



*Sir William Osler (1849-1919)*

# *The Osler Institute*

*Excellence in Continuing Medical  
Education*

## *General Surgery Review Course Table of Contents*

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# *The Osler Institute*

*Excellence in Continuing Medical  
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## *General Surgery Review Course Disc 1 Notes*

Oncologic Principles

Breast Surgery

Sarcomas

Skin & Melanoma

Small Bowel, Appendix, & Spleen

Esophageal Disorders

Head & Neck Surgery

Mediastinum & Chest Wall

Questions & Answers

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# Cellular homeostasis

- Proliferation is properly timed and DNA fidelity is maintained
  - *Chromosome segregator genes*
- Results in normal function and architecture of tissue of which cell is a component
- Tissue population controlled by balance of involution and proliferation
  - *Apoptosis*
- DNA damage is promptly repaired
  - *Tumor suppressor genes*

# Neoplasia

- Result of deregulation of:
  - Programmed cell death (apoptosis)
    - Loss of contact inhibition
      - Key factor is downregulation of TGF-beta or upregulation of EGF or similar growth promoters
    - Interference with tumor suppressor gene activity
    - Immortalization due to induction of telomerase, a ribonucleoprotein
      - Telomere is sequence cap at chromosome end that shortens with each replication
- Induction of neovascularization (angiogenesis)

# Tumor clonality

- Almost all “liquid” tumors and most solid tumors in their early stages exhibit *clonal dominance*
- As solid tumors “mature”, they become polyclonal due to:
  - Accelerating DNA alterations
  - Environmental pressures, e.g., low oxygen tension, host defenses

# APOPTOSIS

- Also known as “active cell death” or “programmed cell suicide”
- Morphologically different from usual mechanism of cell lysis:
  - Chromatin and cytosol condensation *prior to loss of membrane integrity or dissolution cytoplasmic organelles*
  - DNA fragmentation pattern also distinct
  - No or minimal inflammatory response
    - Results in “ghost cells”

# How genes go bad

- Somatic genetic changes (coding)
  - Loss of heterozygosity
    - Non-disjunction of chromosomes or mutation
    - Can be detected with microsatellite instability assays
  - Amplification of oncogenes or proto-oncogenes
  - Mutation
    - Altered proteins or frameshift alteration
- Epigenetic changes (methylation)
  - No coding alteration
    - Affects cytosine which predominates in promoter regions
    - Silences the affected allele

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# Loss of heterozygosity (LOH)

## (Two-hit theory)

- Concept initially studied in *rb1* model since deletion leading to retinoblastoma is easily seen cytogenetically (karyotypes)
- Germline mutation of one allele becomes phenotypically apparent due to somatic mutation in normal (or “wild-type) allele
- Normal allele acts as a tumor suppressor gene

## Loss of Heterozygosity--2

- Key difference from dominant oncogene model is that both alleles need to be damaged for the neoplastic process to express itself
- The mutation in the somatic cell allele does not need to be the same as the germline mutation for cancer induction

# Tumor suppressor genes

- p53, rb1, BRCA (via p53)
- Germline mutations in these genes associated with the hereditary cancer syndromes (e.g., Li-Fraumeni)
  - However, double deletions rare
  - Li-Fraumeni still usually the result of LOH
- p53 LOH is seen in at least 50% of all non-hereditary adenocarcinomas

## How does p53 “work”?

- Chromosomal damage leads to “cellular hibernation” at G1 checkpoint
- Genome amplification is suppressed until DNA repair is completed (not a p53 function)
- If damage is irreparable, apoptosis is induced in cells with wild-type p53

# Tumor Suppressor Genes

- Caretaker genes
  - p53, etc.
  - Maintain DNA integrity during replication, repair and recombination
  - Telomere maintenance
  - Protect the DNA from nucleases and other adversities
- Chromosome segregator genes
  - BUB1, BUBR1
  - Responsible for centromere stability, assembly of the spindle apparatus and sister chromatid cohesion

# Tumor Suppressor Genes

Gene	Familial Syndrome	Sporadic
APC	FAP, Turcot	Colon, brain
BRCA 1	Breast/ovary	Same, prostate
BRCA 2	Breast	Same, ovary, pancreas
p16	Melanoma	Glioblastoma, melanoma, pancreas
Rb1	Retinoblastoma	Osteosarcoma, lung bladder
SMAD4	Juvenile polyposis	Pancreas, colon, lung

# Dominant oncogenes

- Presence may override activity of normal genomic sequences; usually requires more than one mutation in this class of genes to induce neoplastic change
  - Ligand
  - Membrane
    - her-2 neu, EGFR (her-1), N-Ras, H-Ras
    - Normal cellular membrane receptors are either overexpressed or oncogene product is “locked-on” (constitutively activated) resulting in excess number of signals per chromosome

# Dominant oncogenes--2

- **Signal transducers**
  - K-ras series
  - Alters post-receptor signal transduction
- **Nuclear**
  - myc series, fos, tcf3
  - All activate transcription of growth-promoting genes in the nucleus by an unknown mechanism

# Proto-oncogenes

- RET
- Precursor gene codes for signal transduction proteins
  - Persistence in genome implies some past advantage and, in some cases, present function
- Transformation, thought to occur with either viral insertion, point mutation, or chromosomal rearrangement, leads to over-activation (amplification) and conversion to an oncogene

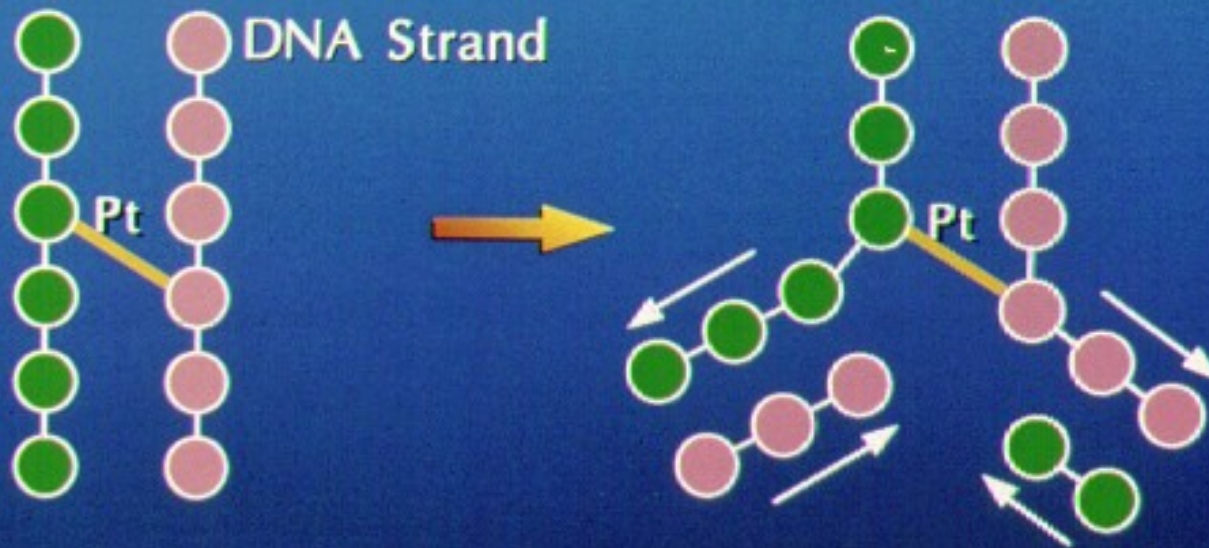
# Penetrance

- Not all patients who carry cancer mutations express them, even in those carrying dominant oncogenes
  - Assumption is that oncogenesis is a multi-step process impacted upon by as yet undiscovered genes
- Studying homogenous groups with high rate of mutation and disease expression overestimates penetrance (BRCA)

# ANTHRACYCLINES

- COMMON AGENTS
  - Doxorubicin
  - Mitoxantrone
- USED IN:
  - Breast
  - “Liquid tumors”
  - Sarcomas
- TOXICITIES
  - Cardiomyopathy
    - SUDDEN DEATH
    - CONGESTIVE FAILURE
  - Hepatotoxic
  - Emetogenic
  - Vesicant

## ALKYLATING AGENTS /MECHANISM OF ACTION



Replication  
impaired

# AKYLATING AGENTS

- COMMON AGENTS

- Cytosin
- Ifosfamide

- USES

- Lymphomas
- Sarcomas
- Non-GI  
Adenocarcinoma

- TOXICITIES

- Severe pancytopenia
- Pulmonary fibrosis
- Second malignancy
- Hemorrhagic cystitis

# PLATINUMS (Alkylators)

- COMMON AGENTS

- Cis-platinum
- Carboplatin
- Oxaliplatin

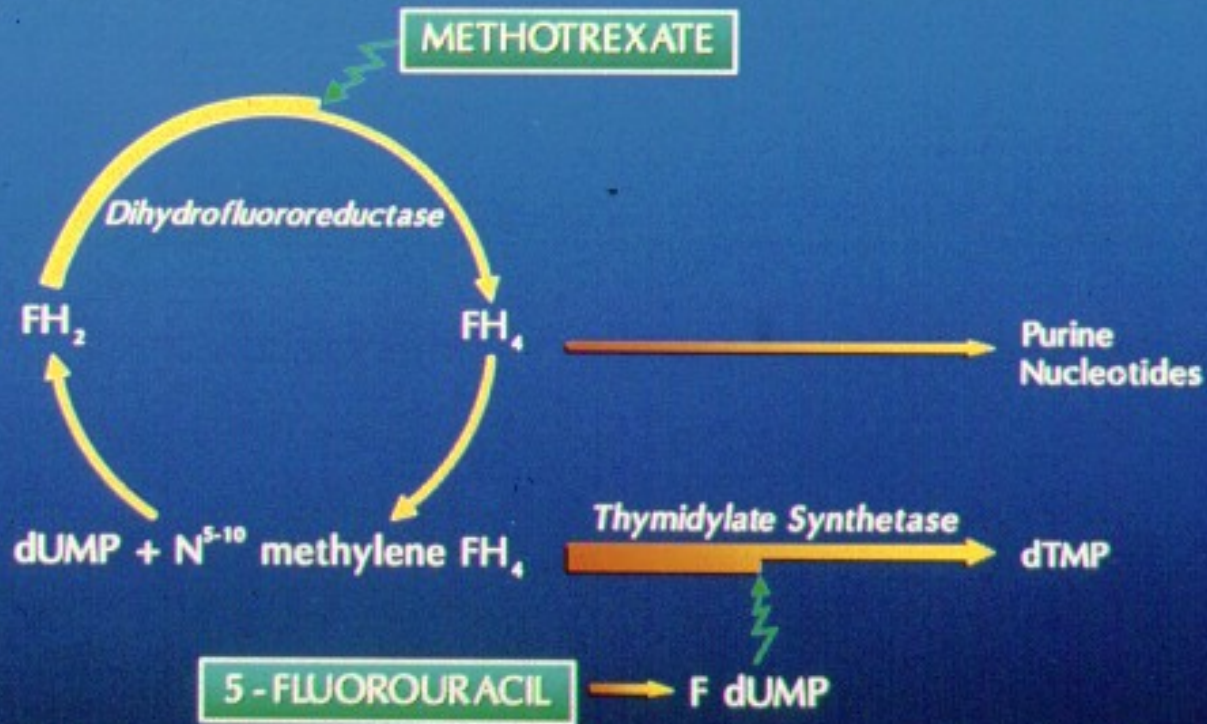
- USES

- Lung
- Squamous cell Ca
- Ovarian
- Germ cell tumors
- Colon cancer (oxaliplatin)

- TOXICITIES

- Nephrotoxic
- Ototoxic
- Hypocalcemia/  
hypomagnesemia
- Peripheral neuropathy
- Highly emetogenic

# ANTIMETABOLITES /MECHANISM OF ACTION METHOTREXATE AND 5-FLUOROURACIL

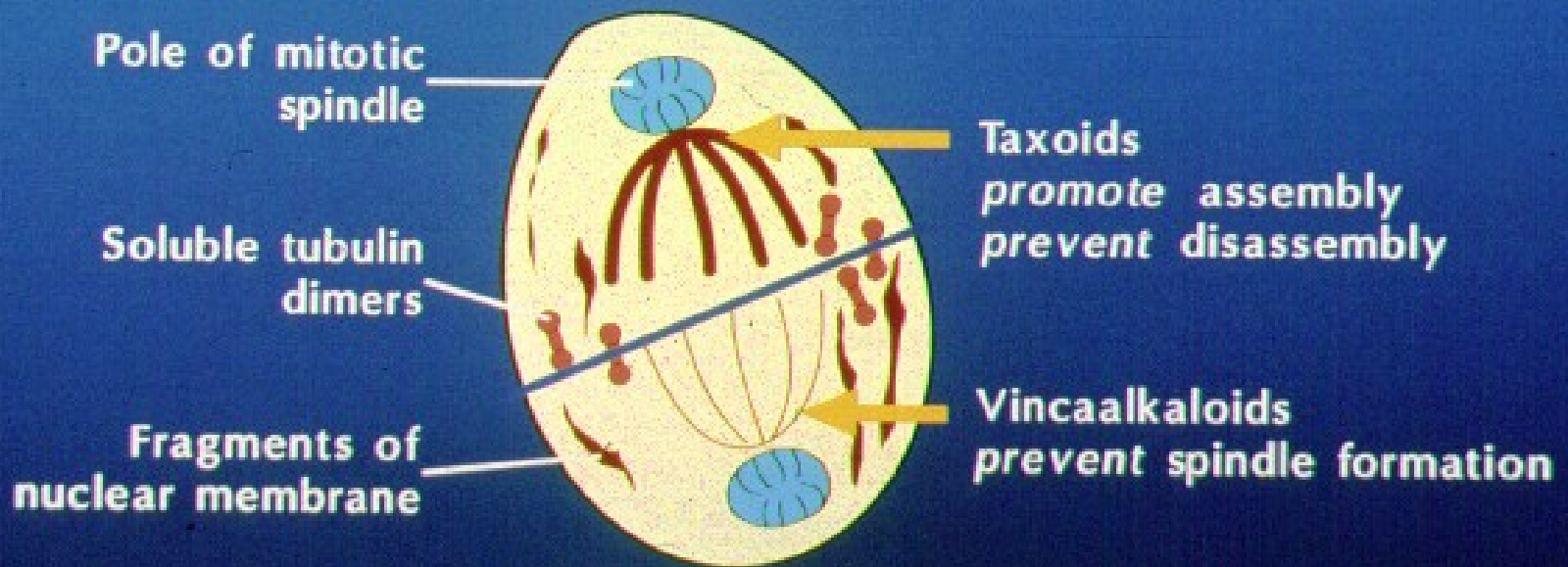


# ANTI-METABOLITES

- COMMON AGENTS
  - 5-FU
  - Xeloda
  - Methotrexate
- USES
  - 5-FU: any adenoCa except lung, radiosensitizer for SCC
  - MTX: liquid tumors
- TOXICITIES
  - 5-FU
    - Oral ulceration
    - Diarrhea
    - Stevens-Johnson
  - MTX
    - Hepatitis
    - Encephalopathy
    - Nephrotoxicity

# SPINDLE POISONS /MECHANISM OF ACTION CELLULAR LEVEL

## Mitosis : Premetaphase



# TAXANES

- COMMON AGENTS

- Taxol
- Taxotere

- USES

- Breast
- Ovary
- Lung

- TOXICITIES

- Pancytopenia
- Cardiotoxicity when used with adriamycin
- Peripheral neuropathy
- Allergic reactions
- Peripheral edema

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# Common drug regimens

Breast cancer	AC +/- T, CMF, FAC, TAC, TCH
Colon cancer	FOLFOX
Esophageal and gastric cancer	FDDP + RT, FDDPT
Melanoma	Interferon
Non-Hodgkin's lymphoma	CHOP

# MISCELLANEOUS DRUGS

- CAMPTOSAR (irinotecan, CPT-11)
  - Initially approved as salvage therapy for colorectal cancer
  - IFL
- GEMCITABINE
  - First used for pancreatic cancer, now being investigated for wide range of adenocarcinomas

# Other drug notes

- Tamoxifen
  - Pre and postmenopausal women
- Raloxifene
  - Prevention role only
- Aromatase Inhibitors-postmenopausal only
  - Arimidex
  - Letrozole
  - Exemestane
- Somatostatin

# Monoclonal antibodies

- Herceptin (trastuzumab)
- Anti-VEGF
  - Avastin (bevacizumab)
    - Causes bowel perforations and inhibits healing
- Anti-EGFR
  - Iressa (gefitinib)
  - Tarceva (erlotinib)
  - Erbitux (cetuximab)

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# SVC SYNDROME-INITIAL THERAPY

- Confirm diagnosis with chest X-ray and non-invasive venous study
- Elevate head
- Administer diuretic
- Oxygen
- Consider heparinization

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## Emergency RT Rarely Used

- Obtain chest CAT scan to R/O intrinsic process vs. extrinsic compression
- Percutaneous approach for biopsy
- Offer therapy, radiation or chemo, based on pathology

# Malignant Pleural Effusions

- TREAT ONLY IF SYMPTOMATIC
- Confirm diagnosis with fluid cytology
- Drain chest with thoracostomy tube, then sclerosis with:
  - Tetracycline
  - Talc
  - Bleomycin
  - Thorascopic abrasion

# Malignant Ascites

- Usually a pre-terminal event
- Treat only if causing pain or early satiety
- Option is peritoneal venous shunt (high rate of failure due to obstruction) vs. peritoneal dialysis catheter (works more reliably, but higher infection risk and protein losses)

# Cancer-associated Endocrinopathies

- MAY OCCUR IN UP TO 15% OF  
CANCER PATIENTS
  - Hypercalcemia
  - Cushing's syndrome
  - SIADH
  - Hypoglycemia

# Hypercalcemia

- OSTEOLYTIC  
PROCESS

Multiple Myeloma

Breast Cancer

Prostate Cancer

Lung Cancer

- PARANEOPLASTIC  
(parathormone-  
related)

Non-small cell lung

Hepatoma

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# Malignancy-Associated Hypercalcemia

- Symptoms
  - Anorexia
  - Nausea/vomiting
  - Polyuria
  - Drowsiness to stupor to coma
  - Cardiac arrhythmias

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# Treatment

- Need to correct volume deficit first
  - Augment diuresis with Lasix after urine output re-established
- Calcitonin not particularly effective in this setting
- Preferred agents are **bisphosphonates**, with Zometa being the most potent
- Steroid may also be helpful, especially with lymphomas

# Cushing's Syndrome

- Associated with:
  - Small cell of the lung
  - Carcinoid
  - Medullary thyroid cancer
  - Melanoma
  - Prostate

# Presentation of Cushing's

- SYMPTOMS/SIGNS

- Muscle weakness
- Weight loss
- Edema/polyuria
- Hypertension
- Hyperpigmentation
- May not be “Cushingoid” due to cancer cachexia

- LAB FINDINGS

- Hypokalemic alkalosis
- Hyperglycemia
- Elevated blood cortisol with no diurnal variation

# Provocative testing in cancer-associated Cushing's

- Very elevated serum ACTH ( $>200$  pg/ml) if tumor is elaborating ACTH (50% of small cell of the lung) or unmeasurable if other trophic hormone
- Low-dose dexamethasone test will be non-suppressible
- High-dose dexamethasone test will be non-suppressible

# Treatment of malignancy-associated Cushing's

- Excise or debulk the causative neoplasm
  - May lead to hypocortisolism due to suppression of pituitary-adrenal axis
- Steroidogenesis blockers
  - ketoconazole
  - Aminoglutethimide
- Consider bilateral adrenalectomy

# SIADH

- ASSOCIATED WITH:

- Small cell of the lung
- Carcinoids
- Infrequently: pancreas, esophagus, prostate, AML, Hodgkin's

- SYMPTOMS/SIGNS

- May be none
- Mild cases usually complain of anorexia, nausea and vomiting
- Severe cases manifest with weight gain, restlessness, confusion, irritability, coma and convulsions

# SIADH

- DIAGNOSIS

- No signs of fluid overload, e.g. edema, ascites
- Hyponatremia with decreased serum osmolality, with inappropriately high urine sodium and osmolality

- TREATMENT

- Fluid restrict for mild case
- Demeclocycline, lithium, and phenytoin for moderate disease
- Slow infusion hypertonic saline if severe changes

# Hypoglycemia

- Think either **diffuse hepatoma** or bulky **mesenchymal tumor** of the mediastinum or retroperitoneum
  - Most common is mesothelioma
  - Fibrosarcoma, neurofibrosarcoma, liposarcoma, rhabdomyosarcoma

# Hypoglycemia--Etiology

- Tumor-derived insulin (suppressible)
- Tumor factor interfering with hepatic gluconeogenesis
- Elaboration insulin-like growth factor I (non-suppressible)
  - Most common scenario
- Liver replacement by hepatoma

# Hypoglycemia-Treatment

- Small frequent meals with carbohydrate restriction if inducible insulin expression is suspected
- Steroids
- Diazoxide is rarely helpful
- Treat primary tumor if possible

# CNS Metastases

- Common in lung, breast, melanoma and renal cell carcinoma
- Life expectancy short if breast is primary, longer in lung and renal cell, longest if melanoma
- While headache is only seen in ~50% of patients, cognitive difficulties are almost universally present

## CNS Metastases--2

- Focal motor deficits are more frequently seen than visual changes, aphasia, or seizures
- Get CAT or MRI
- LP only if lymphoma is suspected as this will present with no mass on scan but CSF cytology is often positive

# Treatment--CNS Metastases

- Temporize with hyperventilation, head elevation, Decadron and mannitol
- Most chemotherapeutic drugs cannot traverse the blood:brain barrier
- Radiation therapy is usual approach, although can consider resection of isolated metastases, esp. melanoma, if in location felt to be accessible by neurosurgeon

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# Pregnancy in Cancer: Rx Options

	Surgery	Chemo	XRT
First Trimester	OK	NO	NO
Second Trimester	OK	OK	NO
Third Trimester	OK	OK	NO

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**Breast**

# BREAST CANCER

## RISK FACTORS

3. Carrier of BRCA-1 and BRCA-2 mutation.

# BREAST CANCER

## Prevalence of BRCA-1/2 Mutation

General population	<0.1%
Ashkenazi Jews	2.5%
Breast Cancer < 35 years	10%



# BREAST CANCER

## OVARIAN CANCER IN BRCA

BRCA-1

20% - 45%

BRCA-2

10% - 25%