PATHOLOGY TEACHING FACULTY LIST

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INTRODUCTION

Pathology – study of the essential nature of diseases and the structural and functional changes produced by them. (Pathos= suffering; ologos = study)

Pathology consists of two major subdivisions.

1. **ANATOMIC PATHOLOGY (AP)**
   This covers surgical pathology, cytopathology, and autopsy pathology.

2. **CLINICAL PATHOLOGY (CP)**
   This deals with analyses of body fluids and tissues and involves various disciplines of microbiology, serology, clinical chemistry, hematology, transfusion medicine, cytogenetics, etc.

General and systemic pathology (AP) and clinical laboratory sciences (CLS) will be taught throughout the year. General pathology emphasizes cellular and molecular biology, biochemistry, and immunology as they relate to the pathogenesis of disease. Systemic pathology deals with diseases of various “organs and systems”.

The clinical laboratory sciences (CLS) course deals with laboratory medicine involving lab testing.

It is that branch of clinical pathology that applies scientific laboratory methods relevant to patient care, health promotion and disease prevention.

**The three pillars of evidence-based medicine are:**

A. What are the results?
B. Are the results valid?
C. How are the results applicable to patient care?

The CLS course will attempt to answer the above utilizing a clinical “case format”. The significance and implications of lab testing, frequency of tests, turn-around-time (TAT), limitations of lab data, quality control and cost effectiveness will be discussed. The overall approach is to emphasize Lab Testing and how it relates to CLINICAL DIAGNOSIS AND MANAGEMENT.

**RECOMMENDED TEXTBOOKS**

   HIGHLY RECOMMENDED.

2. Robbins Basic Pathology by Kumar, Abbas, Foster, 9th edition.

**For the CLS course: - NEED NOT PURCHASE**

1. Henry’s Clinical Diagnosis and Management by Laboratory Methods by McPherson and Pincus, 22nd edition, Saunders Publishing Company

2. Interpretation of Diagnostic Tests by Jacques Wallach, M.D., 8th edition, Lippincott, Williams, and Wilkins Publishers (cost about $65.00).

EXAMINATIONS
There will be four interim and one final examination. The interim examinations are generated within the department; the final examination is the NBME subject (shelf) examination in pathology supplied and scored by the National Board of Medical Examiners. Note that the NBME reports a percent correct score along with a scaled score. It is this score that will be used in the final weighting described below.

All the questions on the interim exams are multiple choice. There are approximately 80 questions on exam I, 90 questions on exam II, 90 questions on exam III, and 55 questions on exam IV. These numbers are subject to change as thought appropriate by the faculty. Questions on the laboratory sessions will be incorporated as pictures (images) into the examination when applicable. Each of the interim examinations will be weighted in proportion to the number of questions on that examination. Together the four interim examinations will constitute 75%, and the final examination (shelf exam – 125 multiple choice questions) 25% of the total weighted score. Should a student fail to achieve a minimum passing level (MPL = 60%) for the examination series, the M-2 guidelines as determined by the Office of Student Affairs (including remedial work and a make-up examination) will be followed. The pathology department reserves the right to determine the type of make-up exam. (internal or NBME).

NOTE: UI CHICAGO MAY IMPLEMENT A NEW MPL SYSTEM; YOU WILL BE NOTIFIED ONCE AN ADMINISTRATIVE DECISION IS MADE.

Please note that:
1. Students undergoing remediation must take and pass the pathology make-up exam before being allowed further progress in their academic work.
2. The pathology make-up exam will be scheduled on the second Monday in June, 2013 (exact time, place, and type of exam. will be announced later).
3. Delays will not be permitted. Extenuating circumstances will be considered by the Pathology Department on a case by case basis.

If you have any questions regarding the curriculum, the course, or the examinations, do not hesitate to contact Dr. Gregory Freund, Head, Department of Pathology, Dr. Steve Nandkumar, Pathology Course Director and Coordinator, or Brent Beenders PhD, Pathology Teaching Assistant.

Faculty
Department of Pathology

“Be not the first by whom the new are tried
Nor yet the last to lay the old aside.”

Alexander Pope
Dear Second Year Medical Students:

Congratulations on successfully completing the M-1 year and welcome to the M-2 year! As your teaching assistant for Pathology, I will set up teaching sessions and office hours for all M-2 students. Although the sessions are not mandatory, they are highly recommended. The time for our meetings will be determined after school begins and may vary from week to week as we try to find times that work with both your schedules and mine.

Most students find pathology to be the most challenging course they have taken so far in medical school. The course content is large and you are required to know the material at a surprising level of detail. I will be providing practice questions, and I hope to take away some of the stress of wondering what the level of questioning will be like.

As far as book resources go, the recommended book for the course is “Big” Robbins (Pathologic Basis of Disease; ISBN 978-1-4160-3121-5). Take care not to confuse this book with “Baby” Robbins (Basic Pathology; ISBN 978-14377-1781-5), which is smaller because it removes all of the explanatory text and is often much more difficult to understand than “Big” Robbins.

Robbins Review of Pathology (ISBN 0721682596) is a question book that I found to be almost indispensable when I took the course. Past students have also recommended Pretest Pathology. You don’t need to buy them as long as you don’t mind sharing the library copies. I think the questions in these books may be a little harder than a typical exam question, but they are representative of the level of difficulty of questions on the NBME pathology shelf-exam that you will take in the spring. Q banks from Kaplan and USMLE World are useful.

There are various pathology resources available on the internet. One that I found to be particularly useful was Webpath (http://www-medlib.med.utah.edu/WebPath/webpath.html). This site features images and a large set of review questions. Also, the GRIPE website http://peir.net is available for viewing digitized images.

One final note on books: BRS Pathology is a quick review book for USMLE or for organizing your thoughts, but the level of detail in this book may not be sufficient for you to pass the pathology course.

Please feel free to contact me by e-mail (beenders@life.illinois.edu) with any questions, comments, concerns, or suggestions as the year goes by.

Brent Beenders PhD
GOALS AND OBJECTIVES

Department of Pathology

(please visit the M2 website and go to learning objectives; this password protected site will give you the lecture titles and their objectives)
Pathology Course Goals and Objectives

By the end of the course, successful students will achieve the level of competence expected of a medical student completing the M2 year, studying for USMLE Step 1, and preparing for the M3 year and patient care responsibilities through the following broad goals and objectives. Specific learning objectives for large and small groups are included at the time of each section. Students will be expected to:

Medical Knowledge:
- Demonstrate an investigative and analytic approach to clinical and pathological problems. (See “introduction to pathology” in chapter 1 in the latest edition of Robbins and Cotran).
  - Demonstrate applied knowledge of Pathology, by describing the four aspects of the major disease processes covered in the course:
    - Cause (etiology)
    - Mechanisms of development (pathogenesis)
    - Biological and structural alterations induced in the cells and organs (molecular and morphologic changes)
    - Functional consequences of the molecular and morphologic changes (clinical significance)
- Apply the basic and clinically supportive sciences appropriate to pathology (such as anatomy, biochemistry, histology/histopathology, cytogenetics, and physiology).

Patient Care:
- Gather and apply essential information from patient cases necessary to discuss clinicopathologic processes in Small Group Discussions.
- Develop a differential diagnosis when presented with clinical information or a histopathologic finding.
- Utilize laboratory studies to diagnose and monitor disease states and conditions.

Practice-based Learning and Improvement:
- Demonstrate the ability to support self-education (i.e., active learning).
  - Demonstrate the ability to find additional information when confronted with a question or unfamiliar term, particularly when preparing for case-based exercises.
  - Demonstrate the ability to appropriately use a medical dictionary and to use appropriate terminology.
- Use information technology to access on-line medical information.
- Facilitate the learning of peers, as appropriate.

Interpersonal and Communication Skills:
- Exhibit effective listening and communication skills to result in effective information exchange among peers.

Professionalism:
- Demonstrate respect, compassion, and integrity in interactions with peers, faculty, and support staff.
- Perform assigned in a dependable and responsible manner.
- Demonstrate commitment to ethical principles pertaining to the course.

Systems-based Practice:
- Demonstrate an understanding of how the practice of pathology fits within the larger context of medical practice.
General Pathology Objectives 2005-2006

GRIPE Objectives Committee

Roger Geiss, MD

Byron Crawford, MD

Kuldeep Teja, MD

June 2005
### General Pathology Objectives

**2005-2006**

<table>
<thead>
<tr>
<th>Topic*</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 – PATHOLOGY AS A SPECIALTY</td>
<td>3</td>
</tr>
<tr>
<td>12 - GENERAL ASPECTS OF DISEASE</td>
<td>4</td>
</tr>
<tr>
<td>21 – CELL INJURY AND NECROSIS</td>
<td>5</td>
</tr>
<tr>
<td>22 – INFLAMMATION</td>
<td>7</td>
</tr>
<tr>
<td>23 – HEALING AND REPAIR</td>
<td>9</td>
</tr>
<tr>
<td>24 – GROWTH DISTURBANCES AND NEOPLASIA</td>
<td>11</td>
</tr>
<tr>
<td>25 – GENETIC AND DEVELOPMENTAL DISORDERS</td>
<td>17</td>
</tr>
<tr>
<td>31 – PHYSICAL INJURY</td>
<td>20</td>
</tr>
<tr>
<td>32 – CHEMICAL AND DRUG INJURY</td>
<td>22</td>
</tr>
<tr>
<td>33 – INFECTIOUS DISEASE</td>
<td>24</td>
</tr>
<tr>
<td>34 – IMMUNOPATHOLOGY</td>
<td>35</td>
</tr>
<tr>
<td>35 – HEMODYNAMIC DISORDERS</td>
<td>38</td>
</tr>
<tr>
<td>36 – METABOLIC DISORDERS</td>
<td>43</td>
</tr>
<tr>
<td>37 – MINERALS AND PIGMENTS</td>
<td>47</td>
</tr>
<tr>
<td>38 – NUTRITIONAL DISEASE</td>
<td>48</td>
</tr>
<tr>
<td>39 – AGING</td>
<td>50</td>
</tr>
<tr>
<td>51 – FORENSIC PATHOLOGY</td>
<td>51</td>
</tr>
<tr>
<td>56 – BLOOD BANK AND IMMUNOHEMATOLOGY</td>
<td>53</td>
</tr>
</tbody>
</table>

*Topic number refers to MCA topic designation in the GRIPE question banks.
11 - PATHOLOGY AS A SPECIALTY

The student will be able to:

1. Define and use in proper context:
   - accuracy
   - analytic variable
   - anatomic pathology
   - autopsy
   - biopsy
   - clinical pathology
   - coefficient of variation
   - exfoliative cytology
   - false negative
   - false positive
   - fine needle aspiration
   - frozen section
   - histopathology
   - incidence
   - monitoring test
   - necropsy
   - pathologic
   - postanalytic variable
   - preanalytic variable
   - precision
   - predictive value
   - prevalence
   - reference range
   - screening test
   - sensitivity
   - specificity
   - specimen
   - standard deviation
   - true negative
   - true positive
   - turnaround time

2. Describe the activities of pathologists, including subdivisions of anatomic and clinical pathology (laboratory medicine).

3. Outline appropriate uses of:
   - clinical laboratories
   - necropsies (autopsies)
   - surgical pathology
   - frozen sections
   - cytopathology

4. State the individual responsible for authorizing a necropsy (autopsy) when death is due to natural causes, as well as when it occurs under unnatural circumstances.

5. Discuss relationships between:
   - pathology and basic sciences
   - pathology and clinical sciences

6. Calculate sensitivity and specificity from a 2 X 2 table

7. Compare and contrast precision and accuracy

8. Discuss development of "normal range", including reference group method, prognosis/treatment derived, threshold value, and therapeutic drug reference range.

9. Compare and contrast pre-analytical, analytical, and post-analytical variables in laboratory testing, and give examples of each

10. Discuss the effects of sample handling on laboratory results, including turnaround time, type of tube used for blood collection, timing of collection, transport, and storage
12 - GENERAL ASPECTS OF DISEASE

The student will be able to:

1. Define and use in proper context:
   - brain death
   - diagnosis
   - differential diagnosis
   - disease
   - etiology
   - exacerbation
   - factitious
   - functional
   - abnormality
   - iatrogenic
   - idiopathic
   - lesion
   - morphology
   - mortality rate
   - natural history
   - nosocomial
   - pathogenesis
   - pathognomonic
   - psychosomatic
   - remission
   - sign
   - somatic death
   - structural
   - abnormality
   - symptom
   - syndrome

2. Distinguish between disease and non-disease.

3. Outline a classification of causes of disease, basic responses of the body to injury, and manifestations of disease; and classify common examples in each category.

4. State the three most common causes of death in this country.
21 – CELL INJURY AND NECROSIS

The students will be able to:

1. Define and use in proper context:
   - agenesis
   - cellular swelling
   - hyaline (hyalin)
   - lipofuscin
   - anthracosis
   - (hydropic change)
   - hyperplasia
   - melanin
   - aplasia
   - dysplasia
   - hypertrophy
   - metaplasia
   - apoptosis
   - heat-shock protein
   - hypoxia
   - neoplasia
   - autolysis
   - gangrene
   - hypoplasia
   - necrosis
   - autophagy
   - hemosiderin
   - infarct
   - pyknosis
   - bilirubin
   - heterophagy
   - karyolysis
   - steatosis
   - autolysis
   - hemosiderosis
   - ischemia
   - steatosis

2. Compare cell and tissue adaptation, reversible cell injury, and irreversible cell injury (cell death) on the basis of:
   - etiology
   - pathogenesis
   - morphologic appearance (ultrastructural and histologic)

3. Compare and contrast cell death and somatic death, on the basis of:
   - causes
   - pathogenesis
   - histologic appearance

4. Outline the relationships between:
   - biochemical
   - light microscopic
   - ultrastructural
   - changes in the processes of cell injury and death

5. Compare:
   - coagulative (coagulation) necrosis
   - liquefactive (liquefaction) necrosis
   - gangrenous necrosis
   - caseous necrosis
   - fat necrosis
   - fibrinoid necrosis
   - apoptosis

   in terms of:
   - common sites or tissues involved and reasons for this
   - common causes or causative mechanisms
   - gross and microscopic appearance
   - types and extent of healing

6. Compare and contrast the following types of cell injury:
   - reperfusion
   - free radical-induced
   - chemical
   - in terms of biochemical and molecular mechanisms
7. List the types of subcellular alterations that can occur in cell injury, with respect to the following organelles:
   - lysosomes
   - endoplasmic reticulum
   - mitochondria
   - cytoskeleton

8. Discuss the significance of intracellular accumulations of:
   - lipids
   - proteins
   - glycogen
   - pigments (exogenous and endogenous)

9. Compare fatty change (steatosis) and fatty infiltration on the basis of:
   - causes
   - pathogenesis
   - organs commonly involved
   - histologic appearances

10. Compare dystrophic and metastatic calcification in terms of:
    - definition
    - etiology and pathogenesis
    - morphologic appearance
    - sites and associated diseases
    - clinical significance
22 - INFLAMMATION

The student will be able to:

1. Define and use in proper context:
   - abscess
   - autocrine
   - cellulitis
   - chemotaxis
   - cytokine
   - edema
   - effusion
   - emigration
   - endocrine
   - erosion
   - exudate
   - fibrinous
   - granulation tissue
   - granuloma
   - inflammation
   - margination
   - paracrine
   - phagocytosis
   - purulent
   - pyogenic
   - resolution
   - serosanguineous
   - serous
   - suppurative
   - transudate
   - ulcer

2. Describe the classic vascular changes and cellular events of the inflammatory reaction.

3. Discuss the five cardinal signs of inflammation in terms of pathogenesis and underlying morphologic changes.

4. Discuss the following chemical mediators of inflammation, in terms of origin (cells vs. plasma) and chief in vivo functions:
   - vasoactive amines
   - proteases of clotting, kinin, complement systems
   - arachidonic acid metabolites
   - platelet activating factor
   - cytokines/chemokines
   - nitric oxide
   - lysosomal granule contents
   - oxygen-derived free radicals
   - neuropeptides

5. Discuss each of the following in terms of the associated type of inflammation and their role therein:
   - platelets
   - mast cells/basophils
   - neutrophils
   - endothelial cells
   - monocytes/macrophages/histiocytes
   - lymphocytes
   - plasma cells
   - eosinophils
   - giant cells
   - fibroblasts
   - cell adhesion molecules

6. Describe the steps involved in the isolation and destruction of an infectious agent by polymorphonuclear leukocytes (neutrophils). Describe important related extracellular and intracellular factors.

7. Compare and contrast acute, chronic, and granulomatous inflammation in terms of:
   - etiology
   - pathogenesis
   - histologic appearance
   - laboratory findings
   - characteristic cells involved
   - outcome
   - systemic effects

8. Compare and contrast resolution and organization with respect to the termination of an inflammatory response.

9. Compare and contrast lymphangitis and lymphadenitis, in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical features and course

10. Develop and utilize the nomenclature used to describe inflammation in the various tissues and organs.
The student will be able to:

1. Define and use in proper context:
   - angiogenesis (neovascularization)
   - cicatrix
   - contact inhibition
   - contracture
   - dehiscence
   - fibrosis (fibroplasia)
   - granulation tissue
   - haptotaxis
   - keloid
   - organization
   - regeneration
   - repair
   - scar
   - stricture

2. Describe the cell cycle and define the single-lettered abbreviations (M, G\textsubscript{0}, G\textsubscript{1}, S, G\textsubscript{2}).

3. Distinguish between labile, stable, and permanent cells, and place each of the following cell/tissue types into the appropriate category:
   - hematopoietic
   - muscular (smooth, skeletal, cardiac)
   - glandular parenchymal
   - neuronal
   - epithelial
   - glial
   - osseous and chondroid
   - connective

4. Discuss the basic aspects of collagen synthesis, degradation, and function, and state the tissue(s) in which collagen types I-IV are predominantly localized.

5. Discuss basement membranes with regard to morphology, composition, and function.

6. Compare and contrast:
   - resolution
   - regeneration
   - repair
   - organization

   in terms of:
   - type of antecedent injury
   - tissue involved
   - cellular response
   - time course
   - ultimate outcome
   - classic/common examples of each

7. State the role of each of the following components of the extracellular matrix:
   - collagen
   - laminin
   - elastin
   - integrin
   - fibrillin
   - matricellular proteins
   - fibronectin
   - proteoglycans
   - hyaluronin

8. Describe how cells are attached to the extracellular matrix, and how these attachments may alter cell gene expression.

9. Describe the four steps of tissue repair, including the cell types and growth factors involved, and the approximate timetable for the tissue repair process.

10. Describe angiogenesis with regard to the time course and biochemical factors (growth factors, enzymes, etc.).
11. Discuss the role of each of the following in the repair reaction:
   • cell migration
   • integrins
   • growth factors

12. Describe the role of each of the following in the process of wound healing:
   • myofibroblasts
   • endothelial cells
   • fibroblasts
   • macrophages
   • collagen

13. Compare healing by first intention (primary union) and second intention (secondary union) in terms of time, sequence of events, morphologic changes, and final outcome.

14. Describe the local and systemic factors that influence wound healing, stating whether each of these influences accelerates or retards the rate of healing.

15. List the complications of wound healing.
24 - GROWTH DISTURBANCES AND NEOPLASIA

The student will be able to:

1. Define and use in proper context:
   - adenoma
desmoplasia
metastasis
sarcoma
anaplasia
DNA repair gene
microinvasion
scirrhous
angiogenesis
dysplasia
mixed tumor
serous
 aplasia
endophytic
mucinous
stage
atrophy
exophytic
neoplasm	
tumor
benign
grade
occult malignancy
tumor associated antigen
borderline malignancy
hamartoma
oncogene
tumor marker
cachexia
heterotopia
oncogenic
tumor specific antigen
cancer
hyperplasia
oncology
tumor suppressor gene
carcinoid
hypertrophy
papilloma
carcinogen
hypoplasia
paraneoplastic syndrome
carcinoma
in situ
parenchyma
carcinosarcoma
initiation
Philadelphia chromosome
choristoma
intraepithelial
pleomorphism
contact inhibition
invasion
point mutation
cystadenoma
leukoplakia
polyp
cystadenocarcinomas
low malignant potential
premalignant
differentiation
malignant
progression
dermoid
medullary
promotion
desmoid
metaplasia
protooncogene

2. Discuss the following:
   - anaplasia
   - hyperplasia
   - aplasia
   - hypoplasia
   - atrophy
   - metaplasia
   - dysplasia
   - neoplasm
   - hypertrophy

   in terms of:
   - etiology
   - pathogenesis
   - morphology
   - functional sequelae
   - specific examples

3. Outline the classification and nomenclature for benign and malignant neoplasms, using appropriate prefixes and suffixes and indicating specific exceptions to rules of nomenclature.

4. Compare and contrast the following in terms of tissue of origin, gross and microscopic features, and mode of spread:
   - normal vs. neoplastic tissue
   - adenoma vs. carcinoma
   - carcinoma vs. sarcoma

5. List the general cytologic, biochemical, antigenic, metabolic, karyotypic, and molecular genetic changes found in neoplastic cells.

6. List the most common sites of origin of:
7. Compare and contrast grading vs. staging of neoplastic disease, in terms of:
   general principles
   clinical significance

8. Cite local and general mechanisms which are believed to affect the rate of tumor growth.

9. Discuss how tumor growth rates can be evaluated using mitotic rate and cell proliferation markers.

10. List four major pathways by which neoplasms spread.

11. Discuss metastasis of malignant neoplasms, in terms of:
    • molecular genetics
    • cellular adhesion
    • mechanisms of invasion of extracellular matrix
    • mechanisms of vascular dissemination and homing of tumor cells
    • tissues and organs in which metastases are:
      o common
      o uncommon
    and cite possible reasons for lack of metastases in some instances when cancer cells are spilled into the blood stream.

12. Describe carcinogenesis, in terms of:
    • initiation and neoplastic progression
    • sequence of gene mutations
    • tumor stemline and sidelines

13. Evaluate critically the role of each of the following in the development of human cancer, citing general significance and at least one specific neoplasm associated with each:

    physical agents  genetic diseases
    chemical agents  genetic predispositions
    infectious agents  hormones
    chronic inflammatory conditions  immune response
    benign tumors

14. Match the following agents or conditions with neoplasms for which there has been a suggested relationship:

    cyclophosphamide  hepatitis B and C viruses
    circumcision  Epstein-Barr virus
    tobacco  human papillomavirus (HPV)
    smoked fish  human immunodeficiency virus (HIV)
    aniline dyes  human T cell leukemia/lymphoma virus, type 1 (HTLV-1)
    aflatoxin  ultraviolet radiation
    asbestos  ionizing radiation
    benzene  radon
    2-naphthylamine  heredity
    vinyl chloride  hormonal imbalance
15. Discuss precancerous lesions (incipient malignancies), in terms of:
   • definition
   • etiology
   • pathogenesis/growth kinetics
   • common examples

Describe the metaplasia→dysplasia→carcinoma-in-situ→invasive carcinoma sequence.

Discuss, compare, and contrast the following theories of origin of neoplasia:
   multifactorial theory
   genetic mutations
   viral oncogene
   epigenetic theory
   immune-surveillance dysfunction
   monoclonal origin
   field origin

List the DNA viruses which have been linked to tumor formation in man and animals.

List the connections between viruses and tumors in terms of:
   • epidemiology
   • interactions of virus proteins with cell regulatory proteins
   • modulation of the host immune system

Contrast the mechanisms of neoplasm formation by DNA viruses with those by RNA viruses.

Discuss the relationship between protooncogenes and oncogenes, as well as the relationship between cellular oncogenes and viral oncogenes.

Compare and contrast protooncogenes and tumor suppressor genes, in terms of genotypic vs. phenotypic expression.

Explain the concept of recessive cancer gene.

Describe the following cancer-susceptibility syndromes:
   ataxia-telangiectasia
   Bloom syndrome
   xeroderma pigmentosum
   hereditary nonpolyposis colon cancer
   Fanconi anemia
   Li-Fraumeni syndrome
   Cowden syndrome
   familial adenomatous polyposis coli
   von Hippel-Lindau disease

in terms of:
   o genetic abnormality
   o mechanisms of oncogenesis
   o clinical features
   o associated neoplasms

Describe the following genes:
   APC
   DCC
   p53
   Rb
   brca
   bcl-2
   ras
   myc
   c-erb B2

in terms of:
   o chromosomal location
   o mechanisms of oncogenesis
   o associated neoplasms

Discuss the following chromosomal translocations:
• t(8;14)
• t(9;22)
in terms of:
  o mechanisms of oncogenesis
  o associated neoplasms

Discuss dose dependency in chemical carcinogenesis.

Explain the carcinogenic effect of irradiation.

Cite evidence for estrogens as carcinogens.

Describe the body’s immune system and its role in the development of neoplasms, and explain the following concepts:
  • anti-tumor immunity
  • immunologic surveillance

Discuss the different types of escape mechanisms utilized by neoplasms to evade the immunosurveillance system of an immunocompetent host.

Discuss tumor specific antigens and tumor related antigens, in terms of:
  • their presence on normal cells
  • their importance in anti-tumor immunity

Compare tumors transmitted by:
  • dominant inheritance
  • recessive inheritance

on the basis of:
  o examples
  o incidence

Compare and contrast:
  acquired cancer-causing genetic mutations
  germline cancer-causing genetic mutations

Describe the indications, advantages, and disadvantages of the following diagnostic procedures and laboratory tests used to diagnose, and monitor the progression of, neoplasms:

  Imaging
  • conventional radiography
  • computed tomography (CT)
  • magnetic resonance imaging (MRI)
  • ultrasound
  • nuclear medicine
  • positron emission tomography (PET)

  Histologic
  • needle biopsy
  • open biopsy
  • frozen section
  • immunohistochemistry
  • electron microscopy

  Cytologic
  • exfoliative cytology
  • fine needle aspiration (FNA) cytology

  Biochemical
  • tumor markers
Molecular

- flow cytometry
- genetic analysis

List the secretions or other fluids which are examined by cytologic means in the diagnosis of malignancy.

List the organs in which cytology plays an important role in cancer case findings.

Discuss the epidemiology of malignant neoplasms, in terms of:
  - incidence
  - prevalence
  - geographic associations
  - environmental factors
  - age associations

Discuss the following cancers:
  - carcinoma of lymphomas
  - large bowel leukemias
  - breast bone cancer
  - lung skin cancers (squamous, basal cell, melanoma)
  - prostate brain tumors
  - bladder sarcoma in general
  - endometrium carcinoma in general
  - stomach squamous cell carcinoma
  - pancreas adenocarcinomas
  - cervix
  - ovary

in terms of:
  - relative frequency
  - relative fatality ratio
  - relative age and sex frequency
  - effects of medical care and age on incidence and mortality

For both males and females, list in descending order:

- the five most common cancers
- the five most common causes of cancer death

List the relative incidence of, and mortality due to, cancer for each sex and decade.

Discuss the mechanism by which neoplasms produce each of the following, listing neoplasms that are commonly associated with each effect:

- anemia
- jaundice
- ischemia
- obesity
- fever
- masculinization
- leukocytosis
- episodic flushing
- leukopenia
- hypercalcemia
- infection
- hemorrhage
- obstruction
- thrombophlebitis
- pain
- endocrine effects
- itching
- fracture

Match each of the following public health measures with appropriate neoplasms in which the measure may be of some use:

- cytologic examination
- routine x-rays
avoidance of ionizing radiation  
avoidance of excessive sunlight  
avoidance of tobacco  
cancer genetic studies  
self-examination  
routine laboratory studies  
routine physical examination

Cite examples of variations in types of neoplasms and incidence of neoplasms related to:
• geographic location  
• age  
• sex  
• race  
• occupation  
• socioeconomic status

Cite at least three neoplasms that produce the same hormones as the organ from which the tumor arises.

Cite at least three examples of paraneoplastic syndromes.

Match each of the following tumor markers with the specific neoplasm(s) with which it is associated:
• human chorionic gonadotrophin (HCG)  
• calcitonin  
• catecholamines  
• α-fetoprotein (AFP)

Contrast the effects of benign and malignant tumors on the host.

List the common signs and symptoms of malignancy.

List the common causes of death from cancer.
25 – GENETIC AND DEVELOPMENTAL DISORDERS

The student will be able to:

1. Define and use in proper context:
   - agenesis
   - aneuploid
   - aplasia
   - autosomal
   - balanced polymorphism
   - Barr body
   - buccal smear
   - carrier
   - chromosome
   - codon
   - congenital abnormality
   - congenital disease
   - deformation
   - deletion
   - developmental anomaly
   - diploid
   - DNA
   - dominant
   - double minute
   - dysmorphogenesis
   - embryonic period
   - embryopathy
   - euploid
   - expressivity
   - familial disease
   - fetal period
   - fragile site
   - gene
   - genetic disease
   - genetic heterogeneity
   - genotype
   - hemizygous
   - hereditary disease
   - hereditary disease
   - hereditary disease
   - hereditary disease
   - homogeneously stained
   - homozgyous
   - inversion
   - karyotype
   - linkage
   - Lyon hypothesis
   - meiosis
   - monosomy
   - mRNA
   - malformation
   - meiosis
   - mitosis
   - monosomy
   - mosaicism
   - mRNA
   - multifactorial inheritance
   - mutation
   - neonatal
   - nongenetic stained
   - operator gene
   - operon
   - genetic disease
   - genetic heterogeneity
   - genet type
   - genetic disease
   - genetic disease
   - genetic disease
   - genetic disease
   - homogeneously stained
   - homozgyous
   - inversion
   - karyotype
   - linkage
   - Lyon hypothesis
   - meiosis
   - mitosis
   - monosomy
   - mosaicism
   - mRNA
   - multifactorial inheritance
   - mutation
   - neonatal
   - nonhomogenously stained
   - operator gene
   - operon
   - genetic disease
   - genetic disease
   - genet type
   - genetic disease
   - genetic disease
   - homogeneously stained
   - homozgyous
   - inversion
   - karyotype
   - linkage
   - Lyon hypothesis
   - meiosis
   - mitosis
   - monosomy
   - mosaicism
   - mRNA
   - multifactorial inheritance
   - mutation
   - neonatal
   - nonhomogenously stained

2. List at least three common congenital anomalies that involve each of the following organ systems:
   - general
   - soft tissues
   - bone

3. Provide at least three examples of:
   - causes
   - pathogenetic mechanisms
   - disturbed function
   - for the development of congenital malformations

4. Discuss the following abnormalities:
   - anencephaly
   - bile duct atresia
   - cleft palate
   - atresia small intestine
   - atrial septal defect
   - diaphragmatic hernia
   - hypospadias
   - polycystic kidney
   - umbilical hernia
   - bifid uterus

   in terms of:
   - cause
5. Identify factors which influence the type and extent of congenital anomalies produced by teratogenic agents.

6. List a maternal therapeutic agent which has been implicated in each of the following malformations:
   - phocomelia
   - goiter
   - clear cell carcinoma of the cervix

7. Describe the morphologic features of the embryopathies associated with ingestion of the following substances during pregnancy:
   - alcohol
   - hydantoin

8. Discuss the possible influence on oogenesis and spermatogenesis of maternal and paternal exposure to toxic agents.

9. Discuss five common genetic abnormalities in terms of:
   - pathogenesis
   - common feature
   - classification
   - examples

10. List three examples of each of the following types of genetic diseases:
    - simple (autosomal) dominant
    - simple (autosomal) recessive
    - sex-linked recessive
    - multifactorial inheritance

11. Given a family history, construct a pedigree using proper diagramming technique.

12. Given the mode of inheritance or a family history involving a disease with classic Mendelian inheritance, predict the likelihood of various phenotypes and genotypes in family members.

13. Discuss the use of chromatin (Barr) body identification in the recognition and diagnosis of chromosome disorders.

14. Compare chromosome analysis (karyotyping) and Barr body count (buccal smear) in terms of:
    - basic steps in performance of test
    - appropriateness in various types of clinical situations
    - costs and time involved
    - accuracy

15. Outline pathogenetic mechanisms of importance in the production of:
    - mutations
    - acquired congenital anomalies
    - nondisjunction
16. Discuss chromosomal abnormalities in terms of:
   - pathogenesis
   - classification
   - specific features of the more common examples

17. List probable causes and examples of mutation and acquired congenital anomalies.

18. Given photographs of karyotypes, determine the abnormalities in sex or autosomal chromosomes.

19. Distinguish on the basis of clinical signs and symptoms among:
   - trisomy 21 (Down) syndrome
   - trisomy 13 (D) syndrome
   - trisomy 18 (E) syndrome
   - Turner syndrome
   - Klinefelter syndrome
   - triple X female
   - double Y male
   and determine the sex and recognize the disease in each case from a photograph of a karyotype thereof.

20. Compare translocation and mosaic types of Down syndrome on the basis of:
   - karyotype
   - maternal factors
   - inheritance


22. Compare rubella infection and thalidomide ingestion in pregnant women in terms of epidemiology and developmental effects on the embryo and fetus.

23. Discuss the usefulness of the following laboratory tests in regard to genetic disorders and congenital malformations:
   - amnionic fluid analysis
   - tissue culture
   - buccal smear
   - chromosomal analysis

24. Discuss the following lysosomal storage diseases:
   - Tay-Sachs disease
   - Niemann-Pick disease
   - Gaucher disease
   - mucopolysaccharidoses
   - glycogen storage diseases
   in terms of:
     o enzyme deficiency
     o accumulating metabolite
     o key phenotypic features

25. Outline the pathogenesis of abnormalities in:
   - rubella syndrome
   - congenital small intestinal atresia
   - adrenogenital syndrome
   - congenital cerebral palsy
   - alcoholic embryopathy
   - aganglionosis
   - midgut volvulus

26. Discuss the various biochemical consequences of single gene defects.

27. Discuss the various methods of molecular hybridization in DNA probe analysis.
28. Outline the basic principles of recombinant DNA techniques and their applications in the detection of genetic diseases.
31-PHYSICAL INJURY

The student will be able to:

1. Define and use in proper context:
   - abrasion
   - acute radiation syndrome
   - avulsion
   - caisson disease
   - carcinogen
   - contusion
   - flashover
   - fouling
   - frostbite
   - full thickness burn
   - gray (Gy)
   - gunshot wound
   - heat cramps
   - heat exhaustion
   - heat stroke
   - hyperthermia
   - hypobaropathy
   - hypothermia
   - incision
   - injury
   - laceration
   - malignant hyperthermia
   - mutagen
   - oncogen
   - partial thickness burn
   - puncture wound
   - rad
   - radiation
   - radiation sickness
   - radon
   - rem
   - rule of nine
   - shotgun wound
   - stab wound
   - stippling
   - teratogen
   - the bends
   - the chokes
   - the staggers
   - wound
   - yaw

2. Compare and contrast:
   - abrasion
   - avulsion
   - contusion
   - incision
   - laceration
   - puncture wound
   - stab wound

   in terms of:
   - type of force (blunt vs. sharp) responsible
   - mechanism of production

3. Discuss, with specific examples, the ways in which clinical/gross and microscopic examination of injuries can aid in the following determinations:
   - antemortem vs. postmortem injury
   - age of antemortem in juries
   - instrument responsible for injury/death
   - including, for gunshot and shotgun wounds:
     - entrance vs. exit wound
     - range of fire

4. Describe the effects of the following characteristics of bullets, on the appearance and clinical effects of gunshot wounds:
   - mass
   - shape
   - deformation
   - fragmentation
   - yaw
   - velocity

5. Compare and contrast partial-thickness vs. full-thickness burns, in terms of:
   - morphology
   - systemic consequences
   - complications

6. Discuss hyperthermic reactions and hypothermic reactions, in terms of:
   - mechanisms
   - clinical manifestations
   - prognosis

7. Discuss the effects of electrical injuries in terms of:
   - resistance of tissue and voltage.
   - thermal vs. non-thermal effects
8. Discuss radiation injury in terms of:
   - sources of radiation
   - molecular effects
   - cellular effects
   - growth/developmental abnormalities
   - major morphologic changes [acute (early) vs. delayed (late)] in:
     - blood vessels
     - gastrointestinal tract
     - skin
     - hematopoietic/lymphoid tissues
     - heart
     - central nervous system
     - lungs

9. Discuss the following syndromes associated with whole-body exposure to ionizing radiation:
   - hematopoietic (bone marrow) syndrome
   - gastrointestinal syndrome
   - central nervous system (brain) syndrome
   in terms of:
     - etiologic radiation dose
     - pathogenesis
     - clinical manifestations
     - time to death

10. List the clinicopathologic effects on the human fetus of in utero exposure to ionizing radiation, and discuss these in terms of dosage and timing of radiation required.

11. List the adverse effects of:
    - microwave radiation
    - electromagnetic fields
    - ultrasound

12. Discuss the following types of atmospheric pressure-related injury:
    - high altitude illness
    - blast (air vs. immersion) injury
    - air/gas embolism
    - decompression disease
    in terms of:
      - mechanisms
      - clinicopathologic manifestations
32 - CHEMICAL AND DRUG INJURY

The student will be able to:

1. Define and use in proper context:
   - adverse drug reaction
   - alcoholism
   - amphbole
   - analgesic nephropathy
   - anthracosis
   - asbestos
   - asbestosis
   - bagassosis
   - berylliosis
   - bioaccumulation
   - bioaerosal
   - biologic effective dose
   - biortransformation
   - bird-fancier’s lung
   - byssinosis
   - Caplan syndrome
   - chrysotile
   - cirrhosis
   - drug
   - drug abuse
   - drug-abuser's lung
   - emphysema
   - environmental health
   - environmental pathology
   - farmer's lung
   - fatty change
   - ferruginous body
   - fetal alcohol syndrome
   - fetal tobacco syndrome
   - lead line
   - macule
   - Mallory body
   - mesothelioma
   - mycotoxin
   - nodule
   - ozone
   - pack-year
   - passive (sidestream) smoking
   - photochemical oxidant smog
   - phytotoxin
   - pleural plaque
   - pneumoconioses
   - pollutant
   - progressive massive fibrosis
   - reducing smog
   - salicylism
   - serpentine
   - silicosis
   - silo-filler’s disease
   - synergism
   - toxicity
   - toxicology
   - track mark
   - tumor initiator
   - tumor promoter

2. Discuss the following:
   - ozone
   - nitrogen dioxide
   - sulfur dioxide
   - acid aerosols
   - bioaerosols
   - carbon monoxide
   - cyanide
   - asbestos
   - in terms of:
     o role in indoor vs. outdoor air pollution
     o clinicopathologic effects

3. List the various substances found in cigarette smoke and their health effects.

4. Discuss the effects of:
   - active tobacco smoke
   - passive (sidestream) tobacco smoke
   - smokeless tobacco
   - in terms of:
     o magnitude of problem
     o resultant diseases

5. Outline the basic pathogenesis of pneumoconioses.

6. Compare and contrast the following pneumoconioses:
   - coal workers' pneumoconiosis
   - silicosis
   - asbestosis
   - berylliosis
   - in terms of:
     o types of occupational exposure
     o pathogenesis
7. Compare coal workers' pneumoconiosis with simple asymptomatic anthracosis.

8. Discuss Caplan syndrome in relation to coal workers' pneumoconiosis, asbestosis, and silicosis.

9. Give examples of different forms of silica and differentiate between silicoproteinosis and classic nodular silicosis

10. Describe the ways in which the following factors influence chemical injuries:
    - route of absorption
    - route of excretion
    - rate of excretion
    - biotransformation
    - bioaccumulation
    - physical properties of chemical
    - age of patient
    - nutritional status of patient
    - drug interactions

11. Compare and contrast toxic reactions to the following:
    - ethanol
    - methanol
    - ethylene glycol
    - cocaine
    - amphetamines
    - narcotics
    - hallucinogens
    - carbon monoxide
    - cyanide
    - hydrocarbons
    - lye
    - vinyl chloride
    - lead
    - mercury
    - organochlorine
    - insecticides
    - organophosphate
    - insecticides

    in terms of:
    - population(s) at risk
    - relative frequency
    - mechanism(s)
    - clinicopathologic manifestations
    - complications

12. Discuss ethanol in terms of:
    - effects ethanol on society
    - blood alcohol levels and their effects
    - metabolism and systemic effects of:
      - acute alcohol ingestion
      - chronic ethanol abuse

13. Discuss the following:
    - fetal alcohol syndrome
    - association of ethanol with cancer

14. Compare and contrast the two major types of adverse drug reactions (ADRs), in terms of:
    - mechanisms
    - agents most frequently implicated in each

15. Compare and contrast adverse reactions due to:
    - estrogens
    - oral contraceptives (OCPs)
    - salicylates
    - acetaminophen
    - antineoplastics
    - immunosuppressives
    - antimicrobials

    in terms of:
    - relative frequency
    - mechanism(s)
    - clinicopathologic manifestations
33 - INFECTIOUS DISEASES

The student will be able to:

1. Define and use in proper context:
   - acid-fast stain
   - acquired immunodeficiency syndrome (AIDS)
   - bacillary angiomatosis
   - bacteremia
   - bacterium
   - botulism
   - carbuncle
   - carrier
   - cellulitis
   - chancro
   - chlamydia
   - chorioamnionitis
   - coinfection
   - condyloma acuminatum
   - condyloma lata
   - Councilman body
   - Cowdry type A inclusion
   - culture
   - cutaneous larva migrans
   - cyst
   - dermatophyte
   - diarrhea
   - dysentery
   - ectoparasite
   - encephalitis
   - encephalomyelitis
   - endemic
   - endocarditis
   - endosporism
   - endotoxin
   - enteritis
   - epidemic
   - erisipelas
   - exotoxin
   - FTA-ABS
   - furuncle
   - gametocyte
   - gas gangrene
   - Ghon complex
   - Gram stain
   - Guarnieri body
   - gumma
   - helminth
   - hydatid
   - hypha
   - inclusion body
   - infection
   - infestation
   - koiocytosis
   - lepra cell
   - leprosy
   - lockjaw
   - lymphadenopathy
   - mad cow disease
   - meningitis (leptomeningitis)
   - meningococcal infection
   - merozoite
   - mold
   - molluscum body
   - mycelium
   - mycoplasma
   - myocarditis
   - Negri body
   - normal flora
   - oocyst
   - opportunistic infection
   - oral hairy leukoplakia
   - pandemic
   - parasite
   - pathogen
   - pathogenic
   - pelvic inflammatory disease
   - plague
   - pleocytosis
   - pneumonia
   - poliomyelitis
   - primary atypical pneumonia
   - prion
   - prion protein (PrP)

2. List and describe the different mechanisms of host barriers to infectious diseases

3. List host factors that predispose to infection

4. List three general ways in which infectious agents damage tissues

5. Discuss the different mechanisms of dissemination and transmission of microbial organisms.
6. Discuss the different mechanisms of bacterial-induced cellular and tissue injury including mechanisms of adhesions, exotoxins, and endotoxins.

7. Compare endotoxins and exotoxins on the basis of:
   - sources
   - effects
   - immunologic response

8. Discuss the specific mechanisms by which viruses enter host cells, replicate, and kill host cells.

9. Explain the events by which viruses may cause cell lysis or destruction in a permissive versus persistent infection.

10. Describe mechanisms by which infectious agents can evade the immune system.

11. Discuss the significance of:
    - pyogenic inflammation
    - granulomatous inflammation
    - caseous necrosis
    - gangrene
    - liquefactive necrosis

    in terms of:
    - possible causative agents
    - mechanism of reaction
    - morphologic features

12. Identify granulomatous inflammation and enumerate special stains needed to differentiate infectious etiologies thereof.

13. Compare and contrast the following types of infectious diseases:
    - bacterial
    - mycobacterial
    - fungal
    - rickettsial
    - viral
    - protozoan
    - helminthic
    - prion

    in terms of:
    - immunologic reactions
    - laboratory tests
    - histologic reaction
    - organ and tissue distribution

14. Compare and contrast respiratory infections due to the following agents:
    - rhinovirus
    - respiratory syncytial virus (RSV)
    - influenza virus
    - hantavirus
    - SARS-associated coronavirus (SARS-CoV)
    - pyogenic bacteria
    - Legionella pneumophila
    - Mycobacteria
    - Histoplasma capsulatum
    - Coccidiodes immitis
    - Blastomyces dermatitidis
    - Pneumocystis carinii

    in terms of:
    - characteristics of etiologic agent
    - epidemiology
    - agent and host factors related to transmission, invasion, survival, growth
    - pathogenesis
    - morphologic features
    - radiologic features
    - clinical features
    - laboratory findings
15. Compare and contrast gastrointestinal infections due to the following agents:
   - viral enteric pathogens
   - Shigella
   - Campylobacter
   - Yersinia
   - Salmonella
   - Escherichia coli
   - Vibrio cholerae
   - Clostridium difficile
   - Entamoeba histolytica
   - Giardia lamblia
   - Cryptosporidium parvum

   in terms of:
   - characteristics of etiologic agent, including toxin activity
   - epidemiology
   - agent and host factors related to transmission, invasion, and growth
   - region of gut affected
   - pathogenesis
   - morphologic features
   - clinical features
   - laboratory findings

16. Compare, contrast, and be discuss sexually transmitted diseases due to:
   - human immunodeficiency virus (HIV) 1 and 2
   - herpes simplex virus (HSV) 1 and 2
   - human herpes virus (HHV) 6 and 8
   - human papillomavirus (HPV)

   with regard to:
   - natural history
   - pathogenesis
   - morphology
   - clinical features and prognosis

17. Differentiate the oncogenic potential of the following types of HPV:
   - 6
   - 11
   - 16
   - 18

18. List extragenital pathologic processes produced by human papillomavirus

19. Describe genital molluscum contagiosum infection, in terms of:
   - etiologic organism
   - location of lesions
   - morphology
   - clinical consequences

20. Compare and contrast the following sexually transmitted diseases:
   - syphilis
   - gonorrhea
   - granuloma inguinale
   - chlamydial infections
   - chancroid
   - herpes simplex virus (HSV) infection
   - bacterial vaginosis
   - trichomoniasis
   - condylomata acuminata
   - crab louse infestation

   in terms of:
   - differences in males and females
   - etiologic agent
   - epidemiology
   - site and appearance of lesions
   - basic tissue response
   - clinical course
   - complications and prognosis
   - diagnostic procedure
21. Discuss staphylococcal infections with regard to:
   • species causing disease
   • pathogenesis
   • syndromes
   • morphology

22. Discuss streptococcal infections with regard to:
   • species (groups) causing disease
   • pathogenesis
   • syndromes
   • morphology

23. Compare and contrast streptococcal and staphylococcal infections, in terms of:
   • epidemiology
   • body sites involved
   • tissue reaction
   • clinical features
   • laboratory findings

24. Discuss Pseudomonas infections with regard to
   • associated conditions
   • pathogenesis
   • syndromes
   • morphology

25. Compare and contrast anaerobic infections caused by Clostridia with those caused by non-spore-forming anaerobes, in terms of:
   • characteristics of etiologic agent
   • epidemiology
   • agent and host factors related to transmission, invasion, growth, survival
   • pathogenesis
   • morphologic features
   • clinical features
   • laboratory findings

26. Discuss listeriosis in terms of:
   • etiology/morphology of the organism
   • epidemiology
   • food products linked to the disease
   • pathogenesis
   • morphologic changes in organs commonly involved
   • clinical presentation and course
   • methods of diagnosis

27. Compare and contrast actinomycosis and nocardiosis, in terms of:
   • epidemiology
   • etiology
   • pathogenesis
   • morphologic features of organism, including Gram and acid-fast staining reactions
   • tissue changes in organs commonly involved
   • clinical presentation
   • methods of diagnosis
   • clinical course

28. Compare and contrast the following infections:
   • measles (rubeola)
   • rubella
• mumps
• poliovirus infection
• varicella-zoster infection

in terms of:
  o etiologic agent
  o epidemiology
  o agent and host factors related to transmission, invasion, survival, growth
  o pathogenesis
  o morphology/organs involved
  o clinical features in children and adults
  o laboratory findings

29. Compare and contrast whooping cough and diphtheria, in with regard to:
  • etiologic organism
  • epidemiology
  • pathogenesis
  • morphology
  • clinical presentation

30. Discuss cytomegalic inclusion disease (CID) with regards to:
  • etiologic organism
  • modes of transmission
  • associated conditions
  • morphology
  • clinical presentation

31. Compare and contrast the following fungal diseases:
  candidiasis  histoplasmosis
  blastomycosis  mucormycosis
  cryptococcosis  sporotrichosis
  aspergillosis  dermatophytosis

in terms of:
  name and morphology of etiologic organisms
  morphology of lesions
  associated conditions  inflammatory response
  syndromes  organs involved
  pathogenesis  clinical features

32. Discuss:
  • Pneumocystis carinii infections
  • cryptosporidial intestinal infections
  • Toxoplasma gondii infections

in terms of:
  o associated conditions
  o inflammatory response
  o pathogenesis
  o morphology
  o clinical features

33. Discuss:
  plague  relapsing fever
  tularemia  rickettsial infections
  anthrax  arboviral encephalitides
  cat-scratch disease  Colorado tick fever
  Lyme disease  dengue fever
yellow fever
viral hemorrhagic fevers
babesiosis
malaria
in terms of:
  o etiologic organisms
  o vectors of transmission
  o morphology of lesions
  o clinical syndromes
  o diagnostic tests

34. Compare and contrast lepromatous leprosy and tuberculoid leprosy, in terms of:
  • epidemiology
  • etiology
  • epidemiology
  • pathogenesis
  • location/morphology of lesions
  • prognosis

35. Name the etiologic agent and vector of transmission responsible for each of the following:
  typhus fever
  rickettsialpox
  scrub typhus
  Q fever
  Rocky Mountain spotted fever
  ehrlichiosis

36. Discuss the following chlamydial diseases:
  • trachoma
  • inclusion conjunctivitis
  • lymphogranuloma verereum (LGV)
  • non-gonococcal urethritis
  • ornithosis
  in terms of:
    o etiologic organisms
    o epidemiology
    o pathogenesis
    o clinical features
    o morphologic features
    o diagnostic tests

37. Compare and contrast the following diseases:
  leishmaniasis
  African trypanosomiasis
  schistosomiasis
  Chagas disease
  in terms of:
    epidemiology
    associated conditions
    etiologic organisms
    vectors of transmission
    pathogenesis
    syndromes
    morphology/organisms
    involved
    laboratory findings

38. Discuss the following helminthic diseases:
  hookworm disease
  trichinelliosis
  cysticercosis
  hydatid disease
  in terms of:
    o etiologic organisms
39. Discuss the pathogenetic pathway of the infection of B lymphocytes by Epstein-Barr Virus (EBV) including the lytic phase and latent (cellular immortalization) phase. Compare the disease processes in each phase.

40. Compare and contrast the immune response to an EBV infection in an immunocompetent patient vs. that in an immunodeficient patient.

41. Using serological testing, differentiate between a patient with subclinical EBV infection, acute infectious mononucleosis, previous infection, reactivated infection, Burkitt lymphoma and nasopharyngeal carcinoma. Describe antibody reactions in immunodeficient patients exposed to Epstein-Barr Virus.

42. Discuss the following disorders:
   Burkitt lymphoma
   nasopharyngeal carcinoma
   in terms of:
   - epidemiology
   - pathogenesis
   - serologic findings
   - relationship to EBV

43. Compare and contrast the following central nervous system (CNS) infections:
   - acute meningitis (leptomeningitis)
   - aseptic meningitis
   - chronic meningitis
   - encephalitis
   - cerebritis
   - neurosyphilis
   in terms of:
   - etiologic agents
   - pathogenesis
   - morphology (gross and microscopic)
   - clinical presentation
   - methods of diagnosis
   - findings in cerebrospinal fluid

44. Discuss CNS abscesses and subdural empyema in terms of:
   - pathogenesis,
   - etiologic agents
   - morphologic features

45. Discuss the following viral encephalitides:
   - rabies
   - arbovirus infections
   - herpes simplex virus infection
   - cytomegalovirus infection
   - papalovirus infection
   - subacute sclerosing panencephalitis
   in terms of:
   - etiopathogenesis
   - clinical features
List three common arbovirus infections of the CNS in the United States.

46. Discuss the following types of spongiform encephalopathy caused by prions:
   - kuru
   - Creutzfeldt-Jakob disease (CJD)
   - variant CJD
   - Gerstmann-Sträusmann-Scheinker syndrome
   - fatal familial insomnia
   in terms of:
   - epidemiology
   - pathogenesis
   - clinical features
   - morphology

47. Discuss the following human immunodeficiency virus (HIV) infections of the CNS:
   - HIV meningoencephalitis (AIDS dementia)
   - vacuolar myelopathy
   in terms of:
   - pathogenesis
   - morphologic features
   - clinical manifestations

48. Discuss the following CNS complications of acquired immunodeficiency syndrome (AIDS):
   - toxoplasmosis
   - progressive multifocal leukoencephalopathy (PML)
   - primary CNS lymphoma
   in terms of:
   - etiologic agents
   - pathogenesis
   - morphologic features
   - clinical manifestations

49. Discuss human immunodeficiency virus (HIV) infections, in terms of:
   - characteristics of the etiologic agent
   - epidemiology
   - agent and host factors related to transmission, invasion, survival, and growth
   - pathogenesis
   - morphologic features
   - clinical course and complications
   - laboratory findings

50. List the most frequent infectious and neoplastic complications of acquired immunodeficiency syndrome (AIDS)

51. Discuss infectious diseases in patients with the following types of congenital primary immunodeficiency syndromes:
   - X-linked agammaglobulinemia (Bruton)
   - common variable immunodeficiency
   - IgA deficiency
   - hyper IgM syndrome
   in terms of etiologic organisms and pathogenesis.

52. Discuss septicemia in terms of:
53. Compare and contrast the acute and subacute forms of infectious endocarditis, in terms of:
   - epidemiology
   - etiologic organisms
   - associated conditions
   - pathogenesis
   - complications
   - clinical presentation
   - laboratory diagnosis
   - clinical coarse
   - prognosis

54. Discuss viral myocarditis in terms of:
   - etiologic organisms
   - pathogenesis
   - morphology
   - clinical presentation
   - clinical course

55. Discuss infectious diseases to which burn patients are predisposed, in terms of etiologic organisms and pathogenesis

56. Discuss infectious diseases to which patients with diabetes mellitus are predisposed, in terms of etiologic organisms and pathogenesis

57. Compare and contrast hepatitis caused by the following viruses:
   - hepatitis A virus (HAV)
   - hepatitis B virus (HBV)
   - hepatitis C virus (HCV)
   - hepatitis D (delta) virus (HDV)
   - hepatitis E virus (HEV)
   - hepatitis G virus (HGV)
   - cytomegalovirus (CMV)
   - Epstein-Barr virus (EBV)
   - in terms of:
     - biological characteristics of virus
     - nomenclature of antigens and antibodies
     - epidemiology
     - pathogenesis
     - clinical presentation
     - laboratory findings
     - serologic findings at various stages in course of disease
     - clinical features and complications, including propensity for chronicity
     - carrier state
     - differentiation from alcoholic and drug induced hepatitis

58. Compare and contrast acute, chronic, and xanthogranulomatous pyelonephritis with regard to:
   - clinical presentation
   - laboratory findings
   - associated conditions
   - etiology and pathogenesis
   - morphology
   - clinical course and prognosis

59. Compare hematogenous and ascending pyelonephritis in terms of pathogenesis and usual bacterial etiology.

60. Compare obstructive and reflux types of chronic pyelonephritis with regard to:
   - pathogenesis
   - morphology
   - clinical course.
61. Discuss the following genitourinary infectious processes:
   • acute cystitis
   • xanthogranulomatous cystitis
   • malacoplakia

   in terms of:
   o etiology
   o pathogenesis
   o morphology
   o clinical features

62. Discuss prostatitis in terms of:
   o etiologic organisms
   o morphology
   o clinical features

63. Discuss post-streptococcal glomerulonephritis in terms of:
   o pathogenesis
   o clinical presentation,
   o morphology,
   o laboratory diagnosis
   o course/prognosis

64. Discuss the different mechanisms producing increased susceptibility of sickle cell patients to infections.

65. Discuss infections to which sickle cell disease patients are prone, in terms of:
   o etiologic agents
   o complications caused by the infectious agents sickle cell patients are predisposed to.

66. Discuss the utilization of blood cultures in the diagnosis of infectious diseases in terms of:
   o indications
   o quantity of blood cultures
   o timing of specimens
   o technique
   o false negative/false positive results.

67. Discuss the utilization of the following techniques in the diagnosis of upper and lower respiratory tract infections:
   • throat culture
   • sputum culture
   • tracheal aspirate
   • bronchoalveolar lavage (BAL)

   in terms of:
   o indications
   o techniques
   o adequacy of specimens
   o special procedures
   o interpretation of results

68. Discuss the utilization of urine cultures in the diagnosis of infectious diseases of the genitourinary tract in terms of:
   o indications,
   o technique
   o interpretation of results
69. Discuss the utilization of feces in the diagnosis of infectious diseases of the gastrointestinal tract in terms of:
   o indications
   o special procedures
   o technique
   o interpretation of results

70. List the types of specimen used in the diagnosis of:
   • wound infections
   • abscesses
   • skin lesions (vesicles, pustules)
   • body fluids other than CSF

72. Describe appropriate uses of the following techniques in the diagnosis of infectious diseases:
   direct smear
   KOH preparation
   cytologic examination
   histologic examination
   Gram stain
   silver stain
   acid-fast stain
   immunohistochemistry
   electron microscopy
   culture

73. Enumerate the methods for diagnosing viral infections
34 - IMMUNOPATHOLOGY

The student will be able to:

1. Define and use in proper context:
   - acute cellular rejection
   - acute necrotizing vasculitis
   - acute serum sickness
   - acute vascular rejection
   - allergen
   - amyloid
   - anaphylaxis
   - anergy
   - antibody
   - antibody-dependent cell mediated cytotoxicity
   - antibody-mediated cellular dysfunction
   - antigen
   - anti-nuclear antibodies (ANA)
   - antiphospholipid antibody syndrome
   - Arthus reaction
   - atopy
   - autoimmune hemolytic anemia
   - autoimmunity
   - cellular rejection (cell mediated)
   - central and peripheral tolerance
   - chronic transplant rejection
   - complement-dependent reaction
   - contact dermatitis
   - CREST syndrome
   - discoid and butterfly rash
   - drug induced lupus erythematosus
   - endotheliitis
   - epithelioid macrophage
   - erythroblastosis fetalis
   - graft arteriosclerosis
   - graft-versus-host disease
   - granuloma

   hematoxylin body
   - histamine
   - human leukocyte antigen (HLA) complex
   - humoral rejection
   - hyperacute rejection
   - hypercoagulable state
   - hypersensitivity reaction
   - immunity
   - immunologic tolerance
   - keratoconjunctivitis sicca
   - LE cell
   - lupus anticoagulant
   - Mikulicz syndrome
   - onion skin lesions
   - opsonization
   - pemphigus vulgaris
   - phagocytosis
   - post transplantation lymphoproliferative process
   - proliferative arteritis
   - rheumatoid factor
   - sicca syndrome
   - T cell mediated cytotoxicity
   - transfusion reaction
   - transthyretin
   - tubulitis
   - wire loop lesions
   - xerostomia
   - β2-microglobulin
   - β-amyloid protein

2. Compare and contrast the four (4) types of immunologically mediated (hypersensitivity) disorders, in terms of:
   - terminology
   - pathogenesis
   - examples
   - definition
   - mediators involved
   - morphologic features
   - stimulating
   - cells involved
   - clinical features
   - antigens
   - tissues involved

3. Compare and contrast the following types of type II hypersensitivity reaction:
   - complement dependent
   - antibody dependent cell mediated cytotoxicity
   - antibody mediated cellular dysfunction

   in terms of:
   - pathogenesis
   - examples
   - clinical features
4. Compare and contrast acute serum sickness and Arthus reaction, in terms of:
   - definitions
   - pathogenesis
   - morphology
   - resultant clinical features

5. Compare and contrast delayed-type hypersensitivity and T cell-mediated cytotoxicity in terms of:
   - definitions
   - pathogenesis
   - clinical examples

6. Compare and contrast the following types of transplant rejection:
   - hyperacute rejection
   - acute rejection
   - chronic rejection
   - in terms of:
     - etiology
     - pathogenesis
     - general morphology

7. Discuss bone marrow transplantation in terms of:
   - indications
   - acute and chronic graft vs. host disease
   - pathogenesis
   - clinical presentation
   - complications.

8. Compare and contrast renal, heart and liver transplants in terms of general morphology of hyperacute rejection, acute rejection and chronic rejection, and other complications.

9. Define immunologic tolerance and discuss different mechanisms of a tolerant state.

10. Discuss different mechanisms by which immune tolerance is lost in the general pathogenesis of autoimmune diseases.

11. Discuss the pathogenesis of autoimmune diseases in terms of genetic factors and effects of microbial agents.

12. Discuss the following disorders:
    - systemic lupus erythematosus (SLE)
    - discoid lupus erythematosus (DLE)
    - drug-induced lupus erythematosus
    - Sjögren syndrome
    - systemic sclerosis (scleroderma)
    - CREST syndrome
    - dermatomyositis
    - polymyositis
    - rheumatoid arthritis (RA)
    - juvenile rheumatoid arthritis (JRA)
    - ankylosing spondylitis
    - Reiter syndrome
    - enteropathic arthritis
    - mixed connective tissue disease
    - polyarteritis nodosa
    - in terms of:
      - incidence and prevalence
      - genetic factors
      - age and sex association
      - clinical criteria for diagnosis
      - etiology
      - associated disorders

      - pathogenesis
      - laboratory diagnosis
      - morphology
      - clinical course
      - prognosis
13. Compare and contrast the five patterns (classes) of lupus nephritis, in terms of:
   - terminology
   - relative frequency
   - morphology (light, immunofluorescent, and electron microscopic)
   - clinical features
   - prognosis

14. Correlate each of the following patterns of immunofluorescent staining for antinuclear antibodies with the specific antibody represented by each, and disease(s) associated with each:
   - homogeneous (diffuse)
   - rim (peripheral)
   - speckled
   - nucleolar

15. Match each of the following autoantibodies with the major autoimmune disease(s) with which it is associated:
   - antinuclear (ANA)
   - anti-Smith (Sm)
   - anti-double-stranded DNA
   - antiphospholipid
   - antihistone
   - anti-SS-A (Ro) and anti-SS-B (La)
   - anti-Scl-70
   - anti-nuclear RNP
   - anti-Jo-1

16. Compare and contrast the following immune deficiency syndromes:
   - X-linked agammaglobulinemia of Bruton
   - common variable immunodeficiency
   - DiGeorge syndrome (thymic hypoplasia)
   - severe combined immunodeficiency syndrome
   - Wiskott-Aldrich syndrome
   - C2 deficiencies
   - deficiency of C1 inhibitor (hereditary angioedema)
   - chronic granulomatous disease
   - myeloperoxidase deficiency
   in terms of:
     - genetics
     - etiology
     - pathogenesis
     - immunologic defect
     - morphology
     - clinical features
     - methods of diagnosis
     - therapeutic approach
     - complications and prognosis

17. Discuss secondary immunodeficiency syndromes in terms of etiologies.

18. Discuss acquired immunodeficiency syndrome (AIDS), in terms of:
   - definition and diagnostic criteria
   - incidence
   - epidemiology
   - risk factors
   - etiology
   - pathogenesis
   - immunologic defects
   - laboratory testing
   - associated infections and neoplasms
   - morphology
   - therapeutic approaches
   - complications and prognosis
35 – HEMODYNAMIC DISORDERS

The student will be able to:

7. Define and use in proper context:
   - hemostasis
   - coagulation
   - clot
   - thrombosis
   - thrombocytopathy
   - thrombocytopenia
   - thrombocytosis
   - thrombophlebitis
   - phlebothrombosis
   - embolism
   - embolus
   - lines of Zahn
   - organization
   - recanalization
   - infarct
   - pale
   - red
   - bland
   - septic
   - von Willebrand factor
   - idiopathic thrombocytopenic
   - purpura (ITP)
   - thrombotic thrombocytopenic
   - purpura (TTP)
   - hemorrhage
   - occult bleeding
   - hemostasis
   - coagulation
   - clot
   - thrombosis
   - thrombocytopathy
   - thrombocytopenia
   - thrombocytosis
   - thrombophlebitis
   - phlebothrombosis
   - embolism
   - embolus
   - lines of Zahn
   - organization
   - recanalization
   - infarct
   - pale
   - red
   - bland
   - septic
   - von Willebrand factor
   - idiopathic thrombocytopenic
   - purpura (ITP)
   - thrombotic thrombocytopenic
   - purpura (TTP)
   - hemorrhage
   - occult bleeding
   - fibrin degradation products
   - d-dimer
   - Virchow’s triad
   - Trousseau syndrome
   - tissue plasminogen activator (tPA)
   - stasis
   - shock
   - reversible
   - irreversible
   - hyperemia
   - congestion
   - congestive heart failure
   - edema
   - inflammatory
   - noninflammatory
   - renal
   - lymphedema
   - anasarca
   - effusion
   - ascites
   - exudate
   - transudate

8. Outline the process of normal hemostasis, in terms of:
   - intrinsic pathway
   - extrinsic pathway
   - final common pathway
   - fibrin formation and fibrinolysis
   - protein C/protein S pathway
   - role of platelets
   - role of vascular integrity
   - events in dissolution of a thrombus
   - describing the role and interaction of each element involved in the process

9. Compare acute and chronic hemorrhage in terms of:
   - common causes
   - clinical manifestations
   - compensatory mechanisms

10. Describe thrombi in terms of:
    - types of thrombotic material
    - factors conditioning the development of thrombi
    - possible fate of thrombi

11. Distinguish between venous thrombi and arterial thrombi on the basis of:
    - etiologic and precipitating factors
• common sites of occurrence
• type and size of vessel involved
• morphologic appearance
• organs commonly involved
• local and distant effects
• fate of lesions and prognosis
• clinical and laboratory features

12. Compare the following types of emboli:
   arterial thrombotic
   venous thrombotic
   paradoxical
   fat
   bone marrow
   in terms of:
   • defining morphologic features
   • etiologic/precipitating factors
   • common sites of occurrence
   • organs commonly involved
   • type and size of vessels involved
   • complications
   • fate of lesion
   • common clinical manifestations

13. Compare and contrast arterial and venous infarcts on the basis of:
   • location
   • pathogenesis
   • morphology
   • clinical manifestations

14. Describe the morphologic appearance and natural history of infarcts of:
   • heart
   • kidney
   • lung
   • spleen
   • bowel
   • brain

15. Define, state the significance of, and identify on a peripheral blood smear each of the following:
   • platelet
   • giant platelet

16. Discuss thrombocytopoiesis in terms of:
   • morphology of megakaryocytes
   • fate of megakaryocytes
   • life span of platelets
   • factors which influence thrombocytopoiesis
   • abnormal morphologic forms of platelets and megakaryocytes

17. Discuss thrombocytopenia in terms of:
   • differential diagnosis
   • clinical features
   • bone marrow morphology and
   • laboratory features

18. Compare and contrast bleeding due to:
   • vascular defect (localized or generalized)
   • platelet defect
   • coagulation defect
   in terms of:
   • etiologic/precipitating factors
   • common sites of occurrence
   • organs commonly involved
   • type and size of vessels involved
19. Discuss thrombocytosis in terms of diagnosis and differential diagnosis.

20. Outline the process for stepwise evaluation of a:
   - bleeding patient
   - patient with suspected platelet disorder
   - patient with suspected hypercoagulability

21. Compare and contrast the following disorders of platelets:
   - Glanzmann thrombasthenia
   - Chediak-Higashi syndrome
   - Bernard-Soulier disease
   - Hermansky-Pudlak syndrome
   - Gray platelet syndrome
   - von Willebrand disease
   - HIV-associated thrombocytopenia
   - Drug-induced thrombocytopenia

   in terms of:
   - definition
   - genetics
   - laboratory features including platelet aggregation patterns
   - clinical features

22. Categorize and discuss acquired disorders of platelet function in terms of etiology and pathogenesis.

23. Compare and contrast:
   - idiopathic thrombocytopenic purpura (ITP)
   - thrombotic thrombocytopenic purpura (TTP)
   - hemolytic-uremic syndrome (HUS)

   in terms of:
   - etiology
   - pathogenesis
   - clinical features
   - morphologic findings
   - clinicopathologic diagnosis

24. List and discuss the laboratory diagnostic procedures used to approach patients with:
   - bleeding disorders
   - thrombotic disorders

25. Compare and contrast bleeding disorders due to:
   - factor VII deficiency (hemophilia A)
   - factor IX deficiency (hemophilia B)
   - factor XI deficiency (hemophilia C)
   - von Willebrand disease
   - vitamin K deficiency
   - liver disease

   in terms of:
   - etiology (including genetics as appropriate)
   - pathogenesis
   - clinical presentation
   - laboratory diagnosis
   - clinical course
26. Discuss coagulopathies associated with systemic lupus erythematosus in terms of:
   - clinical presentation
   - pathogenesis
   - laboratory diagnosis
   - clinical course

27. Discuss disseminated intravascular coagulopathy (DIC) in terms of:
   - etiologies
   - pathogenesis
   - morphologic features
   - clinical presentation and course
   - laboratory diagnosis
   - complications and prognosis

28. Define the hypercoagulable state in terms of Virchow's triad

29. Describe the mechanism(s) by which the following affect hemostasis:
   - aspirin
   - coumadin (warfarin)
   - heparin
   and discuss the methods by which each is monitored

30. Describe the following stages of shock:
   - non-progressive (compensated)
   - progressive (decompensated)
   - irreversible
   in terms of:
   - pathophysiology
   - morphologic changes
   - prognosis

31. Compare and contrast the following types of shock:
    - neurogenic
    - normovolemic
    - hypovolemic
    - hemorrhagic
    - septic
    - cardiogenic
    - anaphylactic

   in terms of:
   - pathogenic mechanism
   - common causes
   - structural changes
   - functional changes
   - clinical features and prognosis

32. List the morphologic changes and functional effects of shock on:
   - lungs
   - kidneys
   - adrenals
   - brain
   - gastrointestinal tract

33. Compare and contrast:
   - respiratory acidosis
   - respiratory alkalosis
   - metabolic acidosis
   - metabolic alkalosis
in terms of:
  o etiologies
  o pathophysiology
  o laboratory findings
  o clinical features

34. Compare:
   • right, left, and combined heart failure
   • acute and chronic heart failure

   in terms of:
     o pathogenic mechanisms
     o common causes
     o morphologic features
     o clinical manifestations

35. Compare and contrast active hyperemia and passive congestion, in terms of:
   • mechanisms of development
   • clinically important examples

36. Describe chronic passive congestion of:
   • lungs
   • liver
   • kidneys
   • spleen

   in terms of:
     o morphologic features
     o functional alterations

37. Discuss the pathogenesis of edema, giving examples associated with the following mechanisms:
   • altered plasma oncotic pressure
   • inflammation
   • venous obstruction/stasis
   • lymphatic obstruction

   and classify each in terms of localized vs. generalized

31. Compare edema of:
   • subcutaneous tissue
   • lungs
   • brain
   • kidneys

   on the basis of:
     o pathogenesis
     o morphologic changes
     o clinical effects
36 - METABOLIC DISORDERS

The student will be able to:

1. Define and use in proper context:
   - acute phase reactant
   - apolipoprotein
   - Bence-Jones protein
   - beta-gamma (β−γ) bridging
   - cholesterol
   - chylomicron
   - cryoglobulin
   - electrophoresis
   - gammopathy
   - high density lipoprotein (HDL)
   - immunofixation
   - isoelectric point
   - lecithin:cholesterol acyltransferase (LCAT)
   - low density lipoprotein (LDL)
   - MGUS
   - monoclonal (M) protein
   - oligoclonal band
   - paraprotein
   - prealbumin
   - total protein
   - triglyceride
   - very low density lipoprotein (VLDL)

2. Describe the major zones found in serum/urine/cerebrospinal fluid protein electrophoresis, and the major protein constituents of each zone.

3. Discuss the following conditions:
   - inflammation (acute, chronic)
   - nephrotic syndrome
   - cirrhosis
   - protein-losing enteropathy
   - hypoalbuminemia
   - α-1-antitrypsin deficiency
   - Tangier disease
   - hypo/agammaglobulinemia
   - cryoglobulinemia
   - polyclonal gammopathy
   - monoclonal gammopathy
   - light chain disease
   - multiple myeloma
   - Waldenström macroglobulinemia

   in terms of:
   - pathogenesis
   - results expected on the following lab tests:
     - serum and urine albumin
     - serum and urine total protein
     - serum and urine protein electrophoresis
     - urine Bence-Jones protein

4. List common benign and malignant causes of monoclonal proteins

5. Discuss multiple sclerosis in terms of:
   - pathogenesis
   - results expected on cerebrospinal fluid electrophoresis

6. List the causes of:
   - hypoalbuminemia
   - hyperlipoproteinemia
   - hyperglycemia
   - hypoglycemia

7. Compare and contrast the genetic hyperlipoproteinemias, in terms of:
   - electrophoretic phenotype
   - genetic defect
   - increased lipoprotein class(es)
   - increased lipid class(es)
   - relative frequency
8. Discuss the significance of:
   o decreased HDL
   o increased LDL
   o elevated chylomicrons
   o markedly decreased cholesterol

9. Discuss the significance of:
   o decreased HDL
   o increased LDL
   o elevated chylomicrons
   o markedly decreased cholesterol

10. Discuss the proposed relationships between dietary lipids, serum lipids, and atherosclerosis.

11. Discuss the pathogenesis of fatty change of the liver and list diseases associated with this finding.

12. Describe normal insulin physiology in terms of:
   o glycogen formation
   o nucleic acid synthesis
   o protein synthesis
   o regulation of blood glucose levels

13. Describe insulin receptor concentration, and list conditions of decreased insulin receptor concentration.

14. List tissues for which glucose transport requires insulin as well as those for which glucose transport does not require insulin.

15. Define diabetes mellitus and list the distinguishing features of type 1 and type 2 diabetes in terms of:
   o etiology and pathogenesis
   o role of inheritance and environmental factors
   o age and frequency
   o mode of onset
   o clinical and morphologic manifestations
   o insulin and glucose levels
   o insulin requirements
16. Describe the following lesions that may be found in diabetics:
- insulitis
- amylin deposition
- atherosclerosis
- diabetic microangiopathy
- pyelonephritis
- diffuse glomerulosclerosis
- nodular (intercapillary) glomerulosclerosis (Kimmelstiel-Wilson disease)

in terms of:
- pathogenesis
- morphologic appearance
- prevalence in diabetes
- relationship to severity and duration of diabetes
- specificity for diabetes
- relationship to serious manifestations of the disease
- prevention and treatment

17. Compare the incidence and distribution of micro- and macroangiopathy in diabetes.

18. Discuss diabetes mellitus in pregnancy in the context of:
- its incidence
- its effect on the mother
- its effect on the fetus and neonate

19. List diseases or conditions in which diabetes occurs as a secondary or accompanying phenomenon.

20. Discuss methods of screening patients for, and monitoring patients with, diabetes mellitus and impaired glucose tolerance, stating appropriate usage of the following laboratory tests:
- blood glucose concentration
- blood insulin concentration
- urine glucose concentration
- ketone bodies
- glucose tolerance test
- glycosylated hemoglobin level
- urine protein concentration

21. Discuss the relationship of diabetes mellitus to hypercholesterolemia, hypertriglyceridemia, and pregnancy (gestational diabetes)

22. Describe tests used to diagnose reactive hypoglycemia

23. Define and use in proper context:
- gout
- pseudogout
- tophus

24. Outline the sequence of pathogenetic biochemical and morphologic changes in gout

25. Compare and contrast:
- acute and chronic gout
- primary and secondary gout

In terms of:
- age and sex incidence
- etiology
- pathogenesis
26. Define and use in proper context:
- amyloid
- β-pleat
- transthyretin
- β2-microglobulin
- β-amyloid protein
- amyloid precursor protein (APP)

27. Describe amyloid in terms of:
- distribution (organ and architecture)
- gross appearance
- microscopic and ultrastructural appearance
- tinctorial properties

28. Compare and contrast the following:
- immunocyte dyscrasias with amyloidosis (primary amyloidosis)
- reactive systemic (secondary) amyloidosis
- hemodialysis-associated amyloidosis
- heredofamilial amyloidosis
- localized amyloidosis
- amyloid of aging
- senile cerebral amyloidosis
- endocrine amyloid
- isolated atrial amyloidosis

in terms of:
- chemical nature of amyloid involved
  major fibril protein
  chemically related precursor protein
- etiology and pathogenesis
- immunologic abnormalities
- distribution of amyloid
- associated diseases or conditions
- clinical features
- methods of diagnosis
37- MINERALS AND PIGMENTS

The student will be able to:

1. Define and use in proper context:
   • dystrophic calcification
   • metastatic calcification
   • hemosiderosis
   • hemochromatosis

2. Compare and contrast dystrophic and metastatic calcification, in terms of:
   • pathogenesis
   • location of lesions
   • associated diseases

3. List the mechanisms of iron deficiency and serum ferritin excess, along with common examples, and predict effects on serum iron and iron binding capacity

4. Compare and contrast hemosiderosis and hemochromatosis on the basis of:
   • etiology
   • pathogenesis
   • effects

5. Describe the major sites and steps of hemoglobin degradation

6. Indicate laboratory tests that would help determine the diagnosis and severity of each of the following:
   • hemolytic anemia
   • hepatocellular disease
   • partial bile duct obstruction
   • complete bile duct obstruction

7. Distinguish features of the following pigments:
   • carbon
   • lipofuscin
   • melanin
   • hemosiderin
   • hematoidin
   • bilirubin

   on the basis of:
   • color of pigment in routine (H and E-stained) sections
   • staining characteristics of pigment with special stain(s) used for identification
   • exogenous vs. endogenous origin
   • mechanism of deposition in tissue
   • common site(s) of deposition
   • diseases associated with each
38 – NUTRITIONAL DISEASES

The student will be able to:

1. Define and use in proper context:
   - anorexia nervosa
   - kwashiorkor
   - scurvy
   - Bitot spot
   - malnutrition
   - secondary (conditional)
   - body mass index (BMI)
   - marasmus
   - malnutrition
   - bulimia
   - osteomalacia
   - starvation
   - cachexia
   - osteopenia
   - trace element
   - cheilosis
   - pellagra
   - undernutrition
   - craniotabes
   - pernicious anemia
   - visceral protein compartment
   - dry beriberi
   - rickets
   - vitamin
   - exophthalmia
   - pigeon breast deformity
   - Wernicke-Korsakoff
   - flag sign
   - primary malnutrition
   - syndrome
   - frontal bossing
   - protein-energy (protein-calorie) malnutrition (PEM)
   - wet beriberi
   - glove dermatitis
   - rachitic rosary
   - xerophthalmia
   - Harrison groove
   - keratomalacia
   - rickets

2. List the five main categories of nutritional disorders

3. List the five major causes of undernutrition in the United States

4. Compare and contrast the following types of protein-energy malnutrition:
   - marasmus
   - kwashiorkor
   - secondary protein-energy malnutrition

   with regard to:
   - etiology and pathogenesis
   - effects on protein stores
   - physical findings
   - laboratory findings
   - morphologic features

5. List the fat-soluble vitamins and the function of each, and discuss deficiency states of each with regard to:
   - nomenclature
   - incidence
   - morphologic changes
   - clinical findings

6. List the water-soluble vitamins and the function of each, and discuss deficiency states of each with regard to:
   - nomenclature
   - incidence
   - morphologic changes
   - clinical findings

7. Compare and contrast deficiency of folate vs. that of vitamin B₁₂, with regard to:
   - incidence
   - etiology
   - hematopoietic manifestations
   - neuropathologic manifestations
   - laboratory findings
   - clinical features
8. Compare and contrast the skeletal changes of vitamin D deficiency with those of vitamin C deficiency, with regard to pathogenesis and morphology.

9. List the principle morphologic and clinical manifestations of toxicity due to:
   - vitamin A
   - vitamin D

10. List the morphologic changes and clinical manifestations caused by deficiency of:
    - calcium
    - phosphorus

11. Discuss the following trace elements:
    magnesium    zinc    selenium    fluoride
    iron    iodine    copper

   with regard to:
   - function
   - clinicopathologic manifestations of deficiencies thereof

12. Compare and contrast deficiency states resulting from:
    - loss of pancreatic function
    - celiac sprue
    - ileal disease
    - bile duct disease/obstruction
    - gastric dysfunction

   with regard to:
   - specific etiologic entities
   - pathogenesis
   - clinicopathologic manifestations

13. Describe the effects of malnutrition on cellular and humoral immunity.

14. Compare and contrast:
    - anorexia nervosa
    - bulimia

   in terms of:
   - pathophysiologic manifestations
   - clinical findings
   - complications

15. Discuss obesity in terms of:
    - epidemiology
    - clinical measurements
    - etiology
    - genetics
    - types of obesity
    - complications

16. Discuss the effects of diet on the pathogenesis of:
    - atherosclerosis
    - diabetes mellitus
    - hypertension
    - colonic diverticulosis
    - aging
    - neoplasia

17. Describe clinical laboratory measurements helpful in making a nutritional assessment of a hospitalized patient.
39 - AGING

*The student should be able to:*

1. Define and use in proper context:
   - aging
   - senescence
   - glycation
   - progeria

2. List the postulated actions in the various “wear and tear” and genome-based theories of aging.

3. List cellular alterations which occur with aging.

4. Discuss the changes which occur in the following with aging:
   - immune system
   - skin/hair
   - cardiovascular system
   - musculoskeletal system
   - genitourinary tract
   - central nervous system

5. Contrast the incidence of neoplasms above and below the age of 55.

6. List the changes in body composition with aging.

7. List four reasons for the increased incidence of adverse drug reactions in the elderly.
51 - FORENSIC PATHOLOGY

The student will be able to:

1. Define and use in proper context:
   - abrasion
   - accident
   - adipocere
   - algor mortis
   - asphyxia
   - avulsion
   - cause of death
   - certification of death
   - chain of custody
   - contusion
   - coroner
   - decomposition
   - drowning
   - electrocution
   - forensic
   - forensic pathology
   - gunshot wound
   - homicide
   - incision (incised)
   - injury
   - laceration
   - livor mortis
   - manner of death
   - mechanism of death
   - medical exam
   - mummification
   - pronouncement of death
   - puncture wound
   - putrefaction
   - rigor mortis
   - sudden death
   - sudden infant death
   - suicide
   - toxicology
   - toxidrome (SIDS)

2. Given the circumstances of death and the postmortem findings, correctly complete a death certificate.

3. List the five types of manner of death.

4. State the types of death which should be reported to the coroner/medical examiner.

5. Discuss the role of each of the following in the medicolegal investigation of death:
   - investigation of circumstances
   - scene investigation
   - necropsy (autopsy)
   - radiologic examination
   - chemical/toxicologic studies

6. Discuss forensic toxicology, in terms of:
   - appropriate specimens for a toxicologic screen
   - appropriate specimens for quantitation of a toxic substance
   - principles of interpretation of:
     - screening analyses
     - quantitative analyses

7. Discuss, with specific examples, the ways in which clinical/gross and microscopic examination of injuries can aid in the following determinations:
   - antemortem vs. postmortem injury
   - age of antemortem injuries
   - instrument responsible for injury

   including, for gunshot wounds:
   - entrance vs. exit wounds
   - range of fire

8. Compare and contrast partial thickness burns vs. full-thickness burns, in terms of:
   - Definitions
   - Morphology
   - systemic consequences
   - complications

9. Discuss electrical injuries in terms of factors determining effect of electric current, as well as thermal vs. non-thermal effects on tissue.
10. Discuss sudden infant death syndrome (SIDS) in terms of:
   o defining features
   o epidemiology
   o morphology
   o pathogenesis

11. List the most frequent causes of death from natural disease seen by coroners/medical examiners
56 – BLOOD BANK AND IMMUNOHEMATOLOGY

The student will be able to:

1. Define and use in proper context:

   - alloantibody
   - allogeneic
   - American Association of Blood Banks (AABB)
   - antibody panel
   - antibody screen
   - antiglobulin (Coombs) test
     - direct (DAT)
     - indirect (IAT)
   - apheresis
   - autoantibody
   - autologous transfusion
   - cold agglutinin
   - crossmatch
   - ΔOD 450
   - directed donor transfusion
   - elution
   - erythroblastosis fetalis
   - exchange transfusion
   - graft-versus-host (GVH) disease
   - hemapheresis
   - hemochromatosis
   - hemolytic disease of the newborn (HDN)
   - hemosiderosis
   - hydrops fetalis
   - immunohematology
   - intraoperative salvage
   - kernicterus
   - leukapheresis
   - Liley curve
   - massive blood transfusion
   - neocytes
   - percutaneous umbilical blood sampling (PUBS)
   - plasmapheresis
   - residual risk
   - Rhogam
   - transfusion reaction
   - transfusion related acute lung injury (TRALI)
   - type and crossmatch
   - type and screen

2. Discuss basic qualifications of a potential blood donor including reasons for deferral and routine laboratory tests performed on donor blood.

3. Describe the methods by which whole blood is collected and processed into the following components:
   - packed red blood cells (RBCs)
   - additive solution packed RBCs
   - fresh-frozen plasma (FFP)
   - platelets
   - cryoprecipitate

4. Describe how ABO and Rh antigens are formed, including the genetic bases thereof

5. Describe the basic identification procedures, incidence, and inheritance of the ABO and Rh blood groups

6. Compare and contrast the precursor substance which forms the backbone of the Lewis antigens with the precursor of the ABH antigens

7. Discuss the following blood group systems:
   - Lewis
   - Duffy
   - Kidd
   - Kell

   in terms of:
   - importance of transfusion history
   - modes of acquisition of antibodies
   - clinical significance of antibodies
   - transfusion reactions
   - hemolytic disease of newborn (HDN)
8. Describe the methods used for the following procedures, along with approximate time required to complete:
   - ABO forward type
   - ABO reverse type
   - Rh type
   - Antibody screen
   - Antibody identification panel
   - Crossmatch
   - Direct antiglobulin test (DAT)
   and determine compatible units by ABO-Rh with recipients based on ABO-Rh type

9. Discuss routine pre-transfusion compatibility testing in terms of:
   - Significance of positive antibody screens
   - Clinical significance of common alloantibodies

10. Discuss alternatives to the standard crossmatch, and clinical situations in which they may be indicated.

11. Discuss the philosophy behind changing ABO and Rh blood types in an emergency.

12. Given a patient's clinical condition and results of complete blood count and coagulation tests:
   - Determine if transfusion is indicated
   - Select proper component
   - Calculate amount needed
   - State proper methods of checking, handling, and administering a transfusion

13. List the hazards and late complications of blood transfusion.

14. Compare and contrast the following blood products:
   - Packed RBCs
   - Frozen RBCs
   - Washed RBCs
   - Leukocyte reduced RBCs
   - Granulocytes
   - Platelets
   - Neocytes
   - Fresh frozen plasma (FFP)
   - Cryoprecipitate
   - Albumin
   - Immune serum globulin
   - Rh immunoglobulin
   - Factor VIII concentrate
   - Factor IX concentrate

   In terms of:
   - Contents
   - Volume
   - Usual dose
   - Shelf life
   - Relative cost
   - Storage conditions
   - Clinical indications for transfusion
   - Expected post-transfusion hematologic effects from one unit
   - Optimum post-transfusion time for laboratory assessment of effect of transfusion
   - Complications of transfusion

15. Compare and contrast IgG and IgM alloantibodies produced in response to RBC transfusion in terms of:
   - Relative size
   - Ability to cause direct agglutination in vitro
   - Ability to cross placenta and cause HDN
   - Likelihood of causing:
     - Intravascular hemolysis
     - Extravascular hemolysis
   - Usual thermal range (room vs. body temperature)

16. Compare and contrast the following types of transfusion reactions:
   - Acute hemolytic
   - Delayed hemolytic
   - Febrile nonhemolytic
   - Allergic (urticarial)
   - Anaphylactoid
   - Transfusion-related acute lung injury (TRALI)
   - Bacterial contamination
   - Fluid overload
17. Discuss the transmission, via transfusion, of the following infectious agents

- *Treponema pallidum*
- hepatitis B virus (HBV)
- hepatitis C virus (HCV)
- human immunodeficiency virus (HIV)
- human T cell lymphotropic virus (HTLV)
- cytomegalovirus (CMV)
- West Nile virus (WNV)
- prions

   in terms of:
   - risk
   - blood product(s) implicated
   - prevention

18. Discuss therapeutic apheresis in terms of AABB guidelines categorizing:
   - effectiveness
   - indications
   - general technique
   - complications

19. Compare and contrast autologous transfusions and directed donor transfusions in terms of:
   - indications
   - presurgical blood donation procedures
   - reasons for deferral of donors/donated blood

20. Discuss the intraoperative salvage of RBCs in terms of:
   - indications and contraindications
   - general technique
   - expected results

21. Discuss massive blood transfusions in terms of:
   - indications
   - complications and treatment thereof

22. Discuss neonatal transfusions, including:
   - percutaneous umbilical blood sampling (PUBS)
   - exchange transfusion

   in terms of:
   - unique characteristics of transfusion of neonates as opposed to adults
   - indications for each of the above procedures

23. Discuss hemolytic disease of the newborn (HDN) in terms of:

   - etiology
   - pathogenesis
   - detection
   - morphologic features
   - clinical manifestations
   - laboratory findings
   - treatment
   - prevention

24. Outline the principles of paternity testing
Systemic Pathology Objectives
2005-2006

GRIPE Objectives Committee

Roger Geiss, MD
Byron Crawford, MD
Kuldeep Teja, MD

June 2005
Systemic Pathology Objectives
2005-2006

<table>
<thead>
<tr>
<th>Topic*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>61 – HEART</td>
<td></td>
</tr>
<tr>
<td>62 – VESSELS</td>
<td></td>
</tr>
<tr>
<td>63 – HEMATOPOIETIC SYSTEM</td>
<td></td>
</tr>
<tr>
<td>64 – RESPIRATORY SYSTEM</td>
<td></td>
</tr>
<tr>
<td>71 – ORAL REGION</td>
<td></td>
</tr>
<tr>
<td>72 – ALIMENTARY TRACT</td>
<td></td>
</tr>
<tr>
<td>73 – LIVER AND BILIARY TRACT</td>
<td></td>
</tr>
<tr>
<td>74 – PANCREAS</td>
<td></td>
</tr>
<tr>
<td>82 – LOWER URINARY TRACT</td>
<td></td>
</tr>
<tr>
<td>83 – MALE GENITAL SYSTEM</td>
<td></td>
</tr>
<tr>
<td>84 – FEMALE GENITAL SYSTEM</td>
<td></td>
</tr>
<tr>
<td>85 – BREAST</td>
<td></td>
</tr>
<tr>
<td>87 – DISORDERS OF FETUS AND PREGNANCY</td>
<td></td>
</tr>
<tr>
<td>88 – PEDIATRIC PATHOLOGY</td>
<td></td>
</tr>
<tr>
<td>91 – SKIN</td>
<td></td>
</tr>
<tr>
<td>92 – BONES, JOINTS, AND SOFT TISSUE</td>
<td></td>
</tr>
<tr>
<td>93 – SKELETAL MUSCLE</td>
<td></td>
</tr>
<tr>
<td>94 – NERVOUS SYSTEM</td>
<td></td>
</tr>
<tr>
<td>95 – SPECIAL SENSE ORGANS</td>
<td></td>
</tr>
</tbody>
</table>

Topic number refers to MCA topic designation in the GRIPE question banks.
The student will be able to:

1. Define and use in proper context:
   - anastomosis
   - aneurysm
   - angina pectoris
   - arrhythmia
   - Aschoff body
   - beriberi heart disease
   - carcinoid heart disease
   - disease
   - cardiac tamponade
   - cardiogenic shock
   - cardiomyopathy
   - chronic ischemic heart disease
coa
cor conduction system of
  the heart
congenital heart disease
congestive heart failure
  contraction band
  necrosis
  cor bovinum
  - cor pulmonale
  - myocardial infarct
  - coronary artery disease
  - dextrocardia
  - diastole
  - Dressler syndrome
  - ductus arteriosus
  - Ebstein
  - anomaly/malformation
  - endocardial
  - fibroelastosis
  - endocarditis
  - foramen ovale
  - heart failure
  - hemopericardium
  - hypertensive heart disease
  - hypertrophy of the myocardium
  - ischemic heart disease
  - Libman-Sacks
  - endocarditis
  - marantic endocarditis
  - mitral valve prolapse
  - myocarditis
  - pancarditis
  - pericarditis
  - Prinzmetal angina
  - reperfusion injury
  - rheumatic fever
  - rheumatic heart disease
  - ring abscess
  - stenosis
  - sudden cardiac death
  - systole
  - tetralogy of Fallot
  - transposition of great vessels
  - truncus arteriosus
  - unstable angina
  - valvular insufficiency
  - valvular regurgitation
  - valvular stenosis
  - vegetation
  - verruca

2. List the most common forms of heart disease in the United States

3. Compare and contrast the following:
   - congestive heart failure
   - high-output heart failure
   - forward heart failure
   - backward heart failure
   - left-sided heart failure
   - right-sided heart failure
   - cor pulmonale

   in terms of:
   - etiology
   - pathogenesis
   - compensatory mechanisms
   - morphology
   - clinical features

4. Discuss cardiogenic shock in terms of:
   - etiologic factors
   - pathogenesis
   - morphology
   - stages
5. Discuss congenital heart disease in terms of:
   o genetic and environmental factors
   o types which result in:
     - left-to-right vs. right-to-left shunt
     - cyanotic vs. acyanotic disease
   o types which present in:
     - infancy
     - childhood
     - adulthood

6. Compare and contrast the following forms of congenital heart disease:
   atrial septal defect (ASD)          patent ductus arteriosus (PDA)
   ostium primum                      transposition of the great vessels
   ostium secundum                    coarctation of the aorta
   ventricular septal defect (VSD)    preductal
   tetralogy of Fallot                 postductal
   endocardial cushion defects        anomalous pulmonary venous return
   hypoplastic left heart syndrome

   in terms of:
   - incidence
   - embryologic abnormality
   - pathogenesis
   - gross morphology
   - hemodynamic abnormalities
   - associated defects
   - clinical features
   - complications
   - treatment
   - prognosis

7. Discuss:
   • endocarditis
   • myocarditis
   • pericarditis
   • pericardial effusion
   • cardiac tamponade
   • pancarditis

   in terms of:
   o classification/types
   o epidemiology
   o etiology/pathogenesis
   o morphology
   o clinical features
   o prognosis

8. Compare and contrast:
   • acute rheumatic fever.
   • chronic rheumatic heart disease

   in terms of:
   o pathogenesis
   o diagnostic criteria
   o morphology (cardiac and extracardiac)
   o complications
   o laboratory findings
9. Compare and contrast the following forms of valvular heart disease:
   - calcific aortic stenosis
   - aortic insufficiency
   - mitral stenosis/insufficiency
   - mitral valve prolapse
   - mitral annular calcification
   - tricuspid insufficiency
   - pulmonic insufficiency
   - endocarditis
   - infective
   - noninfective
   - carcinoid heart disease

   in terms of:
   - epidemiology
   - etiology
   - pathogenesis
   - morphology (cardiac and extracardiac)
   - clinical features
   - complications
   - prognosis

10. List long term complications associated with prosthetic heart valves

11. Compare and contrast:
   - dilated (congestive) cardiomyopathy
   - hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis (IHSS)
   - restrictive cardiomyopathy
   - endomyocardial fibrosis
   - eosinophilic (Loeffler) endomyocarditis
   - endocardial fibroelastosis

   in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical course

12. Discuss coronary artery disease, in terms of:
   - epidemiology
   - risk factors
   - etiologic factors
   - pathogenesis
   - complications

13. Discuss myocardial infarct, in terms of:
   - etiologic factors
   - risk factors
   - pathogenesis
   - morphology
     - evolution of morphologic changes with time
     - correlation of morphologic distribution of infarct with site of coronary artery disease
   - clinical, laboratory, and electrocardiographic findings with increasing time after event
   - complications, including timing thereof after event
   - prognosis, including most common causes of death with increasing time after event
14. Discuss sudden cardiac death, in terms of:
   o causes
   o relationship to arrhythmias
   o cardiac morphology

15. Discuss the following cardiac tumors
    • myxoma
    • rhabdomyoma
    • lipoma
    • metastatic
    cardiac effects of noncardiac neoplasms
62 - VESSELS

The student will be able to:

1. Define and use in proper context:

- aneurysm
- angiitis
- arteriolosclerosis
- arteriosclerosis
- arteriovenous fistula
- arteriovenous malformation
- arteritis
- atheroma
- atherosclerosis
- deep vein thrombosis (DVT)
- false aneurysm
- fatty streak
- fibromuscular dysplasia
- fibrous cap
- fibrous plaque
- fusiform aneurysm
- gangrene
- hemorrhoid
- hypertension
- leukcytoclastic vasculitis
- lymphedema
- Marfan syndrome
- mycotic aneurysm
- obliterative endarteritis
- phlebosclerosis
- phlebothrombosis
- pseudoaneurysm
- pyogenic granuloma
- Raynaud disease
- Raynaud
- saccular aneurysm
- superior vena cava syndrome
- thrombophlebitis
- varicose veins
- vasculitis

2. Discuss mechanisms of blood pressure regulation, including:

- cardiac influences
- neural factors
- hormonal factors
- vasoactive agents
- renin-angiotensin system

3. Compare and contrast the following types of hypertension:

- essential
- malignant
- renovascular
- secondary

in terms of:

- etiology
- pathogenesis
- level of blood pressure elevation
- vascular morphologic findings
- clinical features
- prognosis

4. Discuss the morphologic effects of hypertension on:

- heart
- brain
- kidneys
- placenta

and enumerate the clinical consequences thereof

5. Describe the development, anatomy, and clinical consequences of the major congenital malformations of arteries.
6. Discuss the following vascular diseases:
   - arteriosclerosis
   - atherosclerosis
   - arteriolar sclerosis
   - Mönckeberg medical calcific sclerosis
   - vasculitis

   in terms of:
   - etiologic/predisposing factors
   - morphologic features
   - type and size of vessels involved
   - organs involved
   - complications of lesions
   - fate of lesions
   - clinical features and prognosis

7. Discuss the following forms of vasculitis:
   - infectious vasculitis
   - giant cell (temporal) arteritis
   - Takayasu arteritis
   - polyarteritis nodosa
   - Kawasaki (mucocutaneous lymph node) syndrome
   - microscopic (hypersensitivity) polyangiitis
   - Wegener granulomatosis
   - thromboangiitis obliterans (Buerger disease)

   in terms of:
   - incidence
   - age distribution
   - etiology
   - pathogenesis
   - size, type, and distribution of vessels involved
   - morphology of lesions
   - laboratory findings
   - clinical features, complications, and prognosis

8. Compare and contrast the following disorders:
   - atherosclerotic aneurysm
   - syphilitic aneurysm
   - aortic dissection (dissecting hematoma)
   - berry aneurysm
   - Charcot-Bouchard microaneurysm

   in terms of:
   - incidence
   - etiology
   - pathogenesis
   - type and distribution of vessels involved
   - morphology
   - clinical features
   - complications and prognosis

9. Compare and contrast thoracic and abdominal aortic aneurysms on the basis of:
   - etiologic factors
   - incidence
• complications

10. Discuss the effects of the following on the pathogenesis and prevalence of atherosclerosis:
   • age
   • sex
   • geographic location
   • risk factors

11. Outline the development of the atherosclerotic lesion with respect to:
   • pathogenic mechanisms
   • morphology
   • clinical manifestations
   • complications

12. Compare and contrast:
    • hyaline arteriolosclerosis
    • hyperplastic arteriosclerosis

    in terms of:
    o pathogenesis
    o morphology
    o clinical significance

13. Compare and contrast the following vascular tumors:
    vascular ectasias  glomus tumor (glomangioma)
    hemangioma  angiosarcoma
    hemangioendothelioma  bacillary angiomatosis
    hemangiopericytoma  Kaposi sarcoma
    lymphangioma

    in terms of:
    o age distribution
    o etiology
    o pathogenesis
    o morphology
    o clinical features
    o prognosis
63 – HEMATOPOIETIC SYSTEM

The student will be able to:

38. Define and use in proper context:
achlorhydria
acute leukemia
agnogenic myeloid metaplasia
aleukemic leukemia
amyloidosis
anemia
autosplenectomy
basophilic stippling
Bence Jones protein
Birbeck granule (HX body)
bronchus-associated lymphoid tissue (BALT)
chronic leukemia
circulating pool
coa
gulation
complete blood count (CBC)
cryoglobulinemia
direct antiglobulin (Coombs) test
dyserythropoiesis
dysmegakaryocytopoiesis
echymoses
erythropoiesis
erthropoietin
extramedullary hematopoiesis
e extravascular hemolysis
ferritin
G6PD screen
granulocytopenia
granulopoiesis
Ham test
haptoglobin
hematocrit
hematoma
hemoglobin electrophoresis
hemostasis
hyperviscosity syndrome
hypochromia
idiopathic thrombocytopenic purpura (ITP)
indirect antiglobulin (Coombs) test
ineffective hematopoiesis
intra
vascular hemolysis
intrinsic factor
left shift
leukemia
leukemoid reaction
leukocytosis
leukoerythrolei
blastosis
leukopenia
lymphoma
macrocytosis
maturation/storage pool
mean cell hemoglobin (MCH)
mean cell hemoglobin concentration (MCHC)
mean cell volume (MCV)
microcytosis
mucosa-associated lymphoid tissue (MALT)
myelodysplastic syndrome
myelophthisis
myeloproliferative disorder
nuclear-cytoplasmic asynchrony
pancytopenia
petechiae
Philadelphia chromosome
Plummer-Vinson syndrome
poikilocytosis
polychromasia
proliferating pool
purpura
red cell distribution width (RDW)
reticulocyte count
Schilling test
sickle cell disease
sickle cell prep
sickle cell trait
stem cell
sugar water test
thalassemia
thrombocytopathy
thrombocytopenia
thrombocytopenia
thrombocytopenia
thrombocytosis
thrombopoiesis
thrombopoietin
thrombotic thrombocytopenic purpura (TTP)
total iron binding capacity (TIBC)
transferrin
von Willebrand factor
39. Define, state the significance of, and identify on a peripheral blood smear each of the following:

- erythrocyte (discocyte)
- reticulocyte
- acanthocyte (spur cell)
- echinocyte (burr cell)
- codoocyte (leptoocyte, target cell)
- stomatocyte
- schistocyte
- rouleaux
- ringed sideroblast
- Cabot ring
- Howell-Jolly body
- Pappenheimer body
- neutrophil
- band (stab) form
- basophil
- eosinophil
- monocye

39. Define, state the significance of, and identify on a bone marrow smear each of the following:

- pronormoblast
- normoblast
- megaloblast
- myeloblast
- promyelocyte

41. Explain:

- the concept of reference (normal) range
- the theory of the automated cell counter
- the components of the complete blood count (CBC) and its application in patient evaluation

42. Compare and contrast the reporting of leukocyte differential counts as relative percentages vs. absolute numbers, in terms of the advantages and disadvantages of each system.

43. Discuss the stages of erythropoiesis in terms of:

- morphology of each stage
- stages in which hemoglobin is produced
- lifespan of reticulocytes and mature red blood cells
- mechanisms of degradation of senescent erythrocytes
- factors (vitamin, minerals and hormones) which influence erythropoiesis

44. Discuss the stages of granulopoiesis in terms of:

- morphology of each stage
- time to form and life span of mature granulocytes
- basic functions of the different types of maturing granulocytes
- factors which influence granulopoiesis.

45. Discuss the stages of development of lymphocytes, plasma cells, and monocytes, in terms of:

- morphology
- life span of mature forms
- functions of mature forms
- factors which influence production.

46. Discuss thrombocytopoiesis in terms of:

- morphology of megakaryocytes
• fate of megakaryocytes
• life span of platelets
• factors which influence thrombocytopoiesis
• abnormal morphologic forms of platelets and megakaryocytes

47. Discuss the following classification of anemia in terms of rationale for its use, and specific examples in each category:
• hypochromic-microcytic
• normochromic-normocytic
• macrocytic

48. Categorize and discuss laboratory test procedures used in the diagnosis of anemia, outlining the basic workup of a patient who presents with anemia.

49. Assess bone marrow function in the diagnosis of the anemic patient, on the basis of:
• reticulocyte count (relative, absolute, and corrected)
• serum bilirubin
• urobilinogen concentration

50. Discuss the following types of anemia:
- iron deficiency anemia
- megaloblastic anemias
- folate deficiency anemia

in terms of:
- incidence
- associated risks
- laboratory diagnostic criteria
- marrow and peripheral blood morphology
- etiology and pathogenesis
- clinical features and course

51. Utilize peripheral blood and bone marrow smears to assess the deviations from normal marrow response which occur in:
• hemolytic anemias
• nuclear maturation defects
• cytoplasmic maturation defects
• hypoproliferative anemias

52. Compare and contrast anemia secondary to acute vs. chronic blood loss in terms of:
• etiology
• pathophysiologic changes
• clinicopathologic diagnosis

53. Discuss the following types of anemia:
• sickle cell anemia
• the thalassemia disorders
• hereditary spherocytosis
• glucose-6-phosphate dehydrogenase (G6PD) deficiency
• pyruvate kinase deficiency
• paroxysmal nocturnal hemoglobinuria
• mechanical hemolytic anemia
• malaria

in terms of:
- genetics - molecular changes
- incidence
- etiology
- pathogenesis
- morphology
  - peripheral blood
  - bone marrow
54. Compare and contrast warm vs. cold antibody immunohemolytic anemias in terms of:
   • etiology
   • pathogenesis
   • associated risks-diseases
   • laboratory diagnosis
   • clinical features and course

55. Compare and contrast intravascular vs. extravascular hemolysis, in terms of:
   • etiology
   • pathogenesis
   • laboratory diagnosis
   • clinical findings and course

56. Compare and contrast:
   • acute lymphoblastic leukemia (ALL)
   • acute myeloblastic leukemia (AML)
   • chronic lymphocytic leukemia (CLL)
   • chronic myeloid leukemia (CML)
   • hairy cell leukemia (HCL)
   in terms of:
     o incidence and age distribution
     o cytogenetics
     o morphology (bone marrow and peripheral blood)
     o immunophenotyping
     o laboratory diagnosis (including cytochemical stains)
     o clinical features
     o prognosis

57. Describe the FAB (French-American-British) classification of acute myeloblastic leukemias in terms of:
   • nomenclature
   • incidence of each type
   • general features of each type

58. List the major etiology and pathogenesis of the following:
   leukopenia atypical lymphocytes
   leukemoid reaction eosinophilia
   neutropenia (relative and absolute) monocytosis
   lymphocytosis (relative and absolute) basophilia
   left shift leukoerythroblastic reaction

59. Distinguish between leukemia and leukemoid reaction on the basis of:
   • etiology
   • pathogenesis
   • laboratory data

60. Morphologically differentiate a blast form from a monocyte and lymphocyte.

61. Discuss the following myelodysplastic syndromes:
   • refractory anemia
   • refractory anemia with ringed sideroblasts
   • refractory anemia with excess blasts (RAEB)
   • refractory anemia with excess blasts in transformation (RAEB-IT)
• chronic myelomonocytic leukemia (CMML)

in terms of:
  o clinical presentation
  o etiology
  o genetics
  o morphology of peripheral blood and bone marrow
  o laboratory diagnosis
  o clinical course
  o prognosis

62. Define and classify the myeloproliferative disorders.

63. Discuss the following myeloproliferative disorders:

• chronic myeloid leukemia
• polycythemia vera
• myeloid metaplasia with myelofibrosis
• essential thrombocythemia

in terms of:
  o incidence
  o clinical presentation
  o genetics
  o pathogenesis
  o morphology - peripheral blood and bone marrow
  o laboratory diagnosis
  o clinical course and complications
  o prognosis

64. Compare and contrast:

• polycythemia vera
• relative polycythemia
• secondary polycythemia

in terms of:
  o etiology
  o diagnostic criteria
  o clinical course and complications

65. Describe the proper mode of submission of a lymph node biopsy to the surgical pathology laboratory for workup of a suspected lymphoproliferative disorder.

66. Define, state the significance of, and identify in a microscopic section of a lymph node or extranodal site of involvement each of the following:

- lymphocyte (normal)
- Hodgkin cell
- small cleaved lymphocyte
- Reed-Sternberg cell
- large lymphocyte
- "popcorn" cell
- macrophage
- lacunar cell

67. Compare and contrast:

• follicular hyperplasia
• follicular lymphoma

on the basis of:
  o histologic criteria
  o clinical significance

68. Discuss general features of non-Hodgkin lymphomas in terms of:
• incidence
• immunophenotyping (T vs B cells)
• morphologic patterns (diffuse vs. follicular)
• principles of:
  o classification
  o grading
  o staging
• laboratory methods of diagnosis
• clinical features
• prognosis
• extralymphatic organs involved
• likelihood of a leukemic phase

69. Compare and contrast:
• small lymphocytic lymphoma
• follicular lymphoma
• diffuse large cell lymphoma

in terms of:
  incidence clinical presentation
  associated conditions laboratory diagnosis
  age and sex distribution clinical features
  morphology prognosis
  immunophenotyping

33. Compare and contrast:
• lymphoblastic lymphoma
• small noncleaved cell (Burkitt) lymphoma

in terms of
  incidence immunophenotyping
  associated conditions laboratory diagnosis
  age/sex distribution clinical features
  morphology prognosis

34. Discuss Hodgkin disease in terms of:
  classification morphology of each types
  incidence of each type laboratory diagnosis
  etiology clinical features
  pathogenesis prognosis

35. Compare and contrast:
• non-Hodgkin lymphomas
• Hodgkin disease

in terms of:
  o clinical features
  o methods of staging

36. Discuss:
• mantle cell lymphoma
• marginal zone lymphoma
• peripheral T-cell lymphoma
• adult T-cell lymphoma/leukemia
• cutaneous T-cell lymphoma

in terms of:
37. List benign and malignant etiologies of lymphoadenopathy and splenomegaly.

38. Categorize and discuss the different types of plasma cell dyscrasias in terms of definitions and clinical presentation.

39. Discuss multiple myeloma in terms of:
   - clinical presentation
   - etiology
   - clinicopathologic diagnosis
   - morphology and sites of lesions

40. Discuss Waldenström macroglobulinemia in terms of:
   - clinical presentation
   - morphology with immunophenotyping
   - associated conditions

41. Compare and contrast:
   - plasmacytoma
   - monoclonal gammopathy of uncertain significance (MGUS)
   - heavy chain disease
   in terms of:
   - incidence
   - clinical presentation
   - clinicopathologic diagnosis
   - clinical course
   - differentiation from multiple myeloma

42. Discuss the different laboratory procedures used in the clinicopathologic diagnosis of the different plasma cell dyscrasias.

43. List benign and malignant etiologies of monoclonal gammopathies.

44. Discuss Langerhans cell histiocytosis in terms of:
   - definition
   - classification
   - clinicopathologic diagnosis
   - morphology
   and for each type, discuss:
   - age of onset
   - distribution of lesions
   - clinical course/prognosis

45. Classify major causes of changes in size of spleen, in terms of both increase and decrease.

46. Enumerate the gross and microscopic characteristics of involvement of the spleen by:
   - infarcts
   - sickle cell disease
   - extramedullary hematopoiesis
   - passive congestion
   - amyloid
   - leukemia
   - lymphoma
   - rupture

47. List the major complications of splenomegaly.

48. Briefly describe the morphologic features and clinical findings in:
   - histiocytoses
• Gaucher disease
• Neimann-Pick disease
• Tay-Sachs disease

49. Discuss thrombocytopenia in terms of:
   • differential diagnosis
   • clinical features
   • bone marrow morphology and
   • laboratory features

50. Discuss thrombocytosis in terms of diagnosis and differential diagnosis.

51. Outline the role of platelets in normal hemostasis.

52. Outline the process for stepwise evaluation of a patient with suspected platelet disorder.

53. Compare and contrast the following disorders of platelets:
   Glanzmann thrombasthenia  gray platelet syndrome
   Chediak-Higashi syndrome  von Willebrand disease
   Bernard-Soulier disease   HIV-associated thrombocytopenia
   Hermansky-Pudlak syndrome drug-induced thrombocytopenia

   in terms of:
   o definition
   o genetics
   o laboratory features including platelet aggregation patterns
   o clinical features

54. Categorize and discuss acquired disorders of platelet function in terms of etiology and pathogenesis.

55. Compare and contrast:
   • idiopathic thrombocytopenic purpura (ITP)
   • thrombotic thrombocytopenic purpura (TTP)
   • hemolytic-uremic syndrome (HUS)

   in terms of:
   o etiology
   o pathogenesis
   o clinical features
   o morphologic findings
   o clinicopathologic diagnosis

55. List and discuss the laboratory diagnostic procedures used to approach patients with:
   • bleeding disorders
   • thrombotic disorders

56. Discuss disseminated intravascular coagulopathy (DIC) in terms of:
   etiologies clinical presentation and course
   pathogenesis laboratory diagnosis
   morphologic features complications and prognosis
64 – RESPIRATORY SYSTEM

The student will be able to:

1. Define and use in proper context:

   - acute interstitial pneumonia (AIP)
   - adult respiratory distress syndrome (ARDS)
   - allergic bronchopulmonary aspergillosis (ABPA)
   - alveolar-capillary membrane
   - anthracosis
   - asbestos
   - asbestosis
   - asteroid body
   - asthma
   - atelectasis
   - bagassosis
   - barrel chest
   - "benign mesothelioma"
   - bird-fancier's disease
   - bleb
   - blue bloater
   - branchial cleft cyst
   - bronchial cyst
   - bronchiectasis
   - bronchiolitis obliterans
   - bronchogenic carcinoma
   - bronchogenic cyst
   - bronchopulmonary sequestration
   - bulla
   - byssinosis
   - Caplan syndrome
   - Charcot-Leyden crystal
   - chronic bronchitis
   - chronic obstructive pulmonary disease (COPD)
   - chylothorax
   - coal macule
   - coal nodule
   - coin lesion
   - consolidation
   - cor pulmonale
   - cryptogenic fibrosing alveolitis (CFA)
   - cryptogenic organizing pneumonia (COP)
   - Curschmann spiral
   - diffuse alveolar damage (DAD)
   - diffuse parenchymal lung disease (DPLD)
   - dyspnea
   - emphysema
   - empyema
   - extrinsic allergic alveolitis (EAA)
   - farmer's lung
   - ferruginous body
   - Ghon complex
   - Goodpasture syndrome
   - Hamman-Rich syndrome
   - heart failure cell
   - hemoptysis
   - hemotherax
   - histiocytosis X
   - honeycomb lung
   - Horner syndrome
   - hyaline membrane
   - hydrothorax
   - hypersensitivity pneumonitis (HP)
   - hypertrophic pulmonary osteoarthropathy
   - idiopathic interstitial pneumonia (IIP)
   - idiopathic pulmonary fibrosis (IPF)
   - jagziekte
   - juvenile laryngeal papillomatosis
   - Loeffler syndrome
   - lymphangitic carcinomatosis
   - Meigs syndrome
   - middle lobe syndrome
   - nasopharyngeal carcinoma
   - non-small cell lung cancer (NSCLC)
   - obstructive lung disease
   - organizing pneumonia
   - Pancoast tumor
   - paraneoplastic syndrome
   - pigeon-breeder's lung
   - pink puffer
   - plexiform lesion
   - pneumoconiosis
   - pneumothorax
   - progressive massive fibrosis (PMF)
   - pulmonary edema
   - pulmonary embolism
   - pulmonary veno-occlusive disease (PVOD)
   - rales
   - Reid index
   - restrictive lung disease
   - rhonchi
   - saddle embolus
   - scar carcinoma
   - Schaumann body
   - severe acute respiratory syndrome (SARS)
   - silicatosis
   - silicosis
   - silo-filler's disease
   - singers' node
   - small airways disease
   - status asthmaticus
tension pneumothorax  vocal cord nodule
tumorlet

2. Describe the mechanisms by which the following pulmonary defense mechanisms accomplish their functions:
   - nasal clearance
   - laryngeal (including epiglottic) action
   - tracheobronchial clearance
   - alveolar clearance

3. Explain the pathogenesis of each of the following manifestations of pulmonary disease:
   - pain
   - cough
   - dyspnea
   - sputum production
   - cyanosis
   - clubbing of fingers
   - hypertrophic pulmonary osteoarthropathy
   - secondary polycythemia
   - hemptysis
   - cor pulmonale

4. Discuss the following pulmonary congenital anomalies, in terms of morphology and clinical consequences:
   - agenesis
   - hypoplasia
   - congenital lobar overinflation ("emphysema")
   - congenital cyst
   - bronchopulmonary sequestration
     - intralobar
     - extralobar

5. Compare and contrast:
   - obstruction (resorption) atelectasis
   - compression atelectasis
   - contraction atelectasis
   - microatelectasis
   - patchy
   in regards to:
   - predisposing factors
   - etiology
   - pathogenesis
   - morphologic findings
   - clinical features

6. Contrast obstructive and restrictive pulmonary disease, in terms of:
   - morphologic features
   - radiologic manifestations
   - pulmonary function test results
   - clinical manifestations

7. Compare and contrast the etiologies and effects of airflow obstruction that occur in lesions involving the airways with those that involve the alveolar parenchyma.

8. Compare and contrast:
   - emphysema
   - chronic bronchitis
   - bronchial asthma
   - bronchiecstasy
   in terms of:
   - etiology
o pathogenesis
o morphologic features
o radiologic features
o clinical manifestations
o complications and prognosis

9. Compare and contrast the following forms of bronchial asthma:
   • atopic
   • non-atopic
   • drug-induced
   • occupational
   in terms of etiology and pathogenesis

10. Compare and contrast
    centriacinar (centrolobular) emphysema
    panacinar (panlobular) emphysema
    paraseptal (distal acinar) emphysema
    focal emphysema
    interstitial emphysema
    senile "emphysema"
    congenital lobar "emphysema"
    in terms of:
        incidence
        age and sex distribution
        etiology
        pathogenesis
        gross and microscopic morphology
        physiologic changes
        radiologic features
        clinical presentation, course, and prognosis

11. Discuss the Reid index, in terms of a normal index vs. an index indicative of chronic bronchitis

12. Discuss respiratory bronchiolitis of smokers (small airways disease) in terms of:
    • pathogenesis
    • morphology
    • clinical presentation

13. Discuss bronchiectasis, in terms of:
    • predisposing conditions
    • the types of organisms typically cultured from bronchi
    • sequelae

14. Compare and contrast neonatal and adult respiratory distress syndrome in terms of:
    • predisposing factors/associated conditions
    • pathogenesis
    • morphology
    • complications
    • clinical course

15. Compare and contrast the following forms of diffuse parenchymal lung disease (DPLD):
    • diffuse alveolar damage (DAD)
    • bronchitis obliterans-organizing pneumonia (BOOP)
    • usual interstitial pneumonia (UIP)
    • desquamative interstitial pneumonia (DIP)
    • lymphoid interstitial pneumonia (LIP)
    • nonspecific interstitial pneumonia (NSIP)
    in terms of:
        synonyms
        associated diseases
        etiopathogenesis
        morphologic features
        radiologic features
        clinical manifestations
        treatment
        prognosis

16. Discuss the following disorders:
sarcoidosis
Goodpasture syndrome
idiopathic pulmonary hemosiderosis (IPH)
hypersensitivity pneumonitis (HP)
pulmonary alveolar proteinosis
pulmonary eosinophilic granuloma
pulmonary infiltrates with eosinophilia (PIE)
lipid pneumonia
Wegener granulomatosis
lymphomatoid granulomatosis

in terms of:
- associated conditions
- etiopathogenesis
- morphologic features (pulmonary and extrapulmonary)
- radiologic features
- clinical manifestations
- treatment
- prognosis

17. Discuss pulmonary involvement in autoimmune ("collagen-vascular") diseases, noting the major morphologic manifestations in the lung of:
   - systemic lupus erythematosus (SLE)
   - rheumatoid arthritis (RA)
   - progressive systemic sclerosis (PSS)

18. Discuss the basic pathogenesis of pneumoconioses.

19. Compare and contrast the following pneumoconioses:
   - coal workers' pneumoconioses
   - silicosis
   - asbestosis
   - berylliosis

in terms of:
- occupational exposure
- pathogenesis
- gross and microscopic morphology
- complications
- clinical course

20. Discuss the following asbestos-related lung diseases:
   - fibrous pleural plaques
   - pleural effusion
   - asbestosis
   - bronchogenic carcinoma
   - malignant mesothelioma

in terms of:
- epidemiology
- etiopathogenesis
- morphology
- clinical features
- prognosis

21. Discuss the acute and chronic stages of radiation lung injury, in terms of:
   - temporal features
   - pathogenesis
   - morphology
   - consequences

22. Discuss drug-induced lung disease, enumerating drugs most commonly associated with the following pulmonary reactions:
• bronchospasm
• pulmonary edema
• hypersensitivity pneumonitis (HP)
• eosinophilic pneumonia
• diffuse alveolar damage (DAD)
• pulmonary fibrosis

23. Enumerate the general indications for lung transplantation, and discuss the following complications thereof:
• pulmonary infection
• acute rejection
• chronic rejection
  in terms of:
  o etiology
  o pathogenesis
  o morphology
  o clinical features

24. Discuss the pulmonary features of cystic fibrosis (CF), in terms of:
• frequency of involvement of lung in CF
• pathogenesis
• morphology
• functional alterations
• clinical manifestations
• pulmonary complications
  o obstructive
  o infectious (including most common organisms involved)
• treatment
• prognosis

25. Compare and contrast:
• bronchopneumonia
• lobar pneumonia
• primary atypical pneumonia
• aspiration pneumonia
• lung abscess
• pulmonary infiltrates in the immunocompromised host
  in terms of:
  predisposing factors
  etiologic organisms
  pathogenesis
  morphologic features
  radiologic features
  clinical manifestations
  prognosis

26. Describe the four classic stages of the inflammatory response in lobar pneumonia, in terms of:
• temporal features
• morphology

27. Discuss the following specific respiratory tract infections:
  anthrax
  Legionnaire's disease
  actinomycosis
  nocardiosis
  tuberculosis
  atypical mycobacteriosis
  mycoplasma pneumonia
  psittacosis
  histoplasmosis
  coccidioidomycosis
  blastomycosis
  cryptococcus
  aspergillosis
  mucormycosis
respiratory syncytial virus (RSV) infection
influenza pneumonia
adenovirus pneumonia
cytomegalic inclusion disease (CID)
in respiratory syncytial virus (RSV) infection, influenza pneumonia, adenovirus pneumonia, and cytomegalic inclusion disease (CID), in terms of:
  - characteristics of organism
  - predisposing factors
  - associated conditions
  - pathogenesis

severe acute respiratory syndrome (SARS)
Pneumocystis carinii pneumonia (PCP)
toxoplasmosis
strongyloidiasis

in terms of:
  - morphology, including use of special stains
  - radiologic features
  - clinical features
  - prognosis

28. Differentiate among tuberculosis, sarcoidosis, and granulomatous fungal disease on the basis of:
   - etiopathogenesis
   - morphologic features, including use of special stains
   - organs involved
   - radiologic features
   - clinical presentation
   - diagnostic tests
   - laboratory findings
   - prognosis

29. Discuss pulmonary edema, embolism, and infarction in terms of:
   - predisposing factors and etiology
   - pathogenesis
   - morphologic features
   - radiologic features
   - clinical manifestations

30. Compare and contrast pulmonary embolism caused by:
    - thrombus
    - bone marrow
    - fat
    - amniotic fluid
    - air
    - talc

in terms of:
  - predisposing factors
  - pulmonary pathophysiology
  - incidence
  - complications
  - morphology
  - clinical course

31. Compare and contrast primary and secondary pulmonary hypertension, in terms of:
   - predisposing factors/associated conditions
   - pathogenesis
   - age and sex distribution
   - clinical manifestations
   - size and type of vessels involved
   - morphologic features (including reversible vs. irreversible lesions)
   - hemodynamic consequences
   - prognosis

32. Discuss:
   - pulmonary circulatory disease associated with congenital heart disease
   - persistent fetal circulation

in terms of:
  - etiopathogenesis
  - size and type of vessels involved
  - morphologic features
  - pulmonary pathophysiology
  - prognosis
33. Compare and contrast the following thoracic tumors:
   squamous cell carcinoma of lung  pulmonarv hamartoma
   bronchogenic adenocarcinoma  malignant lymphoma
   bronchioalveolar carcinoma  Hodgkin disease
   small cell carcinoma of lung  metastatic neoplasm to thorax
   large cell carcinoma of lung  pleural fibroma (solitary fibrous tumor)
   bronchial carcinoid  malignant mesothelioma of pleura
   in terms of:
   epidemiology  clinical manifestations (pulmonary, extrapulmonary)
   etiology  staging
   pathogenesis  treatment
   morphologic features  prognosis
   radiologic features

34. Compare central and peripheral neoplasms of the lung in terms of:
   • clinical presentation
   • radiographic presentation
   • histologic types
   • clinical course
   • prognosis

35. Enumerate the different types of mediastinal masses based on location in:
   • superior mediastinum
   • anterior mediastinum
   • posterior mediastinum
   • middle mediastinum

36. Compare and contrast:
   • thymoma
   • malignant thymoma
   • thymic carcinoma
   in terms of:
   o associated conditions and syndromes
   o clinical presentation and course

37. List likely etiologies and expected effects on pulmonary function of:
   hydrothorax  pneumothorax
   empyema  tension pneumothorax
   hemothorax  pleural adhesion
   chylothorax

38. Discuss pleural fluid collections on the basis of fluid type and common associations

39. List appropriate diagnostic procedures for patients clinically suspected of having pleural effusions

40. Compare and contrast:
   nasal polyp
   sinonasal papilloma
   laryngeal nodule (singers' node)
   laryngeal papilloma
   juvenile laryngeal papillomatosis
   laryngeal squamous cell carcinoma
   nasopharyngeal carcinoma
in terms of:
  - etiology
  - morphology
  - clinical features
  - prognosis
71 - ORAL REGION

The student will be able to:

1. Define and use in proper context:
   - carcinoma ex pleomorphic adenoma
   - erythroplasia
   - glossitis
   - leukoplakia
   - Mikulicz syndrome
   - sicca syndrome
   - xerostomia

2. Describe the following congenital anomalies:
   - cleft lip/palate
   - branchial cleft cyst
   - in terms of:
     - embryonic developmental pathogenesis
     - morphology
     - clinical features

3. Describe dental caries and periodontal disease, in terms of:
   - epidemiology
   - etiology and pathogenesis
   - complications
   - prophylaxis

4. Describe the following oral lesions:
   - primary herpetic gingivostomatitis
   - perioral herpes simplex
   - aphthous ulcer
   - oral candidiasis
   - hairy leukoplakia
   - in terms of:
     - epidemiology
     - etiology and pathogenesis
     - clinical and morphologic features

5. State the relationship of carcinoma of the oral mucosa to:
   - leukoplakia
   - erythroplasia
   - jagged teeth
   - tobacco
   - ill-fitting dentures

6. Describe the development of squamous cell carcinoma, in terms of:
   - predisposing factors
   - specific sites within organ
   - morphology
   - clinical features and course
   - prognosis
   - associated predisposing lesions
   - patterns of metastasis

   for each of the following anatomic sites:
   - lip
   - pharynx
   - tongue
   - larynx
   - floor of mouth
   - trachea
7. List the signs, symptoms, and usual etiology of acute epiglottitis

8. Compare and contrast laryngeal nodules ("singer's nodes") and laryngeal papillomas, in terms of:
   - age of onset
   - etiology
   - morphology
   - biologic behavior
   - relationship to carcinoma

9. Describe the following salivary gland lesions:
   - sialadenitis
   - sialolithiasis
   - pleomorphic adenoma (mixed tumor)
   - adenolymphoma (Warthin tumor)
   - acinic cell tumor

   in terms of:
   - relative frequency
   - location
   - morphology
   - prognosis

10. Describe the following odontogenic lesions:
    - odontogenic cyst
    - dentigerous cyst
    - ameloblastoma

    in terms of:
    - pathogenesis
    - morphology
    - prognosis

11. List defining features and significance of the following oral lesions:
    - peripheral giant cell granuloma (epulis)
    - mucocele
    - pyogenic granuloma ("pregnancy tumor")

12. Compare and contrast the following lesions of the nasal cavity and paranasal sinuses:
    - acute rhinitis
    - nasal polyps
    - angiofibroma
    - Wegener granulomatosis
    - polymorphic reticulosis (lethal midline granuloma)
    - olfactory neuroblastoma (esthesioneuroblastoma)

    in terms of:
    - age and sex predilection
    - etiology
    - clinical and radiologic features
    - morphology
    - course and prognosis
72 - ALIMENTARY TRACT

The student will be able to:

1. Define and use in proper context:
   - achalasia
   - acute gastritis
   - adhesion
   - angiodysplasia
   - appendicitis, acute
   - atresia
   - Barrett esophagus
   - carcinoid syndrome
   - carcinoid tumor
   - chronic gastritis
   - chronic inflammatory bowel disease
   - Crohn disease
   - Curling ulcer
   - Cushing ulcer
   - d-xylene absorption test
   - diarrhea
   - diverticulum
   - dysentery
   - dysphagia
   - dysplasia
   - enterocolitis
   - enterotoxin
   - erosion
   - esophageal varices
   - esophagitis
   - gastritis, atrophic
   - gastritis, autoimmune
   - gastritis, chronic idiopathic
   - gastrectomy, chronic idiopathic
   - gastroesophageal reflux disease
   - Helicobacter pylori
   - hematomas
   - hematuria
   - hernias
   - Hirschsprung disease
   - hypergastrinemia
   - hyperplastic polyp
   - inflammation (polyp)
   - intestinal metaplasia
   - juvenile polyp
   - Krukenberg tumor
   - linitis plastica
   - Mallory-Weiss syndrome
   - Meckel diverticulum
   - melena
   - mucocoele
   - necrotizing enterocolitis (NEC)
   - odynophagia
   - peptic ulcer
   - pernicious anemia
   - Plummer-Vinson syndrome
   - pseudomembranous colitis
   - pseudomyxoma peritonei
   - pyloric stenosis
   - reflux esophagitis
   - sprue (celiac, tropical, nonropical)
   - superficial gastritis
   - transmural inflammation
   - ulcer
   - ulcerative colitis
   - Whipple disease
   - Zenker diverticulum

2. Describe the following disorders of the esophagus:
   - esophagitis
   - hiatal hernia
   - achalasia
   - Mallory-Weiss syndrome

   in terms of:
   - etiology
   - pathogenesis
   - clinical features and course
   - morphologic features

3. Describe the clinical presentation and morphology of the following esophageal lesions:
   - congenital stenosis/atrophy and associated tracheal lesions
   - mucosal webs
   - diverticula

4. Discuss the etiology, pathogenesis, gross appearance, histopathology, clinical course, and the route of metastasis of esophageal carcinoma.
5. Describe esophageal varices, their pathogenesis and typical complications.

6. Discuss the following congenital gastric anomalies:
   - pyloric stenosis
   - diaphragmatic hernia
   - gastric heterotopia
   in terms of:
     - incidence
     - morphology
     - clinical presentation and course

7. Compare and contrast acute (erosive), autoimmune, atrophic, and chronic gastritis, in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical presentation and course

8. Discuss the pathogenesis and the morphology of stress ulcers.

9. Contrast and compare duodenal and gastric peptic ulcers, and their typical complications.

10. Compare and contrast the following types of gastric polyp:
    - hyperplasic
    - fundic gland
    - adenomatous
    in terms of:
      - incidence
      - pathogenesis
      - morphology
      - malignant potential

11. Describe typical gross and histologic features of gastric carcinoma.

12. Discuss the epidemiology and risk factors of gastric carcinoma.

13. Correlate the pathologic findings and clinical symptoms of gastric carcinoma.

14. Discuss gastrointestinal stromal tumors (GIST), in terms of:
    - histogenesis
    - morphology
    - prognosis

15. Discuss gastrointestinal lymphoma, in terms of:
    - epidemiology
    - etiology and pathogenesis
    - level of the alimentary tract most frequently affected
    - morphologic features
    - clinical features and course

16. Compare and contrast the following diseases:
    - celiac sprue
    - tropical sprue
    - Whipple disease
    in terms of:
17. Compare and contrast ulcerative colitis and Crohn disease, in terms of:
   • epidemiology
   • pathogenesis
   • morphology
   • clinical features and course
   • complications
   • malignant potential

18. List the most important viral, bacterial and parasitic pathogens causing enterocolitis.

19. Contrast and compare diarrheal disease caused by enterotoxin-producing bacteria and diarrhea due to enteroinvasive microbes.

20. Compare and contrast:
   • necrotizing enterocolitis (NEC)
   • infectious enterocolitis
   • pseudomembranous colitis
   • ischemic colitis
   • collagenous colitis
   • lymphocytic colitis

   in terms of:
   • etiology
   • pathogenesis
   • morphology
   • clinical features and course

21. Discuss the following intestinal processes:
    hernia   Hirschsprung disease   volvulus
    adhesion    diverticulosis   angiodysplasia
    intussusception   diverticulitis

   in terms of:
   • age predilection
   • etiology
   • pathogenesis
   • morphology
   • clinical features and course
   • complications

22. Compare and contrast the following small intestinal neoplasms:
   • adenoma
   • adenocarcinoma
   • carcinoid
   • stromal tumors

   in terms of:
   • benignity vs. malignancy
   • morphology
   • clinical presentations and course

23. Discuss the following types of colonic polyps:
• hyperplastic
• juvenile
• adenomas (tubular, villous, tubulovillous)

in terms of:
  o incidence
  o morphology
  o clinical features and course
  o malignant potential

24. Compare and contrast the following syndromes:
  • Peutz-Jeghers syndrome
  • familial adenomatous polyposis (FAP)
  • Gardner syndrome
  • Turcot syndrome
  • Hereditary nonpolyposis colorectal cancer (Lynch) syndrome (HNPCC)

in terms of:
  o genetics
  o morphology, types, and malignant potential of lesions produced
  o clinical features and course

25. Describe colorectal carcinoma, in terms of:
  • etiology
  • pathogenesis, including genetic and molecular factors
  • morphology, including grading and staging criteria
  • clinical features and course

26. Contrast and compare the morphology and the clinical presentation of carcinoma of the right vs. left colon.

27. Discuss carcinoid tumors of the colon, rectum, and appendix, in terms of:
  • pathogenesis
  • morphology
  • clinical features (including extra-colonic manifestations)
  • course and prognosis

28. Describe the etiology, pathogenesis, and morphology of appendicitis, and list the most common complications.

29. Compare and contrast:
  • mucocele of appendix
  • mucinous neoplasms (cystadenoma/cystadenomcarcinoma) of appendix
  • pseudomyxoma peritonei

in terms of:
  o interrelationships with one another
  o morphology
  o clinical features and course

30. List the clinical situations in which stool examination may be helpful in the diagnosis of alimentary diseases.
73 - LIVER AND BILIARY TRACT

The student will be able to:

1. Define and use in proper context:
   - acidophil body
   - acidophil body
cirrhosis
   - liver function test
   - acute yellow atrophy
   - Councilman body
   - macronodular cirrhosis
   - alcoholic hepatitis
   - Crigler-Najjar disease
   - Mallory body (hyaline)
   - alcoholic liver disease
   - delta hepatitis
   - massive necrosis
   - alpha-1-antitrypsin deficiency
direct vs. indirect bilirubin
   - micronodular cirrhosis
   - ascites
   - Dubin-Johnson syndrome
   - nutmeg liver
   - bile
   - fatty liver
   - peliosis hepatis
   - bile duct hamartoma
   - focal nodular hyperplasia
   - porcelain gallbladder
   - bile lake
   - galactosemia
   - portal hypertension
   - bile stones
   - gallstone ileus
   - primary biliary cirrhosis
   - biliary atresia
   - Gilbert disease
   - primary sclerosing cholangitis
   - bilirubin
   - hemochromatosis
   - Reye syndrome
   - bridging fibrosis
   - hemosiderosis
   - Rokitansky-Aschoff sinus
   - bridging necrosis
   - hepatic coma
   - schistosomiasis
   - Budd-Chiari syndrome
   - hepatic encephalopathy
   - secondary biliary cirrhosis
   - cardiac sclerosis
   - hepatitis
   - splenomegaly
   - centrilobular necrosis
   - hepatorenal syndrome
   - steatohepatitis
   - cholangitis
   - hyperbilirubinemia
   - steatosis
   - cholecystitis
   - hypoalbuminemia
   - strawberry gallbladder
   - choledocholithiasis
   - icterus
   - submassive necrosis
   - cholelithiasis
   - interface hepatitis
   - von Meyenburg complex
   - cholestasis
   - jaundice
   - Wilson disease
   - cholesterolosis
   - kernicterus

2. Describe the formation of bile and explain the main abnormalities that could cause jaundice.

3. Discuss the following laboratory tests:
   - alanine aminotransferase (ALT, SGPT)
   - anti-smooth muscle antibody
   - aspartate aminotransferase (AST, SGOT)
   - bilirubin: total, conjugated, unconjugated
   - alkaline phosphatase (ALP)
   - ceruloplasmin
   - alpha-fetoprotein
   - gamma-glutamyl transferase (GGT)
   - ammonia
   - urobilinogen
   - anti-mitochondrial antibody

   in terms of:
   - indications
   - hepatobiliary parameter measured
   - diseases associated with elevations thereof

4. Discuss:
   - congenital hepatic fibrosis
   - polycystic liver disease

   in terms of:
   - inheritance pattern
   - etiology/pathogenesis
   - clinical and laboratory features
   - prognosis
5. Compare and contrast
   - Crigler-Najjar syndrome, type I
   - Crigler-Najjar syndrome, type II
   - Gilbert syndrome
   - Dubin-Johnson syndrome
   - Rotor syndrome
   in terms of:
   - inheritance pattern
   - defect(s) in bilirubin metabolism
   - morphology of liver
   - laboratory diagnosis
   - clinical features and course

6. Compare and contrast biliary atresia and neonatal hepatitis, in terms of:
   - etiology and pathogenesis
   - morphology
   - laboratory findings
   - clinical features and course
   - complications

7. Describe the principal clinical and morphologic findings in chronic liver disease.

8. Compare and contrast hepatitis cause by the following viruses:
   hepatitis A virus (HAV)
   hepatitis B virus (HBV)
   hepatitis C virus (HCV)
   hepatitis D (delta) virus (HDV)
   hepatitis E virus (HEV)
   hepatitis G virus(es) (HGV)
   cytomegalovirus (CMV)
   Epstein-Barr virus (EBV)
   in terms of:
   - nomenclature of antigens and antibodies
   - epidemiology
   - modes of transmission
   - incubation period
   - laboratory findings
   - serologic findings at various stages in course of disease
   - morphologic findings
   - clinical features and course, including propensity for chronicity
   - carrier state
   - complications


10. Compare and contrast:
    - alcoholic hepatitis
    - nonalcoholic steatohepatitis
    - viral hepatitis
    - granulomatous hepatitis
    - drug-induced
    - toxic hepatitis
    in terms of:
    - etiology
    - pathogenesis
    - morphology
    - clinical features and course
11. Discuss the pathogenesis, morphology, and clinical course of the following alcohol-induced liver diseases:
   - fatty change (steatosis)
   - alcoholic hepatitis
   - fibrosis
   - cirrhosis

12. Classify types of cirrhosis, in terms of:
   - etiology
   - pathogenesis
   - morphologic pattern (gross and microscopic)
   - relationship to neoplasia

13. Differentiate among the following disease processes, based on clinicopathologic data:
    - alcoholic cirrhosis
    - cirrhosis due to:
      - postnecrotic cirrhosis
      - primary biliary cirrhosis
      - secondary biliary cirrhosis
      - hemochromatosis
      - Wilson disease
      - α₁-antitrypsin deficiency

14. Discuss portal hypertension in terms of:
   - etiologic factors
   - pathogenesis
   - clinical features and course

15. Compare predictable and unpredictable drug induced liver disease.

16. Classify the following hepatotoxic drugs/chemicals:
    - acetaminophen
    - carbon tetrachloride
    - halothane
    - phenothiazines
    - tetracyclines

    in terms of:
    - whether or not toxicity is dose-related
    - pattern of reaction (cholestasis vs. hepatocellular necrosis vs. fatty change)

17. Compare and contrast:
    - autoimmune hepatitis
    - primary biliary cirrhosis
    - secondary biliary cirrhosis
    - primary sclerosing cholangitis

    in terms of:
    - associated conditions
    - incidence
    - sex predilection
    - etiology
    - pathogenesis
    - laboratory diagnosis
    - clinical features
    - prognosis

18. Describe typical infectious liver diseases caused by bacteria, protozoa and helminths; in terms of clinical and morphologic findings.

19. List causes of fatty change (steatosis) of the liver, in terms of:
• size of fat vacuoles
• zonal distribution of fat

20. Describe the etiopathogenesis and consequences of:
• hepatic encephalopathy
• portal hypertension
• esophageal varices
• hepatic vein thrombosis
• ascites

21. Compare and contrast the following tumors:
- bile duct hamartoma
- bile duct adenoma
- hepatic adenoma
- focal nodular hyperplasia of liver
- hepatoblastoma
- hepatocellular carcinoma
- fibrolamellar variant
- hepatic angiosarcoma
- cholangiocarcinoma
- metastatic carcinoma to liver

in terms of:
- relative frequency
- etiology and pathogenesis
- relation to cirrhosis
- morphology
- methods of diagnosis
- clinical findings and course
- complications

22. Describe cholelithiasis in terms of:
• risk factors
• mechanisms of stone formation
• composition of stones
• morphology of stones and gallbladder

• clinical features
• complications, including complications of therapy

23. Compare and contrast acute and chronic cholecystitis, in terms of:
• epidemiology
• associated diseases
• morphology
• clinical findings
• complications, including complications of therapy

24. Compare and contrast empyema and hydrops of the gallbladder, in terms of:
• etiology
• pathogenesis
• morphology
• clinical findings

25. Discuss carcinoma of the gallbladder and extrahepatic bile ducts, in terms of:
• epidemiology
• relationship to cholelithiasis
• morphology
• clinical findings and course

26. Describe the indications, benefits, and hazards of liver transplantation.

27. Describe the morphology of liver transplant rejection.
74 - PANCREAS

The student will be able to:

1. Define and use in proper context:
   - cystic fibrosis (CF)
   - CFTR
   - mucoviscidosis
   - sweat chloride test
   - pancreatitis
   - amylase
   - lipase
   - pseudocyst
   - mucinous cystadenoma
   - mucinous cystadenocarcinoma
   - mucinous cystadenocarcinoma
   - insulinoma
   - gastrinoma
   - glucagonoma
   - somatostatinoma
   - VIPoma
   - PP-secreting islet cell tumor
   - Whipple triad
   - Zollinger-Ellison syndrome

2. Compare and contrast:
   - exocrine pancreatic insufficiency
   - endocrine pancreatic insufficiency
   - causes
   - clinical manifestations
   - laboratory abnormalities

3. Discuss cystic fibrosis, in terms of:
   - genetics
   - primary defect
   - morphologic findings in:
     - pancreas
     - lung
     - liver
     - salivary glands
     - male genital tract
   - laboratory manifestations
   - clinical findings and course
   - therapy, including gene therapy

4. List the difference between acute edematous and acute hemorrhagic pancreatitis with regard to histopathology and clinical outcome.

5. Compare and contrast acute and chronic pancreatitis, in terms of:
   - etiologic/predisposing factors
   - pathogenesis
   - morphologic features
   - laboratory manifestations
   - clinical findings and course
   - complications

6. Compare and contrast adenocarcinoma of the:
   - pancreatic head
   - pancreatic body/tail
   - ampulla of Vater
   - incidence
   - risk factors
7. Discuss islet cell tumors of the pancreas, in terms of:
   - incidence
   - morphology
   - benignity vs. malignancy
   - immunohistochemical characteristics
   - endocrine function
   - clinical features and course

8. Discuss indications and complications of pancreatic islet cell transplant.
81 - KIDNEY

The student should be able to:

1. Describe the normal anatomy (gross and microscopic) of each of the following:
   • kidney
   • ureter

2. Define and use in proper context:
   - anuria
   - azotemia
   - bacteriuria
   - Bence-Jones protein
   - cast
   - dysuria
   - glomerulonephritis
   - hematuria
   - hepato-renal syndrome
   - hydronephrosis
   - Kimmelstiel-Wilson disease
   - nephrocalcin
   - nephrolithiasis
   - nephrosclerosis
   - nocturia
   - oliguria
   - polycystin
   - proteinuria

3. List the criteria for the diagnosis of:
   • nephritic syndrome
   • nephrotic syndrome
   • acute renal failure
   • chronic renal failure

   and list:
   o the renal diseases commonly causing each of the above
   o the clinical and laboratory findings in each of the above

4. Discuss the proper use of the following laboratory tests in the evaluation of urinary tract disease:
   • creatinine
   • urea (blood urea nitrogen, BUN)
   • urinalysis

   and interpret abnormalities of these parameters in clinical context

5. Discuss the following congenital renal anomalies:
   • renal agenesis
   • double ureter
   • horseshoe kidney
   • aberrant renal artery
   • ectopic kidney

   in terms of:
   o morphology
   o clinical manifestations
   o complications

6. Compare and contrast the following cystic diseases of the kidney:
   • autosomal dominant (adult) polycystic kidney disease
   • autosomal recessive (childhood) polycystic kidney disease
   • acquired (dialysis-associated) cystic disease
in terms of:
  o incidence
  o etiology and pathogenesis
  o morphologic (gross and microscopic) appearance
  o clinical presentation, course, and prognosis
  o complications

7. Define the following terms as they apply to glomerular histopathology:
   • focal
   • diffuse
   • segmental
   • global

8. Discuss the following glomerular diseases:
   • minimal change disease
   • membranous glomerulonephritis
   • focal segmental glomerulosclerosis
   • membranoproliferative glomerulonephritis
   • acute proliferative (poststreptococcal, postinfectious) glomerulonephritis
   • rapidly progressive glomerulonephritis
   • IgA nephropathy (Berger disease)
   • hereditary nephritis
   • Henoch-Schönlein purpura
   • chronic glomerulonephritis

   in terms of:
   o relative frequency
   o etiology and pathogenesis
   o clinical presentation, course, and prognosis
   o laboratory findings
   o microscopic (light, immunofluorescent, ultrastructural) appearance

9. Describe the major clinical and histopathologic findings associated with renal involvement by the following systemic diseases:
   • diabetes mellitus
   • amyloidosis
   • gout
   • multiple myeloma

10. Discuss lupus nephritis in terms of:
   • etiology and pathogenesis
   • clinical presentation
   • nomenclature, morphologic features, and prognosis of each of the five classes

11. Discuss the following renal tubular diseases:
   • acute pyelonephritis
   • chronic pyelonephritis
   • xanthogranulomatous pyelonephritis
   • acute drug-induced interstitial nephritis
   • drug-induced analgesic nephropathy
   • acute tubular necrosis
in terms of:
- etiology and pathogenesis
- clinical presentation and course
- laboratory findings
- morphologic (gross and microscopic) appearance
- treatment and prognosis

12. Discuss the significance of unilateral renal artery disease, including:
   - usual causes
   - mechanism(s) of clinical effects
   - morphologic changes in contralateral kidney
   - tests used for detection and localization

13. Describe the pathophysiology of hypertension induced by renal artery constriction

14. Compare and contrast benign and malignant nephrosclerosis with regard to:
   - pathogenesis
   - morphologic (gross and microscopic) appearance
   - clinical presentation, course, and prognosis

15. List the three major thrombotic microangiopathies, and describe their renal effects, with regard to:
   - pathogenesis
   - microscopic appearance
   - clinical presentation, course, and prognosis

16. Discuss renal vein thrombosis in terms of:
   - etiology/pathogenesis
   - morphology
   - method(s) of diagnosis
   - clinical and laboratory features

17. Discuss urolithiasis in terms of:
   - composition and relative incidence of various types of stones
   - pathophysiologic abnormalities associated with the common types of stones
   - etiology and pathogenesis of stone formation
   - effect of location of stones on clinical and anatomic findings
   - clinical course and complications

18. Discuss hydronephrosis in terms of:
   - etiologic factors and their relative frequencies
   - pathogenesis
   - morphology (gross and microscopic)
   - clinical course and prognosis

19. Discuss the following renal neoplasms:
   - cortical adenoma
   - medullary fibroma
   - renal cell carcinoma
   - oncocytoma
   - angiomyolipoma
   - Wilms tumor (nephroblastoma)
   - urothelial (transitional cell) carcinoma of renal pelvis
in terms of:

- genetics/associated syndromes
- incidence
- age and sex distribution
- etiology
- morphologic (gross and microscopic) appearance
- laboratory features
- clinical presentation, course, and complications
- treatment
- routes of spread
- prognosis, including assessment of prognostic factors
82 – LOWER URINARY TRACT

The student will be able to:

1. Describe the normal anatomy (gross and microscopic) of each of the following:
   - ureter
   - urinary bladder
   - urethra

2. Define and use in proper context:
   - bacteriuria
   - cystitis
   - cystitis cystica
   - cystitis glandularis
   - dysuria
   - pyuria
   - exstrophy
   - hematuria
   - hypospadias
   - hematuria
   - neogenetic (cord) bladder

3. Discuss the proper use of urinalysis in the evaluation of lower urinary tract disease, and interpret abnormalities of this test in clinical context

4. Discuss obstruction at various levels of the urinary tract in terms of:
   - site and nature of lesion
   - etiology and pathogenesis
   - alteration in renal function
   - morphologic effect on kidney

5. Discuss diverticula of the urinary bladder, in terms of:
   - etiology
   - pathogenesis
   - morphology
   - complications

6. Discuss urolithiasis in terms of:
   - relative incidence of various types of stones
   - pathophysiologic abnormalities associated with the common types of stones
   - etiology and pathogenesis of stone formation
   - effect of location of stones on clinical and anatomic findings
   - clinical course and complications

7. Discuss the following congenital anomalies:
   - patent urachus
   - hypospadias
   - epispadias
   - exstrophy of the bladder
   - duplications of the collecting system
   - urethral valves

   in terms of:
   - frequency
   - morphology
   - complications
8. Compare and contrast the following inflammatory conditions:
   • infectious cystitis
   • interstitial cystitis
   • malacoplakia
   
   with regard to:
   o etiology and pathogenesis
   o clinical course and complications
   o morphologic (gross and microscopic) appearance

9. Discuss the following neoplasms of the lower urinary tract:
   • urothelial (transitional cell) carcinoma
   • squamous cell carcinoma
   • adenocarcinoma
   
   in terms of:
   o incidence
   o age and sex distribution
   o etiology
   o morphologic (gross and microscopic) appearance
   o laboratory features
   o clinical presentation, course, and complications
   o treatment
   o routes of spread
   o prognosis, including assessment of prognostic factors
83 – MALE GENITAL SYSTEM

The student will be able to:

1. Describe the normal anatomy (gross and microscopic) of each of the following:
   - penis
   - prostate
   - testis

2. Define and use in proper context:
   - balanitis
   - balanoposthitis
   - choriocarcinoma
   - chylecele
   - condyloma acuminatum
   - cryptorchidism
   - embryonal carcinoma
   - epispadias
   - gonadoblastoma
   - hematocele
   - hydrocele
   - hypospadias
   - orchitis
   - paraphimosis
   - prepuce
   - prostatic intraepithelial hyperplasia (PIN)
   - prostatitis
   - seminoma
   - Schiller-Duval body
   - Sertoli-Leydig cell tumor
   - smegma
   - spermatocytic seminoma
   - teratoma
   - yolk sac tumor

3. Discuss the following congenital anomalies:
   - hypospadias
   - epispadias
   - in terms of:
     - frequency
     - morphology
     - complications

4. Discuss the following neoplasms:
   - squamous cell carcinoma of penis and scrotum
   - adenocarcinoma of prostate
   - germ cell tumors of testis
   - sex cord-stromal tumors of testis
   - malignant lymphoma of testis
   - in terms of:
     - incidence
     - age distribution
     - etiology
     - morphologic (gross and microscopic) appearance
     - laboratory features (including tumor markers)
     - clinical presentation, course, and complications
     - treatment
     - routes of spread
     - prognosis, including assessment of prognostic factors
     - ovarian counterparts of testicular tumors

5. Compare and contrast the following inflammatory conditions:
   - prostatitis (acute, chronic granulomatous)
   - orchitis (nonspecific, mumps, granulomatous)
   - torsion of spermatic cord
with regard to:
  o etiology and pathogenesis
  o clinical course and complications
  o morphologic (gross and microscopic) appearance

6. Discuss the following disorders:
   • nodular hyperplasia of the prostate
   • cryptorchidism

   in terms of:
   o incidence
   o etiology
   o pathogenesis
   o morphologic (gross and microscopic) appearance
   o clinical presentation and treatment
   o complications
   o relationship to malignancy

7. Classify anatomically the causes of male infertility.
84 - FEMALE GENITAL SYSTEM

The student will be able to:

1. Define and use in proper context:

   - adenomyosis
eenosis
   - arrhenoblastoma
   - atypical endometrial hyperplasia
   - borderline ovarian tumor (BOT)
   - Brenner tumor
   - Call-Exner body
   - carcinoma in situ (CIS)
   - carcinosarcoma
   - cervical intraepithelial neoplasia (CIN)
   - chocolate cyst
   - colposcopy
   - condyloma acuminatum
   - condyloma latum
   - cone biopsy
   - curettage
   - cystadenocarcinoma
   - cystadenofibroma
cystadenoma
   - dysfunctional uterine bleeding (DUB)
   - dysgerminoma
dysmenorrhea
dysplasia
   - embryonal carcinoma
   - endodermal sinus tumor
   - endometriosis
   - fibroma
   - flat condyloma
   - follicular cyst
   - gonadoblastoma
granulosa cell tumor
   - gynandroblastoma
   - hematosapinx
   - HPV
   - HSV
   - hydrosalpinx
   - koilocytosis
   - Leukoplakia
   - low malignant potential (LMP)
   - luteal cyst
   - malignant mixed Müllerian tumor (MMMT)
   - Meigs syndrome
   - menometrorrhagia (MMR)
   - menorrhagia
   - microinvasive carcinoma
   - nabothian cyst
   - Pap smear
   - pelvic inflammatory disease (PID)
   - pseudomyxoma peritonei
   - pyosalpinx
   - sarcoma botryoides
   - Schiller-Duval body
   - Sertoli-Leydig cell tumor
   - squamous intraepithelial lesion (SIL)
   - Stein-Leventhal syndrome
   - teratoma
   - thecoma
   - vaginal intraepithelial neoplasia (VAIN)
   - vulvar intraepithelial neoplasia (VIN)

2. Describe the following congenital anomalies, including their embryologic bases:
   - imperforate hymen
   - bicornuate uterus
   - pseudohermaphroditism

3. List the common organisms which cause:
   - Bartholin abscess
   - vulvitis
   - vaginitis
   - cervicitis
   - endometritis
   - salpingitis

4. Discuss the following vulvar lesions:
   - Bartholin cyst
   - lichen sclerosis
   - squamous hyperplasia
   - condyloma acuminatum
in terms of:
  o etiology
  o clinical presentation
  o morphology
  o differential diagnosis

5. Compare and contrast trichomonal and monilial vaginitis, in terms of:
   • predisposing factors
   • etiology
   • pathogenesis
   • symptoms
   • methods of detection

6. Compare and contrast:
   • vulvar condyloma
   • vulvar and vaginal intraepithelial neoplasia (VIN, VAIN)
   • carcinoma of the vulva and vagina
   • sarcoma botryoides
in terms of:
  o age predilection
  o incidence
  o etiology
  o clinical presentation
  o morphology
  o biologic behavior

7. Define discuss general features of extramammary Paget disease, in terms of:
   • clinical presentation
   • morphology
   • associated malignancies
   • clinical course

8. Discuss vaginal adenosis and vaginal adenocarcinoma, in terms of
   • epidemiology
   • etiology
   • pathogenesis
   • morphology
   • clinical significance

9. Compare and contrast the following cervical lesions:
   • cervical intraepithelial neoplasia (CIN)
   • microinvasive squamous cell carcinoma
   • invasive squamous cell carcinoma
   • adenocarcinoma
in terms of:
   incidence                        morphology
   age distribution                 grading and staging
   risk factors                     clinical features
   pathogenesis                     prognosis
   diagnostic modalities for detection

10. Discuss the screening and diagnostic procedures for cervical cancer in terms of methodology, indications, and utilization.

11. Discuss cervicovaginal cytology, in terms of:
    • technique of obtaining specimen
    • utility in diagnosis of inflammatory conditions
• types and significance of abnormalities
• utility in diagnosis of:
  o CIN of cervix
  o carcinoma of cervix
  o carcinoma of endometrium

12. Outline the morphologic effects of oral contraceptive agents (oral contraceptive pills, OCP's) on the endometrium, in relation to mode of action and possible adverse complications

13. Compare and contrast endometriosis and adenomyosis in terms of:
• incidence
• clinical presentation
• pathogenesis
• morphology
• organs involved
• complications.

14. Discuss the following endometrial processes:
• atrophy,
• hyperplasia
• polyp
  in terms of:
  o etiology
  o morphologic types
  o differentiation from one another and from neoplasia
  o clinical course/significance of the different types

15. Discuss endometrial carcinoma in terms of:
  incidence
  age distribution
  risk factors
  clinical presentation
  epidemiology
  predisposing factors
  pathogenesis
  morphology including common types
  methods of detection
  grading and staging
  prognosis

16. Compare and contrast:
• endometrial stromal tumors
• myometrial leiomyoma
• myometrial leiomyosarcoma
  in terms of:
  o clinical presentation
  o pathogenesis
  o morphology
  o clinical features
  o prognosis

17. List the conditions which result in non-neoplastic enlargement or cysts of the ovary

18. Discuss polycystic ovarian disease in terms of clinical presentation and morphology

19. Compare and contrast the following ovarian neoplasms:
• surface epithelial tumors
  o benign
  o borderline
  o malignant
• sex cord-stromal tumors
• germ cell tumors
• metastatic malignancy to ovary
  in terms of:
  - incidence
  - age predilection
  - different types
  - laterality
  - morphology
  - tumor markers
  - hormonal effects
  - clinical features
  - prognosis
  - complications
  - testicular counterparts

20. Compare and contrast ovarian vs. placental (gestational) choriocarcinoma, in terms of:
  - cell of origin
  - pathogenesis
  - morphology
  - clinical features
  - treatment and prognosis

21. List the most common primary sites of metastatic malignancy to the ovary

22. List and differentiate among clinical etiologies of:
  - pelvic pain in reproductive age group
  - vaginal bleeding in reproductive age group
  - vaginal bleeding in post-menopausal age group
  - vulvar lesions in older women
85 - BREAST

The student will be able to:

1. Define and use in proper context:

   - adenosis
   - blue dome cyst
   - comedocarcinoma
   - cribriform pattern
   - fibrocystic change
   - gynecomastia
   - "Indian filing"
   - inflammatory carcinoma
   - intraductal papilloma
   - microcalcification
   - minimally invasive breast biopsy (MIBB)
   - peau d’orange
   - scirrhous
   - terminal duct-lobular unit (TDLU)
   - triple test

2. Describe the hormonally-induced morphologic changes which occur in the female breast during the following stages:
   - neonatal
   - pubertal
   - menstrual
   - gestational
   - lactational
   - postmenopausal

3. Describe the following congenital abnormalities of the breast:
   - amastia
   - polythelia
   - polymastia
   - neonatal enlargement

   in terms of:
   - incidence
   - morphology
   - clinical significance

4. Discuss the following reactive breast conditions:
   - fat necrosis
   - acute mastitis
   - periductal mastitis
   - granulomatous mastitis
   - plasma cell mastitis
   - mammary duct ectasia
   - galactocele

   in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical features
   - differential diagnosis

5. Discuss silicone breast implants, in terms of:
   - morphologic changes in adjacent breast
   - known epidemiologic relationships with autoimmune disease

6. Compare and contrast fibroadenoma and phyllodes tumor in terms of:
   - incidence
   - clinical presentation
   - morphology
   - clinical features and prognosis
7. Discuss fibrocystic change of the breast in terms of:
   - age predilection
   - incidence
   - etiology
   - general morphology
   - mammographic appearance
   - relationship to carcinoma of the breast
   - clinical presentation

8. Compare and contrast the following morphologic manifestations of fibrocystic change of the breast:
   • apocrine metaplasia
   • sclerosing adenosis
   • intraductal hyperplasia
   in terms of:
     - pathogenesis
     - morphology
     - relationship to carcinoma of the breast

9. Compare and contrast the following:
   • intraductal papilloma
   • intraductal hyperplasia without atypia
   • intraductal hyperplasia with atypia (atypical ductal hyperplasia)
   • ductal carcinoma-in-situ (DCIS, intraductal carcinoma)
   • atypical lobular hyperplasia (ALH)
   • lobular carcinoma-in-situ (LCIS)
   in terms of:
     - age predilection
     - incidence
     - etiology
     - pathogenesis
     - morphology
     - pattern of spread
     - methods of detection
     - principles of management
     - clinical features and course
     - relationship to breast carcinoma, including the influence of family history thereupon

10. Discuss female mammary carcinoma in terms of:
    - genetics
    - risk factors
    - incidence
    - etiology
    - pathogenesis
    - clinical presentation
    - gross morphology
    - patterns of spread
    - methods of diagnosis
    - clinical course
    - staging
    - prognostic indicators
    - treatment options
    - survival rates

11. Compare and contrast the following types of invasive mammary carcinoma:
    • invasive ductal carcinoma, no special type (NOS)
    • medullary carcinoma
    • colloid (mucinous) carcinoma
    • tubular carcinoma
    • invasive lobular carcinoma
    • Paget disease
    in terms of:
      - age predilection
      - microscopic morphology
      - grading
12. Discuss the following diagnostic procedures for evaluating breast masses:
   - self-examination
   - mammography
   - fine needle aspiration cytology
   in terms of
     - indications
     - methodology
     - general interpretative features
     - relative sensitivity and specificity

13. List the most common causes of breast mass in females during the following stages of life:
   - under 35 years of age
   - 35-50 years of age
   - over 50 years of age

14. Compare and contrast the following diseases of the male breast:
   - gynecomastia
   - carcinoma
   in terms of:
     - etiology/pathogenesis
     - clinical features
     - prognosis
The student will be able to:

1. Describe the normal embryology, anatomy, histology, and hormonal physiology of the:
   - pituitary gland
   - adrenal glands
   - thyroid gland
   - parathyroid glands
   - endocrine pancreas
   - pineal gland

2. Define and use in proper context:
   - 17-hydroxy-corticosteroids
   - 17-ketosteroids
   - acromegaly
   - Addison disease
   - adrenocorticotropic hormone (ACTH)
   - aldosterone
   - angiotensin
   - angiotensin-converting enzyme
   - angiotensinogen
   - bronzed diabetes
   - catecholamine
   - congenital adrenal hyperplasia (CAH)
   - corticotropin-releasing hormone (CRH)
   - cortisol
   - cortisol-binding globulin (CBG)
   - cretinism
   - Cushing disease
   - Cushing syndrome
   - dexamethasone suppression test
   - diabetes insipidus
   - diabetes mellitus
   - diabetic ketoacidosis
   - ectopic ACTH
   - endemic goiter
   - epinephrine
   - euthyroidism
   - free thyroxine index (FTI)
   - gestational diabetes
   - glycosyation (glycation)
   - goiter
   - goitrogen
   - growth hormone (GH)
   - growth hormone-releasing hormone (GHRH)
   - humoral hypercalcemia of malignancy (HHM)
   - hyperadrenocorticism
   - hypercalcemia
   - hyperinsulinism
   - hyperosmolar nonketotic coma
   - hyperparathyroidism
   - hyperpituitarism
   - hyperthyroidism
   - hypocalcemia
   - hypoparathyroidism
   - hypopituitarism
   - hypothyroidism
   - impaired glucose tolerance
   - insulin resistance
   - ionized calcium
   - maturity-onset diabetes of young (MODY)
   - metabolic syndrome (syndrome X)
   - metanephrine/normetanephrine
   - metyrapone test
   - microalbuminuria
   - myxedema
   - norepinephrine
   - parathyroid hormone (PTH)
   - parathyroid hormone-related protein (PTHrP)
   - plasma renin activity (PRA)
   - plasma renin concentration (PRC)
   - polydipsia/polyphagia/polyuria
   - primary aldosteronism (Conn syndrome)
   - primary diabetes
   - pseudohypoparathyroidism
   - radioactivity iodine uptake (RAIU)
   - radioimmunoassay
   - renin
   - secondary aldosteronism
   - secondary diabetes
   - Sipple syndrome
   - somatomedin (IGF)
   - somatostatin
   - sporadic goiter
   - steroid hydroxylase enzymes
   - thyroglobulin
   - thyroid hormone binding ratio (THBR, T3U)
   - thyroid stimulating hormone (TSH, thyrotropin)
   - thyrotoxicosis
   - thyrotropin releasing hormone (TRH)
   - thyroxine (T4)
   - thyroxine binding globulin (TBG)
   - triiodothyronine (T3)
   - urinalysis free cortisol (UFC)
   - Wernicke syndrome
   - Zollinger-Ellison syndrome
3. Compare thyroglossal duct cyst and branchial cleft cyst in terms of:
   • anatomic site in the neck
   • gross and microscopic features
   • complications

4. Compare and contrast hyperthyroidism, hypothyroidism, and euthyroid sick syndrome (ETS) in terms of:
   • etiologies
   • pathogenesis
   • clinical features
   • laboratory features
   • complications and prognosis

5. List the commonly used thyroid function tests and their indications.

6. Compare and contrast infectious, subacute (granulomatous), subacute lymphocytic, Hashimoto’s, and Riedel’s thyroiditis, in terms of:
   • age and sex distribution
   • etiology and pathogenesis
   • clinical, functional, and laboratory features
   • gross and microscopic features
   • complications and prognosis

7. Discuss the utilization of fine-needle aspiration (FNA) of the thyroid, in terms of:
   • basic methodology
   • indications
   • sensitivity
   • specificity

8. Discuss the calcium homeostatic mechanisms.

9. Discuss hypocalcemia and hypercalcemia, in terms of:
   • etiologies
   • clinical presentation
   • laboratory testing

10. Compare and contrast primary hyperparathyroidism, secondary hyperparathyroidism, tertiary hyperparathyroidism, and hypoparathyroidism, in terms of:
    • etiology
    • pathogenesis
    • clinical features
    • laboratory features
    • complications and prognosis

11. Discuss the biosynthesis of adrenal steroids, and the enzymatic defects which lead to adrenal hyperplasia.

12. Name the tests used in evaluating plasma glucocorticoids, their indications, and their interpretation.

13. Discuss how plasma concentrations of cortisol and aldosterone are controlled.

14. Name the tests for evaluating adrenal androgens, their indications, and their interpretation.

15. Discuss the biosynthesis of the adrenal catecholamines and their urinary metabolites.

16. Discuss the use of growth hormone stimulation tests.
17. Describe the following hyperfunctional and hypofunctional conditions:

- acromegaly
- gigantism
- Sheehan syndrome
- empty sella syndrome
- diabetes insipidus
- Graves disease
- Addison disease
- diffuse nontoxic (simple) goiter
- multinodular goiter
- myxedema
- parathyroid hyperplasia
- congenital adrenal hyperplasia
- inappropiate ADH secretion
- hypercortisolism (Cushing syndrome)
- primary aldosteronism (Conn syndrome)
- ectopic ACTH production
- hypercortisolism
- 1° acute adrenocortical insufficiency

in terms of:

- etiology and pathogenesis
- laboratory abnormalities
- clinical manifestations
- morphology (gross and microscopic)

18. List the distinguishing features of type 1 and 2 diabetes mellitus, in terms of:

<table>
<thead>
<tr>
<th>Etiology and Pathogenesis</th>
<th>Clinical and Morphologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Insulin and glucose levels</td>
</tr>
<tr>
<td>Age and frequency</td>
<td>Principles of treatment</td>
</tr>
<tr>
<td>Mode of onset</td>
<td>Response to insulin</td>
</tr>
</tbody>
</table>

- insulinitis
- amylin (islet amyloid polypeptide) deposition
- atherosclerosis
- diabetic microangiopathy
- fatty change of the liver
- nodular (intercapillary) glomerulosclerosis
- (Kimmelstiel-Wilson disease)

in terms of:

- pathogenesis
- specificity for diabetes
- morphologic appearance
- relationship to serious manifestations of diabetes
- frequency in diabetes
- prevention and treatment
- occurrence early or late in the disease

19. Discuss the following lesions that may be found in diabetes mellitus:

- insulitis
- amylin (islet amyloid polypeptide) deposition
- atherosclerosis
- diabetic microangiopathy
- fatty change of the liver
- nodular (intercapillary) glomerulosclerosis
- (Kimmelstiel-Wilson disease)
- diffuse glomerulosclerosis
- pyelonephritis
- necrotizing papillitis
- diabetic retinopathy
- diabetic cataracts
- glaucoma
- peripheral neuropathy

in terms of:

- pathogenesis
- specificity for diabetes
- morphologic appearance
- relationship to serious manifestations of diabetes
- frequency in diabetes
- prevention and treatment
- occurrence early or late in the disease

20. Outline methods of screening patients for, and following patients with, diabetes mellitus, stating appropriate usage of the following laboratory tests:

- blood glucose concentration
- blood insulin concentration
- urine glucose concentration
- ketone bodies
- glucose tolerance test
- glycosylated (glycated) hemoglobin level
- urine protein concentration

21. Describe the following neoplasms:

- anterior lobe pituitary neoplasms
- craniopharyngioma
- thyroid adenomas
- thyroid carcinomas
- parathyroid adenoma
- parathyroid carcinoma
- adrenal cortical adenomas
- adrenal cortical carcinomas
- pheochromocytoma
- neoplasms of extra-adrenal paraganglia
- neuroblastoma
- ganglioneuroma
- pancreatic islet cell neoplasms
- pinealomas

in terms of:

- epidemiology
- immunohistochemical characteristics
- associated syndromes
- endocrine function
- etiology and pathogenesis
- complications and prognosis
gross and microscopic appearance

22. Describe the various types of multiple endocrine neoplasia (MEN) syndromes, in terms of clinical, laboratory, and morphologic features, as well as prognosis.
The student will be able to:

1. Define and use in proper context:
   - abortion
   - abruptio placenta
   - amnion
   - chorioamnionitis
   - choriocarcinoma
   - chorion
   - chorial villi
   - circumvallate placenta
   - cellotrophoblast
   - amnion
decrease
diameter
dichorionic
eclampsia
ectopic pregnancy
funisitis

2. Discuss the placenta in terms of:
   - development
   - normal gross and microscopic anatomy
   - formation and quantity-regulating factors of:
     - amniotic fluid
     - human chorionic gonadotropin (HCG)
     - most frequent morphologic abnormalities

3. Discuss twin placentaion, in terms of:
   - mechanisms of occurrence of twin pregnancies
   - morphology of twin placentas
   - determination of zygosity through placental examination

4. Compare contrast preeclampsia and eclampsia in terms of:
   - clinical presentation
   - morphology
   - clinical course.

5. Discuss ascending infections and hematogenous infections of pregnancy in terms of:
   - etiology
   - pathogenesis
   - morphology
   - methods of diagnosis

6. Compare and contrast placenta previa and abruptio placentae in terms of:
   - morphology
   - clinical presentation, course, and complications.

7. Compare and contrast:
   - hydatidiform mole (complete and partial)
   - invasive mole
   - gestational (uterine) choriocarcinoma
   - ovarian choriocarcinoma
   - in terms of:
   - genetics
• incidence
• predisposing factors
• clinical presentation,
• laboratory findings
• morphology
• clinical course including follow-up and complications.

8. Discuss ectopic pregnancy in terms of:
• incidence
• risk factors
• clinical presentation
• morphology
• clinical course
• complications

and differentiate ectopic pregnancy from pelvic inflammatory disease and acute appendicitis based on clinicopathologic data.

9. List the three major categories of factors which may underlie intrauterine growth retardation (IUGR) of the fetus.

10. Discuss the pathogenesis of deformations, and give examples of underlying factors which may lead to deformation by such pathogenetic mechanisms

11. List the most common birth injuries

12. List the most common congenital malformations

13. Describe the two phases of the intrauterine development of humans, and indicate the period of greatest susceptibility to teratogenic agents

14. List the different levels at which teratogens may act in producing malformations

15. Discuss maternal diabetes mellitus in terms of:
• methods of diagnosis
• effects on fetus
88 - PEDIATRIC PATHOLOGY

The student will be able to:

1. Define and use in proper context:
   - Apgar score
   - bronchopulmonary dysplasia (BPD)
   - caput succedaneum
   - cephalhematoma
   - choristoma
   - congenital deformation
   - hamartoma
   - hereditary
   - heterotopia
   - hyaline membrane disease (HMD)
   - hydrops fetalis
   - immature
   - kernicterus
   - malformation
   - premature
   - small-for-gestational-age (SGA)
   - sudden infant death syndrome (SIDS)
   - teratogen
   - teratogenesis

2. Discuss the pathogenesis of deformations, and give examples of underlying factors which may lead to deformations via such pathogenetic mechanisms

3. List the most common birth injuries

4. State the most common cause of death in children, as well as the most common non-traumatic cause of death in children:
   - under one year of age
   - between one and four years of age
   - between five and fourteen years of age

5. List the most common congenital malformations

6. List the most common underlying causes of perinatal asphyxia

7. Describe the following disorders:
   - fetal alcohol syndrome
   - congenital rubella syndrome
   - cytomegalic inclusion disease
   - hemolytic disease of the newborn (HDN)
   - respiratory distress syndrome (RDS) of the newborn
   - bronchopulmonary dysplasia (BPD)
   - necrotizing enterocolitis (NEC)
   - phenylketonuria (PKU)
   - galactosemia
   - cystic fibrosis (CF, mucoviscidosis)
   - Hirschsprung disease
   - sudden infant death syndrome (SIDS)
   - pediatric acquired immunodeficiency syndrome (AIDS)

   in terms of:
   - incidence and epidemiology
   - etiology and pathogenesis
   - morphology
   - clinical course
8. Discuss the following pediatric neoplasms:
   - hemangioma
   - lymphangioma
   - acute leukemia
   - malignant lymphoma
   - neuroblastoma
   - retinoblastoma
   - medulloblastoma
   - Wilms tumor (nephroblastoma)
   - teratoma
   - rhabdomyosarcoma
   - Ewing sarcoma
   - osteosarcoma

   in terms of:
   - frequency
   - age of onset
   - role of genetics and environment
   - morphology
   - clinical behavior
   - prognosis
91 - SKIN

The student will be able to:

1. Define and use in proper context:
   - acantholysis
   - acanthosis
   - acrochordon
   - atopic
   - Auspitz sign
   - Bowen disease
   - bulla
   - comedone
   - compound nevus
   - condyloma
   - CREST syndrome
   - dermatitis
   - dermatofibroma
   - dyskeratosis
   - eczema
   - elastosis
   - ephile
   - exocytosis
   - granuloma pyogenicum

   acantholytic
   - halo nevus
   - hereditary angioneurotic edema
   - (HANE)
   - hyperkeratosis
   - intradermal nevus
   - lentiginous
   - lentigo
   - leukoplakia
   - liquefactive degeneration
   - macule
   - mole
   - Munro microabscess
   - mycosis fungoides
   - nevus
   - nodule
   - panniculitis
   - papule
   - parakeratosis
   - Pautrier microabscess
   - pseudoepitheliomatous
   - hyperplasia
   - psoriasiform
   - pustule
   - target lesion
   - tinea barbae
   - tinea corporis
   - tinea cruris
   - tinea pedis
   - verruca
   - vesicle
   - wheal

2. Compare and contrast:
   - vitiligo
   - albinism

   in terms of:
   - etiology
   - pathogenesis
   - clinical presentation
   - histomorphology

3. Discuss urticaria in terms of:
   - types of clinical presentation
   - pathogenesis
   - histomorphology

4. Compare and contrast the following types of dermatitis
   - contact
   - atopic
   - seborrheic
   - photoeczematous

   in terms of:
   - anatomic site(s) involved
   - clinical presentation
   - etiology/pathogenesis
   - histomorphology
   - clinical course

5. Compare and contrast:
   - erythema multiforme
   - erythema induratum
   - erythema nodosum
6. Compare and contrast:
   • psoriasis
   • lichen planus
   • lichen simplex chronicus

   in terms of:
   o associated conditions
   o clinical presentation
   o pathogenesis
   o histomorphology

7. Compare and contrast:
   • pemphigus vulgaris
   • bullous pemphigoid
   • dermatitis herpetiformis
   • cutaneous lupus erythematosus

   in terms of:
   o etiology
   o pathogenesis
   o anatomic site(s) affected
   o clinical presentation
   o morphology (light and immunofluorescent microscopic)
   o clinical course

8. Compare and contrast:
   verruca
   molluscum contagiosum
   herpes simplex infection
   acne vulgaris

   impetigo
   tinea
   arthropod assaults

   in terms of:
   o etiology
   o pathogenesis
   o clinical presentation
   o cutaneous structure(s) involved
   o histomorphology

9. Compare and contrast:
   • systemic sclerosis (scleroderma)
   • CREST syndrome
   • systemic lupus erythematosus (SLE)
   • discoid lupus erythematosus (DLE)

   in terms of:
   o etiology
   o pathogenesis
   o clinical cutaneous manifestations
   o morphology (light and immunofluorescent microscopic)
   o clinical course/complications
10. Compare and contrast:
   • lentigo simplex
   • lentigo senilis (solar lentigo)
   • lentigo maligna
   in terms of:
     o etiopathogenesis
     o age at presentation
     o clinical appearance
     o histomorphology
     o clinical course

11. Compare and contrast
   • seborrheic keratosis
   • actinic keratosis
   • squamous cell carcinoma
   • keratoacanthoma
   • basal cell carcinoma
   in terms of:
     age at presentation  anatomic site(s)
     etiology/pathogenesis  clinical presentation
     associated syndrome(s)  histomorphology
     predisposing lesion(s)  biologic behavior

12. Discuss:
   • basal cell nevus syndrome
   • dysplastic nevus (BK mole) syndrome
   in terms of:
     o genetics
     o clinical manifestations

13. Compare and contrast the following types of nevocellular nevi:
   congenital  spindle and epithelioid cell (Spitz)
   junctional  blue
   compound  halo
   intradermal  dysplastic
   in terms of:
     o clinical presentation (including age)
     o histomorphology
     o clinical significance

14. Compare and contrast the following types of malignant melanoma:
   • lentigo maligna melanoma
   • superficial spreading melanoma
   • nodular melanoma
   • acral lentiginous melanoma
   in terms of:
     o age at presentation
     o etiopathogenesis
     o clinical morphology
     o microscopic morphology
     o staging criteria (Clark and Breslow)
     o clinical course
     o prognosis
15. Discuss the following skin tumors (i.e., masses):
   - cutaneous cysts
   - adnexal (appendage) tumors
   - Merkel cell carcinoma
   - fibrous histiocytoma
   - dermatofibrosarcoma protuberans
   - nevus flammeus
   - hemangioma
   - angiosarcoma
   - Kaposi sarcoma
   - metastatic neoplasia

   in terms of:
   - etiopathogenesis
   - clinical presentation
   - histomorphology
   - clinical course

16. Compare and contrast:
   - epidermolysis bullosa
   - porphyria

   in terms of:
   - etiology
   - pathogenesis
   - clinical presentation
   - histomorphology

17. Discuss the cutaneous manifestations of the following diseases:
   - leukemia
   - malignant lymphoma
   - Langerhans cell histiocytosis
   - mastocytosis
   - sarcoidosis
   - diabetes mellitus
   - acanthosis nigricans
   - xeroderma pigmentosum
   - neurofibromatosis
   - acquired immunodeficiency syndrome (AIDS)

   in terms of:
   - clinical presentation
   - histomorphology
   - associated visceral diseases
   - clinical course
The student will be able to:

1. Define and use in proper context:
   - alkaline phosphatase
   - Brodie abscess
   - callus
   - cancellous bone
   - chondrocyte
   - triangle
   - cortical
   - bonediphysiseburnatione
   - piphysis
   - Felty syndrome
   - Heberden node
   - involucrum
   - lamellar bone
   - metaphysis
   - osteoblast
   - osteocalcin
   - osteoclast
   - osteocyte
   - osteoid
   - osteomalacia
   - osteopenia pannus
   - Pott disease
   - sequestrum
   - synarthrosis
   - synovium
   - tophus
   - woven bone

2. Discuss the following hereditary disorders, in terms of pathogenesis, morphology, and clinical presentation:
   - achondroplasia
   - osteopetrosis
   - osteogenesis imperfecta

3. Describe the morphologic sequence of normal bone growth, as well as of repair following fracture of a long bone. Indicate the way(s) in which age, mobility, nutritional state, and infection influence the repair process.

4. Discuss the following non-neoplastic bone disorders, in terms of etiology, pathogenesis, morphology, and clinical findings and course:
   - osteoporosis
   - Paget disease
   - hyperparathyroidism
   - renal osteodystrophy
   - osteonecrosis
   - osteomyelitis

5. Describe the following tumors (i.e., masses) of bone, joint, and soft tissue:
   - multiple myeloma
   - nonossifying fibroma
   - fibrous dysplasia
   - bone cysts (solitary and aneurysmal)
   - osteoma
   - osteoid osteoma
   - osteoblastoma
   - osteochondroma
   - chondroma
   - chondroblastoma
   - chondromyxoid fibroma
   - osteosarcoma
   - chondrosarcoma
   - giant cell tumor of bone
   - Ewing sarcoma
   - metastatic malignancy to bone

   in terms of:
   - biology (neoplastic vs. nonneoplastic, benign vs. malignant)
   - age distribution
   - etiology and pathogenesis
   - cell type and site of origin
6. Compare osteoarthritis (degenerative joint disease) and rheumatoid arthritis, in terms of:
   - age and sex incidence
   - etiology
   - pathogenesis
   - laboratory findings
   - morphologic findings
   - clinical findings and course

7. Discuss the following disorders:
   - ankylosing spondylitis
   - Reiter syndrome
   - psoriatic arthritis
   - juvenile rheumatoid arthritis
   - infectious arthritis
   - gout
   - calcium pyrophosphate crystal deposition disease

   in terms of:
   - age and sex incidence
   - etiology
   - pathogenesis
   - findings (laboratory, morphologic, clinical)
   - clinical course
93 - SKELETAL MUSCLE

The student will be able to:

1. Define and use in proper context:
   - arthrogryposis
   - chromatolysis
   - dermatomyositis
   - dystrophin
   - dystrophy
   - fasciculation
   - fiber type grouping
   - fibrillation
   - floppy infant syndrome
   - Gower maneuver
   - hypotonia
   - myopathy
   - myotonia
   - nemaline rod
   - neuropathy
   - pseudohypertrophy
   - rhabdomyolysis
   - ring fiber
   - target fiber
   - type I fiber
   - type II fiber
   - Werdnig-Hoffmann disease

2. Describe the structural features of normal skeletal muscle in terms of:
   - gross morphology
   - light microscopic appearance
   - electron microscopic appearance
   - histochemistry

3. Describe proper skeletal muscle biopsy procedure, in terms of:
   - choice of site
   - biopsy technique
   - techniques of fixation, processing, staining
   - common artifacts seen
   - limitations

4. Describe the neuromuscular apparatus, and list disease processes and histopathologic findings of diseases affecting the following components:
   - neuron
   - myelin
   - axon
   - neuromuscular junction
   - muscle
   - blood vessel
   - supporting tissue

5. Discuss the utility of the following:
   - clinical evaluation
   - electromyography
   - serum levels of:
     - creatine kinase (CK)
     - aldolase
     - aspartate aminotransferase (AST)
   - muscle biopsy
   - in the diagnosis of:
     - neurogenic disorders
     - dystrophic myopathies
     - inflammatory myopathies
     - congenital myopathies
     - vacuolar myopathies
     - metabolic myopathies

6. Discuss the following reactions of skeletal muscle:
   - atrophy
   - fiber type grouping
   - inflammatory infiltrates
   - perifascicular atrophy
7. Compare and contrast the following types of skeletal muscle disorders:
   - neurogenic disorders
   - dystrophic myopathies
   - inflammatory myopathies
   - vacuolar myopathies
   - congenital myopathies
   - endocrine myopathies
   - toxic myopathies
   - metabolic myopathies

   in terms of:
   - etiology
   - pathogenesis (including target cell affected)
   - clinical presentation
   - histopathologic findings
   - prognosis

8. Compare and contrast the following types of muscular dystrophy:
   - Duchenne
   - Becker
   - limb girdle
   - myotonic

   in terms of:
   - mode of inheritance
   - morphologic features
   - age and sex incidence
   - clinical manifestations
   - muscles primarily involved
   - prognosis
   - pathogenesis

9. Discuss the following disorders involving skeletal muscle:
   - spinal muscular atrophy
   - glycogenoses
   - myasthenia gravis
   - Lambert-Eaton myasthenic syndrome
   - AIDS-associated myopathy
   - viral myositis
   - trichinosis
   - cysticercosis
   - polymyositis

   in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical features
The student will be able to:

1. Define and use in proper context:
   - agryria
   - AIDS dementia
   - Alzheimer type II cell
   - amyloid angiopathy
   - Antoni A pattern
   - arrhinencephaly
   - aseptic meningitis
   - astrocytosis
   - ataxia
   - Bergmann gliosis
   - central nervous system (CNS)
   - cerebral
   - cerebral palsy (CP)
   - cerebritis
   - cerebrospinal fluid (CSF)
   - cerebrovascular accident (CVA)
   - choreiform
   - chromatolysis
   - closed head injury
   - concussion
   - contrecoup injury
   - contusion
   - corpora amylacea
   - coup injury
   - cranial
   - dementia
   - demyelination
   - Duret hemorrhage
dysmyelination
   - encephalitis
   - encephalocele
   - encephalomylitis
   - encephalopathy
   - ependymitis
   - etat marbre
   - germistocytic
   - Gitter cell
   - gliosis
   - glomeruloid body
   - granulovacuolar degeneration
   - herniation
   - Hirano body
   - holoprosencephaly
   - hydranencephaly
   - hydrocephalus
   - hydrocephalus ex vacuo
   - inborn error of metabolism
   - kernicterus
   - lacunar infarct
   - lacunar state
   - Lafora body
   - laminar necrosis
   - leptomeningitis
   - leukencephalopathy
   - leukomalacia
   - Lewy body
   - lissencephaly
   - "mad cow" disease
   - megalencephaly
   - meningitis
   - meningocle
   - meningencephalitis
   - meningomyelocele
   - meningovasculitis
   - microcephaly
   - multiple sclerosis plaque
   - myelitis
   - Negri body
   - neuritic plaque
   - neurofibrillary tangle
   - neuronophagia
   - neuropathy
   - Nissl substance
   - open head injury
   - ophthamoplegia
   - pachygryia
   - pachymeningitis
   - paresis
   - parkinsonism
   - peripheral nervous system (PNS)
   - phakomatosis
   - Pick body
   - pleiocytosis
   - polymicrogyria
   - porencephaly
   - presenilin
   - prion
   - prion protein (PrP)
   - radiculitis
   - Rosenthal fiber
   - rosette/pseudorosette
   - satellitosis
   - schizencephaly
   - spina bifida
   - spongiform
   - status marmoratus
   - storage disease
   - stroke
   - syringomyelia
   - tabes dorsalis
   - transient ischemic attack (TIA)
   - ulegyria
   - von Recklinghausen disease
   - Wallerian degeneration
   - watershed (border) zone

2. Describe the following CNS cells:
   - neurons
   - astrocytes
   - oligodendrocytes
   - ependymal cells

   in terms of:
   - derivation
   - morphology
   - function
3. Compare CNS myelin with PNS myelin, in terms of:
   - cells of elaboration
   - structure and function
   - reactions to injury and destruction
   - regenerative potential

4. Discuss normal CSF in terms of:
   - sites of formation
   - circulation patterns
   - sites of absorption
   - pressure
   - glucose and protein levels
   - cell types present

5. Describe the blood-brain barrier (BBB) in terms of:
   - physiologic definition
   - anatomic counterparts
   - morphologic alterations
   - areas of absence

6. Describe the following processes:
   - central chromatolysis
   - neuronophagia
   - axonal swelling
   - ischemic neuronal necrosis
   - gliosis
   - liquefactive necrosis
   - coagulative necrosis
   - caseous necrosis
   - nerve regeneration
   - segmental demyelination
   - dysmyelination

   in terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinicopathologic significance

7. Compare and contrast the following types of cerebral edema:
   - cytotoxic
   - vasogenic
   - interstitial

   in terms of:
   - mechanism of formation
   - morphology
   - clinicopathologic significance

8. Compare and contrast the following types of herniation of the brain:
   - subfalcine (cingulate gyrus)
   - transtentorial (uncal)
   - foraminal (tonsillar)

   in terms of:
   - etiopathogenesis
   - morphology
   - clinical findings
   - sequelae (morphologic and clinical)
9. Correlate destructive lesions in specific areas of the CNS with corresponding functional consequences.

10. Compare and contrast:
   - communicating hydrocephalus
   - non-communicating hydrocephalus
   - hydrocephalus *ex vacuo*

   in terms of:
   - etiopathogenesis
   - morphologic findings
   - clinical manifestations

11. Discuss the following congenital abnormalities:
   - anencephaly
   - hydrocephalus *ex vacuo*
   - Chiari type I malformation
   - Chiari type II (Arnold-Chiari) malformation
   - Dandy-Walker malformation
   - holoprosencephaly
   - porencephaly
   - encephalocele
   - spina bifida/meningomyelocoele
   - polymicrogyria
   - schizencephaly
   - agenesis of corpus callosum
   - syringomyelia (syrinx)
   - hydromyelia

   in terms of:
   - relative frequency
   - gestational age of occurrence
   - etiology
   - pathogenesis
   - morphology
   - clinical features

12. Compare and contrast the following inborn errors of metabolism:
   - Tay-Sachs disease
   - Niemann-Pick disease
   - Gaucher disease
   - mucopolysaccharidosis
   - Krabbe disease
   - metachromatic leukodystrophy
   - adrenoleukodystrophy
   - Leigh disease
   - Canavan disease
   - Wilson disease
   - galactosemia
   - phenylketonuria (PKU)

   in terms of:
   - genetics
   - metabolic abnormalities
   - effects on neurons and glia
   - morphology
   - clinical features

13. Describe the effects of hypoxia/ischemia on the late gestational/perinatal brain, including the pathophysiologic mechanisms underlying the following:
   - hydranencephaly
   - multicystic encephalopathy
   - germinal matrix hemorrhage
   - ulegyria
   - periventricular leukomalacia
   - cerebral palsy (CP)
   - etat marbre (status marmoratus)
14. Discuss the following processes:
   - cerebral contusion
   - diffuse axonal injury
   - epidural hematoma
   - subdural hematoma
   - subarachnoid hemorrhage
   - intracerebral hemorrhage

   In terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical course and prognosis

15. Compare and contrast the following types of central nervous system aneurysms:
   - saccular ("berry")
   - atherosclerotic
   - Charcot-Bouchard
   - mycotic

   In terms of:
   - incidence
   - etiology
   - pathogenesis
   - anatomic distribution
   - morphology
   - clinical presentation
   - complications

16. Compare and contrast the following types of CNS vascular malformations:
   - arteriovenous malformation
   - cavernous angioma
   - capillary telangiectasia

   In terms of:
   - anatomic location
   - morphology
   - clinical manifestations
   - complications

17. List the ways in which hypertension may cause destruction of brain tissue

18. Compare and contrast:
   - hypertensive encephalopathy
   - hypoxic encephalopathy
   - multiinfarct dementia

   In terms of:
   - etiology
   - pathogenesis
   - morphology
   - clinical features and course

19. Compare and contrast the following types of CNS infarct:
   - nonhemorrhagic (pale, anemic)
   - hemorrhagic (red)
   - border zone (watershed)
• incomplete
• spinal cord

in terms of:
  o predisposing conditions
  o etiology
  o pathogenesis
  o morphologic evolution
  o clinical features
  o complications

20. Compare and contrast the clinical presentations of infarcts of areas supplied by the following arteries:
  • middle cerebral
  • vertebrobasilar
  • internal carotid

21. Describe the interrelationship between hypotension and watershed infarcts

22. Explain the basis of the reperfusion theory of causation of hemorrhagic cerebral infarcts

23. Compare and contrast:
  • skull fracture
  • parenccymal brain injury
  • vascular brain injury

in terms of:
  o mechanisms
  o clinicopathologic effects

24. Compare and contrast open vs. closed head injury, in terms of complications and prognosis

25. Compare and contrast the following neuropathologic entities:
  • pyogenic meningitis
  • tuberculous/mycobacterial meningoencephalitis
  • viral meningoencephalitis
  • fungal meningitis
  • neurosyphilis
  • neuroborreliosis (Lyme disease)
  • rickettsial infection
  • protozoal infection

in terms of:
  o predisposing factors
  o etiology
  o pathogenesis
  o morphology
  o cerebrospinal fluid findings
  o clinical features and course

26. List the common bacterial agents of acute pyogenic meningitis, and the age group that each most frequently affects

27. Compare and contrast:
  • brain abscess
  • subdural empyema
  • extradural abscess
in terms of:
  - etiology
  - usual locations
  - morphologic components
  - pathophysiologic consequences

28. Discuss the following types of viral meningoencephalitis:
   - arboviral encephalitides
   - herpes simplex viral encephalitis
   - varicella-zoster viral encephalitis
   - cytomegalovirus (CMV) encephalitis
   - poliomyelitis
   - rabies
   - human immunodeficiency virus (HIV) infections
     - HIV meningoencephalitis (subacute encephalitis)
     - vacuolar myelopathy
   - progressive multifocal leukoencephalopathy (PML)
   - subacute sclerosing panencephalitis (SSPE)

in terms of:
  - predisposing factors
  - epidemiology
  - etiology
  - pathogenesis
  - morphologic features
  - clinical manifestations
  - prognosis

29. Discuss the following prion diseases:
   - Creutzfeldt-Jakob disease (CJD)
   - variant CJD (vCJD, "mad cow" disease)
   - kuru
   - scrapie

in terms of:
  - etiology
  - pathogenesis
  - mode of transmission
  - host immune response
  - morphologic features
  - clinical manifestations and course

30. Compare and contrast the following degenerative diseases:
    Alzheimer disease    olivopontocerebellar atrophy
    Pick disease         Huntington disease
    Parkinson disease    spinocerebellar degeneration
    progressive supranuclear palsy amyotrophic lateral sclerosis (ALS)
    corticobasal degeneration Friedreich ataxia
    striatonigral degeneration ataxia-telangiectasia
    Shy-Drager syndrome
31. Describe multiple sclerosis (MS) in terms of:
   • geographic distribution
   • etiology
   • age at onset
   • distribution of lesions
   • morphology
   • clinical course

32. Discuss the following nervous system disorders:
   - kernicterus
   - acute ethanol intoxication
   - chronic ethanol abuse
   - methanol poisoning
   - carbon monoxide poisoning
   - radiation damage
   - central pontine myelinolysis (CPM)

   in terms of:
   • pathogenesis
   • distribution of lesions
   • morphology
   • clinical findings and course

33. Discuss the following nutritional disorders:
   - Wernicke encephalopathy
   - Korsakoff psychosis
   - neuropathic beriberi
   - subacute combined degeneration

   in terms of:
   • etiologic deficiency
   • pathogenesis
   • morphology
   • clinical findings

34. Explain the concepts of benignity vs. malignancy, as applied to central nervous system neoplasms

35. Compare and contrast the following neoplasms:
   - colloid cyst of third ventricle
   - choroid plexus papilloma
   - astrocytoma
   - anaplastic astrocytoma
   - pilocytic astrocytoma
   - fibrillary astrocytoma
   - glioblastoma multiforme
   - oligodendroglialoma
   - ependymoma
   - neuroblastoma
   - ganglioneuroblastoma
   - ganglioneuroma
   - medulloblastoma
   - gangglioglioma
   - meningioma
   - hemangioblastoma
   - chordoma
   - germinoma
   - pheochromocytoma
   - pineocytoma
   - craniopharyngioma
   - primary CNS lymphoma
   - neurofibroma
   - plexiform neurofibroma
schwannoma (neurilemoma)  metastatic malignancy to CNS
malignant peripheral nerve sheath tumor

in terms of:
  genetics  radiologic findings
  relative frequency  morphology
  age distribution  clinical features
  etiopathogenesis  prognosis
  common sites of origin

36. Compare and contrast the following phakomatoses:
   neurofibromatosis type 1  Sturge-Weber syndrome
   neurofibromatosis type 2  ataxia-telangiectasia
   tuberous sclerosis  von Hippel-Lindau syndrome

in terms of:
   o incidence
   o genetics
   o morphologic manifestations
     CNS
     PNS
     skin
     visceral
   o clinical features and course

37. Discuss the following disorders of the PNS:
   myasthenia gravis  Refsum disease
   Guillain-Barré syndrome  paraproteinemia-associated neuropathy
   herpes zoster (shingles)  spinal muscular atrophy
   hereditary neuropathies  compression neuropathy
   diabetic neuropathy  traumatic neuroma
   AIDS-associated peripheral neuropathy  plantar (Morton) neuroma
   hereditary motor & sensory neuropathy (HMSN)
     type I [Charcot-Marie-Tooth disease (CMT) I]
     type III (Dejerine-Sottas disease)

in terms of:
   o etiology (including genetics, if applicable)
   o pathogenesis
   o morphology
   o clinical findings
95 – SPECIAL SENSE ORGANS

The student will be able to:

1. Define and use in proper context:
   - arcus senilis
   - arteriovenous nicking
   - astigmatism
   - blepharitis
   - blepharochalasis
   - blindness
   - buphthalmos
   - cataract
   - chalazion
   - cherry-red macula
   - cholesteatoma
   - coloboma
   - cotton-wool spots
   - cyclitic membrane
   - dacryocystitis
   - deafness
   - diabetic retinopathy
   - background
   - proliferative
   - drusen
   - ectropion
   - emmetropia
   - entropion
   - epiphora
   - esophoria
   - esotropia
   - exophthalmos
   - glaucoma
   - hordeolum
   - iris bombe
   - iritis
   - keratic precipitate
   - keratitis
   - keratoconus
   - keratomalacia
   - keratopathy
   - leukoma
   - mastoiditis
   - myopia
   - myringitis
   - nevula
   - opthalmoplegia
   - otosclerosis
   - papilledema
   - phakoanaphylaxis
   - photophobia
   - phthisis bulbi
   - pinguecula
   - presbycusis
   - presbyopia
   - proptosis
   - pterygium
   - scotoma
   - sympathetic ophthalmia
   - synecchia
   - tinnitus
   - uveitis
   - vertigo
   - xanthelasma
   - xerophthalmia

2. Discuss the anatomy of the orbit in general

3. Describe ocular findings in the following congenital conditions:
   - trisomy 13
   - trisomy 21
   - congenital rubella
   - congenital syphilis

4. Discuss the following inflammatory conditions of the eye and orbit:
   - conjunctivitis
   - acute (pink eye)
   - chronic
   - inclusion
   - trachoma
   - ophthalmia neonatorum
   - blepharitis
   - hordeolum
   - chalazion
   - pseudotumor
   - dacryocystitis
   - keratitis
   - iridocyclitis
   - granulomatous inflammation
   - sympathetic ophthalmia (uveitis)

   in terms of:
   - etiology (including most common organism, if applicable)
   - pathogenesis
   - morphology
   - natural course
5. Discuss the three major types of corneal stromal dystrophies, in terms of:
   - genetics
   - histomorphology
   - clinical course

6. Compare and contrast the following types of glaucoma:
   - congenital
   - primary angle-closure
   - secondary angle closure
   - open-angle
   
   in terms of:
   - etiology
   - morphology
   - clinical course

7. Discuss the following degenerative conditions:
   band keratopathy
   blepharochalasis
   entropion
   ectropion
   xanthelasma
   pinguecula
   pterygium
   arcus senilis
   keratoconus
   keratomalacia
   
   in terms of:
   - etiopathogenesis
   - morphology
   - clinical significance

8. Discuss cataracts with regard to:
   - associated diseases
   - etiology
   - classification
   - morphology

9. Discuss the following diseases:
   - retinopathy of prematurity (retrolental fibroplasia)
   - retinitis pigmentosa
   - macular degeneration
   - retinal detachment
   
   in terms of:
   - etiology
   - morphology
   - ophthalmoscopic findings
   - clinical course

10. Compare and contrast the following vascular disorders:
    - central retinal artery occlusion
    - central retinal vein occlusion
    - hypertensive retinopathy
    - arteriosclerotic retinopathy
    - diabetic retinopathy
      background
      proliferative
in terms of:
  o incidence
  o etiopathogenesis
  o histomorphology
  o ophthalmoscopic findings
  o clinical course

11. State the ocular lesions associated with:
   • vitamin A deficiency
   • methanol toxicity

12. List the most frequent primary and metastatic malignancies of the:
    • lid
    • conjunctiva
    • uvea (uveal tract)
    • optic nerve

13. Discuss the following malignancies of the eye:
    • malignant melanoma
    • retinoblastoma
    • metastatic malignancy
    in terms of:
      o genetics
      o incidence (including age, race)
      o sites of origin
      o clinical presentation
      o morphology
      o prognosis

14. Discuss the following diseases of the optic nerve:
    • papilledema
    • optic neuritis
    • optic atrophy
    in terms of:
      o etiopathogenesis
      o morphology
      o prognosis

15. State:
    • the two most common causes of blindness in the world
    • the four most common causes of blindness in the United States

16. Describe the following congenital anomalies:
    • preauricular pit
    • preauricular tag
    • branchial cleft cyst
    in terms of:
      o embryonic developmental pathogenesis
      o morphologic features
      o clinical features
17. Discuss the following diseases of the external ear:
   - cauliflower ear
   - otitis externa
   - chondrodermatitis nodularis chronicis helicis
   - keloid
   - myringitis
   - aural polyps
   - neoplasms

   in terms of:
   - etiology
   - morphology
   - clinical course

18. Discuss the following diseases of the middle ear:
   - otitis media
   - cholesteatoma
   - chemodectoma

   in terms of:
   - etiopathogenesis
   - morphology
   - clinical course

19. Discuss the following diseases of the inner ear:
   - labyrinthitis
   - otosclerosis
   - Meniere disease
   - acoustic trauma
   - endolymatic duct tumor
   - acoustic schwannoma ("neuroma")

   in terms of:
   - associated syndromes (if any)
   - age incidence
   - etiopathogenesis
   - morphology
   - clinical features
GENERAL PATHOLOGY LECTURES

PPTs. ON THE FOLLOWING LECTURES WILL BE AVAILABLE ON THE PATH. WEB SITE.

DR. BRETT BARTLETT  GENERAL PATH.  6 SESSIONS

DR. RICHARD TAPPING  IMMUNOPATH.  3 SESSIONS

DR. NICOLE HOWELL  NEOPLASIA  3 SESSIONS

DR. MICHAEL SCHNEIDER  GENETICS  2 SESSIONS
GENETIC AND PEDIATRIC DISEASES

Christine A. Weaver, MD, PhD
SET 1

GENETIC AND PEDIATRIC DISEASE SLIDES

Christine A. Weaver, M.D., Ph.D.
Genetic & Pediatric Disease

Christine A. Weaver, M.D., Ph.D.

Genetic And Pediatric Disease

- Overview Genetic Disease
  - Basic concepts
  - Recent advancements in testing
  - Metabolic disease
  - Malformation syndromes
- Overview Pediatric Disease
  - Intrauterine growth retardation
  - prematurity and related diseases
  - sudden infant death syndrome
  - Malformation/birth defects
  - childhood neoplastic disease

Question

- What is a genetic disorder?
  A. Condition due to mutation in defined genes
  B. Condition due to combination genetic and environmental factors
  C. Condition due to any alteration of DNA
  D. Condition due to alteration in DNA that results in disease

Question

- How are genetic diseases classified?
  A. According to the type of DNA change causes disease
  B. According to whether a change is visible by chromosome evaluation or not
  C. According to DNA and environmental factors
  D. All of the above

Genetic Conditions Are Currently Classified As

- Chromosomal
  - Due to changes visible by chromosome evaluation
- Nonchromosomal
  - Due to genetic changes not detectable by chromosome evaluation
- The line between these is blurring as our technology advances
  - Probes to detect single gene defects on chromosomes are available

Nonchromosomal Genetic Conditions

- Single Gene disorders
  - Are further classified according to their pattern of inheritance
- Multifactorial disorders
  - due to the interaction of multiple gene mutations and environment
Examples of genetic mutations that influence risk of common human diseases

- ApoE4: Alzheimers
- HLA: Autoimmune disease
- CCR5: HIV infection
- CTLA4: Graves disease
- NOD2: IB
- SQA1: Hypertension: IB
- Neuregulin: schizophrenia
- Apo A5: Coronary Artery Disease
- LPL: Coronary Artery Disease
- G6PD: Malaria

Single Gene Disorders

- Have simple patterns of inheritance
- Recurrence risks are determined based on reported patterns of inheritance
- Are categorized according to primary organ systems involved
- However, in reality all are multi-system and best understood based on pathogenesis

Autosomal Dominant Disorders

- Have variable expressivity
- May not have 100% penetrance
- Often have delayed onset
- Due to either dominant negative effects or detrimental gain of function
- Associated with new mutations during gametogenesis
- May have gonadal mosaicism

Autosomal Dominant Disorders

- Nervous
  - Loeys-Dietz syndrome
  - Marfan's disease
  - Ehlers-Danlos syndrome
  - Nephrotic syndrome
- Urinary
  - Polycystic kidney disease
- Cardiorenal
  - Secondary hypertension due to kidney disease
- Retinosclerotic
  - Secondary hypertension due to kidney disease
- Skeletal
  - Hereditary osteopetrosis (osteoclast growth)
  - Osteopetrosis (Rickets)
  - Ectodermal dysplasia
- Neuroendocrine
  - Familial hyperadrenocorticism
  - Adrenocortical dysplasia
- Other
  - Secondary adrenal gland disease (SAD) and SED

Question

- Why do autosomal dominant disorders have variable expressivity?
  A. They involve a single mutation which varies in position in the gene
  B. They require mutations in other genes for expression
  C. The effect of mutation is influenced by other factors which vary between individuals
  D. They are associated with new mutations that occur during gametogenesis
  E. C and B
Which of the following are True of dominant disorders?

A. Most have 100% penetrance
B. HNPCC is known to require mutations in multiple genes for the development of colon cancer
C. 100% of cases of fatal neonatal osteogenesis imperfecta are due to new mutations
D. Neurofibromatosis type I requires somatic mutations in the NF1 gene for the development of neurofibroma
E. All of the above

Neurofibromatosis Type I

NF1 is due to hundreds of different mutations in Neurofibromin, the NF1 tumor suppressor gene product.

- Results in multisystem affects including:
  - Multiplicity of benign hamartomas of neural crest origin: café au lait spots and neurofibroma of skin and deeper periphermal neurofibroma
  - Migration CNS abnormalities—learning disabilities and seizures
  - Abnormalities in growth of bone or soft tissues—scoliosis, sphenoid dysplasia and pseudotumors
  - Huge Variability of expression between individuals with NF1 even in the same family

Diagnostic Criteria for NF1

- Diagnostic requires two of the following:
  - 6 or more café au lait spots
  - Axillary freckling
  - Cutaneous neurofibroma
  - Plexiform neurofibroma of nerve sheath
  - Lisch nodules of iris
  - Dysplasia of the sphenoid bone
  - Cotic glioma
  - PMH of NF1
  - NF1 gene DNA testing identified mutation

Variability of NF1

- Incidence of finding demonstrates the variability in expressivity
  - 57% have café au lait spots by age 6
  - 80% Cafe au lait freckling
  - 90% Lisch nodules
  - 90% Plexiform neurofibroma
  - 16% Bone dysplasia including sphenoid and tibial
  - 40% have learning difficulties
  - 20% of patients develop malignancy, including: optic glioma, neurofibrosarcoma, schwannoma and pheochromocytoma
- Diagnosis is very important to guide surveillance protocols

Male with disfiguring cutaneous Neurofibroma which arise in the dermis and have nervous, fibrous and metaplastic elements, café au lait spots.
Autosomal Recessive Disorders

- Are due to loss of function
- Generally, but not always have complete penetrance
- Expressivity tends to be less variable
- Tend to be early onset
- Severity of phenotype is more related to genotype
Cystic Fibrosis

Severe mutations like delta F508 result in complete loss of CFTB with markedly increased sweat Chloride, severe pancreatic insufficiency, meconium ileus at birth, liver cirrhosis, infertility & fatal lung disease.

Cystic Fibrosis - Genotype & Phenotype

Figure 11-21

XXX: intracellular cystic fibrosis changes in the pancreas. The ducts are dilated and plugged with eosinophilic mucus, and the pancreatic glands are contracted and replaced by fibrous tissue.
Cystic Fibrosis - Genotype & Phenotype

X-linked Recessive Disorders
- Generally do not affect females but may with unfavorable X-inactivation
- Are passed from mother to son
- Are not passed from father to son
- All daughters of affected fathers are carriers
- Tend to have high penetrance in males

X-Linked Recessive Disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td>Fragile X Syndrome</td>
</tr>
<tr>
<td>Blood</td>
<td>Hemophilia A &amp; B</td>
</tr>
<tr>
<td>Cyanotic</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Immune</td>
<td>Acquired immunodeficiency</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Wiskott-Aldrich Syndrome</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Duchenne muscular dystrophy</td>
</tr>
</tbody>
</table>

Fragile X Syndrome
- Fragile X - most common form of hereditary mental retardation
- 100% of males, and 50% of females with full mutation are affected
- Males tend to be more severely affected than females
- Clinical characteristics are highly variable, developmental delay is single consistent feature
- Focus on development of accurate testing based on commonness of disorder and lack of clinical criteria

Clinical Features of Fragile X Syndrome
- Delayed development in infancy
- Delayed speech and language
- Hypotonia
- Seizures
- Small stature
- Microcephaly
- Hypotonia
- Motor difficulties
- Elbow contractures
- Joint laxity
- Hypogonadism
- Late puberty
- Infertility
- Behavioral problems
- Intellectual disability

Demonstrates the multisystem nature of Fragile X Syndrome
Fragile X Syndrome

- Due to mutation in the FMR-1 gene which involves expansion of a trinucleotide CGG repeat sequence
- Normal FMR-1 function with <50 repeats, unstable premutation 50-200, expands metastically up to 2000
- Risks of premutation expansion is directly related to the repeat number
- Expansion results in hypermethylation and inactivation of the Fragile X gene
- FMRP is an RNA binding protein known to bind a subset of brain-specific transcripts

Advancements in Genetic Testing

- Rapid advancements in supportive diagnostic testing for genetic disorders have occurred in all areas
  - High resolution chromosome evaluation, specialized techniques to characterize subtle anomalies.
  - Biochemical testing for metabolic/connective tissue disorders
  - Direct mutation testing for single gene disorders, including: PCR-based testing for point mutations or trinucleotide repeat expansions and DNA sequencing

Genetic Testing

- There are multiple approaches to Direct DNA-based mutation analysis for single gene disorders
- The most outstanding recent advancement for mutation detection in single gene disorders include PCR allowing selection of the DNA segment to be amplified using DNA primers which bind to the sequence of interest.
- The PCR enzyme copies that sequence thousands of times in the process
- The PCR amplified DNA can then be analyzed for the presence of absence of a mutation

Selected Diseases Associated with Unstable Repeat Expansions

<table>
<thead>
<tr>
<th>Repeating Sequence</th>
<th>Disease</th>
<th>Transmission</th>
<th>Protein Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGG - CGG</td>
<td>Fragile X</td>
<td>AD</td>
<td>FMR1</td>
</tr>
<tr>
<td>CGG - CGG</td>
<td>DiGeorge</td>
<td>AD</td>
<td>Protein kinase</td>
</tr>
<tr>
<td>CGG - CGG</td>
<td>MODY</td>
<td>AD</td>
<td>P1A</td>
</tr>
<tr>
<td>CGG - CGG</td>
<td>Thrombocythemia</td>
<td>AD</td>
<td>Thrombocyte</td>
</tr>
<tr>
<td>CGG - CGG</td>
<td>Megalocytes</td>
<td>AD</td>
<td>Megalocytes</td>
</tr>
</tbody>
</table>

Expansions Affecting Coding Regions

- Fragile X syndrome
- Fragile X is a family of neurodegenerative disease caused by unstable repeat expansions
- There are several patterns of inheritance, depending on the mechanism of disease
**Mutation Analysis Using Radiolabeled Oligos and Differential Hybridization**

- Intensity of signal of DNA samples on filter paper is determined by probe usage.

**Advancements in DNA Testing**
- The most outstanding recent advancement in supportive diagnostic testing for single gene disorders is DNA sequencing.
- DNA sequencing uses PCR Primers to select the sequence of interest and methodology allows analysis of each base pair systematically from 5' to 3' of the gene.
- Rapidly evolving improvements in DNA sequencing allows for highly accurate testing even for very large genes with many disease causing mutations.
- Examples of disorders for which DNA sequence analysis is available include NF1, CF, Hereditary Nonpolyposis Colon Cancer, FAP and BRCA1 & 2.
- Breast and ovarian cancer syndromes.

**Genetic Testing**
- Advancements facilitate diagnosis of neurodegenerative disorders.
- Predictive testing for hereditary cancers.
- Understanding and diagnostic support for malformation syndromes.
- Increasing knowledge of true spectrum and frequency of specific genetic disorders.

**LAST SLIDE**

**Virtually All Diseases Have a Genetic Component**

- Genetic Component
- Environmental Component

Cystic Fibrosis  AIDS
SET 2

GENETIC AND PEDIATRIC DISEASE SLIDES

Christine A. Weaver, M.D., Ph.D.
Genetic & Pediatric Disease

Christine A. Weaver, M.D., Ph.D.

Pediatric Disease
- Overview Pediatric Disease
  - Intrauterine growth retardation
  - Prematurity and related diseases
  - Sudden infant death syndrome
  - Congenital anomalies/birth defects
  - Childhood neoplastic disease

Pediatric Disease
- Common causes of morbidity and mortality in the Pediatric population (birth to 14 years)
- First lecture focuses on causes in the first years
- Second lecture will focus on Pediatric malignancies, most common cause of morbidity and mortality in later childhood

Causes of Death by Age in Pediatric Population

<table>
<thead>
<tr>
<th>Causes</th>
<th>Rate per 100,000 deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 1 year: All Causes</td>
<td></td>
</tr>
<tr>
<td>Prematurity complications (requiring a bath)</td>
<td></td>
</tr>
<tr>
<td>Intrauterine growth retardation (low birth weight)</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease syndrome</td>
<td></td>
</tr>
<tr>
<td>Exudative diathesis</td>
<td></td>
</tr>
<tr>
<td>Birth trauma</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies/birth defects</td>
<td></td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td></td>
</tr>
<tr>
<td>Infections &amp; Pneumonias</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders/neonatal diarrhea</td>
<td></td>
</tr>
<tr>
<td>1-4: All Causes</td>
<td>43.3</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td></td>
</tr>
</tbody>
</table>

Causes of Death and Age in Pediatric Population

<table>
<thead>
<tr>
<th>Causes</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9: All Causes</td>
<td>18.5</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td></td>
</tr>
<tr>
<td>10-14: All Causes</td>
<td>18.5</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>Diseases of the heart</td>
<td></td>
</tr>
</tbody>
</table>

Mortality In Pediatric Disease
- Highest mortality rate in childhood is in the first year
- The most prominent causes in infancy are conditions that result in:
  - Intrauterine growth retardation, prematurity including respiratory distress syndrome & congenital anomalies
- Others in the first year of life include:
  - sudden infant death syndrome, birth trauma & infection
Causes of Death in the First Year

- Perinatal conditions
- Intrauterine growth retardation/low birth weight
- Preterm delivery
- Respiratory distress syndrome
- Intrauterine hypoxia
- Birth trauma
- Congenital anomalies/birth defects
- Sudden infant death syndrome
- Infections & Pneumonia
- Gastrointestinal disorders/neonatal necrotizing enterocolitis

Intrauterine Growth Retardation (IUGR)

- Birth weight below the 10th percentile for gestational age
- Studies have indicated that infants born below the 10th percentile for gestational age are at high risk for multiple medical complications
- Complications include: increased risk for infection, birth defects, continued growth failure and developmental delay

Causes of Intrauterine Growth Retardation are categorized as:

- Fetal
- Placental
- Maternal

Intrauterine Growth Retardation

- Fetal
  - Most are unknown
  - Intrauterine infections include: Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Syphilis (TORCHS) are known to be risks
  - Genetic conditions are commonly associated with intrauterine growth retardation

- Placental Insufficiency
  - Placental abruption
  - Previa
  - Infarction
  - Chromosomal mosaicism (chromosome 7)

Intrauterine Growth Retardation

- Maternal Factors include:
  - Hypertension
  - Toxemia
  - Teratogens (ETOH)
  - Are felt to be the most common cause of IUGR
**Sudden Infant Death Syndrome (SIDS)**

- New evidence indicates SIDS due to abnormalities in brainstem regulation of breathing involving serotonin
- Appears causally heterogeneous
- Risk factors include prone sleeping and thermal stress

**Factors Associated with SIDS**

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young (&lt;20 years of age)</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Unmarried</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>Short intrauterine period</td>
<td>Male sex</td>
</tr>
<tr>
<td>Low socioeconomic group</td>
<td>Product of multiple birth</td>
</tr>
<tr>
<td>Postterm</td>
<td>Not first sibling</td>
</tr>
<tr>
<td>Premature</td>
<td>SIDS in prior sibling</td>
</tr>
<tr>
<td>Black race</td>
<td>Low birth weight</td>
</tr>
</tbody>
</table>

**Congenital Anomalies**

- Are one of the most common causes of morbidity and mortality in childhood
  - 3% of children are born with a major congenital anomaly
  - 25% of children dying in the perinatal period have a major error in morphogenesis

**Congenital Anomalies**

- Malformation-abnormal development of a structure due to an intrinsic factor—gene mutation, drugs, TORCH infection
- Deformation-later alteration of an already formed structure by mechanical forces—uterine constraint
- Disruption-destruction of forming structures by either extrinsic or intrinsic Bectra-amniotic bands, vascular insult, TORCH infection, drugs
Ventriculoapical defect of the heart – a malformation

Infant with oligohydramnios sequence – a deformation
Note flattened facial features and deformed right foot (talipes equinovarus)

Schematic diagram of the pathogenesis of the oligohydramnios sequence

Oligohydramnios

Amniotic band syndrome. Note placenta at right of diagram and band of amnion extending from top portion of amniotic sac to encircle leg of fetus – A disruption

Associated features of Fetal Alcohol Syndrome (FAS) include malformation and disruption

<table>
<thead>
<tr>
<th>Area</th>
<th>Frequent</th>
<th>Occasional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Prominent nasion, epicanthal fold</td>
<td>Microphthalmia, exophthalmos</td>
</tr>
<tr>
<td>Ears</td>
<td>Prominent auricle</td>
<td>Ear anomalies</td>
</tr>
<tr>
<td>Limbs</td>
<td>Prominent palmar creases</td>
<td>Hand anomalies, ulnar deviation</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cyanosis, especially in early childhood</td>
<td>Ventricular septal defect, congenital anomalies, tetralogy of Fallot</td>
</tr>
<tr>
<td>Renal</td>
<td>Ureteral abnormalities</td>
<td>Hypertension, renal insufficiency</td>
</tr>
<tr>
<td>Omental</td>
<td>Hypertrophied kidneys</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Hypoplasia, especially in long bones</td>
<td>Hypoplasia</td>
</tr>
<tr>
<td>Muscular</td>
<td>Hypotonia, decreased muscle mass</td>
<td>Hypoplasia, especially in long bones, muscle wasting, dysmorphic features, decreased muscle mass</td>
</tr>
</tbody>
</table>

Child with FAS has severe IUGR, microcephaly, smooth philtrum, thin upper lip, cleft palate and ventriculoapical defect
Developmental Field

- Represents a group of tissues that react as a coordinated unit during embryogenesis.
- Most important developmental field is the midline failure of midline morphogenesis can result in:
  - Holoprosencephaly, cleft lip/palate, congenital heart defect, omphalocele, hypospadias, imperforate anus, spina bifida.

Developmental Field

- Monotopic field defects like midline involve anatomically connected structures with a coordinated response to inductive factors.
- Polytopic developmental field defects are anatomically distant defects that are dependent on the same inductive forces.

Sirenomelia: a monotopic field defect due to failure of the caudal biotena resulting in failure of caudal structures with fusion of the lower limb buds and is multifactorial - more frequent in diabetic mothers.

Apert Syndrome
Polytopic due to FGFR-3 Mutation

Teratogens

- External factors that become internalized & disrupt developmental fields resulting in malformation.
- Often have critical periods of exposure.
- Thalidomide by six weeks gestation to get limb reduction defects.
- Rubella infection by eight weeks to get congenital heart disease and cataract.
- CMV infection usually occurs after 12 weeks which can result in mental retardation, deafness and hepatosplenomegaly but not malformation, as opposed to IUGR and microphthalmia with infection in early first trimester.
Teratogens May Act Through Many Different Mechanisms
- Cell migration
- Cell-cell interaction
- Cell-matrix interaction
- Programmed cell death
- Molecular mechanisms of many teratogens are poorly understood
- Retinoic Acid embryopathy is well characterized at the molecular level

Data on Causes of Malformation

<table>
<thead>
<tr>
<th>Genes</th>
<th>Malformed both lines %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic factors</td>
<td>10-15</td>
</tr>
<tr>
<td>Environmental</td>
<td>3-5</td>
</tr>
<tr>
<td>Maternal effects</td>
<td>4-6</td>
</tr>
<tr>
<td>Paternal effects</td>
<td>1</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>20-25</td>
</tr>
<tr>
<td>Other</td>
<td>80-100</td>
</tr>
</tbody>
</table>

Genes That are Determinants of Developmental Fields
- There is a rapidly growing list of well-characterized genes numbering in the 1000s
- HOX genes are transcriptional regulators implicated in patterning of limbs, vertebrae and craniofacial structures during embryogenesis
- Mutation of many genes including HOX, PAX & WT-1 have been implicated in both malformation and oncogenesis

Malformation Syndromes
- A group of congenital malformations that is recognizable as a specific genetic condition
- Consist of two or more developmental field defects
- May be chromosomal or nonchromosomal

LAST SLIDE
SET 3

GENETIC AND PEDIATRIC DISEASE SLIDES

Christine A. Weaver, M.D., PhD.
Genetic Malformation Syndromes
Nonchromosomal

Christine Weaver, M.D., Ph.D.

Nonchromosomal Syndromes

- Examples of well characterized syndromes include:
  - Opitz Syndrome
  - Marfan Syndrome
  - Ehlers-Danlos Syndrome
  - Velocardiofacial/DiGeorge Syndrome
  - Prader Willi/Angelman Syndrome

Opitz Syndrome

- Opitz Syndrome – X-linked dominant disorder characterized by midline defects including:
  - hypertelorism, cleft palate, laryngotracheal clefts and hypopigmentation.
  - A new gene has been identified (MID1), which is mutated in Opitz Syndrome patients.
  - Mid 1 encodes a member of B-box family of proteins, which contain protein-protein interaction domains implicated in fundamental processes such as body axis patterning and control of cell proliferation.
  - Association of MID 1 mutation with Opitz Syndrome suggests important role in midline development.

Child with Opitz Syndrome with Hypertelorism (wide set eyes)

Cleft Lip and Palate in Opitz Syndrome
**Hypoplastic larynx results in risk for aspiration pneumonia**

**Esophageal Hypoplasia Can Result in Severe Reflux**

**Hypospadias May Require Surgical Repair**

Multiple midline defects in Opitz make it an excellent example of hundreds single gene disorders affecting midline developmental field.

**Marfan Syndrome**

Autosomal dominant disorder due to a large number of different mutations in the gene encoding Fibrillin-1, a structural connective tissue protein

- Frequency approximately 1:3,000
- 100% penetrance but great variability of expressivity even within the same family
- 30% have no FMH, represent new Fibrillin-1 mutations
- DNA-based testing has recently become available that involves sequencing of the Fibrillin-1 gene but has a sensitivity of 90%

*The Diagnosis of Marfan Syndrome Remains Clinical!

**Diagnosis of Marfan Syndrome**

Clinical diagnostic criteria requires two of the following

- 4 major skeletal features:
  - Pectus deformity, scoliosis, dolichostenomelia, pes planus, elbow contractures, thumb or wrist sign or craniofacial features
- Diagnostic finding in one other system
  - Cardiovascular: aortic dilation or aneurysm
  - Ocular: ectopia lentis
- FMH of Marfan Syndrome
- Or Fibrillin-1 gene mutation
Variability of Marfan Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root dilatation</td>
<td>100</td>
</tr>
<tr>
<td>Arachnodactyly</td>
<td>98</td>
</tr>
<tr>
<td>Upper segment lower segment at base ≥ 50% for age</td>
<td>77</td>
</tr>
<tr>
<td>Vertical diameter</td>
<td>68</td>
</tr>
<tr>
<td>High, narrow palate</td>
<td>62</td>
</tr>
<tr>
<td>Height greater than 95th percentile for age</td>
<td>60</td>
</tr>
<tr>
<td>Hypertelorisis</td>
<td>56</td>
</tr>
<tr>
<td>Strabismus</td>
<td>44</td>
</tr>
<tr>
<td>Ptosis</td>
<td>40</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>32</td>
</tr>
<tr>
<td>Family History</td>
<td>24</td>
</tr>
<tr>
<td>Septal defect</td>
<td>22</td>
</tr>
<tr>
<td>Spontaneous cases (new mutations)</td>
<td>22</td>
</tr>
</tbody>
</table>

Variability of Marfan Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>70</td>
</tr>
<tr>
<td>Esophageal reflux</td>
<td>60</td>
</tr>
<tr>
<td>Hypertelorisis</td>
<td>44</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>98</td>
</tr>
<tr>
<td>Myopathic click only</td>
<td>30</td>
</tr>
<tr>
<td>Mitral and aortic regurgitation only</td>
<td>18</td>
</tr>
<tr>
<td>Aortic regurgitation only</td>
<td>10</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>6</td>
</tr>
<tr>
<td>Prosthetic aortic valve</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal echocardiogram</td>
<td>96</td>
</tr>
<tr>
<td>Aortic enlargement</td>
<td>89</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>48</td>
</tr>
</tbody>
</table>

Diagnosis of Marfan Syndrome

Is Life Saving

- Accurate diagnosis results in optimal management includes:
- Annual echocardiogram
- Activity restrictions
- β-Blockers prevent aortic dissection in multiple clinical trials

Medial Degeneration of the Aorta Leads to Dissection and Death

Ehlers Danlos Syndromes

- Due to abnormalities multiple different collagen genes
- Structural proteins critical to integrity of skin, joints, eye, and cardiovascular structures
Classification of the Ehlers-Danlos Syndromes

- **Type**
- **Clinical Manifestations**
- **Inheritance**

1. **Soft, velvety, marked hyperextensibility; easily bruising; unusual joint mobility; premature osteoarthritis; connective tissue weakness**
   - AD
2. **Unilateral hyperextensibility, marked hypermobility**
   - AD
3. **Markedly hyperextensible skin and joint hypermobility**
   - AD
4. **Skin, joint, and arterial anomalies**
   - AD
5. **Skin fragility and hyperextensibility, joint hypermobility**
   - AD
6. **Skin fragility and joint hypermobility**
   - AD
7. **Skin fragility, joint hypermobility, vascular anomalies**
   - AD

Ten different types of EDS are due to mutations in different collagens genes or collagen modifying genes—most of which are not characterized.

---

**Ehlers-Danlos Syndromes**

- **Skin & joint hypermobility in type 1**
- **Mutiloscopy in type 1**

---

**Derangement of Collagens in Ehlers-Danlos Syndromes**

- **Type I Skin**
- **Type III Skin**
- **Type IV Skin**
- **Type V Skin**
- **Type VI Skin**

---

**Skin hyperextensibility and fragility in type I**

---

**Ocular Fragility in type VI**
**Microdeletion Syndromes**

- Have recognizable patterns of malformation
- Result from small chromosomal microdeletions
- Represent the impact of deletion of several contiguous genes or one critical gene
- Require special techniques (FISH or microarray analysis) to detect

**Microdeletion Syndromes**

- Can be passed on in a dominant fashion
- Usually are de novo/occurred during gametogenesis
- Some like Prader-Willi/Angelman Beckwith – Wiedermann and retinoblastoma involve imprinting
- Imprinting involves epigenetic changes including differential methylation between males and females

**Chromosome 22q11.2 Microdeletion: Clinical Features**

- Craniofacial
  - Cleft of secondary palate
  - Retrognathia
  - Prominent nose with squared nasal root
  - Minor anomalies of the ear
- Cardiovascular
  - Conotruncal involving the aortic arch, including Tetrology of Fallot

**Chromosome 22q11.2 Microdeletion: Clinical Features**

- Central nervous system
  - Learning disability
  - Hearing loss
  - Hypotonia
- Endocrinologic/Immunologic
  - Hypoplastic adenoids
  - Parathyroid dysfunction
  - Absent or small thymus
**Chromosome 22q11.2 Microdeletion:**
- Velocardiofacial syndrome
- DiGeorge syndrome
- Isolated conotruncal cardiac anomalies
- Tbx1 is the candidate gene - in mouse knockouts results in conotruncal cardiac defects absent thymus, cleft palate, parathyroid hypoplasia

**CATCH 22:** Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia

---

**Fish Test Results**

![Fish Test Results](image)

- Normal
- 22q Deletion

46,XY,i del(22)(q11.2q11.2)

---

**Velocardiofacial syndrome:**
Two affected older sisters with unaffected younger sister. Both have learning disabilities, prominent nasal bridge, narrow eyes, and soft cleft palate. One had hypoplasia of the ears.

---

**Prader-Willi & Angelman Syndromes**

**Prader-Willi**
- 70% microdeletions of 15q11.2 (paternal)
- 25% uniparental disomy (maternal)
- **Prader-Willi=no Papa**
- 5% imprinting defect of RnRNA gene

**Angelman Syndrome**
- 65-70% have microdeletion (maternal)
- 3-7% have UPD (paternal)
- 10% have mutation in UBE3A gene
TRISOMIC CONCEPTION (most non-viable)

UPD  DISOMIC FETUS  Normal

Prader-Willi & Angelman Syndromes

Prader-Willi Syndrome

Hyptonia, mild NR, hypophagia, morbid obesity, small striae and hands, and hypogenitalism

Angelman Syndrome

- Absent speech
- Intractable seizures
- Puppet-like gait
- Inappropriate laugh
- Profound mental retardation

Genomic Imprinting

- Results in different phenotypes if mutation is inherited from male vs. female parent
- Mechanism involves differential methylation of chromosome 15q11.2
- There is a growing number of genetic conditions where imprinting seems to play a role
- Testing for methylation abnormalities has been developed for some of these disorders

LAST SLIDE
Williams Syndrome

7q11 microdeletion

De Lups G, Valera MC, Jurado LA
Servicio de Genetica, Hospital Universitario La Paz, Madrid, Spain

Williams syndrome (WS) is a neurodevelopmental disorder affecting several systems and characterized by characteristic facial features and cardiovascular abnormalities. It is caused by a deletion of the chromosomal region 7q11.23. The deletion is transmitted from an affected parent to the offspring. The severity of the disorder varies among affected individuals. The face is usually symmetrical and possesses a long, narrow face with a small nose, a high, narrow palate, and a protruding jaw. The cardiovascular abnormalities include aortic stenosis, coarctation of the aorta, and patent ductus arteriosus. The WS associated with heart defects (WS-ASD) is less common than WS without heart defects. The WS-ASD has a higher incidence of heart defects and a higher mortality rate. The typical features of WS include a high, narrow palate, a small jaw, and a long, narrow face. The WS-ASD is associated with a higher incidence of heart defects and a higher mortality rate.

Medical Problems in Children with Williams Syndrome

<table>
<thead>
<tr>
<th>Problem</th>
<th>Percentage (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart problems</td>
<td>47</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>97</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>90</td>
</tr>
<tr>
<td>Musculoskeletal problems</td>
<td>48</td>
</tr>
<tr>
<td>Neurological problems</td>
<td>45</td>
</tr>
<tr>
<td>Otological problems</td>
<td>47</td>
</tr>
<tr>
<td>Dental problems</td>
<td>49</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>33</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8</td>
</tr>
</tbody>
</table>

Medical Problems in Children with Williams Syndrome

<table>
<thead>
<tr>
<th>Problem</th>
<th>Percentage (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defects</td>
<td>47</td>
</tr>
<tr>
<td>Ventricular septal defects</td>
<td>34</td>
</tr>
<tr>
<td>Craniofacial defects</td>
<td>47</td>
</tr>
<tr>
<td>Musculoskeletal problems</td>
<td>47</td>
</tr>
<tr>
<td>Neurological problems</td>
<td>47</td>
</tr>
<tr>
<td>Otological problems</td>
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<td>33</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8</td>
</tr>
</tbody>
</table>

Nonchromosomal Malformation Syndromes

- Single gene conditions can have any pattern of inheritance.
- Single gene conditions are models for the impact of a specific genetic change on growth and development.
- There are greater than 5000 catalogued, genes have been isolated and characterized for 1000.
Malformations in Patients with Opitz Syndrome

- Tongue
- Bifid uvula
- Epiglottis
- Hypoplastic larynx
- Esophagus
- Carina (high bifurcation)

Technology Used for Detection of Microdeletion: FISH

Fluorescence in Situ Hybridization (FISH) allows detection of even single gene deletion and duplication

DNA Probe Technology

- DNA molecule
- Target DNA
- DNA probe
- Hybridization
SET 4

GENETIC AND PEDIATRIC DISEASE SLIDES

Christine A. Weaver, M.D., PhD.
Genetic Malformation Syndromes
Chromosomal
Christine A. Weaver, M.D., Ph.D.

Chromosomal Malformation Syndromes
- Are associated with alterations in chromosome # or structure observable by high resolution chromosome evaluation
- Represent extensive and potentially profound genetic changes
- Tend to be associated with a very high rate of malformation, growth failure and developmental delay
- Are common—1/250 children are born with a clinically significant chromosomal abnormality

Chromosomal Disorders
- Developmental delay
- Growth failure
- Malformation
- The indications for a Chromosome Analysis

Chromosome Evaluation
- Visualization of the genetic material by Light Microscopy
- Allows detection of only gross rearrangements
- Can be performed on any culturable cell type

High Resolution Chromosome Evaluation
- Culture cells (leukocytes, amniocytes, CVS, Bone marrow)
- Arrest cells in prometaphase
- Stain Chromosomes with giemsa to produce bands
- Observe under high power light microscopy

High Resolution Chromosome Evaluation
- Photograph chromosomes and arrange them in order from the longest to shortest (karyotypes)
- Total # of bands observed determines the level of resolution (high resolution = 550 bands)
- The higher the resolution the higher the likelihood of picking up subtle changes
Chromosome Nomenclature

- Internationally Standardized
- Total #, sex complement, rearrangement with bands
  - Examples:
    - 46, XY, del(22)q11.2 – for male with DiGeorge Syndrome
    - 45X/47X+21 – for Mosaic, male with Down Syndrome
    - 46,X; 46,X,i(Xq); 46X(X) – for Turner Syndrome
  - p and q refer to short arm and long arms. Bands are numbered from the centromere to telomere.
  - i-refers to isochromosome-contains duplicate material on both sides of centromere from transverse division
  - r-refers to ring chromosome, which represents a partial deletion forming after loss of telomeres

Cytogenetic Terms

- Polyploidy-having more than two complete chromosome complements (eg. 69 is triploidy)
- Inversion-two breaks with subsequent rotation and fusion of the involved segment
- Reciprocal translocation exchange between two chromosomes, rate of carrier is 1/30
- Robertsonian involves the combining of the long arms two small acrocentric translocation, rate of carrier is 1/1000

Robertsonian 14:21 Translocation Carrier

X-Chromosome Demonstrating Cytogenic Nomenclature

Duchenne muscular dystrophy gene is at Xp21.1

Have a 1 in 3 risk of having a child with Trisomy 21 – Down Syndrome
Chromosome painting is a recent advance used to better identify translocations.

FISH Analysis Allows Detection of Small Deletion and Duplication and is also used for more rapid detection of trisomies in newborns.

Autosomal Aneuploidy
- Deletion and duplication results in partial chromosomal monosomy or trisomy and often results in very significant medical risks
- Full monosomy—not viable
- Full trisomy—have limited viability
- Trisomy 13, 18 and 21

Chromosome Conditions
- Autosomal abnormalities
  - Trisomy 21 (Down Syndrome) 1 in 700 births
  - Trisomy 18 1 in 7,000 births
  - Trisomy 13 1 in 12,000 births

Common Autosomal Trisomies
- Trisomy 13, Trisomy 18 and Trisomy 21
- Associated with intrauterine growth retardation
- Very high rate of malformation
- High rate of developmental delay
- High mortality rate—90% in first year for Trisomy 13 & 18
Rate of Malformation in Trisomy 21 Down Syndrome

<table>
<thead>
<tr>
<th>Findings</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial</td>
<td>43</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>31</td>
</tr>
<tr>
<td>Hypertelorhin</td>
<td>26</td>
</tr>
<tr>
<td>Exophthalmia</td>
<td>22</td>
</tr>
<tr>
<td>Staphylia</td>
<td>22</td>
</tr>
<tr>
<td>Oligophalange</td>
<td>17</td>
</tr>
<tr>
<td>Urogenital</td>
<td>12</td>
</tr>
<tr>
<td>Genital</td>
<td>10</td>
</tr>
<tr>
<td>Cryptorchidity</td>
<td>10</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>8</td>
</tr>
<tr>
<td>Esophageal</td>
<td>8</td>
</tr>
<tr>
<td>Tracheoesophageal</td>
<td>5</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>3</td>
</tr>
<tr>
<td>Diaphragmatic</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
</tr>
</tbody>
</table>

Rate of Malformations in Trisomy 21

<table>
<thead>
<tr>
<th>Findings</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>19</td>
</tr>
<tr>
<td>Pterygium</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary cornucomus</td>
<td>3</td>
</tr>
<tr>
<td>Corneal high pressure</td>
<td>11</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>4</td>
</tr>
<tr>
<td>Oligophalange</td>
<td>10</td>
</tr>
<tr>
<td>Urogenital</td>
<td>8</td>
</tr>
<tr>
<td>Cryptorchidity</td>
<td>8</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>5</td>
</tr>
<tr>
<td>Esophageal</td>
<td>5</td>
</tr>
<tr>
<td>Tracheoesophageal</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>2</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
</tr>
<tr>
<td>Brainstem</td>
<td>1</td>
</tr>
</tbody>
</table>

Deletions and Duplications

- Represent partial monosomy or trisomy visible by chromosome evaluations
- Vary tremendously in their associated medical risks
- Risks can be predicted based on case series
- Correlate as much to chromosome location as size
- Often have critical bands that have been identified
**Common Deletion Syndromes**

- Deletion 4p Syndrome (Wolf-Hirschhorn) del 4p16.3
- Deletion 5p Syndrome (Cri-du-chat) del 5p15.2

Both associated with growth failure, mental retardation and a high risk for malformation including:
- Cleft lip and palate (in 25%)
- Cardiac Defects (in 50%)
- Characteristic Craniofacial Dysmorphism

**Sex Chromosomal Aneuploidy**

- Associated with a lower rate of medical concerns
- Lower rate of developmental delay and malformation
- Problems relating to sexual development and fertility
- Often do not present until after puberty, eg. 47, XXY
- Multiply X females and 47, XYY males have no phenotype

**Rates of Sex Chromosome Abnormalities**

- Klinefelter syndrome: 1 in 1000 males
- XYY syndrome: 1 in 1000 males
- Triple X syndrome: 1 in 1000 females
- Turner syndrome: 1 in 2000-5000 females
Klinefelter Syndrome
47, XXY and Variants eq. 48XXXY and Mosaic Forms
- One of the most common causes of hypogonadism in men
- Generally not identifiable before puberty
- Characteristics include primary hypogonadism, eunuchoid habitus, gynecomastia, small atrophic testes & small penis
- Testicular tubules are atrophied and replaced by hyaline
- Not associated with a significant risk malformation

Rates of Malformation in Turner Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage or Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachydactyly</td>
<td>30%</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>25%</td>
</tr>
<tr>
<td>Deletion</td>
<td>10%</td>
</tr>
<tr>
<td>Heart defects</td>
<td>10%</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>10%</td>
</tr>
<tr>
<td>Renal anomalies</td>
<td>10%</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>10%</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>10%</td>
</tr>
<tr>
<td>Hystoplasticism</td>
<td>5%</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>5%</td>
</tr>
<tr>
<td>Club foot</td>
<td>5%</td>
</tr>
<tr>
<td>Conotruncal defect</td>
<td>5%</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>5%</td>
</tr>
</tbody>
</table>

Klinefelter Syndrome

Rates of Malformation in Turner Syndrome

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<td>5%</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>5%</td>
</tr>
</tbody>
</table>
### Comparison of Trisomy 13 & 18 Syndromes

*Features Common to Both Syndromes*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trisomy 13 Syndrome (%)</th>
<th>Trisomy 18 Syndrome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac defects</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>Occipital plagiocephaly</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>Mosaic figure</td>
<td>86</td>
<td>70</td>
</tr>
<tr>
<td>Prenatal death</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>High arched palate</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>88</td>
<td>60</td>
</tr>
<tr>
<td>Hemihypoplasia</td>
<td>97</td>
<td>60</td>
</tr>
<tr>
<td>Ureteral anomaly</td>
<td>93</td>
<td>67</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>90</td>
<td>33</td>
</tr>
</tbody>
</table>

### A Comparison of Trisomy 13 & Trisomy 18

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trisomy 13</th>
<th>Trisomy 18</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal heart sound</td>
<td>87</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>94</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>99</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Occipital plagiocephaly</td>
<td>73</td>
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</tr>
<tr>
<td>Oligohydramnios</td>
<td>90</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>
Hall's 10 Cardinal Features Of Trisomy 21 Syndrome in the Newborn

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripod ankle</td>
<td>85%</td>
</tr>
<tr>
<td>Poor Moro reflex</td>
<td>85%</td>
</tr>
<tr>
<td>Hyporeflexibility of joints</td>
<td>80%</td>
</tr>
<tr>
<td>Oligosyndactyly of the toes</td>
<td>80%</td>
</tr>
<tr>
<td>Flat facial profile</td>
<td>55%</td>
</tr>
<tr>
<td>Hip contracturesal of adductores</td>
<td>50%</td>
</tr>
<tr>
<td>Ocular hypertelorism</td>
<td>40%</td>
</tr>
<tr>
<td>Ophthalmologic abnormalities of the fifth toe</td>
<td>40%</td>
</tr>
<tr>
<td>Single Palmar crease</td>
<td>95%</td>
</tr>
</tbody>
</table>

[Diagram of chromosomes]
Metabolic Disorders

Inborn Errors of Metabolism

Christine A. Weaver, M.D. Ph.D.

Metabolic Disorders

- Taken as a whole are common
- There are over 800 defined – the number is growing
- As is our understanding and ability to diagnose and treat
- Diagnosis is critical as treatment can prevent potentially fatal complications

Inborn Errors of Metabolism

Can be roughly divided into two groups based on cellular localization and clinical presentation

- Group 1
  - Predominantly cytoplasmic
  - Catabolism of organic acids, amino acids, fatty acids and carbohydrates
  - Present acutely after a brief asymptomatic period
  - Presentation may include coma, respiratory distress, hypotonia, seizures, poor
- Group 2
  - Predominantly organelar
  - Lysosomal storage and mitochondrial
  - Have a more chronic course
  - Often do not present until late childhood or adulthood

Metabolic Disorders

- Due to inherited reduced activities of proteins involved in the synthesis, breakdown or transport of amino acids, organic acids, fats, carbohydrates and complex macromolecules.
- Most are autosomal recessive due to mutations that result in reduced enzyme activity or reduced amount of enzyme.
- Pathogenesis may include: accumulation of a toxic intermediate, reduced amount of a necessary end product or activation of an alternate pathway.

Inborn Errors in Metabolism

- Group 1 - Cytoplasmic
  - Organic acidoses
    - Maple syrup urine disease
    - Methylmalonic acidemia
    - Biotinidase deficiency
    - Propionyl-CoA carboxylase deficiency
    - Linear mitochondrial disorders
- Group 2 - Lysosomal and mitochondrial
  - Phenylketonuria
  - Urea cycle disorders
  - Homocystinuria
- Carbohydrate metabolic disorders
  - Galactosemia
  - Glycogen storage disease
Inborn Errors in Metabolism

- Group 2 - Organellar
  - Lysosomal storage disorders
  - Mitochondrial disorders (respiratory chain)

Disorders of Metabolism

Organic and Amino Acids

- Many involve the accumulation of organic acid, acidaosis, low glucose and elevated NH₃
- Present with anion gap metabolic acidosis
- Results in altered mental status/lethargy in early childhood

Metabolic Disorders-Testing

- There are two different types of testing for metabolic conditions-screening tests and disease-specific diagnostic testing.

- Screening tests allow you to detect the presence of a particular class of conditions and includes:
  - Serum electrolytes (looking for evidence of acidosis), glucose & ammonia levels are also screening tests
  - Blood and urine amino acids for disorders of amino acid metabolism
  - Urine organic acids for disorders of organic metabolism acid
  - Acylcarnitine profile for disorders of fatty acid
  - Blood lactate and pyruvate for disorders of carbonic acid metabolism and mitochondrial disorders

Metabolic Disorders of Amino Acid Metabolism

- Maple syrup urine disease
- Methylmalonic acidemia
- Urea cycle disorders
- Homocystinuria
- Phenylketonuria
Clinical Presentation of Amino Acid Disorders

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Abnormal Amino Acid</th>
<th>Presumed Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute neurologic deficit with convulsions</td>
<td>Tyrosine, Cysteine</td>
<td>Organic Acid Disorders</td>
</tr>
<tr>
<td>Acute neurologic deficit with hypoglycemia</td>
<td>Arginine, Ornithine</td>
<td>Urea cycle disorders</td>
</tr>
<tr>
<td>Heterozygous, growth retardation</td>
<td>Heterozygous</td>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Severe, developmental delay</td>
<td>Phenylalanine</td>
<td>Phenylketonuria</td>
</tr>
</tbody>
</table>

Homocystinuria

Elevated homocysteine levels affect collagen results in a Marfanoid habitus, ectopic lenses, mental retardation and strokes.

Disorders Of Amino Acid Metabolism
Phenylketonuria

- There are two forms of phenylketonuria
- Most common form involves a deficiency of phenylalanine hydroxylase
- Rare form involves biotinidase deficiency
- Treatment of the two forms is different and is effective

Disorders Of Amino Acid Metabolism
Phenylketonuria

- Is an autosomal recessive condition resulting from the accumulation of phenylalanine
- Phenylalanine is neurotoxic
- Results in rapid decline of IQ to 50 in first year if untreated due to neurotransmitter affects
- Newborn screening is done in all states

Phenylalanine Hydroxylase System

\[ \text{Phenylalanine} + \text{O}_2 \rightarrow \text{Tyrosine} + \text{H}_2\text{O} \]
\[ \text{Phenylalanine} + \text{O}_2 \rightarrow \text{Tetrahydrobiopterin (BH}_4) + \text{NAD} \]
\[ \text{Phenylalanine} + \text{O}_2 \rightarrow \text{Dihydrobiopterin (BH}_2) + \text{NADH} \]

- Treatment of classic PKU involves dietary restriction of phenylalanine
- Treatment of biotinidase deficiency is biotin which must be measured to determine its presence

Disorders Of Carbohydrate Metabolism
Galactosemia
Glycogen Storage Disorders
Disorders of Carbohydrate Metabolism

Galactosemia

- The most prevalent disorder of carbohydrate metabolism
- Due to galactose-1-phosphate uridyl transferase deficiency
- Presents in newborn period after lactose exposure in milk
- Vomiting, failure to grow and liver failure
- Complications are preventable with galactose-free diet
- Diagnosis is based on RBC G-1-P uridyl transferase level
- Newborn screening is available in all states

Findings include: liver failure with lactic acidosis & coagulopathy, hemolysis, renal tubular dysfunction with proteinuria
- Neutrophil dysfunction results in infection - *E. Coli* sepsis
- If not treated by galactose dietary restriction early mortality is very high
- Histologically liver shows hepatocellular loss, with extensive fibrosis
- At high power cholestasis with ductal proliferation, steatosis and extensive fibrosis

Liver in patient dying of galactosemia: hepatocellular loss, cholestasis, steatosis due to activation of FA production and fibrosis

Disorders of Carbohydrate Metabolism

Glycogen Storage Disorders

- Disturbance in the breakdown or synthesis of glycogen
- There are many enzymes regulating glycolysis and many different glycogen storage diseases
- They can be generally categorized into hepatic and myopathic forms based on the location of the involved enzyme which determines the organs affected
- Complex carbohydrate diet helps control complications
- Enzyme replacement is available

Principle Groups of Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Pathogenesis</th>
<th>Laboratory Findings</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Liver failure, hypoglycemia, fatigue, convulsions, mental retardation, skin rash</td>
<td>Deficiency of glucose-6-phosphatase</td>
<td>Reduced glucose-6-phosphate, increased lactate</td>
<td>Hyponatremia, hyperkalemia</td>
</tr>
<tr>
<td>Type II</td>
<td>Liver, heart, skeletal muscle failure, hypoglycemia, mental retardation, rhabdomyolysis</td>
<td>Deficiency of glycogen phosphorylase</td>
<td>Decreased glycogen, increased lactate</td>
<td>Myopathy, cardiomyopathy</td>
</tr>
<tr>
<td>Type III</td>
<td>Leber hereditary optic neuropathy, seizures, ataxia, hypoglycemia, failure to thrive</td>
<td>Deficiency of respiratory chain enzymes</td>
<td>Variable, elevated lactate</td>
<td>Visual disturbances, growth retardation</td>
</tr>
<tr>
<td>Type IV</td>
<td>Myopathy, hypoglycemia, lactic acidosis, rhabdomyolysis</td>
<td>Deficiency of cytoplasmic muscle proteins</td>
<td>Elevated lactate, muscle enzymes</td>
<td>Skeletal muscle weakness</td>
</tr>
<tr>
<td>Type V</td>
<td>McArdle syndrome, exercise intolerance, muscle cramps, myoglobinuria</td>
<td>Deficiency of phosphorylase</td>
<td>Decreased glycogen, increased lactate</td>
<td>Myoglobinuria, rhabdomyolysis</td>
</tr>
</tbody>
</table>

Principle Groups of Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Specific Type</th>
<th>Enzyme Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Type I</td>
<td>McArdle disease</td>
<td>Muscle phosphorylase</td>
</tr>
<tr>
<td>Type II</td>
<td>McArdle syndrome</td>
<td>Muscle phosphorylase</td>
</tr>
<tr>
<td>Type III</td>
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</tr>
</tbody>
</table>
Pathology M – Genetic & Pediatric Disease

**Lysosomal Storage Disorders**

- Due to dysfunction of acid hydroxylases, required for the breakdown of complex macromolecules in lysosomes
- Categorized according to the accumulated product
- Complications are determined by both where the product is produced and where it is broken down

**Lysosomal Storage Disorders**

- Lysosomal acid hydrodases are very complex enzymes
- All require adequate targeting to the lysosome
- Some involve disturbance of export of digested product from lysosome
- Many require enzyme and/or substrate activators
- Disturbance in any of these can result in disease
- Measurement of accumulated urine products may be helpful for many

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme Deficiency</th>
<th>Major Accumulating Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen storage</td>
<td>pH 2-6 (Fanconi disease)</td>
<td>Glucose</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>α-L-iduronidase</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Niemann-Pick A</td>
<td>H2O2 hydrolysis</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Niemann-Pick B</td>
<td>α-L-iduronidase</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Hurler’s disease</td>
<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
<td>Glucosylceramide</td>
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<tr>
<td>Morquio A disease</td>
<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Morquio B disease</td>
<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
<td>Glucosylceramide</td>
</tr>
<tr>
<td>Hunter’s disease</td>
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<td>Glucosylceramide</td>
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<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
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<td>Acid sphingomyelases, acid ceramidase, sphingomyelin</td>
<td>Glucosylceramide</td>
</tr>
</tbody>
</table>
Lysosomal Storage Disorders

Most common that you need to know:
- Tay-Sachs Disease
- Gaucher Disease
- Niemann-Pick Disease
- Hunter & Hurler Syndromes

Lysosomal Storage Disorders
Tay-Sachs Disease

- GM2 Gangliosidosis accumulates
- Ashkenazi Jewish predominance
- Some involve disturbance of export of digested product of the lysosomes
- Due to deficiency of Hexosaminidase A
- Activity requires a complex of proteins
- Hex A, Hex B and Activator protein deficiencies cause GM2 Gangliosidosis

GM2 Gangliosidoses

- Most affects function in central nervous system
- Developmental arrest around 6 mos.
- Progressive cognitive decline
- Vegetative state & death by 2-3 years
- Cherry red spot in macula due to GM2 in retina
- Large lipid-engorged neurons

Brain in Tay-Sachs disease

Shows massive neuronal loss throughout all areas
Gaucher Disease
- Glucocerebrosidase deficiency
- Glucocerebrosides accumulate in phagocytes
- Type 1 - hepatosplenomegaly, hypersplenism, bone pain
- Type 2 & 3 have CNS involvement with developmental decline, due to more severe mutations
- Type 1 is treatable with enzyme replacement which is the new standard of care and reverses most disease
- Gaucher cells are diagnostic when seen in bone marrow with lipid-filled lysosomes

Niemann-Pick Disease
- Sphingomyelinase deficiency
- Ashkenazi Jewish predominance
- Type A - severe CNS, visceral-wasting & death by 3rd year
- Type B - organomegaly but no CNS, live to adulthood
- Bone marrow transplantation is standard of care
- Accumulation of foamy-appearing sphingomyelin lipid in phagocytic cells

Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme Deficiency</th>
<th>Metabolite</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I, Hunter</td>
<td>alpha-L-iduronidase</td>
<td>dermatan sulphate</td>
<td>enzyme replacement</td>
</tr>
<tr>
<td>MPS II, Hunter</td>
<td>beta-D-glucuronidase</td>
<td>mucopolysaccharide</td>
<td>enzyme replacement</td>
</tr>
</tbody>
</table>

Clinical And Pathological Ultrastructure Of Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Manifestation</th>
<th>Ultrastructure of Stored Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS type I, Hunter</td>
<td>Teicho: short stature, developmental delay, joint deformities, hepatic and splenic enlargement, heart defects</td>
<td>Has teratoma mesenchymal cells in bone, cartilage, and skin</td>
</tr>
<tr>
<td>MPS type II, Hunter</td>
<td>Short stature, short neck, joint contractures, convolutional brain, and scalp defects, corneal clouding</td>
<td>Has teratoma mesenchymal cells in bone, cartilage, and skin</td>
</tr>
<tr>
<td>MPS type V, Hunter</td>
<td>Short stature, short neck, joint contractures, corneal clouding, and skin defects</td>
<td>Has teratoma mesenchymal cells in bone, cartilage, and skin</td>
</tr>
</tbody>
</table>
Mitochondrial Disorders

- Classically involve mutations in mitochondrial DNA
- Follow a maternal pattern of inheritance
- Highly variable with regard to penetrance and expressivity based on the variability in tissue distribution of abnormal mitochondria

Mitochondrial Syndromes Presenting in Childhood to Adult

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Most Common Clinical Presentation</th>
<th>Other Clinical Features</th>
<th>mt DNA Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETFE, PEO, PEOE</td>
<td>Neurologic, Ophthalmologic, Cardiac</td>
<td>Enzymatic deficiency</td>
<td>Deletion of mt DNA</td>
</tr>
<tr>
<td>D. Myelomeningocele</td>
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</tr>
</tbody>
</table>

Mitochondrial Disorders

- Involve global abnormality in aerobic metabolism
- Growth impairment, development delay & multiple organ dysfunction for tissue dependent on aerobic metabolism
- Common abnormalities include myoclonic seizures & myopathy
- Elevated blood lactate and pyruvate
- Can actually have any pattern of inheritance (90% of proteins are encoded in nucleus)
Inborn Errors in Metabolism

- Group 1 (cytoplasmic)
  - Aminoacidopathies
  - Phenylketonuria
  - Urea Cycle disorders
  - Homocystinuria
  - Nonketotic hyperglycinemia
  - Carbohydrate metabolic disorders
    - Galectosemia
    - Glycogen storage disease

- Group 2 (organellar)
  - Lysosomal storage disorders
  - Mitochondrial disorders (respiratory chain)
  - Peroxisomal disorders
  - Endoplasmic reticulum disorders
    - A-1-antitrypsin deficiency
    - Carbohydrate deficient glycoprotein disorder
  - Cell membrane transport disorders
    - Cystic fibrosis
    - Lysinuric protein intolerance

Metabolic Acidosis

- Due to accumulation of an abnormal organic acid (accumulated product)
- Involves an anion gap metabolic acidosis
- Calculated based on Na, K, Cl and CO₂ in ABG
- Anion gap = (Na + K) - (Cl + CO₂)
- Confirmed by Arterial Blood Gas (ABG)
Genetic and Pediatric Disease - Overview

The following is an overview of genetic disease, patterns of inheritance, recent advancements in genetic testing, congenital abnormalities and Pediatric Disease.

Genetic disorders are classified as single gene, multi-factorial or chromosomal.

Single gene or Mendelian disorders generally have a simple predictable pattern of inheritance within a family and are conferred by alteration in the structure of a single gene. Multifactorial disorders are due to the interaction of multiple genes and the environment and are also called polygenic or multigenic. Examples of pediatric multigenic disorders include: isolated malformations like cleft palate, congenital heart disease and congenital pyloric stenosis. The rate of a single gene disorder in a family is usually predictable based on the pattern of inheritance and carrier frequency in the population. The rate of multifactorial conditions within a family can be predicted based on empiric population data, given the relationship of the individual to the affected family member and observed recurrence risks for specific malformations.

Genetic disease is very common - 1/20 children are born with a specific clinically significant genetic disorder. 1/100 in the population at large have a single gene disorder.

Rate of multifactorial disorders is even higher (due to the interaction of multiple gene mutations and environment). It is estimated that 67/100 individuals in the U.S. will develop multigenic disorders in their life time. Common multigenic disorders of adult onset include: NIDDM, HTN and CAD. But, in point of fact probably all disease has a genetic component.

Our ability to determine the genetic contribution to any specific disease has traditionally been based on twin and other population studies. But the accuracy of determining the genetic contribution to any particular disease is expected to dramatically improve with the isolation and characterization of gene mutations that predispose to disease, due to advancements from Human Genome research.

Single gene/Mendelian disorders are traditionally characterized by their patterns of inheritance and the primary organ system involved.

However, genetic conditions are multisystem and progressive and best understood in the context of the underlying genetic abnormality.

Autosomal dominant conditions are characterized by variability in expressivity and penetrance. Expressivity refers to the spectrum of medical problems which can be seen in individuals with a particular condition. Penetrance refers to the % of individuals with a causal gene mutation that have the condition. The variable nature of autosomal dominant conditions is related to the molecular mechanisms that determine their dominant nature. These mechanisms involve either an altered gene product that has a gain
in function which has a detrimental effect on other gene products or an altered gene product that interferes with the function of the normal gene product (a dominant negative effect). In either case the outcome is heavily dependent on the interaction of the altered gene product with other cellular factors and these other cellular factors vary from individual to individual. This is in contrast to recessive conditions where the molecular mechanism that causes disease is generally due to loss in function of the gene product.

Neurofibromatosis type 1 (NF 1) is an excellent example of an autosomal dominant condition with highly variable expressivity. NF 1 is due to mutation in the Neurofibromin gene which encodes a Ras-related GTPase that regulates the differentiation of neural crest cells and results in a high risk for the formation of multiple benign hamartoma (cutaneous and plexiform neurofibroma, café au lait spots, axillary freckling, and Lisch nodules of the iris), as well as neural-crest derived malignancies (optic glioma, schwannoma, and pheochromocytoma). In NF1, it is not uncommon for a severely affected child with multiple neurofibroma and café au lait spots, scoliosis or another boney dysplasia and learning disabilities to have a previously unrecognized parent with only a few café au lait spots and axillary freckling.

Age of onset for many autosomal dominant conditions is often delayed, and there is a subset which represent new mutations, occurring during gametogenesis, where no family history can be identified. However, there are exceptions to every rule and in genetics exceptions to the rule are common. Take for example, Achondroplasia, an autosomal dominant skeletal dysplasia which is due to mutation in the Fibroblast Growth Factor receptor-3 gene. Achondroplasia has early onset (all characteristics being apparent at birth), very consistent expressivity and 100% penetrance.

For any autosomal dominant disorder, if there is no family history and the condition appears to be due to a new mutation which occurred during gametogenesis, there is a chance that one of the parents might be the carrier of multiple germline mutations, a condition called gonadal mosaicism. In this case, the risk for recurrence of having another affected child is significantly higher than if gonadal mosaicism is not present, but it is not accurately predictable. However, in some AD conditions like the neonatal lethal form of Osteogenesis imperfecta (Type IV) in which 100% of cases are due to new mutations, the rate of gonadal mosaicism and rate of recurrence have been determined.

In autosomal recessive disorders the expression of the defect tends to be more uniform. Complete penetrance is common and onset is frequently early in life. This is due to the fact that autosomal recessive conditions are generally due to loss of function of the gene product. Cystic fibrosis is an excellent example of a well characterized autosomal recessive condition which usually has early onset and complete penetrance. Cystic fibrosis is due to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which results in defective regulation of epithelial chloride transport in exocrine glands. Decreased resorption of chloride in sweat glands results increased sweat chloride; and decreased chloride secretion in airways and in the exocrine pancreas, with increased sodium and water resorption, results in thickened mucous secretions and mucous plugging of ducts with resultant pancreatic insufficiency and related growth failure, male infertility, hepatic cirrhosis and in the lung bronchiectasis and recurrent infection and pulmonary insufficiency. There are hundreds of mutations in the CFTR gene that result in cystic fibrosis. The most common (F508) is a three nucleotide deletion results in defective protein folding and degradation before the CFTR protein reaches the membrane. Patients homozygous for the F508 mutation tend to have severe disease. However, there are other patients with other genotypes that result in an abnormal but partially functional CFTR protein who have much less severe complications including in some cases only recurrent sinusitis. In general, the severity of disease correlates to sweat chloride levels. A great deal of work is being done to determine genotype phenotype correlations. There are specific mutations that are known to incur isolated congenital absence of the vas deferens and related azoospermia.
X-linked recessive disorders are transmitted from unaffected females to affected males. Females rarely express the condition (unless they have unfavorable X-inactivation). Affected males do not pass the condition to their sons and all daughters are carriers.

Fragile X syndrome, the most common cause of inherited developmental delay is an unusual case of not truly X-linked recessive but semi-dominant as half of females with full mutation are affected. It is representative of diseases associated with unstable nucleotide repeat expansions where the unaffected parent is the carrier of a premutation and can have an affected child if the premutation undergoes meiotic expansion to a full mutation (in the carrier female).

Multiple neurologic and neuromuscular diseases have been identified with variable patterns of inheritance which involve unstable nucleotide repeat expansions including: Fragile X syndrome (FMR1 gene, XD), myotonic dystrophy, (myotonin protein kinase, AD) Fredreich ataxia (Frataxin gene, AR) progressive myoclonus epilepsy (cystatin B, AR), spinobulbar muscular atrophy/Kennedy disease (androgen receptor, XR), Huntington Disease (Huntington gene, AD), and spinocerebellar ataxia type 1 (ataxin 2 gene, AD). The last three involve mutations in the coding sequence, the first four are in non-coding regions. In some cases, the affect on gene function is known as in Fragile X syndrome where expansion results in hypermethylation of the region and the gene is turned off. The point (number of repeats) at which the premutation becomes unstable and undergoes meiotic expansion to a full mutation varies between conditions, but the cutoff is between 40 and 200.

Two other unusual patterns of inheritance are that of maternal inheritance of mitochondrial-encoded genes and that involving genomic imprinting.

Disorders involving mutations in genes encoded in the mitochondria follow a pattern of maternal inheritance where sometimes affected mothers pass the condition with unpredictable frequency to both affected sons and daughters. However, the disease is not passed on by affected fathers as mitochondria are passed in oogenesis only. Disorders involving mitochondria) genes tend to be highly variable with regard to expressivity as well as penetrance. This is related in part to variable tissue distribution of abnormal mitochondria.

Finally, the phenomena of imprinting is known to occur for only a few disorders (including Prader-Willi and Angelman Syndromes) where in rare families these conditions are passed from parent to child. If the genetic change (deletion of chromosome 15g1 1) is inherited from the father, it results in Prader-Willi; if inherited from the mother, it results in Angelman syndrome-markedly different conditions. Genomic imprinting is believed to be due to gene inactivation which is different between males and females. Mechanism of imprinting is not completely understood but appears to involve differential DNA methylation.

Recent advancements in genetic testing are rapidly improving the accuracy of genetic diagnosis, including advancements in all areas of supportive diagnostic testing for both chromosomal and nonchromosomal disorders. There are basically two different types of supportive diagnostic testing for genetic conditions: screening tests and disease specific testing. Screening tests allow you to ask the question of whether a child might have a particular class of conditions, for instance a chromosomal disorder (which would require a high resolution chromosome evaluation) or a particular class of metabolic disorder (which would require screening biochemical testing to look for the presence of metabolites in the involved pathways, for e.g. blood or urine amino acids, organic acids, fatty acids or oligosaccharides). We will discuss screening testing in more detail in lectures devoted to chromosomal disorders and metabolic disease.

With regard to disease-specific supportive diagnostic testing, there are two recent techniques which are revolutionizing our approach: Polymerase Chain Reaction (PCR) and significant advancements in DNA
sequencing (which is becoming the approach of choice for clinical testing for many conditions because it is so comprehensive). PCR has been applied to both direct and indirect approaches to the detection of genetic disease. Direct DNA testing using PCR allows for the identification of a specific disease causing mutations by amplification of the region involved and subsequent evaluation for the presence of the specific mutation by one of several approaches. PCR primers are hybridized to the region involved and polymerase chain reaction allows for the production of multiple copies of that region. In one approach to direct mutation analysis the change in sequence do to the mutation results in the loss of a recognition site for a restriction endonuclease which can be identified by sizing the DNA fragments on a gel following restriction digestion. In another approach, the PCR products are hybridized to radiolabeled probes containing either the normal or mutant sequence and the presence or absence of mutation is detected by the presence or absence of signal for that probe. For trinucleotide expansion mutations as in Fragile X syndrome, PCR primers are used to amplify the involved region and the products are sized on gels to determine what the length of the repeat expansion is and whether the DNA fragment size is in the normal, premutation or full mutation range. With regard to indirect DNA testing, this is used in cases where the specific gene mutation involved is not known but there are sequences linked to the mutant or normal gene which are different and can be used as markers to determine which gene was inherited. In the case of restriction fragment length polymorphisms, the presence or absence of a restriction site in a marker gene linked the gene of interest can be used to detect the inheritance of the mutant or normal gene based on the restriction fragment length generated by digestion of an individuals DNA and hybridization with radiolabeled DNA from the marker gene in Southern blot analysis. Alternatively, polymorphisms in repetitive DNA linked the gene of interest can be used to determine whether the mutant or normal gene were inherited. Both of these approaches to indirect mutation analysis represent linkage studies. There are several limitations to linkage studies as compared to direct mutation analysis: 1) several family members must be available for evaluation including often an affected family member, 2) Certain family members must be heterozygous for the analysis to be informative, and 3) Recombination can occur between the marker and disease gene and the likelihood of this depends on how closely linked the two are.

Genetic conditions are a prominent cause of morbidity and mortality throughout childhood. This is in large part due to the relationship of genetic disease to growth failure and to malformation. The highest mortality rate in childhood is by far in the first year of life. The most common causes of mortality in the first year of life are due to conditions which result in the intrauterine growth retardation (IUGR) and prematurity. Intrauterine growth failure is defined as birth weight that falls below the 5th % for gestational age. Infants with IUGR are considered small for gestational age (SGA) and for any gestational age growth retardation seriously influences mortality-for example a 1500 gm infant born at 33 weeks gestation has a 6% mortality rate while a 500 gm infant born at the same gestational age has a 60% mortality rate. The morbidity and mortality related to IUGR is due to complications related to the underlying cause for the growth failure. Common causes of IUGR include: genetic conditions, intrauterine infections, placental abnormalities (uteroplacental insufficiency due to umbilical placental anomalies including placental abruption and multiple gestations) and maternal factors (maternal HTN, toxemia, teratogen/drug use).

With regard to prematurity, infants born before 37 weeks gestation are at significantly increase risk for morbidity and mortality due to the immaturity of vital organs. Common functionally or structurally impaired organs in the premature infant include lungs, kidneys, liver and brain.

Lung maturation is directly related to gestational age. At 22 weeks, the airways of the lungs are a series of branching tubes with terminal bronchioles being lined by undifferentiated cuboid epithelium. By 32 weeks gestation, capillaries begin to approximate the terminal airways and primitive alveoli are present with type I but very few Type II pneumocytes. Prematurity is the most common cause of Respiratory Distress Syndrome (RDS). Prematurity results in reduced alveolar surfactant production and increased alveolar surface tension with atelectasis and hypoventilation. Subsequently, hypoxemia,
carbon dioxide retention and acidosis lead to pulmonary vasoconstriction and hypoperfusion with epithelial damage and plasma leak into the alveoli and the formation of hyaline membrane. Histologically in Hyaline membrane disease there is alternating atelectasis and dilation of the alveoli with eosinophilic thick hyaline membranes lining the dilated alveoli

Sudden Infant Death Syndrome (SIDS) is also a common cause of death in infancy in the U.S. Up to 1/200 infants succumb to SIDS. The cause is unknown, but there are risk factors which have been identified, including prematurity and being small for gestational age, multi-priority and having a sibling with SIDS. Approximately 10% are believed to be due to an undiagnosed metabolic condition.

In addition to IUGR, prematurity and SIDS, congenital malformations are a common cause morbidity and mortality in infancy and remain a common cause of mortality throughout childhood until adolescence when accidents, homicide and suicide take over.

Malignant neoplasms are also a common cause of mortality after the first year of life and we will discuss childhood malignancy further in the last lecture on Pediatric and Genetic Disease which is devoted to pediatric neoplasia.

Congenital malformations are errors in morphogenesis which are present at birth. Approximately 3% of newborns have a major malformation. Up to 25% in infants dying in the perinatal period have a major malformation.

With regard to congenital errors in morphogenesis there are three basic mechanisms, which have been defined: malformation, deformation and disruption.

Recognizing the difference between different types of abnormalities in morphogenesis is very important in the process of evaluation of a child with congenital anomalies as it relates to the underlying etiology.

Malformations are due to an intrinsic abnormality in the embryo or fetus (like a critical gene mutation, intrauterine infection or intracellular teratogen). Examples of malformation include: cleft palate, congenital heart defects and renal anomalies.

Deformations arise later in fetal development and represent alteration in a formed structure due to mechanical factors. An excellent example is the Potter sequence where oligohydraminos from any number of different causes including renal agenesis (a malformation) results in fetal compression and Potter sequence with pulmonary hypoplasia, altered facies and positioning defects of the limbs. The child with potter/oligohydramnios sequence has a flattened features, low set elongated ears and constraint deformities of the hands and feet including talipes equinovarus. Maternal factors that can result in deformation anomalies include amniotic leak small or malformed uterus and multiple gestation.

Finally, disruptions are due to destruction or interference with established structures. Disruptions may be caused by either extrinsic factors like amniotic bands or intrinsic factors like vascular insults. They tend to result in asymmetric anomalies, for example a unilateral limb reduction defect is often due to a vascular insult. Amniotic bands resulting from the rupture of the amnion during fetal development may attach to and encircle limbs and other structures resulting in partial or complete disruption of that structure. Common features of amniotic band sequence/syndrome include: asymmetric reduction defects of arms, legs, fingers or toes, occipital encephalocele, facial clefting, omphalocele, and umbilical cord strangulation (leading to fetal death).

With regard to congenital malformations, the resulting malformation sequence depends not only on the specific agent but also the timing of the insult in gestation. The greatest risk for malformation is in
early embryogenesis between the third and ninth weeks of gestation. The zygote/embryo is generally not susceptible to teratogens in the first two weeks of gestation, prior to implantation and so intrauterine death at this time is usually due to intrinsic factors like genetic factors. The rate of chromosomal abnormalities in spontaneous abortion at 2 weeks gestation is 78%. Within the first trimester (before week 20) the rate is 62% and includes those with 45,X, polyplody and autosomal trisomy.

Some teratogenic agents are known to have critical periods during which exposure must occur for the embryo to be at risk for malformation. For example, rubella viral infection which must occur by 60 days gestation to result in congenital cataracts and cardiac defects and thalidomide exposure which must occur by 40 days gestation to result in limb reduction defects. Teratogens may act on several cellular processes: cell migration, cell-cell interaction, cell-matrix interaction and programmed cell death. Many agents act on a particular developmental field which is a group of tissues which react as a coordinated unit to inductive effects during embryogenesis. There are genes which have been found to be critical to normal development in certain developmental fields. For example the Wilms tumor gene in urogenital development, Fax genes in development of the eye and specific homeobox genes in individually determining patterning of limbs, vertebrae and craniofacial features. All of these are highly conserved DNA-binding proteins which regulate transcription of multiple other genes involved normal development within the involved development field(s).

In most cases, at this point in time, details of the mechanism of malformation are not known. However, the cellular effects of some are being worked out. For example, for Retinoic acid embryopathy, it is known that retinal enters cells bound to the retinal binding protein and is the converted to retinoic acid in the cytoplasm which enters the nucleus, binds to nuclear steroid-like retinoic acid receptors and binds to and activates multiple genes involved in the regulation of patterning, including I-IOX genes. Abnormal expression of these genes at inappropriate times in embryogenesis results in a host of malformations collectively termed Retinoic acid embryopathy.

Genetic conditions are the single greatest cause of congenital malformations (chromosomal accounting for 10-15%, Mendelian for up to 10% and multifactorial for up to 25%). Environmental factors taken all together (including congenital TORCH infections, maternal diabetes and intrauterine drug exposure) account for less than 15% of malformations.

The pattern of congenital malformations associated with an underlying genetic condition are used to diagnose well-described syndromes (both chromosomal and nonchromosomal). Malformation syndromes consist of two or more developmental field defects or one major field defect and several minor defects.
**Genetic and Pediatric Diseases-Nonchromosomal Syndromes**

Genetic syndromes represent a collection of clinical findings which taken together are recognizable as a specific condition.

Clinically, genetic syndromes are classified chromosomal and nonchromosomal.

Chromosomal syndromes are associated with specific cytogenetic changes evident by chromosome evaluation.

Nonchromosomal syndromes result from genetic changes which are usually not identifiable by high resolution chromosome evaluation. Most non-chromosomal genetic syndromes are single gene disorders with simple patterns of inheritance that run the gamut from autosomal recessive or dominant to X-linked recessive or dominant. Some appear to be multifactorial.

Microdeletion syndromes fall in between—generally require special techniques (fluorescence in situ hybridization/FISH analysis or PCR analysis) to appreciate but were originally identified by the associated finding of a cytogenetically visible deletion.

Genetic syndromes have traditionally been named for the geneticist who first described the condition—unfortunate because the identity of the individual with the condition is at risk for getting lost in the diagnostic process.

Nonchromosomal genetic syndromes that represent single gene disorders are models for the impact of a specific genetic change on growth and development.

There are as many different underlying genetic mechanisms for genetic syndromes as there are cellular processes which genes impact.

Examples of non-chromosomal syndromes:

1) **Opitz Syndrome** - mutations in the mid 1 gene have been associated with Opitz Syndrome. The mid 1 gene encodes the midin protein which belongs to a family of proteins with multiple protein-protein interaction domains which are involved in regulating body axis patterning in other organisms. The midin protein is associated with microtubules and has multiple interactions with other proteins known to be involved in midline development. Opitz Syndrome is an X-linked dominant condition which involves multiple abnormalities in midline structures including: cleft palate, laryngotracheal clefts, hypospadias and imperforate anus.

2) **Marfan Syndrome** - is an autosomal dominant disorder characterized by a marfanoid habitus (with increased leg length and arm span for height), tall stature and craniofacial dysmorphism including midface flattening, microgathia and a high arched palate. Marfan Syndrome is due to mutations in the Fibrillin-1 gene and results in a multisystem disorder involving disturbance of bone, joint, ocular and cardiovascular function. Fibrillin-1 is a major connective tissue protein which is critical to the integrity of skin, bones, joints, major arteries and the lens of the eye. Other common medical concerns in Marfan Syndrome include: easy bruisibility, skin striae, joint hypermobility, scoliosis, pes planus, pectus excavatum, aortic root dilatation or
aneurysm and ectopia lentis. There is an established clinical diagnostic criteria for Marfan Syndrome which requires rigorous systematic evaluation. Fibrillin-1 gene mutation testing is not yet readily available although with advancements in gene sequencing probably will be. The most common cause of death in Marfan syndrome is aortic dissection and/or rupture due to medial cystic degeneration with loss of integrity of the media resulting in intimal tearing. This is preventable by beta blocker treatment.

3) Ehlers Danlos syndromes (EDS) are a group of disorders due to abnormalities in various collagen proteins. Disturbance in collagen function results in effects on multiple organ systems, including: skin, joint, cardiovascular and ocular dysfunction. The complications of the particular type of EDS tend to reflect the distribution of collagen involved. The underlying genetic defects for the Ehlers-Danlos Syndromes have in some cases been very well defined and in other cases, not so well. Many involve mutations in collagen genes. These are inherited in an autosomal dominant fashion due to the dominant negative affect of the abnormal collagen on collagen structure and function. Mutations in Type V collagen have been found in individuals with the Type I and Type II EDS. Others involve mutations in enzymes modifying collagen (e.g. lysyl hydroxylase) and these are recessive. Type IV (the cardiovascular form) is well defined and involves mutations in type III collagen which results in incompetence of large arteries resulting in risk for a number of cardiovascular complications including carotid and other large artery dissection and rupture (see table 3). Along with collagen gene testing for collagen-related disorders. Skin biopsy can be used for diagnosis in a limited number of collagen disorders (including Ehlers-Danlos Syndrome Type IV).

Examples of Microdeletion Syndromes (so-called contiguous gene syndrome because they are believed to represent the impact of deletion of a number of contiguous genes):

1) Velocardiofacial Syndrome - is a microdeletion syndrome associated with chromosome 22q11 deletion with craniofacial dysmorphism including palatal insufficiency and submucosal cleft palate as well as a variety of cardiac defects including tetralogy of fallot and defects affecting the aortic arch. DiGeorge Syndrome has also been associated with 22q11 microdeletions in the same region and is associated with disturbances in the development of the 3rd and 4th pharyngeal pouch in addition to the aortic arch resulting in parathyroid and/or thymic hypoplasia.

2) Williams Syndrome - involves a microdeletion of chromosome 7 (ql l) detectable by FISH analysis in greater than 95% of cases using a probe for the Elastin gene. There is also a recently described transcription factor gene which is deleted in some cases. William syndrome involves short stature, supraavalvular aortic stenosis, developmental delay and craniofacial dysmorphism resulting in an "elfin" facies. Familial supraavalvular aortic stenosis has been associated with mutations in the elastin gene; some family members appear to have a mild form of William Syndrome. So, the degree of contribution of the elastin gene to the phenotype is controversial.

3) Prader-Willi and Angelman Syndromes have been mapped to 15g11. Microdeletions of this region using the same FISH probe account for approximately 80%—those resulting in Prader Willi Syndrome are paternal in origin while those associated with Angelman Syndrome are maternal and believed to represent differences in imprinting in this region. Methylation differences between maternal and paternal chromosomes have been found and methylation testing is available and increases the sensitivity of detection over deletion analysis to greater than 90%.

Prader-Willi Syndrome involves craniofacial dysmorphism with almond-shaped palpebrae, short stature, hypogonadism, hypotonia and early childhood onset hyperphagia with weight gain acceleration and early obesity.
Angelman Syndrome involves microcephaly, hypotonia, absent speech, seizures and ataxic gait.
Genetic and Pediatric Disease-Chromosomal Conditions

Conditions that are correlated with alterations in chromosome number or structure observable by light microscopy represent extensive and potentially profound genetic changes.

These are not surprisingly often associated with global effects on growth and development which in many cases result in recognizable patterns of malformation, intrauterine growth retardation, and or postnatal growth retardation, cognitive impairment and increased mortality.

The usual procedure for high resolution chromosome evaluation involves culturing the appropriate cells (leukocytes from blood, amniocytes, chorionic villous or bone marrow), arresting the cells in prometaphase with colchicine and staining the chromosomes usually with Giemsa' (G-banding) which results in the formation of a series of light and dark bands that can be visualized by high power light microscopy. This allows for careful examination of the chromosome number and structure. A karyotype is a standard arrangement of chromosomes in which the chromosomes are paired and arranged in order of decreasing length. The small arm is referred to as p (for petit) and the long are q. The regions, bands and subbands are numbered from the centromere out. For example deletion of the small arm of the X chromosome in region 2, within band 1 involving subband 2 would be reported as del Xp21.2 (duplication would be dupXp21.2). The number of total bands observed determines the resolution and therefore the quality of the study. If there are 550 bands or greater detected, the study is considered high resolution. When the results of the study are reported the total # of chromosomes is given, then the sex complement, then the description of any abnormalities, separated by commas. For example 46,XX,delXp21.2 or for a male with Down syndrome 47,XY,+21.

Newer techniques for characterizing chromosomal abnormalities include Fluorescence In Situ Hybridization (FISH) analysis (using fluorescently labeled probes that correspond to certain regions of chromosomes and can be identified by light microscopy). Because it is more sensitive, FISH can aid in the identification of a deletion or duplication when these are not discernible by high resolution chromosome evaluation. Spectral analysis (using multi-colored fluorescent probes which "paint" entire chromosomes) can aid in identification of chromosome segments involved in a rearrangement (e.g. translocation).

There are a few cytogenetic terms that you should know. Aneuploidy refers to an unbalanced state due to the loss or addition of whole or pieces of chromosomes-always considered deleterious. Monosomy is lack of a whole chromosome. Trisomy refers to having an additional whole chromosome. Deletion refers to loss of part of a chromosome and duplication refers to having an additional copy of part of one chromosome. Translocation refers to a reciprocal exchange between two chromosomes which is balanced in the carrier but which can subsequently result in loss or gain of chromosomal material in the offspring following segregation in meiosis and thereby result in partial monosomy or trisomy. Polyploidy refers to having more than two complete of chromosome (eg.69 is triploidy). Inversions require two breaks and subsequent fusion.
following rotation of the involved segment-if both breaks are on the same side of the centromere it is paracentric, if on opposite sides of the centromere it is pericentric. An isochromosome contains duplicate material on both sides of the centromere and arise from transverse rather than longitudinal division of the centromere. Mosaicism refers to two or more chromosomally distinct cell lines in the same individual.

1/200 children are born with a chromosomal abnormality. In most cases these are de novo (parents chromosomes are normal). There are several different types of rearrangements which can result in clinically recognizable syndromes. Deletion (partial monosomy), duplication (partial trisomy) and ring chromosomes (partial deletion) have a high risk for associated medical complications.

Balanced translocations, inversions and isochromosome formations generally do not result in abnormalities in the carrier but carry significant risks for abnormal offspring due to subsequent formation of genetically abnormal gametes carrying partial or complete monosomy or trisomy (depending on whether it is a reciprocal or robertsonian translocation).

Complete monosomies are not viable, except those involving sex chromosomes.

Of the three trisomies commonly recognized only trisomy 21 (Down syndrome) has a high rate of long-term viability. All are associated with a similar spectrum of concerns including IUGR and organ malformations.

The spectrum of malformations is similar in all three trisomies and includes: craniofacial dysmorphism, brain malformations, congenital heart defects, intestinal malformations and renal anomalies. The frequency and level of severity of malformations is much greater in trisomy 18 and trisomy 13 compared to trisomy 21.

Craniofacial features are more specific among these trisomies, although all are associated with microcephaly (small head and brain). Trisomy 21 is associated with flattened occiput, upslanting palpebrae and a flattened facial profile. While trisomy 18 is associated with a prominent occiput, micrognathia and overlapping fingers and trisomy 13 with microophthalmia and premaxillary hypoplasia/agenesis resulting in cleft lip and palate.

Moral: It's the whole picture that tells the story.

In fact, with regard to Down Syndrome the ten cardinal diagnostic features do not involve specific organ malformation, but flat facial profile, upslanting palpebrae, abnormal auricles, excess nuchal skin (remnant of embryonic cystic hygroma), hypotonia, poor hyperextensibility of joints, dysplasia of pelvis, brachymesophalangy of 5th finger single palmer crease.

Moral: Little things can be specific if taken in the whole context.
The genes responsible for the Down syndrome phenotype are in the process of being isolated and characterized. The Down syndrome critical region is known to include 21q22.

As noted above, smaller cytogenetic changes can result in recognizable syndromes with similar risks for growth failure, malformation, cognitive impairment and mortality including: Wolf-Hirschhorn (del 4p), cri-du-chat (del 5p) and Jacobson syndrome (11 q23-qter).

Abnormalities involving sex chromosomes tend to be less severe and include Turner Syndrome (classic: 45,X), Klinefelter syndrome (47,XXY) and multiple X females. In general they result in problems relating to sexual development and fertility and are often not diagnosed until puberty. Klinefelter Syndrome involves a eunuchoid body habitus and primary hypogonadism with small testes. There are forms of Klinefelter with multiple X chromosomes which can be more significantly affected with hypospadias. Trisomy X females generally are not significantly affected, although the risk for cognitive impairment goes up in females with greater numbers of X chromosomes.

Among the sex chromosomal aneuploidies, Turner Syndrome has the greatest potential for significant associated malformation. Reported malformations include craniofacial dysmorphism, neck webbing (lymphatic hyperplasia), shield chest, cubitus valga, lymphedema, cardiac defects (bicuspid aortic valve, coarctation of the aorta), renal malformations and cysts, and streak gonads.

Many individuals with Turner Syndrome are mosaic and a large variety of karyotypes (including: 46XY/45X, 46XXq- and 46XXp-) may result in Turner Syndrome. Those with a Y chromosome are at risk for germ cell malignancies if their gonads are not removed. Turner Syndrome critical regions for the phenotype on both q and p arms are being delineated.
Pediatric and Genetic Disease - Metabolic Disorders

Disorders of metabolism involve mutations that result in reduced activities of proteins involved in the synthesis, break down or transport of amino acids, fats, carbohydrates, and complex macromolecules (e.g. gangliosides, mucopolysaccharides).

Most metabolic disorders are inherited as autosomal recessive conditions due to mutations in the gene encoding the enzyme with reduced activity either by affecting the rate of catalysis or the amount of enzyme produced. Others involve proteins which modulate enzyme activities (e.g. by direct interaction with the enzyme or by affecting post translation modification of the enzyme).

The pathogenesis of metabolic disease is based on the biochemical consequences of the resulting enzyme defect and may include: accumulation of a toxic intermediate; or decreased amount of a necessary end product (e.g. Lesch-Nyhan syndrome which is due to reduction in activity of hypoxanthine guanine phosphoribosyltransferase resulting in a lack of PRPP end product which causes uncontrolled production of purines by an alternate pathway).

There are two different types of testing for metabolic disease. Screening and disease-specific diagnostic testing. Screening tests allow you to ask the question of whether there is a particular class of disorder. Types of screening tests include: Blood amino acids and urine amino acids (for disorders of amino acid metabolism); Urine organic acids (for disorders of branched chain amino acids and fatty acid disorders); Blood acylcarnitine levels (for disorders of fatty acid metabolism); Blood lactate and pyruvate (for disorders of carbohydrate metabolism and mitochondrial disorders); Urine oligosaccharides or mucopolysaccharides (for disorders of complex macromolecules). In addition, because many metabolic disorders result in metabolic acidosis and hypoglycemia, when considering a metabolic disorder, it is critical to get serum electrolytes (Na, K, Cl, CO_2), ammonia, glucose, and ketone levels. With regard to specific diagnostic disease testing, clinical testing for specific enzyme activities is available for most metabolic disease that is highly specific and sensitive. Disease specific enzyme/protein activity assays vary a great deal in terms of tissue requirements; many can be done on blood, but others require skin, liver or muscle biopsy. In general, confirmation of the findings from screening tests by specific enzyme assay is recommended.

Many disorders of amino acid metabolism result from the accumulation of a toxic metabolite including phenylketonuria.

Most phenylketonuria results from a deficiency of phenylalanine hydroxylase. This results in the accumulation of phenylalanine with low blood tyrosine. Phenylalanine is neurotoxic and unless patients are on a low phenylalanine diet, the IQ drops precipitously to an average of 50 in the first year of life. Biopterin deficiency is an unusual form of phenylketonuria due to deficiency in biopterin reductase which is involved in both phenylalanine and tyrosine breakdown, so both are elevated in biopterin deficiency. The treatment for biopterin deficiency is biopterin not low phenylalanine diet.
Maple Syrup Urine Disease is a disorder due to deficient breakdown of branch chain amino acids resulting in branch-chain ketoaciduria and ketoacidosis. Clinical presentation includes poor feeding, vomiting, tachypnea and CNS depression. It is rapidly fatal if not treated and treated by dietary limitation of branch chain amino acids.

Abnormalities further down the metabolic pathway of many amino acids, result in disturbance of organic acid breakdown and so-called organic acidurias. The production of propionate and methylmalonate is a metabolic branch point for late steps in the breakdown of multiple amino acids (ile, val, thr, met) and odd chain fatty acids. Deficiency in propionyl carboxylase and methylmalonyl mutase results in propionic acidemia and methylmalonic academia (MMA). These conditions result in severe metabolic acidosis, hypoglycemia (due to inhibition of gluconeogenesis), hyperammonia (due to disturbance in hepatic function) and hyperglycinemia. Clinical presentation includes severe feeding difficulties, lethargy, vomiting or in less severe cases poor feeding, failure to thrive (FTT), episodic vomiting, seizures, and development delay. Organic acidemias are identified by the findings of specific organic acids on urine organic acid evaluation. Some forms of MMA are treatable with vitamin B12, a cofactor for the involved enzyme. There are other organic acidemias which involve late degradation pathway for other amino acids, glutaric aciduria is one that is unusual in several regards, has dysmorphic craniofacial features and often presents later (3months-2 years) with progressive hypotonia, loss of head control, dystonia, athetosis, chorea, and seizures.

Multiple defects in the urea cycle have been identified---resulting in profound hyperammonenemia (20 - 100 X normal NH₃). Clinical features are poor feeding, hypotonia, apnea, vomiting and seizures. Arginosuccinate lyase is not associated with persistent elevation in NH₃ because arginosuccinate is easily cleared by the kidney and does not accumulate.

There are multiple disorders of fatty acid oxidation, which involve deficiencies of either carnitine-linked transport of fatty acids (FA) into the mitochondria or break down of fatty acids. Because of the dependence of multiple systems (including muscle) on FA during fasting and the inhibitory affect of the accumulation of FA intermediates on gluconeogenesis and ketosis, disorders of FA oxidation generally present with fasting hypoketotic hypoglycemia. Examples include: carnitine palmytoyl tranferase, medium chain acylCoA dehydrogenase and long chain acylCoA dehydrogenase deficiencies. Common clinical findings in addition to potentially life-threatening fasting hypoglycemia include: exertional myalgia, recurrent rhabdomyolysis and myopathy including cardiomyopathy. Treatment includes avoiding fasting, carnitine and a high carbohydrate, low fat diet. Expanded newborn screening allows for dictation of disorders of fatty acid metabolism because it includes testing for fatty acid metabolites.

There are a large number of disorders of carbohydrate metabolism of clinical interest including those disrupting glucose metabolism involving disturbances in glycolysis, pyruvate metabolism, gluconeogenesis, TCA cycle, electron transport and oxidative phosphorylation. Disorders involving glycolysis (e.g. pyruvate kinase deficiencies) generally affect RBCs and result in hemolytic anemia. Those involving pyruvate metabolism have much broader effects-disorders of gluconeogenesis (e.g. pyruvate
carboxylase) result in fasting hypoglycemia, lactic acidosis, poor feeding, FTT, hypotonia and hyporeflexia. Pyruvate dehydrogenase deficiency results in profound lactic acidosis and associated changes in the CNS including arrest of brain growth with microcephaly and developmental delay.

Mitochondria) disorders involving the electron transport or oxidative phosphorylation result in multisystem disease. Lactic acidosis is common (often low level and intermittent). These have a more chronic course with any combination of the following depending on the specific condition: microcephaly, short stature, FTT, generalized cerebral dysfunction, cranial nerve dysfunction, optic atrophy, retinal abnormalities, sensorineural hearing loss, seizures, migraines, cyclic vomiting, stroke-like episodes, myopathy, hepatic dysfunction, renal dysfunction, endocrine dysfunction (diabetes). These conditions tend to be highly variable in expressivity even within the same family due to differences in the number and distribution of abnormal mitochondria (heteroplasmy). Many have recently been characterized (MERRF, MELAS) that involve mutations in mitochondrial DNA and these have a maternal pattern of inheritance. Some involve specific consistent mutations in mitochondria) genes which are easily tested in the clinical laboratory.

Galactosemia is one of the most commonly recognized disorders of carbohydrate metabolism which is caused by deficiency of galactose-1-phosphate uridyltransferase. Lactose is the primary carbohydrate from milk being split into glucose and galactose. Clinically galactosemia presents neonatally when the infant is fed milk and exhibits vomiting, diarrhea, FTT, hepatic insufficiency (with hepatomegaly, jaundice, hypoglycemia, coagulation defects) also sometimes renal tubular dysfunction. Galactose-1-phosphate accumulates in tissues, as well as galactitol (generated by activation of alternative pathways). Fatty change in the liver occurs early with fibrosis resembling cirrhosis. Loss of nerve cells and gliosis occurs in the brain. There is a high rate of E. Coli septicemia. Removal of galactose from the diet is the treatment. Glucokinase deficiency results in accumulation of galactitol only and neonatal cataracts in homozygotes and cataracts in early adulthood in heterozygotes.

The glycogenoses represent storage diseases that involve disturbances in the synthesis or breakdown of glycogen. The pathology and clinical presentation of glycogen storage diseases depends on the tissue/organ distribution of the involved enzyme. Enzyme deficiencies have been reported in the branching enzyme (involved in glycogen synthesis), liver phosphorylase kinase, liver and muscle phosphorylase, debranching enzyme, glucose-6-phosphatase, phosphofructokinase and lysosomal acid maltase (alpha-glucosidase).

These deficiencies may be simply categorized into: hepatic forms, myopathic forms and those associated with glycogen storage in multiple organs (acid maltase deficiency/ Pompe disease and brancher enzyme, which result in multiple organ failure and early death). Hepatic forms (glucose-6-phosphatase deficiency/ Von Gierke Disease, debranching enzyme and muscle phosphorylase deficiencies) result in hypoglycemia, lactic acidosis (depending on the severity), hepatomegaly and hepatic insufficiency, cirrhosis and hepatoma (in Von Gierke Disease). Myopathic forms of glycogen storage disease (including muscle phosphorylase deficiency/ McArdle disease and muscle
phosphofructokinase deficiency) are associated with muscle weakness, exercise induced myalgia, and rhabdomyolysis.

Lysosomal storage disorders are a group of conditions involving disturbance in activity of lysosomal acid hydrolases which break down a variety of complex macromolecules leading to the accumulation of incompletely digested large nondiffusible macromolecules.

There are several distinctive separable lysosomal storage diseases.

The clinical outcome of a lysosomal storage disorder depends on not only the specific enzyme involved but also on the site where most of the material is accumulated and/or the primary site of degradation.

The lysosomal storage diseases are categorized according to the biochemical nature of the accumulated metabolite and include glycogenosis, sphingolipidoses, sulfatidoses, mucopolysaccharidoses and mucolipidosis.

Lysosomal storage disease can be due to several specific cellular changes which affect lysosomal acid hydrolases including: mutations in the gene encoding the enzyme that affect catalytic activity, defects in post-translational modifications adding mannose-6-phosphate that result in the enzyme not being targeted to the lysosome, lack of an enzyme activator or protector protein, lack of a substrate activator, and lack of transport of digested material from lysosomes.

Tay-Sachs Disease and Sandhoff Disease are GM2 gangliosidoses due to deficiencies in N exosaminidase A and B, respectively. The breakdown of Gm2 gangliosides requires a complex of proteins that includes hexosaminidase A and B and an activator protein. Loss of activity of any of these results in accumulation Gm2 gangliosides in many tissues most prominently the brain. Accumulation of Gm2 gangliosides in neurons results in ballooning with markedly distended lysosomes. There is progressive destruction of neurons. Gm2 gangliosides also accumulate in the retina at the margins of the macula resulting in a cherry red spot. The affected infant, normal at birth, suffers relentless motor and mental deterioration beginning at 6 months. Over a 1-2 year period, a vegetative state is reached and death usually occurs between the ages of 2 and 3 years. Carrier detection is possible by enzyme assays and DNA analysis.

Niemann Pick types A and B are characterized by accumulation of Sphingomyelin resulting from deficiency of sphingomyelinase. Type A is a severe infantile form with extensive neurologic and visceral involvement that results in progressive wasting and death by age 3. Type B is a much milder form with no central nervous system involvement, but organomegaly. The mutations responsible for Type A and B in the Sphingomyelinase gene are different. In Type A, a missense mutation causes almost complete deficiency.

Gaucher Disease results from mutations in the glucocerebrosidase gene. Glucocerebrosides accumulate in massive amounts within phagocytic cells throughout the body. Distended phagocytic cells, Gaucher cells, are found in the spleen, liver, bone marrow, lymph nodes and peyer patches. Gaucher cells are enlarged with an eccentrically placed nucleus and fibrillary (crumpled tissue paper) cytoplasm, not vacuolated. In type I Gaucher disease, there is no CNS involvement, but prominent visceral involvement with hepatosplenomegaly, bone marrow dysfunction and bone pain secondary to accumulation in marrow. In types II and III, central nervous system deterioration predominates although visceral involvement occurs. Mutations responsible for the three types are different. Diagnosis can be made by evaluation of glucocerebrosidase activity in blood or skin fibroblasts. Mutation testing by DNA analysis can be used to detect carriers. Enzyme replacement therapy
ameliorates the hematologic manifestations and hepatosplenomegaly.

Mucopolysaccharidoses are a group of disorders that result from deficiencies of enzymes involved in the breakdown of glycosaminoglycans (mucopolysaccharides) which are long chain complex carbohydrates linked to proteins (proteoglycans). The enzymes involved cleave terminal sugars and when they are deficient, large complex mucopolysaccharides accumulate in lysosomes of multiple tissues including: liver, spleen, bone, heart, blood vessels, skin, joints and brain. Common clinical features include: coarsened facial features, corneal clouding, hepatosplenomegaly, joint stiffness and progressive cognitive decline. There is a somewhat specific spectrum of skeletal abnormalities (dysostosis multiplex). The seven different types of mucopolysaccharidosis are classified according to the enzyme involved. They also vary in terms of the predominant organ system(s) and severity of course. In most forms urine mucopolysaccharides are elevated. Specific enzyme analysis can be performed for most types using white blood cells.
PEDIATRIC TUMOURS: CANCER, TUMORS, AND TUMOR-LIKE LESIONS AND THE ROLE OF GENETICS IN THEIR PATHOGENESIS

Notes by Judy Miller, MS
For independent learning
Genetic Diseases Lecture:

**Pediatric Tumors:**

*Cancer, Tumors, Tumor-like Lesions*

*And the Role of Genetics in Their Pathogenesis*

M-2 Pathology Section
September 2006
Judy Miller, MS

**Goals:**

1. Explain what is meant by “cancer is, in essence, a genetic disease.”
2. Be aware of chromosomal changes related to specific malignancies.
4. Explain the difference between childhood and adult malignancies.
5. List and define the common malignant neoplasms of infancy and childhood:
   - Examples:  Wilms’ tumor
   - Hepatoblastoma
   - Rb
6. Define the common nonmalignant tumors of childhood (hamartoma, heterotopic and teratoma) and know examples of inherited conditions with these tumors.
7. Know the classification of vascular anomalies as described in this handout, especially the definition of hemangioma.

**Reading:** From Baby Robbins: Ch 6 Neoplasia, section “Carcinogenesis: The Molecular Basis of Cancer” and Chapter 7 Genetic and Pediatric Diseases, section “Tumors and Tumor-Like Lesions of Infancy and Childhood.”

Following are 2 excellent texts if you wish more information (not required):


**Part I Chromosomal Defects in Neoplasia**

*And the Philadelphia Chromosome*

**Introduction**

“Cancer is, in essence, a genetic disease.”

**Types of genetic alterations observed in tumor cells (almost all are somatically acquired):**

1. Subtle alterations (small deletions, insertions, and single base pair changes)
2. Chromosome number changes.
   
   This is seen in most cancers. Ranges from 1 copy of a particular chromosome to 4 or more copies.
3. Chromosome translocations.
   Both balanced and unbalanced translocations are seen frequently. In common cancers of epithelial origin (e.g., breast, colon, prostate, stomach), the translocations appear to be random. In contrast, leukemias and lymphomas generally contain characteristic translocations.

4. Amplifications.
   Definition: a five to hundred-fold multiplication of a small region of a chromosome (0.3 to 10 Mb). The “amplicon” contains 1 or more genes whose expression can endow the cell with enhanced proliferative activity.

5. Exogenous sequences.
   Certain human cancers are associated with tumor viruses which contribute genes that result in abnormal growth.

Cytogenetics – including new techniques such as FISH may be used in all except #1.

**Philadelphia Chromosome**


The Philadelphia chromosome is important because it was the first genetic abnormality consistently associated with a particular type of cancer, chronic myeloid leukemia (CML) (previously known as chronic granulocytic leukemia), a pluripotent stem cell disease.

A consistent association of CML and a cytogenetic abnormality characterized by short chromosome 22 was first recognized in 1960 (in cancer research laboratories in Philadelphia). In 1973, with the advent of banding techniques, it was determined that the Philadelphia chromosome (Ph chrom) constituted a reciprocal translocation involving chromosomes 9 and 22. In 1980, it was shown that both the breakpoints for the translocation were within the coding region for cellular oncogenes – the t(9:22) involved genetic translocation of cellular oncogenes. We now understand much on a molecular level about this translocation.

**abl gene** is on chromosome 9 at q34. The normal gene product is a proto-oncogene, a regulated non-receptor tyrosine kinase. Tyrosine kinases regulate key events in signal transduction pathways that control cell shape and growth. The mRNA of the normal gene is 6 or 7 kb and the protein product is located in the nucleus. The breakpoint region involved in the translocation is located within a 200 kb region of abl.

**bcr gene** (for Breakpoint Cluster Region) is at chromosome 22 q11, and the physiologic function of the normal bcr gene product is unknown. Two regions of the gene appear to be involved in translocations, the Mbcr (major breakpoint cluster region) which is about 5.8 kb, and mbcr (minor breakpoint cluster region). The precise site of the break does not seem to have any clinical relevance as far as disease is concerned, only in testing for the presence of the translocation.
The t(9;22) chromosome has a fused bcr-abl oncogene containing 5’ bcr and 3’ abl sequences, and expresses a fusion protein with the N-terminus from bcr and the C-terminus from abl with a molecular weight of 210 kd. This fusion protein has upregulated tyrosine kinase activity, is located in the cytoplasm and is involved in tyrosine phosphorylation of several cytoplasmic proteins. This fusion tyrosine kinase is now an oncogene and is believed to be central to tumorigenesis although the specific events are not well understood. It is known that hematopoietic cell in vitro, when transfected with the bcr-abl fusion gene, can have the properties of a cancer cell.

Diagram showing how the Ph ch arises by a reciprocal translocation involving chromosomes 9 and 22, and how this event joins the bcr and abl genes. The abl gene is located on band q34 of ch 9; bcr is at q11 of ch 22. In the diagrams of the genes, boxes denote exons (these appear as vertical lines for small exons), and horizontal lines represent DNA. Figure 27-13, taken from “Molecular Biology of the Gene, 4th Edition”

Philadelphia Chromosome – Clinical
The Philadelphia chromosome is present in 95% of patients with CML, and we now know that the other 5% have a variant of the translocation and fusion protein that requires molecular methods to detect. That is, this 5% of patients do not have the Ph chrom (the visible t(9;22) chromosome), but they do have the fusion bcr-abl gene. About 90% of untreated patients have the Ph chromosome in 100% of the metaphases. In addition, the Ph chromosome is present in
about 3 to 5% of children and 20 to 40% of adults with Acute Lymphocytic Leukemia (ALL). (Routine karyotyping does not distinguish between the fusion protein in CML and ALL, but molecular analysis shows differences.) Philadelphia chromosome positive leukemia is five times more common in adults than in children. The Ph chromosome is only found in the leukemia cells – all the other cells of the patient have normal chromosomes.

Today – the presence of the Ph chromosome is a requirement for the diagnosis of CML, but it is NOT specific to CML. However, it appears that the tumor-inducing potential of the bcr-abl chimeric gene is restricted to hematopoietic cells.

**Laboratory methods**
1. Conventional cytogenetics or routine chromosome analysis for diagnosis and monitoring treatment response. Provides more information than FISH.
2. FISH (Results available quicker than cytogenetic analysis)
3. Molecular methods: Southern blot analysis of DNA from either the bone marrow or the peripheral blood; PCR (specifically RT-PCR because of large size of gene) is exquisitely sensitive and is a powerful tool for detecting minimal residual disease.

**Since the discovery of the Philadelphia chromosome:** Studies in cancer tissues of fusion proteins/genes/translocations/cytogenetic loss of heterozygosity have resulted in:
- identification of more than 90 different protein tyrosine kinases
- identification of about 26 tumor suppressor genes
- specific translocations have been associated with many lymphoid malignancies
- and most importantly, targeted treatment!

**Targeted Treatment for Ph ch malignancies:** The drug Imatinib (Gleevec) was designed and is used to treat chronic myelogenous leukemia (CML). It acts by specifically blocking the kinase activity of the proteins abl protein and bcr-abl protein.

For an up-to-date discussion of this topic, see Science, 26 May 2006 (312 (5777)), a special issue “Cancer Treatment gets Personal,” and especially the article in that issue on p 1175, “Targeting Tyrosine Kinases in Cancer: The Second Wave,” by Jose Baselga.

**Part II: Common Malignant Neoplasms of Infancy And Childhood**
(Tables and Figure below are from the “Molecular Basis of Cancer” – ref on p 1.)

1. **Biologic and genetic features of childhood tumors are distinct from tumors commonly occurring in adults.**
   - They have a different histological appearance
   - They arise in different cell types, occur in different tissues.
   - Tumors of childhood frequently resemble the embryonic precursor of the cell type in which they arise.
2. Childhood tumors occur prominently in association with a variety of different hereditary cancer susceptibility syndromes.
Knudson theory (or law). Knudson studied the 3 tumors we will discuss, all of which have bilateral or multicentric cancer. Bilateral tumors have an age on onset 1 to 2 years earlier than that of unilateral tumors. By comparing the incidence of the unilateral versus bilateral retinoblastoma in patients with a positive family history, Knudson found that the data fit the Poisson distribution for a single rare event. Loss of the second allele (which represents the second hit) is seen most commonly as a wholesale loss of a chromosome or chromosome recombination event in somatic tissues. These events have been of critical importance for mapping studies of the tumor suppressor genes involved with retinoblastoma and Wilms’ tumor.

Understand the terms:

Inherited cancer susceptibility syndrome
Germline mutation
De novo mutation
Germinal mutation
Congenital tumor
Constitutional mutation

Neuroblastoma:
A tumor of the postganglionic sympathetic nervous system – that is, affecting neural crest
deriving cell lineages. It is the most common extracranial solid malignancy of childhood, with a
prevalence of about 1 case per 7500 live births. Neuroblastoma accounts for about 15% of all
childhood cancer deaths.
Neuroblastoma is characterized by great clinical variability and histological heterogeneity, and
may arise anywhere in the sympathetic nervous system from the head to the pelvis. Primary
tumors generally arise in the adrenal gland (50%) or elsewhere in the abdomen or pelvis (30%).
20% arise in the chest.

Diagnosis: tissue biopsy or characterization of cells in the bone marrow. Catecholamine
metabolites are elevated in the urine in over 90% of cases.
International Neuroblastoma staging system is used for categorizing the extent and resectability
of the primary tumor and the presence or absence of metastases.
Metastases usually are found in the regional lymph nodes, bone, bone marrow, skin or liver.
Most important factors that influence prognostic information are the stage of the tumor and the
age of the patient.
Molecular and genetic analysis of these tumors also provide prognostic information:
- Deletion of the short arm of ch1 (ch1p36) – usually associated with aggressive disease
  MYCN amplification – poor prognosis
  Deletions of short arm of ch 3 distal 11q) often observed – a subset without MYCN
  amplification seen in aggressive neuroblastomas. The deletion results in the loss of the
  VHL gene.
  Gain of 17q – more aggressive subset of neuroblastomas
  Tumor cell ploidy
Tumor pathology is a prognostic variable – presence of ganglion cells and Schwann stroma is
associated with favorable prognosis.

Histological: Neuroblastic tumors can be immature (neuroblastoma), partially mature
(ganglioneuroblastoma), or completely mature (ganglioneuroma).

Future therapeutic approaches may be aimed at: induction of differentiation or programmed cell
death; the product of mycn gene; the 1p36 tumor suppressor gene; or other specific genetic
changes.

Screening of infants for neuroblastoma by measuring urinary catecholamine metabolites has
resulted in a doubling of the apparent incidence rate in infants with no decrease in advanced
disease in older children. WHY?

No environmental exposures or agents have been associated with an increased risk of
neuroblastoma.

**Hereditary predisposition to neuroblastoma:** accounts for less than 5% of neuroblastomas
(NB) and is probably heterogeneous. Previously it was thought that about 22% of all NB may be
a result of a germline mutation and that Knudson’s law appeared to apply (only 2 mutations
needed for tumor development). More recently the thought is that familial NB cannot be
modeled as a Mendelian monogenic trait. Instead, an oligogenic mode of inheritance might explain the existence of different NM loci genetically interacting to cause and/or modify the disease phenotype. One predisposing gene for hereditary neuroblastoma was recently identified (Oct 2005), a paired-like homeobox 2B (PHOX2B) gene, involved in the development of neural crest deriving cells. However, only a few NB families but not others have been shown to carry PHOX2B mutations.

Characteristics of familial NB include: earlier age of onset, tumors at multiple primary sites. Genetic counseling is available and may be helpful although definitive information is not yet available.

**Retinoblastoma**

The most common intraocular malignancy in children. Incidence of approximately 1 in 20,000 births. Occurs almost invariably in early childhood. Unusual in that it can be present before birth.

Thought to arise in the embryonic retinal epithelium. Characterized by the rapid growth of undifferentiated neuroblastic precursors derived from various layers of retinal ganglion cells.

Histologically, RB resembles other embryonal solid tumors of childhood. Typically, RB tumor cells appear very undifferentiated with evidence of ganglionic differentiation such as the presence of Flexner-Wintersteiner rosettes.

Typically presents with characteristic cat’s eye reflex, a papillary reflex termed leukokoria (results from the replacement of the vitrous by the tumor, or by a tumor growing in the macula).

Management depends upon the size of the tumor and the extent of tumor invasion. Surgery and irradiation are the mainstays of treatment. More than 90% of children with local disease can be cured of RB. Patients with bilateral RB do not have as high a survival rate as patients with unilateral disease because of the frequent occurrence of second tumors in these patients.

**Retinoblastoma is the prototypic example of a genetic predisposition to cancer.** The childhood cancer studied by Knudson in development of his model of carcinogenesis, it literally is due to “two-hits,” in which the second hit always occurs somatically.

Bilateral or multifocal disease is assumed to be caused by a germline mutation in the RB1 gene. Approximately 50% of patients with bilateral disease have an inherited RB1 mutation. The other 50% have a de novo mutation. Overall, about 60 to 70% of all tumors are associated with a germline mutation.

Familial RB is transmitted as a typical AD trait with virtually full penetrance (penetrance of a germline mutation is about 95%). **WHY DOES THE PATHOLOGY TEXT DESCRIBE RB AS A CANCER THAT IS RECESSIVE?**
Gene identified as RB1 gene on ch 13q14. Function of RB1 gene product is well described. It is a critical mediator of cell growth, suppressing cell proliferation, and is considered a tumor suppressor gene.

Genetic counseling is important.

**Wilms’ Tumor**

Nephroblastoma.
One of several distinct kidney tumors and the most common of the childhood kidney tumors. Among the more common tumors of childhood, occurring in about 1 out of every 7000 children younger than 16 years.

Embryonal tumor
Most distinctive characteristic of tumor – characterized pathologically by a remarkable histologic diversity of cell types. It is classified as a primitive, multilineage malignancy of renal stem cells. Described as a “triphasic” tumor, including blastemal, epithelial and stromal components (see figure in text) all of which are thought to arise from the malignant stem cell. Epithelial and stromal “differentiation” is not uncommon. Persistent nephrogenic rests (benign foci of embryonal kidney cells that persist abnormally into postnatal) life have been seen within the normal kidney of children with Wilms’ tumor, and are thought to be precursor lesions of Wilms’ tumors. They are comprised of primitive blastemal cells with varying degrees of differentiation. Presentation: typically as an asymptomatic abdominal mass. Approximately 20% of patients have distinct metastatic disease at time of diagnosis. Most cases occur between the ages of 2 and 5 years.

**Diagnosis/testing.** The workup of a child with suspected Wilms tumor begins with appropriate diagnostic imaging studies. Ultrasonography is the recommended first-line test because it provides a panoramic view of the abdomen. Computed tomography (CT) can also visualize pelvic and abdominal structures as well as lymph nodes. Magnetic resonance imaging (MRI) may facilitate the distinction between Wilms tumor and nephrogenic rests. The definitive diagnosis of Wilms tumor can be made only by surgical resection or biopsy.

Approximately 5-10% of children with Wilms tumor have bilateral or multicentric tumors. The average age at presentation is 42-47 months for children with unilateral Wilms tumor and 30-33 months for those with bilateral Wilms tumor.

**Genetic susceptibility to Wilms’ tumor:**
In 10-15% of affected individuals, Wilms tumor is considered to be heritable, with genetic heterogeneity. However, only about 1 to 2% of individuals with Wilms tumor have at least one relative also diagnosed with Wilms tumor.

To date, only one Wilms tumor gene, WT1, a tumor suppressor gene (a transcription factor?) on ch11p13, has been identified.
The vast majority of children with genetic susceptibility to Wilms’ tumor have nephrogenic rests in the otherwise normal kidney. Intralobar rests, which are usually solitary are associated with two syndromes associated with WT1 mutations: WAGR and Denys-Drash syndrome. Perilobar rests, which are often multiple, are associated with Beckwith-Wiedemann syndrome. The syndromes in which germline WT1 mutations occur are:

1. WAGR syndrome (Wilms tumor-aniridia-genital anomalies-retardation), a contiguous gene syndrome, caused by deletions of chromosome 11p13 that include both PAX6 and WT1. The incidence of Wilms’ tumor is <50%.

2. Denys-Drash syndrome (XY individual with undermasculinized external genitalia that can range from ambiguous to normal appearing female, diffuse mesangial sclerosis, and Wilms tumor) is caused by missense mutations in WT1, almost invariably in exons 8 and 9.

3. Frasier syndrome (XY individuals with undermasculinized external genitalia that can range from ambiguous to normal appearing female, focal segmental glomerulosclerosis, gonadoblastoma) caused by point mutations in the WT1 intron 9 donor splice site; and genitourinary (GU) anomalies without renal failure.

Mutations in WT1 are not implicated in most families with Wilms tumor predisposition. Syndromes not associated with germline WT1 mutations:

1. Beckwith-Wiedemann syndrome (BWS), characterized by (predisposition to) organomegaly, hemihypertrophy, abdominal wall defects, macroglossia, neonatal hypoglycemia and the development of embryonal solid tumors. The chromosome locus is 11p15 with a complex critical region of about 5 different genes, with both maternal and paternal imprinting effects. The gene that is the Wilms’ tumor gene is not established yet. Wilms tumor is observed in fewer than 5% of children with BWS.

2. Other inherited multisystem disorders are associated less frequently with Wilms tumor.

3. Linkage analysis has mapped Wilms tumor predisposition genes to 17q (locus name FWT1) and 19q (locus name FWT2). Because some families do not show linkage to WT1, FWT1, or FWT2, the existence of one or more other familial Wilms tumor genes is likely.

4. Familial Wilms’ tumor. Rare (less than 1% of Wilms’ tumor patients). Genetic linkage to chromosome 17q12-22.

Genetic counseling is recommended.

Part III: Common Benign Tumors/Tumor-like Lesions of Childhood

Benign tumors/tumor-like lesions are common in childhood. They are often as little concern medically but occasionally are quite serious. Many have been considered “developmental
aberrations,” especially if isolated (no other physical findings present in the child). However, as our genetics knowledge base increases, we are continuing to learn that even isolated findings can have a genetic cause. It may be that, analogous to the situation in cancer, we may learn that all tumors/lesions have a genetic basis. In this next section, I will try to give examples of inherited genetic conditions which may predispose to the tumor under discussion, as it may be that understanding the etiology of the inherited disorder may provide clues to the pathogenesis of the tumor/ lesion.

SPECIFIC BENIGN TUMORS

1. Heterotopia
Definition: microscopically normal cells or tissues present in abnormal locations
Pathology text describes heterotopic pancreatic tissue and adrenal cells

Two genetic examples are disorders of neuronal migration, characterized by certain brain malformations which can be seen on cranial MRI. The malformations are most often observed in epilepsy patients.

1. Periventricular nodular heterotopia, X-linked. This disorder is sometimes misdiagnosed as tuberous sclerosis because of the similarity in the brain lesions. This neuronal migration disorder is characterized by the presence of uncalcified nodules of neurons ectopically situated along the surface of the lateral ventricles. Affected individuals are predominantly heterozygous females (therefore X-linked dominant condition); males show early lethality. Affected females present with seizures at an average of 14-15 years; intelligence ranges from normal to borderline functioning. The risk for stroke and other vascular/coagulopathic problems appears to be increased.

The causative is loss-of-function mutations in the FLNA (chr X) gene, which encodes the filamin-A protein. [NOTE: Missense mutations in the same gene are associated with a very different group of genetic disorders, the otopalatodigital spectrum disorders, characterized primarily by skeletal dysplasia, not associated with heterotopia]. The filamin class of actin-binding proteins is known to regulate cell stability, protrusion, and motility across various biological systems. A direct mechanism can be drawn with the association of filamin and integrins, which have been implicated in cell adhesion and migration.

Filamins coordinate and integrate cell signaling and subsequent remodeling of the actin cytoskeleton. The complexity of these integrative functions make the implication of individual functions in the pathogenesis of these conditions difficult. However, filamin associates with integrins, which regulate such cellular processes as cell adhesion and neuronal migration. Filamin A may have a similar influence on neuroblast migration during cortical development within the central nervous system. Disruption of this process likely results in the formation of periventricular heterotopias. Similarly, filamins regulate signal transduction by transmembrane receptors and second messengers, the disruption of which could lead to developmental defects such as those observed in the OPD spectrum disorder phenotypes.
2. Sub-cortical band heterotopia (SBH) (aka double cortex syndrome), characterized by a striking band of heterotopic gray matter located just below the cortex. Gene is the “double coticin gene,” DCX. This is also an X-linked disorder, with heterozygous females having double cortex syndrome and hemizygous males having X-linked lissencephaly. Patients with SBH have a mild to severe mental retardation with epilepsy of variable severity and type.

2. Hamartoma
Definition: a focal malformation that resembles a neoplasm grossly and even microscopically, but results from faulty development in an organ; composed of an abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present in the site, which develop and grow at virtually the same rate as normal components, and are not likely to result in compression of adjacent tissue (in contrast to a neoplasm).

Many examples of hamartomas are seen in genetic disorders associated with dysregulation of cell growth.
1. Lisch nodules
   Seen in Neurofibromatosis type 1, a disorder that predisposes affected individuals to multiple abnormalities of embryonic neural crest cells. Lisch nodules are benign age-dependent hamartomas that start to appear at about age 5 years and by about 20 years of age are seen in virtually all individuals affected with NF-1. The gene associated with NF-1 appears to function as a tumor suppressor gene.

2. Tuberous Sclerosis has been described as a neurocutaneous, hamartomatous syndrome. Some of the hamartomas seen in TS:
   Cortical tubers
   Rhabdomyoma (most common primary cardiac tumor of infancy and childhood)
   Retinal hamartoma
   Sub-ependymal lesions
Two genes appear to account for all the cases of TS. The protein product for the TSCI gene is called hamartin. The functions of hamartin and tuberin, the gene product for TSC2, are not fully understood. Hamartin and tuberin have been shown to form heterodimers, suggesting that these two proteins may act in concert to regulate cell proliferation.

3. Teratoma
A teratoma is a type of germ cell tumor typically found in the gonads or the midline. The common feature of teratomas is that they all appear to arise from postmeiotic germ cells. By definition, teratomas include components derived from all 3 embryonic layers (ectoderm, endoderm and mesoderm). Several theories about the origin of these tumors exist. The best evidence suggests that most teratomas are due to abnormal differentiation of fetal germ cells – totipotent germ cells that are capable of forming tissues from at least 2 of the 3 embryonic layers that are foreign to the anatomic region in which they arise. Normal migration of these germ cells may cause gonadal tumors (especially in the ovary and testis), whereas abnormal migration may produce extragonadal tumors. They may also occur at any site in the midline where germ cells
have stopped in their migration to the gonads; common sites are the brain, the neck and mediastinum.

**Sacrococcygeal teratomas** are the most common germ cell tumors of childhood, accounting for about 40% of all teratomas. They present as a mass protruding between the coccyx and rectum, nearly always arising from the tip of the coccyx.

About 10 to 15% of sacrococcygeal teratomas are associated with congenital anomalies: imperforate anus, sacral bone defects, duplication of the uterus or vagina, spina bifida, meningomyelocele.

**Inherited condition with teratomas: the Currarion triad.** Characterized by ano-rectal anomalies (particularly ano-rectal stenosis), a sacro-coccygeal defect, and a presacral tumor (that may be a sacral meningocoele, a teratoma, a cyst, or a mixture of these). At least 50% of cases of the triad are familial with AD inheritance. Gene has been identified as a homeobox gene (\(HLXB9\)) on ch7q36. (def homeobox gene: gene that contains a conserved 180 basepair coding region termed a homeobox. The amino acid residues of the homeobox protein encode a DNA binding-domain, which is consistent with the role of homeobox genes in regulating gene expression, particularly in development).

**VASCULAR ANOMALIES**

Vascular anomalies occur mainly in the skin. The terminology used to describe congenital vascular anomalies has been a source of confusion, in particular, the term “hemangioma,” which has been used to describe a wide variety of vascular anomalies, most of which we now understand are not hemangiomas. New research in vasculogenesis and angiogenesis has facilitated a more accurate classification of congenital vascular anomalies. A precise classification of vascular anomalies is important:

- For better understanding of the developmental etiologies
- For providing prognosis
- Because correct classification can have a direct impact on patient management
- For accurate genetic counseling

These are excellent references on the topic of classification of vascular anomalies:


Note: The classification of vascular anomalies presented here and in these publications has been accepted by the International Society of the Study of Vascular Anomalies (in 1996).
Vascular anomalies can be divided into vascular tumors and vascular malformations, which differ clinically and histologically. We will discuss hemangioma as a true vascular tumor, and several vascular malformations.

**Hemangioma**
A hemangioma is a rapidly growing vascular tumor of infancy, and is the most common tumor of infancy. This benign tumor is usually not present at birth, appears during the first 2 weeks of life, and undergoes a natural regression within 5 to 10 years. That is, there is a proliferative phase followed by apoptosis and at the end of the life cycle, the tumor is in its involuted phase. Hemangiomas do not occur in adolescents or adults.

They are composed of plump, rapidly dividing endothelial cells. Studies using immunohistochemical markers throughout the life cycle of the hemangioma have demonstrated a pattern, changing during the course of the hemangioma, of up-regulation of several different proteins, peptides and specific molecules suggesting genetic control. However, there is no evidence of Mendelian inheritance of hemangioma although occasionally siblings are affected. The initiating “trigger” has not yet been identified.

**Vascular Malformation**
Vascular malformations are usually, but not always, obvious at birth. They never regress, they grow proportionately with the patient, and sometimes they expand. Vascular malformations (VM) can be subcategorized based on channel morphology and rheology as either slow-flow or fast-flow, into the simple forms (arterial, venous, capillary or lymphatic), and the combined forms (such as arteriovenous and capillary-venous-lymphatic malformations). VM has a bluish-purple color, and may be emptied by compression. They are most often located in the skin and/or mucosal membranes, but visceral lesions do occur. The lesions are typically multifocal – not all vessels are affected.

Most VMs are sporadic, but families with Mendelian inheritance (usually dominant) have been reported for a variety of VMs, allowing for genetic analysis. Several causative genes have been identified, for example, the receptor tyrosine kinase, TIE-2, a receptor expressed specifically in endothelial cells. Only veins in the mucocutaneous tissues are affected in individuals carrying a TIE-2 mutation. It is not known whether TIE-2 mutations are involved in apparently sporadic VMs. Research is ongoing, and studies have implicated other chromosome loci, so it is clear that there is genetic heterogeneity.

In addition to genetic studies, immunohistochemical studies have begun to elucidate the molecular basis of VMs. The 2 most important components of blood vessel walls are the endothelial and smooth muscle cells. Apparently there is no proliferation of endothelial cells, and a deficiency of smooth muscle cells in VMs. Histology of VMs shows large ectatic channels with thin walls.

**Inherited disorder with lesions that are characteristic of both hemangioma and vascular malformation:** **Von Hippel-Lindau disease.** An AD, tumor predisposition syndrome characterized by benign and malignant tumors and cystic lesions, and by overgrowth of the blood vessels. The most common site is the retina – lesions referred to both as retinal angiomomas and
retinal capillary hemangioma. Histologically, the retinal lesions are identical to cerebellar hemangioblastomas. Other hallmark lesions of VHL include hemangioblastomas of the cerebellum and spinal cord, and renal cell carcinomas. At least 25 manifestations of VHL have been described.

Caused by mutations in the VHL gene (ch3p25). The VHL protein does not have homology to other proteins. The gene appears to function as a tumor-suppressor gene. The most striking feature of the clinical manifestation of VHL is angiogenesis. Efforts are ongoing to understand the mechanism by which the VHL protein acts as a tumor suppressor. It appears to down-regulate the transcription of certain genes.

**Vascular Birthmarks.** These are also known as “stork bite,” “salmon patch,” “strawberry birthmarks,” or “angel’s kiss.” They are harmless macular stains of neonates, occurring in 30 to 40% of newborns, usually in the nuchal region, eyelids, glabella, and lips. These stains typically disappear within 1 year without leaving a trace. They are not capillary malformations or pathologic lesions and their etiology is unknown.

**Capillary Malformations (CM)**

**“Port-Wine” Stain (aka “nevus flammeus”)** is a CM that does not disappear. It gradually darkens from pink to purple, and some facial lesions exhibit soft tissue hypertrophy. Skeletal overgrowth in the region of CM can also occur, especially in the maxillary region.

A genetic disorder with capillary malformation: **Sturge-Weber syndrome (SWS).** Sturge-Weber syndrome (also called “encephalotrigeminal angiomatosis”) is a congenital disorder characterized by vascular birthmarks and neurological abnormalities. Symptoms of the disorder vary widely among patients. The most apparent symptom is a facial capillary malformation (or nevus flamus) or part wine stain that is present at birth and usually involves at least one upper eyelid and the forehead. It is also characterized by angiomas (excessive blood vessel growth) of the leptomeninges that cause seizures. A wakening or loss of use of the side of the body opposite the port wine stain (hemiparesis) may also develop. Developmental delay of motor and cognitive skills may occur. SWS syndrome rarely affects other body organs.

This is a sporadic condition. A gene has not been identified. It has been suggested that SWS may only be viable in the mosaic state.

**Lymphatic Malformations**

Lymphatic-derived channels can also comprise abnormalities that are similar to those that occur in capillaries and veins. Lymphatic malformation (LM) is a defect of cutaneous and subcutaneous lymphatic vessels. An LM is composed of clusters of dilated lymphatic channels (vesicles) with both thick and thin muscular layers (smooth and skeletal), filled with clear proteinaceous fluid, and not connected to normal lymphatic vessels. These lesions occur mostly in the cervicofacial area, although they can also occur in solid organs, in skeletal tissue, and in multiple organ systems.
Familial LM has not been reported. It is postulated that all sporadic cases of LM could be caused by *de novo* dominant mutations, or perhaps LM may only be viable in the mosaic state. Infants with Turner syndrome (45,X) often have a nuchal LM (usually called a cystic hygroma).
GENERAL PATHOLOGY OF INFECTIOUS DISEASE

Self Study Notes

by

Dixie D. Whitt, PhD

Reading Assignment: Robbins and Cotran
*Pathologic Basis of Disease*

OBJECTIVE: See College Objectives
Introduction to Pathology of Infectious Diseases

Dixie Whitt, September 2007

Learning the ways in which infectious diseases could be controlled was one of the greatest medical triumphs of the last two centuries. Starting in the 1800s, with the realization that many diseases were caused by microorganisms, great strides have been made in identifying and preventing diseases that once took millions of lives. Vaccines were developed against some of the most feared diseases. The discovery of antimicrobial compounds made it possible for the first time to cure infectious diseases. Smallpox was eradicated, the first such global success. As late as 1970, the human victory over disease-causing microbes seemed unassailable. Then, the cracks in the façade of human invulnerability began to appear. Acquired immunodeficiency syndrome (AIDS), a new viral disease, emerged. And new bacterial diseases such as Legionnaire’s and Lyme diseases were documented. Tuberculosis reappeared in developed countries. An epidemic of cholera, a disease previously seen mainly in Europe and Asia, swept through South America. Large and widespread outbreaks of food-borne disease began to occur with depressing regularity. Medication failed in some patients infected with bacteria that were resistant to many antibiotics. Humans were learning a new lesson. It doesn’t pay to underestimate an adversary with a three-billion-year evolutionary head start. An overview of the leading infectious disease killers in the world based on 1998 data from the World Health Organization is shown in Figure 1.

Emerging and Reemerging Infectious Diseases

Complacency gives disease-causing microbes another chance

Scientists in Pasteur’s time knew that effective prevention of disease required constant vigilance. By the 1950s, however, this principle did not seem so important. Physicians, elated by the success of antimicrobial compounds, began to think that infectious diseases were no longer a problem, except for those few viral diseases for which no effective drugs were available. Scientists stopped investigating life-threatening bacterial diseases, such as pneumonia and tuberculosis, and programs for the prevention of tuberculosis were dismantled. Pharmaceutical companies, faced in the 1960s with a glut of antibiotics on the market, began to cut back or shut down completely their antibiotic research and discovery programs. This meant that by the 1990s, fewer and fewer antibiotics entered the market each year. Because it takes at least 10 to 20 years to bring a new antibiotic from the lab bench to the market, the impact of decisions made in the 1960s was not felt until much later. Complacency was not limited to the developed countries. Worldwide, the control of the major infectious diseases continued to have a low priority compared to other investments such as arms expenditures.

Although the medical community forgot about bacteria and eukaryotic microbes, the microbes did not forget their human targets. Bacterial resistance to antibiotics rose steadily, until some strains of bacteria were treatable by only one antibiotic or were not treatable at all. Physicians were slow to admit that resistance to antibiotics was a problem, because they assumed there would always be new antibiotics to treat the resistant strains. Hospital administrators were the first to become alarmed about resistance to antibiotics, because of escalating costs and increased time patients must spend in the hospital because of infections caused by resistant microbes.
Figure 1. Role of infectious diseases as cause of death worldwide in 1998. (A) Microorganisms are responsible for millions of deaths each year. In 1998, the major killers of children younger than 5 years of age were acute respiratory infections and diarrheal diseases, whereas the major killers of those older than five were acute respiratory infections, AIDS, and tuberculosis. (B) In children between birth and 4 years, infectious diseases accounted for 63% of deaths. (C) Infectious diseases accounted for almost half (48%) of all deaths between birth and 44 years. (Data from the World Health Organization, 1999).
Changes in disease patterns

The unexpected appearance of new diseases in the last decades of the 20th century and the beginning of the 21st century was something of a shock to the medical community. In most cases, the microorganisms had been around for years, but the opportunities to infect humans had not been frequent enough to produce disease outbreaks. Changes in human practices that increased the frequency and conditions of contact with microbes created situations in which disease could occur. An example of this is the connection between air-conditioning and Legionnaire’s disease. Medicine itself produced some new diseases. Cancer chemotherapy and organ transplants created new populations of people whose immune systems were severely compromised during attempts to stop tumor growth or prevent rejection of new organs. To make matters worse, these people often were collected together in hospitals, thus increasing the likelihood of disease transmission. Microbes that had been thought to be incapable of causing human disease became a serious problem in these immunocompromised people.

Individuals infected with human immunodeficiency virus (HIV) swelled the ranks of those who were hypersusceptible to many diseases. Crowding in homeless shelters and prisons increased the likelihood of disease spread. The increasing number of elderly people, whose immune systems had begun to deteriorate and who were often placed together in nursing homes, provided still another disease opportunity for enterprising microbes. The media began to publish alarmist reports of “killer bugs” and an imminent return to the pre-antibiotic era. Physicians began to realize that new antibiotics were no longer appearing with the frequency they had a decade before. Alarm bells were going off on many different fronts.

The pharmaceutical industry sprang belatedly into action on the antibiotic discovery front, but with distinctly less enthusiasm than in the first half of the century. Antimicrobials had become much less economically attractive for these companies, because it was more difficult to discover new antimicrobials and much more expensive to conduct the clinical trials needed to establish safety and efficacy and to satisfy the requirements of regulatory agencies. Moreover, antibiotics usually cured patients after a short course of therapy. By contrast, other pharmaceuticals, such as antidepressants and blood pressure medications, were administered daily for long periods of time and were thus much more profitable. Anti-HIV medications became an exception to this rule, because they must be taken daily for life, but most antimicrobials were unprofitable compared with other categories of drugs. New antibiotics are now once again beginning to move toward the market, but it will take years to achieve the levels of effectiveness and abundance that characterized antibiotic therapy in the 1950s and 1960s.

Tuberculosis, which had been virtually eradicated in developed countries, showed up again in big cities beginning in the 1980s. Concurrently, government policies that led to moving many patients from mental institutions into the mainstream caused the ranks of the homeless to swell, contributing enormously to the spread of antibiotic resistant tuberculosis. Homeless shelters provided places where disease transmission could occur easily. The regimen of antituberculosis drugs was complicated, and many patients were unsupervised, leading to low compliance and the rise of drug-resistant strains of tuberculosis. International travel boomed, and travelers became vectors of disease. Malaria cases appeared in developed countries, brought home by citizens traveling
overseas. Travelers also brought penicillin-resistant strains of *Streptococcus pneumoniae*, the most common cause of bacterial pneumonia, from Europe to the Americas.

**Fortunately, not all the news was bad**

At the same time that health officials were waking up to the realization that infectious diseases had by no means been conquered, scientists discovered that “new” infectious diseases were bringing renewed hopes for cures for diseases previously thought to be incurable. The first such breakthrough was the discovery that a gram-negative bacterium, *Helicobacter pylori*, causes most gastric ulcers. This discovery led to a pharmaceutical cure for ulcers and has dramatically increased the quality of life for ulcer sufferers. In addition, *H. pylori* also appears to be responsible for gastric cancer, one of the most deadly forms of malignancy. Thus, curing ulcer patients early may also reduce the incidence of gastric cancer. The *H. pylori* success story generated a veritable gold rush to find a bacterial cause for chronic incurable diseases. Atherosclerosis, rheumatoid arthritis, coronary artery disease, colon cancer, and inflammatory bowel disease are among the diseases now being reconsidered. How many actually prove to be microbial in origin remains to be determined, but if even one of these diseases is moved from the incurable to the curable list, a giant advance will have been made. Another sort of good news is the complete eradication of a microbial disease. The first success was the eradication of smallpox, and efforts to eradicate polio are ongoing.

**Bioterrorism**

The CDC defines bioterrorism as "the intentional release of bacteria, viruses or toxins for the purpose of harming or killing civilians." Agents that can be used in bioterrorism attacks are classified into three categories (A, B, and C). See p. 346 in your text for the agents that fall into each of these categories.

**Types of Pathogenic Microbes**

The different types of pathogenic microbes include viruses, bacteria, fungi, protozoa, and metazoal parasites. Strictly speaking, metazoal parasites are not “microbes” because adult forms of many of them can be seen with the unaided eye, but they are usually included under the heading of microbes because some of their developmental stages including the diagnostic forms, can only be seen with a microscope.

**Viruses**

*Viral structure.* Viruses are the smallest and simplest of the pathogenic microbes. They have a nucleoprotein core, which contains the viral genome and proteins needed to initiate their replication cycle. The nucleoprotein core is protected by the capsid, which consists of tightly packed proteins (capsomeres). The shape and charge properties of the capsomeres dictate how the capsomeres will interact with each other. Capsid shape is one of the traits used to classify and identify viruses. Some viruses have an envelope that surrounds the capsid (enveloped viruses). The envelope consists of a phospholipid bilayer
(derived from host cell membranes) containing embedded proteins (encoded in the viral genome). Whereas other types of pathogenic microbes have double-stranded DNA genomes, viruses can have genomes that are composed of single-stranded RNA, double-stranded RNA, single-stranded DNA, or double-stranded DNA. The replication strategy of a virus is dictated by the characteristics of its genome.

**Viral replication cycle.** Some features of the viral replication cycle are common to most viral pathogens. The surface proteins of the virus (i.e., the capsid proteins of naked viruses and envelope proteins of enveloped viruses) mediate attachment of the virus to a specific molecule on the surface of a host cell (receptor). The receptor can be the carbohydrate moiety of a host cell glycoprotein or glycolipid, or it can be a host cell membrane protein. The tissue distribution of this receptor determines what tissues the virus can infect (tissue tropism). For example, the virus that causes rabies passes through neurons and infects the brain because its envelope proteins recognize a receptor that is located only on neurons. After the attachment to the target host cell, the virus is internalized and enters the host cell cytoplasm. In the process, the envelope and capsid are removed, releasing the nucleoprotein core. This step is called uncoating. The nucleoprotein core then directs production of viral proteins and more copies of the viral genome. Many viruses provide the enzymes needed to reproduce the viral genome, but they utilize nucleic acid precursors produced by the host cell and they rely on the host cell’s protein synthesis machinery for production of viral proteins. After many copies of the viral genome are made and viral proteins are produced, the viral particle is assembled and the virus exits the host cell either by lysing the host cell (a common feature of naked viruses) or budding through the host cell membrane (the preferred exit mechanism of enveloped viruses). The phospholipids of the viral envelope are acquired from the host cell membrane, into which viral envelope proteins have been inserted.

**Implications for diagnosis and treatment of viral infections.** The parasitic nature of viruses has some important implications for diagnosis and treatment of viral infections. Since viruses only replicate inside eukaryotic cells, they must be cultivated in tissue culture cells or embryonated eggs. Many viruses produce characteristic changes in host tissues or in tissue culture cells, which can be seen with a light microscope even though the viruses themselves cannot. These characteristic changes are called cytopathic effects and can be useful in identifying a viral pathogen. For example, to determine if an animal is rabid, sections of the animal’s brain are examined under a light microscope for the characteristic lesions caused by the virus that causes rabies. The need to use tissue culture cells for viral cultivation can make diagnostic tests based on cultivation of the virus expensive and time-consuming. Using an electron microscope to visualize the virions is even more expensive because it requires a complex and expensive piece of equipment, as well as personnel trained to use it. Accordingly, diagnosis of a viral infection is often based on tests that either employ antibodies to detect the virus in clinical specimens or use viral proteins to detect antibodies against that particular virus in the patient's blood.

The fact that viruses make such extensive use of host cell biosynthetic machinery limits the number of potential targets for chemicals that stop viral replication (antiviral agents). An effective antiviral agent must inhibit viral replication without causing undue toxicity to the host. Thus, antiviral agents must target viral proteins that are specific to the virus. Most of the currently available antiviral agents either target the uncoating step or steps involved in replication of the viral genome, although agents that prevent viral
attachment or budding of the virus from the host cell are also under investigation. The fact that viruses differ so much from each other with respect to the nature of their genome and their replication strategies explains why most antiviral agents are effective only against certain types of viruses.
Bacteria

Comparison with eukaryotes. Bacteria are unicellular prokaryotes, which have double-stranded DNA genomes. A comparison of features of prokaryotes and eukaryotes are summarized in Table 1. Eukaryotes have multiple linear chromosomes, but most bacteria have a single circular chromosome. Some unusual bacteria have more than one chromosome and some even have linear chromosomes. *Borrelia burgdorferi*, the cause of Lyme disease, is an example of a bacterium with a linear chromosome. The prokaryotic genome, like the genome of a eukaryote, is concentrated into a compact mass (nucleoid) but unlike the eukaryotic nucleus the bacterial nucleoid does not have a nuclear membrane. The genes of eukaryotes are monocistronic, i.e., each mRNA contains information from a single gene. Prokaryotes frequently transcribe several genes in a single mRNA, i.e., their messages can be polycistronic. Prokaryotes, like eukaryotes, use DNA polymerases to replicate their DNA and DNA-dependent RNA polymerases to make RNA. The polymerases of prokaryotes and eukaryotes have substantially different properties, however, and chemicals that inhibit bacterial DNA or RNA polymerases generally do not inhibit eukaryotic polymerases and vice versa. Some clinically important antibiotics are chemical compounds that inhibit the activities of bacterial DNA or RNA polymerases.

Table 1. Comparison of prokaryotes and eukaryotes

<table>
<thead>
<tr>
<th>Type of microbe</th>
<th>Prokaryotes</th>
<th>Eukaryotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>dsDNA, usually single circular chromosome</td>
<td>dsDNA, multiple linear chromosomes</td>
</tr>
<tr>
<td>Nuclear membrane</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Genes</td>
<td>Monocistronic or polycistronic</td>
<td>Monocistronic</td>
</tr>
<tr>
<td>Nucleic acid synthesis</td>
<td>DNA-dependent DNA and RNA polymerases</td>
<td>DNA-dependent DNA and RNA polymerases</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>Ribosomes (30S, 50S subunits)</td>
<td>Ribosomes (40S, 60S subunits)</td>
</tr>
<tr>
<td>Site of energy generation</td>
<td>Cytoplasmic membranes, cytoplasm</td>
<td>Mitochondria, cytoplasm</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>External cell wall</td>
<td>Peptidoglycan (some exceptions)</td>
<td>Fungi and some metazoal parasites</td>
</tr>
<tr>
<td>Size</td>
<td>0.3-40 µm (average 1-2 µm)</td>
<td>Fungi - 4.0-25.0 µm; Protozoa - 2.0-50.0 µm; Metazoa - highly variable (&gt;20 µm)</td>
</tr>
</tbody>
</table>
Prokaryotes, like eukaryotes, use ribosomes for protein synthesis, and the ribosomes of prokaryotes have a structure that resembles the structure of eukaryotic ribosomes (one small subunit and one large subunit), but the size and composition of the prokaryotic ribosome are different from those of eukaryotic ribosomes. For example, the prokaryotic ribosome has a size of 70S (where S is a unit of sedimentation used to measure the sizes of large multiprotein complexes), and the subunits of a prokaryotic ribosome are 30S and 50S in size. Eukaryotic ribosomes are 80S in size, with subunits of 40S and 60S. The proteins and ribosomal RNA (rRNA) molecules that make up prokaryotic and eukaryotic ribosomes are also different. The differences between prokaryotic and mammalian ribosomes are sufficiently great that antibiotics capable of inhibiting prokaryotic protein synthesis have little or no effect on mammalian ribosomes. Accordingly, the protein synthesizing machinery of prokaryotes is the target of many clinically important antibiotics.

In eukaryotes, glycolysis occurs in the cytoplasm and products of glycolysis are further converted into energy by organelles called mitochondria. Prokaryotes also have their glycolytic enzymes in the cytoplasm, but the energy generating processes analogous to those mediated by mitochondria occur in the prokaryote's cytoplasmic membrane. The majority of pathogenic bacteria use glycolysis as part of their energy-generating metabolism, but some use other energy-generating pathways.

Eukaryotic cells have an internal cytoskeleton that helps to determine their structure and anchors them to a substratum. Prokaryotes have no internal cytoskeleton. Instead, most prokaryotes have a rigid cell wall, which covers the cytoplasmic membrane. This cell wall consists of a network called peptidoglycan, which is composed of a polysaccharide backbone cross-linked with peptide segments. Because mammalian cells do not have peptidoglycan, antibiotics that inhibit bacterial peptidoglycan synthesis are unlikely to have toxic effects on mammalian cells. Bacterial peptidoglycan synthesis is another major target of clinically used antibiotics. Finally, prokaryotes differ from eukaryotes in size. Pathogenic bacteria range in size from 0.3 to 40 µm (average = 1.0 to 2.0 µm), and are generally large enough to be seen with a light microscope at high magnification (200x). Eukaryotic pathogens are usually larger, and can be seen with a light microscope at lower magnification.

Motility and adherence. Some bacterial pathogens are motile, a feature that allows them to swim to mucosal surfaces once they enter the human body. A common form of motility is mediated by flagella, long flexible helical shaped protein fibrils that extend outward from the surface of the bacterium and move it by rotating, much as an outboard motor propels a boat. Many pathogenic bacteria have surface proteins that allow them to attach to the surface of host cells (adhesins). It is advantageous for bacteria to be able to adhere to host surfaces if they are trying to colonize areas such as the small intestine or bladder, where the rapid flow of fluids through the area can wash them out of the site. Adherence to a host cell surface is the first step in invasion of host tissues. One type of bacterial adhesin has a fibrillar structure. These adhesive structures are called fimbriae or pili. Other adhesins, called afimbrial adhesins, are not organized into fibrillar structures. Bacterial adhesins, like viral surface proteins, are specific for certain host cell receptors, and this specificity determines the tissue tropism of the bacterial pathogen.
Endospores. A few bacterial pathogens can change from their replicating form (vegetative form) into tough survival forms, called endospores. Endospores are nonreplicating and metabolically inactive but can survive disinfectants or harsh conditions such as the low pH of the stomach.

Bacterial morphology and staining characteristics. Bacteria come in several different shapes, including straight rods (bacilli), curved rods, spheres (coccis) and spirals. The shape of a bacterium can be useful for identification, but since many different genera and species can have the same shape, shape alone is usually not sufficient to identify a bacterium. Bacteria also differ in the thickness of their peptidoglycan layer and in the presence or absence of a second membrane, the outer membrane, which covers the peptidoglycan layer. The peptidoglycan layer plus the outer membrane is called the cell envelope. Bacteria can be classified into two types based on the characteristics of their cell envelope. These two types of bacteria are easily differentiated from each other because their differences lead to differences in the ability to retain the dye crystal violet when washed with an ethanol-acetone mixture during the Gram stain. One type of bacterium is covered by a shell consisting of many layers of peptidoglycan studded with proteins. These are the gram-positive type of bacteria because they retain crystal violet during the staining process. The second type of bacterium has only one or a few layers of peptidoglycan, covered by and linked to a second membrane (outer membrane). These bacteria with a thinner cell wall and an outer membrane stain gram-negative. The shape and gram-stain reactivity of a bacterium are important traits used to identify bacterial pathogens. Although microscopic examination of a gram-stained slide containing material from a clinical specimen is seldom sufficient to provide a final diagnosis, this information can often allow a presumptive diagnosis to be made so that therapy can be initiated while further diagnostic tests are being completed. The Gram stain has the advantage that it is inexpensive and requires less than 15 minutes to perform.

Extracellular and intracellular pathogens. Most bacteria that cause human disease are capable of replicating outside host cells. Some, however, can only replicate inside a host cell. These are called obligate intracellular pathogens. An example of an obligate intracellular bacterial pathogen is Chlamydia trachomatis, a cause of nongonococcal urethritis and pelvic inflammatory disease. Unlike viruses, obligately intracellular bacteria carry out most of their own biosynthetic reactions (i.e., have their own DNA and RNA synthesizing enzymes and their own ribosomes). They are obliged to replicate inside host cells because they lack the ability to make some essential nutrient. C. trachomatis, for example, is unable to make nucleotide triphosphates and must obtain these from the host cell. Some bacteria that are capable of replicating outside host cells nonetheless prefer to grow inside host cells during an infection because this replication strategy helps to protect them from the host's immune system and provides them with additional sources of nutrients. Such bacterial pathogens are called facultative intracellular pathogens. Bacteria that grow primarily outside of host cells during an infection are called extracellular pathogens.

Bacterial replication. Bacteria divide by binary fission. This means that bacterial numbers increase exponentially, by orders of 2, during growth. Bacteria differ
considerably with respect to their rate of growth. *Escherichia coli*, a cause of urinary and gastrointestinal tract infections, can divide as frequently as once every 20 minutes in laboratory medium, whereas *Mycobacterium tuberculosis*, the cause of tuberculosis, is able to divide only once every 24 hr. In the body, bacterial growth seldom occurs at the maximum rate because essential nutrients are limiting. Even so, bacterial growth rates in the body can be high enough for the disease to progress rapidly. This is why some bacterial diseases such as pneumonia and meningitis can develop so quickly, whereas diseases like tuberculosis, which are caused by slow-growing bacteria, may take many months to develop.

Because most pathogenic bacteria can be cultivated in cell-free laboratory medium, cultivation of bacteria is generally easier and less expensive than cultivation of viruses. Cultivation is usually done on the solid surface of agar medium. If a specimen containing bacteria is spread onto agar medium, individual bacteria give rise to isolated colonies. Even motile bacteria do not migrate far from the place where they were originally deposited, so the colonies develop as localized mounds of bacteria. The surface properties of bacteria and the pigments some of them produce give colonies a characteristic appearance that can be useful for identification. For example, *Staphylococcus aureus*, a common cause of skin and wound infections, forms colonies that have a golden color and this trait is what gave this species its name (*aureus*, derived from the Latin word for gold).

A problem that arises in connection with cultivation of bacterial pathogens is that different pathogens may require substantially different media and atmospheric conditions for growth. For this reason, it is important to have some idea of what type of bacterial pathogens might be responsible for a patient's symptoms. Fortunately, the nature of the symptoms and the location from which the specimen is obtained generally suggest a limited number of possible pathogens. Also, a Gram stain of the appropriate clinical specimen can provide valuable clues as to the possible identity of the bacterial pathogen. Another problem with cultivation-based identification procedures is that it usually takes at least 24 hr to obtain isolated colonies. Subsequent identification tests needed for a definitive diagnosis extend the time period even longer. In many cases, the clinician cannot wait for the test results before initiating treatment. The clinician must use the patient's symptoms and history to arrive at a tentative diagnosis, then order treatment on that basis. Such therapy is called empiric therapy. Later when test results are available, the therapy can be adjusted if necessary. As already mentioned, rapid tests such as the Gram stain may aid the clinician in a tentative diagnosis.

**Pathogenic Eukaryotes: Fungi**

*Characteristics of Fungi - Implications for Therapy.* Fungi are eukaryotes, but they differ from mammalian cells in that they have a thick polysaccharide cell wall (Table 1). Enzymes involved in fungal cell wall biosynthesis are an important target for antifungal agents. Although the fungal cell wall plays the same role as bacterial peptidoglycan, it has a completely different composition and is produced by a different set of biosynthetic enzymes. For this reason, antibacterial compounds that inhibit peptidoglycan synthesis have no effect on pathogenic fungi. The fungal cell wall generally consists of more than one type of polysaccharide, and different fungal species have different types of cell wall.
Accordingly, an antifungal agent that targets the synthesis of one type of cell wall polysaccharide is not effective against all fungi.

Another important difference between fungi and mammalian cells is that fungi have ergosterol rather than cholesterol as an essential component of their membranes. Enzymes involved in ergosterol biosynthesis are the targets of a number of antifungal agents. In many other ways, fungi are similar to mammalian cells. That is, they have similar mechanisms for synthesizing their DNA, RNA and proteins. Nonetheless, there are enough differences between the fungal proteins that catalyze these processes and those of mammalian cells that fungal nucleic acid and protein synthetic machinery can be used as a target for antifungal agents. These antifungal agents can have toxic side effects, however, because they usually have some effect on mammalian enzymes, even if their effect on fungal enzymes is greater.

**Yeast, Mycelium, and Spore - Developmental Stages of Fungi.** Fungi can exist in a unicellular or multicellular form. The unicellular form (yeast) is an ovoid cell that reproduces by budding. Yeasts can also produce spores, which have the same general traits and functions as bacterial endospores and help the yeast to persist in the face of adverse environmental conditions. The multicellular form (mycelium) is a fibrous network of tubes called hyphae. A hyphal segment contains end-to-end cells that may be separated by a cell wall (septate hyphae) or have pores between cellular constituents that connect the cytoplasms of adjacent cells (nonseptate hyphae). Hyphal segments grow from the tip. Proteases and other degradative enzymes are produced in the growing tip. These enzymes help the hyphal tip to penetrate the substratum on which the fungi are growing and release nutrients for use by the fungus. As the mycelium develops, spores are produced at various points along the hyphae.

Some pathogenic fungi, such as the fungi that cause athlete's foot, grow only in the mycelial form. Others can assume the yeast form when they enter the human body. Fungi that can switch between the mycelial and yeast form are the most serious fungal pathogens because switching to the yeast form facilitates their spread throughout the body. A fungal pathogen that grows in the mycelial form at temperatures less than 30°C and in the yeast form at 37°C is called a dimorphic fungus. Usually the distinction between the form of the fungus seen in the human body compared to that seen in the environment is not as marked as this definition implies. Dimorphic fungi are usually seen both as yeast and hyphal forms in the human body, although the hyphae are not as long and do not form the extensive branched network associated with the mycelial form. Yeasts with short hyphal extensions are called pseudohyphae. Hydrolytic enzymes produced at the hyphal tip help the pseudohyphae to penetrate host tissue and thus contribute to fungal invasiveness.

**Diagnosis of fungal infections.** Yeast forms of different fungal species tend to look alike, but the appearance of hyphae and the location and appearance of spores differs considerably from one species to another. In fact, the morphology of the mycelial form can be used to identify the species of a fungal pathogen. Because of the tough fungal cell wall, yeasts and mycelia retain their structures when exposed to 10% KOH, a treatment that dissolves mammalian cells. Thus, if a fungal pathogen is suspected, the clinical specimen is treated with KOH to eliminate tissue cells and make it easier to see the
fungal structure. Special stains, such as calcifluor (which binds to β-glucans in the fungal cell wall) help to make the fungi visible.

Fungi, like bacteria, are free-growing and can form colonies on agar. The appearance of these colonies can be useful for identification. Yeasts commonly produce colonies that have a smooth surface. Colonies of fungi growing in the mycelial form have a fuzzy appearance, with characteristic patterns of pigmentation. The fuzzy appearance is due to the branched nature of the mycelial network and pigmentation is generally due to structures that contain spores. A problem with using colonial morphology to diagnose a fungal infection is that fungi grow very slowly. Whereas a bacterial colony may appear within one or a few days, fungal colonies usually become visible only after a week or more of incubation. This means that special medium, which discourages the growth of possible bacterial contaminants, must be used to cultivate pathogenic fungi. Given the long time required to obtain fungal colonies, visualization of fungal pathogens in clinical specimens assumes particular importance and is frequently the only early clue that a patient has a fungal infection.

More Pathogenic Eukaryotes: Protozoal Parasites

*Characteristics of protozoal parasites.* Protozoal parasites are unicellular eukaryotes. They differ from fungi in that they do not have a rigid cell wall and do not have a multicellular form. Protozoa come in a variety of shapes and some have multiple nuclei. Although they do not switch from unicellular to multicellular forms as fungi do, protozoa commonly have more than one developmental stage. An example is provided by *Giardia intestinalis*, the cause of a type of chronic diarrhea called giardiasis. *G. intestinalis* has two forms: the replicating form (trophozoite) and the survival form (cyst). The cyst has the same function as the bacterial or fungal spore. Since it survives much longer in the environment than the fragile trophozoite form and can survive passage through the stomach, the cyst form is the infective form. Many of the protozoa with simple life cycles are motile. *G. intestinalis* moves by means of flagella. Protozoa of this type are called flagellated protozoa. Other protozoa move by pseudopod formation (amebas) or by the motion of numerous short filaments (cilia). Some protozoa have complex life cycles. The different forms they assume are specially adapted to different human tissue and cell types that are parasitized by the protozoan as it moves through the body. An example of a protozoan with a complex life cycle is *Plasmodium vivax*, a cause of malaria. This protozoan has two types of hosts, insects and mammals, and it assumes different forms as it moves from one host to another. Within the human body, it assumes different forms as it passes through liver and blood cells and finally assumes the sexual forms that are ingested by the mosquito during a blood meal.

*Diagnosing Protozoal Infections.* Many infectious protozoa cannot be cultivated in the laboratory or can only be cultivated with difficulty. Thus, diagnosis of protozoal infections relies heavily on microscopic detection of diagnostic forms of the organism.
Diagnostic forms are forms of the parasite that are unique and that are found in easily obtained specimens such as feces, urine, or blood. For example, visualization of the red blood cell stages of *P. vivax* in a blood sample is used to diagnose malaria. Serological and nucleic acid-based tests are now available for diagnosing some protozoal infections such as giardiasis, but in many cases microscopic examination of clinical specimens for diagnostic stages of the protozoan remains the gold standard.

*Targe ts of antiprotozoal drugs.* Protozoa have the usual characteristics of eukaryotic cells, such as a nuclear membrane and a cytoskeleton, but some of them do not have mitochondria and some have unusual organelles such as the kinetoplast, a DNA-containing organelle distinct from the nucleus and mitochondria. Such unusual organelles have proved to be good targets for antiprotozoal drugs. In addition, the biosynthetic machinery of protozoa is usually different enough from that of mammalian cells to allow drugs that interfere with protozoal DNA or protein synthesis to be used to combat protozoal infections. Some antibacterial antibiotics can be used to treat protozoal infections because there are similarities between certain metabolic pathways of bacteria and protozoa. For example, humans require preformed folic acid, which serves as an essential cofactor in several biochemical pathways. Bacteria and protozoa make their own dihydrofolic and tetrahydrofolic acid. Chemical compounds that inhibit steps in this pathway are effective against some protozoa as well as bacteria.

**Still More Pathogenic Eukaryotes: Metazoal Parasites**

Metazoal parasites (also called helminths) are multicellular eukaryotes. There are three types of pathogenic metazoa: trematodes (also called flukes), cestodes (also called tapeworms) and nematodes (also called roundworms). An example of a trematode is *Schistosoma mansoni*, the cause of schistosomiasis. *S. mansoni* passes through several larval stages, some of which occur in aquatic snails and some of which occur in the human body. The adult form is a worm that has two sexes and mates in the human bloodstream to produce eggs, which are excreted in urine or feces. The egg has an unusual hook type appendage that allows it to become lodged in small blood vessels. The egg is the diagnostic form of the parasite.

An example of a cestode is provided by *Taenia saginata*. Cestodes are flat, segmented worms that have a head (scolex) that is used to anchor the worm in the human intestinal lining. The segmented portion of the worm (strobila) attached to the scolex is made up of a series of proglottids. Cestodes do not have a digestive tract, but each proglottid of the worm has a complete reproductive tract. As new segments are added at the scolex, the older segments mature and eggs appear in the reproductive tract. The mature segments, called gravid proglottids, break off and are excreted in feces. Cysticerci, which are the larval forms that develop in the egg, are the infective form of the cestode. Depending on the species of cestode, gravid proglottids or eggs are the diagnostic stage.

An example of a nematode is provided by *Trichinella spiralis*, the cause of trichinosis. The developmental cycle of nematodes begins with an egg and proceeds through various larval forms to produce a mature worm. Mature worms and larvae have a single digestive tract and a single reproductive tract. Mature worms are either males or
females and mate to produce eggs. The egg is the diagnostic form of most nematodes, although larvae and fragments of the adult worm are sometimes excreted and can be used in diagnosing the infection.

Metazoal parasites vary considerably in size. Trematodes are generally very small, and most stages are only visible with a microscope. Cestodes and nematodes range in size from a few mm to several meters in length. The eggs and gravid proglottids are too small, however, to be seen without a microscope. Targets of antimezoal agents include the nervous system, energy-generating pathways, DNA-synthesizing, and protein synthesizing machinery of the parasite.

Host Defenses

To cope with the enormous variety of microbes it encounters, the human body has evolved sets of overlapping defenses that are effective against most pathogenic microbes. One set of defenses does not target specific microbes. These defenses are called innate defenses. Examples of innate defenses are skin and mucosal surfaces, phagocytic cells, the complement system, and the cytokine system. The innate defenses are always available and come immediately into play regardless of whether the microbe has been encountered previously. A second set of defenses is specific for a particular type of microbe (adaptive defenses). When the microbe is first encountered, the adaptive defenses are not immediately available, and will not begin to appear for several days. It can take weeks after the initial exposure for the adaptive defenses to rise to their full strength. In subsequent encounters with the same microbe, however, the adaptive defenses appear almost immediately. We will focus on the innate defenses here.

Although the distinction between innate and adaptive defenses is useful for emphasizing the basic differences between these defenses, it is somewhat artificial because the innate and adaptive defenses interact with each other in a number of ways. For example, phagocytic cells, which are normally considered to be an innate defense, can also act as antigen-presenting cells, which potentiate the antibody and cytotoxic T cell responses. Similarly, cytokines are bioactive proteins that are produced by cells of the innate and adaptive defense systems. Cytokines regulate both adaptive and innate defenses. Antibodies help phagocytes to ingest and kill microbes. Antibodies also interact with the complement system. Thus, the innate and adaptive defenses act in concert to protect the body from infection. The collection of phagocytic, cytotoxic, and antibody-producing cells that protect the body from infection is called the immune system. The innate and adaptive defenses respond to material the body views as foreign and ignore the body's own tissues.

Epithelia. Epithelia, the layers of cells that cover the surface of the body and body cavities, are an important initial defense against pathogenic microbes. Epithelia found in different body sites differ considerably in their properties, but all have some features in common. First, epithelia consist of tightly packed cells, which are attached to each other by protein structures called tight junctions and desmosomes. The tight binding of epithelial cells to each other prevents microbes from transiting the epithelial layer through the space between the cells. To get through epithelia, microbes must take advantage of wounds or natural openings in the epithelium, or they must be capable of
invading epithelial cells and passing through them to underlying tissue. By contrast, the
cells that line blood vessels or lymphatic vessels (endothelium) are not tightly bound to
each other, and microbes can move into and out of blood and lymphatic vessels by
moving between the cells.

A second common feature of epithelial cells is that they are attached to a basement
membrane (basal lamina), which consists of a matrix of glycoproteins. The surfaces of
an epithelial cell that are attached to other cells or to the basal lamina (basolateral
surfaces) have a different protein composition from the surface that faces outward (apical
surface). Cells with this property are said to be polarized. Influenza virus provides an
example of how epithelial cell polarization can affect the course of an infection.
Influenza viruses recognize specific proteins on the apical surface of respiratory tract
cells and enter the cells by this route, but they are unable to exit through the basal surface
of the respiratory epithelial cells because that surface has a different protein composition
from the apical surface. This is why influenza viruses cause infection that is localized to
the respiratory tract and do not enter the bloodstream.

Epithelial layers that cover surfaces where absorption or secretion is taking place,
e.g., in the intestinal tract, usually consist of a single layer of epithelial cells (simple
epithelium). Other surfaces are covered with many layers of epithelial cells (stratified
epithelium). Epithelial cells in different sites vary in shape. Some have a flattened shape
(squamous cells), some are cube shaped (cuboidal), and some are tall and thin (columnar
cells). Simple epithelia are more vulnerable to microbial invasion than stratified epithelia
because invading microbes must pass through only one layer of cells to gain access to
underlying tissue. Most of the surfaces that are exposed directly to the environment (e.g.,
skin, mouth) are covered by stratified epithelia, whereas simple epithelia are found in
internal areas such as the intestinal tract. Both simple and stratified epithelial surfaces
are protected by a variety of defenses, which are summarized in Table 2.

Defenses of Skin

*Chemical and physical barriers to microbial colonization.* Few pathogenic microbes are
able to penetrate intact skin unaidered. This is why skin infections are so often associated
with wounds, burns, or insect bites. Why is intact skin such an effective barrier to
microbial invasion? A number of characteristics combine to make skin inhospitable to
microbial growth as well as difficult to penetrate (see Table 2). Skin is composed of two
layers, the epidermis (outer layer) and the dermis (inner layer). The epidermis consists of
stratified squamous cells, most of which are keratinocytes. The cells in the outermost
portion of the epidermis are dead, a feature that prevents viral replication in these cells
and thus prevents viral invasion through the skin. The surface cells of the epidermis are
constantly being shed. Thus, bacteria and pathogenic eukaryotes that bind to epidermal
cells are constantly being removed from the body. Skin is dry and has an acidic pH (pH 5),
two features that inhibit the growth of many pathogenic microbes, which prefer a wet
environment with a neutral pH. Also, the temperature of skin (34°- 35°C) is appreciably
lower than that of the body interior (37°C). Accordingly, microbes that succeed in
colonizing skin must be able to adapt to the very different internal environment of the
body if they invade to underlying tissue.
Table 2. Examples of Innate Defenses of Epithelial Surfaces

<table>
<thead>
<tr>
<th>Compartment or Epithelial Surface</th>
<th>Characteristics</th>
<th>Protectants</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Stratified, squamous; keratinized epidermis</td>
<td>Dry, acidic, &lt; 37°C</td>
<td>Limits microbial growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sloughing cells</td>
<td>Removes microbes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resident microbiota (Mainly Gm+ bacteria)</td>
<td>Competes for colonization sites, nutrients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Langerhans cells (epidermis), macrophages (dermis)</td>
<td>Recognize invaders, trigger adaptive defenses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrophages</td>
<td>Ingest and kill microbes</td>
</tr>
<tr>
<td>Mucus</td>
<td>Glycoprotein matrix</td>
<td>Lysozyme</td>
<td>Digests peptidoglycan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactoperoxidase</td>
<td>Creates reactive forms of oxygen, toxic form microbes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactoferrin</td>
<td>Sequesters iron, prevents growth of microbes</td>
</tr>
<tr>
<td>Mouth</td>
<td>Stratified, squamous</td>
<td>Washing action of fluids</td>
<td>Removes microbes from area</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resident microbiota (Mainly Gm+ cocci)</td>
<td>Competes for colonization sites, nutrients</td>
</tr>
<tr>
<td>Upper respiratory tract, bronchi</td>
<td>Pseudostratified (Layer of cells of different heights)</td>
<td>Mucus, goblet cells</td>
<td>Mucus traps microbes</td>
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<tr>
<td></td>
<td></td>
<td>Ciliated cells</td>
<td>Propel mucus out of airway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resident microbiota (Mainly Gm+ cocci)</td>
<td>Competes for colonization sites, nutrients</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>Simple, squamous</td>
<td>Alveolar macrophages</td>
<td>Ingest and kill microbes</td>
</tr>
<tr>
<td>Stomach</td>
<td>Simple, columnar</td>
<td>Low pH, proteases</td>
<td>Toxic for most microbes</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Simple, columnar</td>
<td>Mucus</td>
<td>Traps microbes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rapid flow of contents</td>
<td>Removes microbes, mucus from area</td>
</tr>
<tr>
<td>Organ</td>
<td>Structure</td>
<td>Description</td>
<td></td>
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<tr>
<td>----------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Simple, columnar</td>
<td>Mucus Traps microbes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resident microbiota (Mixture of Gm+, Gm- bacteria)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Competes for colonization sites, nutrients</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Stratified, mixture of types</td>
<td>Washing action of fluids Removes microbes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acidic pH of urine Prevents growth of some microbes</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Sphincter at opening Physical barrier to microbes</td>
<td></td>
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<tr>
<td>Vaginal tract</td>
<td>Stratified, squamous (cervix); stratified columnar (vaginal wall)</td>
<td>Mucinous secretions Trap microbes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resident microbiota (Mostly Gm+ rods) Competes for colonization sites</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucus plug in cervical opening Prevents microbes from entering uterus</td>
<td></td>
</tr>
</tbody>
</table>

The keratinocytes of the epidermis are so named because of their ability to produce the protein keratin. Keratinocytes also help to keep the pH of the skin acidic. Keratinocytes divide rapidly in the layers nearest the dermis, then mature as they are pushed closer to the surface of the skin. During maturation, they begin to produce keratin and by the time they reach the skin surface, they have a high content of this protein. Since most microbes do not readily degrade keratin, this layer of keratinized cells is highly resistant to invasion. Nails and hair, which are also composed of keratinized tissue, are similarly resistant to microbial invasion. Only a few pathogenic microbes are capable of growing in highly keratinized tissues such as those in skin, nails, and hair. One example is the fungi that cause athletes foot and jock itch (dermatophytes). Dermatophytes are able to infect keratinized tissue because they produce keratin-degrading enzymes. The dermatophytes also provide an example of how a limited ability to adapt prevents a microbe from being invasive. Dermatophytes grow only in the mycelial form and cannot switch to the yeast form at 37°C. The yeast form is better adapted than the mycelial form to survive and spread inside the human body. Thus, although the dermatophytes can infect skin, nails, and even hair, they are unable to infect underlying tissue.

Another defense of the epidermis is the Langerhans cells, a type of cell that processes invading microbes and activates the adaptive defenses (antigen-presenting
cell). A second type of antigen-presenting cell, the macrophage, protects the dermis. Macrophages also ingest and kill microbes.

Hair follicles, their associated sebaceous glands, and sweat glands offer natural breaches in the skin that could be used by infectious microbes to bypass the barrier provided by skin. These natural breaches are protected by lipids that are toxic to many microbes and by the enzyme lysozyme, which degrades the peptidoglycan wall of bacteria. Some pathogenic microbes are capable of infecting hair follicles or sweat glands. This is why some skin infections such as boils or furuncles are commonly centered around hair follicles.

**Resident microbiota of the skin.** The defenses of the skin do not completely prevent microbial growth, and some microbes are capable of colonizing and persisting on the surface of skin. These consist primarily of gram-positive bacteria, a mixture of cocci and rods. These bacteria do not normally cause human infections. A microbial population, which is found continuously in some body site without causing disease, is called the resident microbiota of that site. The skin microbiota helps to protect against pathogenic microbes, because members of the resident microbiota occupy sites that might be colonized by pathogenic microbes and compete with incoming pathogens for essential nutrients. Pathogenic microbes can sometimes colonize the skin, but such colonization events are usually of limited duration. Although members of the resident microbiota are not normally pathogenic, they are not completely innocuous. Some of them can cause infections if they are introduced into the body through a wound. Such infections are especially likely to occur in immunocompromised patients. Microbes that can cause infection if host defenses are depressed, but cannot infect otherwise healthy people, are called opportunists.

**Defenses of Mucosal Surfaces**

**Mucus and sloughing cells.** The respiratory tract, gastrointestinal tract, and vaginal tract are technically inside the body, but they are exposed constantly to the outer environment and foreign materials. These mucosal surfaces have a temperature of around 37°C, a pH of 7.0 to 7.4, and most are bathed in fluids. These are ideal conditions for the growth of pathogenic microbes. These vulnerable mucosal surfaces are protected from microbial colonization by a formidable array of chemical and physical barriers (see Table 2). An important protection of mucosal surfaces is mucus. Mucus is a mixture of glycoproteins produced by goblet cells, a specialized cell type incorporated into the epithelial layer. Mucus has a viscous, slimy consistency, which allows it to act as a lubricant. It also plays a protective role because it traps microbes and prevents them from reaching the mucosa. Mucus is constantly being produced and excess mucus is shed in blobs into the lumen of the tract. Microbes trapped in mucus are thus eliminated from the site. In the gastrointestinal and urinary tracts the flow of liquids through the area removes the mucus blobs. In the respiratory tract and fallopian tubes, there are specialized mucosal cells, ciliated cells, whose cilia are constantly waving in the same direction. The waving action of the cilia propels mucus blobs out of the area.

Another protective role of mucus is to sequester proteins and other chemicals that prevent the growth of microbes (see Table 2). Lysozyme is an enzyme that digests the
peptidoglycan cell wall of bacteria. It is most effective against gram-positive bacteria, but can digest the gram-negative cell wall if membrane-disrupting substances such as the bile salts found in the intestine make breaches in the outer membrane. Lactoperoxidase is an enzyme that generates peroxide, a chemical that is toxic for many microbes. Lactoferrin, an iron-binding protein, sequesters iron and deprives microbes of this essential nutrient. Toxic peptides, called defensins, form channels in microbial membranes that destroy the structural integrity of the microbe.

Mucosal cells are constantly being replaced and old cells are ejected into the lumen. In fact, mucosal cells are one of the fastest dividing populations of cells in the body. Thus, microbes that manage to reach and colonize a mucosal surface are constantly being eliminated from the mucosal surface and can only remain in the area if they can grow rapidly enough to colonize newly produced cells. Defenses like lactoferrin help to reduce the growth rates of microbes sufficiently to allow ejection of mucus blobs and sloughing of mucosal cells to clear the microbes from the area.

Special defenses of specific sites. The defenses described in the preceding section are characteristic of mucosal surfaces in general. Other defenses are specific to a particular site (see Table 2). These will be covered in detail in later chapters of your textbook on infections of specific organs, but some examples will be given here to illustrate the variety of strategies used by the body to prevent microbial colonization of mucosal surfaces. The mucus-coated hairs of the nose trap microbes inhaled in air, and the sneeze reflex helps to expel them. The curvature of the airway, together with the turbulence created by breathing makes it likely that inhaled microbes not trapped on nasal hairs will be trapped in mucus somewhere in the upper airway. Ciliated cells in the respiratory epithelium propel bacteria-laden mucus blobs upward out of the airway (the mucociliary elevator). The lung contains macrophages (alveolar macrophages) that ingest and kill any bacteria that reach the lung and also serve as antigen-presenting cells to activate the adaptive defenses. The surfactant proteins of the lung, whose main role is to facilitate gas exchange between the lung and the bloodstream, may also have an antimicrobial function because some of them can coat microbes and make it easier for the alveolar macrophages to ingest and kill them. The stomach protects the intestine from infection because the acidic pH of the stomach and the proteases found in gastric secretions are lethal for many microbes. The rapid flow of contents through the small intestine further helps to reduce the microbial load by washing microbes out of the area. The contents of the small intestine have a high concentration of bile salts, detergents which disrupt the envelopes of viruses and the membranes of many bacteria and eukaryotes. The mucosa of the small intestine and colon contains crypts in which the stem cells divide to produce the columnar epithelial cells. Cells in these crypts, called Paneth cells, produce a type of defensin called cryptdins. Cryptdins help to protect vulnerable stem cells from microbes passing through the intestine. The bladder is protected by the sphincter action of the opening of the urethra. The bladder is further protected by the washing action of urine. The uterus is protected by a mucus plug that separates it from the bacterium-laden vaginal tract.

Resident microbiota. Many mucosal surfaces are protected by a resident microbiota that consists primarily of bacteria. Because different parts of the body offer such different
conditions, it is not surprising that each colonized body site has its own distinctive microbiota. The mouth and upper respiratory tract contain a dense population of microbes, which grow on the numerous surfaces available in these sites (teeth, mucosa of airway, cheek, and tongue). Most of these are gram-positive cocci, although low numbers of yeasts can sometimes be detected. The population of bacteria that colonizes the crevices at the base of teeth is somewhat more complex, consisting of a mixture of gram-positive and gram-negative bacteria. The small intestine has a relatively sparse microbiota, except near the ileocecal valve, which separates it from the microbe-rich colon. The colon contains a dense population of bacteria, which are packed in the lumen of the colon rather than adherent to the colonic mucosa. Bacteria account for approximately half of the volume of feces. Low numbers of yeasts and protozoa are also present. The colonic microbiota is complex, consisting of at least 500 bacterial species. Most types of bacteria are represented: gram-negative rods, gram-positive cocci, and gram-positive rods. The vaginal microbiota is as complex as that of the colon, but gram-positive rods predominate, and the bacteria grow in layers on the vaginal wall and cervix rather than in the lumen. As in the colon, low numbers of yeasts and protozoa are commonly found in the vagina.

Although the microbiota of the mouth, upper respiratory tract, colon, and vagina generally play a protective role, some of them can also contribute to disease. For example, pathogenic microbes are often present in low numbers in the microbiota of the mouth, colon, and vaginal tract. They do not normally cause disease because competition from the predominant species of bacteria keeps them from reaching high enough concentrations to cause disease. However, if antibiotics depress the numerically predominant bacteria, these pathogens can overgrow the area and cause disease. Also, as was the case for the skin microbiota, some of the numerically predominant species of oral, intestinal, and vaginal bacteria are opportunists, which can cause infections if they are introduced into otherwise sterile areas of the body. Opportunistic infections are a serious problem for hospitalized patients. A substantial fraction of patients who are hospitalized for some other cause suffer hospital-acquired infections. Many of these infections are caused by members of the resident microbiota of the patient or of hospital staff members. Because of the widespread use of antibiotics in hospitals, hospital-acquired infections are likely to be caused by microbes that are resistant to antimicrobial agents.

The lungs, bladder, and uterus are generally considered to be sterile, but how sterile they actually are is still a matter of contention. The term "sterile," as it applies to microbes, means "completely free of microbes." In practice, since these organs are adjacent to areas that carry a high population of bacteria, it is likely that they are regularly exposed to low numbers of bacteria, which are quickly removed from the site.

A fetus is normally free of microbes during gestation. During birth, the infant begins to acquire its resident microbiota. Surface colonization by the vaginal microbiota starts the process. Subsequent ingestion of bacteria during feeding, and as a result of the general propensity of infants to sample any accessible object by putting it in their mouths, completes the process. The resident microbiota reaches its full development by about 2 years of age.

**Phagocytes, Natural Killer Cells, and Eosinophils: Defenders of Blood and Tissue**
The defenses of epithelial surfaces are highly effective in preventing pathogenic microbes from entering underlying tissue and blood, but from time to time microbes succeed in breaching these surfaces and enter underlying tissue and blood. Here the microbes encounter a formidable defense force, the phagocytes and nonspecific cytotoxic cells. Phagocytes are cells that ingest and kill microbes. Nonspecific cytotoxic cells kill microbes or microbe-infected cells, but they do so by attaching to them and bombarding them with toxic substances. This distinction is not absolute because phagocytic cells sometimes kill by a bombarding mechanism rather than ingesting their prey, especially if their target is infected host tissues that are too large to ingest. For our purposes, however, the distinction between phagocytes and cytotoxic cells is a useful one. The phagocytes include neutrophils (also called polymorphonuclear leukocytes or PMNs), monocytes, and macrophages. Nonspecific cytotoxic cells include the eosinophils and natural killer cells. Another type of cytotoxic cell, the cytotoxic T cell, belongs to the adaptive defense system.

Both phagocytes and cytotoxic cells store their toxic proteins in granules. During an infection, phagocytes and cytotoxic cells are stimulated to merge their granules with cell membranes, releasing the contents of the granule. In the case of phagocytes, the granule contents are released into a vesicle containing the ingested microbes, whereas cytotoxic cells expel granule contents into the surrounding environment. PMNs and macrophages are examples of phagocytes that ingest and kill microbes. They can also attack infected host cells. The role of natural killer cells is to kill microbe-infected host cells, especially virally infected cells. Eosinophils target metazoal pathogens, some of which are too large for the phagocytes to tackle.

Phagocytes and cytotoxic cells have another important role: release of bioactive proteins called cytokines, which regulate the deployment and activation of cells of the innate defense system and stimulate cells of the adaptive defense system. Macrophages and other antigen-presenting cells initiate the process that leads to production of antibodies and cytotoxic T cells.

**Measures of Infectivity and Virulence**

How do scientists define infectivity and virulence in quantitative terms? A measure of infectivity is the infectious dose 50 (ID$_{50}$), which is defined as the number of microbes needed to infect 50% of animals exposed to them. Usually the ID$_{50}$ is measured using laboratory animals instead of human subjects, especially in the case of virulent microbes or microbes for which no effective therapy is available. Infectivity in human populations can be deduced from the attack rate of an infection. The attack rate is defined as the number of cases of clinically apparent disease divided by the number of susceptible people in the population. A measure of virulence is the lethal dose 50 (LD$_{50}$), which is defined as the number of microbes required to kill 50% of the animals exposed to them. A measure of virulence in human populations is the case fatality rate of a disease. The case fatality rate is defined as the number of deaths from a particular disease divided by the number of clinically apparent cases of that disease.

The practical importance of terms such as these is evident from discussions of bioterrorism. A popular focus for bioterrorists has been the bacterium that causes anthrax.
Bacillus anthracis is a spore-forming gram-positive bacterium. The fact that it produces spores, which are quite hardy and survive for years, makes B. anthracis easy to store and disperse. In pulmonary infections, B. anthracis is a highly virulent bacterium that kills most of the people who develop symptomatic pulmonary disease. Death results from septic shock. Anthrax clearly has a high case fatality rate. Up until the attack by bioterrorists in the fall of 2001, we did not have any estimate of the attack rate. Bioterrorists had sprayed B. anthracis spores in the past, but no documented cases of disease resulted. The most recent bioterror attack indicates that the attack rate must be fairly low considering how many people were probably exposed. By contrast, native Americans in the 16th century who came into contact with smallpox virus for the first time had a very high attack rate and high case fatality rate. In Europe, where the disease had been around for centuries, the attack rate and case fatality rate were lower, probably because of some degree of immunity acquired from occasional contacts with individuals shedding low numbers of the virus.

Proving Cause and Effect in Microbial Infections

Today, the idea that organisms too small to be seen by the unaided eye could cause disease is taken for granted, but this was not always the case. During the 1800s, the hypothesis that microbes were the cause of diseases like tuberculosis or cholera was quite controversial.

Koch's postulates

In an attempt to devise a rational basis for proving that a specific microbe could cause a specific disease, the microbiologist Robert Koch (1843–1910) proposed a set of postulates for proving that a microorganism is a pathogen. Koch's postulates, first stated in 1882, are listed in Table 3. The first postulate states that the microorganism must be associated with lesions of the disease. The second postulate asserts that the microorganism can be isolated in pure culture from a person with the disease, preferably from the lesions associated with the disease. This has proved to be difficult in some diseases, because of a failure to cultivate the causative organism. Few people doubt that syphilis is caused by the bacterium Treponema pallidum, because antibiotic treatment that eradicates this bacterium from the body cures the disease. However, despite the fact that these spirochetes can be seen in lesions of the disease, the bacterium has never been grown in the laboratory. The third postulate states that the microorganism isolated from a person with the disease must be administered to another person or animal and shown to produce the disease in that person or animal. This is often the hardest postulate to satisfy, especially for diseases caused by microorganisms that are human specific and do not readily infect animals. Finally, Koch's fourth postulate states that the microorganism must be re-isolated in pure culture from the animal or human that was infected experimentally to satisfy the third postulate.

Table 3. Koch’s Postulates

| Postulate 1. | The microbe must be present in all people with the disease and should be associated with the |
lesions of the disease

Postulate 2. The microbe must be isolated in pure culture from a person who has the disease.

Postulate 3. The isolated microbe, when administered to humans or animals must cause the disease.

Postulate 4. The microbe must be isolated in pure culture from the human or animal infected to satisfy postulate 3.

*Koch’s postulates are still relevant today*

Today, scientists are more prone to accept the idea that a particular microorganism causes a disease, especially if the appropriate antimicrobial therapy predicted by this understanding of the disease effects a cure. In fact, some scientists thought that Koch's postulates had been relegated to a dusty shelf of the library, when the controversy surfaced over whether *H. pylori* caused most gastric ulcers. Scientists and pharmaceutical companies with vested interests in the theory that ulcers were caused by stress found it hard to believe that bacteria might be the culprits. At issue were some of the most lucrative drugs sold by pharmaceutical companies, medications that had to be taken daily for life. The news that a patient who once spent thousands of dollars a year for anti-ulcer medication could now spend a few hundred dollars for a short course of antibiotics that would quickly cure the disease and prevent recurrences was devastating to some pharmaceutical companies. Understandably, if these companies were going to accept this new theory of ulcers, they wanted proof, with all the i's dotted and t's crossed. Koch's postulates assumed center stage once again, especially the third postulate. Animal models for gastric ulcers have allowed scientists to satisfy Koch’s third postulate. Moreover, the discovery of an antibiotic combination that eliminated the bacteria from the stomach and stopped ulcer recurrences provided even more convincing proof that ulcers were caused by *H. pylori*.

What Makes a Microbe Pathogenic or Virulent?

Characteristics of microorganisms that allow them to cause disease are called virulence factors or pathogenicity factors. Defining these factors has been a major focus of research in recent years, and some basic answers have been obtained. In retrospect, these answers seem intuitively obvious to those who view disease as a shift in the equilibrium between microorganisms and the defenses of the human body. The fact that they seemed revolutionary when first proposed gives a good indication of how much the view of infectious disease has changed over the past few decades. Some of the features of pathogenic microbes are listed in Table 4.

**Table 4. Features of Pathogenic Microbes**

- Attach to host
- Evade host defenses
- Obtain iron and other essential nutrients
Produce symptoms

Possess virulence factors

**Virulence factors that allow microbes to cause an infection**

A microbe must first get to the body site it targets. For example, a bacterium or virus that infects the intestinal tract must be able to survive passage through the stomach and must be able to attach to the intestinal lining to prevent being washed out of the site. Thus, most bacteria and protozoa that cause intestinal infections have flagella, which allow them to swim to the intestinal wall, and pili or other mechanisms of adhesion that help them adhere to the intestinal mucosal cells. Viruses that infect the intestine must be able to attach to and infect intestinal cells or be able to transit the intestinal wall and gain entry into the bloodstream. A microbe that can live inside a biting insect has a natural system for getting itself injected into the human bloodstream.

As mentioned earlier, the human body is protected from infection by a variety of defenses so a second characteristic that disease-causing microorganisms have is the ability to evade or subvert one or more of these defenses. Microbes have evolved a variety of mechanisms for doing this. Capsules protect microbes from phagocytosis. Some bacteria are able to live in and kill unactivated phagocytes. Other microbes make themselves invisible to the immune system by making their surfaces resemble host tissues. Still others attack the cells of the immune system directly.

A third characteristic of most disease-causing microbes is their ability to obtain essential nutrients from human tissues. Iron is a very important nutrient for virtually all microorganisms, but the concentration of available iron in human tissues and blood is low, because the body produces iron-binding proteins such as transferrin or lactoferrin that bind iron very tightly. Disease-causing microbes either have very efficient iron-uptake systems that allow them to scavenge what little free iron is available, or they are able to remove the iron from transferrin or lactoferrin. The human body is potentially a rich source of carbon and nitrogen, but these elements are normally not free but rather are found as part of complex molecules, that is polysaccharides or proteins. A number of microbes that infect tissue produce polysaccharidases or proteases, which damage tissue as they release carbon and nitrogen.

Pathogenic microbes are those that can produce symptoms in the host by a variety of processes. The major virulence factors that allow such microbes to cause damage are described below.

**Nonprotein microbial toxins**

In an earlier chapter of your text, the ability of bacterial surface molecules, such as lipopolysaccharide and lipoteichoic acid, to activate the inflammatory response was described. Lipopolysaccharide has been called endotoxin, because it is part of the bacterial cell (endo) and is only released during cell lysis. The term endotoxin was meant to differentiate it from exotoxins, protein toxins that are usually released from the cells
without lysis. Yeasts and protozoa also elicit an inflammatory response, but the molecules that do this have not been well characterized.

For microbes that are unable to survive attack by neutrophils, molecules such as lipopolysaccharide are a liability. But for microbes that can survive the inflammatory response, this response is advantageous, because it liberates nutrients by killing tissue cells. In addition, if the region of dead tissue becomes large enough, it protects the bacteria from the immune system, because immune cells move through the blood or lymph to a site. If there has been enough damage to cut off the blood supply, this will inhibit migration of immune cells to the site where the microbes are growing.

Macrophages and neutrophils can migrate in tissue but do not do this as well in areas of extensive tissue damage. Similarly, antimicrobial compounds may not diffuse readily into a damaged site. This is why, in cases of gas gangrene, a bacterial disease characterized by extensive tissue damage, it is necessary to remove the dead tissue surgically (debride the wound) before antibiotics and the defense system can bring the bacteria under control. In cases where debridement is not successful, amputation of the limb is necessary. Gas gangrene is an interesting example of how bacteria cause damage. Here, tissue damage is not only the result of microbe-produced proteases and polysaccharidases (although these contribute to the damage), but also results from the physical pressure of the copious amounts of carbon dioxide produced by the bacterium *Clostridium perfringens* as it utilizes the carbon sources from the dead human cells.

**Protein toxins (exotoxins)**

A-B toxins. Protein toxins are individual proteins or protein complexes that attach to eukaryotic cells and damage them. Bacteria produce these protein toxins. Fungi, algae, and some bacteria produce low molecular weight toxic substances that are not proteins. A common type of protein toxin is the A-B type toxin (Fig. 2). A-B toxins consist of a B part, which binds to specific receptors on the surface of the human cell and facilitates the entry into that cell of the A part, which actually does the damage. The B part, by itself, is nontoxic. The A part is only active if it is introduced into the target cell by the B part. The B portion may consist of a single protein or a complex of several proteins. The A part is usually an enzyme, consisting of one or two proteins.

**Figure 2. Structure and mechanism of action of an A-B type toxin.** The B portion of the toxin binds to the target host cell. The active A portion then enters the host cell, where it produces an effect. The B portion of many A-B type toxins consists of several subunits. The A portion often catalyzes an ADP-ribosylation reaction, in which ADP-ribose is transferred to a host cell protein, thus altering or inhibiting its activity.
The A portion of most A-B type toxins catalyzes a reaction called adenosine-diphosphate (ADP)-ribosylation, in which it removes the ADP-ribosyl group from nicotinamide adenine dinucleotide (NAD) and attaches it to a human protein. ADP-ribosylation inactivates the protein. The results of this inactivation depend on what protein is ADP-ribosylated. In the case of *Escherichia coli* strains that produce a heat-labile enterotoxin called LT, a regulatory protein is inactivated, causing ion channels that control the flow of water across cell membranes to go out of control. The result is water loss from tissue, leading to dehydration and diarrhea. In the case of diphtheria toxin, the target is a step in which amino acids are added to a growing peptide chain. The result is cessation of protein synthesis and death of the cell. In the case of tetanus toxin, the proteins inactivated are in nerve cells that control the transmission of neuronal signals.

Most A-B toxins are secreted by the bacteria into the extracellular fluid. The toxin then finds and binds to the type of cell it targets. An interesting variation on this action that was discovered only in the past decade, is a type of toxin delivery system called a type-III secretion system. Bacteria with type-III secretion systems actually bind to the target cell and inject the toxin directly into the cell interior. An example of a bacterium that uses this strategy is *Yersinia pestis*, the cause of bubonic plague.

Superantigens. Superantigens are another type of protein toxin. They attach to the T cell receptors of T helper cells and the major histocompatibility complexes (MHCs) of the antigen-presenting cells (APCs). Usually these cells associate only when the T cell recognizes an antigen that is being presented on the MHC of the APC. Superantigens force the cells into an unnatural association that they would not otherwise form, because they are not presenting or recognizing antigens at the time. Whereas only a fraction of a percent of T helper cells would normally be interacting with antigen-presenting cells during an immune response, superantigens can cause up to 20% of T helper cells to attach to antigen-presenting cells and become activated. This is why the toxins are called superantigens. The unnatural activation of so many T cells is toxic, because it results in the release of large amounts of cytokines by the immune cells. Such a release can cause a form of septic shock.

In the 1990s, lurid news articles described a new disease characterized by extensive tissue damage: “THE BACTERIUM THAT ATE MY FACE.” The gram-
positive bacterium *Streptococcus pyogenes* was responsible for the massive tissue
destruction experienced by some people. *S. pyogenes* has caused a number of diseases
over the past century, ranging from scarlet fever and rheumatic heart disease to wound
infections. Scarlet fever and rheumatic heart disease have virtually disappeared, but *S.
pyogenes* is still around. The modern strains cause extensive tissue damage around a
wound (called cellulitis) or deadly systemic infections. This bacterium produces a
superantigen. This cellulitis was reminiscent of a disease called streptococcal gangrene,
which was experienced in the early 1900s by soldiers with battle wounds. *S. pyogenes* is
unusual, even among bacteria, for the variety of different conditions it has caused.

**Roles of toxins in disease.** Toxins can be the sole cause of a disease or simply a
part of the microorganism’s array of virulence factors. Some examples of the roles of
toxins in disease are shown in Figure 3. Food-borne disease caused by *Staphylococcus
aureus* and botulism are examples of diseases in which the bacteria do not infect, but
instead produce the toxin in food. The toxin is ingested with the food. Botulism is caused
by a gram-positive, spore-forming bacterium *Clostridium botulinum. C. botulinum* is
closely related to *Clostridium tetani*, the bacterium that causes tetanus.

Botulism toxin, like tetanus toxin, is a neurotoxin that causes a flaccid paralysis.
Death is usually caused by collapse of the respiratory system. The toxin of *S. aureus* is
much less dangerous. It stimulates the nerve ends in the stomach that control peristalsis,
causing projectile vomiting and severe abdominal pain. The disease lasts only a day or
two and is not fatal. Note that the difference in lethality between botulism toxin and *S.
aureus* toxin (called enterotoxin) is accounted for by the difference in the cells they
target. Both target nerve cells, but their effects on the nervous system are quite different
and thus have different impacts on the human body.

Diphtheria, caused by *Corynebacterium diphtheriae*, and tetanus, caused by *C.
tetani*, are diseases in which the bacteria do infect tissue but most of the disease
symptoms are the result of a toxin released into the bloodstream. *C. diphtheriae* colonizes
the throat, and *C. tetani* colonizes deep wounds. *C. diphtheriae* is spread from person to
person. *C. tetani* is found in soil, especially soil contaminated by animal feces.

An example of a bacterium that infects tissues and causes damage by a number of
mechanisms has already been mentioned: *S. pyogenes*, a common cause of wound
infections. It usually causes inflammation in the area of the wound, resulting in a red,
painful area with lines radiating out from the wound site. These lines are caused by
bacteria migrating in the tissue. Polymer degrading enzymes produced by the bacteria
allow it to break down tissue and spread outward from the wound. In some cases,
however, where *S. pyogenes* enters the body through very tiny wounds and does so little
damage in the wound area that the infected person does not realize at first that infection
has occurred. The most dangerous infections caused by *S. pyogenes* are cellulitis and the
ones where bacteria enter the bloodstream. *S. pyogenes* has lipoteichoic acid, which can
trigger septic shock. The superantigen it also produces contributes to toxic shock. *S.
pyogenes* is a human-specific pathogen that is carried in the mouth and throat, where it
rarely causes disease. This location, however, allows it easy access to any wounds that
might occur.
**Figure 3. Roles of toxins in disease.** *Staphylococcus aureus* and *Clostridium botulinum* produce toxins when they grow in food. The toxin is ingested and produces the effect. *Clostridium tetani* and *Corynebacterium diphtheriae* colonize the host and produce toxins once they are in the host. The toxins, but not the bacteria, enter the bloodstream and move to the target cells. *Streptococcus pyogenes* infects the host and enters the bloodstream, where it produces a toxin that is a superantigen. The actions of the superantigen result in shock.

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The mystery of toxin function. For those who believe that microbes are out to get us, toxins are easy to understand. On closer inspection, however, this view would need to embrace the idea that microbes are so vindictive that they do things to injure humans, even when these actions have no benefit for the microbes themselves. Consider botulism to: 

- *Clostridium botulinum* produce botulism toxin. These toxins are produced in foods but do not help the bacteria to infect. Instead, the bacteria pass through the intestinal tract without causing infection, leaving the toxins behind to cause disease. Even diphtheria and tetanus toxin are difficult to understand as aids to microbial survival. Not all strains of *C. diphtheriae* produce diphtheria toxin. Yet the toxin nonproducers are just as successful as the toxin producers in colonizing the human throat. Similarly, tetanus toxin has no known function in aiding the bacteria to colonize wounds.

The story becomes more complex and more puzzling when you consider that many of the toxin genes are carried on bacteriophages. Thus only bacteria that acquire a lysogenic phage produce the toxin. This means that toxin genes in the bacteria themselves did not necessarily evolve to ensure the survival of the bacteria but were acquired in chance encounters with bacteriophages. And why would a bacterial virus be carrying genes that encode a neurotoxin or a diphtheria toxin? One explanation is that the genes we call toxin genes and that are carried by bacterial viruses play some role in regulating the viral life cycle and just happen to be toxic to human cells.

**Where Do Pathogenic Microbes Come From?**

Interest in the evolution of pathogens has been growing because of the need to understand how new diseases can continue to emerge and why new forms of "old" pathogens continue to appear. Understandably, most of the attention given to this topic
has focused on recent evolution of pathogens. There are two ways evolution can occur in microbes: existing genes in the microbe's genome can mutate, or new genes can be acquired from other microbes (horizontal gene transfer).

**Evolution by mutation**

Eukaryotic viruses seem to favor the first strategy, especially those viruses with ribonucleic acid (RNA) genomes. RNA is less stable chemically than deoxyribonucleic acid (DNA). Moreover, enzymes that reproduce RNA molecules tend not to have the kind of proofreading capability found in enzymes that reproduce DNA. The result is that RNA-reproducing enzymes tend to make more mistakes. Together, the chemical instability of RNA and the lack of proofreading functions in many of the viral enzymes that reproduce RNA give viruses with RNA genomes the potential to mutate very rapidly. Not surprisingly, two RNA viruses, HIV (the cause of AIDS) and influenza virus (the cause of influenza) are among the most rapidly mutating viruses known. Mutants of HIV have been seen to appear in the same patient over the course of the infection--a very short time span for evolution. By mutating rapidly, HIV and influenza are able to avoid the body's immune responses. HIV is definitely mutating to greater resistance against the new antiviral compounds. This type of evolution to resistance to antiviral compounds has been slower in the case of influenza virus but may well occur. There is one case in which viruses become more virulent by horizontal gene transfer: influenza virus has a genome that comes in segments. The most virulent strains are ones that have acquired a new segment from another influenza virus. Such acquisitions can make them virtually invisible to the immune system that normally controls them.

**Evolution by horizontal gene transfer**

Bacteria also undergo mutations, and this contributes to the evolution of strains resistant to the fluoroquinolone antibiotics, an important class of antibiotics. The bacterium that causes tuberculosis becomes resistant to the antituberculosis drugs by mutating the genes that are the targets for the drugs. Aside from these examples, however, bacteria seem to prefer to take advantage of horizontal gene transfer to acquire new traits. The reason for this seems obvious. Changing by random mutation ensures that many unsuccessful mutants will die in the process, whereas acquiring a gene that has already developed in some other microbe is a lot less hazardous and more likely to produce immediate results. Antibiotic-resistance genes are clearly being transferred widely among bacteria. Pathogenic bacteria can acquire these genes from each other or from bacteria that do not cause disease but are present in the same site. The human intestinal tract, for example, contains a huge population of bacteria that do not usually cause disease in healthy people. Yet when these bacteria are exposed to antibiotics, they can become resistant and transfer these resistance genes to pathogenic bacteria that happen to pass through the intestinal tract.

Horizontal gene transfer can also increase the virulence of a bacterium. *E. coli* provides a good example of this. Most strains of *E. coli* do not cause intestinal disease, but a subset of strains can do so. For example, a type of *E. coli* called *E. coli* O157:H7, which has been in the news because of its ability to cause bloody diarrhea and kidney
failure in children, seems to have arisen when a strain of *E. coli* that could cause a mild form of diarrhea acquired toxin genes from *Shigella*, a bacterium that causes bloody diarrhea and kidney failure. *Shigella* has been largely eliminated from the food and water supplies of developed countries, but *E. coli* is still very much in evidence. The *Shigella* toxin genes entered *E. coli* on a bacteriophage. The study of pathogen evolution is still in its infancy, with most work focused on viruses and bacteria, but a better understanding of how pathogens arise may help to predict and prevent the emergence and spread of new pathogens.

**Evolution of virulence**

An interesting question that arises in connection with pathogen evolution is which direction does pathogen evolution take: toward increased or reduced virulence. Most people take the pessimistic line and assume that pathogens want to cause disease. From the microbe's point of view, however, this is not a very smart strategy. Severe diseases that kill rapidly not only kill the supplier of all sorts of goodies but also reduce the likelihood that the causative organism will be transmitted before the infected person dies. Pathogens that cause severe diarrheal disease are swept out of the intestine into a presumably less attractive and certainly less nutrient-rich environment. One could argue that the most successful pathogens are those that colonize the body without causing noticeable symptoms, establishing an asymptomatic carrier state that can persist for months or even years. If this view is correct, microbes that are initially virulent should mutate in the direction of lesser virulence, a better fit with their human host. One case in which this may have occurred is syphilis. Science historians suspect that the rapidly fatal disease called leprosy in the Middle Ages might actually have been syphilis. If so, the syphilis of today is a much milder pathogen, taking years rather than months to finish off the person it infects. Unfortunately, scientists have so far been unsuccessful in testing this hypothesis. If syphilis has indeed mellowed with age, the process took rather a long time from a human perspective: centuries. Of course, the change in the virulence of syphilis, if indeed it has occurred, could reflect better nutrition and less exposure to the pathogen rather than a change in the ability of the bacterium to cause disease.

Another confounding factor is the as yet inexplicable shift that can occur in the strains of microbes prevalent at any given moment in history. In the late 1800s, scarlet fever (a disease caused by the bacterium *S. pyogenes*) was a disease with a high rate of fatality. It was characterized by a diffuse red rash that gave the disease its name. Some parents lost child after child to scarlet fever. By the 1930s and 1940s, *S. pyogenes* had changed its spots somewhat. Scarlet fever had become a mild childhood disease, rather like chicken pox. However, many young adults, especially military recruits living in the types of crowded conditions that encourage the spread of disease, were contracting a form of *S. pyogenes* infection that damaged the heart valves. The disease had different symptoms and affected a different age range than those seen in scarlet fever. Some infected people died immediately, but many felt the effects of damaged heart tissue only much later in life, when they were more susceptible to infections of the heart valves (endocarditis, an often fatal disease). This heart-damaging form of *S. pyogenes* infection was called rheumatic fever. Inexplicably, rheumatic fever, like scarlet fever, virtually disappeared for several decades, but this type of *S. pyogenes* has resurfaced during the
past 10 years as a more severe form of scarlet fever in children. In adults, *S. pyogenes* was back in yet another form: our friend "the flesh-eating bacterium," a severe form of cellulitis. Another version of *S. pyogenes* that caused a rapidly fatal disease in adults also appeared, then disappeared. Scientists believe that this shifting pattern of *S. pyogenes* diseases has been caused by one strain of *S. pyogenes* supplanting another. Diseases can submerge as well as emerge, but we still don't understand why.

A better understanding of the coevolution of humans and their attendant microbes is particularly important if we are to answer the question: how many disease-causing microbes are out there? Is there any limit to the number of microbes that are capable of causing human disease? Microbiologists are fond of stating that only a tiny minority of the microbes in nature cause disease, but is this really true? Protozoa are similar in many ways to the bacteria-killing cells that are one of the human body's main defenses against bacterial infection. This suggests that virulence factors first began to evolve not after the arrival of animals and humans on the evolutionary scene, but much earlier, when protozoa first appeared. If this view of the evolution of pathogens is correct, most types of bacteria and other microbes have experienced the selective pressures directing evolution toward a form that would, if opportunity presented itself, make them capable of surviving an important part of the human defense system. And the number of microbes capable of causing disease is almost limitless.

**Diagnosis of Infectious Diseases**

*Diagnosing microbial infections*

Some symptoms (what the patient reports) and signs (what the physician observes) in infectious disease direct the physician to suspect a patient has a microbial infection. These symptoms and signs are listed in Table 5. All are indications of the inflammatory response being mounted by the body against the microbial invader. Before trying to decide what microbe is causing the infection, it is helpful to establish that the patient actually does have an infection. One test that helps to identify a bacterial infection is the concentration of neutrophils in the patient’s blood. This is usually high in patients experiencing a bacterial infection, but, because the concentration of neutrophils varies widely among different people in different settings, a high neutrophil count is an indication rather than positive proof of infection. The symptoms of a microbial infection are often too nonspecific to serve as good diagnostic tools. Moreover, in immunocompromised people, symptoms can be even less clear, because of impairment of the body’s defenses, which are responsible for many of the symptoms.

**Table 5. Signs and Symptoms Commonly Associated with Infectious Diseases**

- Skin or mucosal lesions
- Inflammation (red, swollen, painful area)
- Pus or purulent discharge; pseudomembrane
- Painful urination, vaginal itching and burning
- Swollen lymph nodes, enlarged spleen
Fever
Generalized aches and pains
Changes in mentation (confusion, lethargy)
Unintended weight loss
Loss of appetite (anorexia)
Vomiting
Diarrhea, dysentery

At one time, a good guess about the identity of the microbe responsible for the disease was all a physician needed in order to prescribe appropriate antimicrobial therapy. As the incidence of resistant strains has risen, an educated guess is becoming more of a crapshoot. In critically ill patients, such as those manifesting signs of septic shock, the identity of the causative agent becomes less important than which antimicrobials will be effective. Here, antimicrobial susceptibility tests become critical. Such tests are most highly developed for bacteria, which cause the majority of serious infectious diseases. Similar tests can be used for yeast infections. Tests for susceptibility of viruses and protozoal pathogens are more complicated and are not performed routinely in hospitals. This may change in the future. As HIV becomes more resistant to antiviral drugs, tests to detect mutations that confer resistance may be performed more frequently.

Some of the tests for identifying microorganisms that are often carried out in hospital laboratories are described below. However, keep in mind that many new types of tests such as microarray tests are being developed at a rapid pace, and many of the “classics” are becoming less useful.

**Stains.** The simplest microbiological tests, and the first tests done by laboratory personnel are staining tests, such as the Gram stain for bacteria and the calcifluor stain for fungi (see Table 6). Fungi and many protozoa can also be seen in a gram-stained slide, but special stains are used when pathogenic prokaryotes are suspected to make it easier to see them and, in some cases, to obtain a rapid presumptive identification. Calcifluor is fungus-specific, because it binds to β-glucans, a common component of fungal cell walls not found in the cell walls of bacteria, protozoa, and metazoa. Bound calcifluor is fluorescent and provides a clear picture of fungal morphology. These and other commonly used stains are summarized in Table 6. Stains can be particularly useful in identifying fungi, protozoa, and metazoa because the shapes of these microbes or the shapes of their products (spores, eggs) are species-specific. Thus, if enough are in a specimen to be found by the microscopist, a species identification can usually be made by staining alone. Speciating bacteria, however, requires cultivation of the bacteria and metabolic or immunological tests to determine their species. The result of the Gram stain indicates what further tests are needed to determine the species of a bacterium.

**Table 6. Stains commonly used to detect pathogenic microbes.**

<table>
<thead>
<tr>
<th>Type of microbe</th>
<th>Stains</th>
</tr>
</thead>
</table>
Viruses

- Immunoperoxidase

Bacteria

- Gram stain
- Acid-fast (*Mycobacterium* spp.)

Fungi

- Calcifluor
- Giemsa
- Periodic acid-Schiff base
- Lactophenol cotton blue
- India ink
- Gomori methenamine-silver nitrate

Protozoa

- Acid-fast
- Iron-hematoxylin
- Giemsa
- Gomori methenamine-silver nitrate

Metazoa

- Iron-hematoxylin
- Giemsa

**Metabolic Tests.** The important thing to know about metabolic tests is that identification of bacteria or fungi follows an identification algorithm. In a bacterial identification algorithm, the first step is always the Gram stain. Depending on whether the bacterium is gram-positive or gram-negative, rod or coccus, a second test is done, the results of which dictate further tests, eventually leading to a species identification. Metabolic tests can be ability to grow in air (aerobic), enzyme assays (e.g., catalase), or can measure the ability of the microbe to utilize a particular substrate. Since the microbe must first be isolated in pure culture before such tests can be performed, metabolic testing can take days to weeks to complete, depending on how rapidly the microbe grows. An example of a slow-growing microbe is the bacterium that causes tuberculosis, *Mycobacterium tuberculosis*. Using conventional media, it can take over 4 weeks for this bacterium to form an easily visible colony on solid medium. Not only does this mean that results will not be available for a long time, but special precautions have to be taken to prevent faster-growing contaminants from overgrowing the medium. The same problem is encountered with fungi, which usually grow much more slowly than most bacteria. A faster way of tentatively identifying *M. tuberculosis*, which could also be applied to other slow-growing microbes, is illustrated by the BACTEC system (Becton-Dickinson Diagnostic Instrument Systems, Sparks, Md.) A specimen suspected of containing *M. tuberculosis* is inoculated into liquid medium, which contains $^{14}$C-labeled substrate. *M. tuberculosis* converts the substrate into CO$_2$. The system measures the evolution of radioactive CO$_2$. Production of CO$_2$ is generally detectable within 10 days, long before colonies would be visible on laboratory medium. Recently, a nonradioactive version of this test has been introduced that works in the same way except that CO$_2$ is detected colorimetrically. At the point where CO$_2$ production is detectable, the culture
can be centrifuged to pellet the bacteria and the pellet stained with a special stain for detecting *M. tuberculosis* (acid-fast stain).

Historically, special media have been used to speed the identification process. Some media have an indicator that turns a different color depending on a metabolic activity of the bacteria. For example, some bacteria lyse red blood cells (hemolysis) and produce a clear zone around colonies growing on agar that contains red blood cells. This type of medium is called a differential medium. Inclusion of antibiotics and dyes in the medium inhibit the growth of normally occurring bacteria and select for growth of pathogenic microbes. This type of medium is called a selective medium. Differential media, selective media, and media that are both selective and differential are still widely used for the rapid identification of some bacterial pathogens.

Another popular approach to rapid identification is to dispense the bacterial pathogen isolated from a clinical specimen into a series of wells in a microtiter plate containing different reagents that detect different enzyme activities. If the bacterium has an enzyme that can hydrolyze the substrate in a particular well, a visible color reaction occurs. The pattern of colors provides a species identification of the pathogen. Different sets of reactions are used for gram-positive and gram-negative bacteria. That is, this type of testing procedure follows the same algorithm approach mentioned in an earlier paragraph. Failure to follow all the steps in the algorithm can lead to inaccurate results.

**DNA Hybridization Tests.** The classical tests for identification of bacteria and fungi, which are based on their metabolic characteristics, are still widely used to identify bacteria that grow rapidly in culture. In recent years, DNA-based tests have become more popular, especially for use in identifying microbes that are difficult to cultivate. An example of a DNA-based test is the DNA hybridization test. DNA hybridization also is being used for viruses. A clinical specimen is treated to lyse tissue host cells and microbes, releasing their DNA. The DNA is rendered single-stranded by treatment with base and is cross-linked to a paper or plastic matrix by heat or UV light. A single-stranded DNA probe, which hybridizes specifically with a DNA segment found in the genome of one microbial species, but not other species, is incubated with the specimen. If the homologous DNA sequence is found in the specimen, the probe will form stable Watson-Crick base pairs. After unbound probe is washed off, the bound probe is detected by measuring the label on the DNA probe. This label can be a radioactive compound or a fluorescent molecule. The main shortcoming of DNA hybridization tests is their lack of sensitivity.

**Polymerase Chain Reaction (PCR).** A solution to the problem of low sensitivity is a form of DNA amplification called polymerase chain reaction. Two DNA segments, called primers, are designed to bind at a short distance from each other on either side of a species-specific DNA segment. The two primers bind to different strands of the target DNA. The clinical specimen is boiled to release DNA from any microbes it contains and to make the DNA single-stranded. The released DNA is mixed with the two single-stranded primers, which bind to the homologous DNA sequences. Then, a thermostable DNA polymerase is added. DNA polymerase is an enzyme that synthesizes DNA from a single-stranded template, but it starts synthesis at a double-stranded region. DNA polymerase thus synthesizes a second strand of both strands of the target region. After a
few minutes, the mixture is heated to 90°C to stop DNA synthesis and separate the strands of newly synthesized DNA, then the mixture is cooled to allow the primers to bind again and DNA polymerase to synthesize the DNA segment between the primers. This cycle is repeated up to 30 times and produces a huge increase (amplification) in the amount of the DNA segment between the primers. This amplified segment can be detected by DNA hybridization or by incorporating fluorescently labeled bases during the amplification process. The use of PCR for diagnosis is still somewhat limited, but it is most useful for identification of microbes such as the bacterium, *Mycobacterium tuberculosis*, which grows very slowly and is thus difficult to identify rapidly by growth-based techniques.

**Use of Tissue Culture Cells.** Cultivation and identification of viruses and certain obligately intracellular bacteria require the use of tissue culture cells or embryonated eggs. Some viruses produce cytopathic effects in tissue culture cells, which can be used to identify them. In other cases, an ELISA type test is used to stain tissue culture cells to determine if the particular virus detected by the ELISA is present. It is sometimes necessary to cultivate the viruses in tissue culture cells because the numbers of viruses in a clinical specimen are not high enough to detect the virus directly. Viruses can also be visualized with an electron microscope but few hospital laboratories have such specialized equipment or personnel trained to use it.

**Tissue Changes in Infection**

The material in Chapter 8 in Robbins, p. 361-363 classifies the tissue changes by the type of inflammation that occurs. I prefer to present the damage caused by type of organism, e.g., obligate intracellular pathogens, etc. In your outline I have included the material as I will give it to you in lecture. It is just a slightly different way of looking at it, and if you consider both types of classification you should find one that will work best for you.
CHAPTER OUTLINE

I. Attempts to control infectious diseases
   A. Emerging and re-emerging diseases
   B. Infectious diseases are major cause of death worldwide
   C. Change in disease patterns
      1. Change in human practices
      2. Immunosuppression
      3. Antibiotic resistance of microbes

II. Types of pathogenic microorganisms
   A. Viruses
      1. Structure
         a. Nucleoprotein core
         b. Capsid
         c. Genome
      2. Replication cycle overview
         a. Attachment
         b. Uncoating
         c. Replication of genome
         d. Protein synthesis
         e. Assembly
         f. Exit from cell
      3. Diagnosis of viral infections
         a. Cultivation in tissue culture
b. Cytopathic effects (CPE) in specimens or cultured cells

c. Serological tests

4. Therapy
   a. Limited because viruses use host machinery
   b. Narrow spectrum – usually virus-specific

B. Bacteria

1. Prokaryotes
   a. Double-stranded DNA genome – usually have one circular chromosome; no nuclear membrane
   b. mRNA may be polycistronic
   c. Ribosomes – different size from eukaryotic; target of antibiotics
   d. No mitochondria – energy generated in cytoplasmic membrane
   e. Peptidoglycan cell wall – target of antibiotics

2. Motility and adherence
   a. Flagella – motility
   b. Adhesins
      1) Pili or nonfimbrial adhesins
      2) Specific for host cell receptors

3. Endospores – tough survival forms

4. Morphology and staining characteristics
   a. Rods, cocci, curved rods, spirals
   b. Gram stain divides into two groups
      1) Gram-positive
         a) Thick peptidoglycan layer
b) No outer membrane

2) Gram-negative
   a) Thin peptidoglycan
   b) Outer membrane

5. Extracellular and intracellular pathogens
   a. Some bacteria are obligate intracellular pathogens, i.e., unable to make some essential nutrient
   b. *Chlamydia, Rickettsia* are examples

6. Bacterial replication
   a. Binary fission
   b. Range 20 min – 24 hr/division
   c. Most bacteria grow well on agar plates
      1) Different species require different media or conditions
      2) Takes at least 2-3 days to identify microbe growing on plate

C. Fungi

1. Structure
   a. Eukaryotes
   b. Thick polysaccharide cell wall
   c. Ergosterol in cytoplasmic membrane

2. Developmental stages
   a. Yeast – single cells
   b. Mycelium – multicellular; hyphae; proteases help invasion of host tissue
c. Dimorphic – switch between yeast and mycelial forms
d. Spores are survival forms

3. Diagnosis
   a. Mycelial morphology useful in species identification
   b. Stains (e.g., calcifluor)
   c. Can be cultivated on agar but grow very slowly

D. Protozoal parasites

1. Unicellular eukaryotes

2. Some form cysts – *Giardia*

3. Some have complex life cycle involving more than one host – *Plasmodium*

4. Many are motile
   a. Pseudopods
   b. Cilia

5. Diagnosis
   a. Diagnostic forms found in specimens
   b. Serological tests
   c. Nucleic acid-based tests

6. Targets of drugs
   a. Unusual organelles such as kinetoplast

E. Metazoal parasites – helminths

1. Multicellular

2. Trematodes – flukes, e.g., *Schistosoma*

3. Cestodes – tapeworms, e.g., *Taenia*
4. Nematodes – round worms, e.g., *Trichinella*

5. Most have complex life cycles

6. Diagnosis based on diagnostic forms in specimens, e.g., eggs, larvae, proglottids

7. Targets of drugs variable
   a. Nervous system
   b. Energy-generating pathways
   c. DNA and protein synthesis

III. Host defenses

A. Adaptive defenses – antibodies, cytotoxic T cells, activated macrophages

B. Innate defenses

   1. Epithelia
      a. Cover skin and body cavities
      b. Tightly packed cells – prevent access of microbes
      c. Attached to basement membrane-polarized

   2. Defenses of skin
      a. Covered by many layers of cells
      b. Dry
      c. Acidic
      d. Keratinocytes – produce keratin, acid
      e. Langerhans cells – APCs
      f. Macrophages in dermis
      g. Resident microbiota
1) Out-competes pathogens

2) Produces antimicrobial compounds

3) May cause infections under the right conditions

3. Defenses of mucosal surfaces
   a. Mucus
      1) Traps microbes
      2) Sequesters antimicrobial compounds, e.g., lysozyme, lactoperoxidase, defensins
   b. Sloughing of cells – carry attached microbes along

4. Respiratory tract
   a. Nose hairs and sneeze reflex
   b. Resident microbiota
   c. Curvature of tract
   d. Ciliated cells in epithelium (mucociliary elevator)
   e. Alveolar macrophages
   f. Surfactants

5. Gastrointestinal tract
   a. Low pH of stomach
   b. Gastric proteases
   c. Rapid flow of contents through small intestine
   d. Bile salts and detergents in small intestine
   e. Resident microbiota of colon
   f. Defensins in colon
6. Urogenital tract
   a. Sphincter at urethral opening
   b. Washing action of urine
   c. Uterus protected by mucus plug where it joins vagina
   d. Resident microbiota of vagina

7. Defenses of blood and tissue
   a. Phagocytes (neutrophils, monocytes and macrophages) – ingest and kill microbes
   b. Cytotoxic cells (eosinophils and natural killer cells) – bombard microbes with toxins
   c. Both types of cells produce cytokines

IV. Measures of infectivity and virulence
   A. ID$_{50}$, attack rate
   B. LD$_{50}$, case fatality rate

V. Koch’s postulates
   A. Microbe must be present in lesions of everyone infected with the disease
   B. Microbe must be isolated in pure culture
   C. Isolated microbe must be able to cause same disease when given to human or animal
   D. Microbe must be reisolated from subject infected to satisfy postulate 3

VI. Properties that make a microbe pathogenic
   A. Microbe must get to appropriate host cell and attach
   B. Ability to avoid host defenses
1. Avoid phagocytosis – e.g., capsules
2. Survive in and kill unactivated macrophages
3. Make surfaces resemble host tissues
4. Change surface properties frequently
5. Attack immune cells directly

C. Ability to get nutrients from human tissues
   1. Efficient iron-uptake systems, or ability remove iron from host proteins
   2. Degradative enzymes that release carbon and nitrogen from polysaccharides and proteins

D. Major virulence factors
   1. Nonprotein toxins
      a. LPS (endotoxin) and LTA of bacteria activate inflammatory response
      b. Yeasts and protozoa elicit inflammation by uncharacterized means
   2. Exotoxins (proteins)
      a. A-B type toxins
         1) B – binding component; may have several subunits
         2) A – active component; ADP-ribosylating common, different results depending on target
            a) *E. coli* LT or cholera toxin disrupt flow of water across cell membrane—diarrhea
            b) Diphtheria toxin blocks protein synthesis—cell death
            c) Tetanus toxin and botulism toxin cleave synaptobrevin proteins in nerve cells—tetanus toxin causes spastic paralysis, botulism toxin causes flaccid paralysis
b. Superantigens (proteins)

1) Cause activation of large numbers of T helper cells nonspecifically

2) Results in release of massive amounts of cytokines—can lead to a form of septic shock

3) May cause severe cellulitis—streptococcal gangrene

3. Roles of toxins in disease

a. Bacteria may not infect; effect due only to ingested toxin (e.g., *Staphylococcus aureus* food-borne disease, botulism)

b. Bacteria infect tissues; most of effect due to toxin (e.g., *Clostridium tetani, Corynebacterium diphtheriae*)

c. *Streptococcus pyogenes* infects tissues

1) Polymer-degrading enzymes damage tissue; spread to bloodstream, other tissues

2) LTA and superantigens trigger septic shock

VII. Source of “new” pathogens

A. Mutations

1. Common in RNA viruses (HIV, influenza)

   a. Allow virus to avoid immune responses

   b. Cause of drug resistance

2. Unusual in bacteria

   a. Resistance to fluoroquinolones

   b. *Mycobacterium tuberculosis* resistance to anti-tuberculosis drugs

B. Horizontal gene transfer

1. Antibiotic resistance

2. Toxin genes, e.g., *Shigella* toxin gene in *E. coli* = *E. coli* O157:H7
VIII. Diagnosis of infectious disease

A. Signs and symptoms important

B. Stains – vary for different types of organisms

C. Metabolic tests
   1. Used mainly for bacteria in identification algorithm
   2. Measure ability to grow in air, enzyme activity, ability to use substrates
   3. Special differential or selective media often used

D. DNA hybridization tests – used for microbes that are hard to culture

E. PCR linked with DNA hybridization can be used to detect pathogens directly in patient specimens

F. Tissue culture used for viruses and obligate intracellular bacterial species; some viruses produce CPE

IX. Tissue changes in infection

A. Tissue damage caused by infectious agents
   1. Obligate intracellular organisms
      a. Cell necrosis
      b. Cell swelling
      c. Inclusion body formation
      d. Giant cell formation
      e. Latent viral infections
   2. Facultative intracellular organisms
   3. Extracellular organisms
      a. Release of degradative enzymes
      b. Production of vasculitis
c. Release of toxins

1) Endotoxin

2) Exotoxins, superantigens

B. Tissue changes caused by the host response to infection

1. Acute inflammation

2. Suppurative inflammation

3. Chronic inflammation

4. Combined suppurative and granulomatous inflammation
NUTRITIONAL DISEASES

Steve Nandkumar, MD
NUTRITIONAL DISEASES

NUTRITION AND VITAMINS
- **Recommended Dietary Allowance (RDA)** is the estimated amount of nutrient required (per day) by 95% of the U.S. population. Set in excess of minimal requirements for many nutrients; amounts vary with age, sex, physiological state.

- **Energy Requirements:**
  - Male ~ 2,900 kcal
  - Female ~ 2,100 kcal
  - Energy content of foods (1 kcal = 4.128 kJ):
    - Carbohydrates, 4 kcal/g
    - Protein, 4 kcal/g
    - Fat, 9 kcal/g
    - Alcohol, 7 kcal/g
  - Energy use for a sedentary person:
    - Basal metabolic rate (60%)
    - Thermic effect of food (10%)
    - Light activity (30%)

- **Macronutrients:** Fat, carbohydrate, protein
- **Micronutrients:** Vitamins, minerals

![Figure 27.2](image_url)
*Figure 27.2* Recommended dietary allowances for selected nutrients for 70 kg males, age 25 to 50. Vitamins shown in black boxes; minerals shown in white boxes.

![Figure 27.3](image_url)
*Figure 27.3* Energy available from the major food components.
An appropriate diet should provide the following:
1. Adequate carbohydrates, fats, and proteins for daily metabolic needs
2. Essential and non-essential amino acids and fatty acids for synthesis of structural and functional proteins and lipids
3. Vitamins and minerals which function as co-enzymes or hormones in metabolic pathways or serve as structural components; e.g., calcium and phosphorus

MALNUTRITION

Insufficient intake of protein and energy causes loss of both body mass and adipose tissue, leading to malnutrition.

The common causes are:
1. Inadequate nutrients in diet/lack of food; e.g., starvation, diet restriction, etc.
2. Ignorance and poverty
3. Malabsorption
4. Impaired utilization and storage
5. Excess loss of nutrients
6. Increased need for nutrients

Some of the above causes are seen in chronic alcoholism, drug therapies, total parenteral nutrition (TPN), and acute or chronic illnesses.

1. PROTEIN-ENERGY MALNUTRITION (PEM)

   - Defined as “a dietary intake of protein and calories INADEQUATE for the body’s metabolic needs.” Usually common in children – (25% cases in third-world countries).

Protein Storage Occurs as Follows:

   - SOMATIC PROTEIN COMPARTMENT – protein stored in skeletal muscles
   - VISCERAL PROTEIN COMPARTMENT – storage in viscera (e.g., liver)

Diagnosis of PEM is based on:

   - Compare body weight for a given height with standard tables (BMI < 16kg/meter squared)
   - Evaluation of fat stores – thickness of skin (and subcutaneous tissue) folds
   - Muscle mass – measurement of mid-arm circumference
   - Measurement of serum proteins (albumin, transferring, etc.) – it measures visceral compartment proteins

PEM is of Two Types:

   A. MARASMUS – (Greek marasmus – to waste away)

   - Weight falls to 60% of normal for sex, height, and age = marasmus.
   - If body weight is < 80% of normal = malnourished.
Clinical Features:

1. Growth retardation
2. Loss of muscle mass mainly affecting the SOMATIC compartment (protein breakdown yields amino acids as a source of energy!) → emaciation
3. Loss of subcutaneous fat (used as fuel) decreases leptin levels and increases cortisol levels → lipolysis → emaciation; extremities appear emaciated; head appears too large for the body
4. Lack of vitamins causes anemia/vitamin deficiency states
5. T-cell mediated immune deficiency predisposes to infections (worms and parasites)
6. SERUM ALBUMIN IS NORMAL OR MINIMALLY REDUCED, AS THE VISCERAL COMPARTMENT IS MINIMALLY AFFECTED!

B. KWASHIORKOR (In Ghana means “red boy”)

- Defined as a condition where PROTEIN LACK IS RELATIVELY MORE THAN REDUCTION IN TOTAL CALORIES.
- Occurs more commonly in Southeast Asia and Africa due to the weaning habits, (mainly carbohydrate diet) malabsorption (diarrhea) or protein loss (kidney or GI diseases, burns, etc.)

Clinical Features:

1. Growth failure
2. Protein loss affects the VISCERAL COMPARTMENT. Hence, serum ALBUMIN IS LOW. HYPOALBUMINEMIA causes edema (water retention in tissues).
3. Relative sparing of muscle mass
4. Relative sparing of subcutaneous fat
5. Skin lesions of hyperpigmentation, desquamation, and hypopigmentation (FLAKY PAINT APPEARANCE)
6. Hair changes → loss of color (linear depigmentation with alternating bands of pale and dark hair – FLAG SIGN), straightening, fine texture, loss of attachment to scalp (easily plucked hair)
7. ENLARGED FATTY LIVER due to reduced synthesis of carrier proteins for lipids.
8. T-cell immune deficiency → infection (worms, parasites)
9. Vitamin lack → anemia; vitamin deficiency
10. Small bowel → mucosal atrophy; loss of villi and micro villi; loss of enzymes → diarrhea
11. Thymus and lymphoid atrophy

NOTE: Kwashiorkor is MORE SEVERE than marasmus.

II. SECONDARY PEM

- Also called CACHEXIA
- Occurs in chronic illnesses and wasting diseases such as cancers, AIDS
- Loss of subcutaneous fat
- Loss or wasting of muscles
- Ankle or sacral edema
- BMR (basal metabolic rate) is high (whereas in starvation, BMR is low)
- May be associated with cytokines, such as TNF-α, IL-1, IL-6, and interferon-γ; protein and lipid inhibiting factors also occur. Lipid Mobilizing Factor (LMF) increases fatty acid oxidation leading to lipolysis.

NOTE: Proteolysis inducing factor (PIF) causes skeletal muscle breakdown through the NF-κB induced activation of ubiquitin proteosome pathway leading to degradation of myosin heavy chain gene. Loss of dystrophin also causes muscle atrophy.
III. **ANOREXIA NERVOSA**

- Defined as “self-induced starvation resulting in marked weight loss.”
- Occurs in usually healthy young girls/women obsessed with attaining thinness (like models)

**Clinical Features:** Similar to those of PEM.

**Other changes seen are:**

1. Endocrine system:
   1. Amenorrhea due to decrease in FSH and LH following decrease in GRH
   2. Low estrogens cause decrease in bone density
   3. Hypothyroidism due to decrease in TSH
   4. Skin is dry and scaly; it turns yellow due to excess carotene in blood (obtained from ingested green, leafy, yellow vegetables)

Anemia, lymphopenia, hypoalbuminemia occur

**Complications:** **Hypokalemia** may lead to cardiac arrhythmia and sudden death

IV. **BULIMIA NERVOSA**

- Defined as “binge eating of food, mainly carbohydrates, followed by induced vomiting.”
  1. **WEIGHT AND GONADOTROPIN LEVELS ARE NEAR NORMAL.**
  2. Menstrual irregularities; e.g., amenorrhea (50% of cases) occur.

**Complications:**

- **HYPOKALEMIA** (electrolyte imbalance) due to vomiting and the use of diuretics/laxatives
- **PULMONARY ASPIRATION** of gastric contents
- **RUPTURE OF GASTRIC CARDIA AND ESOPHAGUS**

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<table>
<thead>
<tr>
<th></th>
<th>ANOREXIA NERVOSA</th>
<th>BULIMIA NERVOSA</th>
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<tbody>
<tr>
<td>Prevalence Rate</td>
<td>0.5%</td>
<td>1-3%</td>
</tr>
<tr>
<td>F : M</td>
<td>10:1</td>
<td>10:1</td>
</tr>
<tr>
<td>Age</td>
<td>Mid adolescence</td>
<td>Late adolescence/early adulthood</td>
</tr>
<tr>
<td>Binge Eating</td>
<td>20-50%</td>
<td>100%</td>
</tr>
<tr>
<td>Menses</td>
<td>Absent</td>
<td>Absent in 25-50% of cases</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Moderate to marked</td>
<td>Usually normal weight</td>
</tr>
<tr>
<td>Prognosis</td>
<td>25-50% recover fully</td>
<td>Good</td>
</tr>
<tr>
<td>Mortality</td>
<td>5% per decade due to:</td>
<td>Low</td>
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<tr>
<td></td>
<td>- Chronic starvation</td>
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<tr>
<td></td>
<td>- Depression/suicide</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** The exact cause of these two disorders is unknown – perhaps altered serotonin metabolism may play a role in the genesis of these diseases.
**VITAMIN DEFICIENCIES**

Vitamin deficiency usually involves a combination of fat- and/or water-soluble vitamins and may present as a part of PEM.

**Table 10-21. VITAMINS: MAJOR FUNCTIONS AND DEFICIENCY SYNDROMES**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Functions</th>
<th>Deficiency Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat-Soluble Vitamin A</td>
<td>- A component of visual pigment</td>
<td>- Night blindness, xerophthalmia, blindness</td>
</tr>
<tr>
<td></td>
<td>- Maintenance of specialized epithelia</td>
<td>- Squamous metaplasia</td>
</tr>
<tr>
<td></td>
<td>- Maintenance of resistance to infection</td>
<td>- Vulnerability to infection, particularly measles</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>- Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone</td>
<td>- Rickets in children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteomalacia in adults</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>- Major antioxidant; scavenges free radicals</td>
<td>- Spinocerebellar degeneration</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>- Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, and X; and protein C and protein S</td>
<td>- Bleeding diathesis</td>
</tr>
<tr>
<td>Water-Soluble Vitamin B₁ (thiamine)</td>
<td>- As pyrophosphate, is coenzyme in decarboxylation reactions</td>
<td>- Dry and wet beriberi, Wernicke syndrome, Korsakoff syndrome</td>
</tr>
<tr>
<td>Vitamin B₂ (riboflavin)</td>
<td>- Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism</td>
<td>- Ariboflavinosis, cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization</td>
</tr>
<tr>
<td>Niacin</td>
<td>- Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate involved in a variety of redox reactions</td>
<td>- Pellagra—the three “D’s”: dementia, dermatitis, diarrhea</td>
</tr>
<tr>
<td>Vitamin B₆ (pyridoxine)</td>
<td>- Derivatives serve as coenzymes in many intermediary reactions</td>
<td>- Cheilosis, glossitis, dermatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>- Requisite for normal folate metabolism and DNA</td>
<td>- Combined system disease (megaloblastic pernicious anemia and degeneration of posterolateral spinal cord tracts)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>- Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen</td>
<td>- Scurvy</td>
</tr>
<tr>
<td>Folate</td>
<td>- Essential for transfer and use of 1-carbon units in DNA synthesis</td>
<td>- Megaloblastic anemia, neural tube defects</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>- Incorporated in coenzyme A</td>
<td>- No nonexperimental syndrome recognized</td>
</tr>
<tr>
<td>Biotin</td>
<td>- Cofactor in carboxylation reactions</td>
<td>- No clearly defined clinical syndrome</td>
</tr>
</tbody>
</table>
THIAMINE

Widely available in diet.

Following absorption in gut, Thiamine $\rightarrow$ Thiamine pyrophosphate

Phosphorylation

Its main functions are:

1. Regulates oxidative decarboxylation of $\alpha$-keto acids leading to ATP synthesis.

DEFICIENCY

- Occurs in SE Asia where diet consists mainly of polished rice; also seen in chronic alcoholics, debilitating illnesses, diarrhea, pernicious vomiting of pregnancy, etc.

A. POLYNEUROPATHY (Dry Beriberi)

- A symmetric non-specific, peripheral polyneuropathy with myelin degeneration involving axons of sensory, motor and reflex arcs.
  - Progressive sensory loss, muscle weakness, lack of reflexes
  - Toe drop, foot drop, wrist drop occur

B. HEART DISEASE (Wet Beriberi)

- Peripheral vasodilation, edema
- Enlarged heart, thrombi seen, high output HEART FAILURE due to AV shunting of blood

C. WERNICKE – KORSAKOFF SYNDROME

- Wernicke’s encephalopathy includes ophthalmoplegia, nystagmus, ataxia, confusion, apathy, listlessness, disorientation.
- Korsakoff psychosis involves retrograde amnesia, inability to acquire new information, confabulation.

CNS LESIONS SEEN ARE:
Changes of hemorrhage, necrosis, neuronal degeneration and cystic lesions with surrounding hemosiderin containing macrophages.

OCCUR IN:

1. Mammillary bodies
2. Periventricular regions of thalamus
3. Floor of third and fourth ventricle
4. Anterior cerebellum

NOTE: What does Beri-beri mean?
NIACIN  
(Nicotinic acid, Nicotinamide)

Nicotinamide is a component of co-enzymes NAD and NADP. NAD activates dehydrogenases in metabolism of fats, carbohydrates, and amino acids. NADP participates in HMP (Hexose Monophosphate) shunt of glucose metabolism.

SOURCE

1. Endogenous from tryptophan
2. Exogenous – grains, legumes, seed oil, meat

NOTE: Niacin in maize (corn) is in a bound form and hence not absorbed easily.

DEFICIENCY

Niacin deficiency occurs in chronic alcoholics, HIV, protracted diarrhea, debilitating diseases, long-term drug use (Isoniazid, mercaptopurine).

PELLAGRA (Pella-skin; agere – catch)

The features include:

A. DERMATITIS
   - Red, thick, rough skin with scaling desquamation, fissures and chronic inflammation
   - Bilaterally symmetric lesions on exposed areas of the body
   - Mouth and vagina may be involved

B. DIARRHEA
   - Atrophy of GI mucosa, inflammation and ulceration

C. DEMENTIA
   - Degeneration of brain neurons and tracts in the spinal cord.
VITAMIN A

It is a group of related natural and synthetic chemicals with a hormone-like function

**Figure 8-17**

Interrelationships of retinoids and their major functions

I. **DIETARY SOURCES OF VITAMIN A**

A. **Animal Sources:**
   - Liver, fish, eggs, milk, and butter (contain preformed Vit.A)

B. **Vegetable Sources:**
   - **CAROTENOIDS** (β-CAROTENE) ARE PRO VITAMINS found in green and yellow leafy vegetables, carrots, squash, and spinach. They are metabolized to active Vitamin A. They provide 30% of Vit. A.

C. **Retinoids:**
   - Natural and synthetic chemicals structurally related to vitamin A, but may not have any “activity”

II. **METABOLISM OF VITAMIN A**

Vitamin A (Carotenes or Retinoids) → bile → **Digestion and Absorption**

- pancreatic enzymes
- anti-oxidants

**In LIVER, uptake by Apo E receptors**, undergo esterification. Stored as **RETINOL ESTER** (90% of Vitamin A in Ito cells)-a six month supply

When vitamin A is needed, retinol esters release retinol, which binds to retinol-binding protein (a carrier protein produced by the liver). Tissues needing retinol express receptors specific for RBP. Retinol is transported across the cell membrane, where it binds to cellular RBP. It is stored in tissues or oxidized to retinoic acid.
III. **VITAMIN A FUNCTIONS**

A. **Maintaining Normal Vision in Reduced Light**

- The retina contains **RODS** and **CONES**.
- Rods contain **RHODOPSIN**, a light-sensitive pigment important in reduced light.
- Cones contain three **IODOPSINS**, each responsive to specific colors in bright light.

\[
\text{RETINOL} \quad \xrightarrow{\text{oxidation}} \quad \text{ALL \, TRANS-RETINAL} \quad \xrightarrow{\text{isomerization}} \quad \text{11-CIS-RETINAL} \quad \xrightarrow{\text{OPsin}} \quad \text{RHODOPSIN (a rod protein)}
\]

Light impinging on the dark-adapted retina (rods) causes rhodopsin to undergo configurational changes to yield all-trans-retinal and opsins. This causes a change in membrane potential, generating a nerve impulse that is transmitted via the neurons to the visual cortex in the brain.

B. **Potentiating Orderly Differentiation of Specialized Mucus-Secreting Epithelium**

- Deficiency of vitamin A causes squamous metaplasia and keratinization of mucus producing epithelium. Possibly, retinoic acid binds to RAR and RXR, attaches to retinoic acid response elements on genes and regulates gene expression of cell receptors (growth factor receptors) and proteins. Loss of retinoic acid causes an abnormal metaplastic change, with loss of mucus secretion.

C. **Host Resistance to Infections**

- Vitamin A metabolite 14-hydroxy retinol stimulates the immune system. Infections decrease RBP synthesis in the liver causing low circulating levels of retinol, so vitamin A availability to tissues is reduced. Vitamin A supplements improve clinical outcome (in measles, pneumonia, and diarrheal diseases). Mortality decreases by 20 – 30%.

D. **9-cis Retinoic Acid Activates**

- Retinoic X receptor (RXR) which interacts with other nuclear receptors involved in drug metabolism, Vitamin D receptors and PPARs (peroxisome proliferator – activated receptors) which regulate fatty acid metabolism, lipoprotein metabolism and adipogenesis.

E. **Retinoids are useful in treating promyelocytic leukemias as part of differentiation therapy**

allows cells to differentiate into mature cells.

13-cis retinoic acid is useful in treatment of childhood neuroblastomas.

IV. **VITAMIN A DEFICIENCY** – occurs in colitis, celiac disease, Crohn disease, following bariatric surgery

1. Night blindness (Nyctalopia)
2. Xerophthalmia (dry eye)
   - Xerosis conjunctivae and dry cornea occur due to loss of lachrymal secretions and mucus production; BITOT’S spots, (small keratinous opaque plaques), corneal erosion with destruction (keratomalacia), and total blindness may follow.
4. Renal and urinary bladder stones.
5. Follicular/papular dermatosis (with hyperplasia and hyperkeratinization of epidermis; ductal plugging of adnexal glands)
6. Immune deficiency.
V. **VITAMIN A TOXICITY** (HYPERVITAMINOSIS A)

**Short or Long Term Excess Vitamin A Usage Can Cause:**

1. **Acute Hypervitaminosis A**
   - Headache, vomiting, dizziness, stupor, blurred vision, and papilledema
2. **Chronic Hypervitaminosis A**
   - Anorexia, nausea, vomiting, weight loss, bone and joint pains.
   - Hyperostosis.
   - Hepatomegaly with damage/fibrosis.
   - Teratogenic effects (congenital malformation) in pregnant women (avoid use!).
   - Osteoporosis and fractures (Vitamin A stimulates osteoclasts).

**NOTE:** Early Arctic explorers ate Polar bear liver and suffered from hypervitaminosis A.

### VITAMIN D

A fat-soluble vitamin, it is present in the following sources:

**EXOGENOUS SOURCES:** deep sea fish, grains, and plants (precursor: ergosterol).

**ENDOGENOUS SOURCE:** 90% of vitamin D (cholecalciferol or Vitamin D3) is synthesized in the skin from a precursor, 7-dehydrocholesterol, via solar/UV light (a photochemical reaction).

I. **METABOLISM OF VITAMIN D**

A. Dietary source/endogenous production in skin

B. Vitamin D in plasma (after absorption) $\alpha_1$-globulin $\rightarrow$ Liver

   D-binding protein

C. In the liver, it is converted $\rightarrow$ to 25-OHD (25-hydroxy vitamin D)

   25-hydroxylase

D. 25-OHD $\alpha_1$-hydroxylase $\rightarrow$ 1,25(OH)$_2$-D (1,25-dihydroxy vitamin D) (MOST ACTIVE FORM)

**Production of 1,25(OH)$_2$-D by the kidneys is REGULATED by**

1. Feedback inhibition of $\alpha_1$-hydroxylase by 1,25(OH)$_2$-D. Increased levels of this form of vitamin D inhibit the enzyme; low levels stimulate the enzyme.
2. Low calcium increases PTH, which activates $\alpha_1$-hydroxylase.
3. Low phosphorus activates $\alpha_1$-hydroxylase (direct action).
II. **FUNCTIONS OF VITAMIN D**

- Vitamin D functions as a steroid hormone. It binds to nuclear receptors and RXR, which bind to regulatory DNA sequences, which in turn induce transcription of mRNA coding for specific proteins that carry out the functions of vitamin D. **VITAMIN D IS NECESSARY FOR MAINTAINING NORMAL PLASMA LEVELS OF CALCIUM AND PHOSPHORUS.**
- 1,25(OH)\(_2\)D also binds to Vitamin D membrane receptors, activates protein kinase C and leads to opening of calcium channels. (This is a non-genomic mechanism).
- Vitamin D also has immunodulatory and anti-proliferative actions.

III. **VITAMIN D AND GUT**

- Vitamin D stimulates intestinal absorption of calcium and phosphorus. Though the exact mechanism is unknown, vitamin D probably binds to mucusal epithelial receptors and RXR, causing synthesis of calcium transport proteins/calcium transport channels (through TRPV6). Phosphorus absorption is independent of calcium transport.

IV. **VITAMIN D AND BONE**

A. Vitamin D is needed for normal bone mineralization. Vitamin D activates osteoblasts to synthesize the calcium binding proteins **OSTEOCALCIN** and **OSTEONECTIN**, resulting in calcium deposition into the osteoid matrix, leading to bone mineralization.

B. Vitamin D, together with PTH, helps resorption of calcium and phosphorus from bone to **MAINTAIN NORMAL PLASMA LEVELS OF BOTH**. Vitamin D enhances osteoclast genesis by favoring differentiation of pre osteoclasts (monocytes/macrophages) to osteoclasts through the **RANK/RANK L** pathway. Osteoblasts and bone stromal cells express RANK L (receptor activated for nuclear factor kB ligand). This binds with RANK expressed on monocytes/macrophages (pre osteocalsts) converting them into osteoclasts (osteoclastogenesis). HCl and cathepsin K dissolve bone and release Ca and P.

V. **VITAMIN D AND KIDNEY**

- PTH and vitamin D help renal reabsorption of calcium. Vitamin D increases calcium influx in distal tubules through increased expression of **TRPV5** (transient receptor potential vanilloid family). Vitamin D does not affect phosphorus reabsorption. **PTH regulates TRPV5 expression in hypocalcemia.**

VI. **NON-SKELETAL EFFECTS OF VITAMIN D**

A. Vitamin D regulates expression of genes that participate in cell proliferation, differentiation, apoptosis and angiogenesis.

B. Vitamin D receptors are present in macrophages, keratinocytes, prostate, breast, and colon. In macrophages, pathogen induced activation of toll-like receptors causes increased Vitamin D synthesis, which in turn stimulates cathelicidin (anti-microbial) formation.

**NOTE:** Vitamin D deficiency may be associated with 30-60% increased incidence of breast, colon, and prostate cancers.

VII. **VITAMIN D DEFICIENCY** – Vitamin D is < 20 ng/ml (normal range = 20-100 ng/ml).

**The common causes are:**
1. Decreased endogenous production of vitamin D, dietetic deficiency
2. Decreased GI absorption
3. Increased degradation of vitamin D; e.g., drugs (phenytoin, rifampin)
4. Impaired synthesis of 25-OH-D; e.g., liver disease
5. Decreased synthesis of 1,25(OH)\(_2\)D
   a. Renal disease
   b. Inherited deficiency of renal \(\alpha_1\)-hydroxylase (rickets type 1)
6. Target organ resistance to 1,25(OH)\(_2\)D
7. Congenital lack of receptors to active vitamin D (rickets type II)
8. Phosphate depletion
   a. Poor absorption as seen in long-term use of antacids
   b. Renal tubular disorders causing increased excretion

**VITAMIN D DEFICIENCY CAUSES HYPOCALCEMIA (LOW LEVELS OF CALCIUM)**, so PTH production is increased, which activates $\alpha_1$-hydroxylase, leading to increased synthesis of active vitamin D.

<table>
<thead>
<tr>
<th>GI</th>
<th>RENAL</th>
<th>BONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Ca absorption</td>
<td>↑ Ca reabsorption</td>
<td>↑ Ca reabsorption</td>
</tr>
<tr>
<td>↑ P absorption</td>
<td>↑↑ P excretion</td>
<td>↑ P reabsorption</td>
</tr>
</tbody>
</table>

Hence there is an increased calcium absorption, increased calcium reabsorption, and increased phosphorus excretion in the bone. As a result, calcium is conserved and returns to **NORMAL LEVEL**, \textbf{BUT} phosphorus level is low. With continued Vitamin D deficiency, the compensatory mechanism fails and both Ca and P are low. Hence, bone mineralization is impaired.

**NOTE:** Fibroblast growth factor 23 (a phosphatonin) blocks absorption of phosphorus in the GI tract and kidney, leading to hypophosphatemia.

A. **HYPOCALCEMIC TETANY**

- If vitamin D deficiency persists, serum calcium levels will eventually decrease (in spite of the PTH-related compensatory mechanism). Calcium in serum exists as
  1. Bound form.
  2. Ionic form (most active).

- Lack of ionized calcium in the extracellular fluid causes continuous neural excitation of muscle, convulsions, and tetany.

**CLINICAL FEATURES:**

1. Carpopedal spasm
2. Laryngospasm (may cause suffocation)
3. Convulsions
4. Latent signs of neural excitation; e.g., Erb’s sign, Chvostek’s sign, Trousseau’s sign, Peroneal sign

**NOTE:** Erb’s sign – increased electrical irritability of motor nerves
Chvostek’s sign – Tap facial nerve, facial muscles twitch
Trousseau’s sign – Pressure on any nerve causes muscle contraction
Peroneal sign – Pressure on peroneal nerve near fibula head, causes dorsiflexion and abduction of foot.

**TREATMENT:**

1. IV calcium gluconate 10%
2. Followed by oral calcium chloride
3. Vitamin D 50,000 IU/day or more
B. **RICKETS AND OSTEOMALACIA**

- Rickets occurs in infants and children before closure of epiphyses, whereas osteomalacia occurs in adults after bone growth stops.

**BONE DEVELOPMENT IS AS FOLLOWS:**

**FLAT BONES**
Intramembranous ossification occurs when mesenchymal cells go to form osteoblasts, which synthesize collagenous osteoid matrix on which calcium is deposited.

**LONG TUBULAR BONES**
Endochondral ossification occurs when the epiphyseal growth plates of cartilage are mineralized, progressively resorbed, and replaced by osteoid matrix which then becomes mineralized with calcium and phosphate leading to bone formation/growth.

- **AN EXCESS OF UNMINERALIZED BONE MATRIX OCCURS IN BOTH RICKETS AND OSTEOMALACIA.**

- The poorly mineralized bones, characterized by overgrowing, poorly calcified cartilage and deposition of osteoid matrix, become enlarged and laterally expanded at the **OSTEOCHONDRAL JUNCTION** (disorganized). Loss of structural integrity leads to microfractures and bony deformities of the skeleton.

**CLINICAL FEATURES IN RICKETS:**

1. Flattening of occipital bones
   - Craniotabes – parietal bones pressed inward by fingers; release of pressure causes bones to snap back due to elastic recoil
2. Frontal bossing – square head due to excess osteoid deposition
3. Rachitic rosary – beaded appearance at the costochondral junction due to overgrowth of cartilage/osteoid tissue
4. Pigeon breast deformity – respiratory muscle pull causes ribs to bend inwards; sternum protrudes anteriorly
5. Harrison groove – caused by inward pull at the diaphragmatic margin
6. Lumbar lordosis and bowing of legs – spine, pelvis and long bones are affected.

**CLINICAL FEATURES IN OSTEOMALACIA:**

- Normal bone remodeling that occurs in life is affected due to defective poorly mineralized osteoid tissue.

   1. Microfractures/fractures of femur and vertebral bodies occur
   2. Osteopenia (weak bones with loss of skeletal mass)

**NOTE:** Osteoporosis (reduced production of osteoid matrix of bone) may be associated with vitamin D receptor defects.

VIII. **VITAMIN D TOXICITY**

- Excess intake of oral Vitamin D can cause calcification of soft tissues and kidney (metastatic calcification), bone pain and hypercalcemia.
**VITAMIN C**

I. SOURCES OF VITAMIN C (ASCORBIC ACID)
   a. ENDOGENOUS: NONE
   b. EXOGENOUS: present in liver, fish, milk, fruits, and vegetables

II. FUNCTIONS OF VITAMIN C
   1. ACTIVATION OF PROLYL AND LYSYL HYDROXYLASES FROM INACTIVE PRECURSORS PROVIDING FOR HYDROXYLATION OF PROCOLLAGEN
   2. ENHANCES RATE OF SYNTHESIS OF PROCOLLAGEN PEPTIDES INDEPENDENT OF ANY EFFECT ON PROLINE HYDROXYLATION
   3. ANTIOXIDANT EFFECT – vitamin C can scavenge free radicals directly and act indirectly by regenerating the antioxidant form of vitamin E.

III. DEFICIENCY OF VITAMIN C
   - Though uncommon, it may occur in elderly people with poor nutrition, alcoholics, infants given milk formulas without vitamin C, and in patients undergoing dialysis. Vitamin C deficiency causes poor hydroxylation of procollagen. This results in the formation of relatively unstable, soluble, easily degradable molecules lacking in tensile strength. The collagen (hydroxyproline) formed is WEAK, affecting BONES and BLOOD VESSELS.

SCURVY
   - Lack of vitamin C causes SCURVY. Children and young adults are affected.
   1. Blood Vessel Changes
      - Poorly formed collagen leads to weak walls of capillaries and venules. Wall defects cause HEMORRHAGES. Purpura, ecchymoses, etc., occur in the skin and gingiva. Minor trauma can cause sub-periosteal hematoma and bleeding into joints. Retrobulbar, subarachnoid, and intracerebral hemorrhage can be fatal.
   2. Skeletal Changes  FORMATION OF OSTEOID MATRIX IS DEFECTIVE
      Changes noted in long bones are:
      1. ‘Palisade’ arrangement of cartilaginous cells is normal.
      2. Calcification (MINERALIZATION) occurs.
      3. INADEQUATE OSTEOID MATRIX FORMATION by osteoblasts
      5. There is cartilaginous OVERGROWTH with widening of epiphyses.
      6. WEAK SCORBUTIC BONES subject to stress of weight bearing and muscle tension become deformed; e.g., bowing of legs.
   3. Skin rash, periodontal infections, poor wound healing, and anemia may also occur.

IV. VITAMIN C TOXICITY
   1. Uricosuria (increased uric acid excretion in urine)
   2. Iron overload (due to increased iron absorption)
OBESITY

Definition:

- A state of increased body weight due to adipose tissue accumulation, producing adverse health effects. Energy intake and energy expenditure are **UNBALANCED**.

- 35% of U.S. adults are overweight; 30% are obese. **300,000 deaths/year in the USA**.

Measurement of Fat Accumulation:

1. BMI (body mass index)

   \[
   \text{BMI} = \frac{\text{weight in kilograms}}{\text{height in meters}^2} = \frac{W}{H^2}
   \]

2. Skin fold measurement

3. Various body measurements: ratio of waist to hip circumference

<table>
<thead>
<tr>
<th>Table 9-25 Body Mass Index Associated Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity Class</td>
</tr>
<tr>
<td>Underweight</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
</tr>
<tr>
<td>Obesity Class I</td>
</tr>
<tr>
<td>Obesity Class II</td>
</tr>
<tr>
<td>Extreme Obesity III</td>
</tr>
</tbody>
</table>


ETIOLOGY OF OBESITY

GENETIC FACTORS

- Obesity genes act as lipostats so that there is regulation of food intake and energy expenditure, depending on the energy stores (adipose tissue).

- Obesity genes control **LEPTIN** (Gr. Leptos = thin) synthesis (a cytokine produced by fat cells). Leptin binds to specific “neuron receptors” in the hypothalamus.
LEPTIN-MELANOCORTIN PATHWAY

- There are 2 major types of receptors in the hypothalamus.

I. NPY-Neuropeptide Y
   AgRP (Agouti-related protein)

   These produce NPY and AgRP, which are appetite stimulating OREXIGENIC, anabolic neurotransmitters

LEPTIN INHIBITS NPY/AgRP SYNTHESIS

II. α-MSH (α-Melanocyte stimulating hormone) and CART (cocaine and amphetamine related transcripts)

- Both are produced from POMC (pro opiomelanocortin). These produce α-MSH and CART which are appetite suppressing, ANOREXIGENIC, catabolic neurotransmitters.

LEPTIN STIMULATES α-MSH and CART SYNTHESIS

ANABOLIC PATHWAY

- NPY/AgRP act on their own receptors (Y 1/5, second order neurons) in the paraventricular nucleus of hypothalamus, resulting in the synthesis of orexins A and B and MCH (melanin-concentrating hormone). They stimulate appetite.

CATABOLIC PATHWAY

α-MSH binds to MC3R and MC4R (melanocortin receptor3 and 4) resulting in:

1. TRH (Thyrotropin-releasing hormone) synthesis which causes increased thermogenesis and appetite suppression.
2. CRH (Corticotropin releasing hormone) synthesis which causes anorexia and activates sympathetic nervous system (nor-epinephrine release). NE release in fat cells causes fatty acid hydrolysis and energy loss through heat dissipation.

MUTATIONS OF LEPTIN GENE OR LEPTIN RECEPTORS may cause obesity. Mutations of MC4R cause 4-5% cases of massive obesity.

LEPTIN RESISTANCE (with high blood levels) also occurs in most cases of obesity. Defective leptin transport, abnormal hypothalamic pathways, etc., may cause obesity.

SYNDROMES OF OBESITY, associated with hypogonadism and mental retardation, are known to be genetically determined. e.g., Prader Willi syndrome (15q 11 – 13 deletion), Laurence-Moon-Biedl syndrome etc.

ADIPONECTIN is produced by adipose cells and stimulates fatty acid oxidation in muscle thereby decreasing fat stores. By binding to receptors Adipose R1 (muscle) and Adipose R2 (liver), cyclic AMP activated protein kinase is formed. This in turn inactivates carboxylase enzyme required for fatty acid synthesis. So fat stores decrease. It also functions as an “insulin sensitizer”.

ADIPOSE TISSUE CYTOKINES. TNF, IL-1, IL-6, IL-8 and chemokines participate in energy balance and metabolism.

GUT HORMONES. Ghrelin, insulin, PYY and Amylin are involved in energy metabolism.
ENVIRONMENTAL FACTORS
Affluent western countries with abundant food supply have an increased incidence of obesity. Immigrants to western nations (with changes in the type and amount of dietary intake) have a higher incidence of obesity. MORE FOOD, MORE OBESITY!

OSTEOPATHY ASSOCIATED DISORDERS

1. **DIABETES MELLITUS (TYPE 2) – DM**
   Obesity is associated with insulin resistance and hyperinsulinemia. Weight loss causes improvement of DM.

2. **HYPERTENSION (HTN)**
   Obesity related hyperinsulinemia causes Na/water retention, blood volume expansion, production of excess NE and smooth muscle proliferation → HTN.

3. **DYSLIPIDEMIA**
   Increased triglycerides and low HDL cholesterol values seen in obesity may increase the risk of CAD (coronary artery disease).

4. **SYNDROME X – A metabolic syndrome characterized by abdominal obesity, insulin resistance, hypertriglyceridemia, low HDL, HTN and increased risk for coronary artery disease.**

5. **HEPATO-BILIARY DISEASE**
   Increase in total cholesterol and its metabolism leads to increased biliary excretion of cholesterol → gall stones. Non-alcoholic Steato-hepatitis (NASH), pancreatitis, etc., can occur.

6. **HYPOVENTILATION SYNDROME (PICKWICKIAN SYNDROME)**
   Respiratory abnormalities in the obese, polycythemia, cor pulmonale (right side heart failure), sleep apnea, hypersomnolence, etc., occur.

7. **OSTEOARTHRITIS (DJD – DEGENERATIVE JOINT DISEASE)**
   More fat, more weight, more trauma to joints (increased wear and tear) causes arthritis in older people.

8. **STROKE/CVA (CEREBROVASCULAR ACCIDENT)**
   This is more a result of HTN and not of obesity. There is an increased risk for venous thrombosis.

9. **CANCER**
   E.g., cancers of breast and endometrium – The relationship between obesity and cancer is well known. Sex hormones play an important role in hormone dependent cancers. Obesity enhances sex hormone synthesis; hyperinsulinemia causes increased cell growth, through insulin-like growth factors.

DIET AND SYSTEMIC DISEASES
Undernutrition, overnutrition, and specific nutritional deficiencies can cause diseases.

The causation and progression of some diseases can be influenced by diet. Dietary therapy is useful in the management of some diseases.

1. **DIET AND AS (Atherosclerosis)**
   Lipid abnormalities are an important risk factor for AS and hence CHD (coronary heart disease). The western diet is usually high in cholesterol and saturated fats (saturated: unsaturated fats=3:1). Decreased consumption of saturated fats may be beneficial. Vegetable oils (corn and safflower oils) and fish oils contain polyunsaturated fatty acids that help reduce serum cholesterol levels. Fish oils (omega 3 fatty acids) are helpful in reducing the risk of CHD.

2. **Hypertension**
   Low-salt or salt-free diet is helpful. Na intake is restricted.

3. **Diabetes mellitus**
   Diabetic diet: sugar free/calorie controlled diet is IMPORTANT.

4. **Diverticulosis of colon**
   Increased fiber (roughage) in the diet causes increased bulk, enhancing bowel movement. Hence, there is a preventive effect against diverticulosis and carcinoma of colon.

5. **Myocardial infarction (MI)**
   Fresh fruits and vegetables may lower homocysteine levels and are thus cardioprotective, whereas meats and processed foods are associated with hyperhomocystinemia, increasing the risk of MI. Garlic is cardioprotective.
6. Immune functions
Calorie restriction slows age-related decline in immune functions in experimental animals.

7. DIET AND CANCER
Dietetic factors may be carcinogenic or may prevent or minimize cancer.

a. Exogenous carcinogens in diet
   - E.g., aflatoxins \(\rightarrow\) liver cancer
   - Cyclamates, saccharin \(\rightarrow\) bladder cancer in animals

b. Endogenous carcinogens in diet
   - E.g., sodium nitrite (used as a food preservative) and nitrates (present in vegetables) are reduced by bacterial flora in the gut. Nitrosamines and nitroso amides formed may induce GASTRIC cancers.
     - High fat intake (in diet) \(\rightarrow\) increased bile acids in gut \(\rightarrow\) microaerophilic bacteria break down bile acids \(\rightarrow\) metabolites may be carcinogenic.
     - High fiber diet is protective. Fiber binds carcinogens and thus protects the mucosa.

c. ANTIOXIDANTS in diet
   - Vitamins C, E, β-carotenes, and selenium may be anticarcinogenic.
ENVIRONMENTAL DISEASES

William Scott, MD, PhD
Environmental Pathology I
Mechanisms of Toxicity
and Personal Exposures

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Humans and the Environment
• Basic concept
  - Genetics — Environment
• Environmental and Occupational Health
  - Diagnosis
  - Treatment
  - Prevention
• Types of exposure
  - Workplace
  - Voluntary
  - Involuntary

Recognition of Occupational
and Environmental Diseases
• Occupational exposures affect
  - 120 million in the US
• Fatal injuries
  - 10,000 in 1992
  - 40% transportation accidents
  - 20% assaults and physical violence
  - 10% falls
  - 5% electrocution
  - 5% explosions and fires

Recognition of Occupational
and Environmental Diseases
• Occupational exposures cont.
  - Nonfatal injuries
    - In the millions in 1992
      - Highest in construction workers, followed by
        - Agriculture
        - Forestry
        - Fishing
        - Manufacturing
  - Economic cost
    - $145 billion

Recognition of Occupational
and Environmental Diseases
• Occupational exposures cont.
  - Occupational illnesses vs. injury
    - Cancer, cardiovascular and cerebrovascular diseases
      - Occupational exposure to chemicals in the range of ppm
    - 842,000 new cases in 1992
    - 60,000 premature deaths
  - Economic cost
    - $25 Billion

Recognition of Occupational
and Environmental Diseases
• Total costs for occupational illnesses and
  injuries are greater than for treatment of
  AIDS and Alzheimer disease
Recognition of Occupational and Environmental Diseases

- Environmental exposures
  - Magnitude and extent of illness difficult to ascertain
    - Over 80,000 chemicals in use in the US
    - 4 million people live within 1 mile of a superfund site
    - 1.8 million workers are employed at hazardous waste sites
    - Environmental exposure to chemicals in the range of µg or µg vs. ppm (as seen in work settings)

Recognition of Occupational and Environmental Diseases

- Regulatory agencies that determine exposure limits for environmental/occupational hazards
  - EPA - Environmental Protection Agency
    - Pesticides, toxic chemicals, water and air pollutants, and hazardous wastes
  - FDA - Food and Drug Administration
    - Drugs, medical devices, food additives and cosmetics
  - OSHA - Occupational Safety & Health Administration
    - Safe working conditions
  - CPSC - Consumer Products Safety Commission
    - Products sold for use in homes, schools, or recreation

Mechanisms of Toxicity

- Definitions
  - Toxicology
  - Toxicity
  - Dose-response curve
  - Threshold dose
  - No observed effect
  - Threshold limit value
  - Ceiling effect
  - External dose
  - Biologic effective dose

Toxicology

- Toxicology is the scientific discipline that studies the detection, effects, and mechanisms of action of poisons.
- All substances are potentially toxic.
- Toxicology try to define the capacity of substances to produce harmful effects (toxicity), measure and analyze the doses at which toxicity occurs (dose-response relationship)

Mechanisms of Toxicity

- Toxicology principles
  - Exposure (dose and duration)
  - Absorption 3 ways (ingestion, inhalation, skin contact)
  - Distribution (some do not require metabolism and some are directly excreted)
  - Metabolism (products may be more or less toxic than the parent compound or conjugation products)
  - Interaction (reach target receptors)
  - Excretion
  - Toxic effect depends on the rate and ability of all the above.

Mechanisms of Toxicity

- Metabolism refers to the chemical transformation of compounds that can occur in an organism as a result of enzymatic reactions. The type of enzymatic reactions that can occur include catabolic or breakdown reactions of oxidation, reduction, and hydrolysis, and synthetic conjugation reactions.
Mechanisms of Toxicity

- Basic principles of xenobiotic metabolism
  - Most xenobiotics are lipophilic (fat interacting)
  - Lipophilic toxicants are metabolized to hydrophilic (water interacting) metabolites in 2 steps
    - Phase I reactions
    - Phase II reactions
  - Genetic variations exist in the level of activity of xenobiotic-metabolizing enzymes
    - Cytochrome P-450 enzymes (deficiency)
    - Glutathione-S-transferases (deficiency)
  - Multiple pathways may be involved in metabolism of a toxicant

Toxicity

- A number of factors influence the rate of biotransformation. These include differences in
  - Age
  - Sex
  - Species
  - Nutritional status
  - Presence of an underlying disease

Mechanisms of Toxicity

Biochemical pathways

- Phase I reactions
  - A polar functional group is added to the parent compound (mostly oxidation reactions)
  - Most important phase I reactions occur in Cytochrome P-450-dependent monoxygenase system (oxidative reaction)
    - Located in the smooth ER - conducts electrons
    - Highest activity in the liver
    - Skin, lung, gastrointestinal tract
    - Different enzymes have different distribution patterns
    - Example: Benz(a)pyrene (hydroxylation/epoxidation)

- Phase II reactions
  - Products of Phase I reactions are conjugated with endogenous substrates prior to elimination
  - Examples:
    1. Glucuronidation
      - Example: Naphthylamine
        - Oxidized by cytochrome P-450 followed by glutathione
        - Occurs in the liver
        - Secondary glucuronide metabolite is excreted in the urine
        - Under acidic conditions (glucuronides) → 4-hydroxy-1-naphthylamine (urate cotransporter) → bladder cancer

Mechanisms of Toxicity

Biochemical pathways

- Phase I reactions cont.
  - Flavin-containing monoxygenase system
    - Located in the smooth ER in the liver
    - Oxidation reaction
    - Example: Miconine (cigarette smoke)
  - Peroxidase-dependent oxidation
    - Located in the smooth ER
    - High activity in the seminal vesicles, kidneys, and urinary bladder
    - Catalyzed by prostaglandin-H-synthase
    - Example: 2-naphthylamine (synthetic dye)

Mechanisms of Toxicity

Biochemical pathways

- Phase II reactions cont.
  - Biodegradation
    - Example: biodegradable mercuric
      - Methylated by aquatic microorganisms → ingested by herbivorous fish → ingested by carnivorous fish eaten by humans
      - An example of biomagnification
      - Mammals, Japan
      - Easily absorbed from the gastrointestinal tract and crosses the BBB and placenta
      - Adults → delayed polyneuropathy and death
      - Fetuses → fetal brain damage, mental retardation and death
Mechanisms of Toxicity

Biochemical pathways
- Phase II reactions cont.
  3. Glutathione conjugation
    - Common pathway for detoxification of primary metabolites
    - Produce water-soluble secondary metabolites
    - (conjugation to reduced glutathione)
    - Readily excreted in the bile and urine
    - Example: Vinyl chloride monomer
    - Vinyl chloride $\xrightarrow{P450}$ reactive intermediates
    - (chlorohydrine and chloromethyl hydroxide) lead to
    - macromolecules or conjugated to GSH and excreted

Toxicity

- Toxicants are primarily eliminated from the body through the Kidney, but also by:
  - Liver and biliary system
  - Lungs
  - Sweat
  - Breast Milk

Toxicity

- An understanding of toxicologic principles can assist the physician in the evaluation of patients who have symptoms or illness that are possibly caused by an exposure. A detailed occupational history helps assess the degree and nature of the individual's contact with toxic material. The Material Safety Data Sheet (MSDS), if available, can provide important information.

Common Environmental and Occupational Exposures

- Personal Exposures
  - Tobacco use
  - Alcohol abuse
  - Drug abuse

Personal Exposures

- Tobacco use
  - Associated with more mortality and morbidity than any other personal environmental or occupational exposure
  - 390,000 premature deaths per year in the US
  - 10 million cases of chronic diseases

Personal Exposures: Tobacco Use

- Mainstream smoke
  - 48 million smokers in the USA
  - Highest among American Indians/Alaskan Natives
  - 42%
  - Increased among ADOLESCENTS
  - 1983-94
  - Greatest in Whites
  - Highest among MALE drop outs
  - 60%
Personal Exposures: Tobacco Use

- Mainstream smoke continues
  - Adults (18 and over)
  - DECLINED 40%
  - Per capita consumption and DAILY smoking in the workplace/public
    - Continues to decline
    - Cost to the Economy
      - Health care ~ $50 Billion
      - Lost productivity ~ $48 Billion

Personal Exposures: Tobacco Use

- Mortality associated with mainstream smoke
  - SINGLE most PREVENTABLE cause of DEATH!
  - 1 out of 3 deaths in the USA
  - 3.0 million worldwide
  - IS DOSE related, i.e., “pack-years”
  - Sources of death
    - COPD - Emphysema/chronic bronchitis
    - Coronary atherosclerotic - MI
    - Lung - 400,000 cancer deaths (1997)
      - 37% were attributed to smoking

Personal Exposures: Tobacco Use

- Tobacco smoke and emphysema
  - Emphysema
    - Abnormal PERMANENT enlargement of the air spaces DISTAL to the TERMINAL bronchi
    - DIRECTLY associated with HEAVY cigarette smoking!
    - ≥ 2 packs/day
    - Men > Women
    - Symptomatic
      - Beginning in the 3rd decade
      - Ventilatory defects
      - Prior to the 5th decade

Personal Exposures: Tobacco Use

- Tobacco smoke and emphysema cont.
  - Theory
    - PROTEASE-ANTIPROTEASE MECHANISMS ----------
      - destruction of ALVEOLAR WALLS!
      - IMBALANCE between proteases and antiproteases
    - Greater numbers of NEUTROPHILS and MACROPHAGES in alveoli
      - Stimulates elastase release from neutrophils
      - Enhances elastolytic protease activity in macrophages
      - Nicotine is CHEMOTACTIC for neutrophils

Personal Exposures: Tobacco Use

- Carcinogenicity and other effects of cigarette smoke
  - Carcinogenic and addictive
    - Over 4,000 chemical compounds
      - ≥34 are CARCINOGENIC substances
    - Low-tar and nicotine, filtered tips
      - Decreased risk of LUNG cancer
    - NO decrease in BRONCHIOLIC cancer
    - No decrease in CHD
    - Nicotine
      - A DRUG in tobacco
      - Causes ADDICTION!

Personal Exposures: Tobacco Use

- Types of Cancer
  - LUNG
    - Attributes to 90% of ALL LUNG cancer
    - EXCEEDS breast cancer deaths in women since 1987
    - Bronchogenic carcinomas
      - > in males
    - Laryngeal, oral cavity and esophageal cancer
      - 7 fold higher in smokers
    - Kidney, urinary bladder, uterine, cervix and pancreas
Personal Exposures: Tobacco Use

- Other effects of cigarette smoke
  - Colds
  - Cerebrovascular disease
  - Acute gastritis
  - COPD
  - Complications associated with pregnancy
  - Fetal
    - Low birth wt, prematurity, increased incidence of spontaneous abortion and SIDS
  - Placental
    - Premature rupture of membranes, placenta previa, abruptio placentae

- Effect of cessation
  - SLOW decrease in mortality
  - Reach baseline after 20 or more smoke-free years
    - Before age of 30 — half the risk of dying in the next 15 years
  - Decreases in
    - Risk of MI after 1 year
    - Bronchogenic CA — 5-9 years
    - Risk of lung/cervical CA — 1-2 years
  - NO decrease in COPD
    - Lung damage associated with emphysema and chronic bronchitis is permanent
    - May become LESS symptomatic

Personal Exposures: Tobacco Use

- Sidestream smoke
  - 1992 EPA classified as a human CARCINOGEN
  - HIGHER concentration of toxic and carcinogenic compounds than mainstream smoke
  - Over 4,000 chemical compounds
    - Among them benzene, 2-naphthylamine, 4-aminobiphenyl and polonium-210
  - 30% higher risk of dying for a non-smoker living with a smoker.
    - Lung cancer
      - 3,000 non-smoking adult die each year
    - Myocardial infarction

Personal Exposures: Tobacco Use

- Sidestream smoke continued
  - Aggravates asthma
  - Increased incidence of bronchitis and pneumonia
  - Impairs blood circulation
  - Irritation of small airways
  - Emphysema
  - COPD

Personal Exposures: Tobacco Use

- Smokeless tobacco
  - Plug, leaf, snuff, dipping snuff
  - Nicotine
    - Absorption via oral tissue
    - Highly addictive
  - Increased use
    - 5 million in the USA, 1996
    - 13.8% male high school students, 1997
    - 50 fold increase in the risk of ORAL cancer in those with 5 or > years of use
**Tobacco Use**

- **Cigars**
  - From 1993-97 the consumption of large cigars and cigarettes increased 68%
  - Greater increase in young men and men with degrees
  - Socially acceptable
  - 1989 Surgeon General's Report
    - Contain MOST of the same carcinogens as cigarettes
    - 5-10 times more likely to cause cancer of the mouth or throat than non-smokers
    - 4-10 times the risk of dying from laryngeal, oral or esophageal cancer than non-smokers

**Personal Exposures**

- Ethyl Alcohol
  - Estimated 15-20 million alcoholics in the USA
  - Accounts for 100,000 deaths per year in the US
    - Economic cost of $100-130 billion
  - Increase in TEENAGE alcohol abuse
  - Genetic and environmental predisposition

**Tobacco Use**

- Whereas smoking is a major risk factor for lung cancer, it also interacts with other environmental & occupational exposures in an additive or synergistic fashion.
- Synergism in asbestos exposure (7 fold).
- Synergism in radon exposure

**Tobacco Use**

- Cigarette smoke exacerbates
  - Bronchitis
  - Asthma
  - Pneumoconiosis
    - Silica
    - Coal dust
    - Grain dust
    - Cotton dust
    - Welding fumes

**Personal Exposures:** **Ethyl Alcohol**

- Blood Alcohol Levels
  - 80 mg/dl
    - Legal definition for drunk driving
  - 200 mg/dl
    - Inebriation
  - 300-400 mg/dl
    - Coma, respiratory arrest and death
  - 700 mg/dl upper tolerance limit for habitual drinkers

- Ethyl Alcohol
  - Decreased fatalities due to
    - Blessed stupor
    - Gastric irritation — vomiting
  - Major effects of alcoholism
    - ACUTE — CNS
    - CHRONIC — CNS + VISCERAL organs
  - Agents responsible for PHYSICAL effects
    - Ethanol
    - Ethanol metabolites
      - ACETALDEHYDE and ACETATE
Personal Exposures: Ethyl Alcohol

- Mechanism of Absorption/Distribution
  - ORAL ingestion
    - Stomach and Small Intestine
      - Small amount metabolized by mucosal dehydrogenase
        - Women have lower levels than men — greater blood levels when drinking equal amounts
  - Level of Distribution
    - ALL TISSUES and FLUIDS in DIRECT proportion to BLOOD LEVELS
    - 2 - 10% is excreted DIRECTLY
    - Breach test
      - Amount EXHALED is in DIRECT proportion to the BLOOD LEVEL

- Metabolism
  - Primarily in the LIVER
    - 1 Major pathway
      - HEPATIC ALCOHOL DEHYDROGENASE — ACETALDEHYDE — ACETATE via ALDEHYDE DEHYDROGENASE
    - 2 Minor pathways
      - MICROSOMAL CYP2E1 (P-450)
      - PEROXISOMAL CATALASE

Personal Exposures: Ethyl Alcohol

- Mechanisms of Pathogenesis
  - ACETALDEHYDE
    - Proposed mediator of widespread tissue damage
    - Increased levels
      - DECREASED oxidative capacity of the liver
  - Free RADICAL activation
    - INCREASED rate of alcohol metabolism
  - FATTY ACID ETHYL ESTER
    - Nonoxidative metabolism of alcohol
  - HEPATOCYTIC ANTIGEN-ANTIBODY injury
    - Immunologic basis

Personal Exposures: Ethyl Alcohol

- Clinical presentation
  - CNS depressant
    - INHIBITORY control centers are DEPRESSED
  - Excitatory pathways are released
    - Stimulant effect
  - Mechanism
    - Affects the cerebral cortical neurons first
    - Impaired mitochondrial and microsomal function
    - Followed by the limbic system, cerebellum, and lower brain stem

Personal Exposures: Ethyl Alcohol

- Morphologic changes
  - Acute alcoholism
    - Usually not evident
    - Liver
      - Small microvesicular lipid droplets (fatty change)
      - Stomach
        - Acute gastritis
      - Cerebral edema secondary to hypoxia
        - If fatal
  - Fact
    - Contributed to 41% of motor vehicle fatalities in 2002

- Chronic alcoholism
  - LIVER
    - Fatty change (macrovesicular lipid droplets) with enlargement
      - Reversible with discontinuation use
    - ALCOHOLIC HEPATITIS
      - Potentially reversible
  - Fatty change — acute liver insufficiency
  - Focal areas of hepatocyte necrosis with neutrophil accumulation — fibrosis, alcoholic hepatitis, Mallory bodies
  - ALCOHOLIC CIRRHOSIS
    - Irreversible
    - Microvillus of regenerating hepatocytes surrounded by dense bands of collagen
    - Potentially fatal
Personal Exposures: Ethyl Alcohol

- Morphologic changes
  - Chronic alcoholism
    - CNS - Korsakoff’s Syndrome
      - Confusion and severe impairment of memory for which the patient compensates by confabulation. Precise pathogenesis is uncertain.
    - Mechanism
      - Infrequently responds to continued thiamine treatment
  - Mechanism
    - Direct neurotoxicity of alcohol, compounded by lack of thiamine

- Ethanol Substitutes
  - Methanol
    - Slowly metabolized by alcohol dehydrogenase
    - Metabolized to formaldehyde and formic acid
      - Metabolic acidosis
    - Clinical signs
      - Dizziness, vomiting, blurred vision or blindness, respiratory distress

Personal Exposures: Ethyl Alcohol

- Morphologic changes
  - Chronic alcoholism
    - CNS - Wernicke’s Encephalopathy cont.
      - Microscopic lesions
        - Foci of Symmetric Discoloration, Congestion, Malacia, and Punctate hemorrhages in the brain
      - Microscopic lesions
        - Vascular dilations, Endothelial proliferation with hemorrhage, Demyelination, Neuronal changes and loss of Purkinje’s cells

Personal Exposures: Ethyl Alcohol

- Clinical Presentation
  - Shortened lifespan
    - Major organs damaged
      - Liver - cirrhosis
      - Brain - cerebellar degeneration/psychiatric neuropathy
      - Stomach - gastric ulceration/bleeding
      - Heart - dilated congestive cardiomyopathy and coronary heart disease
    - Other organ systems damaged
      - Peripheral Nervous System, Vascular, Pancreas
    - Other effects
      - Fetal alcohol syndrome
      - Increased risk of certain types of cancer

Personal Exposures: Ethanol Substitutes

- Ethylene glycol
  - Lethal dose 1.4 ml/kg
  - Metabolized to aldehydes, glycolate, oxalate, lactate
  - Clinical signs
    - Acute renal failure
    - Renal tubular necrosis due to obstruction by oxalate crystals
  - Treatment
    - Ethanol
      - Slows production of toxic metabolites by competing for alcohol dehydrogenase
Personal Exposures

- Drug abuse
  - More than 2 million people in the US are addicted to cocaine
- Sources of drugs
  - Prescriptions
  - Black market
  - Synthesized or extracted from plants
- Classification
  - CNS Depressants
  - CNS Stimulants
  - Narcotics
  - Hallucinogens

Personal Exposures: CNS Depressants

- Ethanol
- Barbiturates ("downers")
  - Induce sedation and decrease anxiety
  - Tolerance develops rapidly
  - Simultaneous use with ethanol is lethal
  - Chronic use induces cytochrome P-450 activity
    - Increased metabolism of other drugs

Personal Exposures: CNS Stimulants

- Cocaine and Crack
  - Source
    - Cocaine hydrochloride
    - Abnormal extract from the leaves of the coca plant
    - Crack (solid crystalline, crackles when heated)
    - Pure alkaloid
    - More potent than cocaine hydrochloride
  - Produces an intense CRAVING vs. a TRUE physical addiction
  - Associated with physiologic TOLERANCE
  - Absorbed from ALL sites

Personal Exposures: CNS Stimulants

- Cocaine and Crack
  - Pharmacologic Actions
    - Crack and cocaine are IDENTICAL
    - Widely used as local anesthetic
    - Is a potent CNS stimulant
      - Blocks the RE-UPTAKE of EPINEPHRINE, DOPAMINE, and SEROTONIN at PREsynaptic terminals
      - INCREASE in POST synaptic receptor sites
      - Increases the synthesis of
        - NE
        - Dopamine

Personal Exposures: CNS Stimulants

- Cocaine and Crack
  - Clinical Presentation
    - Intense EUPHORIA followed by depression
    - Activates the SYMPATHETIC nervous system
      - Vasconstriction
      - Hypertension
    - Sudden death
    - Increased thrombotic tendencies
    - Cardiovascular disease
      - Hypertension
    - Rupture of ascending aorta
    - Tachycardia and arrhythmias
    - MI
    - Myocarditis and dilated cardiomyopathy

Personal Exposures: Narcotics

- Heroin
  - Opiate from the Poggo plant
  - MOST hazardous of ALL street drugs
  - Progressive TOLERANCE and ADDICTION
  - Short-acting
  - Acts on the SAME receptors as ENDOGENOUS opioid peptides
    - Affinity for CNS
    - Endocrine, Gastrointestinal and Cardiovascular system
Personal Exposures: Narcotics

- Heroin
  - Effects
    - Euphoria, somnolence and sedation
    - Adverse physical effects associated with
      - Adulterants
      - Hypersensitivity reactions
      - Infections related to the use of needles
      - Sudden death
        - Loss of tolerance
        - Concentration of the drug - OVERDOSE
          » Respiratory depression, cardiac arrhythmias, arrest and pulmonary edema

Personal Exposures: Hallucinogens

- Marijuana
  - Cannabinoid active plant
  - THC (tetrahydrocannabinol)
    - Active substance
  - Smoked, ingested or injected
    » 50% absorption via lung
    » 10% absorption via gut
  - Non-addictive by itself
  - 1991
    » Used by 50% of high school seniors

Personal Exposures: Nutritional Diseases

- Heroin
  - Morphologic lesions by Organ
    - Lung
      » Edema
      » Septic embolism
      » Abscesses
      » Foreign body granulomas
      » Opportunistic infections
    - Skin and Subcutaneous tissue
      » Most FREQUENT site of lesions
        » Scarring/hypopigmentation
        » Thrombosed veins
        » Abscesses/Cellulitis/Ulceration

Personal Exposures: Hallucinogens

- Hallucinogens
  - Natural and chemical
  - Natural
    » Alkaloid mescaline
    » marijuana
  - Chemical
    » Phencyclidine (PCP)
    » Lysergic acid diethylamide (LSD)
**Personal Exposures: Hallucinogens**

- Marijuana
  - Effects cont.
  - Fetus
    - Retarded development, malformations, lower birth weights, increased frequency of leukemia
  - Upper respiratory system
    - Inflammation, asthma-like symptoms, mild airway obstruction and lung cancer (?)
  - Cardiovascular system
    - Increased heart rate, blood pressure and angina
  - Psychomotor
    - Distorted sensory perception, motor coordination and psychotic breaks

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**Personal Exposures: Hallucinogens**

- PCP – Phencyclidine
  - Used as an anesthetic
  - Ingested, smoked, snorted
  - Inebriation, disorientation, numbness, nystagmus
  - High doses – coma for hours to days
- LSD – Lysergic acid diethylamide
  - Taken orally
  - Rapid absorption
  - Psychic effects, visual illusions and altered perception up to 12 hours

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_The End_
Environmental Pathology II
Therapeutic Drugs
Outdoor and Indoor Air Pollution

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Therapeutic Drugs:
Exogenous Estrogens

- Advantages exogenous estrogens
  - PREVENTS or RETARDS the progress of OSTEOPOROSIS
  - DECREASES cholesterol
    - LDL and VLDL
    - Increases HDL
  - DECREASES insulin resistance in Type II diabetes
    - Mechanism not fully understood

Therapeutic Drugs:
Exogenous Estrogens

- Disadvantages of exogenous estrogens
  - INCREASED risk of ENDOMETRIAL cancer with unopposed estrogens
    - 3 fold to 6 fold after 5 years
    - >10 fold after 10 years
    - Also seen with endogenous estrogens
  - Small INCREASED risk of BREAST carcinomas with unopposed estrogens
    - Not influenced by the addition of progestins
    - Also seen with endogenous estrogens

Therapeutic Drugs:
Exogenous Estrogens

- Exogenous estrogens
  - Types
    - Natural
      - More common and can be given alone
    - Synthetic
      - Steroidal forms of estradiol, estriol
  - Consequences of use
    - Depend on TYPE of estrogen
    - Dosage/dosage schedule
    - Concomitant use of progestins

Therapeutic Drugs:
Oral Contraceptives

- Oral contraceptives
  - Nearly always contain synthetic estrogens and variable amounts of progestin
    - Example: Ethynyl estradiol/19-nortestosterone
    - A few contain only progestins
  - Past OC’s vs. “mini pills” (Current OC’s)
    - Contain smaller amounts of estrogens
    - <50 micrograms/day
Therapeutic Drugs: Oral Contraceptives

- Advantages & Disadvantages of OC's
  - Protective against Ovarian cancer
    - The longer the use the greater the protection
    - Female risks if they are stopped

Therapeutic Drugs: Oral Contraceptives

- Disadvantages of Past and Current OC's
  - Breast cancer
    - Slight increase in risk in women younger than 45
    - Especially younger than 35 years old
    - >45 years old risk is negligible
  - Cervical cancer
    - Some increased risk
    - Duration of use
    - Level of sexual activity
  - Hypertension
    - Slight increase in blood pressure
    - > 10 in older females with history of hypertension

Therapeutic Drugs: Oral Contraceptives

- Advantages of OC's cont.
  - Alleviates Rheumatoid arthritis
    - Estrogen receptors on lymphoid cells and thymic epithelial cells
  - No increased risk of Endometrial cancer
    - Probably protective

Therapeutic Drugs: Oral Contraceptives

- Disadvantages of Past and Current OC's cont.
  - Cardiovascular disease
    - Young women smokers, using the pill are 10X more likely to suffer from MI than users that do not smoke
  - Hepatic Adenoma
    - Risk is correlated with years of use

Therapeutic Drugs: Oral Contraceptives

- Disadvantages of Past OC's
  - Thromboembolism
    - 50 micrograms/day
    - Increased risk of venous thrombosis and pulmonary embolism
    - Due to increased hepatic synthesis of coagulation factors and decreased levels of antithrombin III
  - Gall bladder disease
    - Slight increased risk with older formulations
    - Highly correlated with years of use

Hormone Replacement Therapy

- For peri-menopausal & menopausal sx's.
  - The WHI (Women's Health Initiative).
    - 16,608 women ages 50-79
    - Stopped study early in 2002 because adverse effects.
    - Increase rates of breast cancers
    - Increase rates in strokes
    - Increase rates in heart attacks
    - Increase risk of dementia in women 65 and older.
    - (JAMA May 2003)
Therapeutic Drugs

- **Acetaminophen**
  - Analgesic - antipyretic
  - Wide OTC use ("over the counter")
  - Range between ED (effective dose) and TD (toxic dose) is LARGE, i.e., high MOS (margin of safety)
    - ED = 0.5 gm, TD = 15-20 gm
  - Adverse reaction
    - Hepatic necrosis
  - Clinical signs
    - Nausea, vomiting, diarrhea, shock and liver failure

Therapeutic Drugs: Aspirin

- Clinical signs with chronic toxicity
  - CNS
    - Headache, vertigo, tinnitus, difficulty hearing, mental confusion, drowsiness, convulsions, coma
  - G.I.
    - Acute erosive gastritis
      - Damages mucosal barrier
      - Ulceration + bleeding
    - Nausea, vomiting, diarrhea

Therapeutic Drugs

- **Acetaminophen**
  - Mechanism
    - Metabolism of the drug -- toxic metabolite that is normally DETOXIFIED by binding GLUTATHIONE
    - Phase II reaction
    - Overdose -- Glutathione is DEPLETED -- toxic intermediate binds to liver macromolecules -- INJURY

Therapeutic Drugs: Aspirin

- Clinical signs with chronic toxicity cont.
  - Bleeding tendency
    - Petechial hemorrhages and bleeding from gastric ulcersations
      - Aspirin INHIBITS cyto-oxygenase -- PLATELET dysfunction
    - Analgesic nephropathy
      - Aspirin + phenacetin -- renal papillary necrosis

Therapeutic Drugs

- **Aspirin (Acetyl salicylic acid)**
  - Overdoses are
    - Accidental or suicidal
    - Often fatal before morphologic changes can occur
      - 2-4 gm in children
      - 10-20 gm in adults
    - Chronic toxicity (Salicylism)
      - 3 g grams/day or more
    - Mechanism of toxicity
      - Centers around fluid and electrolyte IMBALANCES
        - Respiratory ALKALOSIS -- metabolic ACIDOSIS which can be FATAL prior to anemic changes

Outdoor Air Pollution

- EPA
  - Role in identification and regulation of pollutants in the ambient air
- Major sources of air pollutants
  - Combustion of fossil fuels
  - Photochemical reactions
  - Powerplant emissions
  - Waste incinerators, industry, smelters
Outdoor Air Pollution

- Ozone
  - Product of a series of photochemical reaction sequences
    - Highly oxidant gas
  - Hydrocarbon vapors
  - Nitrogen dioxide
  - Sunlight
- Ambient atmosphere
  - Peaks late morning or afternoon
  - Declines in the evening
  - Contributes to smog

Outdoor Air Pollution: Ambient Ozone

- Symptoms associated with high level exposure
  - Adults
    - Cough
    - Shortness of breath
    - Pain on deep inspiration
  - Children
    - In general, NO symptomatic responses
  - Asthma
    - Can exacerbate

Outdoor Air Pollutants

- Ozone
- Nitrogen dioxide (NO₂)
- Sulfur Dioxide (SO₂)
- Acid Aerosols
- Particulates

Outdoor Air Pollution: Ambient Ozone

- Effects on the lung
  - Increased respiratory epithelial permeability and reactivity of the airway
  - Decreased ciliary clearance
  - Increased susceptibility to bacterial infection
    - Impaired macrophagocytic activity
- Mechanism
  - Oxidizes polyunsaturated lipids
  - H₂O₂ and lipid aldehydes act as irritants
  - Release of inflammatory mediators

Outdoor Air Pollution: "Atmospheric Ozone"

- Effects at ≥ 80 ppb
  - Decrements in exhaled volume and flow rate
    - Transient
  - Terminal bronchiole epithelial damage and inflammatory changes
    - Progressive
  - Airway hyperresponsiveness
    - Histamine

- Prevents UV light from penetrating the environment
- Chemicals convert O₃ to O₂
- Ozone loss
  - Increase in non-melanomatosus skin cancers
  - Increase in melanomas among Caucasians
**Outdoor Air Pollution: NO\textsubscript{2}**

- Oxide of nitrogen
- Lower reactivity than ozone
- Mechanism of action
  - Dissolves in water in the upper airways → nitric acid and nitrous acid
  - Damages airway epithelial lining
- Asthmatics have increased susceptibility to NO

**Outdoor Air Pollution: Particulates**

- Deposition and clearance of particles in the lung is dependent on size
  - Most hazardous
    - Ultrafine particulates 1-5 micrometers in diameter
- Mechanism for morbidity and mortality
  - Associated with free radical generation at the surface of the fine particles

**Outdoor Air Pollution: SO\textsubscript{2}**

- Source
  - Powerplant emissions
    - Atmospheric formation of sulfates from coal and oil containing sulfur
- Properties
  - Highly soluble in water
    - Absorbed in upper and lower airways
- Mechanism
  - Release H\textsuperscript{+}, HS\textsuperscript{2}O\textsubscript{3}, and SO\textsubscript{2} in the airway → local irritation

**Indoor Air Pollution**

- Associated with increased insulation and decreased ventilation
- Sources
  - Tobacco smoke
  - Gas stoves/furnaces
  - Wood stoves
  - Construction materials
  - Furniture
  - Radon
  - Allergens/bacteria

**Outdoor Air Pollution: Acid Aerosols**

- Source
  - Primary combustion products of fossil fuels
    - Emitted by oil and gas fields
    - Motor and agricultural vehicles
    - Emission of oxides of nitrogen
    - SO\textsubscript{2} and NO\textsubscript{2} oxidized to sulfuric acid and nitric acid
    - Dissolved in water droplets or absorbed to particles
    - Aerosolized acid sulfates contribute to acid rain
    - Alter mucociliary clearance and irritate airway epithelium
    - Asthmatics have decreased lung function on exposure

**Indoor Air Pollution: Types**

- CO and CO\textsubscript{2}
- NO\textsubscript{2}
- Formaldehyde
- Radon
- Asbestos fibers
- Wood Smoke
- Bioaerosols
### Indoor Air Pollution: Carbon monoxide

- **Byproduct of combustion produced with burning gasoline, oil, coal, wood and natural gas**
  - Major pollutant in tobacco smoke
- **Accounts for 900 accidental deaths due to asphyxia per year in the US**
- **Levels**
  - Non-smoking adults - <1% of total circulating COHgb
  - Heavy smokers - COHgb = 5-10%
  - Combustion of fossil fuels/automobile exhaust - 4-7%

### Indoor Air Pollution: Nitrogen dioxide

- **Sources**
  - Gas stoves and kerosene space heaters
  - Levels up to 20-40 ppm in homes
- **Effects**
  - Impairs lung defenses — increased respiratory infections (children more susceptible)
- **Mechanism**
  - Dissolves in water in the upper airways — nitric acid and nitrous acid
  - Damages airway epithelial lining

### Indoor Air Pollution: Carbon monoxide

- **Levels cont.**
  - 2-4 ppm in homes in the winter (levels should not exceed 9 ppm)
- **Effects**
  - Reduced exercise capacity
  - Aggravation of myocardial ischemia (30% or >)
  - High levels — poisoning
- **Clinical signs**
  - Headaches, dizziness, loss of motor control, coma and death

### Indoor Air Pollution: Radon

- **Greatest source or radiation exposure in the US is from natural background radiation**
- **Radon** — Inert gas from the soil. It enters building that are relatively negative pressure (homes). Primarily affects the lower levels of a building.
  - Decay product of radium-226 (parent of uranium-238)
    - Emitted from the earth
      - Present in most soil and rock
      - Continuously generated — UMBROUS
      - Present in homes
    - Average home 1.3 pCi/L
    - 4% of homes have > 4 pCi/L, (above EPA standards)

### Indoor Air Pollution: Carbon monoxide

- **Clinical signs cont.**
  - Death associated with 50-80% saturation of hemoglobin with CO
- **Mechanism**
  - Conversion of oxyhemoglobin to carboxyhemoglobin — hypoxia
  - Inhibitory effects on cytochrome C oxidase
  - Energy metabolism in the brain

### Indoor Air Pollution: Radon

- **Short-lived radioisotopes that emit alpha particles (solid charged particles)**
- **Alpha particles**
  - Most attach to larger aerosols
    - Inhaled into the lungs
Indoor Air Pollution: Radon

* Alpha particles cont.
  - Deposition in the lung
    - Size and branching patterns of airways
    - Rate of mucociliary clearance
    - Thickness of mucous layer
  - Damage to tissue
    - DNA damage → repair, cell death or permanent damage

Indoor Air Pollution: Radon

* Lung cancer
  - Estimated that 10,000 lung cancers per year in the US
    - With or without cigarette smoking
      - Increased risk with cigarette smoking
  - Types
    - Small cell carcinoma
    - Squamous cell carcinoma
    - Adenocarcinoma

Indoor Air Pollution: Radon

* Other Associated Disease Processes
  - Emphysema
  - Interstitial fibrosis
  - COPD
  - Chronic and unspecified nephritis
  - Decline in M/F births
  - Congenital malformation
  - Spontaneous abortion
Environmental Pathology III
Industrial Exposures, Agricultural Hazards and Natural Toxins

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Industrial Exposures

- Occupational exposures contribute to human diseases
  - Alice Hamilton established occupational medicine as an academic discipline
- Spectrum of human diseases
  - Almost ALL organ systems can be affected
    - Acute toxicity/irritation
    - Hypersensitivity reactions
    - Chronic toxicity reactions
    - Fibrosis
    - Cancer

Industrial Exposures

- Potential hazards of environmental exposures
  - 4 toxicant categories
    - Volatile organic compounds
    - Aromatic halogenated hydrocarbons
    - Plastics, rubber and polymers
    - Metals

Industrial Exposures

- Volatile Organic Compounds (VOC's)
  - Aliphatic hydrocarbons
    - Industrial solvents/dry cleaning agents
  - Used in industry and homes
    - Manufacturing, degreasing and dry cleaning, paint removers, aerosol sprays
  - Stored underground in tanks
    - Leakage contamination of underground water supplies

Industrial Exposures

- VOC's cont.
  - Exposure levels
    - High
      - Headache, dizziness and liver or kidney toxicity
    - Low
      - Potential carcinogenicity
      - Adverse reproductive effects
  - Absorption
    - Readily absorbed through the lungs, skin and gastrointestinal tract

Industrial Exposures

- VOC's cont.
  - Effects
    - Acute CNS depression
    - Kidney and liver toxicity
  - Examples
    - Chloroform and carbon tetrachloride
      - Both are carcinogenic in mice
    - Methylene chloride
      - Used in paint removers/pesticides
        - Highly volatile
      - Metabolized by cytochrome P-450 to CO₂ and CO
        - Carboxyhemoglobin
        - Respiratory depression and death
Industrial Exposures

- VOC's cont.
  - Examples cont.
    - Perchloroethylene
      - Used in dry cleaning industry
      - Acute exposure
        - CNS depression, confusion, dizziness, impaired gait, and nausea
        - Repeated exposure
          - Dermatitis
          - Potential human carcinogen

- Industrial Exposures

  - VOC's cont.
    - Examples cont.
      - Aromatic hydrocarbons
        - Benzene, toluene, xylene
        - Widely used solvents in rubber, shoe industry, printing and paper coating
        - Toluene and xylene are NOT carcinogenic
        - Inhalation of benzene is hazardous
          - Bone marrow toxicity, aplastic anemia and acute leukemia
        - Mechanism
          - Benzene metabolized by cytochrome P-450 to benzoquinone + acetaldehyde → bone marrow toxicity

- Industrial Exposures

  - Aromatic halogenated hydrocarbons
    - Polycyclic aromatic hydrocarbons (PAH's)
      - Most potent chemical carcinogens
      - 1775, scrotal cancer in chimney sweeps
      - Variety produced by combustion of fossil fuels, processing of coke, coal and crude oil, iron/steel foundries, cigarette smoke
      - 3 or more fused benzene rings
      - Example
        - Benzo(a)pyrene

- Industrial Exposures

  - PAH's cont
    - Benzo(a)pyrene
      - Metabolism
        - Metabolized by aryl hydrocarbon hydroxylase, conjugated with sulfonic or glucuronide acid, then excreted in the bile or urine
      - Effects
        - Epoxide intermediate bind to DNA
        - Used as markers to document exposure
        - Associated with increased risk of lung/hodder cancer

- Industrial Exposures

  - Plastics, Rubber and Polymers
    - Fabricated into latex fabrics, pipes, cables, flooring, home and recreational products, medical products and food/beverage containers
    - Example: Vinyl chloride
      - 1974, occupational exposure to vinyl chloride monomers found to be associated with angiosarcomas of liver
      - Colorless gas
        - Flammable and explosive
        - Prior to polymerization
          - Can be absorbed through the skin or lungs
Industrial Exposures
- **Plastics, Rubber and Polymers**
  - Vinyl chloride cont.
    - Metabolism
      - Metabolized by cytochrome P=450 to chloroacetaldehyde
        » Covalently binds to DNA and is mutagenic
    - 1,3-butadiene
      - Increased risk of leukemia
    - Plasticizers and additives
      - Potential adverse reproductive effects
        » Testicular injury in rats
      - Mimics proliferative effects of estrogen

- **Lead**
  - Recognized as an occupational hazard in 1839
  - Produced for use in batteries, alloys, exterior red lead paint and ammunition
    - 4 million tons per year
  - Also
    - Mining, smelting, spray painting, recycling and radiator repair
    - Gasoline additive (tetraethyl lead) in some countries

- **Lead cont.**
  - Routes of exposure
    - Inhalation
      - Volatilized Pb - MOST hazardous
        » Lung  →  blood
    - Ingestion
      - Diet, food, and water
      - Urban adults ingest 100 to 150 micrograms per day
      - 10% is absorbed
        » 11%  →  Blood
      » Absorption enhanced by Ca, Fe or Zn deficiency

- **Metals**
  - Occupational exposure in mining and manufacturing
    - Lead
    - Cobalt
    - Tungsten chloride
    - Cadmium
    - Chromium
    - Nickel
  - Associated with acute and chronic toxicity and carcinogenicity

- **Lead cont.**
  - Environmental sources
    - Urban air, contaminated soil and water supplies and house dust
      - Lead-glazed ceramics, lead solder food/drink cans, illegally produced alcoholic beverages

- **Absorption and storage in children**
  - Lead paint and soil
    - 50% is absorbed from the gut.
      - 85-95% taken up by BONE and developing TEETH
      - SKELETAL sequestration (storage)
    - Protective for other organs
      - Chronic lead exposure due to SLOW bone turnover
      - Deposits in the EPiphyseal regions of BONES
    - Has a half-life of 30 years in bone
      - 5-10% accumulates in BLOOD
    - Clear rapidly from the blood
      - Upper perceivable "safe" limit - 10 micrograms/dl
      - Soft tissue deposition
Industrial Exposures

- Multiple biochemical effects of lead cont.
  - Inhibition of membrane-associated enzymes
    - Inhibits 5'-nucleotidase activity
    - Sodium-potassium ions pumps
      - Decreased survival of red blood cells, renal damage and hypertension
    - Impaired metabolism of 1, 25-dihydroxyvitamin D
      - Active metabolite of vitamin D

Industrial Exposures

- Major target organs of lead cont.
  - Blood
    - Abnormalities
      - EARLY and CHARACTERISTIC
        - MICROCYTIC-HYPOCHROMIC mild hemolytic anemia with basophilic stippling
        - Hemolysis
        - Increased ZINC PROTOPORPHRYN (ZPP) or FREE ERYTHROCYTE PROTOPORPHYRIN
      - MECHANISM
        - Lead interferes with ALA-D and ferrokinase
        - Incorporation of iron into hemoglobin
        - Iron is displaced and ZPP is formed
        - Free erythrocyte protoporphyrin

Industrial Exposures

- Major target organs of lead cont.
  - Nervous System
    - Children
      - Varying degrees of BRAIN damage
        - Intellectual impairment, learning disabilities, behavioral abnormalities
      - Anatomical changes with severe exposure
        - Marked edema of the brain
        - *Flattening of gyri
        - *Narrowing of sulci
        - *Demyelination
        - Neuronal death
        - *Inhibition of mitochondrial oxidative phosphorylation

Industrial Exposures

- Major target organs of lead cont.
  - Nervous System
    - Adults
      - Headache, dizziness, memory deficits and decreased nerve conduction velocity
      - Peripheral Demyelination
        - Extensor muscles of the wrist and foot

Industrial Exposures

- Major target organs of lead cont.
  - Nervous System
    - Children
      - Varying degrees of BRAIN damage
        - Intellectual impairment, learning disabilities, behavioral abnormalities
      - Anatomical changes with severe exposure
        - Marked edema of the brain
          - *Flattening of gyri
          - *Narrowing of sulci
          - *Demyelination
          - Neuronal death
          - *Inhibition of mitochondrial oxidative phosphorylation
Industrial Exposures

- Major target organs of lead cont.
  - Gastrointestinal
    - Major source of clinical symptoms in ADULTS
    - "Lead colic"
    - "Lead line"
      - Precipitated Pb sulfide
      - Gingival margins
      - RARE in children
      - NOT pathognomonic for Pb
  - No intestinal morphologic changes!

Industrial Exposures

- Reproductive system
  - Infertility in men
    - Testicular injury
  - Infertility in women
    - Failure of implantation of fertilized ovum
  - Fetus
    - Neurotoxic to the developing nervous system
      - Similar to methyl mercury

Industrial Exposures

- Diagnosis of lead toxicity cont.
  - Adults
    - Abdominal pain, fatigue and arthralgia
  - Treatment
    - Blood chelators
    - Environmental control

Industrial Exposures

- Major target organs of lead cont.
  - Kidney
    - Primary route of excretion
    - Damage to the proximal tubules
      - Intranuclear lead inclusions
      - Renal tubular dysfunction
    - Chronic exposure
      - Diffuse tubulointerstitial nephritis fibrosis, gout and renal failure
        - Fanconi’s syndrome – glycosuria, aminoaciduria, phosphaturia, proteinuria and hyperuricemia
    - Hypertension

Industrial Exposures

- Diagnosis of lead toxicity
  - Both Adults and Children
    - Anemia and basophilic stippling
    - Elevated blood levels of
      - Pb, Free Erythrocyte Protoporphyrin and Zinc Protoporphyrin
    - Increased excretion of ALA in urine
    - Decreased erythrocyte ALA-D activity
  - Children
    - Flocularity of deposits
    - Epiphyses
    - Intellectual, behavioral or motor abnormalities

Industrial Exposures

- Cobalt and tungsten carbide
  - Products fabricated from tungsten carbide with cobalt as a binder
    - Cutting tools, metal grinders, polishers, drilling equipment
  - Target organ
    - Lung
  - Effects
    - Can develop asthma
    - Interstitial lung fibrosis
      - "hard metal disease"
Industrial Exposures

- Cadmium
  - Exposure occurs near mines and smelters
    - Also used in paint pigments, alloys, solder, electroplating, and batteries
  - Target organs
    - Lung and kidney
  - Acute effects
    - Irritation and pulmonary edema
  - Chronic effects
    - Damage to proximal convoluted tubules
      - proximal

- Chromium
  - Exposure occurs in mining and smelting
    - Also used in stainless steel, pigments, and alloys
  - Important occupational carcinogen
  - Mechanism
    - Hexavalent chromium is reduced to trivalent chromium
    - Generation of free radicals and DNA damage

Industrial Exposures

- Nickel
  - Topical exposure
    - Frequently results in contact dermatitis
  - Metallic nickel
    - Widely used in steels, alloys, batteries, fuel cells, electroplating, and ceramics
      - Also emitted from waste incinerators, power plants, and cigarette smoke
  - Major route of exposure
    - Inhalation

- Metallic nickel cont.
  - Effects
    - Particulate nickel compounds are carcinogenic
      - Enter cells after phagocytosis and release nickel ions intracellularly
  - Mechanism
    - Nickel ions generate reactive oxygen species
    - Increase endogenous generation of oxidants and form DNA-protein cross-links
      - Damages heterochromatin selectively and can inactivate T5 genes by hypermethylation

Agricultural Hazards

- Advantage of fertilizers and pesticides
  - Improved agricultural production

- Disadvantages
  - Cause disease in those exposed to them
    - Particularly farmers
  - Pesticide residues on foods and contaminate soil and water supplies
  - Environmental contamination
    - Threat to wildlife
      - Bioaccumulation/bioaccumulation with persistence
        - Organochlorines (DDT) and dioxins (TCDD)

Agricultural Hazards

- Agricultural pesticides
  - 5 categories
    - Insecticides
    - Herbicides
    - Fungicides
    - Rodenticides
    - Fumigants
  - ALL are toxic to some plant or rodent species
    - Higher doses can be toxic to farm animals, pets, and humans
Agricultural Hazards

- Herbicides
  - In general, have low acute toxicity for mammals
- Fungicides
  - Moderately toxic
- Insecticides
  - Range from low to high toxicity
- Fumigants and rodenticides
  - Highly toxic

Agricultural Hazards

- Acute toxicity for agricultural pesticides
  - Well known
  - Safe exposure limits established
- Chronic toxicity for agricultural pesticides
  - Less certain
  - Especially at low dose exposure in food residues or in soil and water
- Examples
  - DDT – biopersistence
  - Organochlorines and PCB's – weakly estrogenic and some are carcinogenic

Agricultural Hazards

- Organochlorines (Insecticides)
  - DDT
    - Low acute toxicity for humans
    - Bioaccumulation in environment and fat tissue
    - Absorbed through the skin, g.i.t. and lungs
    - Role as an endocrine disrupting agent is controversial
    - Example – Chlordane (insecticide)
      - Insecticide
      - Controls termites and soil insects
      - Acute toxicity — hypothermia, tremors, convulsions
      - Also causes immune dysfunction and may act as a non-genotoxic carcinogen (lymphoma in farm workers)

Agricultural Hazards

- Organochlorines (Insecticides)
  - DDT cont.
    - Example – Lindane
      - Isomer of benzene hexachloride
      - Used to control lice and scabies
    - Also used as a wood preservative and household fumigant
    - Causes immune dysfunction and reproductive problems in women

Agricultural Hazards

- Organochlorines (Insecticides)
  - Irreversible inhibitors of cholinesterases
    - Abnormal transmission at peripheral and central nerve endings
    - Absorption through the skin, g.i.t. and lungs
    - Up to 40% of the farm workers in US have a measurable inhibition of red blood cell or plasma cholinesterase activity
      - Fumates have been reported from OP exposure

Agricultural Hazards

- Carbamates (insecticides)
  - Reversible inhibitors of cholinesterase
    - Acute neurotoxic effects similar to OP
    - Example – Carbugyl (Sevin)
      - Potentially mutagenic/teratogenic
      - Poisons the mitotic spindle
Agricultural Hazards

- Herbicides
  - TCDD – a dioxin
    - Vietnam War
      - Defoliant agent orange was contaminated with TCDD
  - Chemical factory explosion
    - Chlorine and increased incidence of leukemia, lymphoma and sarcomas
  - Also produced in the paper pulp industry using chlorine bleach and by waste incinerators
  - Low levels in food, soil and water

- Rodenticides
  - Characteristics
    - Highly toxic
    - Restricted use

Natural Toxins

- Mycotoxin, phytotoxins and animal toxins
  - May contaminate food
  - Example – cyanid flour
    - Plant contains cyanid toxin
    - Associated with a degenerative neurologic disorder
    - Amyotrophic lateral sclerosis
  - Example – ciguatoxin
    - In dinophilagellates
      - Poisoning from eating tropical fish and snails who have ingested dinophilagellates with ciguatoxin
    - Ciguatera poisoning – S. Pacific and Caribbean

- Mycotoxin, phytotoxins and animal toxins cont.
  - Example – saxitoxin
    - Paralytic shellfish poisoning
    - In America
      - Consuming mollusks that have ingested dinophilagellates with saxitoxin
  - Example – aflatoxin B1
    - Fungi found on peanuts, corn and cottonseed
    - Potent carcinogen
    - High incidence of liver cancer in Africa and Far East
ENIRONMENTAL PATHOLOGY IV

PHYSICAL INJURIES

Physical injuries
- Mechanical forces
- Thermal injuries
- Electrical injuries
- Atmospheric pressure change injuries
- Radiation

Mechanical injuries
Result of Mechanical Forces
- Abrasions
  - Superficial epidermis is torn
- Laceration
  - Tearing of skin
- Contusion
  - Small blood vessel damage by blunt force, usually without disrupting the underlying tissues
- Gunshot wound

Thermal injuries
- Thermal burns – factors to consider
  - Depth of burn
  - % of body surface involved
  - Internal injuries from inhalation of hot and toxic fumes
  - Fluid & electrolyte management
  - Prevention or control of infection

Thermal Burns Morphology
- 1st degree
  - Mostly pink and painful
- 2nd degree
  - Blistering & pain is characteristic
- 3rd and 4th degree
  - White or charred, dry and anesthetic
Thermal Burns

% Body Surface

- > 20%
  - Rapid shift of body fluids from vascular to interstitial compartments
  - Hypovolemic shock
  - Protein from blood is lost into interstitial tissue
    - Generalized edema
    - Pulmonary edema
- >50% usually fatal

Thermal Burn Injury to Airways and Lungs

- Direct heat effect to mouth, nose and upper airways
- Inhalation effect due to water-soluble gases
  - Chlorine, sulfur oxide, ammonia
    - React with water to form acids or alkalize upper airway
- Inhalation effect due to lipid-soluble gases
  - Nitrous O₂, products of plastics
    - Reach deeper airways and produce pneumonitis

Thermal Burns

- Infections:
  - ? Leading cause of death in burned patients
  - Pseudomonas
    - Very common infection
  - Antibiotic
    - Resistant strains of hospital-acquired bacteria are becoming more of a problem
      - S. aureus (MRSA)
      - Fungi (candida)

Thermal Exposure

- Hyperthermia
  - Prolonged exposure to elevated ambient temperatures
    - Heat cramps
    - Heat exhaustion
    - Heat stroke

Thermal Exposure

- Heat cramps:
  - Loss of electrolytes via sweat
  - Voluntary muscle cramping
  - Normal core body temperature

Thermal Exposure

- Heat exhaustion:
  - Sudden onset
  - Prostration
    - Sweating
  - Collapse
    - But easily reversible
  - Failure of the cardiac output to keep up due to hypovolemia
    - 2° water depletion
    - Core body temp mildly elevated
Thermal Exposure
- Heat stroke:
  - Sweating ceases but red hot
  - Core body temp. rise (1010 or >)
  - Thermoregulatory mechanisms fail
  - Medical emergency
  - Hypovolemic shock
    - Due to vol. depletion with peripheral vasodilatation
  - Death is common
    - Due to arrhythmias and necrosis of muscle tissue

Electrical Injuries
- May produce multiple effects to no effect
- Many variables are involved
  - Tissue resistance to current
  - Intensity of the current
  - The more resistance, the greater the heat generated
  - Death due to thermal injury, electrical disruption of heart or brain, exploding solid organs

Atmospheric Pressure Changes
- Direction of change, rate of change, magnitude of change
- High-altitude illness
- Blast injury
- Air of gas embolism
- Barotrauma
  - Decompression disease
  - Caisson disease

High-Altitude Illness
- Seen in mountain climbers
  - ≥ 4,000 meters
- Lower oxygen tension increases capillary permeability with pulmonary edema and systemic edema
- Progressive mental deterioration

Blast Injury
- Violent increase in pressure
- Pressure disrupts tissue

Air or Gas Embolism
- Abnormal increase in intra-alveolar air or gas pressure leading to tearing of tissue with air into the interstitium and small blood vessels
- Complication of scuba diving, mechanical positive-pressure ventilation
  - hyperbaric O₂ therapy
Air or Gas Embolism

- Pulmonary, mediastinal, and subcutaneous emphysema may result
- Coalescence of small air or gas emboli that access arterial circulation
- May lead to acute stroke or myocardial ischemia episode

Decompression (Caisson) Disease

- Disorder occurs when a person spends long periods under increased atmospheric pressure conditions
- Seen in deep-sea divers, tunnel or caisson workers
- Under rapidly decreasing pressure environments, air and its accompanying gases dissolve out of the blood
- The formation of minute bubbles of nitrogen and oxygen occur in bloodstream and tissues
- Coalescence of the bubbles for emboli development then travel to organs and disrupt vascular supply

Radiation Injuries

- Radiation is energy distributed across the electromagnetic spectrum as waves of particles
- We know much more about high dose effects of radiation than low dose exposures
- There are 2 types of radiation exposure
  - Non-ionizing
  - Ionizing

Non-ionizing Radiation

- Characterized by long wavelength and low frequency wave

<table>
<thead>
<tr>
<th>Type Radiation</th>
<th>Frequency (Hz)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical power</td>
<td>1-50</td>
<td>?</td>
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<tr>
<td>Radio waves</td>
<td>$10^6-10^{11}$</td>
<td>Thermal effect, cataracts</td>
</tr>
<tr>
<td>Microwaves</td>
<td>$10^9-10^{10}$</td>
<td>Thermal effect, cataracts</td>
</tr>
<tr>
<td>Infrared</td>
<td>$10^{11}-10^{14}$</td>
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<tr>
<td>Visible light</td>
<td>$10^{15}$</td>
<td>Retinal burns</td>
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<tr>
<td>Ultraviolet</td>
<td>$10^{15}-10^{18}$</td>
<td>Skin burns, cancer</td>
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Non-ionizing Radiation

- Exerts its biological effect by vibration and rotation of atoms in biological molecules

Ionizing Radiation

- Characterized by short wavelengths and high frequency particles

- Can ionize biological molecules by ejecting their electrons from atoms
Particulate Radiation (Ionizing)

- Is classified by the type of particles emitted:
  - Alpha
  - 2 neutrons and 2 protons
  - Beta
  - Electrons emitted from the nucleus of atoms
  - Electrons
  - Protons
  - Mesons
  - neutrons

Radioisotopes

- Decay by emission of particles
  - Radon gas - releases alpha particles
  - Alpha particles are very large because they have 2 neutrons and 2 protons
  - Thus Alpha particles have strong ionizing power but low penetration because of their large size

Beta Particles

- Are electron emitters from nucleus of atoms

- Thus have weaker ionizing power but higher penetration

Gamma Rays and X-Rays

- Are strong electromagnetic producing forms of radiation

- They penetrate deeply but interact with relative few molecules per unit distance

The primary target for biological effect of ionizing radiation is the DNA

- Rapidly dividing cells are more radio-sensitive than quiescent cells

Biological effects of ionizing radiation depend on

- Radioactive material
- Dose
- Dose rate
  - total amount at one time
- Types of tissues involved
  - Hematopoetic vs. bone
- Regional dose vs. whole body exposure
- Age of the person
Radiation Syndrome/Sickness

- LD₅₀ for for humans to a single exposure
  - 250 - 400 rads
- 4 clinical syndromes are produced depending on the dose.
  - Prodromal (subclinical) Syndrome
  - Hematopoietic Syndrome
  - Gastrointestinal Syndrome
  - Central Nervous System

Acute Prodromal Syndrome

- Anorexia
- Nausea
- Vomiting
- Begin within a few hours of intense exposure then subside.

Acute Hematopoietic Syndrome

- Main phase of the illness is related to leukopenia and thrombocytopenia which do not give rise to symptoms until the 2nd to 3rd week after irradiation
- Death from infection or hemorrhage may result after the 4th to 6th week if dose is high enough.

Acute Gastrointestinal Syndrome

- Usually after 2 to 3 days after irradiation.
- Abdominal pain, fever, increasing diarrhea, dehydration and toxemia.
- Reaction progresses rapidly, culminating within several day in a fatal, shocklike state.

Acute CNS Syndrome

- Anorexia, nausea, and vomiting begin almost immediately after irradiation.
- Minutes or hours later increasing drowsiness, confusion, ataxia, convulsions, loss of consciousness, and death.

The annual maximum permissible exposure in workers is 1 rem per year for a total of 5 rems in a life time.
THE END

All test materials will be from Robins 8th edition

Good Luck