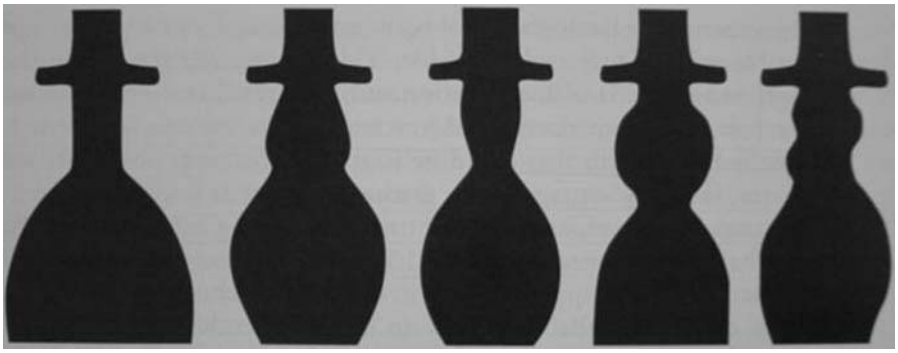
Secondary AEF:

- 90% are graft-enteric fistula (anastomotic) vs. 10% graft-enteric erosion (paraprosthetic)
- 60 – 80% present initially with self-limited sentinel bleed
- Of all patients with GI bleed + history of aortic reconstruction → 2% have AEF (hence, do endoscopy 1st to rule out other causes of UGIB)
- Mortality ≈ 35%
- Document femoral pulses
- CT with IV contrast (minimum of 3 mm cuts) [CT >angio: shows more than lumen]
- Angiography if: (i) symptomatic mesenteric disease, (ii) question of renal disease, (iii) no femoral pulses (need to know targets), (iv) significant PVD/claudication
- Gold Standard repair: graft excision, closure of aortic stump, extra-anatomic revascularization (close duodenum primarily)

Endovascular Stenting:

Endovascular stent-graft placement is widely performed for the treatment of infrarenal abdominal aortic aneurysms. Although advances in graft design have greatly expanded the population of patients who would be considered candidates for endograft placement, there are certain anatomic limitations that place the patient at high risk for a type I endoleak (a lack of, or suboptimal fixation in, the proximal or distal attachment site). Critical information that the vascular surgeon/interventionalist needs to know prior to embarking on an endograft placement procedure includes:

1. Is there a sufficient length of neck (≥ **15 mm**) of normal aorta above the aneurysm?
2. Is the width of the neck < **20 – 26 mm**?
3. What is the degree of angulation of the neck (needs to be < 60°, see figure)?
4. Is the inferior mesenteric artery patent?
5. Are the common iliac arteries aneurysmal?
6. Are the common iliac arteries aneurysmal with respect to the distal aorta?
7. Are the hypogastric arteries patent?
8. Are the external iliac arteries patent?



[Figure taken from talk given by Les Cunningham, 2005]

- 97% success installation
- No study shows decrease mortality (only decreased morbidity)
- Actually increased cost with follow-up
- 1%/year rupture/explant rate
- Up to 50% of patients will develop an endoleak
- 20 – 30% need re-intervention within 2 years
- 5-year survival: 75% (same as open)

<u>Leaks (I, III are worst)</u>

I. Presumed anastomosis site (fixed site leak) → **must be fixed when diagnosed**
II. Graft leak via collaterals (branch vessel leak; back bleeding, usually lumbars) → **must be fixed or converted to open if continues to expand***
III. Tear in graft (graft defect)
IV. Transgraft egression (needle holes/porosity): self-limiting
V. Endotension (controversial): said to occur when there is ↑ intrasac pressure without evidence of endoleak. Unsure of cause.

***Type II** my close spontaneously within first 12 months; hence, if aneurysm sac not expanding → warrants observation for 12 months. Repair if sac persists > 12 months OR sac ↑ in size.

Presently **OVER** (**O**pen **V**s. **E**ndovascular **R**epair of AAA) Trial has randomized > 400 patients

Peripheral Vascular Disease

Claudication:

- History is key: **Reproducible** pain of buttock, thigh and/or calf associated with **ambulation** and **relieved by rest**.
- Initial treatment is smoking cessation, exercise; Pletal > Trental (but ↑ cost); not surgery
- These patients have the same risk of death from cardiovascular disease as patients with known cardiac disease (50% die within 5 years)
- Progresses to gangrene 2 – 3% annually (only 10% ever lose leg)

Rest pain/ulcers → indication for bypass

Clinical manifestations of critical limb ischemia (according to European Consensus Conference):
1. Rest pain requiring analgesia for at least 2 weeks
2. Ankle systolic pressure < 50 mmHg (with or without tissue loss/gangrene)

Exercise Test "positive" if > 20% fall in ankle systolic pressure requiring > 3 min to recover

Arterial Flow is **triphasic**: 1. Forward, 2. Reverse, 3. Late forward (Note: will be normally monophasic in low resistance system, like ICA)

ABI Values:
Calcified (diabetic) > 1.2; normal > 1; Claudication 0.5 – 0.99; Rest pain ≤ 0.3
*Require ABI > 0.5 to heal a lower extremity amputation

1-year survival after amputation for ischemic disease is 75%
2-year survival after amputation for ischemic disease is 60%
3-year survival after amputation for ischemic disease is 50%
4-year survival after amputation for ischemic disease is 45%
50% of patients lose other leg within 5 years of 1st amputation

***Most common site of lower limb atherosclerosis: SFA in region of the adductor canal (Hunter's canal)**
***Cardioatrial emboli most frequently occlude CFA**

Reversed saphenous vein patency (gold standard below inguinal ligament): 80 – 90% at 1 year; 75% at 5 years; persistent smoking is #1 reason for late graft failure (valve leaflet remnants is #1 reason during 1st two years)

Fem-pop bypass:

# Vessel run-off	5-year patency
3	70%
2	35%
1	15 – 20%

Popliteal Artery Aneurysm

- Most common peripheral aneurysm (≈ 70% of all)
- 50% are bilateral and 30% also have AAA
- 20 – 30% of limb loss with distal emboli → elective *repair of all*, regardless of size
- Management options: - medial exploration: proximal/distal ligation & bypass
  - acute thrombosis → preop thrombolytics
  - endovascular repair (not yet accepted)

Tibperoneal Disease (infrapop)*

	1-year	4-year patency
in situ SV vein:	82%	68%
arm vein	73%	58% (3 year)
PTFE	46%	21%
PTFE+coum (2.0)	-	50%
PTFE+vein pat	74%	54% (5 year)

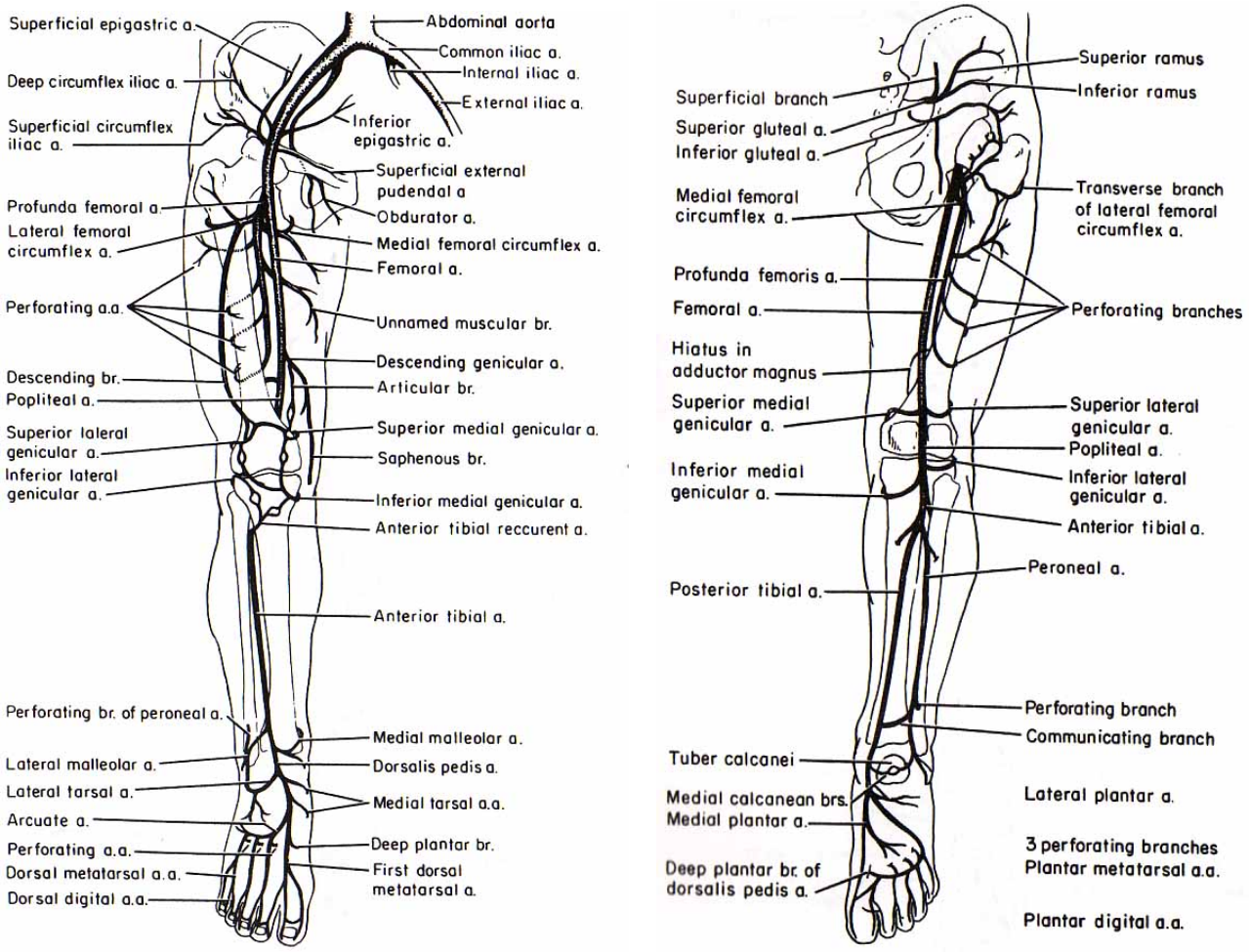
*Peroneal artery is least likely vessel of lower extremity to be occluded by atherosclerosis

Patch/collar reduce turbulence → increase compliance at distal anastomosis → minimize trauma to arterial endothelium → decrease proliferative response (intimal hyperplasia)

Below knee revascularization should only be performed for **limb salvage** (including rest pain)

Contraindications to thrombolytic therapy: recent history (6 months) of TIA or CVA; recent (10 days) operation or GI bleed; presence of intracranial malignancy or vascular malformation; uncontrolled hypertension

Lower Extremity Vascular Anatomy



Anterior view **Posterior View**

[Vascular Surgery, House Officer Series, 3rd Faust and Cohen, 1998]

Evaluating Lower Extremity Ulcers

First diagnose the cause (diabetic, venous insufficiency, arterial insufficiency, vasculitis, IBD, etc.)

The most common are diabetic, arterial, and venous insufficiency:

I. Diabetic: typically occur on pressure points on the foot and are painless secondary to the acquired neuropathy

II. Arterial Insufficiency: extremely painful, associated with rest pain in distal foot, have grayish granulation tissue, surrounded by blue and mottled skin, and do not bleed when debrided. Pain is most common over metatarsal heads, not toes (usually occur at pressure points).

III. Venous insufficiency: large, irregular, shallow, have red granulation tissue, occur around medial and lateral maleoli, and are surrounded by brawny edema and stasis pigmentation. Leukocytes are thought to play an important role in the pathophysiology because they have been found to be sequestered in the ankle region of patients with elevated venous pressures, especially in the dependent position. They plug capillaries and become activated and release their enzymes and superoxide radicals, decreasing flow, leading to ischemia and ulceration

Phlegmasia alba dolens: venous clot results in such increase in venous pressure → edematous, swollen, pale, cyanotic extremity; blanched appearance result of edema; can impair arterial inflow; a surgical emergency requiring thrombectomy ± creation of AV fistula (can use TPA)

Evaluating Limb Ischemia

The presentation of peripheral limb ischemia determines the chronicity
Acute limb ischemia is **60% thrombotic** and **40% embolic**
Always check inflow (femoral pulses)
Absent popliteal pulses imply SFA occlusion or multiple proximal occlusions

When describing angiographic lesions/stenoses use terms like**: none, mild, moderate, severe**, and distinguish between **diffuse** and **focal**

SVS Clinical Classification of Limb Ischemia

	Sensory	**Motor**	**Doppler Arterial¥**	**Doppler Venous¥**
Viable	Normal	Normal	Normal	Normal
Threatened Marginal	+/- toes	Normal	Abnormal	Normal
Threatened Immediate	Beyond toes	Mild-moderate deficit	Abnormal	Normal
Irreversible	Profound	Paralysis	Abnormal	Abnormal

¥ If you hear a monophasic doppler signal → distinguish between arterial and venous (venous will change with sequential calf compression)

Treatment

Viable: heparin‡ → further work-up
Threatened (Marginal): heparin → further work-up
Threatened (Immediate): heparin → to OR for intra-op angiogram +/- intervention
Irreversible: to OR → amputation
‡dose: bolus 80 units/kg followed by drip of 18 units/kg

Thoracoabdominal Aneurysms

The most common cause of ascending aneurysmal disease is cystic medial necrosis (seen in Marfan's syndrome); all other areas of aneurysm (including transverse arch) are most associated with atherosclerotic disease.

Operate if **symptomatic** or **> 6 cm**

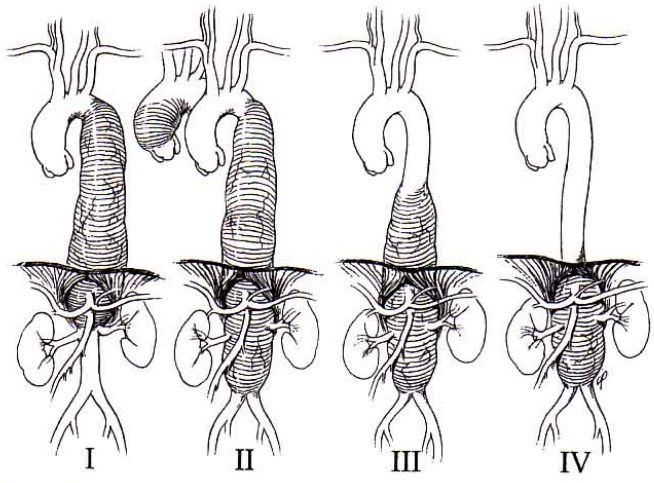
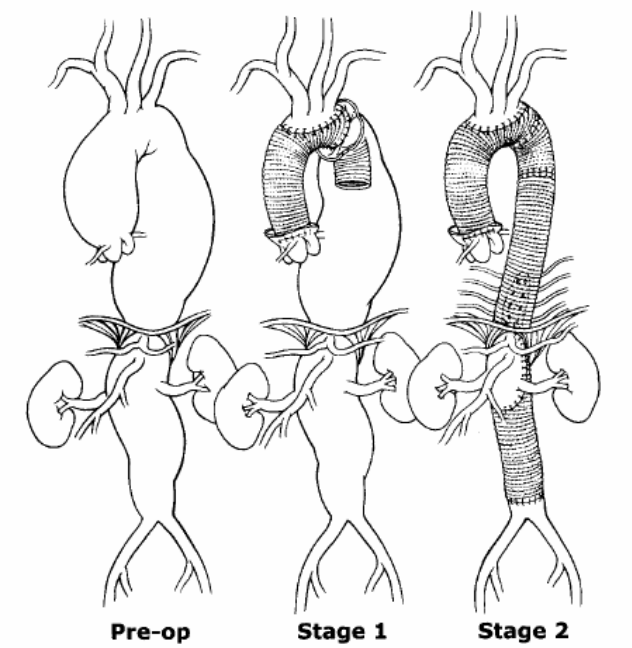


Fig 1. The Crawford classification of thoracoabdominal aortic aneurysms is based on the extent of aortic involvement. Extent I aneurysms begin above the sixth intercostal space (usually near the left subclavian artery) and extend down to encompass the aorta at the origins of the celiac axis and superior mesenteric arteries; although the renal arteries may also be involved, the aneurysm does not extend into the infrarenal segment. Extent II aneurysms also arise above the sixth intercostal space but extend distally into the infrarenal aorta, often to the level of the aortic bifurcation. Extent III aneurysms begin in the distal half of the descending thoracic aorta (below the sixth intercostal space) and extend into the abdominal aorta. Extent IV aneurysms generally involve the entire abdominal aorta from the level of the diaphragm to the bifurcation.

[Ann Thor Surg 2001;71:1233]



[Ann Surg 2004; 240:677]

Risk of paraplegia: **greatest risk – Type II**; I –50% risk; III – 25% risk; IV – 10% risk

Staged Repair to TAA with elephant trunk

Aortic Dissection

Stanford A: involves aortic arch [included DeBakey I (ascending and descending) and DeBakey II (ascending only)]. A surgical emergency, 1% mortality per hour.

Stanford B: involves descending aorta only [same as DeBakey III]. Medical management (i.e. control HTN). Operate only for rupture, occlusion

Splancnic Artery Aneurysms

Site	Incidence	Pathology	Clinical Presentation	Diagnosis	Natural History	Treatment
Splenic	**Most common**; 1/1000	Atherosclerosis F > M **60% occur during pregnancy**	Most asymptomatic 20% with variable symptoms	Often incidental Calcs in LUQ CT Arteriography is gold std	Unclear; if symptomatic, **enlarging** → fix **Pregnant** → fix **> 2 – 3 cm** → fix Some say ok to watch if 1. Asympt + > 60 2. calc + < 1.5 cm	If distal → splenectomy If proximal → ligate at both ends (no need to reconstruct because of short gastrics)
Hepatic	2nd most common splancnic	Infectious most common; Mycotic following sepsis (e.g. bacterial endocarditis); Approx 80% outside of liver	Most symptomatic; Persistent RUQ pain	Rare pre-op; Selective celiac Arteriography is gold std	Unknown, but rupture devastating, so **fix all unless serious contraindication**	Proximal to GDA → aneurysmectomy and ligate (retrograde GDA flow) May do same for PHA, LHA, or RHA, but recon with saphenous vein is best
SMA	3rd most common splancnic	Rarely atherosclerotic; > 50% mycotic (2o to SBE)	Almost always cause symptoms; Intermittent or constant epigastric/back pain	Epigastric pain, tender NONFIXED pulsitile mass	Spontaneous rupture occurs in over 50%; **Operation always warranted**	Aneursymectomy + bypass (vein preferred because of infection); Dacron acceptable
Celiac	Rare; 1/8000	Atherosclerosis; Infectious, also	Usually asymptomatic	Usually incidental	Unknown; probably high risk of rupture	Aneurysmectomy with arterial reconstruction is desired; Greatest risk is intestinal ischemia

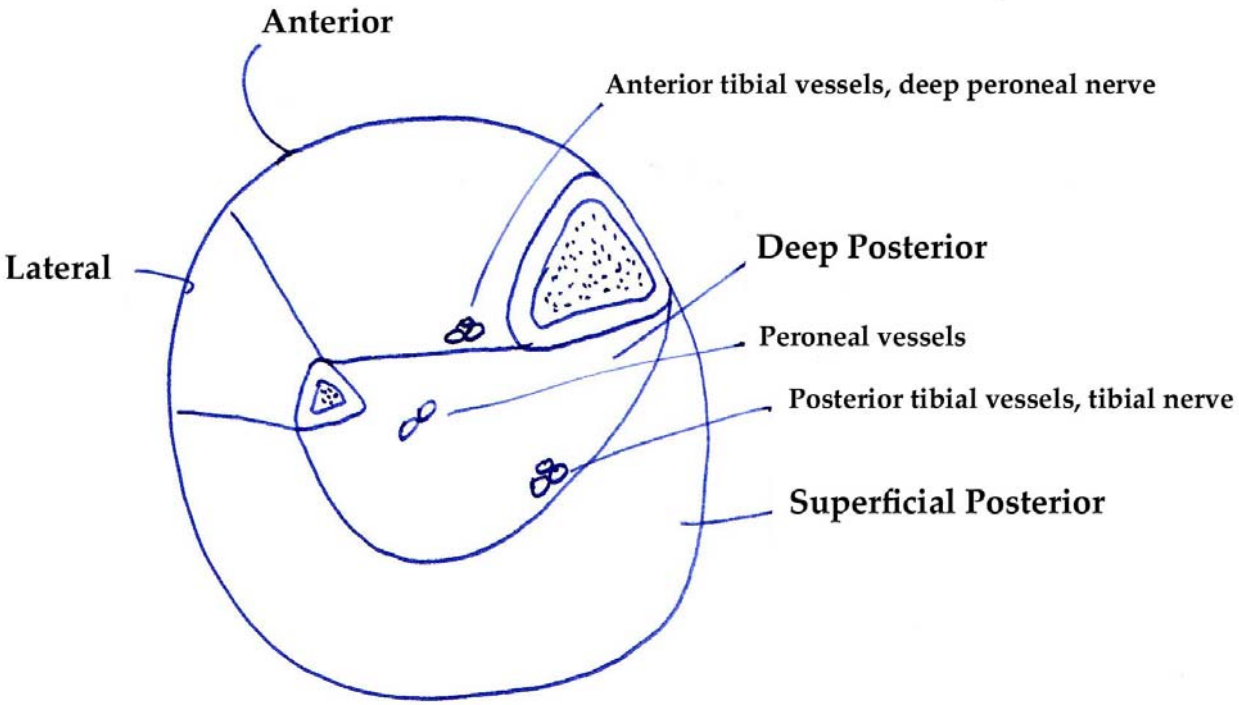
Thoracic Outlet Syndrome: anatomic compression of brachial plexus, subclavian/axillary artery, and/or vein.

- Most patients (95%) have pain or paresthesias
- Most commonly in the C8 to T1 **(ulnar)** distribution [nerve conduction tests demonstrate slower conduction velocity across thoracic outlet: mean of > 80 m/s in normals vs. < 60 m/s in affected]
- Can also cause atrophy of interosseous muscles
- Arterial involvement: can see distal ischemia (similar to Raynaud syndrome), 1%
- Venous involvement: extremity edema, "effort thrombosis" or Paget-Schroetter syndrome, 4%
- In examining the patient → try to reproduce the symptoms with arm elevation (EAST – Elevate Arm, Stress Test: put both arms up and pinch fingers – should be able to for 3 minutes).
- Conservative management appropriate for most
- Generally, the transaxillary approach is best for operative correction
- **For nerve compression**: 1st rib resection, anterior scalenectomy, resection of costoclavicular ligament, and neurolysis of C7, C8, T1
- **For arterial compression (producing thrombosis)**: 1st rib resection, thrombectomy, embolectomy, arterial repair or replacement
- **For venous compression (producing thrombosis)**: via antecubital catheter obtain venogram, perform thrombolytic therapy; after clot lysis → 1st rib resection + other compressive elements. Do venogram 2 weeks later as 50% will require balloon dilatation of stenosis in vein

Subclavian stenosis:

- Can result in subclavian "steal", where use of arm "steals" blood from cerebral circulation via vertebral artery or arm claudication
- Best patency results seen with carotid-subclavian bypass or balloon dilatation

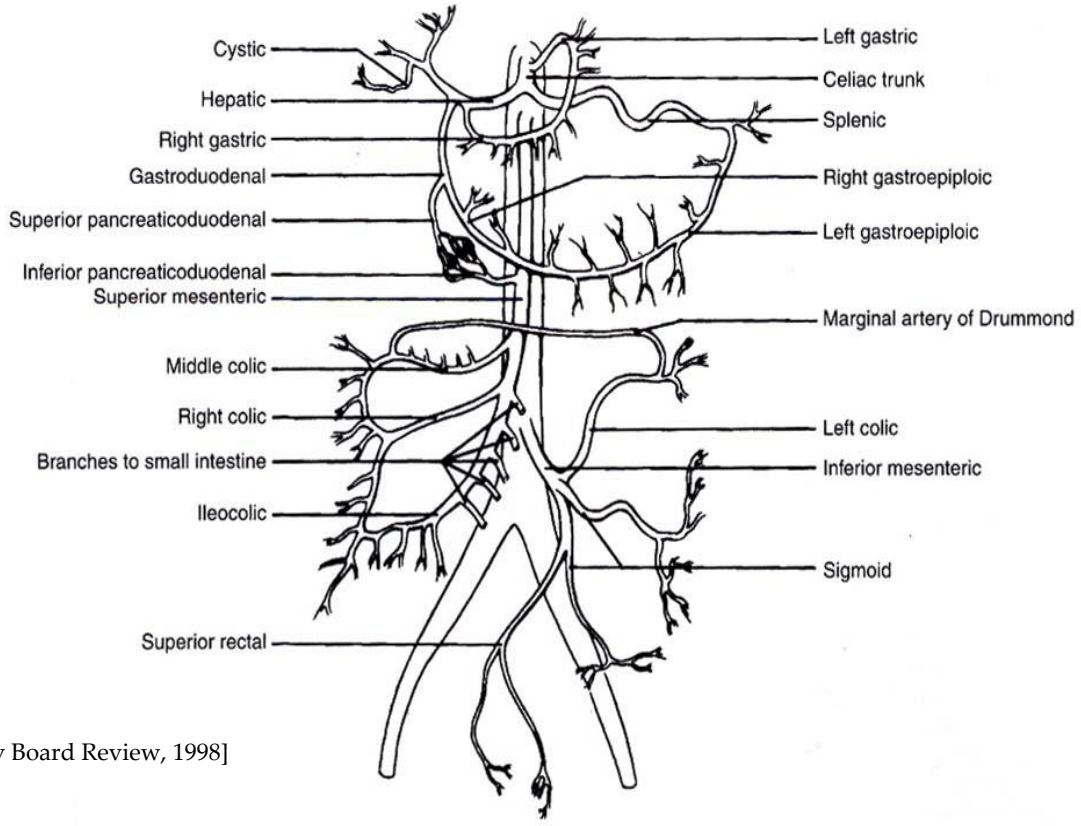
Fascial compartments of lower leg (right):



Fasciotomy should be performed concomitantly on the limb if it has been subjected to > 4 – 8 hours of ischemia (including heparinized patients), and/or in patients with symptoms

Visceral Ischemia

Celiac & SMA collateralize via GDA, PDA
SMA & IMA collateralize via marginal artery of Drummond (arc of Riolan)



[General Surgery Board Review, 1998]

	Incidence (%)	Age	Prior symptoms	Risk factors	Mortality
Arterial Emboli ‡	50	Elderly	Possibly intestinal angina	Systemic atherosclerosis and the risks that accompany it; Afib	Very High
Arterial Thrombosis §	25	Elderly	Usually none	Recent MI, CHF, arrhythmias, Rh fever	High
Nonocclusive (low flow)	20	Elderly	Usually none	Shock, CPB, vasopressors, sepsis, burn, pancreatitis; digoxin can exacerbate; treat underlying condition; OR for gangrenous bowel	Highest
Venous Thrombosis ♣	5	Younger	Possible previous thrombosis; Dx by CT	Hypercoagulable state, portal HTN, inflammatory states, prior surgery, trauma; treat with immediate anticoagulation	Lowest

‡ most commonly lodge at major branch points along SMA, **distal to middle colic**
§ most commonly occlude **proximal SMA**
♣ tends to be more **peripheral** than arterial occlusion → shorter segments involved

*Barium studies are *contraindicated* because of the ↑ intraluminal pressure generated and the potential of the barium to obscure future angiographic studies

Chronic Mesenteric Ischemia: typically need 2/3 vessels occluded. Preferred repair is **antegrade** (aorto-mesenteric) bypass with vein or prosthetic, typically to a single vessel (SMA). Can dilate and stent (especially if older and/or malnourished)

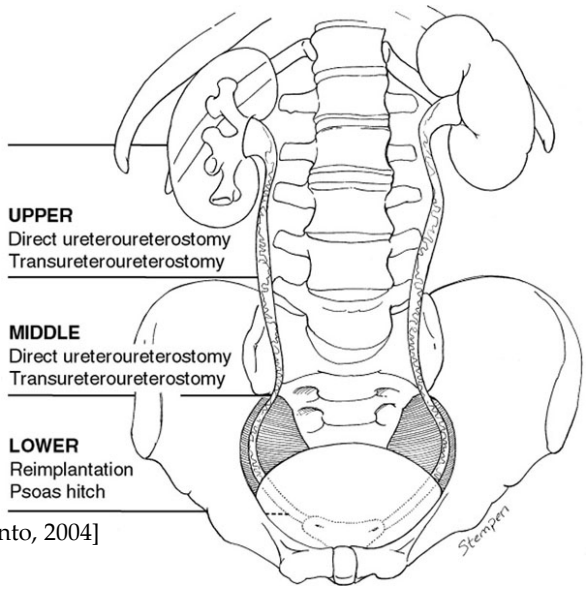
Urology

1. Bladder Body: cholinergic → contracts → empties
2. Bladder Neck: α-adrenergic → contracts internal sphincter → retains

Testicular mass: biopsy is orchiectomy via *inguinal* incision (never trans-scrotal)

Testicular torsion → bilateral orchiopexy

Ureteral injury: use *absorbable* suture, stent, and *drain* (debride and spatulate ends → over stent)
Treatment based on location (upper, middle, lower); middle has worst blood supply → hardest to heal



[Figure taken from a talk by Peter Pinto, 2004]

Varicocele seen more often on left side: left gonadal vein → left renal vein; right gonadal vein → IVC
Right varicocoele present, rule out right renal mass with IVC thrombus

Seminoma

- 20 – 35 years old; Anaplastic subtype is most malignant; **↑βhCG in 5 to 10% of pure seminoma patients**
- 25% have occult mets in stage I
- Very radiosensitive (all stages get RT)
- Node + disease (N1 and N2) gets RT
- Bulky node + disease > 5 cm (N3) gets platinum chemo (BEP) if residual nodes, then surgery, if residual nodes + for tumor, salvage chemo with VIP (vinblastine, ifosfamide, cisplatinum)

Nonseminoma germ cell tumors (choricocarcinoma, embryonal cell, yolk sac, teratocarcinoma)

- May have **↑βhCG** AND **AFP**
- **AFP not elevated in pure choriocarcinoma or seminoma**
- Get LN dissection; chemo if advanced; NOT radiation
- Chemo is **BEP**: bleomycin, etoposide, cisplatin; pulmonary fibrosis is most feared complication due to bleomycin

<u>Lymphatic drainage of testes (if crossover drainage occurs, it is right to left):</u>
Right: interaortocaval nodes & right renal hilum
Left: paraaortic & left renal hilum

Prostate cancer most often arises in *periphery* of gland (peripheral zone); BPH arises in *center* of gland (transitional zone); Prostate mets to bone are osteoblastic (50%), osteolytic (10%) mixed (40%) and radiodense

95% of EPO made by kidney; stimulated by hypoxia

Orthopedic Surgery

Disc herniation and associated nerve root compression:

Disc	Nerve root compression	Symptoms
L3 – L4	**L4**	**Weak knee jerk**; ↓medial foot sensation
L4 – L5	**L5**	**Weak dorsiflexion**; weak big toe; ↓sensation between 1st and 2nd web space
L5 – S1	**S1**	**Weak plantarflexion**; weak ankle jerk; ↓sensation to lateral calf/foot

Hip Dislocation

90% **posterior** → internal rotation + flexed + adducted thigh
Risk of sciatic nerve injury, **AVN** of femoral head

Tibial and Calcaneous fracture: prone to compartment syndrome

Humerus Fracture: may see radial nerve injury (weak wrist extension; Δ in sensation over lateral/dorsal hand)

Shoulder Dislocation: 90% anterior; risk of axillary nerve injury; posterior dislocation seen with extremely violent movement (seizures, electrocution)

Navicular Fracture: tender snuffbox → even with negative x-ray, requires cast to elbow

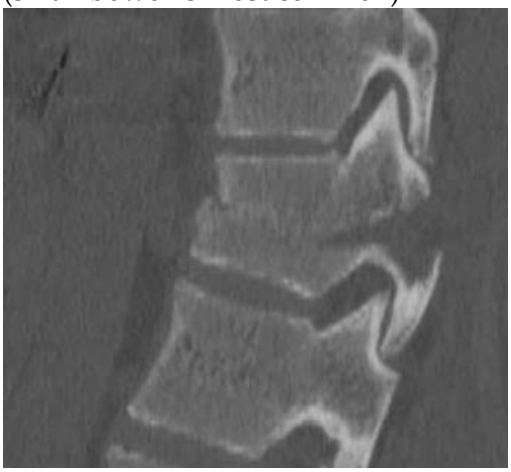
(Closed) Posterior Knee Dislocation: Reduce 1st, then arteriogram; 30 – 45% incidence of popliteal artery injury (intimal tear → disruption)

Femur fracture

Adults: early ORIF → allows early mobilization, ↓ fat emboli/complications
Children: closed reduction and to avoid interference with growth plate

Anterior drawer sign: tear of anterior cruciate ligament (ACL)

Chance Fracture: horizontal fracture thru vertebra (body, pedicles, laminae). Seen with sudden deceleration with lap-only seatbelts; usually L1 or L2; **> 50% chance of underlying hollow viscous injury** (small bowel is most common)



[www.auntminne.com]

Gynecologic Pathology

Ovarian Cancer

- 5 major classes (based on histology and embryologic etiology):
    1. neoplasms derived from celomic epithelium
    2. neoplasms derived from germ cells
    3. neoplasms derived from gonadal stroma
    4. neoplasms derived from nonspecific mesenchyme
    5. metastatic lesions to the ovary (usually GI, breast, or uterine)
- Responsible for half of all gynecologic deaths each year; 25,000 cases/year in US (33% 5-year survival)
- All comers: 20% of ovarian neoplasms are malignant (↑ with age)
- Woman aged 20 – 30: 10% chance of malignancy; ≥ 50: 50% chance of malignancy
- Usually diagnosed in advanced stage (2/3 present as stage III or IV)
- CA-125 of limited use for screening, especially in premenopausal women
- Cytoreductive surgery is most effective treatment (**TAH+BSO; must include omentum, peritoneal washings**; **no need for lymphadenectomy** since tumors spreads by exfoliation of cells)

Uterine Cancer

- Endometrial cancer is the **most common** gynecologic malignancy in US (40,000 cases/year)
- ≈ 75% are diagnosed as stage I, 5-year survival > 75%
- Risk factors are associated with ↑estrogen exposure
- 80% of cases are in postmenopausal women (5% in women < 40)
- Abnormal bleeding is #1 presentation; histology is adenocarcinoma > 90%
- Treatment is **TAH+BSO, peritoneal washings, LN sampling**
- Post-operative radiation (5000 rad over 5 weeks) reserved for: + pelvic nodes, poor differentiation, invasion into myometrium, occult cervical involvement
- Uterine sarcoma has poor prognosis

Cervical Cancer

- Most (> 80%) are squamous cell
- Primarily affects women aged 35 – 45
- Painless bleeding is #1 presentation (pain often signals advanced disease)
- Pap smear allows most to be diagnosed as premalignant lesions
- Highly associated with HPV infection (serotypes 16 and 18 virtually always involved)
- Treatment for early stage: radical hysterectomy (no need for oophorectomy unless >45 or has ovarian pathology)
- Chemoradiation if poor surgical candidate or advanced disease

Post-menopausal HRT is associated with:

Increase in:	Decrease in:
▪ Endometrial cancer ▪ Breast cancer ▪ Venous thrombosis ▪ Stroke ▪ Coronary artery disease ▪ Gallbladder disease	▪ Vasomotor symptoms of post-menopause ▪ Vertebral/hip/pelvic fractures ▪ Osteoperosis ▪ Colorectal Cancer

Surgery during pregnancy:

- Second trimester is preferred
- Both laparoscopic and open procedures during first trimester are associated with ↑ risk of spontaneous abortion and possible risk of teratogenicity
- During the third trimester surgery is associated with ↑ risk of premature labor and damage to the uterus

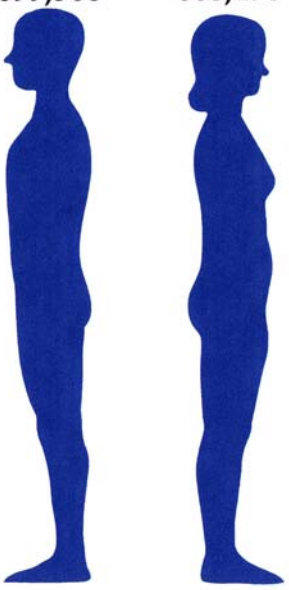
Neurosurgery

Diabetes Insipidus – central or renal (ADH inhibited)	SIADH
▪ ↑ urine output ▪ Low urine Osm, specific gravity ▪ High serum Osm, *hyper*natremic	▪ ↓ urine output ▪ High urine Osm, specific gravity ▪ Low Serum Osm, *hypo*natremic

Peripheral Nerve Injuries

Neuropraxia: focal demyelination → improves
Axonotmesis: loss of *axon* continuity (nerve and sheath intact) → regenerates at 1 mm/day
Neurotmesis: loss of *nerve* continuity → surgery required to repair

2004 Estimated US Cancer Cases*

		Men 699,560	Women 668,470		
Prostate	33%			32%	Breast
Lung & bronchus	13%			12%	Lung & bronchus
Colon & rectum	11%			11%	Colon & rectum
Urinary bladder	6%			6%	Uterine corpus
Melanoma of skin	4%			4%	Ovary
Non-Hodgkin lymphoma	4%			4%	Non-Hodgkin lymphoma
Kidney	3%			4%	Melanoma of skin
Oral Cavity	3%			3%	Thyroid
Leukemia	3%			2%	Pancreas
Pancreas	2%			2%	Urinary bladder
All Other Sites	18%			20%	All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2004.

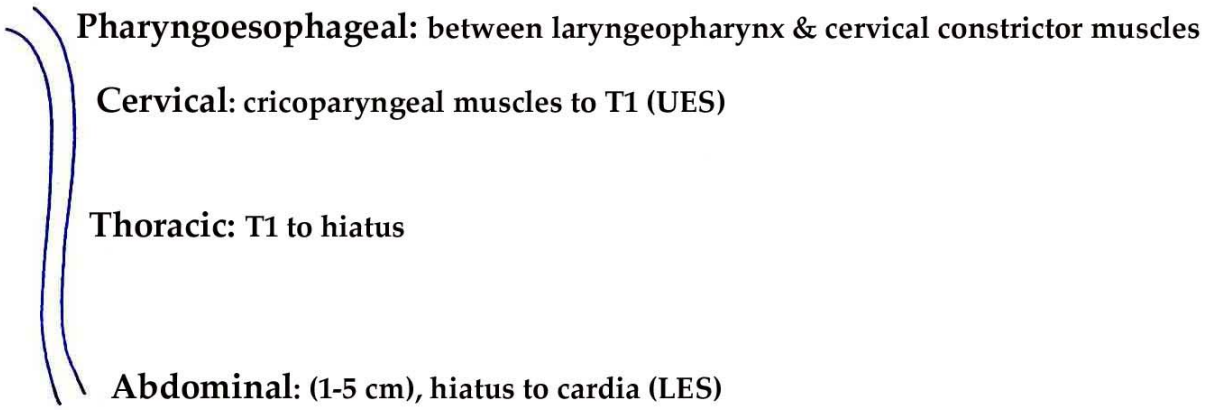
2004 Estimated US Cancer Deaths*

		Men 290,890	Women 272,810		
Lung & bronchus	32%			25%	Lung & bronchus
Prostate	10%			15%	Breast
Colon & rectum	10%			10%	Colon & rectum
Pancreas	5%			6%	Ovary
Leukemia	5%			6%	Pancreas
Non-Hodgkin lymphoma	4%			4%	Leukemia
Esophagus	4%			3%	Non-Hodgkin lymphoma
Liver & intrahepatic bile duct	3%			3%	Uterine corpus
Urinary bladder	3%			2%	Multiple myeloma
Kidney	3%			2%	Brain/ONS
All other sites	21%			24%	All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2004.

Esophageal Disease

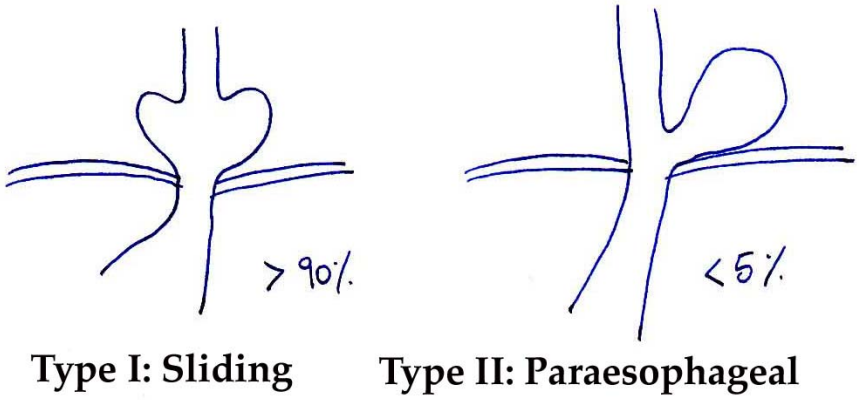
4 Segments:



No serosa; mucosa is strongest layer
Sphincters are contracted at rest; Normal LES tone ≈ 15 – 25 mmHg

Order of events in swallowing: soft palate closes nasopharynx → larynx up → larynx closes → UES relaxes → pharyngeal contraction

Hiatal Hernia



Type I: sliding; most patients with reflux have, but most patients with it don't have reflux
Type II: paraesophageal → repair even if asymptomatic because of risk of infarction
(Also: **Type III**: esophagogastric junction in mediastinum, and **Type IV**: entire stomach in mediastinum)

Benign Esophageal Disorders

I. Primary
Achalasia: ↓ ganglion cells in Auerbach's plexus, absence of peristalsis; esophageal dilation ("bird's beak" on swallow); manometry shows no peristalsis, high LES pressure, & failure to relax; Rx: Botox, pneumatic dilation, Heller myotomy
Diffuse Esophageal Spasm: chest pain; manometry shows high amplitude contractions, normal LES relaxation; Rx: Ca^{++} channel blockers; *if* fail medical management → *thoracic* esophagomyotomy
Nutcracker Syndrome (not = DES): chest pain; extremely high amplitude peristaltic waves (up to 400 mmHg); need long myotomy, occasionally esophagectomy
Hypertensive LES
Nonspecific esophageal motility disorder

II. Secondary
Collagen vascular (SLE, systemic sclerosis, polymyositis, dermatomyositis)
Chronic idiopathic intestinal pseudo-obstruction
Neuromuscular disease
Endocrine disorder

Zenker's Diverticulum
- Loss of compliance in the pharyngoesophageal segment; manifested by increase bolus pressure
- Muscle biopsies have shown histologic evidence of restrictive myopathy correlating with decreased compliance of upper esophagus
- Repetitive stress of bolus through noncompliant muscle → diverticulum through Killian's triangle (between cricopharyngeus and thyropharyngeus muscles)
- **Primary reason**: dyscoordination of the sphincter relaxation with pharyngeal contraction together with impaired sphincter opening
- Dx: with barium swallow; *not* EGD
- Rx: **myotomy** and diverticulectomy (or -pexy if unfit for resection) via left cervical approach

Zenker's and epiphrenic are both false diverticuli (mucosa only); epiphrenic requires **long myotomy at 180^0**

***T*raction** diverticuli are ***T*rue**: located mid-esophagus; associated with ***T*B**/inflammatory diseases

Esophageal Claudication: chest pain caused by a burst of uncoordinated esophageal motor activity under ischemic conditions (i.e. esophageal blood supply is interrupted during these bursts in situations where blood flow may already be compromised)

Esophageal foreign body: usually at points of natural narrowing: below cricopharyngeus, near arch of aorta, behind right mainstem; 95% are immediately below cricopharyngeus muscle → rigid scope under GA is treatment of choice

Esophageal rupture (Boerhaave's): full thickness injury (vs. partial thickness injury of Mallory-Weiss); often left posterior/lateral; 85% die if diagnosis delayed > 36 hours (Rx: early → repair, late → diversion)

Mallory-Weiss Tear: repeated emesis; about 10% present with massive hemorrhage → gastric bleeding (usually lesser curvature); since arterial bleed, pressure tamponade of little help → usually stops spontaneously; Dx with endoscopy → gastrotomy & oversew if doesn't stop

Esophageal Perforation

50% instrumentation, 20% trauma, 15% spontaneous
3/10k EGD, 11/10k rigid

Presentation depends on
1. Location, 2. Size, 3. Elapsed time, and 4. Underlying pathology/etiology

- Cervical: neck pain (especially with flexion), crepitus, right pleural effusion
- Spontaneous: usually distal left

Non-operative Criteria (i.e. contained leak)

1. Intramural Perforation
2. Transmural, not in abdomen → drains well back into esophagus
3. Not associated with obstruction/malignancy
4. Mild symptoms; no evidence of sepsis

Treatment: NPO, antibiotics

Diagnosis:

- Always get: CXR, EKG, gastro swallow
- Poor tissue → resect
- Good tissue (early) → 1° repair
- Reinforced with Gambi stitch & tongue of stomach or parietal pleural patch

Cervical perforations: usually managed with transcervical drainage; repair if technically feasible
Thoracic perforations: if found early → can primary repair (in layers with buttress and thoracic drainage)
Septic/Late perforations: if associated with cancer → **resection**; some favor esophageal exclusion

Following corrosive ingestion:

- EGD only to proximal margin (not at all if suspect perforation)
- Emergent thoracotomy indicated for evidence of mediastinitis or perforation: severe chest pain, cervical subcutaneous crepitus, widened mediastinum, PTX, pleural effusion
- Emergent laparotomy indicated for: signs of perforation or when nasogastric alkali contents from the stomach have been aspirated (direct visualization of stomach necessary to rule out liquefaction)

Benign esophageal tumors: far less common than malignant tumors; leiomyoma is most common → usually found in lower ⅔; DO NOT biopsy; → resect by enucleation

Barrett's Esophagus

Semantics

- **Metaplasia**: A change of cells to a form that does not normally occur in the tissue in which it is found
- **Dysplasia**: An abnormal development of cells, which is not cancerous, but could become cancerous
- **Barrett's Esophagus (classic)**: The presence of a circumferential length of at least 3 cm of intestinal metaplasia in lower esophagus above the GEJ
- **Barrett's Esophagus (current)**: Intestinal metaplasia anywhere in the tubular esophagus
- **Short Segment BE**: Any segment of BE < 3 cm

- Barrett's will develop in 10 – 15% of patients with symptomatic GERD
- Patients with high grade dysplasia (aka CIS), will develop adenocarcinoma in 30 – 50% of cases → need esophagectomy (no debate)
- 30 – 40% increased incidence of adenocarcinoma with Barrett's (compared to general population);
- Risk of cancer progression in Barrett's is 0.2 – 2.1% per year
- Progression to adenocarcinoma associated with loss of p53 heterogenicity on ch17
- Controversy exists for the management of the larger population of patients with Barrett's esophagus but no dysplasia, low grade dysplasia, or indeterminate dysplasia, although they clearly require close surveillance

Esophageal Cancer

Top 10 cancer worldwide
Geographic variation 17/100k U.S. (Adenocarcinoma, Barrett's) → 100/100k Asia (SCC)

Lymphatics run longitudinally in esophagus → straight to thoracic duct; hence small primary can still spread aggressively via lymphatics

T1: to lamina propria (does not breach submucosa)
T2: to muscularis propria (does not breach muscularis propria)
T3: Adventitia
T4: Adjacent structures

No role for adjuvant chemo/XRT (except adjuvant XRT for margin + to decrease local recurrence)

Role of Neoadjuvant Treatment [4 studies]

20 – 25% PR to induction chemo/XRT on final path (50% of those CR)
Survival benefit (including LN +) with more aggressive lymphadenectomy and resection

1. [Kelson NEJM 1998]: 5FU+CDDP+surgery vs. surgery (Prospective randomized): no survival difference at 2 years 35% vs. 37%
2. [Herskovic NEJM 1999]: Nonsurgical patients: 5FU+CDDP+XRT (50 Gr) vs. XRT (6400 Gr) [difference is because these chemo agents make tissue more radiosensitive] 12.9 months vs. 8.9 months (significant survival, local, distal disease)
3. [*Walsh NEJM 1996]: 5FU+CDDP+XRT + surgery vs. surgery alone (10 protocol violations vs. 1); 16 vs. 11 months ($p < 0.01$); 1 & 3 year survivals: 52/32% vs. 44/6% ($p < 0.01$)

*Controversy: (i) Protocol violations (ii) Poor surgical survival compared to previous studies (iii) U/S and CXR for staging (no CT) (iv) Proportion of stage III (13 vs. 38)

4. [Meluch Cancer J 2003]: Phase II trial of Taxol/Carbo/5FU/XRT/Surg: median survival 22 months

What about radical resection?
<u>Stage III 5 year survival</u>
US: 10 – 17% (standard resection)
Japan: 27 – 34% (radical resection)
[Altorki/Skinner Ann Surg 2001 and Altorki Ann Surg 2002]

EUS: valuable tool for staging (better than CT for T-stage; good for N-staging)

Surgical Approaches

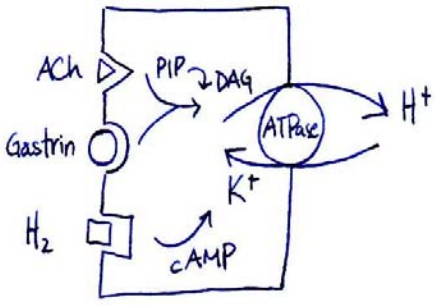
- Cervical esophagus best approached via left neck (cervical esophagus is left of midline)
- Thoracic esophagus best approached via right thoracotomy (Ivor Lewis)
- Lower esophagus best approached via left thoracotomy ± celiotomy

Options for resection include:

- <u>"3 hole"</u> (left neck, right thoracotomy, celiotomy) offers complete exposure, but greatest morbidity (if intrathoracic anastomosis)
- <u>Transhiatal</u>: no thoracotomy, cervical anastomosis (very low morbidity, but higher leak rate)

Stomach & Gut Physiology and Disease

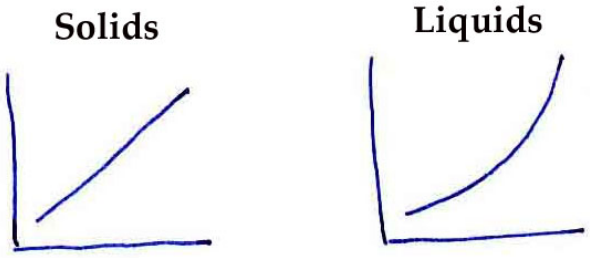
Parietal cells: produce H^+ and IF



Somatostatin: Inhibits release of essentially all GI peptides, including gastrin, insulin, secretin, Ach, and pancreatic/biliary output; stimulated by H^+ in duodenum
CCK: from intestinal mucosa → contracts gallbladder, relaxes sphincter of Oddi, ↑ pancreatic enzyme secretion
Secretin: primary stimulus for pancreatic HCO_3 secretion
Enterokinase: activates trypsinogen → trypsin → activates the other digestive enzymes
Peptide YY: released from TI → inhibits H^+ secretion ("ileal brake")

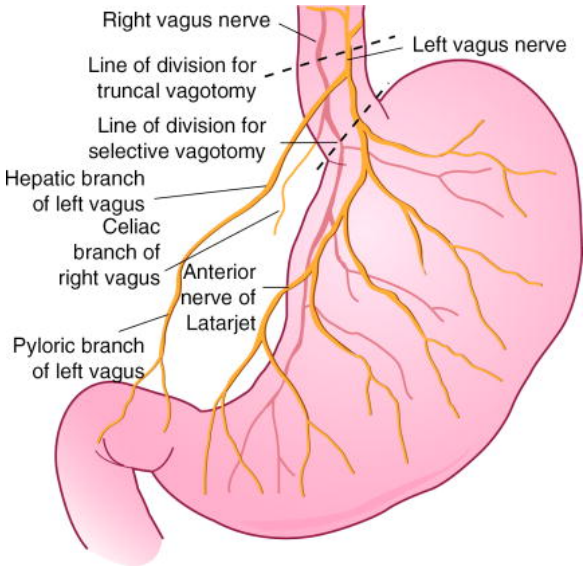
Proximal vagotomy: abolishes receptive relaxation, so ↑ liquid emptying, but ↔ in solid emptying
Truncal vagotomy: also ↑ solid emptying (when pyloroplasty done) and ↓ basal acid output by 80%
#1 symptom post-vagotomy is diarrhea (1/3); Dumping is 10% → almost always responds to diet changes

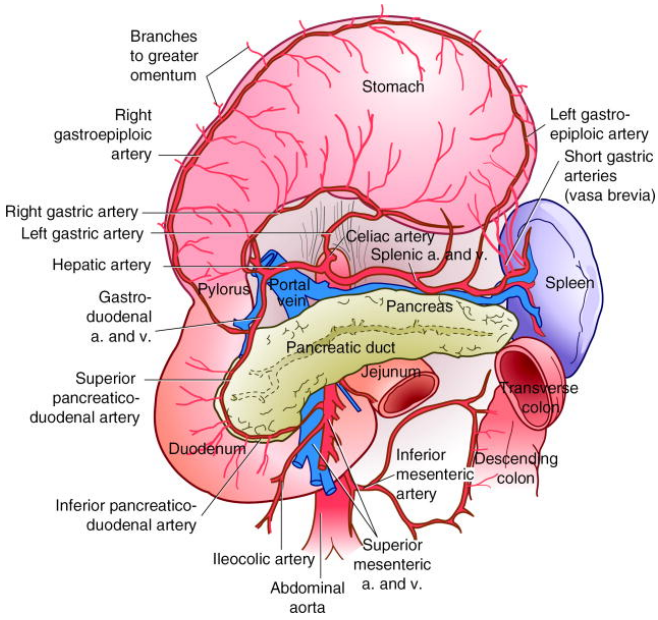
^{99m}Tc: solid emptying study ^{111}I: liquid emptying study



- Left vagus nerve → anterior → hepatic branch;
- Right vagus nerve → posterior → celiac branch & 'Criminal nerve of Grassi' (can keep H^+ levels ↑ if left undivided post-gastrectomy)

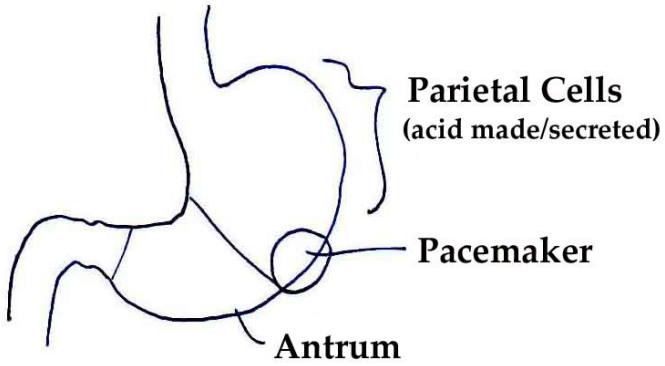
[Figures taken from talk given by JT Lenert, 2005]





Pacemaker in proximal stomach on greater curve: generates ≈ 2 – 3 MMC/minute:
Wave gets stronger as it approaches the pylorus

Diabetes is #1 cause of gastroparesis



PUD: Gastric vs. Duodenal Ulcers

<u>Gastric:</u>

- pain **G**reater with meals
- H. pylori 70%
- Blood type A
- M = F
- 1 – 3% malignant potential

<u>**D**uodenal:</u>

- pain **D**ecreases with meals
- H. pylori 100%
- due to increased acid secretion or decreased mucosal protection
- hemorrhage > perforation
- Blood type O
- NO malignant potential
- M > F

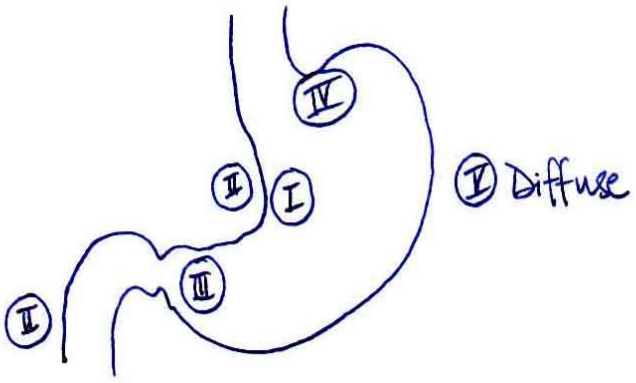
Following repair of *perforated* duodenal ulcer, natural history is such that approximately ⅓ of patients have no further problems, ⅓ have further ulcers amenable to medical management, and ⅓ ultimately require operation;
Following repair of *bleeding* duodenal ulcer, because of higher risk of recurrence, a definitive antiulcer operation should accompany the repair (if sick → TV and antrectomy; otherwise → more selective)

Elevated Fasting Gastrin

I. Elevated acid
- ZES
- G Cell hyperplasia
- retained antrum
- renal failure
- gastric outlet obstruction
- short bowel

II. Low/Normal acid
- pernicious anemia
- chronic gastritis
- gastric CA
- postvagotomy
- on acid suppression

Type I gastric ulcer associated with Type A blood; others with Type O;
II (25%), III (15%): **Too much acid**
I (50 – 60%), IV, V: **Too little mucosal protection**



Surgical Therapy for PUD:
Non-healing despite medical therapy is an indication (especially to rule out cancer)
[algorithm: 6 weeks medical treatment → EGD → repeat 6 weeks medical treatment → EGD → surgery if not healed]

With prolonged vomiting: see $\downarrow Cl^-$, $\downarrow H^+$ ($\uparrow$pH), and $\downarrow K^+$ (because kidney is dumping K^+ to hold H^+)

Distribution of Upper GI Bleeding

PUD	55%
Esophagogastric varices	14%
Arteriovenous malformations	6%
Mallory-Weiss tears	5%
Tumors/erosions	4% each
Other lesions‡	12%

‡ Includes: Dieulafoy's Lesion: dilated aberrant submucosal vessel (usually arterial) usually high in the gastric fundus; can lead to significant bleeding.
Gastric antral vascular ectasia (GAVE): Also known as "Watermelon Stomach" is generally idiopathic, but may be associated with autoimmune disease

Gastric Volvulus: 2 types:

- **Organoaxial** (more common): rotation around the axis of line connecting cardia to pylorus
- **Mesenterioaxial**: axis is orthogonal to above

Gastric Dilation: causes *hypo*tension, *brady*cardia, abdominal pain

Obesity
Class I: BMI > 30
Class II: BMI > 35* → surgery if develop complications of obesity;
*If BMI > 35 + *significant GERD* → Gastric Bypass is much preferred over an anti-reflux procedure
Class III: BMI > 40 → surgery
(Note: previous jejuno-ileal bypasses led to renal failure because of development of CaOxalate stones)

Gastric Cancer

Gastrointestinal Stromal Tumor (GIST)

- Arises from interstitial cell of Cajal (intestinal pacemaker); C-kit mutation/CD117+
- Gain of function tyrosine kinase
- Resect if possible; Gleevac for mets; role of Gleevac in adjuvant being currently evaluated

Adenocarcinoma:

- Resect with **6 cm margins** + draining lymph nodes + omentum; no obvious role for extended lymphadenectomy
- Chronic atrophic gastritis underlies most gastric cancer;
- other risks: adenoma > 2 cm, Type A blood, nitrosamines, pernicious anemia

Lymphoma: distinguish between T-cell, NHL (non-MALT), and MALT
Extranodal marginal Zone B-Cell lymphoma (low grade B-cell lymphoma of Mucosa-Associated Lymphoid Tissue, MALT):

- 50% of patients with gastric NHL have the indolent MALT type
- gastric MALT is frequently associated with chronic gastritis and H.pylori infection

*the standard treatment for MALT patients (who are H.pylori +) is antibiotics and follow-up EGD 3 and 6 months later:

- if CR → done
- if PR → continue antibiotics before XRT (not surgery)

Surgery reserved for complications
Note: the thicker the lesion → the less likely it will regress with eradication of H.pylori alone

Small Bowel Physiology and Disease

MMC: interdigestive motility; 90 minutes cycles; starts in stomach → goes to TI

- Phase I: quiescence
- Phase II: gallbladder contraction
- Phase III: peristalsis
- Phase IV: subsiding electric activity

MMC return to normal 6 – 24 hours after laparotomy; stomach and colon take longer to return to normal tone

- SB transit is approximately 1 inch per minute
- Jejunum absorbs more Na^+ and H_2O (paracellular) than ileum
- 80 – 100 cm (30%) of the small bowel is required for absorption, unless the IC junction is absent, in which case approximately 150 cm is required.
- Derangements seen with SB resection leading to malabsorption/short-gut include:
  1. Fat
  2. B12
  3. Electrolytes
  4. H_2O

Following bowel resection → Ca^{++}/Mg^{++} soap form → ↓cations to complex with oxalate in colon → ↑oxalate absorption (worsened by Vit C consumption). Treat deficiencies with Ca^{++}, Mg^{++}, potassium citrate, Vit B6, and avoid Vit C

Small Bowel Neoplasms

Represent only 5% of GI neoplasms (1 – 2% of all neoplasms)

Most common benign:	Most common malignant:
1. Adenoma (25 – 35%)	1. Adenocarcinoma (50%)
2. GIST	2. Carcinoid
3. Lipoma	3. Lymphoma
	4. GIST

- All should be resected, even if asymptomatic (need path to confirm lack of malignant behavior) → also perform regional lymphadenectomy with resection
- Adenocarcinomas are most common in the duodenum, the remaining malignant tumors are more common distally, with frequency proportional to length of segment (ileum > jejunum > duodenum)
  - Periampullary → Whipple
  - D3/D4 → segmental resection + duodenojejunostomy

GIST arise from multiple mesodermal components (muscle, nervous tissue, connective tissue, vascular elements, fat)

Carcinoids arise from the **Kulchitsky cell** and are found in the appendix 85% of time

- Mets 2% if less than 1 cm; 80 – 90% if > 2 cm
- Most common locations for GI carcinoids: 1. Appendix, 2. Ileum, 3. Rectum 4. Stomach
- Small bowel carcinoids are **multiple ≈ 30%;** appendiceal usually solitary
- Urinary 5-HIAA only elevated if able to bypass first pass (extensive liver mets, drains directly into systemic circulation)
- Metabolizes tryptophan → serotonin → 5-HIAA (measured in urine); carcinoids utilize 60% of body's tryptophan, hence side effects of tryptophan deficiency (3 D's: dermatitis, dementia, diarrhea)

Clinical Manifestations

Depends on location:

i) Foregut: stomach-pain, bleeding; bronchus-hemoptysis, pneumonitis, wheezing

ii) Midgut: appendix-obstructive appendicitis; jejunoilium-obstruction, intusessuption

Localization

CXR, Chest CT, Barium enema, colonoscopy, superior mesenteric angiography in advanced tumors

Biopsy: + argyrophil stain is suggestive, but EM of neurosecretory granules is gold standard

If one found, especially in colon, 36 – 40% incidence of synchronous lesion → look everywhere

Metastatic disease diagnosed ONLY by mets, not histology

Treatment

Appendix: If > 1.5 cm, involving base of appendix, or regional lymphadenopathy present → right hemicolectomy indicated

Gastroduodenal: If < 1 cm → endoscopic resection; >1 cm or mets →subtotal gastrectomy and omentectomy

Rectal: If < 1 cm → endoscopic excision; 1 – 2 cm → resection with negative margins (2 – 3 cm); > 2 cm → low anterior resection (LAR) or abdominal perineal resection (APR) if low

Any tumor with mets → en bloc resection

Outcome > 2 cm portends a poorer prognosis

Noninvasive appendiceal and rectal < 2 cm ≈ 100% 5-year survival

If > 2 cm ≈ 40%; with liver mets: 20 – 40%

Approximately 10% of patients with carcinoid tumor develop the "Carcinoid Syndrome‡" of flushing, sweating, diarrhea, wheezing, abdominal pain, right-sided cardiac valvular fibrosis, and pellagra dermatosis

‡Tumor needs access to venous drainage that escapes portal circulation, such as when:

1. Hepatic mets are present
2. Venous blood from extensive retroperitoneal mets drains into paravertebral veins
3. Primary tumor is outside the GI tract (bronchial, ovarian, testicular)

Carcinoid Crisis: results from overwhelming release of serotonin (liver unable to break down)

- Can occur in OR during manipulation of tumor
- Results in hypo- or hypertension
- Hypertension should be treated with volume expansion, octreotide, and ketanserin (somostatin analog)

Lymphoma: in adults usually NHL B-cell; stage I and II require resection
-in children usually Burkitt's → better survival than adults

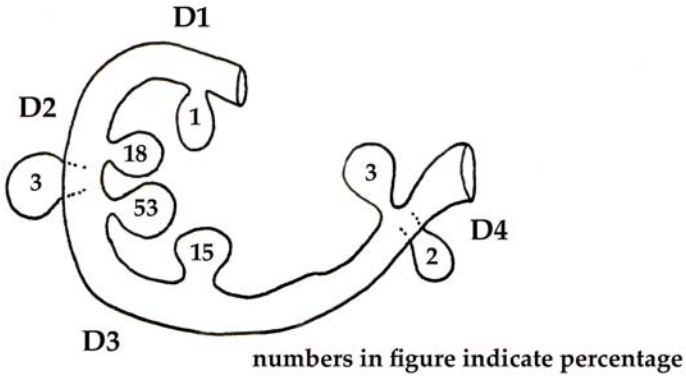
Meckel's diverticulum is #1 cause of small bowel bleeding in those < 30 yrs.
Often contains gastric mucosa (75%) → secretes HCl → peptic ulceration
"Meckel's scan" Tc^{99}-pertechnetate taken up by parietal cells
Most common cause of obstruction is volvulus around persistent fibrous band from tip to umbilicus

Angiodysplasia (Vascular Ectasia): #2 cause of small bowel bleeding in younger patients; #1 cause in those > 50 yrs.

Intussusception (in adults): up to 90% result from underlying pathology (most often a tumor; about half are benign). No role for conservative management → to OR

Ileus: look for colonic and rectal air to differentiate from a mechanical obstruction
4 Categories:
1. Postoperative
2. Paralytic
3. Intestinal pseudo-obstruction
4. Colonic pseudo-obstruction (Ogilvie's)

Diverticula of GI tract: caused by propulsion forces; 10% symptomatic; 5 – 10% develop complications (bleeding, perforation, obstruction, diverticulitis→ RP abscess); surgery is only indicated for complications/symptoms.
Most Common:
1. Colon
2. Meckel's
3. Duodenum* (see figure)



4. Pharynx & esophagus
5. Stomach
6. Jejunum
7. Appendix
8. Ileum (excluding Meckel's)

***If arises in periampullary region → must protect during surgery**

For Meckel's → resect *asymptomatic* patient if:
1. younger than 40,
2. longer than 2 cm,
3. fibrous band persists, or
4. gross evidence of heterotopic mucosa

Most common reasons for surgery (i.e. surgery is reserved for select cases) in patients with Crohn's disease
1. Failure of medical management
2. Obstruction
3. Inflammatory mass or abscess
4. Fistula

Note: If appendicitis suspected → find Crohn's → *do* appendectomy provided the base of appendix *not* involved

Small Bowel Fistula:
"High output" (≥ 500 mL/24 hours) are 3 x less likely to close than low output
Overall mortality: 20% (higher for jejunal; lower for ileal)
In patients with Crohn's disease + high output fistula → TPN does promote fistula closure

Schilling test for Vitamin B12 deficiency: reveals a type of urinary excretion of B12 similarly to that seen with pernicious anemia, except not corrected with the addition of IF, but is corrected with the use of oral tetracycline (nonabsorbable)

Appendix

- A component of the secretory immune system
- Appendicitis is initiated by obstruction of the lumen. In adults → fecalith; in children → lymphoid hyperplasia
- Continued secretion of mucus leads to ↑ pressure (up to 126 cmH_2O within 14 hours) → gangrene & perforation
- The area of the appendix with the poorest blood supply is mid-portion of antimesenteric side, hence location of most frequent gangrene and perforation

Presentation of Appendicitis:
- Classically, abdominal pain begins in periumbilical region (somatic pain from appendiceal distention) → then localizes to site of appendix (e.g. RLQ) as visceral pain once the serosa is involved.
- Anorexia precedes pain
- Vomiting occurs in about 75% of patients and typically follows the onset of pain
- Hence: **anorexia → pain → vomiting** is observed ≈ 95% of time

Acute appendicitis is the most common cause of an acute abdomen in women after the first trimester of pregnancy; they may present with RUQ pain, especially during the last trimester; however, pregnancy does not ↑ risk per se. Immediate operation is warranted. A CT scan is safe during pregnancy.

Colorectal Disease

Colon:

- actively secretes K^+ and HCO_3
- absorbs Na^+ against both concentration and electrical gradients to avoid hyponatremia
- normally absorbs 1 – 2 L of H_2O/day; can absorb up to 5 – 6 L/day

Lower GI bleeding: diverticulosis + angiodysplasia = 90% of causes (for those >50)

Diverticulosis	**Vascular Ectasia**
▪ 50% right-sided ▪ ruptured vasa recta at neck of diverticula → **arterial bleeding**; severe ▪ 25 – 50% re-bleed rate ▪ most visualize on angiography	▪ virtually all right-sided ▪ **venous bleeding** ▪ 85% re-bleed rate ▪ only 8 – 10% extravasation on angiography

Angiography can detect bleeding rates as low as **1 – 5 mL/min** (in some series as low as 0.5 mL/min)
Tag RBC can detect bleeding rates as low as **0.5 – 1 mL/min** (in some series as low as 0.1 mL/min)
1st test to perform on LGIB (i.e. NG aspirate is bilious), after starting resuscitation, is <u>rigid proctoscopy</u>

Volvulus

Cecal (rare); also known as cecal bascule	**Sigmoid**
▪ presents with SBO ▪ young (25 – 35) ▪ OR (only 25% success with scope) → most do R hemi; but some attempt cecopexy	▪ present with colonic obstruction ▪ old, debilitated patients (nursing homes) ▪ 70% success with scope → tube decompression → bowel prep → sigmoid colectomy during that admission

Ulcerative Colitis:

- Limited to mucosa and submucosa
- 5 – 6% develop colorectal cancer; ↑ risk with disease duration, pancolitis, PSC
- Proctocolectomy does not help sclerosing cholangitis or arthritis, but may help skin manifestations
- 20% will require proctocolectomy

Ischemic colitis:

- A disease of small arterioles
- Can occur in any segment of colon, but most common in watershed areas, which rely on "Meandering" arteries, such as splenic flexure (Griffith's point) and distal sigmoid colon (Sudeck's point)
- See thumbprinting on bowel wall
- Dark discoloration on colonoscopy (black/green) is indication for surgical resection

Colorectal Cancer

- 120,000 – 140,000 new cases/year; 60,000 deaths/year in U.S.
- 3rd most common cancer in western society
- 2nd in deaths (to lung)
- 50% mortality
- 80% of patients present eligible for resection (i.e. 20% stage IV); 67% of these will recur; 80% of these recurrences will be intra-abdominal (liver #1)
- 5 cm gross margin for resection in colon; 1 cm distal mucosal margin (UNfixed) is adequate because rectal cancers recur based on radial spread, rather than longitudinal spread; need 3 – 5 cm of distal mesorectal margin, if possible

Staging

Tis: mucosa only
T1: into submucosa
T2: into muscularis propria
T3: into subserosa
T4: into adjacent structure (through serosa)

N0: no nodes
N1: 1 – 3 regional
N2: > 3 regional

Stage I: T1, T2, N0, M0
Stage IIA/B: T3 (A), T4 (B), N0, M0
Stage IIIA: T1-2, N1, M0
Stage IIIB: T3-4, N1, M0
Stage IIIC: any T, N2, M0
Stage IV: any T, any N, M1

Survival

1-year (all): 83%
10-year (all): 55%

5-year survival: I, II: 90%; III: 65%; IV: 9%

Treatment

- Stage I,II colon: Surgery alone (current trials looking into adjuvant chemo for II)
- Stage III colon: Surgery + Chemo (FL ± what other trials throw in)
- Stage II, III rectal: Surgery + Chemo/XRT (adjuvant)

With respect to **adjuvant vs. neoadjuvant XRT**, good evidence of down staging (e.g. to sphincter preserving operation) and decreased local recurrence rates, but no evidence of survival advantage, particularly in era of TME

- Stage IV: 5FU/Leukovorin (FL), Oxaliplatin, CPT-11(Irinotechan), Avastin; all combinations

In 2004: **IFL (Saltz regimen) + Avastin →** increased median survival to 20.3 months from 15.6 months (IFL alone); *BUT NO INCREASE IN 5-YEAR SURVIVAL* **(no regimen has impacted this in nearly 20 years)**

Post-Resection Follow-Up (Debatable)

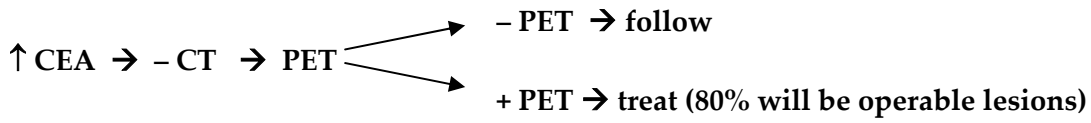
*CEA	q3 months
*colonoscopy	q1 – 3 years
Serial CT	q6 months
Liver enzymes	q2 – 3 months (**LDH** is most important)
CXR	q6 months

*most agree on

Rising CEA (happens in 70% of recurrences)

CT will miss nearly 40% of recurrences, and 60 – 90% of these missed lesions will be intra-abdominal
FDG-PET is 89% sensitive when other modalities are negative, so algorithm is:

Rising CEA → negative CT → PET; if negative, follow; if positive treat accordingly (80% of these will be operable lesions) [Libutti SK, et al. Ann Surg Oncol. 2001 8:779]



Liver Resection For Colorectal Metastases ["Fong score"]:

Prognostic Factor	***p*-value (for predictor of survival)**
Dx-free interval	0.002
Tumors > 3	0.01
CEA > 200	0.05
Size > 5 cm	0.01
Node+ primary	0.05

[Fong Y, et al. Ann Surg. 1999;230:309]

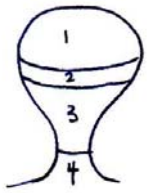
Survival based on criteria

#factors	**5-year survival (%)**	**OS (months)**
0	57	74
1	57	73
2	47	50
3	16	30
4	8	15

Colorectal Polyps

- Classified as Neoplastic (adenoma) or Non-neoplastic (hyperplastic, hamartomatous, inflammatory)
- (Adenoma) Classified histologically as **tubular** (65 – 80%), **villous** (5 – 10%), or **tubulovillous** (10 – 25%). As poly size INCREASES, so too does frequency of VILLOUS histology.
- Approximately 5 – 8% of adenomas have severe dysplasia, and 3 – 5% have invasive cancer at the time of diagnosis
- Risk of cancer at time of diagnosis: **tubular (5%), tubulovillous (22%), villous (40%)**.
  For < 1 cm, risk very low, for > 2 cm approaches 50%
- All polyps detected should be removed endoscopically, although this is controversial for polyps < 5 mm, which should, at the least, be biopsied.
- Pedunculated polyps should be removed via colonoscopy, but this is difficult for large sessile polyps (> 2 cm), which harbor high malignant potential. Alternatively, multiple biopsies taken, and the area is marked with ink tattoo.

- For malignant pedunculated polyps, if there is lymphovascular invasion, poor differentiation, or cancer within 2 mm of resection margin, colon resection is indicated. Sessile polyps with invasive cancer require formal colon resection.



Haggitt Level
Well-differentiated adenocarcinoma in zone 1, 2, or 3 → polypectomy; zone 4 → formal resection
Poorly differentiated in zone 1 → polypectomy; zone 2, 3, or 4 → formal resection

Gardner's syndrome: (FAP) polyposis, desmoid tumors, osteomas
Turcot's syndrome: polyposis and brain tumors
Peutz Jeghers syndrome: polyposis and mucocutaneous pigmentation
Muir-Torre syndrome: polyposis and skin cancer
*Note: the above do not have to be colorectal cancer

HNPCC (Hereditary Nonpolyposis Colorectal Cancer)

- AD inheritance
- Accounts for 2 – 6% of all colorectal cancer
- Average age of CRC development 40 – 45
- Begin colonoscopy at 25
- 60% by 60 years old; lifetime risk 80%
- **Germline mutation in mismatch repair (MMR) genes** + somatic mutation in wildtype allele produces a Micro Satellite Instability (MSI)
- 2 genes account for 90% of mutations (hMSH2 and hMLH1)
- Predominance of R-sided cancer (60 – 70% in right/transverse colon)
- Increased synchronous and metachronous CRC
- "Lynch Syndrome I" CRC only
- "Lynch Syndrome II" CRC + other cancer (endometrial, ovarian, stomach, small bowel, UGI)
- Follows the adenoma-carcinoma sequence, just does so quicker
- Fare better than staged-matched non-HNPCC with CRC (i.e. the cancer is less aggressive)

Surgical Treatment
- Total abdominal colectomy with ileorectal anastomosis recommended for Amsterdam + patients with CRC or MMR carriers
- Prophylactic TAC + IRA as alternative for MMR carries with adenomas or patients with difficult to follow colons

Revised Amsterdam Criteria (II)

1. HNPCC-associated caner in 3 relatives, one a first degree of the other two
2. At least 2 successive generations affected
3. At least 1 diagnosed < 50
4. FAP excluded

FAP (Familial Adenomatous Polyposis)

- AD, 100% penetrant
- Mutation is in **Adenomatous Polyposis Coli (APC) gene**, localized to **5q21**
- Normal APC protein is localized to basolateral membrane
- Truncated, inactive APC appears to allow beta-catenin accumulation in the cell and nucleus, where it turns on genes and stimulates cell growth
- 80% familial, but 10 – 30% cases are new mutations
- Accounts for < 1% of colorectal cancer
- Extraintestinal manifestations: desmoid tumors, osteomas, sebaceous cysts (Gardner's); with brain tumors (Turcot's), CHRPE (hyperplastic retinal complication → blindness)

*Most common extracolonic manifestation is periampullary duodenal malignancy (also pancreatic, biliary, gastric, small intestinal, thyroid)

Desmoid tumors appear in 10% of carries by age 30

<u>Most common genetic alterations</u>:
p53: ch17; most common (≈ 85%), *tumor suppressor*
APC gene: ch5; sporadic & familial (35 & 75%, respectively); *tumor suppressor*
DCC: ch18; 70% cancers/10% adenoma, *tumor suppressor*
K-ras: ch12; 50% cancers; *oncogene*

Summary:

Genetic Pattern	% of Colorectal Cancer	Clinical Features
LOH (loss of heterozygosity)	**60 – 85%**	
1. **Sporadic**	35%	**Distal tumors** (70%); no FH of polyps/CRC; aneuploid DNA; age > 60
2. **Familial**	25%	**Distal tumors**; FH of polyps/CRC in several relatives; aneuploid DNA; age 50 – 60
3. **Inherited (polyposis)**	1 – 3 %	> 100 polyps; early onset disease; mutation of **APC**
▪ **FAP**		-Upper GI polyps and CRC; retinal findings
▪ **Gardner's**		-Desmoid tumors and bone abnormalities
▪ **Turcot's**		-Medulloblastoma
RER (replication error pathway – DNA repair mismatch)	**20 – 35%**	
1. **Sporadic**	20%	**Proximal tumors** (70%); diploid DNA; **better prognosis than LOH**; age > 60
2. **Familial**	≈6%	**Proximal tumors**; diploid DNA; FH of polyps/CRC; age 50 – 60
3. **Inherited**	≈10%	
▪ **Lynch I**		CRC only; **proximal tumors** (70%); 40% with synchronous/ metachronous CRC; age 40 – 45
▪ **Lynch II**		Lynch I + cancers of endometrium, ovaries, pancreas, stomach, small bowel, urinary tract, bile ducts

Rectal Cancer

3 approaches for local excision:

1. Transanal
2. Transsacral (Kraske's procedure)‡
3. Transsphincteric*

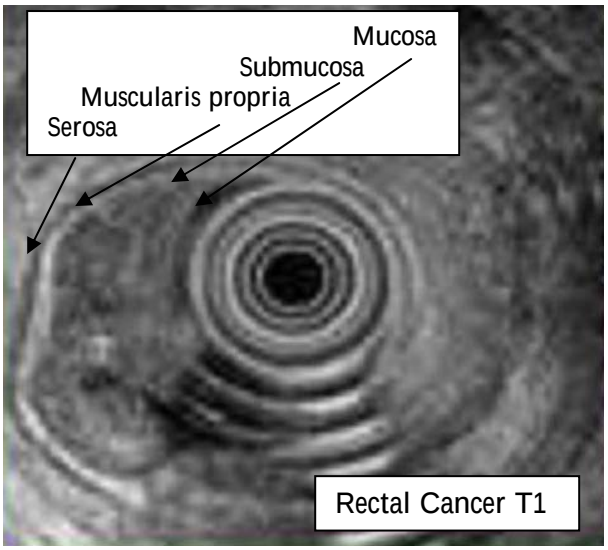
‡Unacceptable rates of perineal fistula, not preferred
*Transsphincteric leads to unacceptably high rates of fecal incontinence, not preferred

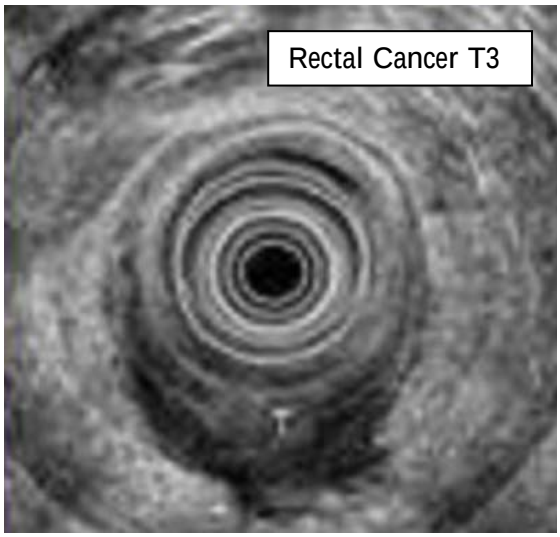
Transanal excision is reserved for tumors less than 8 cm anterior and 10 cm posterior from the anal verge, not involving sphincters (also less than 4 cm in diameter and occupying less than 40% of rectal circumference)

Preoperative staging is important: patients with evidence of transmural (e.g. tethered lesion on physical exam) or regional LN involvement are not candidates for local excision (unless considered medically unfit for major resection)

Evaluation of rectal cancer with Endorectal U/S:

[Figures taken from talk given by J Douglas, 2005]





Three prospective studies [Ota 1992, Bleday 1997, Steele 1999] asked questions of adequacy of local excision ± adjuvant treatment.

Conclusions:

1. Patients with nodal involvement need TME
2. T1 lesions are best candidates for local resection
3. T3 and T4 have high probability of nodal involvement and should have TME
4. T2 lesion can be managed with TME (gold standard), but local excision + adjuvant chemoradiation achieves similar survival rates, but may have higher local recurrence rates (however, can often be salvaged by TME)

- Postop XRT alone ↓ locoregional recurrence, but no impact on survival
- **Postop XRT + chemo ↓ locoregional recurrence AND ↑ survival**
- Preop XRT alone ↓ locoregional recurrence
- Preop XRT + chemo downstages and improves respectability and ↓ locoregional recurrence

Table 2. ACTUARIAL RATES OF LOCAL RECURRENCE (LR), OVERALL RECURRENCE (OR), AND SURVIVAL

			5-Year Actuarial (%)			10-Year Actuarial (%)		
Stage	RT	n	LR	OR	Survival	LR	OR	Survival
T1	–	67	14	19	92	17	24	74
	+	7	17	43	71	17	43	71
T2	–	27	28	37	87	28	37	75
	+	24	24	35	74	24	35	68
All		125	18	27	86	20	30	73

RT, radiotherapy.

[Paty PB, et al. Ann Surg. 2002;236:522]

As with colon cancer must do full colonoscopy, prior to surgery, to look for synchronous lesion (4% chance)

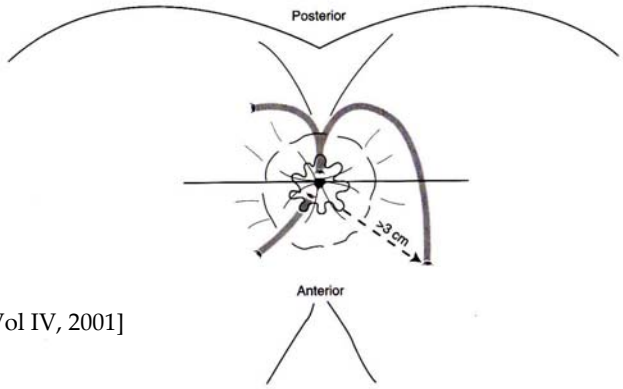
Squamous cell cancer of anal canal:

- Treat with modified *Nigro protocol*: 5FU+mitomycin & XRT (50.4 Gr), including patients with positive inguinal nodes; not surgery (80 – 85% cure rate) → APR for recurrent disease (although up to 50% response to cisplatin in this setting of recurrence)
- Risk of metastatic disease rises, and survival rates fall as **tumor size > 2 cm**

Pouchitis: Nonspecific inflammation of ileal reservoir following ileal pouch/anal anastomosis; occurs in 5 – 40%; usually respond to oral flagyl; chronic problem in 15% of patients

Fissure in Ano: 10% anterior in women; nearly all posterior midline (90% *below* dentate line)
*if fissure not in midline → think of IBD, TB, syphilis, HIV, Herpes, cancer

Goodsall's rule: if the external opening of the fistula is anterior to an imaginary line drawn between the ischial tuberosities → the fistula usually runs directly into the anal canal; if it is posterior → the tract curves to the posterior midline; if > 3 cm from anus → can go either way



[Surgery of the Alimentary Tract, Vol IV, 2001]

Hemorrhoids
External: dilated veins of inferior hemorrhoidal plexus; covered with anoderm (below dentate line); do not band
Internal: exaggerated submucosal vascular cushions, normally located above dentate line, hence covered in mucous membrane of anal canal, not anoderm; can band
When **thrombosed** → best treated by incising the overlying anoderm in an elliptical fashion and evacuating the thrombus
Medical Treatment: bulk agents, stool softeners, local agents (e.g. NTG)

Pediatric Surgery

Gastroschisis

Incidence: 1:10,000 to 1:15,000 (and increasing)

Embryology: Mesodermal and ectodermal defects caused by ischemia resulting from premature involution of the right umbilical vein (this is supposed to happen 6 – 7 weeks *post-conception*) or a vascular accident involving the right omphalomesenteric artery.

Anatomy:

- Full thickness defect of abdominal wall **to the right of the umbilical cord**; umbilical cord has a normal insertion
- Herniation of bowel loops (uncommonly liver): **organs are not covered by a membrane**
- Meconium stained amniotic fluid common, and may be secondary to intestinal irritation

Associated anomalies (5 – 10%): Not associated with chromosomal abnormalities. Ileal/jejunal atresia is most common associated defect; cardiac anomalies are rare

Outcomes: Mortality ranges from 7 – 25%; if liver herniates → mortality increases to 50%:

Management: Vaginal delivery at term, at tertiary care facility. Caesarean may be indicated if liver herniation is present. Primary closure is obtainable in 90% of cases; silo placement and staged reduction necessary in the remaining 10%

Omphalocele

Incidence: 1:5000 to 1:6000 (and decreasing)

Embryology: Improper migration and fusion of lateral embryonic folds. Can be cephalic, caudal, or lateral. Failure of **lateral folds** to fuse results in isolated **omphalocele**; failure of **cephalic folds** results in defects seen in **Pentalogy of Cantrell**.

Anatomy:

- Herniation of the intra-abdominal contents into the base of the umbilical cord.
- Contents are covered with an amnio-peritoneal membrane. Defect is **midline**.
- Bowel, stomach, and liver most frequently herniated; a membrane made up of peritoneum and amnion covers the herniated organs.
- The umbilical cord inserts into the sac.

Associated Anomalies (40 – 60%): Can be seen with chromosomal abnormalities (including trisomy 18, trisomy 13). Also seen as part of *Pentalogy of Cantrell* and *Beckwith-Weidemann syndrome* (see below). Other anomalies seen occur with the following frequencies:

Cardiac defects: 50% (Overall, **VSD** is most common defect seen with omphalocele)

GU anomalies: 40%

IUGR reported in 20% of cases

Beckwith-Weidemann: macroglossia, viceromegaly, hypoglycemia, macrosomia

Pentalogy of Cantrell: 1. Cardiac defects, 2. Diaphragmatic defects (2 specific), 3. Sternal defect, 4. Abdominal wall (midline, supraumbilical) defect, and 5. Ectopic cordis

Outcome: overall mortality 40 – 80% (varies depending on presence of associated anomalies; cardiac abnormalities determine mortality to a large extent)

Management: Cardiac echo and karyotype indicated, as well as search for other anomalies. **Consideration of anomalies has priority unless sac has ruptured.**

Vaginal vs. C/S delivery controversial: important to diagnose potential anomalies that are incompatible with life. C/S for large lesions or lesions containing large portions of the liver seems prudent. Delivery at a tertiary care center needed.

Omphalocele	**Gastroschisis**
▪ midline defect ▪ has a peritoneal sac ▪ covered abdominal contents *within* umbilical cord ▪ 60% cardiac abnormalities ▪ pulmonary hypoplasia ▪ repair can be delayed	▪ defect to *right* of umbilical cord ▪ no sac ▪ few associated abnormalities ▪ 10% associated atresias ▪ immediate intervention required (closure can be delayed, but intervention must be immediate; Silo vs. closure)

Intestinal Atresia

Thought to result from in-utero vascular accidents; associated with maternal cocaine use
10% are multiple
Frequency: generally proximal → distal, although most common is a single jejunoileal atresia
Short bowel most likely to result from jejunal atresia (Type III)
Trisomy 21 most likely associated with duodenal atresia, usually in 2nd portion distal to ampulla (treat with duodenoduodenostomy, not duodenojejunostomy)

Congenital cystic adenomatoid malformation of the lung (CCAM)

Lobar hamartoma; overgrowth of terminal bronchioles
Rare; No sex predilection, usually unilateral. Not associated with other anomalies.

Types: Macrocystic: > 5 mm cyst
Microcystic: < 5 mm cyst or solid; poorer prognosis, more likely to be complicated by hydrops.

Type I macrocystic, generally > 2 cm
Type II microcystic, areas of uninvolved lung
Type III involves entire lobe, no cystic spaces (all solid)

Complications:

- Hydrops: vascular compression by tumor decreases venous return and myocardial contractility
- Polyhydramnios: caused by esophageal compression
- Pulmonary hypoplasia and pulmonary hypertension: compression of otherwise normal lung tissue by tumor (can result in acute respiratory failure)
- Diagnosis is made by U/S findings of non pulsatile intra-thoracic lung mass; resection timing depends on symptoms
- 15% will regress spontaneously

Pulmonary Sequestration

Distinguish between intra- and extralobar (same arteries in, different veins out):

Intralobar: aorta in, *pulmonary veins* out; much more common than extralobar → segmentectomy/lobectomy

Extralobar: aorta in, *systemic veins (azygous, hemiazygous)* out; no bronchial connection; distinct and separate pleural investment (often asymptomatic); resect if symptomatic

Both present with respiratory *infection*, not distress; clue is *low* position of abscesses (vs. upper segments of lower lobes)

Congenital Lobar Emphysema
Massive hyperinflation of a single lobe of lung; usually upper/middle (LUL > RML >> RUL > lower lobes)
⅓ - ½ have respiratory distress at birth; rare presentation after 6 months of age
M:F ratio is 2:1
10% have severe symptoms → lobectomy

Malrotation: Lig Treitz is to **right of vertebral column**; duodenum has a corkscrew configuration (on UGI)

- Ladd's bands (adhesions from R colon to R pericolic gutter) contribute to duodenal obstruction. They are remnants of the RP attachments that would normally secure R colon.
- Most children with malrotation present within first year of life
- **Sudden appearance of bilious vomiting is malrotation until proven otherwise**
- May or may not have abdominal pain/tenderness
- Gold standard for diagnosis is UGI
- If malrotation *with volvulus* or if sick → to OR
- If asymptomatic and no volvulus → elective Ladd's procedure

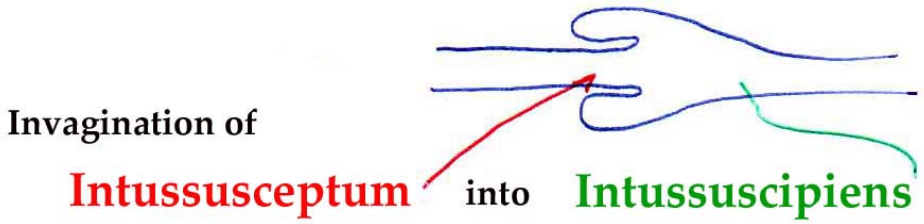
Operation: **counterclockwise** rotation of volvulus; mobilize duodenum → lyse Ladd's bands → widen mesenteric base → rule out obstruction → appendectomy (since cecum no longer in RLQ) → small bowel to right/colon to left (*create* non-rotation)

NEC: Most common surgical emergency in NICU (1 – 7% of NICU admissions)

- Those < 2 kg make up 80% of cases; primarily a disease of premature newborns (30 – 32 weeks)
- can involve any part; most common is SMA watershed area (distal ileum/cecum)
- Risk factors: low birth weight; prematurity; maternal cocaine; indomethacin (for PDA); enteral feeding (formula vs. breast), asphyxia, exchange transfusions, anemia, umbilical arterial/venous catheterization
- Presentation: toxic ↓ platelet count; pneumatosis on AXR (absent in 20%)

*AVOID contrast studies
Surgery indicated for perforation, +paracentesis, clinical deterioration, persistent loop (some have also advocated for PV gas)

Intussusception: frequent cause of bowel obstruction



- 90% in 3 months – 3 years old
- ≈10% have anatomic lead point (hypertrophied lymphoid tissue, polyp, Meckel's, submucosal hemorrhage)
- U/S in noninvasive procedure of choice; can show "pseudokidney" = "target sign"
- Success of air contrast enema in uncomplicated cases ≈ 50 – 90%; can reduce with column up to 80 cmH_2O
- OR: *right transverse supraumbilical incision*
- **Reduce**: proximal milking (NEVER pull intussuceptum out)

Imperforate Anus (Anorectal Malformation – ARM)

Low ARM: may present late; do not require colostomy; dilations first → then anoplasty or limited posterior sagittal anorecto plasty (**PSARP**)

High ARM: fistula to urethra, bladder neck, vagina, or cloaca (common opening)

- Require colostomy (usually a 2-stage procedure)
- PSARP

- Renal abnormalities most common
- May be part of the **VACTERL** syndrome: **V**ertebral anomalies, imperforate **A**nus, **C**ardiac abnormalities, **T**E fistula, **E**sophageal atresia, **R**enal anomalies, and **L**imb abnormalities)

Meckel's Diverticulum: true diverticula; outpouching on antimesenteric side of small bowel

Rule of 2's:

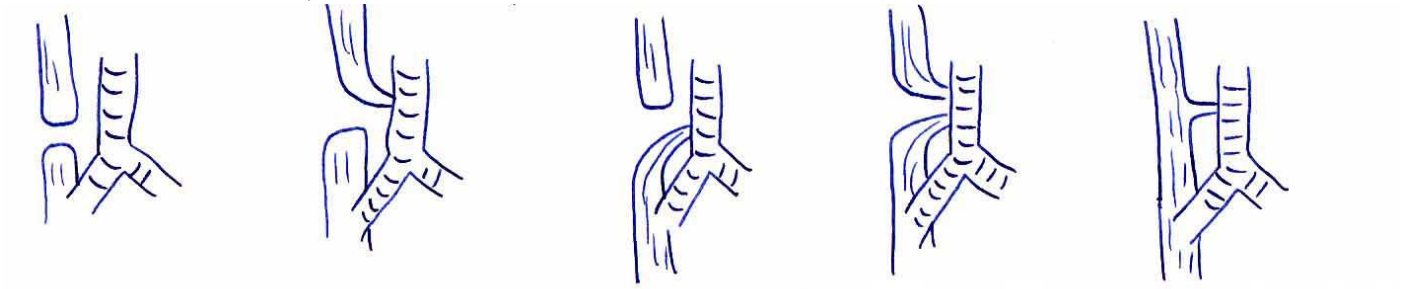
2% of population
2% symptomatic
< 2 feet from ileocecal valve
2 inches long
2 presentations (bleeding and obstruction)
2 types of (heterotopic) mucosa: gastric & pancreatic
Most commonly presents in < 2-years-olds

Biliary Atresia

- hepatic U/S and HIDA to diagnose **early**
- rule out choledochal cyst, giant cell hepatitis, duct hypoplasia
- initial goal of surgery is to confirm diagnosis; if GB identified → perform cholangiogram
- hepatoportoenterostomy (Kasai procedure) for bile drainage most successful if done before **2 months of age** (success much less if child > 3-months-old; ⅓ drain well, ⅓ drain ok, ⅓ no drainage)
- if Kasai failed (poor biliary drainage), late diagnosis, progressive liver failure → require transplant

Tracheoesophageal Fistula (have associated VACTERL syndrome)

Incidence: 1:3000 – 4000; 30% have cardiac abnormalities → ECHO first



Type A: Gastrostomy tube and growth before repair; NGT to drain proximally

Type C: Repair is dependant on health and size of infant; if healthy + > 2500 gm → primary repair;
If not → ligate fistula, gastrostomy, drainage of blind pouch, delayed repair

Type D: Bronchoscopy to confirm presence of 1 or 2 fistula; repair via **right** thoracotomy

Type E: Presents later (weeks) → H is usually high → repair through **neck** incision

Place upright, place NGT for suction, NPO, avoid vigorous bagging, check CXR for tube curl, ECHO

Pyloric Stenosis

- Present in 3/1000 live births
- Most common cause of surgically correctable vomiting in newborn
- Presents with non-bilious, often projectile, vomiting, usually by 3 – 6 weeks of age; 4:1 M:F
- Physical exam reveals "olive" about 90% of the time
- Exam is sufficient to diagnose; UGI if no palpable olive
- Treatment is Ramstedt pyloromyotomy, but not emergently (fix electrolytes first, fluid balance)
- Associated malformations: malrotation, hepatic glucuronyl transferase ability (jaundice)

Congenital Diaphragmatic Hernia

- **Bochdaleck** (posterolateral-usually left) and **Morgagni** (anteriomedial)
- present shortly after birth (may have few normal hours)
- CXR shows loops of bowel and/or stomach in chest
- **Resuscitation/stabilization** is priority over timing of surgery (including ECMO)
- as in adults, repair is via abdomen

Hirschsprung's Disease

- More common in males (70 – 80%)
- Lack of ganglion cells from rectum to stomach (although rare proximal to colon)
- Rectosigmoid is most common location
- Diagnose with **BE** (look for sigmoid/rectum ratio > 1), **suction rectal biopsy (definitive)**
- Treat with resection and pull-through (1-stage vs. 2-stage); 1-stage associated with ↓ anastomotic disruption

Management of **undescended testicle**: may occur spontaneously during first year of life; if not → orchiopexy by 1 year of age (↑risk of infertility, but not risk of cancer: risk 1/4000, i.e. 40-fold increase)

Umbilical hernia: no urgent need for repair, unless very large; if not spontaneously closed when school age → elective repair

Inguinal hernia: repair is most common general surgical procedure performed on infants; M > F (3:1), R>L; all should be repaired at the time of diagnosis; bilateral repair is performed by some up to age 5

Pediatric malignancy

- #1 overall is **leukemia**, #2 is **CNS** (=#1 solid tumor), #3 is **neuroblastoma**
- #1 solid organ tumor (excluding intracranial) is **neuroblastoma**; 90% have ↑ VMA; ↑ HVA → worse prognosis; cells derived from neural crest and may arise anywhere along sympathetic ganglia (adrenal medulla is most common location); 30% cure; associated with N-myc
- Location: 75% adrenal, 20% posterior mediastinum, 4% organ of Zuckerkandel, 1% cervical
- Favorable prognosis: age < 1 year; stage 1, 2, or 4S, low tumor markers, normal N-myc, DNA index > 1.0
- **Wilm's tumor ≡ nephroblastoma** (most common in children > 2-years-old) → 80% cured with nephrectomy; chemo regimen is vincristine, D-actinomycin and doxorubicin (≥ stage III)
- **Hepatoblastoma** is most common liver tumor in children; ↑ AFP often; if ↑ β-HCG → can result in precocious puberty; surgical resection is treatment

Spleen and Splenectomy

Functions:

- Filter abnormal RBCs, store platelets, produce Tuftsin and Properdin (opsins), produce Ab (esp. IgM), site of phagocytosis (Does not store RBCs)
- White pulp: lymphatic
- Red pulp: phagocytic

Blood Supply: splenic artery and short gastric veins (gastroepiploic)
Drainage: splenic vein and short gastric veins (gastroepiploic)
15 – 20% of people have accessory spleens
Spleen is approximately 1% of total body weight → receives 5 – 10% of cardiac output

Most common cause of splenic vein thrombosis: Pancreatitis
Patients with Ulcerative Colitis develop hyposplenism

Definition of Hypersplenism:
Hyperfunctioning spleen, loss of blood elements, large spleen (splenomegaly), hyperactive bone marrow trying to keep up with loss of blood elements; splenic cellular sequestration
Primary: A diagnosis of exclusion → will respond to splenectomy
Secondary: e.g. Result of hepatic disease → no splenectomy

⅓ of total body platelets are stored in spleen

"Delayed Splenic Rupture": A subcapsular hematoma may rupture at a later time after blunt trauma up to 2 weeks later. Present with shock ± abdominal pain

Signs/Sx of Rupture:
Hemoperitoneum and Kehr's Sign (referred pain to tip of left shoulder), LUQ pain and mass (Ballance's Sign)

Diagnosis:
Abdominal CT if stable;
U/S → ex lap if unstable

Treatment:
Nonoperative if: stable, isolated injury without hilar involvement or complete rupture
If unstable: splenectomy or splenorrhaphy (salvage operation with wrapping vicral mesh and topical hemostat agents/ partial splenectomy)

Indications for splenectomy:
Hyperslenism, Gaucher's disease, splenic vein thrombosis, sickle cell disease, thrombocytopenia via drug abuse, sphereocytosis, lymphoma (esp. Hodgkin's), ITP, TTP, splenic tumors/trauma, Felty's syndrome, lymphroproliferative disorders (NHL, CLL), Hairy Cell leukemia, Thal major, **not** G-6-PD Deficiency

- **ITP**: (Immune)
  - Autoimmune (usually anti-platelet Ab) → platelet destruction leading to bleeding and purpura
  - Spontaneous remission occurs in most children; only 25% of adults
  - Splenomegaly is rare
  - #1 cause of failed procedure is missed accessory spleen
- Erythrocytes Membrane Abnormalities
  - **Hereditary spherocytosis**: abnormality of spectrin → ↑ osmotic fragility → splenectomy is only effective therapy. Most common indication for splenectomy in US (non-trauma)
- Red Cell Enzyme Defects
  - **G-6-PD deficiency**: most common enzymatic abnormality of RBC; most patients require no treatment, but some variants improve with splenectomy

Autoimmune Hemolytic Anemia (AIHA):
If secondary to IgG antibodies ("warm" antibody type) → may respond to splenectomy;
But if IgM mediated (cold agglutinin disease) → liver is sight of RBC sequestration → no splenectomy

Treatment of choice for TTP (Thrombotic): Plasmapheresis, steroids (splenectomy as last resort);
TTP is a disease characterized by occlusion of arterioles and capillaries by hyaline deposits composed of aggregated platelets and fibrin

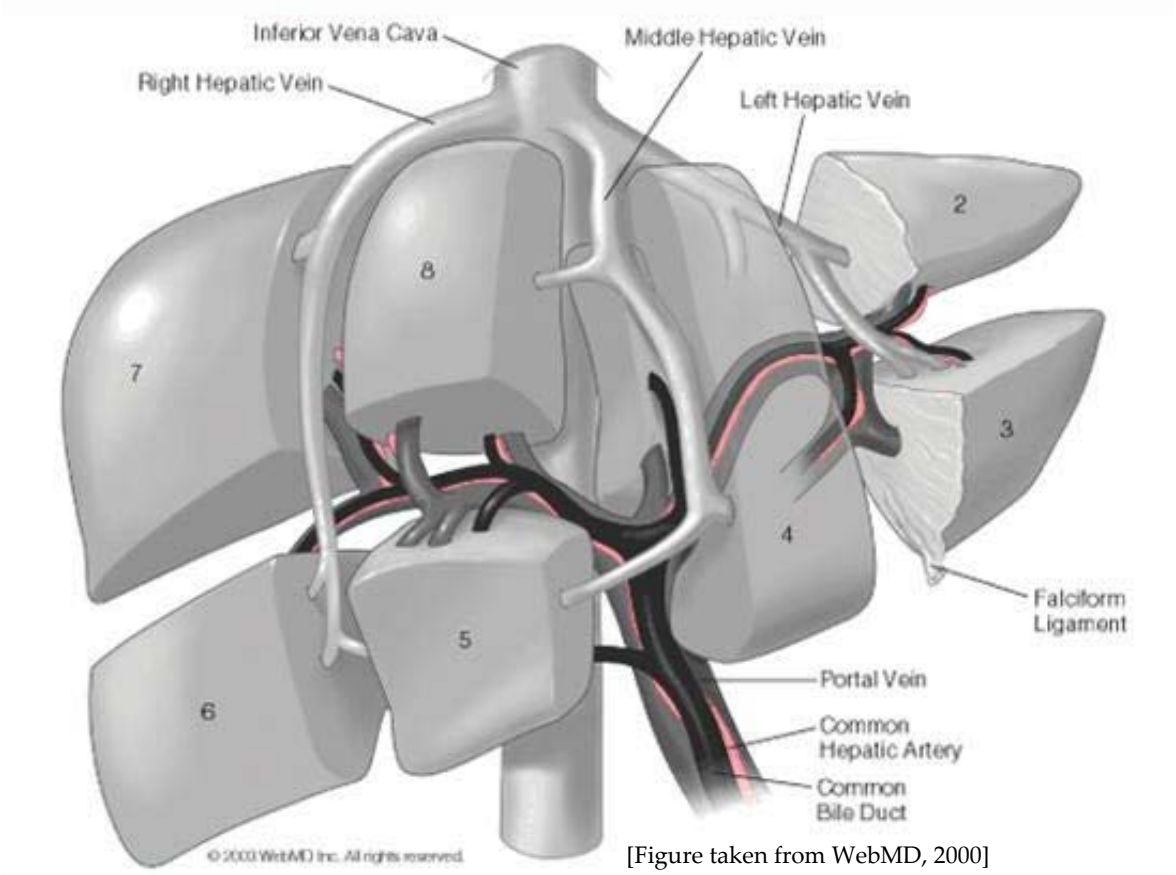
Lab tests following splenectomy: 50% increase in WBC, marked thrombocytosis, Howell-Jolly bodies in peripheral smear (failure to see HJ bodies following splenectomy → missed accessory spleen)

Possible complications:
Thrombocytosis (treat with ASA if platelets > 1 million), subphrenic abscess, gastric dilation, **O**verwhelming **P**ost**S**plenectomy **S**epsis (OPSS)

OPSS:
- < 1% in adults, more common in children (both incidence and mortality)
- More common following splenectomy for hematologic disease (vs. trauma)
- Strep pneumo, Meningococcus, HIB, E.coli
- Vaccinate preop if possible (Pneumcoccus, Meningococcus, HIB)
- Aggressive treatment with PCN for all minor infections

Most common arterial variations:
1. Left hepatic artery arises in part or completely from left gastric artery (23%)
2. Right hepatic artery arises in part or completely from SMA and passes behind head of pancreas (25%)
Practical point: The RHA (or accessory RHA) is the only structure to the right of the CBD

- Anatomically, the liver is divided into **sectors** by the RHV, MHV (80% joins LHV; 20% into IVC directly), and Falciform ligament
- Each sector is subdivided into **segments** by the portal triad (above vs. below); each **segment** has its own portal pedicle
- Right portal vein branches before the left; and left PV rises (i.e. seen on higher cuts on CT)
- On U/S, portal veins have prominent *hyper*echoic walls because of the accompanying intrahepatic Glissonian sheath
- Hepatic veins appear "wall-less"



[Figure taken from WebMD, 2000]

Flow towards liver is termed hepatopedal; Flow away from the liver is termed hepatofugal

Hepatic Abscess
-usually in right lobe

Pyogenic	**Amebic**
▪ entry via biliary tree or portal vein ▪ Rx: drainage ▪ grows E.coli, bacteroides, strep	▪ entry via portal vein ▪ Abx only (flagyl) ▪ culture usually sterile

Hydatid cyst ≡ Echinococcal cyst: + casoni skin test, + indirect hemaglutination; appears as calcified cystic lesion containing many cysts → **resect** (pericystectomy)

Benign Liver Tumors

	Hemangioma	Hepatic Adenoma	Focal Nodular Hyperplasia
History	Often asymptomatic, symptoms if large*; most common	**OC use**; often symptomatic; bleeding or rupture	OC use (less association than adenoma); usually asymptomatic; 2nd most common
CT findings	Peripheral enhancement and delayed central pooling	Hypodense, heterogeneous mass; arterial enhancement	Central "scar", which enhances
MRI findings	T1: hypointense T2: extremely hyperintense	T1: hypointense T2: hyperintense	T1: isointense T2: hyperintense + central scar
RBC scan findings	Pooling on delayed images	No change	No change
Liver Scan	"cold" defect	"cold defect"	No defect; **sulfur-colloid taken up by Kupffer's cells** → lesion blends with surrounding parenchyma
Management	Asymptomatic → conservative + follow-up; Symptomatic → resect by enucleation	**Resect**; rupture or hemorrhage risk related to size; malignant potential	Conservative; Resect only if symptomatic or unclear diagnosis

* Kasabach Merrit syndrome: consumptive coagulopathy or CHF due to hemangioma

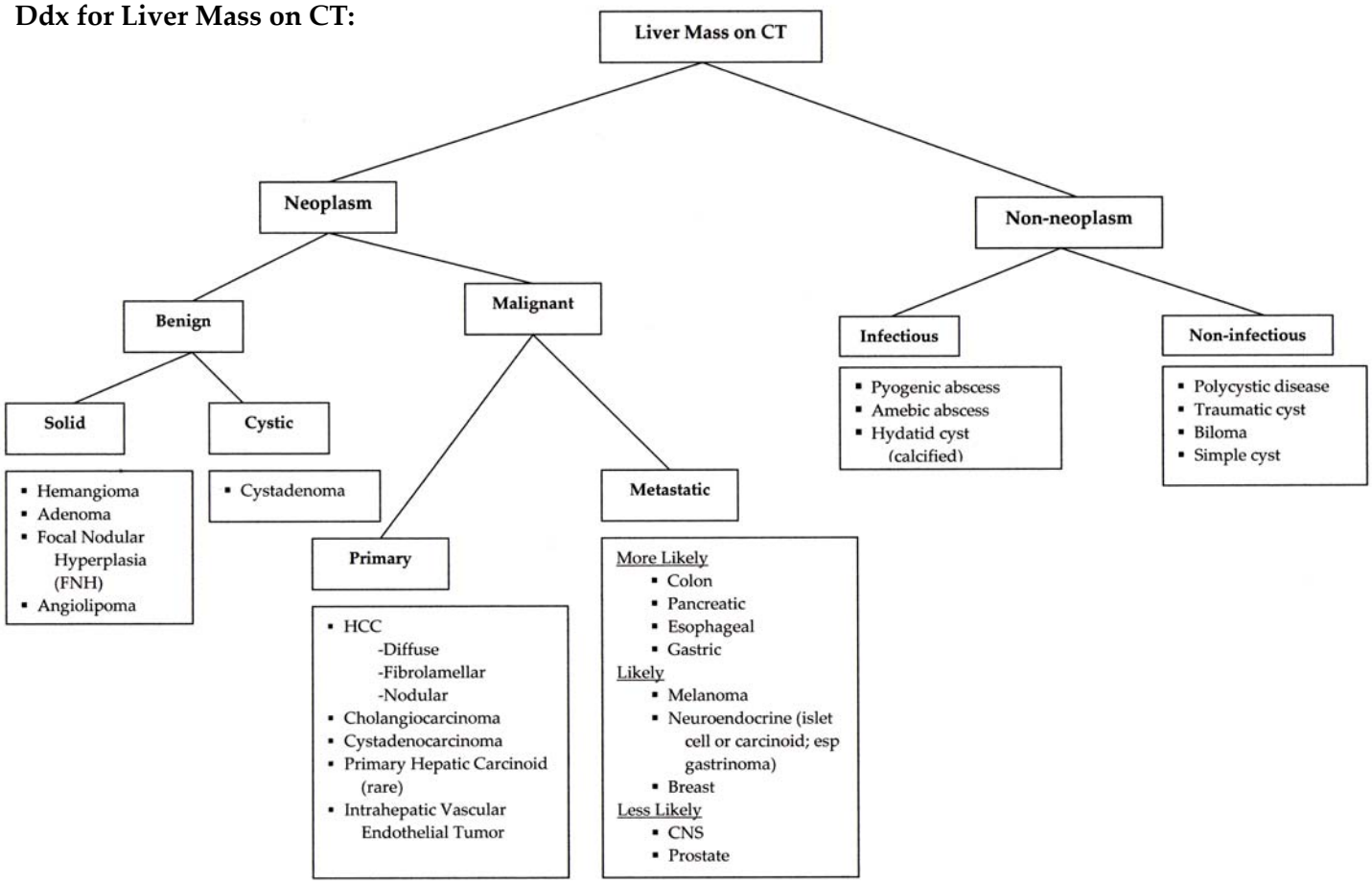
Hepatocellular Cancer

- 3rd highest cancer mortality worldwide (lung is 1st, stomach 2nd as of 2004)
- Risks: Hep B, Hep C, cirrhosis (ethanol, hemochromatosis, PSC, α-1-antitrypsin deficiency), aflatoxins, clonorchis sinensis (flukes)
- Serum AFP ↑ in 55 – 95%
- Size, stage, and histologic grade are important prognostic factors
- Blood supply mostly from hepatic artery → enhances arterial phase; iso/hypodense portal phase (can have central "scar")
- Resection if:
    - Single lesion < 5 cm; up to 3 lesions each < 3 cm
    - Okuda I, CLIP 0 – 1, BCLC 0 or A
    - Childs A and B (*not C*)
    - No portal hypertension (clinically or PVP > 10 mmHg)
    - Tumor recurrence occurs in 70% of cases at 5 years

- Transplant if:
    - Single lesion < 5 cm; up to 3 lesions each < 3 cm (Milan criteria)
    - Okuda I, CLIP 0 – 1, BCLC 0 or A
    - *Childs B or C* (*not A*)

- Fibrolamellar variant *may* have better prognosis

Ddx for Liver Mass on CT:



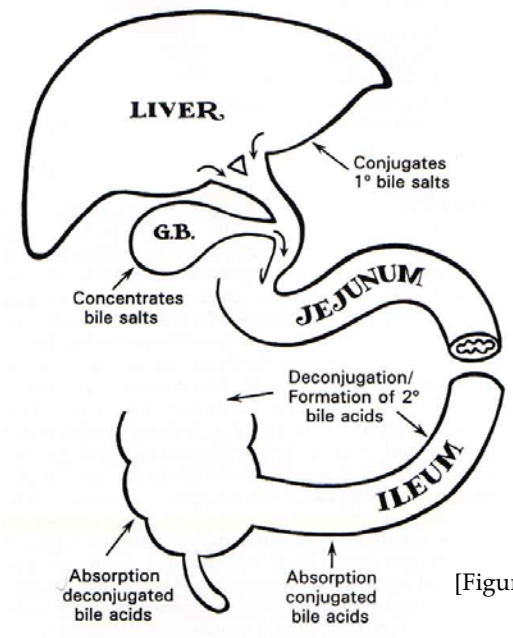
Biliary System:

Blood supply to supraduodenal bile duct arises from RHA and branches of GDA (retroduodenal artery) and lie longitudinally at the 3 and 9 o'clock positions

Bile is required for:
-vitamin D absorption
-bilirubin excretion
-cholesterol excretion (solublized in phospholipids vesicles)

- Stones associated with ileal disease/resection and TPN use are **pigmented stones**, not cholesterol stones (are composed of **calcium bilirubinate**)
- Primary common duct stones (those in duct > 2 years after cholecystectomy) are pigmented and related to biliary stasis and infection, not cholesterol
- **Natural History of Asymptomatic Gallstones**: Symptoms develop in about 1 – 3% of patients per year. Hence, observe asymptomatic stones.
- **Complicated gallstone disease** develops in about 3 – 5% of symptomatic patients per year.

Bile circulation:



[Figure taken from RUSH review of surgery, 2000]

- Hepatic synthesis = fecal losses = 300 – 600 mg/day
- In the presence of acute cholecystitis (calculous or acalculous) → ≈ all gallbladders fail to visualize following technetium-99m pertechnetate iminodiacetic acid (^{99m}Tc) administration, because of cystic duct obstruction (actual or functional)
- Between 8 and 18% of patients with *symptomatic* gallstones have choledocholithiasis
- Small CBD stones can be cleared by flushing the duct following **glucagon** administration (to relax sphincter)
- Acalculous cholecystitis results from gallbladder stasis → distention → ischemia
- Cholangitis: requires *both* bacteria in bile *and* stasis; common duct pressure > 20 cmH_2O

Preop ERCP should be performed if any of the following are present:

1. cholangitis
2. jaundice
3. stones seen on U/S
4. dilated CBD

IOC is not considered adequate unless the following are visualized:

1. Both right and left hepatic ducts (if not → be concerned about duct transaction)
2. CBD without filling defect
3. Free flow of contrast into duodenum (try glucagon if not seeing)

Gallbladder

- Concentrates bile by active absorption of Na^+, Cl^- (H_2O follows); cholecystectomy works by eliminating reservoir → forces a more continuous source of bile and eliminates chance for "sludge" and stone formation.
- 70% of patients with EF < 30% (normal is > 35%) on CCK-HIDA benefit from cholecystectomy, although this may still be controversial
- 10 – 20% of patients with symptomatic gallstones have choledocholithiasis
- By definitions: stones in CBD > 2 years after cholecystectomy are **primary CBD stones** (pigmented, related to biliary stasis and infection), rather than cholesterol stones; → need sphincterotomy and extraction
- Porcelain gallbladder has 30 – 65% risk of cancer → cholecystectomy indicated
- Gallbladder adenocarcinoma: 90% have stones. Cholecystectomy adequate if confined to mucosa; if grossly visible tumor → regional lymphadenectomy, wedge segment V, skeletonize portal triad
- Gallbladder polyps can be malignant; risk is related to size; hence, should remove GB for polyp is symptomatic or > 10 mm; sessile more likely to be malignant; pedunculated more likely benign

Diagnosis of Cholecystitis

Three most sensitive signs of cholecystitis:

1. Sonographic Murphy's sign
2. Wall thickening > 4 mm
3. Pericholecystic fluid

Postop lap chole patient not doing well, think:

- Viscous injury (e.g. duodenum)
- Duct injury
- Bile leak
- Retained CBD stone
- Cystic duct stump leak

Management of **gallstone ileus**:

1. Remove stone (via enterotomy proximal at site of obstruction)
2. Run entire bowel
3. In acute setting, especially elderly, reserve cholecystectomy for later (risk of recurrence ≈ 5 – 10%) & repair biliary-enteric fistula

Rates of Positive Bile Cultures

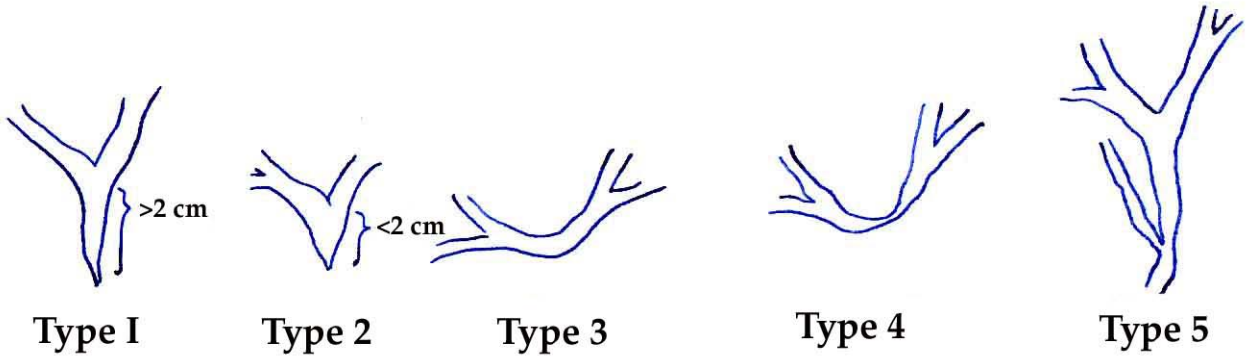
Bile cultures are positive in approximately:

1. 5 – 40% of chronic cholecystitis
2. 30 – 70% acute cholecystitis
3. 60 – 80% of choledocholithiasis
4. 25 – 30% of malignant obstruction
5. 100% of bile duct strictures

Acalculus cholecystitis (pathophysiology involves ischemia) most common in: cocaine use and HIV

Sclerosing cholangitis: ERCP to diagnose; multiple strictures/dilations ("beaded" appearance)

Bismuth classification system of bile duct injury:



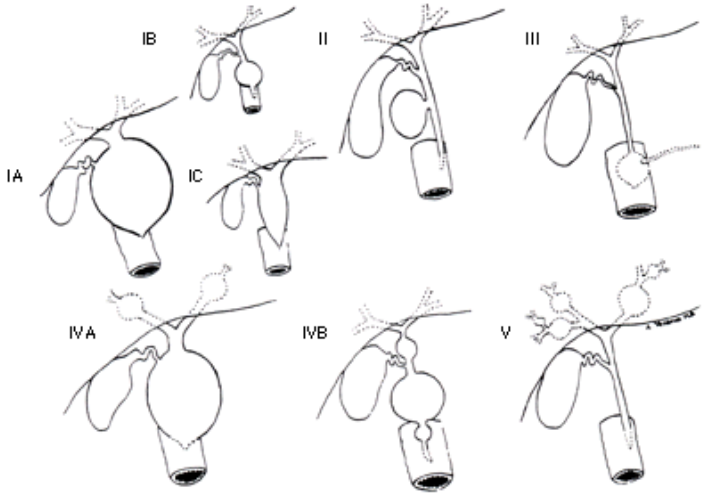
Note: Type 5 injury involves a separate inserting sectoral duct with or without injury of the common duct

Choledochal Cysts – Todani Class

*20-fold increase in bile duct malignancy if left untreated; F:M ≈ 4:1

I Solitary fusiform extrahepatic cyst (82%)
II Extrahepatic supraduodenal diverticulum "second gallbladder" (3%)
III Intraduodenal diverticulum, (choledochocele) (5%)
IVA Fusiform extrahepatic & intrahepatic cysts
IVB Multiple extrahepatic cysts (A+B = 9%)
V Multiple intrahepatic cysts, (Caroli's Disease) (<1%)

*Current theory is that cysts occur because of bile reflux, which results from an *abnormal junction of the biliary and pancreatic ducts*; in other words, the congenital aspect of the disease is the ductal abnormality → the cysts are a consequence of this



[Figure taken from www.uptodate.com]

Management:

I Complete cyst excision with hepaticojejunostomy
II Excision of cyst with primary choledochorrhaphy
III Large sphincteroplasty
IV & V Selective management with hepatic resection if localized bile duct cyst, extrahepatic cyst resection, hepaticojejunostomy with large stents, advanced biliary cirrhosis may require hepatic transplantation

Transport of Bilirubin

Bilirubin is synthesized in the RES from biliverdin. Insoluble unconjugated bilirubin, reversibly bound to albumin, is transported to the liver, and into cytoplasm of hepatocytes. The enzyme **uridine diphosphate-glucuronyl transferase** conjugates the bili with either one or two molecules of glucuronic acid to form water-soluble bilirubin mono- and diglucuronide. This is secreted into the bile canaliculus.

In the terminal ileum & colon, bilirubin is converted to urobilinogen, 10 – 20% of which is reabsorbed back into portal circulation

Bile is 80% bile salts, 15% lecithin, 5% cholesterol. Gallstones can be classified as **cholesterol stones**, **black stones**, and **brown stones**:

- **Cholesterol stones** form when bile becomes supersaturated with cholesterol
- **Black stones** form when bile becomes supersaturated with calcium salts (primarily calcium bilirubinate)
- **Brown stones** from when bile acquires stasis-induced bacterial contamination

GB concentrates bile by active reabsorption of Na^+, Cl^-; → H_2O then follows
Bile pool of 5 g is recirculated q4 hours → lose 0.5 g (10%) daily

Assessment of Jaundice

<u>Ask why?</u>

- Excess bili production?
- Deficient hepatocyte uptake?
- Deficient conjugation?
- Deficient hepatocyte secretion?
- Deficient bili secretion?

Grouped as prehepatic, hepatic, and posthepatic causes

Check fractionated bili levels

1. Predominance of unconjugated (indirect) suggests prehepatic etiology (hemolysis) or hepatic deficiencies of uptake or conjugation
2. Predominance of conjugated (direct) suggests defects in hepatocyte secretion into bile ducts or bile duct secretion into GI tract
3. Combined elevation suggests complex problem, usually acquired liver damage

Laboratory Investigation of Hyperbilirubinemia

Jaundice may result from overproduction of bilirubin (hemolysis), impaired conjugation (Gilbert's syndrome), impaired intracellular metabolism or excretion (drug effect), hepatocyte injury (hepatitis), bile duct injury (primary biliary and sclerosing cholangitis), and large duct obstruction (stone, tumor, sclerosing cholangitis)

First investigate by fractionation:

- **Unconjugated hyperbilirubinemia** (hemolysis, Gilbert's) is usually defined as levels greater than 80% of total bilirubin, which should RARELY exceed 5 mg/dL
- **Conjugated hyperbilirubinemia** (hepatocellular or bile duct disease) exists when the conjugated fraction exceeds 50% of the total level
- **Δ-bilirubin** is an irreversibly (covalently) albumin-bound form of bilirubin found in the setting of long-standing conjugated hyperbilirubinemia; not filtered through kidneys; $T_{1/2}$ = 18 days → reason for slow decline of TB following long-standing hyperbilirubinemia, especially in patients with renal failure
- In general, a bilirubin of 2 – 5 mg/dl, of which most is unconjugated, in an otherwise healthy adult is Gilbert's (2 – 5% of population), hemolysis, or both. The hemolytic component will be more likely LDH and AST (both in RBCs) are also mildly elevated

Alkaline phosphatase comes from liver and bone. Measurement of GGT (gamma-glutamyl transpeptidase) is often used to indicate the source of the AP. Normal GGT suggests non-hepatic source, such as osteoblastic bone lesions, or certain other tumors. Spurious elevations in AP may also be seen after albumin infusion if the albumin is derived from placental blood, which is rich in AP

Sphincter of Oddi

- Regulates flow of bile into duodenum
- Composed of 4 sphincters containing both circular and longitudinal smooth muscle
- Length is about 4 – 6 mm
- Basal (resting) pressure averages 13 mmHg (5 – 15)
- Undergoes phasic contractions with a frequency of 4/min; each with duration of 8 seconds
- Pressure increases to 130 ± 15 mmHg (50 – 150)
- Relaxation occurs with CCK stimulation and parasympathetic stimulation; glucagons (try IV glucagons to pass small stones)
- MSO_4, sympathetic stimulation increases sphincter tone

Portal Hypertension

Defined as PVP that exceeds normal value of 3 – 6 mmHg; either ↑resistance to flow (common) or ↑portal blood flow (uncommon); bleeding requires a pressure > 12 mmHg
Bleeding from ruptured gastroesophageal varices is responsible for greatest mortality and morbidity
May be classified as presinusoidal, sinusoidal, or postsinusoidal:

Presinusoidal‡	**Sinusoidal**	**Postsinusoidal**
Extrahepatic -Portal vein thrombosis (congenital atresia, pylephlebitis, hypercoagulable state, trauma, adjacent inflammation, mechanical obstruction-tumors/nodes) **Intrahepatic** -Schistosomiasis -congenital hepatic fibrosis -myeloprolifertiive disorders -PBC	-fatty metamorphosis -toxic hepatitis -Wilson's disease ***Cirrhosis**	**Extrahepatic** -Budd-Chiari (extrahepatic): congenital webs, compressive neoplasms, trauma -cardiac causes (constrictive pericarditis, CHF) **Intrahepatic** -Budd-Chiari (intrahepatic): veno-occlusive disease, hypercoagulable state

‡ Better prognosis than sinusoidal, postsinusoidal

* Overall most common cause

Also, high-flow portal hypertension resulting from:
-AV fistula (HA-PV, splenic, mesenteric)
-massive splenomegaly

Natural History

- ½ of patients with cirrhosis will develop varices → 20 – 33% will bleed
- with supportive management alone → 30% will re-bleed within 6 weeks and 70% within 1 year
- initial bleed is fatal in 30 – 50% of cirrhotic patients
- factors associated with bleeding: **large** (> small), **tortuosity**, **cherry red spot**, **presence of gastric varices**, **Child's class C** (vs. A, B)
- varices bleed by rupture rather than erosion
- portal-systemic shunts have been shown to have no role in prophylactic management on esophageal varices (but β-blockers do)
- Vasopressin + NTG >> Vasopressin alone [vasopressin causes splanchnic arteriolar vasoconstriction]
- **Octreotide** [50 mcg bolus followed by 50 mcg/hr x 48 – 72 hours] is best 1st treatment for bleeding varices and is as effective as sclerotherapy [Planas R, et al 1994 Hepatology 20:370]

Massive Upper GI Bleed:

All comers: 40% PUD, 18% gastritis, 13% esophageal varices, 9% Mallory-Weiss tear, 9% other
Known cirrhotic: 53% esophageal varices, 22% gastritis, 20% PUD

4 Main complications of cirrhosis

1. portal hypertension
2. ascites
3. hepatic encephalopathy
4. malignancy (primary hepatic)

SAAG (Serum-Ascites Albumin Gradient)

If > 1.1 gm/dL → indicates portal hypertension. Should be responsive to medical management consisting of sodium restriction (2000 mg/day) + oral diuretics (spironolactone + lasix)
Fluid restrict when Na^+ falls below 120 mmol/L

TIPS Indications

- Acute variceal hemorrhage is the most common indication for TIPS, followed by refractory ascites and hepatic hydrothorax.
- TIPS controls bleeding in 75% to 100% of patients; the efficacy is similar for both esophageal and gastric varices, and rebleeding does not usually recur unless there is shunt dysfunction. TIPS, however, may not eliminate isolated gastric varices in up to 50% of patients. When rebleeding occurs in spite of an open shunt, angiographic obliteration of the varices may arrest bleeding. Despite good results for control of bleeding, short-term mortality remains high in patients who have TIPS for variceal bleeding. As a result, better criteria for selection of patients have been sought.
- A recent study showed that patients could be stratified by 4 clinical variables before TIPS in order to predict survival after TIPS placement. Overall, all patients undergoing TIPS had a 19% 1-month and a 48% 1-year mortality. Of all variables available before TIPS the following:
    1. **variceal hemorrhage** requiring emergent TIPS,
    2. bilirubin > 3.0 mg/dL,
    3. alanine transaminase > 100 IU/L, and
    4. encephalopathy

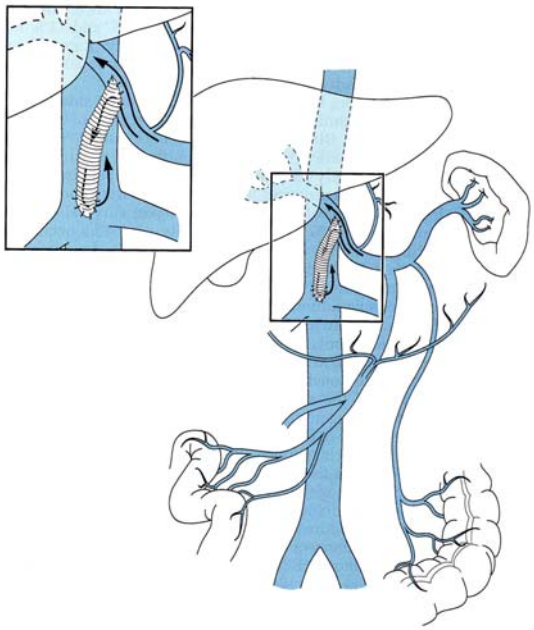
  were associated with a 90% mortality at 1 month. **Variceal hemorrhage requiring TIPS** was the strongest independent predictor of mortality.
- When a patient with TIPS presents with recurrent bleeding/ascites → 1st test to perform is Doppler U/S to rule out shunt thrombosis

Surgical Shunts:

In presence of severe ascites → side-to-side portocaval shunt (or mesocaval shunt) is preferable

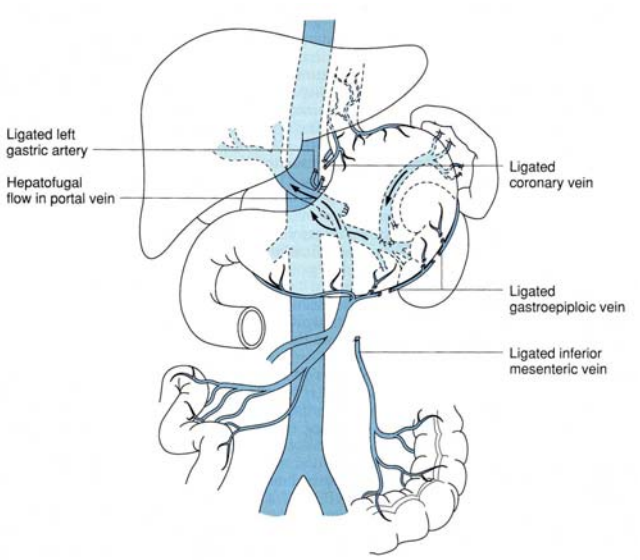
Few indications for direct portal vein anastomosis (rather than splenic/SMV anastomosis)

Small diameter interpositional shunt (Sarfeh)



[Surgery: Scientific Principles and Practice 3rd , 2001]

Warren Shunt (distal splenorenal)



Pancreas

pan (all) + *creas* (meat) → **the only organ that can eat the body**

Ventral bud → uncinate process and inferior portion of head
Dorsal bud → remainder of gland

Islet cells are 1 – 2 % of pancreatic mass, but receive 10 – 25% of arterial blood supply
Of the islet cells, β-cells comprise about 70% and are located at the center of the islet

Annular pancreas: "double-bubble" on AXR; treat obstruction with duodenojejunostomy (no resection of gland)

Pancreatic Enzymes and Function

1. Alpha-amylase: starch digestion, secreted in active form
2. Lipase, phospholipase A, colipase: fat digestion (removes #1, 3 carbon)
3. Proteases (trypsin, chymotrypsin, elastase, carboxypeptidases): protein digestion, secreted as proenzymes
4. Trypsinogen* is converted to active enzyme trypsin by enteropeptidase, a duodenal brush-border enzyme. Trypsin then activates the other proenzymes and trypsinogen (*positive* feed-back)

*PRSS1 mutations are related to hereditary pancreatitis

Stimulation of Pancreatic Functions:

1. Secretin*: stimulates flow of bicarbonate-containing fluid
2. Cholecystokinin (CCK)*: major stimulus for zymogen release; weak stimulus for alkaline fluid flow
3. Acetylcholine: major stimulus for zymogen release, poor stimulus for bicarb secretion
4. Somatostatin: inhibits release of gastrin and secretin

*secreted from duodenum

Secretion Rates

Pancreas:

- Basal exocrine: 0.2 – 0.3 mL/min up to 5 mL/min with maximum secretion (i.e. more than gastric H^+)
- Na^+, K^+ always ≈ plasma;
- At low rates, HCO_3, Cl^- composition ≈ plasma;
- At high rates HCO_3, Cl^- reverse

Bile:

- 1000 – 1500 mL/day (0.4 – 1 mL/min); gallbladder can only store 60 mL of fluid, but can concentrate up to 10 – fold*

*Keep these numbers in mind for patients with bile leaks to assess nature of ductal injury, i.e. how major an injury?

How ethanol causes pancreatitis:

1. Pancreatic duct hypertrophy → ↑ampullary resistance
2. Stimulation of gastric acid secretion → ↑secretin → ↑exocrine secretion

1+2 → enzyme extravasation; exacerbated by
↑acetaldehyde (byproduct of ethanol) → ↑membrane permeability, and
↑TG source of cytotoxic free fatty acids

Ranson's Criteria – Ethanol-associated Pancreatitis

Initial:
- Age > 55
- WBC > 16,000 per mm^3
- Blood glucose > 200 mg/dL
- AST > 250 mg/dL
- Serum LDH > 350 mg/dL

During first 48 hours:
- Hct falls > 10% points
- BUN increases > 5 mg/dL
- Serum calcium < 8 mg/dL
- Arterial PaO2 < 60 mmHg
- Base deficit > 4 mEq/L
- Fluid sequestration > 6 L

Mortality:
- If 0 – 2 signs, then 2%
- If 3 – 4 signs, then 15%
- If 5 – 6 signs, then 40%
- If 7 – 8 signs, then 100%

Note: all you can really conclude is > 3 signs → poor prognosis (in actuality, prognosis is slightly better today because of greatly improved critical care)

Distinguish between **edematous pancreatitis** (resolves) and **necrotizing pancreatitis** (progresses).
Pathogenesis: 1° cell death → local inflammatory response → systemic inflammatory response via portal circulation to entire body.

CT is helpful for diagnosis because dual phase CT allows comparison of non-contrast and arterial phase to delineate the ischemic extent of the process and/or to appreciate extralumenal gas

Antibiotics should only be used for severe episodes (i.e. > 3 of Ranson's criteria)
1st line agent is imipenem (crosses blood/pancreas barrier best)
2nd line agent is ciprofloxin

Operative debridement if:
1. clinical deterioration, despite maximal medical treatment
2. infection of necrotic pancreas (**air in RP, + pancreatic culture**)
3. failure to improve after 3 – 4 weeks

If gallstone pancreatitis → perform cholecystectomy with IOC:
-Quick improvement → lap chole ± IOC during index admission
-Severe disease → lap chole at interval

Pancreatic ascites:
- follows ductal disruption; often caused by blunt trauma/pancreatitis
- abdominal distention with high-amylase fluid
- Rx: nonoperative (NPO, TPN, octreotide)
- if persists > 3 weeks → ERCP + sphincterotomy to delineate anatomy and consider transpapillary stenting; if fails plan Roux-Y vs. distal pancreatectomy

Site of ductal disruption related to collection:
Dorsal rupture → RP collection → can be sucked into chest (= pancreatic pleural effusion)
Ventral rupture → inside lesser sac, if not walled off → pancreatic ascites

Pancreatic Pseudocyst

- Encapsulated collection of pancreatic fluid formed by inflammatory fibrosis (NOT epithelial lining)
- 1 in 10 after alcoholic pancreatitis; chronic alcoholic pancreatitis is #1 cause in U.S.
- Sx: epigastric pain, emesis, fever, weight loss
- Signs: palpable epigastric mass; tender epigastrium; ileus
- U/S, CT (good for multiple) show fluid collection; MRI/MRCP; ERCP (for treatment): contrast will fill cyst if communication with duct
- Ddx: cystadenocarcinoma, cystadenoma, IPMN, solid pseudopapillary tumor, mesenteric cyst, adrenal cyst
- Complications: infection, bleeding into cyst (most common cause of death), fistula, pancreatic ascites, gastric outlet obstruction
- Treatment: it takes 6 weeks (by definition) to mature and wall off so it can hold sutures; if it's going to resolve spontaneously (50% will), it will do so during this time
    - Most agree that if pseudocyst is > 5 cm it should be drained (especially if symptomatic)
    - Size IS an important predictor of resolution
    - Internal (surgical) drainage is successful in 90% of cases
    - External (surgical) drainage is reserved for thin walled and/or infected cysts
    - External drainage should be used only in cases of sepsis
    - Endoscopic drainage may be appropriate in the setting of chronic pancreatitis

Surgical Drainage:

1. If adherent to posterior wall of stomach: cystogastrostomy
2. If adherent to duodenum: cystoduodenostomy (rare)
3. If not adherent to either: Roux-en-Y cystojejunostomy (drain into Roux limb of jejunum)
4. If in tail: resect tail with cyst

*ALWAYS biopsy cyst wall to rule out cystic neoplasia

Cystic Neoplasms of the Pancreas

Account for < 15% of pancreatic cystic lesions (but incidence increasing)

	IPMN*	**MCN‡**	**Serous**
Gender	M = F	2:1	0.8:1
Age	70	50	60 – 70
Location	Head	Tail	Uniform
Ductal component	Yes	Rare	No
Malignant	35%	30%	Rare

*Associated with chronic pancreatitis (and often mistaken for)
‡ By definition must have underlying ovarian stroma

- **EUA + FNA for CEA** is probably most accurate (optimized sensitivity + specificity) measure of malignancy, BUT resection almost always indicated as it is difficult to exclude malignancy on the basis of biopsies [Brugge WR, et al. Gastroenterology, 2004;126:1330]
- **Do not** perform CT-guided percutaneous biopsy (often undiagnostic, potential to cause pancreatitis, bleeding, rupture of capsule)

Endocrine Neoplasm of the Pancreas

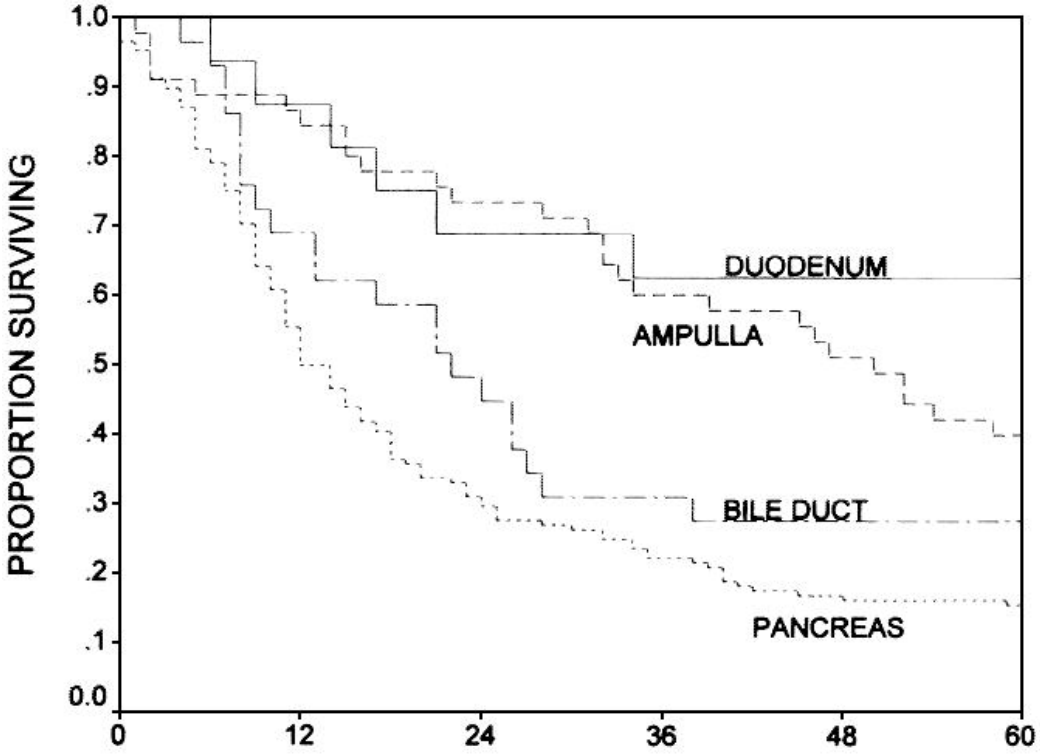
See previous sections on gastrinoma, insulinoma, glucagonoma. In general, pancreatic tumors producing *ectopic* hormones (e.g. ACTH-producing tumor) are very aggressive.

Exocrine Neoplasm of the Pancreas

Four periampullary malignant neoplasms:

1. pancreatic ductal adenocarcinoma of the head, neck, and uncinate process
2. ampullary adenocarcinoma
3. peri-Vaterian duodenal adenocarcinoma
4. distal cholangiocarcinoma

Of these, pancreatic ductal adenocarcinoma accounts for the most (75 – 85%) and has the poorest prognosis (see figure below)

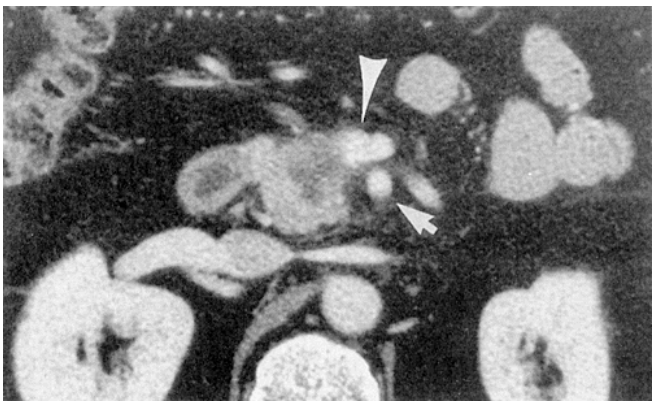


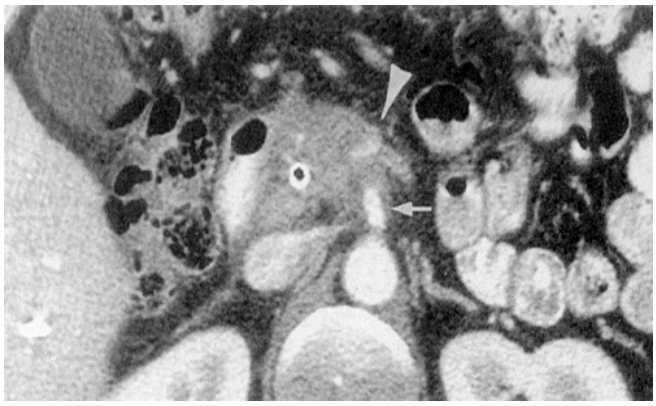
[Yeo CJ, et al. Ann Surg 227:821, 1998]

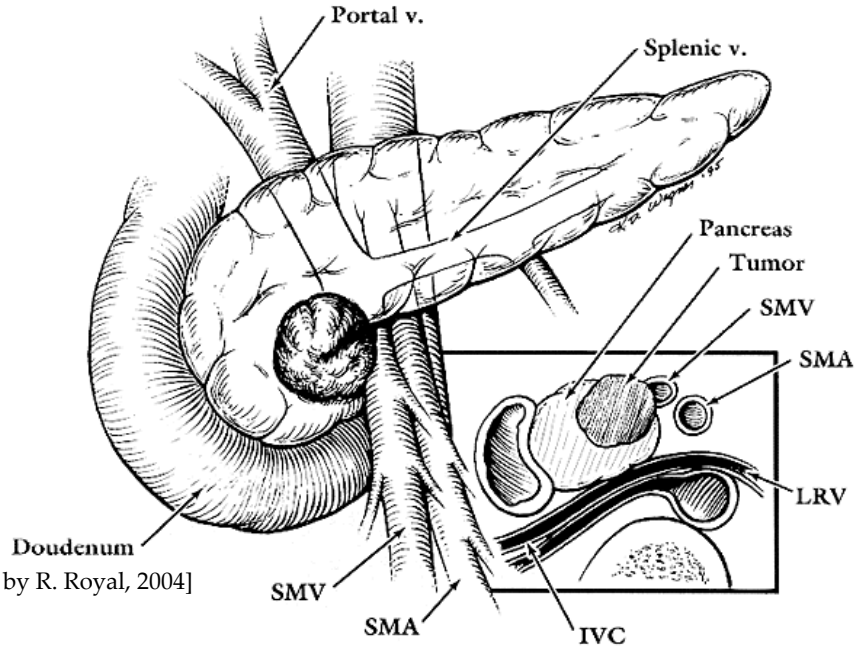
Lethality (death/incidence ratio) of **pancreatic adenocarcinoma** is approximately 0.99

- 15 – 20% of patients presenting with pancreatic cancer are surgical candidates, the remainder have metastatic disease or locally advanced (unresectable) disease
- Of patients with pancreatic adenocarcinoma, the *surgical candidates* have 10 – 20% 5-years survival
- Visualization of fat planes around SMV/PV are predictive of resectability
- Thrombosis of SMV/PV is a contraindication for resection

Resectable **Unresectable**







[Figure taken from talk by R. Royal, 2004]

Outcomes for pancreatic cancer

- Median survival following resection with positive retroperitoneal margin: 6 – 12 months (with chemoradiation)
- Median survival following standard pancreaticoduodenectomy for adenocarcinoma of pancreas: 20 – 22 months (13.5 months without chemoradiation)
- Median survival following reconstruction of PV/SMV: 20 – 22 months
- Median survival following reconstruction of SMA/celiac: 6 – 10 months
- Suggests **venous** involvement a function of location, not biology

Predictors of outcome following resection

1. Resectability – R_0, R_1, R_2 (i.e. margin status)
2. LN involvement
3. Tumor size
4. Adjuvant therapy
5. Molecular genetics (particularly medullary variant with MSI do better)

Sarcoma

8000 cases/year in US; 1% of adult cancers
Mesoderm origin
No predilection for sex, age, race
Overall 5-year survival approx 50%

Most Common: Liposarcoma, fibrosarcoma, leimyosarcoma (MFH is sort of a "wastebasket" term), essentially no change in treatment or survival

Staging (**grade**, size/depth, metasteses; **not histology**):
Stage I: low grade, < 5 cm deep or > 5 cm super, no mets → 99% OS
Stage II: low grade, > 5 cm deep OR high < 5 cm deep/> 5 cm super, no mets → 82% OS
Stage III: high grade, > 5 cm deep, no mets/nodes → 52% OS
Stage IV: metasteses (including nodes) → 20% OS

Sites:
- Lower extremity…32%
- Upper extremity…14%
- Retroperitoneal…15%
- Viscera…16%
- Trunk…11%
- H&N…12%

Biopsy:
- < 3 cm, uncomplicated → Excisional biopsy
- If incisional → longitudinal
- Core needle >>> FNA (not recommended)

Prognosis:
Grade: **low** > high
Depth: **superficial** > deep
Location: **distal** > proximal; **extremity** >> RP/visceral

Treatment:

Low Grade
1. NCI Surgery Branch Prospective Randomized Trial (excluding RP/viscera): surgery + (XRT 6800 rad vs. observation) → **XRT effective in preventing recurrence, but no effect on survival**
2. MSK Prospective Randomized Trial: surgery + (brachy vs. observe) → **no difference in local control or survival**

High Grade
Narrow (< 1 cm) margin→ 50 – 90% recurrence
Wide (> 1 cm) margin →30 – 50% recurrence
Radical resection (entire tissue compartment) < 20% recurrence

Role of XRT:
1. NCI SB PRT: Wide resection + adjuvant chemo (adria + cytoxan) (XRT vs. observe) $p = 0.003$ (0% vs. 22% recurrence), but **no survival difference** ($p = 0.64$)
2. MSK PRT: **consistent with above**

Role of systemic adjuvant chemo: SMAC Meta-analysis [Lancet 1997 350:1647]
Adriamycin vs. others
Found: decreased risk of mets/distant disease, local recurrence
BUT no increase in survival
Overall HR = 0.89 (0.76 – 1.03 95% CI), $p = 0.12$, increased survival from 50 to 54%
Hence, no support of adjuvant chemotherapy.
Current trend favors induction chemoradiation to shrink lesions preoperatively → less aggressive resections

Increase Risk of Recurrence: + margin, previous recurrence, no XRT; **Local recurrence is strongest predictor of ↓ survival**

Predictors of success for metastesectomy (lung):
1. Number of lesions (≤ 5)
2. Disease free interval (>1 year)

Melanoma

Thickness of primary tumor	Margin of resection
in situ	5 mm
< 1 mm	1 cm
1 – 2 mm	1 – 2 cm depending on location (2 is preferred)
2 – 4 mm	2 cm
≥ 4 mm	≥ 2 cm

Lesions of intermediate depth (1 – 4 mm) and lesions ≤ 1 mm that are ulcerating or Clark's level IV or V should receive sentinel node biopsy in the absence of clinically palpable nodes
[summary of trials in Reintgen D, et al. Semin Oncol. 2004;31:363]

Revised AJCC Staging for Melanoma:

Table 3. Survival Rates for Melanoma TNM and Staging Categories

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. + Nodes	Nodal Size	Distant Metastasis	No. of Patients	Survival ± SE			
								1-Year	2-Year	5-Year	10-Year
IA	T1a	1	No	0	–	–	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1	Yes or level IV, V	0	–	–	1,380	99.8 ± 0.1	98.7 ± 0.3	90.9 ± 1.0	83.1 ± 1.5
	T2a	1.01-2.0	No	0	–	–	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	1.01-2.0	Yes	0	–	–	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	2.01-4.0	No	0	–	–	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	2.01-4.0	Yes	0	–	–	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	> 4.0	No	0	–	–	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	> 4.0	Yes	0	–	–	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	Any	No	1	Micro	–	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	Any	No	2-3	Micro	–	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	Any	Yes	1	Micro	–	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	Any	Yes	2-3	Micro	–	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
	N1b	Any	No	1	Macro	–	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	Any	No	2-3	Macro	–	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	Any	Yes	1	Macro	–	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	Any	Yes	2-3	Macro	–	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	N3	Any	Any	4	Micro/macro	–	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	Any	Any	Any	Any	Skin, SQ	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	Any	Any	Any	Any	Lung	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	Any	Any	Any	Any	Other Visceral	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9
Total							17,600				

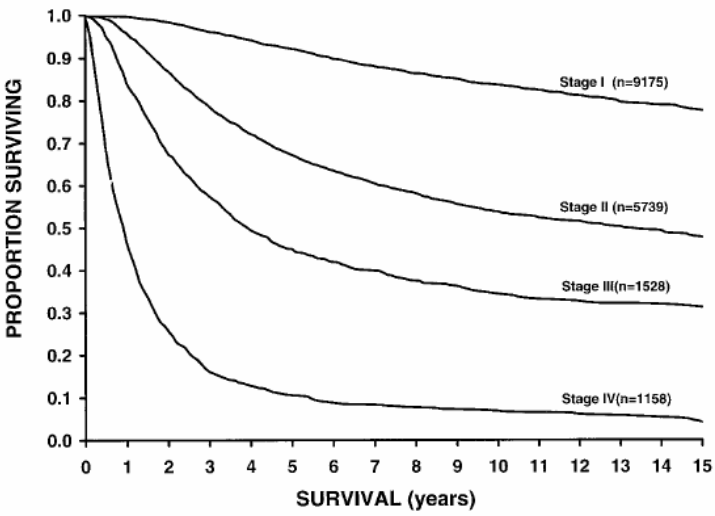


Fig 1. Fifteen-year survival curves comparing localized melanoma (stages II and I), regional metastases (stage III), and distant metastases (stage IV). The numbers in parentheses are patients from the AJCC melanoma staging database used to calculate the survival rates. The differences between the curves are significant ($P < .0001$).

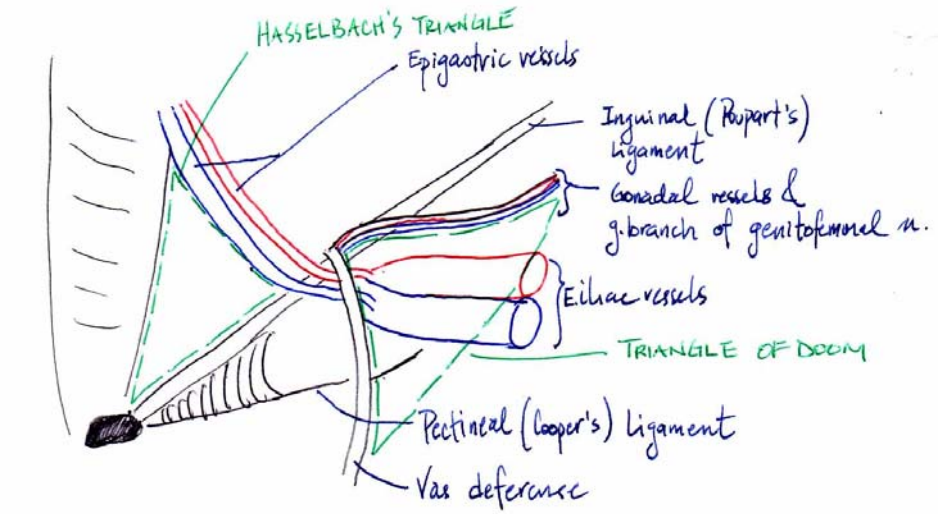
[Balch CM, et al. JCO 2001, 19:3635]

For patients with melanoma of depth **1 – 4 mm** and patients with **ulcerated** melanoma there **is a survival benefit** associated with elective lymph node dissection vs. observation. [Balch CM, et al. Ann Surg Onc 2000, 7:87]

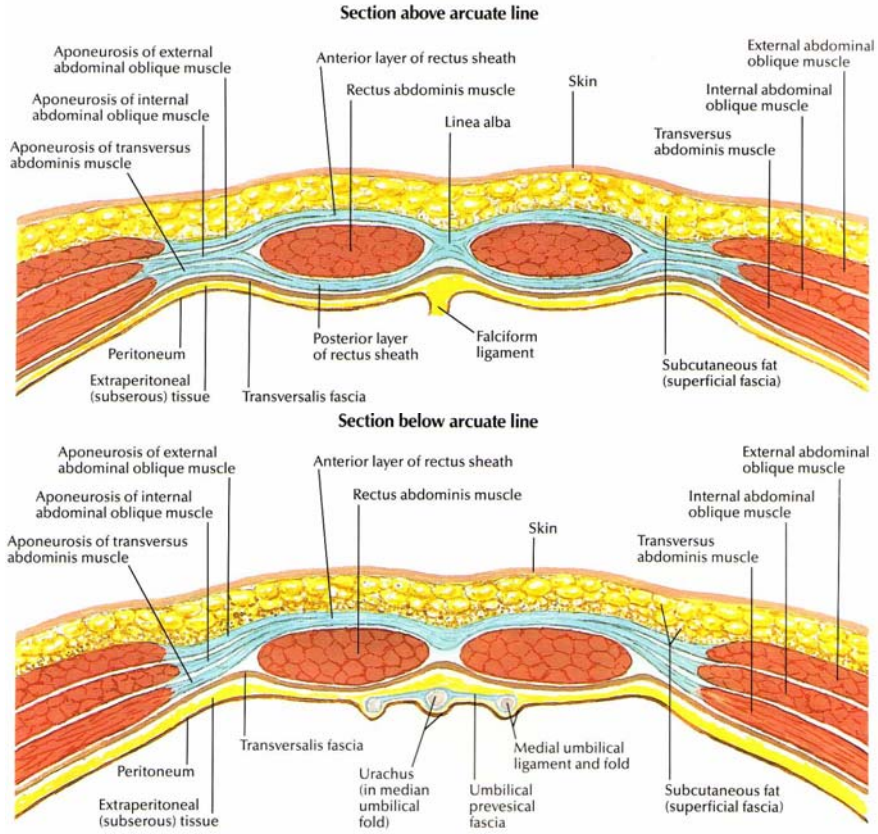
Merkel cell carcinoma: rare skin tumor of neuroendocrine origin. Similar to melanoma in that it typically appears in sun-exposed areas, and lymph node (10 – 30%) and distant sites (25 – 40%) of metasteses are often present

Hernia & Abdominal Wall

Approximately 75% of abdominal wall hernias occur in the inguinal region → ⅔ of which are direct
Males experience ≈ 5 x more than females; in both genders **direct** are more common
Femoral canal is bounded by: Cooper's ligament inferiorly, the ileopubic tract (inferior margin of transversalis fascia) superiorly and medially, and the femoral vein laterally
Posterior view of inguinal anatomy:



If strangulation is suspected → to OR (do not attempt reduction); open sac prior to OR reduction to assess viability of sac contents
Spigelian hernia: inferior to linea *semicircularis (the point at which the inferior epigastric artery enters the rectus sheath)*, through linea *semilunaris*; deep to external oblique → hence hard to diagnose; repair all
Petit's hernia: inferior lumbar triangle: iliac crest, external oblique, latissimus dorsi
Grynfeltt hernia: superior lumbar triangle: 12th rib, internal oblique, lumbosacral aponeurosis



[Netter's Anatomy, 1996]

Trauma Principles

Top 3 causes of **prehospital mortality**

1. Head injury
2. Hemorrhage
3. Airway obstruction

With massive hemorrhage, the most important factor in predicting outcome is **duration of hypotension**

Critical decision for patient with head injury is whether or not **mass lesion** is present

- Multiple injuries, plus widened mediastinum → **decompression of mass lesion in head is still first priority**.
- If patient arrives in shock, with widened mediastinum → bleeding most likely in abdomen (go there first)
- If patient stable with widened mediastinum → CT chest/arterigraphy first, but must RULE OUT abdominal bleeding prior to thoracotomy

The two major injuries associates with **widened mediastinum** (typically > 8 cm): **contained aortic rupture** and **vertebral body fracture** with associated hematoma

When assessing circulation → must discriminate between pump and volume problems:
Pump problems → distended neck veins (tamponade, tension pneumothorax, myocardial contusion, air embolus)

Finite number of sites of **significant** internal bleeding: **Chest, thigh, abdomen, pelvis, RP**

Rib fractures, including those of 1st and 2nd ribs, are related to the MAGNITUDE of deformation;
Thoracic aorta injury is related to the initial SPEED of deformation; hence, not directly related to each other

Amniotic fluid on pelvic exam will be alkaline (deep blue on nitrazine paper); **Kleihauer-Betke (K-B)** blood test detects even small amounts of maternal-fetal transfusion

Low CVP is not a good indicator of hypovolemia, rather its use is helpful when *high* (tamponade, tension pneumothorax)

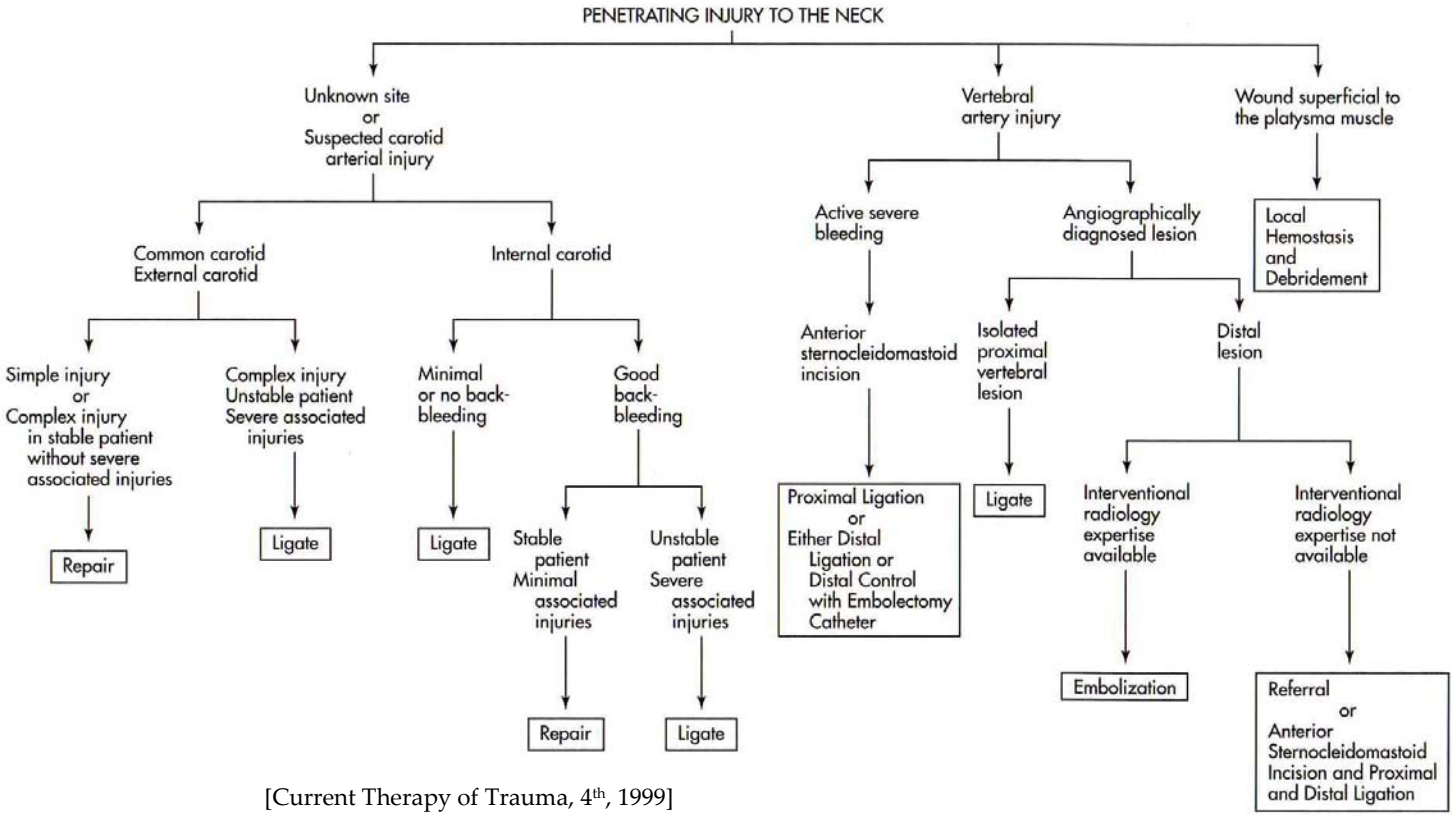
Zone I: clavicle to cricoid; **Zone II**: cricoid to angle of mandible; **Zone III**: angle of mandible to base of skull

In general: Zone II unstable → secure airway → to OR; if stable can do same *or* conservative approach: carotid arteriogram, barium swallow, rigid esophagoscopy, ± bronchoscopy

Brachiocephalic trauma: Zone II → to OR without arteriography; Zone 1 & 3 frequently treated conservatively

Patients with exsanguinating external hemorrhage, expanding hematomas, or neurologic deficits → airway → OR (no diagnostic procedures)

Blunt carotid artery trauma: few signs prior to neurological changes; mortality high (25%) and ½ of survivors have permanent neurological deficit. The lesions are rarely amenable to surgical repair → anticoagulation appears to be the mainstay of treatment



[Current Therapy of Trauma, 4th, 1999]

In general, try to avoid operating on the vertebral artery, even proximally. Angiography + embolization is always the better option.

Carotid artery ligation results in neurologic deficit in only 20% of adults

Use of recombinant Factor VIIa in bleeding trauma patients [Boffard et al. J Trauma 59;8:2005]
Randomized nearly 300 patients with either blunt (143 eligible) or penetrating (134 eligible) trauma to receive either 3 x placebo injections or 3 x rFVIIa (200, 100, and 100 μg/kg) in addition to standard treatment with the first dose following the 8th unit of transfused RBC and subsequent doses administered 1 and 3 hours later. In blunt trauma the treatment group had a significant reduction in RBC requirement and "massive" (>20) transfusion requirements. In the penetrating trauma arm, treatment resulted in trends towards fewer transfusions, but the results did not reach statistical significance. Both groups experienced a trend towards reduced mortality. Adverse events (e.g. thromboembolism) were distributed equally between all groups.

Incisions§

Suspected injury to	Incision for best exposure
Innominate artery	Median sternotomy ± extension into cervical or right supraclavicular incision
Right subclavian artery	Median sternotomy for proximal vessel injury; distal supraclavicular incision for distal injury
Left subclavian artery	Median sternotomy + extension into supraclavicular incision
Carotid artery	Cervical incision
Axillary artery	Inner arm with patient's arm away from side; infraclavicular incision may be necessary proximally

§ In general: median sternotomy is always safest because of better proximal control; never hesitate to resect the clavicle

Pelvic Fractures:

Most common associated with hemorrhage are:

1. Butterfly/Straddle: all 4 pubic rami
2. Open book: diastases of > 2.5 cm
3. Vertical shear: both anterior and posterior elements with vertical displacement > 1 cm

- If unstable → must rule out intraabodominal hemorrhage
- Pelvic fracture associated with urethral injury in 15% of males (very rare in females) and bladder rupture in 7% of patients

Absolute indications for urgent operative repair in **GU trauma**:

1. Avulsion of renal pedicle
2. Acute ischemia resulting from arterial intimal flap

Blood at meatus, high-riding prostate, anterior pelvic fracture, or penetrating injury proximal to urethra require retrograde urethrography before Foley (12 Fr cath without lube 1 to 2 cm in → 20 – 40 mL contrast in). In hemodynamically stable patients without gross hematuria → incidence of renal injury is < 1%

Peripheral Vascular Trauma

- ≈ 20% of patients with serious arterial injuries have normal pulses distal to injury → hence any penetrating injury in path of major artery should be investigated; ABI < 0.9 should raise suspicion
- Posterior knee dislocation → should undergo popliteal arteriography *after* reduction, unless ABI > 0.9
- **"Hard signs" of vascular injury** (pulse defect, pulsatile bleeding, thrill, bruit, expanding hematoma) → **Go directly to OR** (no angiography); administer heparin immediately; reversed saphenous vein graft is interpositional graft of choice, but PTFE ok

Neurologic Trauma

Glasgow Coma Scale (motor is best prognostic indicator of overall neurologic outcome)

Eye Opening	Verbal	Motor
4: spontaneous	5: oriented	6: obeys commands
3: to pain	4: disoriented	5: localizes pain
2: to verbal stimuli	3: inappropriate words	4: withdraws from pain
1: none	2: incomprehensible sounds	3: decorticate posturing
	1: none	2: decerebrate posturing
		1: none

Lesions classified as **focal** and **nonfocal**:

Focal

- epidural/subdural, intraparenchymal hematomas (require urgent surgical decompression for mass effect)
- Indications for OR: midline shift > 5 cm, ICP > 20 mmHg, deterioration in neuro findings
- Subdural >> Epidural (3% of patients with severe head injury); subarachnoid rarely causes mass effect, but vasospasm is biggest concern

Nonfocal

- 3 categories (mild concussion, classic cerebral concussion, DAI)
- Hypotension (prehospital and hospital) is single biggest predictor of poor neuro outcome and death

Tools: CT, ICP, Jugular bulb O_2 saturation (< 50% believed to represent cerebral ischemia), TCD

1995 Aitken Brain Trauma Foundation Guidelines for Treatment of Head Injury
(**Only 3** level one "standards" for patients GCS 3 – 8)

1. **NO** prolonged hyperventilation [Note: respiratory alkalosis causes a reflex vasoconstriction of the cerebral blood vessels → decreasing intracerebral blood volume and pressure; but best used in acute management]
2. **NO** prophylactic steroids
3. **NO** prophylactic anti-seizure meds beyond 7 days

Who gets ICP monitoring?

1. GCS ≤ 8 + abnormal CT, or
2. GCS ≤ 8 + two of the following three: (age > 40, MAP < 90 mmHg, clinical signs of elevated ICP), or
3. ANY TBI patient having an invasive operation/intervention

Skull Fractures

In and of themselves do not cause injury or warrant intervention, but markers of damage
Operate if depressed and: CSF leak, underlying tissue injury, significant deformity

C-Spine Fracture

C1 burst fracture (Jefferson's): caused by axial loading → **stable** (if isolated) → treat with collar

C2 posterior element fracture (Hangman's): caused by extension and distraction → **unstable** → 3 months in halo

Odontoid fracture:

Type I: above base → **stable**;

Type II: at the base → **unstable**; < 5 mm displacement → 3 months halo; > 5 mm → C1/2 fusion or screw fixation

Type III: extend into vertebral body → halo

3 Columns determine the stability of the spine:

1. Anterior: anterior spinous ligament
2. Middle: vertebral body, posterior spinous ligament
3. Posterior: facet/lamina interface

Instability results when at least ⅔ are interrupted. Penetrating injury rarely results in instability.

T- and L-spine fractures (⅔ occur between T11 and L3):

- Fractures that involve the middle or posterior columns are by definition unstable and, because of the narrow spinal canal in this region, can cause severe neurologic injury
- If finger spreading can be accomplished with symmetry and strength, there is no cord injury above C8

Cord Injury

- Most common C6 to T1
- If tip of odontiod (dens) is > 4.5 mm above McGregor's line (hard palate to lowest point on occipital bone) → basilar impression likely
- OR for compression > 50% height of vertebral body or > 30% narrowing of canal

NASCIS 2 Trial demonstrated that in patients with blunt trauma to the spinal cord high-dose methylprednisolone (30 mg/kg bolus followed by 5.4 mg/kg/hour for 23 hours), if initiated within 8 hours of injury, resulted in greater neurologic recovery, which remained at one year [NEJM 322;20, 1990]

A follow-up study further demonstrated that 24 hour treatment was sufficient for patients initiated on treatment within 3 hours, but 48 hour steroid treatment was necessary for patients initiated 3 – 8 hours after injury [JAMA 277;20, 1997].

Neurogenic Shock

- Not to be confused with flaccid spinal shock
- Loss of vasomotor tone in viscera and lower extremities; need volume *first*, peripheral vasoconstriction (e.g. neo) *second*. Hypotension should first prompt search of other causes of shock (such as hypovolemia)
- May see bradycardia and warm, perfused extremities

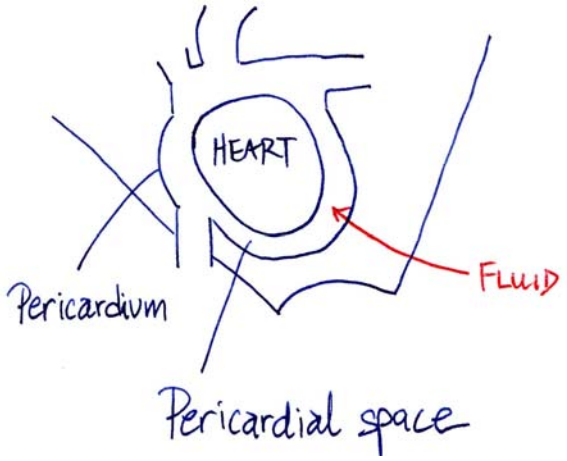
Nexus Criteria

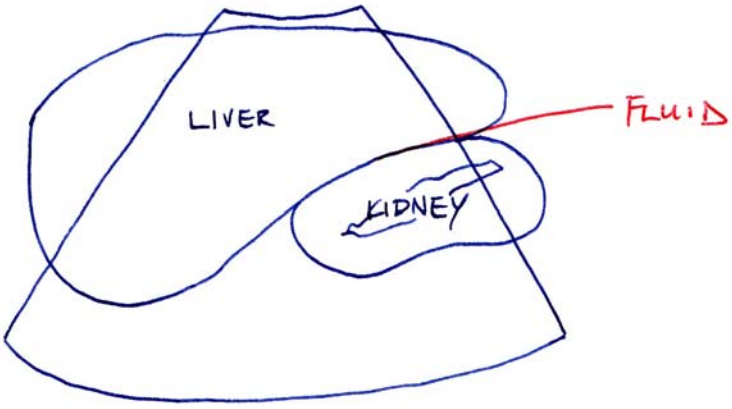
No films if:

- No intoxication, alert, awake, no ΔMS
- No neuro deficit
- No neck pain
- No distracting injury
- Normal neck exam

Focused Abdominal Sonogram for Trauma (FAST) Exam:
Ultrasound can detect as little as 100 mL of free fluid in the peritoneum. Withhold foley placement until FAST is done to facilitate bladder view

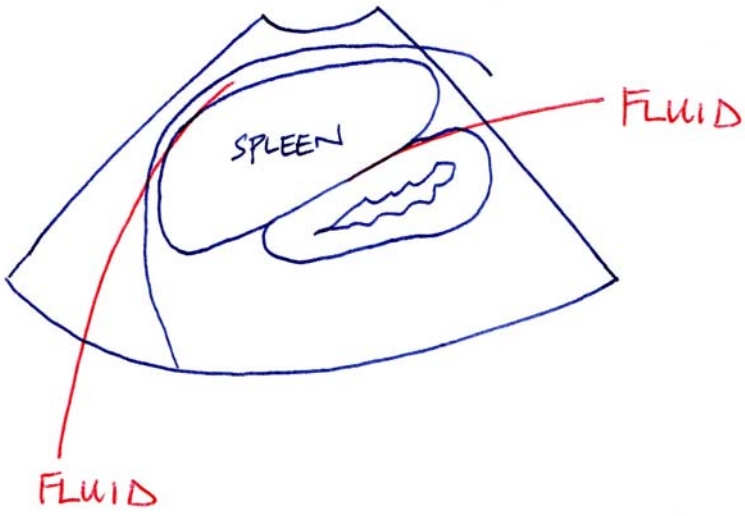
1st View: Subxiphoid, demonstrates a <u>longitudinal</u> cross-section of the heart and pericardial sac

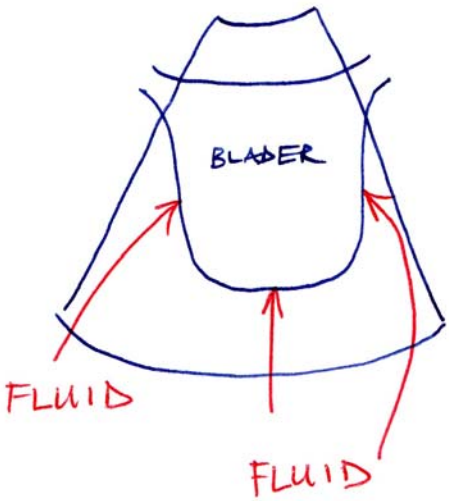




2nd View: RUQ, demonstrates a <u>sagital</u> view of the liver and right kidney

3rd View: LUQ, demonstrates a <u>sagital</u> view of the diaphragm, spleen, and left kidney
(Note: 2 locations for fluid accumulation)





4th view: Pelvis, demonstrates a <u>transverse</u> view of the pelvis

Chest Wall Injuries

Sentinel injuries:

- First rib fracture → can indicate underlying **head and neck** injury or **great vessel** injury
- Scapular fracture → **CNS** injuries, **pulmonary contusion**
- Sternal fracture → **cardiac contusion**, **great vessel** injury
- Bilateral rib fracture, lower rib fracture → **liver**, **spleen**

Flail chest: adjacent ribs, each in two or more places → paradoxical movement on respiration (can be overlooked in positive-pressure ventilation). Three components:

1. Altered chest wall mechanics,
2. Underlying pulmonary contusion (*most significant),
3. Pain → reduced tidal volume

If awake, alert, deserve trial of non-intubation, but adequate IV pain control (consider epidural); if respiratory distress → volume-controlled ventilation

Open Pneumothorax: If the defect is more than ⅔ the diameter of the trachea → on inspiration air will preferentially pass through chest wall rather than airway; initial management is creating a flutter valve-type dressing + chest tube at site remote from defect

Tracheal Injury:

- If penetrating → explore via SCM incision
- Patients presenting with massive subq or mediastinal emphysema should be suspected of having distal tracheal or bronchus injury; Also, constant "bubbling" after chest tube placement; Perform bronchoscopy ASAP to rule out tracheal/bronchial tear
- 80% of traumatic tears occur within 2.5 cm of carina; Airway repair done via right PL thoracotomy

Pulmonary Contusion: ⅓ do not manifest on CXR until > 24 hours; hypoxia may be first sign; consider intubation if $PaO_2 < 60$ mmHg on > 40% O_2 or if $PaCO_2 > 50$ mmHg with normal HCO_3

Pulmonary Laceration*: Thoracotomy indicated for:

1. Entire hemithorax opacified,
2. Shock that is persistent or develops or is persistent as hemothorax is evacuated,
3. Rapid removal of > 1500 mL blood,
4. > 250 mL/hour x 4 – 6 hours,
5. Significant hemoptysis

*Consider tractotomy with GIA stapler over trauma pneumonectomy ("more papers than survivors")

Air Embolism:

- As distributed to end organs, small bubbles cause ischemic damage as they occlude vessels of the microcirculation; Brain and myocardium are most sensitive;
- RCA is anterior in supine patient, hence, receives substantial proportion of AE as they exit aortic root
- Penetrating thoracic trauma causes ⅔ of traumatic AE
- Clues to injury: **Chest injury, without head injury → yet focal neuro signs**
- Treatment: cessation of continued AE; head down, thoracotomy on suspected side with hilar cross-clamping; Interventions that increase PaO_2, CO, BP enhance air bubble dissolution

Fat emboli: long bone fracture; petechia, hypoxia, confusion/agitation; Sudan urine stain for fat

Cardiac Trauma:

- Penetrating heart trauma have 75% prehospital mortality (higher for blunt trauma)
- **RV > LV > RA > LA**
- Major morbidity is coronary artery injury
- Presentation of tamponade: extreme anxiety, hypotension, distended neck veins
- Following thoracotomy and aortic cross-clamping → open pericardium (longitudinally from inferior to superior)
- Fine fibrillation is a bad sign and won't convert to course fibrillation until the pH reaches 7.20
- **s/p blunt cardiac trauma**: new murmur should raise suspicion of valvular prolapse (mitral, tricuspid) or traumatic VSD

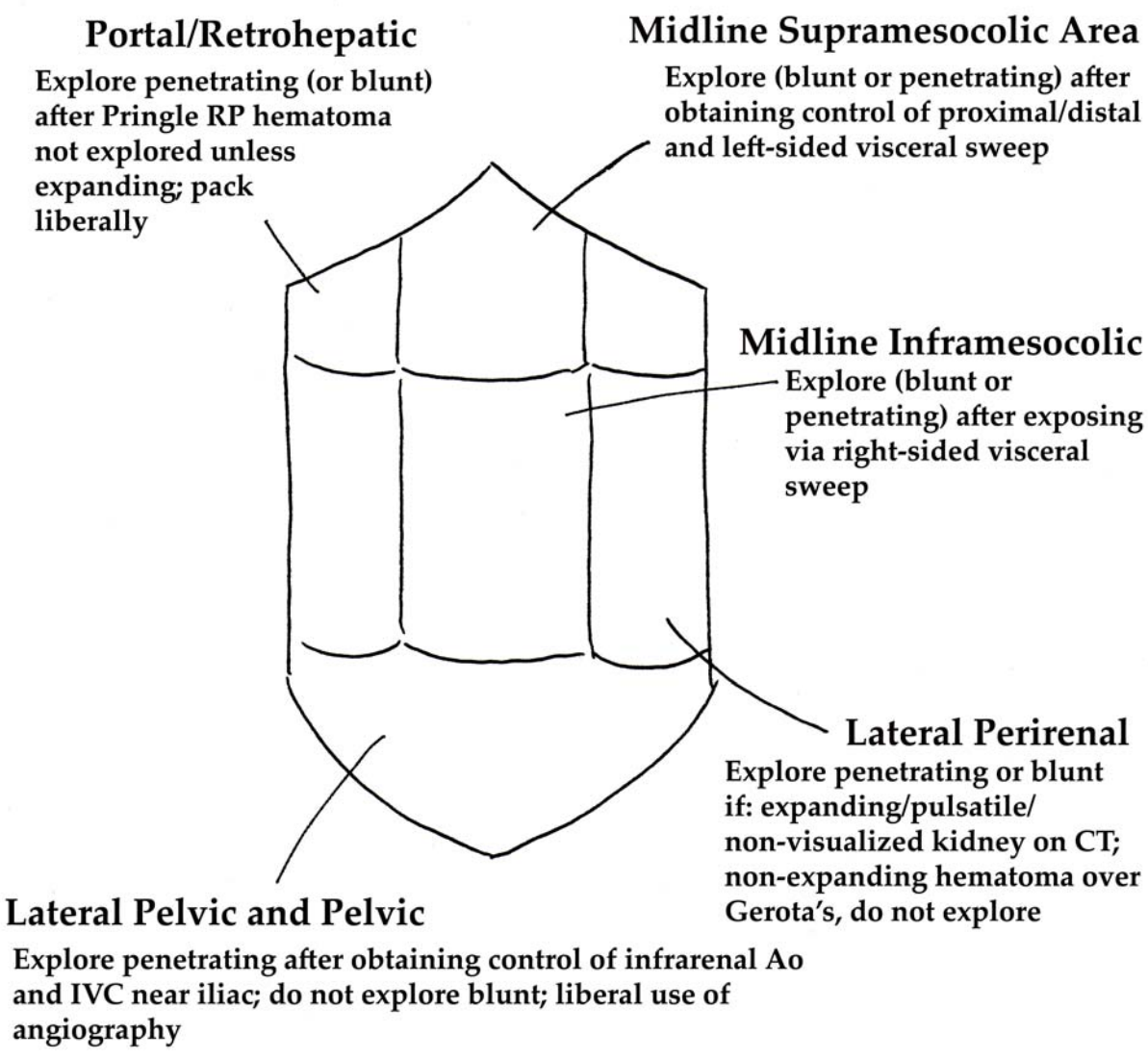
Esophageal Trauma: most common site is cervical (> 80%)
Should be suspected when:

- posterior chest wound,
- transmediastinal injuries,
- penetrations of platysma, and/or
- tracheobronchial trauma;

Gastrograffin can miss up to 15% of injuries and should be followed with dilute barium
Management:
< 24 hours, stable patient: primary closure, buttressed with tissue and drained
> 24 hours; unstable patient: Cervical – simple drainage; if large → spit fistula; Thoracic – close with Grillo (pleural) patch, extensive debridement, wide drainage

Caustic Injuries: scope only to first area of burn, not beyond
First Degree (hyperemia and edema): IV until able to handle own saliva → barium swallow → advance diet as tolerated
Second Degree (hemorrhage, exudates, ulcerations): as above, repeat endoscopy in 3 weeks to rule out stricture
Third Degree (complete obliteration of mucosa, circum ulceration, eschar): controversial; consider esophagectomy

Retroperitoneal Injury Exploration:



Great Vessel Injury: acute hypotension, sudden CV collapse, unusual shadow on CXR
Suggestive physical signs: unequal peripheral pulses, steering wheel contusion on chest, palpable sternal fracture
OR indications: initial blood from chest tube > 1500 mL; > 200 mL/hour x 4 hours; hemopericardium; tamponade; expanding hematoma at thoracic inlet; hemorrhage from supraclavicular wound
Exposure: if unstable: **left AL thoracotomy** with transsternal extension into right chest;
If confirmed thoracic vena cava, ascending aorta, arch, thoracic innominate, carotid → median sternotomy
⅓ of blunt aortic injuries arriving to the hospital (20% of total – 80% die at scene) will have a normal arrival CXR

Diaphragmatic Injury: occurs in 15% and 45% of patients with stab and GSW involving upper abdomen and lower thorax, respectively.
For penetrating injuries: L = R sided injuries (usually small tears), BUT for blunt injuries: L > 5 x R sided lesions (usually larger tears)

Splenic Injury§: most commonly injured abdominal organ in blunt trauma *that requires treatment during celiotomy*
Risk of OPSI is greatest after 1st year, but appears lifelong; greater in children
Nonoperative approach better if: < 55, no substantial hemoperitoneum, no coagulopathy, no vascular blush on contrast CT; Can manage nonoperatively if vascular blush present if no extravasation of contrast and stable hemodynamics.

Liver Injury§: most commonly injured organ in patients with blunt abdominal trauma (30 – 40%)
If deep venous bleeding from over the dome of the liver encountered → grade V or VI injury likely → extend incision into chest without applying traction on liver; Use Heaney's maneuver (clamping supra- and infrahepatic IVC), venoveno bypass, or atriocaval shunting
IV contrast in the gallbladder indicates (abnormal) connection between biliary and vascular systems (several weeks out from liver trauma → indicates hemobilia)

§ Can manage both liver and spleen with angiography if blush present in stable patient

Pancreatic and Duodenal Injury:

- 0.2 – 3% of blunt trauma, slightly more with penetrating trauma
- 90% have at least one other intraabdominal injury, with an average of three
- Duodenum most common site of intramural hematoma following blunt trauma → can present as high-grade proximal obstruction 12 – 72 hours after trauma; (assuming stable) obtain gastrografin SBFT followed by barium swallow; after ruling out other injury can manage with NGT/TPN, but if no resolution in 10 – 14 days → to OR to evacuate

Organ Injury Scale:

I Hematoma-minor contusion **without duct injury**
Laceration-superficial **without duct injury**
II Hematoma-major **without duct injury** or tissue loss
Laceration-major **without duct injury** or tissue loss
III Laceration-**distal** transaction or parenchymal injury **with duct injury**
IV Laceration-**proximal** transaction or parenchymal **injury involving ampulla**
V Laceration-**massive disruption of pancreatic head**

Selective Treatment:
I External drainage
II External drainage; distal pancreatectomy if distal
III Distal pancreatectomy
IV Extended distal pancreatectomy
V Resect (or drain) pancreas, exclude duodenum; consider Whipple

Colon/Mesocolon:
At laparotomy → explore all hematomas or colon wall or mesocolon to identify occult perforations
Primary repair of colonic injuries can be performed unless following:

- > 50% circumferential injury (i.e. destructive injury)
- significant associated injuries, ISS > 25 (i.e. unstable)
- peritonitis
- significant fecal spillage
- hemodynamic instability

Rectal Injuries: 3 Principles:
1. Formation of a proximal, completely diverting colostomy
2. Insertion of presacral drains between anal verge and the coccyx
3. Debridement and primary repair of the injury itself, if it is accessible

SIRS (Systemic Inflammatory Response Syndrome): at lease 2 of the following 4 (in the absence of other explanation):

1. Hyperthermia (> 38 ^{0}C or 100.4 ^{0}F) of hypothermia (< 36 ^{0}C or 94 ^{0}F)
2. Tachycardia (> 90 bpm)
3. Tachypnea (> 20/min or $PaCO_2$ < 32)
4. WBC > 12,000 or < 4,000 per mm^3 (or >10% bands)

Sepsis: Known or suspected presence of infection (bacteremia, toxemia, fungemia, viremia) plus 2 or more SIRS criteria

Severe Sepsis: Sepsis plus evidence of organ dysfunction, hypotension, or evidence of hypoperfusion

Shock: End-organ hypoperfusion. Period. Often manifested by lactic acidosis, oliguria, mental status changes, and hypotension refractory to fluid administration.

Septic Shock: Severe sepsis leading to shock

Pathophysiology of this cascade leading to shock:
It really begins with a "panendothelial organ failure" as a consequence of an inflammatory cascade. Macrophages release TNF (itself a direct myocardial depressant) and IL-1, which results in two detriments:

1. Increased expression of the adhesion molecules CD11, CD18, ICAM-1, and ICAM-2 on endothelial cells and WBCs, resulting in leukoaggregation.
2. Promotion of NO Synthase activity, increasing circulating levels of NO, which does two things: direct myocardial depression, and vasodilation

The endothelium itself becomes the target organ as blood flow is shunted around capillaries (because of obstruction), leading to poor tissue oxygenation

<u>Other etiologies of shock</u>:

1. Cardiogenic
2. Neurogenic
3. Hypovolemic
4. Obstructive
5. Distributive (anaphylaxis)

Catecholamine response to injury is maximal at 24 – 48 hours

- CO = HR * (EDV – ESV)
- Generally, CO↑ as HR↑ (sinus) up to ≈ 160/min
- Atrial kick provides 15 – 20% of EDV
- A reduction in Hct by 50% produces an 8-fold reduction in blood viscosity → mechanism whereby CO↑ in normovolemic anemia

As the arterial waveform propagates distally the systolic pressure increases and diastolic pressure falls slightly so that the MAP remains constant except in certain circumstances like rewarming from CPB or during vasopressor administration in sepsis

Aortic **MAP** and **diastolic** pressures are slightly higher than distal pressure; BUT **systolic pressure rises with distal propagation**

PADP reflects left atrial pressure when no pulmonary vascular hypertension exists. PADP is usually 1 – 2 mmHg **higher** than PCWP and LA pressure; PAOP is not commonly superior to PADP for estimating LAP; A difference between PADP and PAOP of **> 4 – 5 mmHg is indicative of ↑PVR, assuming to valvular disease exists**

Carbon Monoxide Poisoning: few symptoms if level < 10%; most deaths associated with level > 60%
Affinity of CO for Hb is 240x that of O_2 with slow dissociation; $T_{1/2}$ is 250 min in room air; with 100% O_2 → $T_{1/2}$ reduced to 40 minutes

Oxygen Delivery, Uptake, and Extraction

I. Oxygen Delivery (DO_2)

DO_2 = CO * CaO_2, [where CaO_2 = Hg (g/dl) * 1.34 (ml O_2/g Hg) * SaO_2 + 0.003 * PaO_2 (torr =mmHg)]
= CO * [**Bound** + Dissolved]
= CO * [**1.34 * Hg * SaO_2** + 0.003 * PaO_2] → **take-home message: *bound* O_2 is everything when considering delivery, but it is the dissolved component that is necessary for diffusion to the tissues**

II. Oxygen Uptake (VO_2)

VO_2 = CO * (CaO_2 – CvO_2)
≈ CO * 13.4 * Hg * (SaO_2 – SvO_2) * 10

III. Oxygen Extraction Ratio

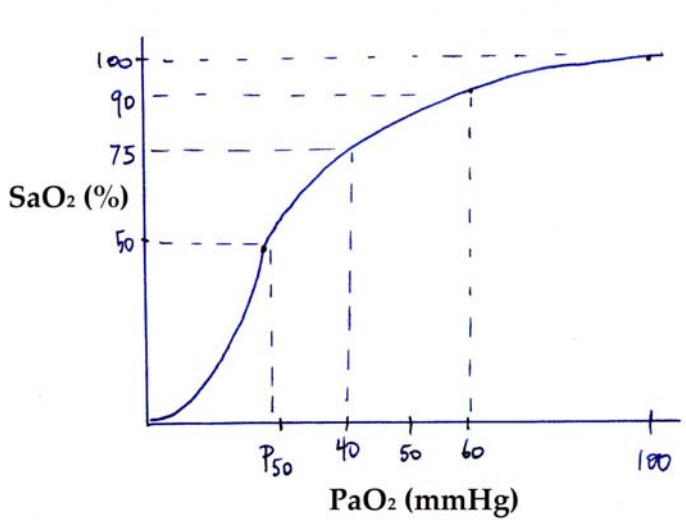
O_2ER = (VO_2/DO_2) * 100 [Normally: 20 – 30%]

Control of O_2 Uptake
VO_2 = DO_2 * O_2ER

Below Critical DO_2 (≈ 300 mL/min/m² or 4 mL/kg/min, but varying from 150 to 1000 in the critically ill), VO_2 becomes DEPENDENT on supply, and energy production becomes oxygen-limited (dysoxia)

Above Critical DO_2, VO_2 does not vary with DO_2, and is essentially constant

Relationship between O_2 saturation and partial pressure:



The Hill Equation:

$$SaO_2 = \frac{PaO_2^N}{PaO_2^N + P_{50}^N}$$

where N = Hill coefficient ≈ 2.4 – 2.6; P_{50} = PaO_2 at which point SaO_2 = 50% ≈ 24 – 26 mmHg

Vasoactive Drugs

Drug	Mechanism	Action	Indication
Amrinone	Phosphodiesterase inhibitor with positive inotropic effects + vasodilator actions	-increase stroke output without an increase in stroke work. -similar to dobutamine, BUT does not stimulate adrenergic receptors (hence, not attenuated by β- antagonists)	-effective single therapy of low-output states caused by systolic failure. -vasodilator → must be adequately pre-loaded
Dobutamine	Synthetic catecholamine considered inotropic DOC for acute management of severe systolic heart failure. Mostly β1	-dose-dependent increase in stroke volume accompanied by a decrease in cardiac filling pressure (measured by wedge pressure) -these changes are matched by a decrease in SVR, hence, arterial pressure remains virtually unchanged, but hypotension can occur especially when low or borderline volume status	-good for low output states (right or left failure) -NOT suitable as monoagent for cardiogenic shock - must be adequately pre-loaded
Dopamine	Endogenous catecholamine serving as a neurotransmitter Effects depend on pattern of receptor activation	Receptor profile changes with dose: Splanchnic → β → α (2 – 5 μg/kg/min) → (5 – 8) → (>10)	-cardiogenic shock, and circulatory shock syndrome associated with systemic vasodilation (e.g. septic shock) -High neurogenic shock (above T3/T4, hypo and *bradycardic*)
Epinephrine	Endogenous catecholamine.	-like DA, β at low does (0.005 – 0.02 μg/kg/min); -α at high does (0.01 – 0.1 μg/kg/min) -severe vasoconstriction: >0.1 μg/kg/min -Blocks histamine release	-cardiac arrest, pulseless VT/VF, AS, PEA -severe anaphylactic reaction -good in children First Line in: 1. anaphylaxis 2. RH failure (massive PE) 3. Heart failure with low BP (too low for inotrope)
Vasopressin	Endogenous hormone (ADH)	-Directly stimulates smooth muscle V1 receptors, resulting in vasoconstriction -"hormonal" levels (0.01 – 0.03 U/min) can help wean off other vasopressors	-sepsis refractory to norepinephrine, phenylephrine.
Norepinephrine	Endogenous catecholamine	- α > β-agonist → often results in reflex bradycardia	-low SVR, in need of inotropic support -drug of choice in severe septic shock -improves renal blood flow
Phenylephrine	Endogenous catecholamine	- Selective α-agonist	-low SVR (provided adequate pre-load); do not use for pump failure

When you see *low SVR* and *normal/high filling pressures* think:

1. Sepsis
2. Adrenal insufficiency
3. Anaphylaxis
4. Neurogenic shock (if high → fluids and dopamine; if low → fluids and phenylepherine)
5. AV fistula (large, central)

Mechanical Ventilation

Distinguish between problems of **ventilation** and **oxygenation**:

Ventilation Problems	Oxygenation Problems
Apnea: head trauma, meds (narcotics), spinal cord injury, OD Hypoventilation: narcotics, head trauma, spinal cord injury, neuromuscular disease, electrolyte abnormality (PO_4), in adequate pain relief Airway Disease: obstruction (foreign body, aspiration), COPD Mechanical Problems: rib fracture (splinting), diaphragmatic rupture, increased abdominal pressure	Shunt: atelectasis and collapse, HTX/PTX, pulmonary contusion, ARDS, cardiogenic pulmonary edema Decreased Inspired O_2: high altitude, smoke-filled rooms, malfunctioning O_2 delivery devices Diffusion Limitations: sarcoidosis, alveolar proteinosis, extreme hyperdynamic states V/Q Mismatches (most common cause of hypoxia): PE, pneumonia, asthma/COPD

Conventional ventilation: I:E (inspiratory:expiratory ratio) of 1:2 (or up to 1:1);
Inverse ratio ventilation (IRV) spends more time on inspiration (up to 4:1) can further ↑ oxygenation by ↑ total PEEP

"Physiologic" PEEP is low-level PEEP (5 cm) to stimulate glottic closure mechanism (which is eliminated by ETT) → shown to ↑ FRC, ↓ shunt fraction, and improve oxygenation
auto-PEEP is defined as PEEP occurring at the alveolar level, which is greater than the PEEP generated by the ventilator

The work of breathing at rest consumes 2% of total body VO_2; can increase up to 50%
Shunt Fraction = pulmonary venous admixture = amount of blood shunted around the lung as a fraction of the CO (measured at the inspired O_2 concentration required to maintain oxygenation)

Ventilator-Induced Lung Injury

- Not caused by high peak airway pressures, but rather by alveolar overdistension, which stretches the alveolus beyond its maximum volume and disrupts the alveolar-capillary membrane, and/or by opening and closing of the alveoli with shear stress causing endothelial injury. Peak pressure is a marker of this, but a poor one.
- Best measure of transmural pressure acting to distend the alveoli during inspiration is the ***plateau pressure*** measured during a 1-second end-inspiratory pause (must be less than 40 cmH_2O to avoid lung injury; **and** must be a mode of ventilation that allows this measurement: IMV, support mode; not PS). ARDS trials show outcome best when plateau pressure < 30 cmH_2O, with a few trials implying ≤ 25 is best.

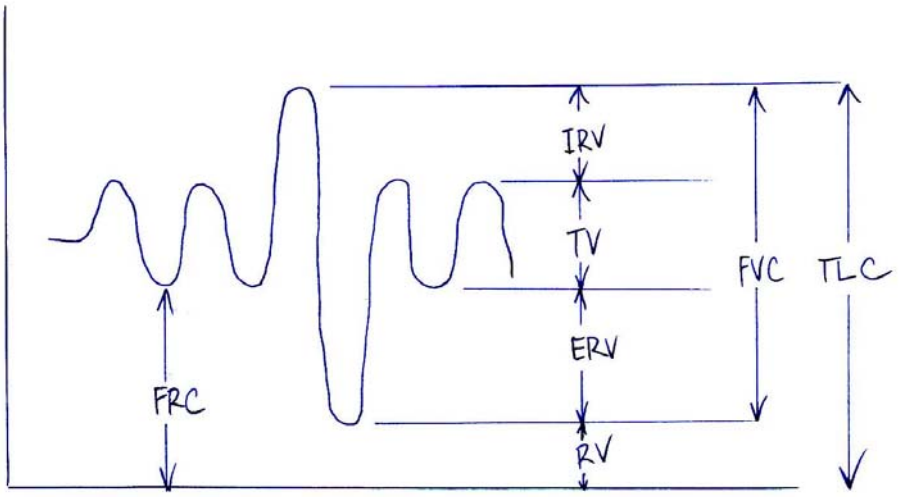
Ventilator-Associated Pneumonia (VAP)

- 2nd most common nosocomial infection (after UTI); 1st in morbidity and mortality
- Within 48 hours → colonization with the prevalent (usually gram-negative) organisms; ETT allows them in, but impairs the normal mucociliary clearance mechanisms
- Highest risk during first 5 – 7 days (3% per day), then days 7 – 10 (2% per day), then 1% per day thereafter [Cook DJ, et al. Ann Intern Med, 129:1998]
- BAL and quantitative culture is gold standard (colony count > 10^4 cfu/mL indicates bacterial pneumonia). [See excellent review in Dodek P, et al. Ann Intern Med, 141:2004]

ARDS:

1. $PaO_2/FiO_2 < 200$
2. PCWP < 18 or no assumption of CHF
3. Diffuse interstitial infiltrates in at least 2 quadrants
4. Decreased compliance (TV/[PIP – PEEP]; normal 60 – 80 cmH_2O)

Lung Volumes:



Tobin (and Yang) Index: "Best" objective data to aid in weaning off vent:

RSBI = RR/VT where V_T is in liters

Rapid Shallow Breathing Index (RSBI): In T-piece trial: **RR/V_T (in Liters)** → if < 80 then likelihood of remaining extubated at 24 hours is about 90%. If RSBI > 105 breaths/min/L likelihood of remaining extubated at 24 hours was about 10%. No need to "wean" if RSBI < 80 → CPAP or T-piece [Yang KL, Tobin M. NEJM 1991, 324:1445]

Dead Space:

$$V_D/V_T = \frac{P_{CO_2} - ET_{CO_2}}{P_{CO_2}}$$

WHERE $P_{CO_2} = K \times \left[\frac{V_{CO_2}}{V_A}\right]$ ← Rate of CO_2 Production; ← Alveolar Ventilation

$$= K \times \left[\frac{V_{CO_2}}{V_E \times \left(1 - \frac{V_D}{V_T}\right)}\right]$$

← Total Expiratory Ventilation

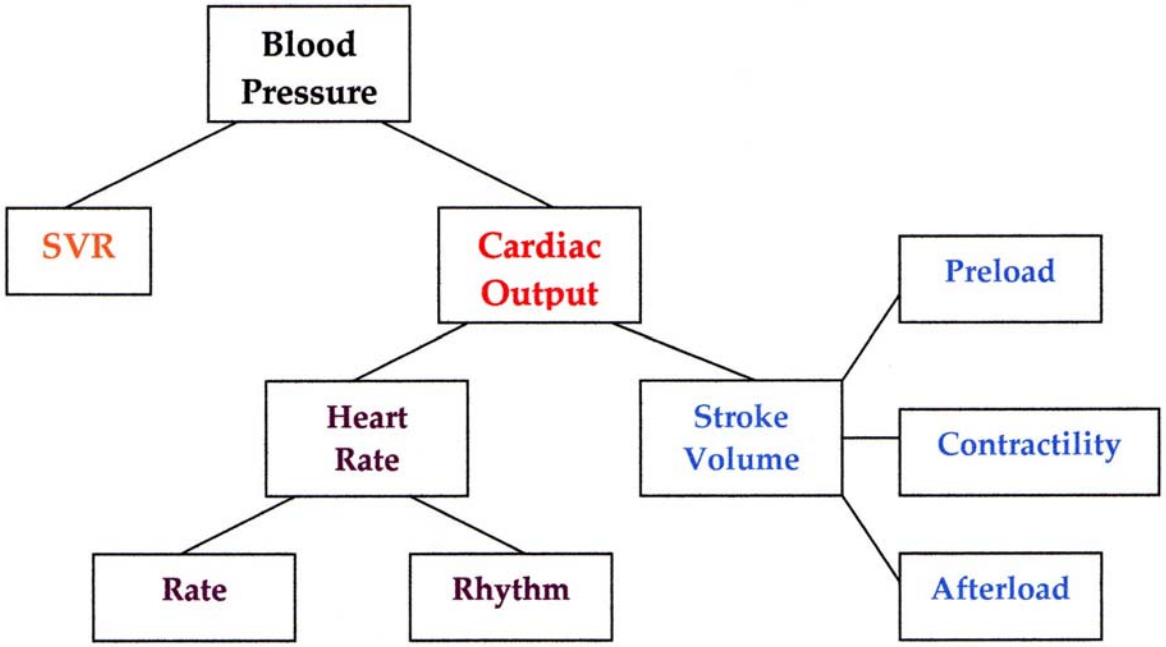
3 reasons for ↑ $PaCO_2$

1. ↑ CO_2 production
2. ↓ Expired volume (hypoventilation)
3. ↑ Dead space → Most common reasons for this include:
    1. PE
    2. Right heart failure
    3. ↑ PEEP/autoPEEP
    4. Hypotensive shock (↓ perfusion/ventilation)

If Deadspace/Tidal Volume (V_D/V_T) > 0.6 → usually not weanable;
Anatomic deadspace (airway → bronchiole) – 150 mL; (in a normal adult ≈ 2 mL/kg)
Physiologic V_D = anatomic V_D + any well ventilated/poorly perfused alveoli

<u>During apnea</u>: $PaCO_2$ ↑ 6 mmHg during the first minute and 3 mmHg per minute thereafter (if CO_2 production normal and constant)

Systematic way to identify etiology of low blood pressure (consider *all* variables in the equation):



6 problems in the torso that must be ruled out quickly in an acutely ill patient

1. Tension pneumothorax
2. Ruptured aneurysm
3. Cardiac tamponade
4. Aortic dissection
5. Myocardial infarction
6. Pulmonary embolism

Most Influential Recent Trials/Papers in Critical Care Medicine (reverse chronological):

Evidence-Based Clinical Practical Guideline for the Prevention of Ventilator-Associated Pneumonia [Ann Int Med 141:305, 2004]

These guidelines provide excellent evidence-based recommendations for the prevention and treatment of VAP. Recommendations included: orotracheal intubation, use of closed suction system, heat and moisture exchangers, and semi-recumbent positioning. Treatments not recommended included: use of sucralfate, use of topical antibiotics. Because of conflicting and/or insufficient data no recommendations were made about: chest PT, timing of tracheostomy, prone positioning, prophylactic IV antibiotics.

Eliminating Catheter-Related Bloodstream Infections in the Intensive Care Unit [Crit Care Med 32;10:2014, 2004]

A prospective cohort control trial in a single institution ICU aimed at eliminating CR-BSI by implementing multifaceted interventions including: hand washing before gloving, using of full sterile technique, and chlorhexidane prep. This study showed a decrease in CR-BSI rate from 11.3/1000 catheter days to 0/1000 days, which was extrapolated to prevent 43 CR-BSIs, 8 deaths, and over $1.9 million

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit [NEJM 350;22:2247, 2004]

A multi-center, randomized, double-blinded trial which compared 28-day outcomes of patient in the ICU who were administered normal saline or 4% albumin for resuscitation. 3500 patients were randomized into each arm and there were no differences found in deaths, organ failure, number of days spent in ICU, number of days in hospital, requirements for mechanical ventilation, or days of renal replacement.

Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults [JAMA 290;19:2588, 2003]

A prospective, randomized, multi-center, double-blinded study to determine if 8 days of antibiotic therapy is as effective as 15 days in patients with microbiologically proven VAP. The patients treated for 8 days had similar rates of mortality and recurrent infections. However, in patients with non-fermenting gram-negative bacilli, including *Pseudomonas aeruginosa*, higher rates of recurrent pulmonary infection (40.6% vs. 25.4%) were seen.

Effect of Treatment with Low Dose of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock [JAMA 288;7:862, 2002]

A placebo-controlled, randomized, double-blind, multi-center trial to assess the role of low dose corticosteroids in the management of patients in septic shock with relative adrenal insufficiency. Over 300 patients were stimulated with corticotripin and responders (appropriate stimulation) and non-responders (inappropriate stimulation) were randomized to receive either steroids (hydrocortisone 50 mg q6 + fludrocortisone 50 μg qd) or placebo. Amongst non-responders there were statistically fewer deaths (53% vs. 63%) and statistically less time spent on vasopressors in the steroid treatment group. Amongst responders there were no differences between steroid and placebo treatments.

Intensive Insulin Therapy in Critically Ill Patients
[NEJM 345;19:1359, 2001]
A prospective, randomized, controlled study involving mechanically ventilated patients to evaluate the impact of tight glucose control in critically ill patients. Over 1500 patients were randomized receive either tight glucose control (maintenance of blood glucose between 80 and 110 mg/dL) or conventional glucose control (insulin only when blood glucose > 215 mg/dL; maintenance between 180 and 200 mg/dL). At 12 months intensive insulin therapy reduced overall mortality from 8% to 4.6% (p<0.04). In addition to 12 month mortality, intensive insulin therapy also led to decreased in-hospital mortality, bloodstream infection, acute renal failure, and red cell transfusion requirements.

Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis
[NEJM 344;10:699, 2001]
A randomized, double-blinded, placebo-controlled, multi-center trial evaluating the use of recombinant activated human protein C in the treatment of severe sepsis. Nearly 1700 patients with SIRS and organ failure due to acute infection were randomized to either treatment (24 μg/kg/hr recombinant activated protein C for 96 hours) or placebo. The mortality in the placebo group was 30.8% vs. 24.7% in the treatment group. There was an absolute reduction in the risk of death of 6.1% (p=0.005). The incidence of serious bleeding was higher in the treatment group (3.5% vs. 2.0%, p=0.06). This study is noteworthy in that it is the first agent (of countless agents) to show a decreased mortality in septic patients.

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation
[NEJM 342;20:1471, 2000]
A randomized, controlled trial in a medical intensive care unit involving 128 patients receiving mechanical ventilation and continuous infusions of sedating drugs. In the treatment group the patients were awaken daily by temporary discontinuation of the sedatives. In the control group the sedation was only discontinued at the discretion of the treating physician. The median duration of mechanical ventilation in the treatment group was 4.9 days vs. 7.3 days in the control group (p=0.004) and the median length of stay in the ICU was 6.4 days vs. 9.9 days (p=0.02). There were also fewer diagnostic studies to assess changes in mental status in the treatment group (9% vs. 27%, p=0.02).

Low-Dose Dopamine in Patients with Early Renal Dysfunction: A Placebo-Controlled Randomised Trial
[The Lancet 356:2139, 2000]
Over 300 patients were randomized in a placebo-controlled, double-blinded study to receive either placebo or "renal-dose" dopamine (2 μg/kg/min) via continuous infusion upon admission to an ICU. Patients with pre-existing renal dysfunction were excluded. Use of dopamine did not confer an advantage in peak serum creatinine, need for renal replacement, length of stay in ICU, or overall hospital stay. This study was essentially the final nail in the coffin of the debate over the myth of "renal-dose" dopamine.

Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome
[NEJM 342;18:1301, 2000]
This trial randomized patients across multiple centers with acute lung injury and ARDS to receive either "traditional" ventilatory tidal volumes of 12 mL/kg (with plateau pressures up to 50 cm H_2O) or "low tidal volumes" of 6 mL/kg (with plateau pressures up to 30 cm H_2O). The trial was stopped after 861 patients were enrolled because mortality was lower in the low tidal volume group (31.0% vs. 39.8%, p=0.007) and the number of days without ventilatory use was also lower.

A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care [NEJM 340;6:409, 1999]

This multi-center study randomized non-bleeding, euvolemic, critically ill patients who had a Hb concentration of ≤ 9.0 g/dL within 72 hours of admission to the ICU to one of two transfusion strategies:

- Liberal transfusions: transfusion was initiated when Hb concentration fell below 10.0 g/dL and was subsequently maintained between 10.0 and 12.0 g/dL
- Restrictive transfusion: transfusion was only initiated when Hb concentration fell below 7.0 g/dL and was subsequently maintained between 7.0 and 9.0 g/dL

Overall, the 30-day mortality was similar between the two groups. However, amongst patients with APACHE II score ≤ 20 (i.e. less ill) mortality was lower in the restrictive group (8.7% vs. 16.1%, p=0.03), as was the case in patients younger than 55 (5.7% vs. 13.0%, p=0.02). There was no difference amongst patients with clinically significant cardiac disease (20.5% vs. 22.9%).

A Prospective Study of Indexes Predicting the Outcome of Trials of Weaning From Mechanical Ventilation

[NEJM 324; 21:6170, 1991]

This study evaluated a number of indexes determined from 36 patients' successful or unsuccessful extubations and prospectively applied them to a cohort of 64 patients in an effort to predict successful extubation. Of all the parameters studied, the rapid shallow breathing index (RSBI, affectionately referred to as the "Tobin" despite the fact that Karl Yang shared authorship with Martin Tobin on this landmark paper) defined as the ratio of respiratory frequency, f, to tidal volume in liters, Tv, was the most accurate predictor of success (RSBI < 80) or failure (RSBI > 105) of extubation, where "success" was defined as not requiring intubation at 24 hours.

Hemostasis & Transfusion

Three reactions mediate the initial hemostasis response following vascular injury:

1. Vascular response to injury (injury exposes subendothelial components and induces vasoconstriction *independent* of platelet function)
2. Platelet adherence and aggregation
3. Generation of thrombin

Aspirin, indomethacin, and most other NSAIDs block formation of PGG_2 and PGH_2 resulting in decreased platelet aggregation

"Normal" bleeding time is 5 – 7 minutes. The value of the bleeding time in clinical evaluation is very limited. It can be normal in patients with platelet disorders, even those who have taken aspirin, and can be prolonged in subjects with normal hemostasis. Therefore, it cannot be trusted. Much of the limitation is probably related to technical issues, such as the depth of the cut, the vascularity of the cut tissue, etc. Also, the "normal" range is logarithmically distributed, making interpretation of 7 – 12 minute BTs impossible.

- PT and PTT only elevate when factors reduce below approximately 20 to 40% of normal (varies with the individual factor and with the individual laboratory methods/reagents. Generally the tests are adjusted to become "abnormal" when any of the factors is in a range that might not support normal hemostasis. A very common cause of a prolonged aPTT in a patient with a negative bleeding history is a "lupus anticoagulant," a laboratory artifact not associated with a bleeding tendency.)
- 20% of normal is usually satisfactory for general hemostasis, but > 50% for major surgery

Pre-operative evaluation:

- If a patient has a positive bleeding history and requires minor surgery: PT, PTT, BT, fibrin clot solubility
- If a patient has a positive bleeding history and requires major surgery: PT, PTT, BT, fibrin clot solubility, platelet function studies, F VIII levels, F IX level, alpha-2-antiplasmin level

<u>As a rule</u>:

1 unit platelets for 2 units RBC. For a total blood volume replacement, expect platelet count of 250,000 to drop to 80,000.

1 mg protamine required for every 100 U of heparin (up to 100 mg total, or 50 mg over 10 min). If the aPTT is measurable (i.e., less than 2 minutes), the plasma concentration of heparin should be low enough (i.e., < 1 U/mL) that 20 – 30 mg protamine will be very effective. However, the protamine may be cleared before the heparin is completely gone. So another dose may be required in an hour or two.

<u>Clotting Factors (see figure below):</u>
Intrinsic (PTT): exposed collagen + XII → XI → IX → X, which activates thrombin → fibrin
Extrinsic (PT): TF + VII → activated X → thrombin → fibrin
Note: X is common to both
VIII is only factor not solely made in liver (made by endothelial cells)

Bleeding Disorder

Von Willebrand disease is the most common inherited bleeding disorder (1% of population; AD)

- symptomatic bleeding in 1/1000
- long PTT and bleeding time (usually)
- associated with variable deficiencies in both vWF and factor VIII; platelet defect is also present (although this is called "platelet type" vWd, it is different from the other types because the defect is in the platelet membrane, not in the vWf).
- + Ristocetin test (Ristocetin "cofactor" [i.e., vWf] activity is the laboratory test for vWf activity, as opposed to antigen level.)
- give DDAVP (releases intracellular stores of vWF) for Type I (low vWF) (The effect only lasts for < 12 hours. Repeat doses may be less effective.) (vWf concentrates are available when extended replacement is needed. These are not the same as standard fVIII concentrates, which contain very little, if any, vWf.)
- give cryo for Type II (qualitatively poor vWF) and III (low vWF)

Hemophilia A (factor VIII deficiency) X-linked recessive; ≥ 5% normal levels fVIII considered mild

- DON'T aspirate hemarthrosis
- Tx with factor VIII concentrates (to 100% pre-op levels)
- ↑ PTT; normal PT

Hemophilia B (factor IX deficiency) X-linked recessive

- Tx with factor IX concentrates
- ↑ PTT; normal PT (to 50% pre-op levels)

Glanzman's thrombasthenia: Platelets have IIb/IIIa deficiency → ↓ aggregation abnormalities due to decreased fibrinogen binding. Extremely rare.

Bernard Soulier: Platelets have Ib deficiency → ↓ adherence to exposed collagen von Willebrand factor. Extremely rare

Hypercoagulable States

APC Resistance: **most common inherited hypercoagulable** state; AD; 90% associated with FV (Leiden) mutation → ≈ 5% prevalence in Caucasian populations, much less in others. Spontaneous DVT typically only occur in thrombophilic families, who probably carry other prothrombotic genes in addition to FVL. In the general population (where FVL is likely to be the only prothrombotic gene in most individuals) FVL is rarely associated with thrombosis.

ATIII Deficiency: rare, 1/5000; don't respond to heparin unless given FFP (to replace ATIII); can't treat DVT without giving FFP The most common forms of "AT deficiency" are identified because the AT molecule does not bind heparin normally. These actually are not associated with an increased risk of thrombosis. Specialized tests are necessary to identify the individuals with the dangerous form of AT deficiency.

Lupus Anticoagulant: anti-phopholipid Abs; dx: long Russell's viper venom time; long PTT; confirmed by assays that demonstrate the dependence of the anticoagulant activity upon the concentration of phospholipid present.

HIT: Heparin induced thrombocytopenia, due to an antibody to the complex of heparin and platelet factor-4, which is secreted by stimulated platelets. Typical onset after 5 – 10 days of heparin, earlier if recent prior heparin exposure. Half of HIT patients will develop thrombosis within 30 days unless they are treated with non-heparin anticoagulants. "White clot" treat with **hirudin** or **argatroban** (direct thrombin inhibitor) or **danaparoid** (indirect thrombin inhibitor); dextran is **not** sufficient for treating clots resulting from HIT

For each ↓ in core body temperature by 1 ^{0}C → blood viscosity ↑ by 2 – 3%

Transfusions:
Banked blood has ↓ 2,3-DPG → left shift (holds O_2 tightly)
Risks: CMV highest; HIV: 1:500,000; Hepatitis C: 1:30,000 – 150,000

Heparin before Coumadin

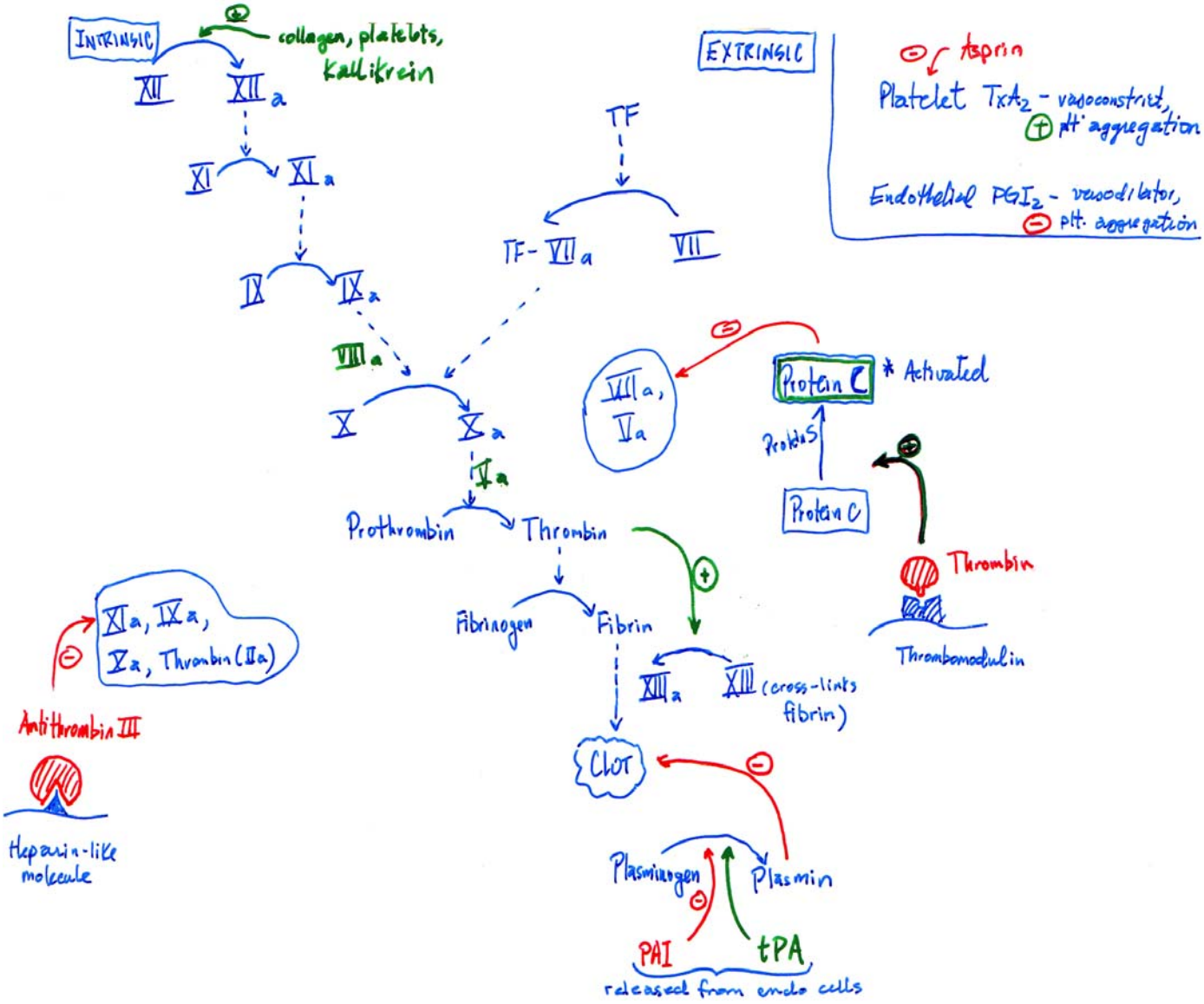
Heparin must be given for 3 to 4 days before coumadin when anti-coagulating patients to protect against coumadin skin necrosis if they have ATIII, Protein C, or Protein S deficiency.
For years cardiologists have started Coumadin without heparin and not recognized any problem, presumably because significant protein C and S deficiency are so rare. However, Coumadin alone is definitely inadequate/deleterious for the treatment of acute thrombosis. Coumadin and heparin can be started together, since the effect of Coumadin does not appear till 2 – 4 days later, after the patient should have been theratpeutically anticoagulated with heparin for several days. It is especially important that patients with HIT not start Coumadin until they have been treated with a non-heparin parenteral anticoagulant.
ALL patients with thrombosis to receive coumadin should receive heparin for 3 – 4 days because the half-life of the *anti*coagulation factor, protein C, is much shorter than the vit K *pro*coagulant factors (II, IX, X).

Table 2—*Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis**

Level of Risk Examples	Calf DVT, %	Proximal DVT, %	Clinical PE, %	Fatal PE, %	Successful Prevention Strategies
Low risk Minor surgery in patients < 40 yr with no additional risk factors	2	0.4	0.2	0.002	No specific measures Aggressive mobilization
Moderate risk Minor surgery in patients with additional risk factors; nonmajor surgery in patients aged 40–60 yr with no additional risk factors; major surgery in patients < 40 yr with no additional risk factors	10–20	2–4	1–2	0.1–0.4	LDUH q12h, LMWH, ES, or IPC
High risk Nonmajor surgery in patients > 60 yr or with additional risk factors; major surgery in patients > 40 yr or with additional risk factors	20–40	4–8	2–4	0.4–1.0	LDUH q8h, LMWH, or IPC
Highest risk Major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state; hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury	40–80	10–20	4–10	0.2–5	LMWH, oral anticoagulants, IPC/ES + LDUH/LMWH, or ADH

*Modified from Gallus et al[60] and International Consensus Statement.[74]

[Geerts WH, et al., 2001 Chest 119:132S]


INTRINSIC
collagen, platelets, kallikrein
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
Xa
Va
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIIIa
XIII (cross-links fibrin)
Clot
Plasminogen
Plasmin
PAI
tPA
released from endo cells
EXTRINSIC
TF
TF-VIIa
VII
aspirin
Platelet TxA2 - vasoconstrict, plt aggregation
Endothelial PGI2 - vasodilator, plt. aggregation
VIIIa, Va
Protein C
* Activated
ProtS
Protein C
Thrombin
Thrombomodulin
XIa, IXa, Xa, Thrombin (IIa)
Antithrombin III
Heparin-like molecule

Metabolism

A number of vital areas of the body (**brain, renal medulla, RBC, WBC, peripheral nerves**) are **glycolytic tissues** (require a glucose source of energy for metabolism) and are unable to utilize fatty acids.

When the limited glycogen stores are depleted, this is accomplished by gluconeogenesis and recycling incompletely metabolized glucose. Primary sources of gluconeogenesis are:

1. Amino acids, derived from the breakdown of muscle proteins,
2. Glycerol, derived from the breakdown of triglycerides in adipose stores

In trauma → the hormonal milieu results in catabolism of protein stores beyond that necessary for energy needs alone
In starvation → body attempts to conserve protein wasting by adapting to allow utilization of fatty acids and ketones for fuel by **non**glycolytic tissues
In prolonged fasting → brain can actually use acetoacetate and β-hydroxybutyrate in place of glucose

Lactate and pyruvate (derived from incomplete glucose utilization) can be recycled into glucose via energy provided by fatty acid oxidation (the Cori cycle)

Late starvation → shift from liver to kidney as the primary source of gluconeogenesis (since alanine is depleted from the liver)

Hemochromatosis:
- Excessive Fe-absorption from gut → afflicts heart, liver, pancreas, pituitary
- Earliest test to become abnormal is **Fe-saturation test**

Wilson's Disease:
- AR
- defect in copper metabolism
- most important lab finding is ↓ **cerulosplasmin level** (< 20 mg/dL)
- liver copper stores elevated on biopsy

Transplant Surgery

I. Types of Rejection:

1. Hyperacute: preformed anti-donor Ab. Destruction in 24 – 48 hours. Rarely occurs with present day crossmatching techniques.

2. Accelerated: as above + memory T-cells in host. Rejection within 5 days

3. Acute: T-cell mediated. Most common. Weeks to months

4. Chronic: usually humoral response. Months to years. Currently no cure.

II. Rejection Prophylaxis, prevention, treatment:

- Corticosteriods (Prednisone): **block cytokine production** (IL-1, 2, 3, 6, TNF)
- Cyclosporin (Neoral): selectively **inhibits IL-2 secretion** and proliferation of T cells (**calcineurin inhibitor**)
- Mycophenolate Mofeil (Cellcept): **inhibit** inosine monophosphate dehydrogenase, (**de novo purine synthesis**) causing selective antiproliferative effect of T and B cells
- Tacrolimus, FK506 (Prograf): **inhibition of calcineurin**-dependent signal transduction in T-cells, **inhibiting cytokine production**
- Sirolimus, (Rapamycin): **blocks** Ca^{++}-dependent cytokine-mediated **signal transduction** (blocks the TOR protein, which arrests cell in G1) → preventing proliferation of T-cells
- Azathioprine (Imuran): **inhibits DNA synthesis** and consequent T-cell activation
- IL-2 Inhibitors (Zenapax, Simulect): monoclonal Abs against IL-2 receptors; used as induction therapy
- CD3 Inhibitors (OKT3): murine monoclonal Abs to CD3 receptor on T-cells
- Thymoglobuline: rabbit polyclonal Ab to multiple T-cell receptors. Used for both induction and rejection treatment

Long term effects of successful simultaneous kidney/pancreas transplant are:
1. *Stabilization* of retinopathy
2. *Reduced* risk of diabetic nephropathy
3. *Improvement* in nerve conduction velocity
4. No reversal of CAD or PVD

Post-transplant DM is seen in 5 – 20% of renal transplant recipients. Steroids, cyclosporine, FK506 are all diabetogenic

Completely mismatched HLA (0/6) LRRT does better than complete HLA match (6/6) cadaveric → ischemic time and quality of organ are most important determinants of graft survival

BK Virus is an important factor associated with graft nephropathy. Prevalent in 90% of population and results in nephropathy in 1 – 8% of transplant recipients (↑ by bouts of rejection, need for rejection treatment (vs. IS), **+** donor to **–** recipient); no adequate anti-viral treatment; instead must ↓ immune suppression, in particular MMF

Post-Transplant Lymphoma

- Lymphoma is 10 – 100 x more common in transplant patients than general population (Ranges from 1% incidence in kidney; 4 – 5% in heart/lung patients); especially seen in CNS
- Usually NHL B-cell lymphoma related to malignant transformation of EBV
- Reduce or withdraw immunosuppression (life before graft)
- High dose acyclovir may be effective; conventional chemotherapy generally not effective

MELD (Model for End-stage Liver Disease) Criteria for liver failure*

Score = **3.8** * ln [**bilirubin** (mg/dL)] + **9.6** * ln [**Cr** (mg/dL)] + **11.2** * ln [**INR**]
[Hepatology 2001; 33: 464-470]

*Formula predicts the risk of death in 3 months; average score for most patients being transplanted currently is 15; additional points given for tumors suspected or confirmed to be HCC

Acute Fulminant Hepatic Failure: the appearance of acute liver disease with hepatic encephalopathy in less than 8 weeks in an individual without previously known liver disease.

Stage I: Prodrome
Stage II: Impending coma (50 – 70% spontaneous recovery)
Stage III: Stupor (40 – 50% survival)*
Stage IV: Deep coma (<20% survival)*
*lactulose of little benefit

Kings College Criteria for acute fulminant liver failure requiring transplant

Acetaminophen Toxicity	**Non-acetaminophen toxicity**
▪ **pH < 7.30** after resuscitation, or ▪ INR > 6.5, ▪ Creatinine > 3 mg/dL, and ▪ Encephalopathy III – IV	▪ **INR > 6.5**, or **3/5 below**: ▪ Age < 10 or > 40 ▪ Drug induced or cryptogenic etiology ▪ Jaundice > 7 days before encephalopathy ▪ INR > 3.5 ▪ Serum bilirubin > 17.5 mg/dL

Upper limits of acceptable cold ischemic times:

Heart:	6 hours
Lung:	4 – 6 hours
Liver:	24 hours
Kidney:	48 hours
Pancreas:	24 – 48 hours

Warm ischemic time must be less than 60 minutes

Hepatic arterial thrombosis is main cause of immediate graft loss following liver transplant:

- 3 – 5 % in adults
- 5 – 8 % in children

HCC patients are candidates for liver transplant provided[§]:

1. A single tumor < 5 cm, or
2. Up to three tumors individually < 3 cm

[§]Milan criteria

Hepatorenal Syndrome

- 10% of hospitalized patients with cirrhosis and ascites develop
- progressive oliguria → ↑Cr, ↓CO, ↓BP
- similar laboratory findings to prerenal azotemia (UOP < 500 mL/24 hours, U_{Na} < 10 mEq/L, Uosm > Posm)
- physiology: splanchnic vasodilation (associated with ↑ NO) → ↓SVR → ↓renal perfusion
- only effective treatment is hepatic transplantation → renal function usually returns to normal

Nutrition

Energy Capacity: (1 calorie = energy to take 1 mL water from 14.5 → 15.5 ^{0}C at 1 atm)
Fat: 9 kcal/g
Protein: 4 kcal/g (but aqueous, so only 1 – 2 kcal/g when utilized)
Carb: 3.4 kcal/g

RQ = ratio of CO_2 produced to O_2 consumed = 1.0 for carbs; 0.7 for fats; >1 for proteins

Essential Amino Acids: **2L, 2T, VIP & Me** (Leucine, Lysine, Threonine, Tryptophan, Valine, Isoleucine, Phenylalanine, & Methionine)

$[N]_{Balance}$ = $[N]_{In} - [N]_{Out}$, where
$[N]_{In}$ = [g protein/6.25 g protein per g N]
$[N]_{Out}$ = [UUN (mg N/100 mL urine) * 1000 mL/L * 24 hour urine volume * g N/1000 mg N + 3]

Branched Chain Amino Acids: **leucine, isoleucine, valine** (metabolized in muscle; **all essential**)

Aromatic Amino Acids: tyrosine, **tryptophan**, **phenylalanine** (⅔ **essential**)

Glutamine is #1 AA in body; most rapidly used in stress; fuel of the enterocytes (when depleted → brush border breakdown); the addition of glutamine to enteral or parenteral feeds may ↓ sepsis [Houdijk AP, et al. Lancet 1998;352:772]
Hydroxybutarate: fuel of colonocyte
Arginine: most important for immune function

In hepatic failure → Minimize aromatic AA; give branched chain only
In renal failure → give essential AA only

Fatty Acid Metabolism:
-medium chain FA can be absorbed directly via portal blood, hence bypassing the lymphatic system
-long-chain FA poorly tolerated by patients with compromised gut function; medium chain better, since absorbed directly

Three Main forms of Fat are found in the body:
1. **Glycerides** (95 – 98% of body stores), essential (see below) or nonessential; most dietary sources are medium (6 C) and long (> 11 C)
2. Phospholipids (mainly in cell membranes and myelin sheaths)
3. Sterols, comprised primarily of cholesterol

Essential Fatty Acids: (unsaturated bond within the last 7 carbons of the FA chain at the methyl end)
linoleic (TPN mostly consists of this), **linolenic**, **arachidonic**; can NOT be synthesized by humans

Ω-6-polyunsaturated fats (linoleic) → precursors for PGs and leukotrienes

Fat digestion: micelles to enterocytes → chylomicrons to *lymphatics* (to junction LIJ/subclavian)

Energy Storage:

- Fats: 25% BW = fat; so if 70 kg → 17 kg fat → **160,000 kcal**
- Carbs: circulating ≈ 80 kcal; Liver glycogen ≈ **300 kcal**;
- Muscle glycogen ≈ **600 kcal** (exhausted in ≈ 24 hours)
- Proteins: 12 kg → **48,000 kcal**; but no access unless late starvation
  (Main advantage of dextrose in IVF is to obviate the need for protein catabolism)

½ glucose + ½ (fructose + galactose) → 40% Liver glycogen + 60% Muscle glycogen

Nonprotein calorie to gm Nitrogen ratio of 150:1 generally appropriate (both adults and children)

*Patients with **major burn** (> 25% TBSA) have greatest caloric requirements

Assessing Nutritional Status:

Albumin: 18 day $T_{½}$
Prealbumin: 24 hour $T_{½}$
Retinol binding protein: 12 hour $T_{½}$ (most sensitive)

Injured patients can maximally oxidize glucose at 5 – 6 mg/kg/min (above this → osmotic diuresis, ↑respiratory quotient)

Remember: Metabolic Alkalosis → require K^+

Marasmus = depletion of **body fat;** relative sparing of visceral protein (simple starvation)
Kwashiorkor = acute **visceral protein depletion** (sparing of fat; acutely ill patients)

Deficiencies:

- **Phosphorus**: weakness, paresthesias
- **Zinc**: perioral rash, alopecia, poor wound healing, impaired immunity, change in taste
- **Copper**: anemia, neutropenia, pancytopenia
- **Iron**: anemia
- **Linoleic acid**: dermatitis, alopecia, blurred vision, paresthesias
- **Selenium**: cardiomyopathy, weakness, alopecia
- **Vitamin A**: night blindness, skin keratosis
- **Chromium**: glucose intolerance (relative diabetes), peripheral neuropathy
- **Biotin**: alopecia, neuritis

Fluids & Electrolytes

Sodium concentration must be corrected by 2 – 3 mEq per 100 mg/100 mL elevation in blood glucose above 100 [i.e. as BG↑ → Na^+↓]

- Gastric losses (vomiting) usually require hypercholoremic replacement
- Post-pyloric losses require balanced salt solution (except pancreatic fistula, which require high HCO_3 replacement)
- Patients with GI losses initially lose isotonic fluid → but the body always tries to protect volume status (even at the expense of tonicity)

Insensible Losses:

- Skin > Lung: total 600 – 900 mL/day
- 0.9% NaCl = 9 gm NaCl per L

HYPO Mg^{++} and Ca^{++} both have HYPERexcitability: ↑reflexes, tetany
Cannot correct ↓Ca^{++} with ↓Mg^{++} since ↓Mg^{++} induces skeletal resistance to PTH and may impair PTH synthesis

Prolonged vomiting: results in hypokalemia, hypochloremia, metabolic alkalosis; early urine is alkaline…BUT as Na^+ is conserved → H^+/K^+ are lost with HCO_3 → resulting in **paradoxical aciduria**

Note: The most important treatment for **hyperkalemia** is **Ca^{++}** (vs. insulin, HCO_3, etc.) because it is the only agent that actually **stabilizes the myocardium**

Mechanisms of Diarrhea:
Osmotic Diarrhea: accumulation of poorly absorbed solutes in lumen → secretion of H_2O into lumen
Secretory Diarrhea: excessive electrolyte secretion (toxins, neuroendocrine tumors) → stimulate cAMP production
Inhibition of Absorption: unabsorbed free fatty acids or bile salts → decreased H_2O absorption

Sweat: normally hypotonic, but can approach isotonicity during periods of high secretion; Na^+ secretion parallels Cl^- (both < plasma); K^+ approaches plasma concentration; urea and NH_3 >> plasma concentrations

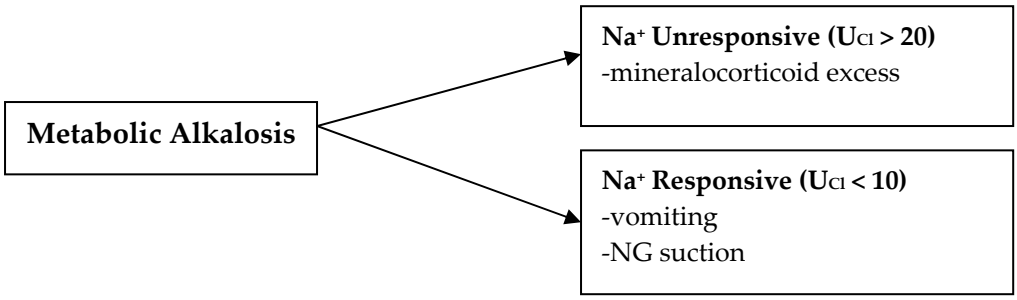
Renal Physiology

Kidney can tolerate ischemia up to 15 minutes without adverse event
15 – 90 minutes produces varying degrees of chronic damage
> 90 minutes usually irreversible damage

In response to ↓ renal blood flow or pressure → juxtaglomerular apparatus releases **renin**, which interacts with the α_2-globuline **angiotensinogen** (synthesized in the liver) to produce **angiotensin I**.
In the lung, **angiotensin I → angiotensin II** (half life: 4 minutes) increases BP by two methods:

1. direct vasoconstrictor properties
2. stimulating the release of aldosterone from the ZG of the adrenal cortex (→ ↑ Na^+ and H_2O absorption in distal tubules)

3 reasons for contraction (metabolic) alkalosis:
1. HypoK^+ (K^+ leaves cell to compensate, HCO_3 follows to maintain electrical neutrality
2. Volume depletion
3. Hyperaldosteronism (diuretics)



Renal Failure Index = $U_{Na} * P_{Cr}/U_{Cr}$ if < 1 → prerenal oliguria

70% of nephron mass is damaged before BUN and Cr levels rise
FENa > 3 and Uosm < 350 mOsm/L represent inability of renal tubule to reabsorb Na^+ and concentrate urine

FENa = $[U_{Na}/U_{Cr}]/[P_{Na}/P_{Cr}]$ < 1%, BUN/Cr > 30, U_{Na} < 20 → all indicate low volume

If patient has received lasix and/or hypertonic NaCl during previous 48 hours → FENa may be of limited value. Instead use **Fractional Excretion of Urea (FEUN):**

FEUN = $[U_{UREA}/U_{Cr}]/[P_{UREA}/P_{Cr}]$ < 35% → suggestive of pre-renal azotemia

Definitions of low urine output state:

Polyuric: >1000 mL/24 hours
Nonoliguric: 400 – 1000 mL
Oliguric: 100 – 400 mL
Anuric: <100 mL

In High Output Renal Failure [↑BUN, u/o > 1500/24h] → mild metabolic acidosis: give Na^+ with *lactate*, since Cl^- will worsen acidosis

Differential Dx of elevated BUN or Cr (one out of proportion to the other):

↑Cr/BUN	**↑BUN/Cr**
Renal failure	Dehydration
Muscle breakdown	+N-balance
	GI bleed
	Hepatic failure

Transtubular K^+ Gradient (TTKG)

[Urine $_K$/Plasma $_K$, *mEq/L***]** divided by **[Urine $_{osm}$/Plama $_{osm}$,** *mosm/kg***]**

Normal is 8 – 9; may be up to 1 with potassium loading
If K^+ is high and TTKG < 7 → implies hypoaldostoronism

Appropriate responses
Hypokalemia <3
Hyperkalemia >10

If the specific gravity of urine is normal → kidney is working, *UNLESS* artificial osmoles are present including:

- Mannitol
- IV contrast
- High glucose load
- Methanol

Immunology/Infections

IgG: opsonin (along with IgM) to fix complement (2 IgG's or 1 IgM), #1 in serum; crosses placenta
IgM: made first; levels ↓ after splenectomy
IgA: in secretions
IgE: allergic reactions, type I hypersensitivity
IgD: largely unknown

Complement:
C3a, C5a and anaphylatocins; C5 – 9: MAC (membrane attack complex)

Hypersensitivity
Type I: immediate; IgE mediated; e.g. anaphylaxis
Type II: cytotoxic reactions; IgG or IgM; e.g. ABO/Rh incompatibility
Type III: immune-complex mediated; deposition of complex; e.g. serum sickness, rheumatoid arthritis
Type IV: delayed-type: T Cells (CD4+); e.g. contact dermatitis

HIV Patients
-have increased risk of developing NHL (high-grade B-cell) and Kaposi's sarcoma

Advantages of Zosyn

I. vs. 3rd generation cephalosporins
-enterococci, MSSA
-pseudomonas, klebsiela
-4+ anaerobes

II. vs. quinolones
-enterococci, MSSA
-pseudomonas
-4+ anaerobes

III. vs. Unasyn
-MSSA
-E.coli, pseudomonas, other G-
-4+ anaerobes

IV. Timentin (better for stenotrophomonas)
-enterococci, MSSA
-E.coli, pseudomonas, other G-
-4+ anaerobes

Remote infection (e.g. UTI) ↑ the risk of surgical site infection by at least 7%

Burns

1. **Silver nitrate**: Broad spectrum, painless, cheap, poor eschar penetration, may cause electrolyte imbalance

2. **Silver sulfadiazine (Silvadine)**: Painless, no electrolyte abnormalities, no occlusive dressing required, little eschar penetration; misses Pseudomonas, idiosyncratic neutropenia; good for small burns

3. **Mafenide**: Penetrates eschars, broad spectrum (but misses staph); pain and burning on application; 7% have allergic reactions; may cause acid-base disturb (metabolic acidosis); agent of choice in already-contaminated burns; water-soluble

Parkland Formula for Burns

Add Maintenance Fluids to below:

1. First 24 hours: 4 mL/kg/%BSA. Half over 8 hours, then rest over 16 hours.
2. Second 24 hours: Fluid requirements are 50 – 75% of the first days. Use weight, electrolytes, UOP & NGT to determine concentration and rate.
3. Withhold K^+ for first 48 hours because of large tissue release.
4. Keep UOP @ 0.5 mL/kg/hour

Burn patients initially have drop in CO → then are HYPERdynamic

Burn Wound Infection

Reduced by:
1. Aggressive resuscitation
2. Early debridement
3. Topical antibiotic therapy

To confirm infection need biopsy with quantitative culture (10^5): must include **normal and burned skin (2x2 cm with normal underlying skin)**

Skin & Wound Healing

Three major stages of wound healing:
1. Inflammatory Phase (10 minutes – 2 weeks)
2. Proliferative Phase (3 – 6 weeks)
3. Remodeling Phase (up to 1 year)

Inflammatory Phase: Hemostasis & Clot formation
- Platelet plug mediated by thromboxane A2, thrombin, PF4, C5a (most important complement)
- Monocytes must be present for normal wound healing
- Collagen and basement membrane proteins → clotting factor activation
- Vasoconstriction → decrease blood loss and allow clot formation (< 24 hours)
- Platelet degranulation: PDGF and TGF-β; chemotaxis and proliferation of inflammatory cells
- Vasodilation (> 24 – 48 hours) → supplies cells and substrates for wound repair

Proliferative Phase:
- Formation of matrix of fibrin and fibronectin
- Initiation of collagen formation
- Proliferation of fibroblasts
- Growth factors from macrophages initiate angiogenesis (especially FGF)
- Cross-linking of collagen → requires Vit C
- Wound is now a scar

Remodeling Phase:
- Collagen equilibrium
- Increase tensile strength (abundance of Type I cross-linking)
- Diminishing capillary density and fibroblasts

Tensile Strength of Wound*:
Early: fibrin
Late: collagen cross-linking
***Tensile strength is never equal to pre-wound**

10^5 organisms/cm^2 is enough to retard wound healing

As time progresses: Type III (proliferation) collagen and Type I (mature)
Ultimately the ratio of I:III is 8:1 (i.e. that of normal skin)

I	Most abundant, found in scar
II	In cartilage
III	In *would healing* (low in Ehler Danlos)
IV	In basement membrane
V	Found in cornea

Pharmacology

Clues to drug overdose:

1. **Eyes**
i) Miosis: opiates, org. phos, barbs
ii) Mydriasis: amphetamines, cocaine, anti-chol, ethanol, mushrooms, LSD
iii) Nystagmus: PCP, phenytoin, ethanol, VPA

2. **Mouth**
i) Dry: anti-chol, opiates, SSRIs
ii) Very salivary: org. phos

3. **Skin** → look for needle tracks
i) Hot, dry: anti-chol
ii) Very pink: CO
iii) Very sweaty: org. phos

Pharmacology

↑P–450	**↓P–450**
Phenobarb	INH
Rifampin	Cimetidine
PTN	Benzos
Carbamazepine	Phenothyazines
	TMP-SMX

Lidocaine toxicity: tinnitus, peri-oral numbness → neuro symptoms → cardiovascular changes

Local Anesthetics (2 classes)

Amino Esters	**Amino Amides***
Tetracaine	L**i**docaine
Cocaine	Mep**i**vacaine
Procaine	Bup**i**vicaine
Chloroprocaine	Et**i**docaine
	* All have an "**i**" before -caine

Malignant Hyperthermia: can be genetically transferred; triggered by halogenated inhalational agents (1 in 250,000); can also be triggered by succinylcholine (1 in 60,000); earliest sign is rise in CO_2; hyperthermia is a relatively late finding; treat with dantrolene.

Ketamine: does not ↓ BP, but does ↑ ICP; good in children; **avoid in head trauma, cardiac disease**

Propofol: rapid onset and short duration; ideal for patients with altered neuro exam to allow for frequent neuro examinations; does ↓ BP; does not provide analgesia

4 Components of (Informed) Consent:

1. Disclosure
2. Comprehension
3. Competency
4. Voluntariness

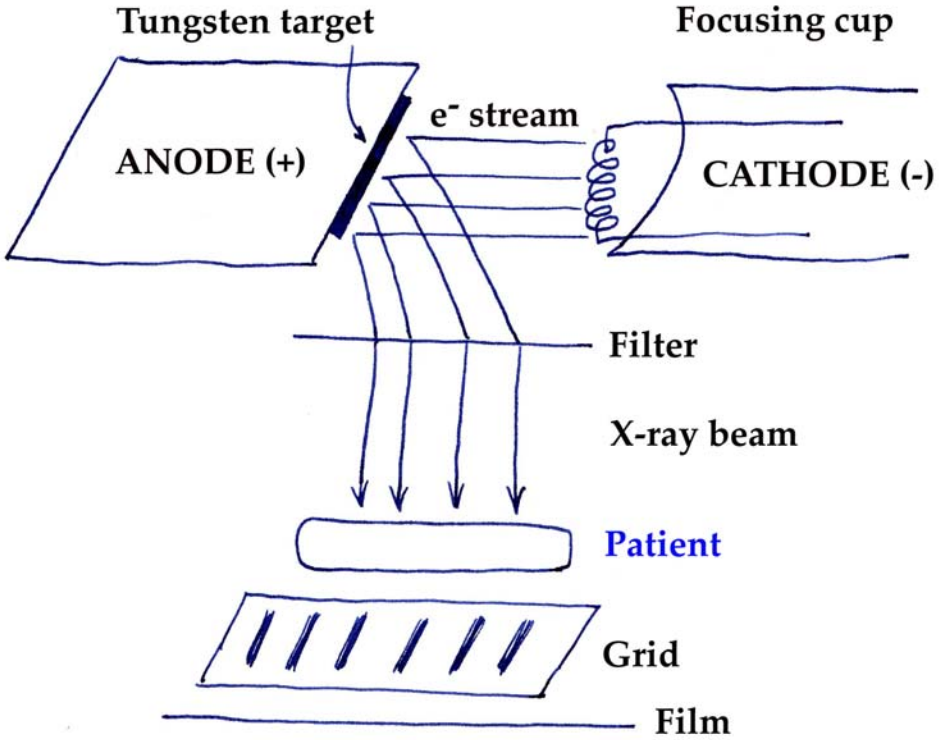
Radiology

Basics

- Each modality emits a source of **energy**. For conventional x-ray and CT the energy emission is a photon generated by an **electron (e^-)** collision with its target. For MRI the energy emission is a spinning dipole of a **proton (H^+)** converted into radiofrequency current. For PET the energy emission is a gamma ray produced by the collision of a **positron (e^+)** and an electron (e^-).
- Distinguish between **imaging** tests (e.g. conventional CT, MRI, U/S) and **functional** tests (e.g. PET, HIDA, U/S for gallbladder ejection time, etc.)

I Basic Roentgenogram

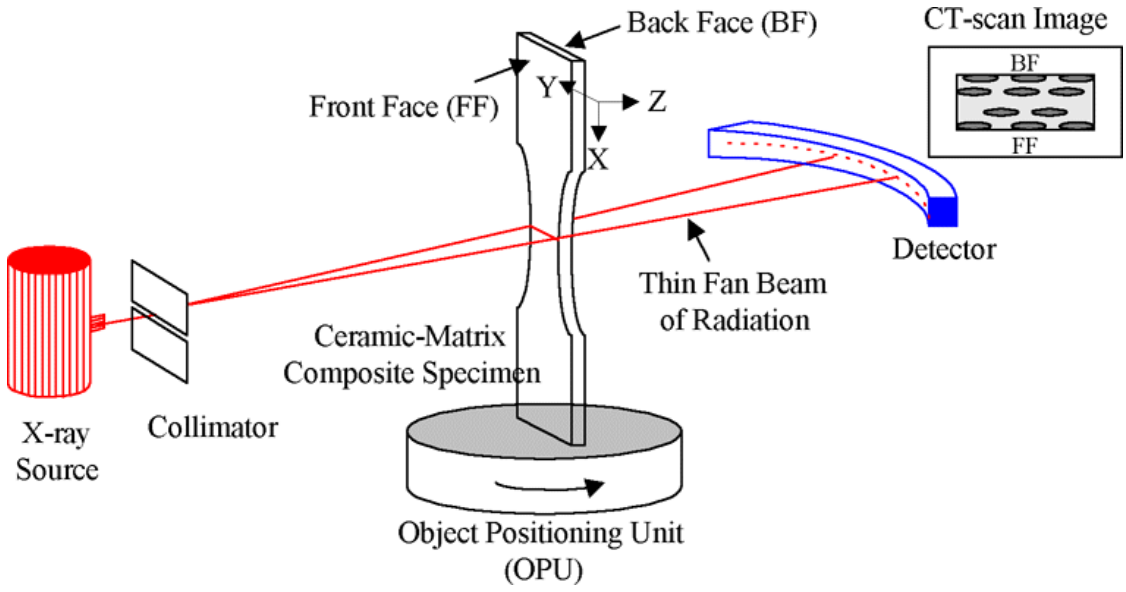
- Discovered by William Roentgen in 1895
- High voltage current (50 – 120 kV) is run through a cathode containing wire coil (filament) providing a constant stream of high speed electrons to a tungsten target on an anode.
- Most of the energy is dissipated as heat, but ≈ 1% of the electron energy is converted to x-rays, which are deflected towards a filter that collimates the beams towards the anatomic portion of interest before they pass through the body of the patient. Collimator also filters out very high energy and low energy x-rays
- The density of the tissue encountered determines the x-ray absorption: less dense tissues (e.g. lung) allow the beam to travel through with minimal deflection; more dense tissues (e.g. bone) cause the x-ray to scatter.
- A grid with lead bars in it removes the scattered beams by absorbing the rays
- Finally, the beam interacts with an x-ray cassette containing a fluorescent plate which emits light when struck by the x-ray onto a light-sensitive film coated with silver nitrate or a phosphor screen that is scanned with a laser or a direct CCD array for digital radiographs
- Hence, more x-ray (less dense tissue) → darker image



II Computed Tomography (CT)

- Essentially, an advanced form of "conventional" x-ray where a series of two-dimensional images (or slices) of a body are constructed by rotating the x-ray source or detector around the body (this gives the information for a given slice) and parallel to the axis of the body (this gives information from one slice to another). Now, volume scans are obtained as the patient moves continuously through the scanner as the beam rotates around subtended a "helix" on the patient. The data are collected as a volume and then computationally divided into "slices" that are displayed.
- Hounsfield units, named after Sir Godfrey N. Hounsfield, the British engineer who developed the first clinically useful CT machine (at the EMI corporation which was also the record company owned by the Beatles at the time. Sir Godrey won the Nobel Prize, unusual for an engineer), are a standardized unit for reporting and displaying the reconstructed x-ray computed tomography values.
- They range from **–1000** for air to **+3095** for lead; **water is 0**; this represents 4096 (or 2^{12}) bits → too many for our eyes to distinguish. Instead we get 2^8 linearly distributed bits
- Two parameters are selected: **window width** and **window level** (i.e. where it is centered). For example, a window of **(400, 40)** means we see between **–160** and **+240**; hence anything **< –160 → black** and anything **> +240 → white**

Tissue	H.U.
Air	-1000
Lung	-600
Fat	-100 → -10
Water	0
Kidney	30
Liver	50
Blood	30 → 80
Clotted blood	60 → 80
Cortical bone	500 → 2000



[*JOM-e* internet journal, Kim and Jiaw, 1998]

Use the **gallbladder** as an **"internal standard"** of 0 H.U. (i.e. water)

If there is contrast in the peritoneum, look for 3 things:

1. **Ruptured viscous (general rules)**
   - Stomach: ↑ free air, ↑ fluid
   - Small bowel: ↓ free air, ↑ fluid
   - Colon: ↑ free air, ↓ fluid

2. **Vessel extravasation**: must see clot and contrast (clotted blood will be *brighter* than "liquid" blood) on pre contrast (but the reverse on post contrast)

3. **Ruptured bladder** (intraperitoneal): must look at delayed views

The **Pouch of Douglass** will normally hold ≈300 – 400 mL of blood before overflowing → usually to **Morrison's Pouch** → then to **right subphrenic recess**

III Magnetic Resonance Imaging (MRI)

An H atom contains a single proton and behaves like a spinning bar magnet that will align with a magnetic field created by the solenoid of the MR scanner. Before a radiofrequency (**RF**) is applied the protons are aligned. The RF deflects them some number of degrees from the Z axis of the magnet → they then "relax" back to being aligned, although, the protons are spinning all the time at the Larmor frequency. The coil picks up the spinning magnetic component that is perpendicular to the main magnetic field and induces a current (Faraday's Law) → this is the signal from MRI.

The RF field is applied to the patient to make the bar magnet stand up at 90^{o} (perpendicular) to the spine. A wire (antenna) parallel to the spine, outside of the patient's body, has an alternating current formed in it, which determines the signal intensity. The magnitude of is proportional to the number of protons and the extent to which their spins are perpendicular to the Z axis. Protons predictably realign with the spine, while continuing to preceess. So there are 2 things at play here:

1. The shortening length of the spinning magnet, and
2. The lengthening magnet parallel to the spine as more and more protons realign.

The longitudinal (or restoration with the main magnetic field) realignment is known as **T1 RELAXATION**. It is a constant for a given tissue and, by definition, it is the time required for 63% of the protons to realign with the main magnetic field. It's exponential, so after 1 T1 63% have realigned, after 2 T1's 86% have realigned, after 3 T1's 95% have realigned, etc. [i.e. $1 - (0.37)^3$]

In reality, the spinning magnet shrinks even faster than predicted by the T1 decay because the spinning protons actually lose coherence and cease to spin in unison. This causes some of the remaining protons to cancel out each other's signal and further reduce the signal generated in the antenna. This process of protons randomly losing coherence and canceling out each other's magnetic fields is known as **T2 RELAXATION**. T1 and T2 are independent of each other but simultaneous and T2 relaxation is usually much faster than T1 relaxation. Again, the 63% decay is chosen to describe the constant T2. For example, after 3 T2's have elapsed the net strength of the magnetic field in the transverse plane will be 5% of original strength.

MRI exploits the fact that different tissues and states of pathology have different T1 and T2. The most common way to do this is to acquire images using a spin-echo pulse sequence, where 2 parameters are utilized: **TR (repetition time)** and **TE (echo time)**. TR is the time between RF pulses. This is the time during which T1 relaxation occurs. At the end of TR, another RF pulse is applied and those protons that have realigned with the magnetic field will be brought up again and produce current in the antenna. So TR adjusts the amount of signal received from a tissue depending on its T1 value (e.g. if TR = 3T1, the signal will be 95% intensity).

TE is the time between the first RF pulse and the observation of signal, that is, the time for T2 relaxation to occur. For example, setting TE = 2T2 would result in 15% net remaining signal intensity produced by the component of the protons in the transverse plane.

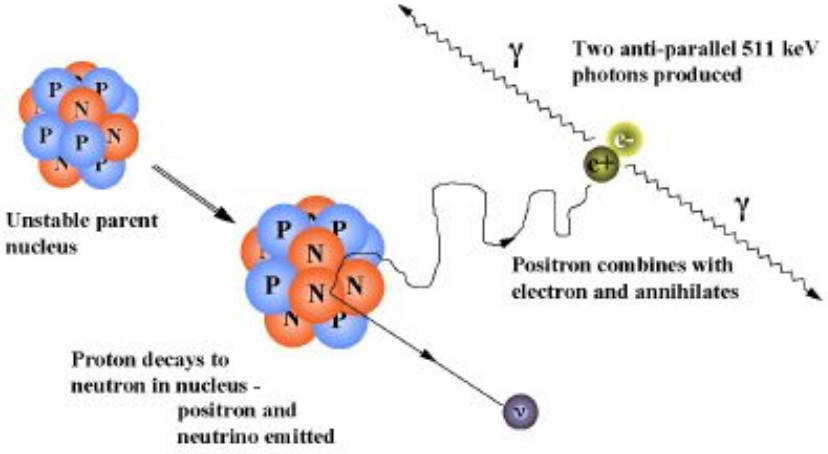
Contrast between the two tissues can be produced by the interaction of the two parameters. A very long TR will eliminate difference between tissues with different T1 (e.g. TR = 2500 ms will allow 5T1's to elapse whether T1 is 250 ms or 500 ms). A very short TE would similarly minimize the difference in T2 decay by different tissues.

- **T1 Weighted Image** utilizes a **short TR (to maximize T1 contrast)** and a **short TE (to minimize T2 contrast)**. Anatomic definition is superior to T2 weighted images. Fat is dark and fluid is bright
- **T2 Weighted Image** utilizes a **long TR (to minimize T1 contrast)** and a **long TE (to maximize T2 contrast)**. Fat is bright, fluid is dark
- **PD (Proton Density)** is somewhere between T1 and T2. It utilizes short TE (14 – 20 ms) and long TR (4000 ms) to eliminate differences in T1 and T2 → i.e. differences are only due to the proton density of each tissue. Fat and fluid are bright.

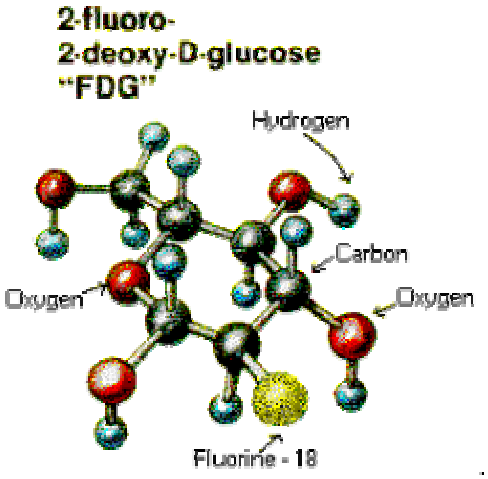
HASTE (**HA**lf-fourier **S**ingle shot **T**urbo spin-**E**cho), **FLAIR** (**FL**uid **A**ttenuation **I**nversion **R**ecovery), **STIR** (**S**hort **T**1 **I**nversion **R**ecovery), etc. are various algorithms based on different TR/TE times and methods of data acquisition. However, the basic principles described above remain the same.

IV Positron Emission Tomography (PET)

PET is a functional study that detects uptake of various radioisotopes. The isotope used most commonly used in clinical (surgical) application is F^{18}, which has favorable chemistry (similar to OH^-) and a reasonable half-life (2 hours). **^{18}FDG** or 2-fluoro-2-deoxy-D-glucose is treated by metabolically active cells like glucose, except that it can not be metabolized. When the FDG molecule enters a cell, the extra proton, which causes the nucleus to be unstable, degrades into a neutron and releases a **positron** (same mass as an electron, but with a positive charge). This very unstable positron leaves the atom and travels some distance, depending on the energy at release (usually 2 – 3 mm), until it collides with an electron, resulting in their mutual annihilation. Two (almost) anti-parallel photons are released from the reaction and travel to a detector outside of the body



[Physics of PET, Badawi, R, 1999]



[Scientific Services, 1998]

Nonpathological cells with high metabolic rates (heart, brain, kidney, and liver) take up FDG in addition to pathologic cells, such as tumor cells. High FDG uptake is not always synonymous with malignant disease, however, as other metabolically active cells, such as those found in infections and inflammatory lesions, may appear indistinguishable from tumor lesions by PET.

V Ultrasound

Ultrasound works by emitting a brief pulse of sound (at a high frequency) and "listening" for the returning echo from the surface within the body.

- Audible sound is in the range: 20 – 20,000 Hz
- Ultrasound is defined as > 20,000 Hz
- Medical (diagnostic) ultrasound operates between **1 – 20 MHz** (e.g. Abdominal U/S ≈ **3 – 5 MHz**)
- Higher frequency → superior resolution, but decreased penetration
- The monitor distinguishes between 256 (2^8) shades of grey: **0** (black) → **256** (white)

Different tissues within the body have different sound-transmission characteristics (acoustic impedances); the denser the tissue → the faster sound travels through

Material	Sound Velocity (m/s)
Air	340
Fat	1450
Water	1480
Soft tissue	1540
Blood	1570
Liver	1535
Kidney	1560
Bone	2100 – 4080

Greater differences in acoustic impedance between adjacent surfaces ("**acoustic mismatch**") → determines the strength of the returning echo

While U/S has several advantages (no deleterious side effects, inexpensive, fast) there are several drawbacks:

1. Sound waves propagate very **poorly through gas** → hence, U/S must have a gasless contact with the body and organ(s) of interest
2. U/S images are very **noisy** compared to x-ray/MR images and produce poorer images
3. Operator dependence
4. Difficult to quantify

Statistics in Medicine

Type I Error: Reject the null hypothesis when you shouldn't (probability α)

Type II Error: Failing to reject the null hypothesis when you should (probability β)

Power: The probability of avoiding Type II error ($1 - \beta$). Anther way of saying this: "The ability of your statistical test to detect a difference between 2 populations should a difference exist". See more on statistical power below.

3 Broad Classes of Statistical Pitfalls

I Sources of Bias
Include errors of *sampling bias* (studied population dose not adequately represent population of interest) and *data gathering* (questionnaires with leading questions).

II Errors in Methodology
Three most common include: designing experiments with *insufficient power* (see below), failing to pay attention to *errors in measurement* (understand the difference between reliability and validity, see below), and going on "fishing expeditions" (making *multiple comparisons*) without appropriately correcting (see the Bonferroni correction, below).

III Interpretation of Results (Misapplication of statistical methods)
Include errors of *statistical assumptions* (e.g. using a method such as ANOVA which relies on assumptions of normality and independence, when such conditions are not met), misunderstandings of *statistical significance*, and assessing *causality* (see below).

Reliability: the ability of a test to measure the same thing each time it is used (How close are the darts to each other after repeatedly throwing them at the dart board?). Even if the test is meaningless, it should yield the same results over time if used on subjects with the same characteristics.

Validity: the extent to which a test measures the outcome it was designed to measure (How close are the darts to the center of the dart board?).

Bonferroni correction: a statistical adjustment for the multiple comparisons often made during statistical "fishing expeditions". This correction raises the standard of proof needed to justify the significance of a finding when evaluating a wide range of hypotheses simultaneously. If testing n outcomes (instead of 1), divide the α by n. For example, if trying to find the association between body weight and 25 different types of cancer, divided the traditional α of 0.05 by 25 (0.05/25 = 0.002) to ensure an overall risk of Type I error equal to or less than 0.05. Be aware, however, that application of the Bonferroni correction can result in a loss of substantial precision.

Causality: Observational studies are very limited in their ability to make causal inferences; doing so requires random assignment. Hence, correlation *can* be used to infer causation if the interventions are randomly assigned (e.g. dose of drug vs. outcome).

The below **Power Table** (to quote my lab mentor, "is the single most important table for someone doing clinical research") provides the number of subjects needed to adequately detect a difference between two populations, should one exist. Power is a direct function of the degree to which the null and alternative distributions overlap (less overlap → more power) and α

For example, if without intervention the rate of an infection is 30%, and you expect your treatment to reduce it to 20%, you will require 411 patients per arm (822 in total) to have 90% power, or 313 per arm (626 in total) to have 80% power. To arrive at these numbers from the table below do the following: subtract the smaller success rate (0.20) from the larger success rate (0.30), 0.30 – 0.20 = 0.10. Align this column with the row corresponding to the smaller of the 2 success rates (in this example 0.20). This leads you to the numbers 411 and 313. The upper number is the number of subjects, *per arm,* required for 90% power, and the lower number the number of subjects, *per arm*, required for 80% power, with a significance of 95%. Glancing at this table from left to right you see that more subjects will be required when the expected difference between the treated and untreated groups is smaller. That is, the less of a difference the treatment is expected to have, the more subjects you will need to find a difference, should one exist.

Number of Patients in Each of Two Treatment Groups (Two-Sided Test)

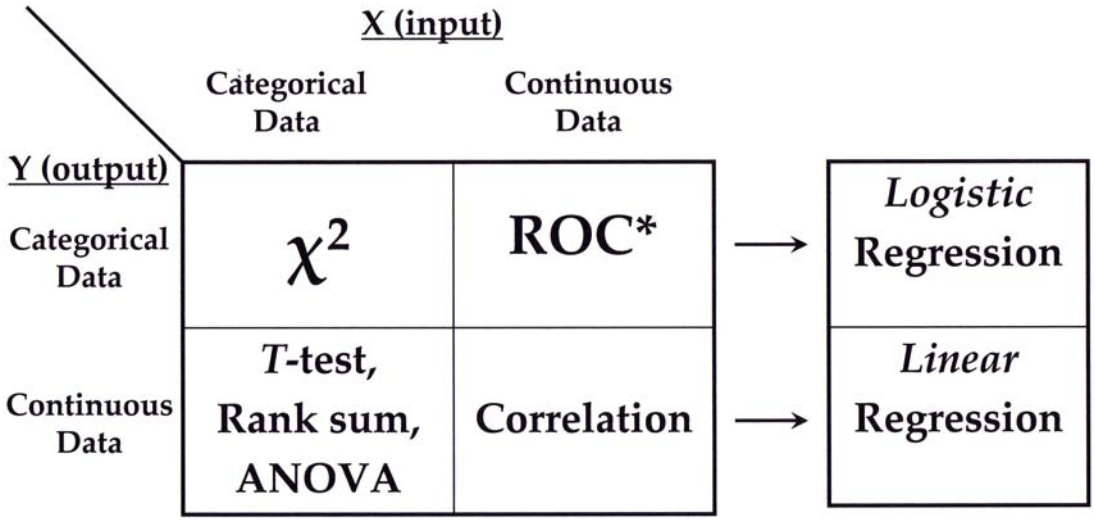
Smaller Success Rate	*Larger Minus Smaller Success Rate*									
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
0.05	620*	206	113	74	54	42	33	27	23	19
	473†	159	88	58	43	33	27	22	18	16
0.10	956	285	146	92	64	48	38	30	25	21
	724	218	112	71	50	38	30	24	20	17
0.15	1250	354	174	106	73	53	41	33	26	22
	944	269	133	82	57	42	32	26	21	18
0.20	1502	411	197	118	79	57	44	34	27	22
	1132	313	151	91	62	45	34	27	22	18
0.25	1712	459	216	127	84	60	45	35	28	23
	1289	348	165	98	65	47	36	28	22	18
0.30	1880	495	230	134	88	62	46	36	28	22
	1414	375	175	103	68	48	36	28	22	18
0.35	2006	522	239	138	89	63	46	35	27	22
	1509	395	182	106	69	49	36	28	22	18
0.40	2090	537	244	139	89	62	45	34	26	21
	1571	407	186	107	69	48	36	27	21	17
0.45	2132	543	244	138	88	60	44	33	25	19
	1603	411	186	106	68	47	34	26	20	16
0.50	2132	537	239	134	84	57	41	30	23	17
	1603	407	182	103	65	45	32	24	18	14

* Upper figure: significance level 0.05, power 0.90.
† Lower figure: significance level 0.05, power 0.80.

[Cancer: Principles & Practice of Oncology 5th, 1999]

However, more is not always better. Too much power can result in statistical significance that lacks practical significance. In other words, if the sample size becomes too large, essentially any difference between the groups, including those with no practical significance, may reach "statistical significance".

Summary of ways to analyze data (i.e. "Which test do I use?")



***ROC**: Receiver Operator Characteristic curve (for those interested, mathematical explanation of the ROC curve is included below)

- With ***logistic*** **regression**: values 0 – 1 → negative association; values > 1 → positive association
- With ***linear*** **regression**: values < 0 → negative association; values > 0 → positive association

Multiple Samples

	Measured Data	**Ranked Data**	**Indication Data (e.g. counts)**
Independent Samples	***T*-test if $n \geq 30$***	**Mann-Whitney U Test (for small samples)**	**χ^2**
Paired Samples	***T*-test if $n \geq 30$***	**Wilcoxan-Rank (for small samples)**	**Sign's Test**

* For $n < 30$ → too much variance to use t-test unless you know the distribution is normal and the selection is random

Summary of Clinical Trials

Phase I: Their purpose is to document the dose level at which signs of toxicity first appear in humans to determine a safe, tolerated, dose. The endpoint of such studies is toxicity.

Phase II: Their purpose is to determine the optimal dose-response range for a new drug and verify its efficacy for the intended disorder.

Phase III: After phases I and II are completed, phase III trials are conducted and continue until the drug is released for general use. They further verify the efficacy of the drug.

Phase IV: Following FDA approval, these studies are often conducted in large populations to further define the role of the drug/treatment in special subpopulations (e.g. children, elderly, pregnant women).

Receiver Operator Characteristic (ROC) Curve

Recall:

Sensitivity = TP/D+ = True Positive / Total Disease + = ***True Positive Rate*** **(TPR)**
Specificity = TN/D- = True Negative / Total Disease -
1 – Specificity = 1 – TN/D- = (D- – TN)/D- **= FP/D-**
= False Positive / Total Disease -
= *False Positive Rate* **(FPR)**

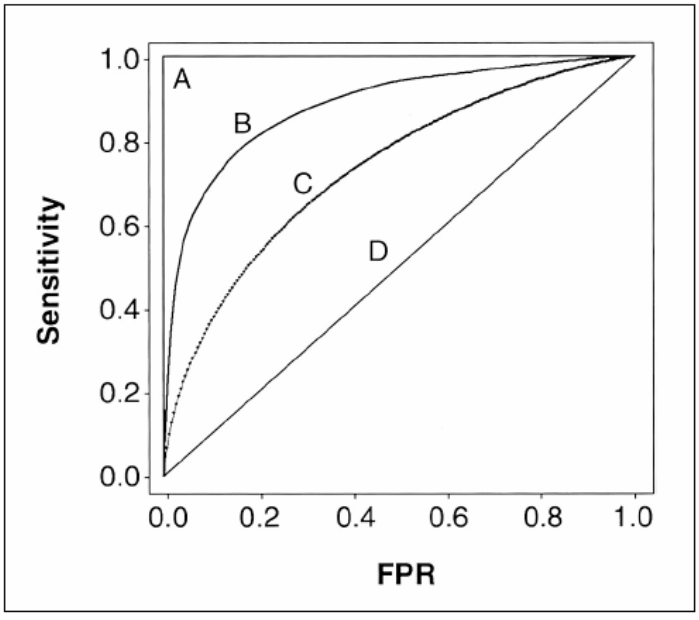
Sometimes the results of a test fall into one of two obviously defined categories → hence: one sensitivity/specificity pair

What if the test is more complicated? For example, use of CEA level as a prognostic tool for deciding if pancreatic cyst fluid is from a benign or malignant pancreatic cystic lesion. If you decide that a low CEA will be your cutoff for accepting the lesion as malignant, you will probably not miss any lesions, but will unnecessarily resect many benign lesions. Conversely, if you decide on a very high CEA as the cutoff, you will likely only resect malignant lesions, but will certainly miss malignant lesions with lower CEA levels. Hence:

As the cutoff decreases → Sensitivity ↑ and Specificity ↓

The **ROC curve** is defined as a plot of test **sensitivity** (true positive rate) as the y-coordinate *versus* its **false positive rate** (1 – sensitivity) as the x-coordinate

This is a very effective method of evaluating the performance of a diagnostic test. What does this look like?



[Koren J Radiol, 5:11, 2004]

AUC = Area under Curve

Test A (best possible): AUC = 1

Test D ("chance diagonal"): AUC = 0.5

Hence,

Test A > Test B > Test C > Test D

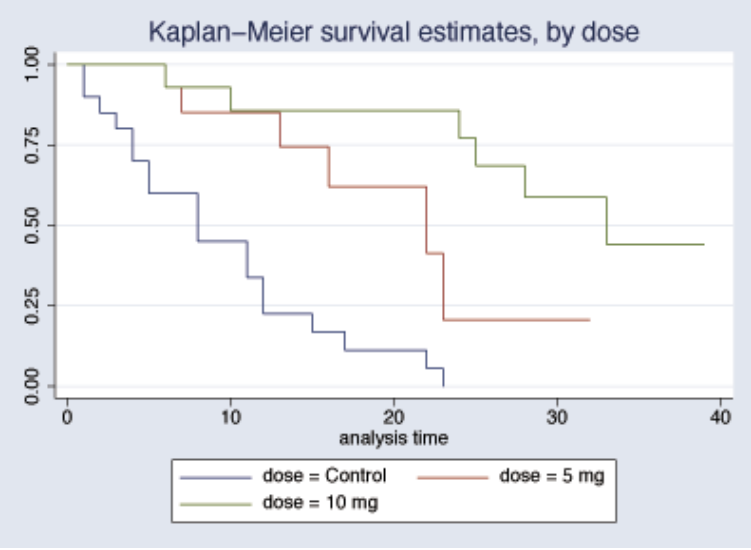
Analysis of Survival

The goal of survival analysis is to estimate the survival of a population based on a sample. There are several methods for doing this, however, the most widely used method is that of **Kaplan-Meier** (in fact, their original article, *Journal of the American Statistical Association 1958;53:457-481*, is one of the top 5 most cited papers in the field of science). The reason this method is so important, in particular for clinical medicine, is based on the fact that rarely in any trial are patients followed for the same length of time. Patient accrual takes place over months to years and patients leave the trial for reasons other the stated endpoints. However, the analysis of survival (or some other measure, such as time to disease recurrence) takes place at one point in time, meaning that not each patient has the same length of follow-up. Hence, the "Holy Grail" of survival analysis is one that allows us to follow a patient for the entirety of their treatment and follow-up, but remove them (statistically) from the analysis when they leave the trial.

For example, a patient participates in a trial of an anti-cancer agent, where the primary endpoint of the trial is survival, but is lost to follow-up (i.e. leaves the trial) at 4 years. The fact that the patient lived 4 years should contribute to the survival data for the first 4 years, but not after that. However, you don't want to consider the patient dead at 4 years, since they may still be alive and well. In clinical practice, most trials have a minimum follow-up time, for example, 3 years. Patients leaving the trial alive in less time than this will not be included in the analysis.

Mathematically removing a patient from the survival analysis is referred to as **censoring** the patient. When patients are censored from the data, the curve does not take a downward step as it does when a patient dies. Rather, ticks, on the horizontal lines, indicate when censoring occurred.

At each time interval the **survival probability** is calculated by dividing the **number of patients surviving** by the **number of patients at risk**. Patients who have died, dropped out, or not yet reached the time for minimum follow-up are not considered to be "at risk", and hence, are not included in the denominator. The probability of surviving to any point is estimated by the product of cumulative probabilities of each of the previous intervals.



[Figure taken from STATA: Statistical Software from Professionals]

Comparing survival curves is one of the most important aspects of survival analysis. If no subjects were censored in any of the treatment arms, the **Wilcoxon rank sum test** can be used to compare median survival times. However, if censored data are present (most situations) other methods must be used to determine if survival differences exist. One such method commonly used is a nonparametric technique known as the **log-rank test**.

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