Biomedical Sciences Department

BMS 6601: General Pathology & Immunology

Syllabus: Fall 2006

Rudolf Virchow (1821 - 1902)

"Epidemics resemble great warning signs on which the true statesman is able to read that the evolution of his nation has been disturbed to a point which even a careless policy is no longer allowed to overlook."

Florida State University
College of Medicine

2006-2007

Rudolf Ludwig Karl Virchow (1821-1902) was born in the small Pomeranian city of Schivelbein, Germany. His early life was in a modest, rural background which he never completely forgot. As a young man he set a gigantic goal for himself: "An all-around knowledge of nature, from the deity down to the stone."

He was educated at the Friedrich-Wilhelms Institut in Berlin which provided medical education for gifted boys in return for service in the Army.

Virchow's early interest and direction was in epidemiology and the history of disease. As a young man, he was an experimentalist (embolism) and biochemist (amyloid, haematoidin, myelin), but his interest turned and developed in microscopic pathology. He became a great oncologist, and his pathological studies made him an important biologist.

Virchow laid the foundation for modern pathology. In 1858 at the age of twenty-six he published "Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre." The results of his investigations on thrombosis and embolism and the essence of Virchow's doctrine: "with his immortal aphorism 'omnis cellula e cellula' " were published in two articles that revolutionized thinking in the medical field. Medicine in Germany turned from "romantic" to modern as observation of clinical findings became the standard. His important discoveries in parasitology and his social approach in medicine and epidemiology set a new standard as a pioneer in modern public health.

Virchow's notable reputation developed from his "civic courage." He fought against militarism, Anti-Socialist Laws, and Anti-Semitism. At his death Germany complained that she lost four great men in one: her leading pathologist, her leading anthropologist, her leading sanitarian, and her leading liberal.[1]

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[1]Sources: 1) Rudolf Virchow Doctor Statesman Anthropologist by Erwin H. Ackerknecht, The University of Wisconsin Press, Madison, 1953; 2) Selected Readings in Pathology From Hippocrates to Virchow, edited by Esmond R. Long, Charles C. Thomas, Springfield, Illinois/Baltimore, Maryland, 1929.

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Fall Term 2006
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BMS 6601 - GENERAL PATHOLOGY & IMMUNOLOGY – Fall 2006Syllabus

Syllabus - Electronic

The "Course Documents" section in Blackboard includes an electronic version of the study notes (included in this Syllabus) for each lecture. The "Powerpoint Lectures" section has an electronic version of the PowerPoint lectures for the course. These are designed to supplement and organize the material in the textbook and the study notes, but not be a complete substitute for it.

Course Objectives

The general pathology course in the Fall semester at FSUCOM covers the basic pathophysiology of mechanisms of disease in medicine. The knowledge gained from study of these basic mechanisms will be applied to systemic pathology in the Spring semester and to clerkships in the 3rd and 4th years. This pathology course will incorporate gross pathologic, microscopic, and radiologic material to assist you in understanding the disease processes and prepare you for licensing examinations. The knowledge gained from a study of pathology will integrate with other courses to provide you with the means for assessment and diagnosis of patients under your care.

Lectures / Discussions / Tutorials

Check locations for lectures in your FSUCOM master schedule, which is posted on the Blackboard site. See the course schedule for dates and times. Note that due to room scheduling conflicts and other exingencies, the schedule is subject to change and the student is advised to check the electronic version of the schedule frequently. Changes in the schedule will also be e-mailed to the class. The lectures are designed to cover the course content in an organized fashion, illustrating the concepts and allowing time for you to ask questions. There are 41 lecture hours and 30 small group, PBL and laboratory hours.

Laboratories / Small Groups/Problem-Based Learning (PBL) Exercises

Check the schedule for times and locations. You will be assigned to one of the learning community rooms. Assignments for small group sessions will be made on the basis of the number of groups and room availability. There are 10 laboratory, 12 PBL, and 8 small group hours.

Required Textbooks

PATHOLOGIC BASIS OF DISEASE, 7th edition, by Robbins.
BASIC IMMUNOLOGY by Abbas and Lichtman.

Computer Resources

Multimedia exercises covering the small groups/laboratories/PBLs, as well as images supporting the lecture and syllabus materials, and the examination question banks, are available via the World Wide Web at:

http://www.med.fsu.edu/webpath/webpath.htm

Contact Person

The course director is Dr. Morton H. Levitt, who can be contacted at 644-0498. Please feel free to stop by the office [Room 2300-G] at any time. Dr. Levitt's e-mail address is:

Morton.Levitt@med.fsu.edu

Faculty

In addition to Dr. Levitt, Dr. Edward C. Klatt serves as faculty for the Course. Dr. Klatt can be reached at 644-9397; his e-mail address is:

Edward.Klatt@med.fsu.edu

From time to time, guest lecturers and facilitators are invited to participate in the course. Small group, laboratory and PBL facilitators are drawn from the FSUCOM faculty.

Examinations/Grading

The material for examinations and quizzes will come from lectures, laboratory, PBL and small group sessions, and the textbook.

The format for examinations will be as follows:

- Written examination items: multiple choice questions (single best answer and extended matching).

- Practical examination items: multiple choice (single best answer) questions based upon illustrations of gross and microscopic lesions or charts and graphs, from material covered in laboratories, small groups, PBLs, and lectures.

- Essay items: a written response (250 words or less, including articles a, an, the) to a question about a particular subject covered in the course. The essay requires that you organize your thoughts and gives you an opportunity to express what you know.

There will be three integrated 4-hour block examinations in the Fall semester. These examinations will cover material in all the courses for the four weeks prior to each examination. The pathology component of each examination may include components follows:

multiple choice written questions
questions with illustrations (multiple choice)
essay question (one page)

There will be 12 small group/laboratory/PBL sessions for Pathology 6601 in the Fall semester. There will be a 5 point quiz given at the beginning of each of these sessions.

Thus, the final grade in Pathology 6601 will be determined as follows:

75% Exams (3 block exams)
25% Small group/laboratory/PBL quizzes (12 quizzes)

100%

Grading for the course is based upon a numeric score calculated as a percentage achieved from all possible points, as follows:

A = > 90 % correct
B+ = 87 – 89.9% correct
B = 80 – 86.9 % correct
C+ = 77 – 79.9% correct
C = 70 – 76.9 % correct
D = 65 – 69.9 % correct
F = < 64.9 % correct

According to our established policy, please note that fractional grades will **not** be "rounded up."

The following Attendance, Remediation, Honor Code, and ADA policies have been adopted by the Florida State University College of Medicine for all courses:

Attendance Policy

FSU COM ATTENDANCE POLICY

COM Philosophy

We believe that:

Professionalism is a major component of our medical curriculum. We believe students should conduct themselves appropriately in the various educational activities of the curriculum. This conduct includes coming to educational activities on-time, using the laptop computers only for course work during the educational activity, and not disrupting the class if late. The faculty should also demonstrate professionalism, by starting and ending all scheduled educational activities on time and providing a course schedule with clearly explained course policies in the course syllabus. Any changes in the schedule should be given to the students in a timely manner.

Students will be accountable and personally responsible for attending all educational activities (small groups, labs, clinical experiences, examinations, lectures, computer sessions, etc.).

Unexcused absences reflect negatively on the goals and objectives of the medical curriculum and demonstrate unprofessional behavior by the respective student.

We owe it to our state legislature and the citizens of the State of Florida to provide a quality educational program that meets the needs of our students in preparing them for the M.D. degree.

Attendance Policy

Students are expected to attend all scheduled activities. Students are expected to be on time. Being on time is defined as being ready to start at the assigned time. If a student has an emergency that prevents her/him from attending a scheduled activity, s/he is to call and notify the Office of Student Affairs (Year 1/2) or the Regional Campus Dean (Year 3/4) and request that they inform the supervisors/professors/clerkship faculty/education director for that activity. If at all possible, the student should also call and at a minimum, leave a message with one of the course/clerkship directors. It is important that students realize that their absence or tardiness negatively impacts a number of other people. Attendance, including tardiness, is part of the student's evaluation for professionalism. Negative evaluations may result in decreased grades and in severe cases, referral to the Student Evaluation and Promotion Committee.

Procedure for Notification of Absence

Year 1/2

If the student knows in advance of an upcoming legitimate absence, the "Advance Request for Absence from Educational Activity(ies)" form should be completed with signatures from the student, the Associate Dean for Student Affairs, the course faculty member and the Course Director. The form will be filed in the Office of Student Affairs. The implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.) will be given to the student by the course director and final decisions regarding these actions shall rest with the course director.

If the absence occurs due to an unforeseen emergency, the student should contact the course director and the Associate Dean for Student Affairs immediately to report the absence including the reason for the absence. The implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.) will be given to the student by the course director and final decisions regarding these actions shall rest with the course director.

Year 3/4 Required Clerkships

If the student requests an absence in advance, the "Advance Request for Absence from Educational Activity(ies)" form should be completed, signed by the student and given to the Regional Campus Dean. Requests for excused absences from a required clerkship should be rare and made only in situations that cannot be rescheduled to occur during a scheduled time off or during an elective. An excused absence from a required clerkship may be allowed when it is determined by the Regional Campus Dean that the student has no alternative (see Fourth Year Scheduling Policies).

The Regional Campus Dean, after consultation with the Education Director and the Clerkship Director, will make the final decision regarding the student's request and give the student the implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.). Final decisions regarding implications for the student's grade shall rest with the Education Director. The Clerkship Director will notify the clerkship faculty member of the decision. The form will be filed in the Office of Student Affairs at the regional campus.

If the absence occurs due to an unforeseen emergency, the student should contact the Clerkship Director and the Regional Campus Dean immediately to report the absence including the reason for the absence. The Regional Campus Dean, after consultation with the Education Director and the Clerkship Director will make the final decision regarding implications of the student's absence. The implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.) will be given to the student by the Regional Campus Dean. Final decisions regarding implications for the student's grade shall rest with the Education Director. The Clerkship Director will notify the clerkship faculty member of the decision. The form will be filed in the Office of Student Affairs.

Year 4 Electives

If the student requests an absence in advance, the "Advance Request for Absence from Educational Activity(ies)" form should be completed, signed by the student and given to the Regional Campus Dean. The Regional Campus Dean, after consultation with the Elective Director, will make the final decision regarding the student's request and give the student the implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.). Final decisions regarding implications for the student's grade shall rest with the Regional Campus Dean, who will notify the Elective Director of the decision. The form will be filed in the Office of Student Affairs.

If the absence occurs due to an unforeseen emergency, the student should contact the Regional Campus Dean immediately to report the absence including the reason for the absence. The Regional Campus Dean, after consultation with the Elective Director, will make the final decision regarding implications of the student's absence. The implications for the absence (e.g., remediation, course grade adjustment, make-up exam, etc.) will be given to the student by the Regional Campus Dean. Final decisions regarding implications for the student's grade shall rest with the Regional Campus dean, who will notify the Elective Director of the decision. The form will be filed in the Office of Student Affairs.

Remediation Policy for Absences from Examinations, Quizzes, Small Group Sessions,

Preceptor visits, and Clerkship Call

The remediation policies for absences from examinations, quizzes, small group sessions, and clerkship call are:

1. POLICY ON MISSED EXAMINATIONS: Students are required to take major in-term and final examinations. Based on Curriculum Committee policy, a student can only be excused from an examination by a course/education director decision based on the personal situation of the student. **All examinations must be made up within 1 week of returning to class.** The Course/Education Director will determine the time of the exam make-up session. Also, according to the Curriculum Committee decision and the existence of the FSU COM honor code, the student will be given the same examination given to the other students.
2. POLICY ON MISSED QUIZZES: Students are required to take scheduled and unscheduled quizzes in the courses/clerkships. A student can only be excused from a quiz by a Course/Education Director decision based on the personal situation of the student. The student must make arrangements with the Course/Education Director to make up a missed quiz. **All quizzes must be made up within 1 week of returning to class** Also, according to the curriculum committee decision and the existence of the FSU COM honor code, the student will be given the same quiz given to the other students.

3. POLICY ON MISSED SMALL GROUP SESSIONS, PRECEPTOR VISITS, AND CLERKSHIP CALL: The student should contact the Course Director, small group leader, Clerkship Director or Education director for instructions on remediation of the missed session and material covered.

Academic Honor Code:

The Florida State University Academic Honor Policy outlines the University's expectations for the integrity of students' academic work, the procedures for resolving alleged violations of those expectations, and the rights and responsibilities of students and faculty members throughout the process. Students are responsible for reading the Academic Honor Policy and for living up to their pledge to ". . . be honest and truthful and . . . [to] strive for personal and institutional integrity at Florida State University." (Florida State University Academic Honor Policy, found at http://www.fsu.edu/~dof/honorpolicy.htm.

Students With Disabilities

Students with disabilities needing academic accommodations should:

(1) Register with the Student Disability Resource Center [SDRC], and provide documentation of their disability.
(2) Bring a letter to the Clerkship Director from the SDRC indicating the need for academic accommodations. This should be accomplished within the first week of the rotation. Specific arrangements should be made with the Clerkship Director five working days prior to any examination for which accommodations are being requested.

Unexcused Absences

"It will be the responsibility of the course/education directors to clearly state in their respective course/clerkship syllabi the implications for having an un-excused absence from a scheduled educational or examination activity in a course or clerkship." **For BMS 6601, students with more than 2 such absences in the Fall Term will not receive academic credit for the course and a grade of "F" will be submitted to the Registrar. Students who have an unexcused absence from an examination or a quiz will lose the entire score (points) awarded for that examination or quiz, and the final grade for the course will reflect this loss.**

Evaulations

Student evaluations throughout the course are an important way of improving medical education, particularly during the founding years of the College of Medicine. Not only are your comments and suggestions valued, but the evaluation process represents one way for you to become familiar with the peer review process. Peer review is an important quality management function in all branches of medicine. In order for peer review to work properly, it must be taken seriously both by the evaluators as well as those being evaluated. Therefore, we ask that you give careful consideration to evaluations. When making comments, consider what you would say if you were face to face with the person to whom the comments are directed. How would you react if the comments were directed at you? Give thought to how learning resources were used in regard to the way you learn best. What worked for you and what did not? How is your time used optimally? Are you making adequate progress? Are you being challenged to improve? Be specific. Ultimately, your use of the evaluation process can help you learn how to improve your own medical practice.

Course Objectives

1. Demonstrate knowledge of general categories of disease conditions.
2. Develop a vocabulary to describe the immune system and its components.
3. Demonstrate knowledge of immune cell structure and function.
4. Demonstrate knowledge of immune cellular interactions.
5. Demonstrate knowledge of the tissues that are part of the immune system.
6. Demonstrate knowledge of the body's immune reactions to infections.
7. Demonstrate problem solving ability and diagnostic reasoning to diagnose immunologic diseases.
8. Demonstrate the ability to correlate microbial infection with immunologic findings.
9. Demonstrate the ability to correlate immunologic conditions with pathologic findings.
10. Develop a vocabulary that allows for description of disease processes and communicating findings to other health care workers and to patients.
11. Demonstrate knowledge of the molecular and cellular basis for inflammatory disease states.
12. Demonstrate knowledge of the molecular basis for neoplastic diseases.
13. Demonstrate knowledge of the pathophysiology of pathologic conditions encountered in clinical practice.

14. Demonstrate the ability to recognize abnormal gross and microscopic findings in the context of the clinical problem.
15. Demonstrate knowledge and interpretation of laboratory findings associated with disease conditions and be able to use the laboratory for diagnostic purposes, including indications for ordering, proper specimen collection, and sending and receiving.
16. Demonstrate appropriate application of autopsy findings to quality assurance for improvement of clinical practice.
17. Demonstrate the ability to form differential diagnoses based upon pathologic findings.
18. Demonstrate the use of clinical-pathologic correlation to understand disease conditions.
19. Demonstrate knowledge of the radiologic findings that accompany pathologic lesions.
20. Demonstrate problem solving ability when presented with patient scenarios including pathologic findings.
21. Demonstrate skills in evidence-based medicine to obtain information involved in solving case-based problems
22. Develop the ability to meet compliance standards when ordering laboratory tests.
23. Demonstrate professionalism in working with colleagues and faculty.
24. Demonstrate an attitude of care and concern for patients and their families affected by pathologic disease states.
25. Treat patients, as represented by laboratory, pathology, and radiologic specimens and records, with respect, dignity, and confidentiality.
26. Demonstrate knowledge of fundamental mechanisms of cell injury, repair and adaptation.
27. Demonstrate knowledge of common neonatal, pediatric and congenital diseases and their diagnosis.
28. Demonstrate knowledge of the pathogenesis and immunologic aspects of aging and principles of aging at the clinical, cellular and sub-cellular levels.

Integration with COM Goals and Objectives:

Knowledge

* Demonstrate the application of the scientific bases of health, disease, and medicine to common and high impact medical conditions in contemporary society.

* Describe the development, structure and function of the healthy human body and each of its major organ systems at the macroscopic, microscopic, and molecular levels.

* Recognize and discuss the implications of altered structure and function (pathology and pathophysiology) of the body and its major organ systems that are seen in various diseases and conditions.

* Identify changes in the structure and function of the human body associated with the aging process and be able to distinguish normal changes associated with aging from those that denote disease.

* Describe the molecular basis of diseases and maladies and the way in which they affect the body (pathogenesis).

* Demonstrate the ability to use basic biobehavioral and clinical science principles to analyze and

solve problems related to the diagnosis, treatment, and prevention of disease.

* Recognize the implications of cultural, social, economic, legal, and historical contexts for patient care.

* Describe strategies to support life long learning via both print and electronic sources to assist in making diagnostic and treatment decisions (e.g., practice guidelines) and to remain current with advances in medical knowledge and practice (e.g., medical information data bases).

Skills

* Demonstrate the appropriate use of laboratory tests and radiographic studies in making diagnostic and treatment decisions.

* Demonstrate the ability to evaluate the patient's medical problems and to formulate accurate hypotheses to serve as the basis for making diagnostic and treatment decisions.

* Demonstrate the ability to acquire new information and data and to critically appraise its validity and applicability to one's professional decisions, including the application of information systems technologies for support of clinical decision-making.

Attitudes/Behaviors

- Demonstrate professionalism and high ethical standards in all aspects of medical practice, specifically competence, honesty, integrity, compassion, respect for others, professional responsibility and social responsibility.

PATHOLOGY 6601, FALL 2006

INTRODUCTION
Dr. Morton H. Levitt
& Dr. Edward C. Klatt

Introduction to BMS 6601 – General Pathology & Immunology

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: Page 1-4)

LEARNING OBJECTIVES: Following study of this handout, the student will be able to:

1. Define what the study of pathology is and what pathologists do.

2. Recognize the relationships between pathology and: (1) basic sciences
   (2) clinical medicine

3. Outline a classification of causes of disease.

4. Outline the major causes of death in the United States.

5. Outline the basic etiologies for disease.

6. Define what is meant by pathogenesis.

PATHOLOGY

A. The study of disease in tissues of the body

1. Gross Pathology: the study of the visual appearances (morphology) of tissues and organs, as biopsies, resected organs from surgery, or at autopsy

2. Microscopic Pathology: the study of cells and tissues by light microscopy

a. Hematoxylin & Eosin (H&E) - the usual way tissues are stained, most of the microscopic slides you will see are stained with H&E; nuclei are blue and cytoplasm is pale pink

b. Special histochemical stains are used to identify cell and tissue components

PAS: stains glycogen, basement membranes, mucin, and fungi

Acid fast: stains mycobacteria

Prussian blue: stains iron

Gomori methenamine silver (GMS): stains fungi and pneumocystis

Trichrome: stains collagen

Congo red: stains amyloid

Oil Red O: stains lipid

c. Papanicolau (Pap) stain - used in cytologic cell screening

d. Immunohistochemistry: - use of specific antibodies tagged with a brown dye to identify antigenic components of cells. The components identified can determine the cell type and function

e. Electron microscopy - used to identify cellular ultrastructure; the

structures identified provide clues to the types of cells and their function

3. Molecular biology: the study of cells by analyzing genetic material

   a. Flow cytometry - analysis of the amount of cellular DNA

   b. Polymerase chain reaction (PCR) - analysis with DNA probes to identify specific components of cells; PCR is highly sensitive

B. Anatomic pathology

1. Surgical pathology: the study of tissue specimens removed from patients, either as a biopsy for diagnostic purposes or as surgical resection of tissues for therapeutic purposes. The findings are used as the:

   a. Establishment of the diagnosis
   b. Basis for further surgery
   c. Basis for further treatment
   d. Analysis of adequacy of treatment

2. Cytopathology: the study of cells removed from patients for diagnosis

   a. Direct scrapings, washings, or smears from organs (e.g., Pap smear of the uterine cervix, bronchoalveolar lavage from lung)
   b. Fine needle aspiration of internal organs of the chest and abdomen
   c. Analysis of body fluids (e.g., thoracentesis, paracentesis, lumbar puncture

3. Autopsy pathology: determine cause of death and make clinical-pathologic correlations that aid in analyzing the effectiveness of diagnostic techniques and of therapy

C. Clinical Pathology

1. Chemical pathology: analysis of blood or body fluids for specific parameters such as sodium, potassium, lactate dehydrogenase, etc. (includes most laboratory tests you will order on your patients)

2. Toxicology: a subset of chemical pathology dealing with detection and measurement of drugs and toxins (e.g., therapeutic drug monitoring, drugs of abuse testing).

3. Hematology: analysis of cellular elements of the blood; known as a "complete blood count" or CBC

4. Coagulation: determine the adequacy of the coagulation system, or determine the cause for abnormal bleeding or clotting.

5. Immunology: analysis of acquired and congenital abnormalities of the immune system. Includes serologic assays for autoimmune diseases, measurement of immunoglobulins and immune cell types.

6. Microbiology: cultures, gram stains, PCR probes, and other techniques for the detection of microorganisms in body fluids and tissues.

7. Immunohematology (blood banking): obtain, prepare, and test blood and its components for transfusion therapy.

D. Forensic Pathology

1. Use of anatomic and clinical pathologic techniques, along with scene investigation, to determine the manner and cause of death.

2. Assist medicolegal functions (criminal, civil litigation)

E. Experimental Pathology: investigation and research of causative agents and mechanisms of disease; pathology represents a bridge between the basic sciences and clinical medicine

MAJOR CAUSES OF DEATH IN THE UNITED STATES

Rank	Cause of Death	Number of Deaths	Death Rate per 100,000
1	Heart Diseases	724,000	268
2	Cancer	542,000	200
3	Cerebrovascular disease (stroke)	158,000	59
4	Emphysema	113,000	42
5	Accidents	94,000	36

6	Pneumonia and influenza	92,000	34
7	Diabetes mellitus	65,000	24
8	Suicide	31,000	11
9	Chronic renal diseases	24,000	10
10	Septicemia	24,000	9
11	Chronic liver disease and cirrhosis	23,000	9
12	Alzheimer's disease	23,000	8
13	Homicide	18,000	7
14	AIDS	14,000	5

There are about 2,300,000 total deaths per year in the U.S.

ACTUAL CAUSES OF DEATH IN THE UNITED STATES
(by behaviors that are modifiable)

Rank	Cause of Death	Number of Deaths	% of Total Deaths
1	Tobacco	450,000	20
2	Diet/Activity patterns	300,000	14
3	Alcohol	100,000	5
4	Microbial agents	90,000	4
5	Toxic agents	60,000	3
6	Motor vehicles	42,000	2
7	Firearms	31,000	2
8	Sexual behavior	20,000	1
9	Illicit use of drugs	15,000	<1

The four modifications of patient behavior that could be reinforced by physicians that would have the greatest impact upon mortality reduction in the U.S. are:

1 Smoking cessation
2 Increased physical activity
3 Diet modification with lipid lowering (decrease cholesterol)
4 Detection and treatment of hypertension

CLASSIFICATION OF CAUSES OF DISEASE

A. Cardiovascular (hypoxia)
B. Traumatic
C. Toxic (drugs, chemicals)
D. Infectious (microbiologic)
E. Immunologic

F. Congenital (inherited)
G. Nutritional
H. Neoplastic

GENERAL APPROACH TO CLASSIFICATION – "The VITAMIN-D" MNEMONIC

Vascular
Infectious
Toxic/Metabolic
Autoimmune/Immune
Mechanical/Environmental/Trauma
Iatrogenic/Idiopathic
Neoplastic
Developmental/Genetic

TERMINOLOGY

Etiology:	Cause of disease. Can be known or unknown (idiopathic).
Pathogenesis:	The sequence of events and mechanisms leading to a disease state.
Clinical Findings:	Includes history taking, performance of physical examination, and performance of tests and procedures (laboratory, radiographic) which document or measure abnormalities or loss of function.
Morphologic Findings:	Gross appearance of organs and tissues, microscopic appearance of tissues and cells.
Morbidity:	The presence of disease in a patient or a population.
Mortality:	Death of the patient, or rate of death in a population.
Iatrogenic:	Caused by health care workers during intervention in the course of diagnosis and therapy.
Sign:	An objective piece of evidence that you perceive from your examination.
Symptom:	Subjective evidence, something the patient tells you is present.
Syndrome:	A set of symptoms, signs, or morphologic appearances that occur together and are related.
Pathognomonic:	Distinctively characteristic of a disease process.

WHY YOU NEED TO KNOW PATHOLOGY

Pathology helps you apply your knowledge of the basic sciences to human diseases. It is the basis for understanding pathogenesis and pathophysiology of disease and the basis for recognizing morphologic appearances and correlating with physical examination and radiologic findings.

You must understand and apply clinical laboratory testing for diagnosis. You must be able to evaluate what you are doing to your patients.

Your understanding of the vocabulary and the meaning of the terms forms the basis for your ability to communicate with other medical personnel and with patients who are becoming increasingly sophisticated with access to a variety of information resources.

ORGANIZATION OF THE COURSES IN PATHOLOGY

A. Pathology 6601 - Mechanisms of Disease

1. With a background training in the basic sciences (anatomy, embryology, histology, biochemistry, genetics) you will learn about the etiologies for and pathogenesis of basic disease processes.

2. Learn the terminology for the disease processes that will be applied throughout your career.

3. Learn basic gross and microscopic morphologic appearances to aid in recognition and understanding of disease processes.

4. Learn to formulate differential diagnoses based upon your recognition of pathologic processes and correlation with clinical findings (history, physical diagnosis, laboratory, radiology).

B. Pathology 6602 - Organ System Pathology

1. Apply the principles learned in Pathology 6601 to specific organs.

2. Correlate the pathologic processes with clinical findings and laboratory testing studied at the same time.

3. Learn the disease processes in more detail and increase your ability in differential diagnosis.

PATHOLOGY 6601, FALL 2006
CELL INJURY 1,2 & 3
Morton H. Levitt, MD

Cell Injury, Cell Death, Adaptations, Intracellular Accumulations, and Cell Aging

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: Page 4-46)

LEARNING OBJECTIVES: At the end of these lectures and upon completion of the reading assignment, the student will be able to:

1. What mechanisms can produce cellular injury? Can any be avoided?

2. Describe reversible and irreversible features of cell injury.

3. Describe patterns of cell death and necrosis and give examples of each.

4. Outline the control mechanisms and the outcomes for apoptosis.

5. Describe and outline etiologies for the following: intracellular accumulations of lipid, protein, glycogen, lipochrome, iron, bilirubin, and calcium. Relate these accumulations to disease processes.

MECHANISMS OF CELLULAR INJURY AND ADAPTATION

How can cells and tissues be injured?

1. Trauma - physical forces or environmental changes (e.g., heat, cold) that damage organs and tissues

2. Ischemia - reduction or lack of blood flow from poor circulation (very common because of atherosclerosis)

3. Toxins (poisons) ingested, inhaled, or contacted

4. Infections by microbiologic organisms

5. Immunologic derangements - autoimmune diseases or failures of the immune system to work properly

6. Genetic diseases, including failure of proper development or the inheritance of an abnormal gene

7. Nutrional problems from either too much food intake (obesity) or the lack of nutrients - starvation, poor diet

8. Neoplasms that replace or impinge upon normal tissues

To recover from an injury, a cell must:

1. Maintain its integrity:

   cell and cytoplasmic organelle membranes

   biosynthetic pathways

   nucleus

2. Be subjected to an injurious agent for a limited time

3. Sustain a lesser degree of injury

4. Be in good condition to begin with

Cells and tissues that are more prone to damage include:

More metabolically active cells, such as those in the myocardium

Actively dividing cells, such as germ cells in gonads, epithelia, and hematopoietic cells

Highly specialized cells that cannot be replaced, such as neurons of the CNS

Reversible injury: the following are cellular events from which the cell can recover. Such a cell will be living, but will have lost function (permanently or temporarily) and/or have undergone a morphologic alteration:

1. Hypoxia with loss of ATP (ischemia)

2. Increased anaerobic glycolysis with acidosis (ischemia)

3. Failure of the sodium pump with cell (and organelle) swelling, known as edema

4. Intracellular accumulations of substances from metabolic pathways. This may include cytoplasmic accumulation of lipid, protein, glycogen, iron, etc

5. Intracellular morphologic alterations: ribosomes detach from the endoplasmic reticulum, nuclear chromatin begins to clump

Microscopic cellular morphologic alterations representing adaptation (potentially reversible) to injury include:

1. Atrophy - the cells undergo a decrease in size in order to compensate.

   This may include autophagocytosis with increased lipofuscin (lipochrome) within individual cells as evidence for the loss of cellular components.

   May be a physiologic event: muscle fibers decrease in size with lack of exercise.

2. Hypertrophy - the cells increase in size

   This may occur to compensate for increased work (a nephrectomy leads to enlargement of remaining kidney) or as a result of exersize (or injury), typical of striated muscle and other cells that cannot divide

3. Hyperplasia - the cells increase in number in response to a stimulus, typical of cells that can still divide:

   a. may be physiologic from hormonal stimulus (breast tissue increases in pregnancy for lactation) or as compensation for loss of normal cells (liver cells regenerate in a cirrhotic liver)

   b. may be pathologic from a continued abnormal stimulus (endometrium in response to abnormal estrogen levels; squamous epithelium in response to viral infection) and be a precursor to neoplasia (so-called "atypical" hyperplasia)

Note: atrophy, hypertrophy, and hyperplasia can be normal physiologic processes; however, the processes listed below are distinctly abnormal and can be premalignant:

4. Metaplasia - one cell type is exchanged for another

   This can occur when the metaplastic cell type is more capable of dealing with noxious stimuli, as in respiratory tract epithelium which becomes squamous epithelium in response to the injurious effects of smoking.

5. Dysplasia - the cells display a disorderly growth pattern in an epithelium.

   This can occur in response to prolonged abnormal stimulation or injury (cervical squamous dysplasia in response to human papillomavirus infection)

Irreversible cell injury: the following are events that occur from cellular injury from which the cell cannot recover:

1. Holes form in the cell membrane

2. Calcium influx occurs with poisoning of mitochondria

Note: both of the above are key events in cell death

3. Lysosomes swell and leak enzymes that digest the cell contents

4. Nuclei become pyknotic (small and dark) and non-functional

Free radical formation - a key feature of cellular injury

1. Free radicals are oxidants that form in response to:

   radiant energy

   ischemia

   metabolism of toxins

   inflammatory cell product accumulation

   aging

2. Cells contain antioxidants such as glutathione and enzymic pathways to degrade free radicals to control this process

3. A greater or more prolonged injury may generate more free radicals than the cells can handle

CELLULAR NECROSIS AND DEATH - PATTERNS

Autolysis: a general term describing the dissolution of cell structure, characterized by:

1. Nuclear pyknosis

2. Karyolysis

3. Karyorrhexis

4. Cytoplasmic organelle loss

Apoptosis: individual cell death

1. A more orderly, natural process with very focal cell death and phagocytosis.

   Individual cells, not all or parts of tissues, undergo necrosis.

2. Apoptosis can be "programmed" in:

   a. embryogenesis (disappearance of embryonic structures in normal development)

   b. response to selective viral infection:

      hepatocytes with viral hepatitis

      CD4 lymphocytes with HIV infection

   c. immunologic reactions, as in graft vs host disease

   d. response to hormonal influences (menstruation with endometrial sloughing)

3. Also, apoptosis occurs with the normal ongoing destruction and phagocytosis (recycling) in tissues as part of normal cellular "turnover" process

4. Lack of apoptosis has been recognized in neoplams, as cells accumulate abnormally, as in some chronic leukemias

5. Some forms of cancer chemotherapy work mainly by more selectively inducing apoptosis in tumor cells

6. Control of apoptosis:

   a. signalling by products of Fas (ligand activation in T lymphocytes) and Bcl-2 (inhibition), Bax (promotion), and Apaf-1 (promotion) genes

a. activation of proteases named caspases

b. endonuclease activity to break down nuclear DNA

c. expression of phosphatidylserine on cell membrane to stimulate phagocytosis

Patterns of tissue necrosis:

1. Coagulative necrosis (ischemic necrosis):

   Cellular proteins are denatured but the cellular outlines remain

   Grossly results in a localized area of necrosis known as an **infarct**. Infarcts have a pale tan to white appearance, have a distribution that coincides with the blood supply to an organ, and are typical of most solid organs (kidney, spleen)

2. Liquefactive necrosis:

   Seen with destruction of tissues with lots of lipid (such as brain)

   Seen with tissue destruction by bacteria or inflammatory cells with release of proteolytic enzymes (as in an **abscess**)

   Grossly leads to a soft or liquefied area of necrosis that, upon resolution, leaves a hole or cystic space

3. Fat necrosis:

   Destruction by enzymes digesting fat; grossly, soaps are present.

   Typical of breast and pancreas.

4. Caseous necrosis:

   A combination of coagulative and liquefactive necrosis

   Grossly has a cheese-like appearance.

   Typical of granulomas formed in response to tuberculosis or fungal infection.

5. Gangrenous necrosis: applies to necrosis of a body part

   Dry gangrene - ischemia with coagulative necrosis predominates

   Wet gangrene - liquefaction with infection predominates

CYTOPLASMIC ORGANELLE DERANGEMENTS

Lysosomal functions

1. Heterophagocytosis: macrophages eat up the debris of damaged cells or eat up foreign material (such as bacteria) to form a phagosome that fuses with lysosomes. A typical body response to clearing up a mess from cellular injury.

2. Autophagocytosis: within an individual cell, intracellular debris is sequestered and fused with lysosomes to form autophagolysosomes. "Residual bodies" of material that cannot be completely digested may remain and are known by light microscopy as lipochrome (lipofuscin) pigment. Autophagocytosis is a key part of:

   Cell differentiation

   Cell injury (gradual or long term)

   Cell atrophy

Mitochondria: many alterations in response to cell atrophy and hypertrophy

Cytoskeletal elements

1. A variety of "intermediate filaments" exist which are between the size of thin (actin) and thick (myosin) filaments which play a role in movement of the cell (best example is chemotaxis)

2. Accumulations occur in response to injury

   a. Mallory bodies (alcoholic hyaline) in liver

   b. Neurofibrillary tangles (Alzheimer's disease) in brain

INTRACELLULAR ACCUMULATIONS

Fatty change (also called fatty metamorphosis or fatty degeneration)

1. Must be distinguished from fatty accumulation (fatty infiltration) which is nothing more than increased fat cells in tissues (usually from obesity)

2. Basic problem: lipid accumulates in the cytoplasm, either as small vesicles or large droplets

3. Etiology: impaired intracellular metabolism or lipoprotein transport

   Toxic injury - alcohol

   Genetic - galactosemia from lack of an enzyme for metabolism of galactose

   Nutritional - kwashiorkor from lack of sufficient dietary protein

Protein accumulations

1. From cellular degeneration

   Amyloid - abnormal protein breakdown products accumulate

   Hyaline - "pink-staining stuff" in tissues

2. Excess synthesis or impaired excretion

   Immunoglobulins - Russell bodies in plasma cells

   Alpha-1-antitrypsin - globules accumulate in hepatocytes

Carbohydrate accumulations. May result from:

1. Glycogen storage diseases from inherited enzyme disorders

2. Altered metabolism - glycosylation of tissues with poorly controlled diabetes mellitus

Lipochrome - intracellular accumulation of autophagolysosomes. Etiologies include:

1. Aging

2. Atrophy (brown atrophy of heart)

Iron - hemosiderin

1. Local - tissue hemorrhage with breakdown of RBC's into heme and globin

   The heme is broken down and collects as hemosiderin granules which may eventually be recycled.

2. Systemic: Accumulation of excess hemosiderin in reticuloendothelial tissues (such as bone marrow, liver, spleen) or elsewhere if severe

   The term "hemosiderosis" implies there is only a simple accumulation of iron, while the term "hemochromatosis" is used when the iron accumulation interferes with organ function.

Etiologies include:

Excessive dietary iron intake or deranged iron absorption

Chronic transfusion therapy for anemia

Bilirubin

The accumulation of this bile pigment leads to a condition known as jaundice

The yellowish color it imparts is also described as "icterus"

Jaundice can result from:

Problems with excretion of bile from liver or biliary tract

Liver injury

Excessive recycling of red blood cells from hemolysis

Anthracosis

Accumulation of carbon pigment in the lungs and lymph nodes

From inhaled dust particles in the air.

Calcium

Dystrophic calcification - calcium is deposited in necrotic or damaged tissues irrespective of blood calcium level

Metastatic calcification - calcium may precipitate in normal tissues in response to hypercalcemia

Questions for discussion:

1. Describe changes that may occur at the cellular level when your patient actually follows your advice and eats less and exercises more.
2. Describe changes that can occur when a patient stops smoking.
2. What are some physical examination findings that could accompany various intracelluar accumulations?

CELL INJURY: Match the numbered disease with the lettered mechanism of injury

1. Meningococcal meningitis
2. Laceration of liver in head on collision
3. AIDS
4. Trisomy 21 (Down syndrome)
5. Acetaminophen overdose
6. Incompatible blood transfusion
7. Pituitary adenoma
8. Renal vein thrombosis
9. Housefire
10. Chronic alcoholism
11. Sickle cell anemia
12. Thiamine (B1) deficiency
13. Systemic lupus erythematosus
14. Occlusive coronary atherosclerosis
15. Obesity
16. Squamous cell carcinoma of lung
17. Diabetic foot
18. High cholesterols “run in the family”

A. Cardiovascular (hypoxia): A derangement of circulation with decreased blood flow and decreased oxygenation of cells and tissues with resultant ischemia and/or infarction.

B. Traumatic: Direct cell injury from physical agents such as blunt force, heat, cold, radiation

C. Toxic (drugs, chemicals): Injury from: (a) damage to cell membranes or cellular biochemical processes; (b) formation of toxic metabolites; (c) formation of free radicals

D. Infectious (microbiologic): An organism invades cells and tissues and grows unchecked

E. Immunologic: The body's immune mechanisms do not act properly or act inappropriately

F. Congenital (inherited, genetic): A disorder is programmed (an abnormal gene or karyotype)

G. Nutritional: Failure to provide enough basic nutrients or an imbalance in nutrient supply

H. Neoplastic: Uncontrolled cellular proliferation with loss of normal function and mass (space occupying) effects

Answers:

1D. Meningococci growing on meninges lead to meningitis with increased intracranial pressure, leading to neuronal cell death

2B. Motor vehicle accident with abdominal blunt force trauma leading to laceration of liver with hemorrhage and shock

3D & E. Cytotoxic viruses such as human immunodeficiency virus (HIV) infection gradually destroys helper lymphocytes, leading to opportunistic infections

4F. A chromosomal anomaly (trisomy) leads to multiple malformations of organogenesis

5C. Acetaminophen overdose leads to liver cell necrosis and death

6E. Incompatible blood is transfused, leading to massive hemolysis

7H. Pituitary adenoma compresses optic chiasm, leading to visual field defects

8A. Venous occlusion (rare): An example would be a renal vein thrombus with renal ischemia and acute renal failure.

9B. Housefire with extensive thermal burns leads to epithelial loss and sepsis

10C. Alcohol produces liver cell injury leading to cirrhosis

11F. The genetic code is altered for production of globin chains (in hemoglobin) in sickle cell anemia. Oxygen carrying capacity is reduced.

12G. Thiamine deficiency leads to myocardial fiber weakness and beri beri

13E. Autoantibodies to a wide variety of normal tissue antigens are formed, leading to a multitude of organ dysfunctions, such as glomerular injury

14A. Arterial occlusion (common): An example would be occlusive coronary atherosclerosis with myocardial fiber hypoxia (ischemia) and cell death (infarction).

15G. Excess caloric intake leads to obesity with insulin resistance and diabetes mellitus

16H. Squamous cell carcinoma of lung invades and destroys normal lung tissue

17A & D. Diabetes mellitus leads to accelerated atherosclerosis with tissue ischemia that predisposes to infection

PATHOLOGY 6601, FALL 2006
INFLAMMATION
Morton H. Levitt, MD

READING ASSIGNMENT: Pathologic Basis of Disease, (7th ed: Page 4-116)

LEARNING OBJECTIVES: Upon completion of the lectures, laboratory and reading assignment on inflammation, the student will be able to:

1. Describe the clinical signs of inflammation.
2. Categorize inflammation as acute, chronic or granulomatous.
3. Describe the sequence of events in inflammation.
4. Outline the major chemical mediators involved in inflammation and what they do.
5. Identify and describe the roles for inflammatory cells: PMN's, lymphocytes, monocytes, macrophages, epithelioid cells, giant cells, plasma cells and mast cells.
6. Outline types of agents that produce inflammatory responses.
7. Describe the possible outcomes of the inflammatory process.
8. Describe the components of cellular growth, division, attachment and migration in the ECM.
9. Describe the mechanisms of repair.
10. Describe the mechanisms producing edema.

INFLAMMATION

Definition: Inflammation is a protective response of tissue that eliminates causative agents and debris and is closely tied to repair.

Nomenclature: "-itis" appendicitis, meningitis, cholecystitis, pericarditis, pneumonitis.

Causes: organisms, chemicals, trauma, autoimmune, neoplasia

Constituents: circulating cells, connective tissue cells, extracellular matrix (ECM) and basement membrane (BM).

Categories depend on time but may not always be distinct and may evolve from one to another:

1. **Acute** - minutes to days / neutrophils and fluid protein exudates

2. **Chronic** - days to years / lymphocytes and macrophages / tissue destruction and repair

3. **Granulomatous -** special type of chronic inflammation with granulomata / epithelioid histiocytes, macrophages and giant cells

4. **Repair -** resolution of inflammation to the previous tissue state, or scar formation

5. Inflammation is terminated when the injurious stimulus is removed and all the mediators are dissipated or inhibited.

Signs of Inflammation:

1. **Rubor** - redness due to erythema & increased blood flow

2. **Tumor** - swelling due to increased fluid

3. **Calor** - heat due to increased blood flow and fever

4. **Dolor** - pain due to chemical mediators

5. **Loss of function** - due to tissue damage, loss or scarring

6. **Transudate -** ultra filtrate of plasma, low in protein, seen in increased hydrostatic pressure, fluid appears clear.

7. **Exudate** - high protein fluid - seen when vessels are permeable and may contain cells , fluid appears cloudy. An exudate is called fibrinous when it contains large amounts of fibrinogen which tend to congeal as fibrin.

8. **Pus** - purulent exudate with neutrophils also called suppurative

9. **Effusion** - accumulation of fluid in a body cavity, it is serous if the fluid is a transudate and serosanguinous if it is blood tinged.

Chemical mediators from plasma or cells amplify the inflammatory stimulus and influence the type and length of response. Inflammation ends when stimulus is removed and mediators have been dissipated, catabolized or inhibited.

Laboratory signs of inflammation:

1. Increased white blood cell count (WBC)

   a. In acute processes see increased neutrophils and bands. A higher percentage of immature forms (bands) is called a “left shift”.

   b. In chronic and viral inflammation lymphocytosis can be seen, but not always.

   c. In parasitic infections and allergic responses, eosinophilia may be seen.

2. Increased sedimentation rate "sed rate" is a non-specific indicator of inflammation and is caused by increased fibrinogen and globulins in the serum.

3. "Acute phase reactants" are blood proteins that increase with the onset of inflammation, ie: ceruloplasmin, fibrinogen, C-reactive protein.

4. Laboratory findings with inflammation:

   a. For clinical situations, laboratory testing on the paient’s blood will provide you with clues to damage to cells in the body. Tests on blood are relatively inexpensive and easy to obtain.

   b. Since damaged cells leak their contents, those contents can show up in the circulating blood in increased amounts.

   c. Certain substances, particularly cellular enzymes, are helpful because they may originate from certain cell types that give a clue as to the organ damage.

   d. Useful enzyme measurements include:

Creatine kinase	muscle
Creatine kinase, MB fraction	heart
Aspartate aminotransferase	liver
Alanine aminotransferase	liver

Lipase	pancreas
Amylase	pancreas
Lactate dehydrogenase	heart, liver, RBC's

ACUTE INFLAMMATION

Sequence of events in the Vessel

A. **Vasodilation:** dilation of arterioles resulting in increased flow to capillaries with resultant appearance of redness and warmth**.**

Vasodilation is mediated by release of:

1. Histamine from mast cells at the site of injury

2. Bradykinin

3. Prostaglandin

B. **Increased permeability of microvasculature:** the vessels become leaky resulting in exudation of fluid and resultant tissue edema**.** Mechanisms for this include:

1. Intercellular Gaps in Endothelium:

a. Immediate transient response: Endothelial cells contract, widening the intercellular gaps in small venules. Mediators act rapidly and last 15 - 30 minutes

Histamine
Bradykinin
Leukotrienes
Substance P

b. Delayed sustained response**:** Endothelial cells undergo cytoskeletal changes that disrupt junctions in venules and capillaries, this takes 4-6 hours after the mediator stimulus and lasts for days.

IL-1
TNF
INF-g
Hypoxia
Sublethal injury

2. Direct injury resulting in endothelial cell necrosis:

   a. Immediate leakage that continues until thrombosis/repair. Affects all types of vessels.

   b. Delayed prolonged leakage after 2 to 12 hours, it lasts for days. Seen with sunburn, and affects venules and capillaries.

3. Leukocyte mediated endothelial injury:

   a. inflammation results in PMN adhesion to vessel, degranulation and local injury to vessel wall. Seen in the lungs and kidneys.

C. Vascular stasis: blood cells slow down in the vessels due to vasodilation and exudation of fluid. This allows the chemical mediators to collect and act on the cells in this area.

Sequence of Cellular Events in Inflammation

Neutrophils respond very quickly but non-specifically to injury.

Neutrophils are non-selective because they release their enzymes and produce their effects on all cells in the vicinity. This response is most prominent in the first day of an inflammatory response.

A. Margination, rolling and adhesion: neutrophils approach the vessel wall during vascular stasis and start to stick, which creates a rolling motion, until they finally adhere to the endothelial cells. Mechanisms and mediators of adhesion include:

1. Activation of Endothelial Cells: Tumor necrosis factor (TNF) and interleukin (IL) stimulate production of E selectin, ICAM. Histamine and thrombin upregulate P selectin.

2. Loose adhesion and rolling begins.

3. Firm adhesion: C5a component of complement increases the avidity of integrins on the neutrophils. IL-1 increases the expression of ICAM

4. Transmigration is mediated by ICAM, PECAM; called diapedesis. The neutrophils follow chemoattractants into the tissues.

B. **Migration:** cells move through the interstitium toward a chemotactic stimulus via diapedesis

C. **Chemotaxis**: mediators draw leukocytes into the area of injury over a chemical gradient. Mediators include:

Bacterial products
C5a
Leukotriene B4
Cytokines IL-8

Chemotactic agents bind to cell membrane receptors which results in a cascade of phosphorylations and transduction within the cell resulting in the release of calcium ions in the cytoplasm. This results in 3 important changes in the cell:

1. Movement via actin myosin contraction

2. Activation of the cell causing: arachidonic acid metabolism, degranulation and modulation of adhesion molecules.

3. Phagocytosis

D. **Attachment of neutrophils** to the offending agent**.** This is done via opsonins which coat the agents:

1. Immunoglobulin (IgG-FC) - naturally occuring Ab to particle

2. Complement (C3b & C3bi) - generated by activation of complement by immune or non-immune mechanisms.

3. Collectins - lectins of plasma bind to microbe walls (innate immunity).

E. **Phagocytosis** of the offending agent by engulfment into a phagosome.

F. **Degranulation** of neutrophils and release of proteolytic enzymes from granules into the phagolysosome to degrade the agent.

Killing/degradation is done in three ways:

1. Reactive oxygen species: Myeloperoxidase which reacts with hydrogen peroxide to form a highly reactive oxidant (hypochlorous radical) that kills bacteria.

$$O2 \xrightarrow{(NADP \text{ø} NADPH)} O2^{-}. \xrightarrow{\text{dismutase}} H2O2 \xrightarrow{(\text{myeloperoxidase} + Cl^{\sim})} HOCl. + H2O$$

2. Enzymes: Products of the neutrophilic granules (lysosomes) contain a number of enzymes which punch holes in the bacterial membranes including lysozyme, lactoferrin, bactericidal permeability increasing protein and defensins.

1. Acid hydrolases: Digest the cellular debris in the phagolysosomes

G. Tissue injury in acute inflammation

1. Degranulation into extracellular space of lysosomal enzymes by regurgitation or frustration, oxygen derived active metabolites by exocytosis and products of AA metabolism all amplify the inflammatory effects. Granule enzymes also include: elastase, collagenase, cathepsin and anti-proteases.

2. Disease caused by abnormal amplification:

ARDS
Asthma
Glomerulonephritis
Transplant rejections
Reperfusion injury
Septic shock
Atherosclerosis
COPD
Arthritis

H. Defects in leukocyte function

1. Adhesion - Patients with defective beta 2 integrins get recurrent infections and have impaired wound healing.

2. Phagocytosis - Patients with abnormal membrane associated protein involved in membrane docking and fusion can not secrete lysozymes into the phagosome. This is called Chediak Higashi Syndrome.

3. Microbicidal activity - Defects in NADPH oxidase result in chronic granulomatous disease

III. Chemical mediators of inflammation

The kinin, complement, clotting and fibrinolytic systems are all activated by Hageman factor (FXII) and interact continuously in the course of inflammation to maintain the area of destruction localized.

A. Kinin system

1. Vasoactive peptides are derived from kininogens by action of kallikreins when contacted by surfaces (ie: collagen, BM).

HMWK + XII → XIIa + Prekallikrein → Kallikrein (activates FXII in loop feedback) + HMXK → Bradykinin

2. Bradykinin - Causes arteriolar dilation

   Increases permeability of venules, rapidly inactivated by kinase

   Causes pain and contraction of smooth muscle

3. Kallikrein activates FXII, converts C5 to C5a and is chemotactic.

B. Complement system

may amplify inflammation by activation of C3a & C5a by plasmin and lysosomal proteases.

1. Classic Pathway: Antigen-antibody (Ag-Ab) complexes initiate the sequence cleaving C1. This is seen in bacterial infections and autoimmune diseases.

2. Alternate Pathway: endotoxin or aggregated IgG initiate the sequence by cleaving C3. Also called the properidin pathway as this is a cofactor.

3. Other pathways: Collectins activate C1r and C1s and plasmin activates C3

4. Effects of the complement mediators:

   a. Anaphylatoxins (C3a & C5a) cause vascular permeability and vasodilation by stimulation of mast cells.

   b. (C5a) causes chemotaxis, activates the AA metabolic path and increases leukocyte adhesion.

   c. Opsonin (C3b & C3bi)

d. Cell lysis (C5-9) lyses microbes (MAC)

5. Regulation is centered on deactivating C3 convertase (DAF) or cleaving C3b (factor I) or binding of active components (C1inhibitor).

C. Clotting & fibrinolytic system

1. Intrinsic Pathway - Hageman Factor (FXII) is activated by surface contact.

2. Extrinsic Pathway - Tissue Factor released at sites of injury activates FVII

3. Results in clotting and fibrinolysis balanced by mediators at the site of inflammation by XIIa → kallikrein → plasmin.

4. Links between coagulation and inflammation:

   a. Thrombin splits fibrinogen to fibrinopeptides which induce vascular permeability and are chemotactic. Thrombin also causes increased leukocyte adhesion and fibroblast proliferation.

   b. Factor Xa increases vascular permeability and leukocyte exudation

   c. Plasmin cleaves C3 & fibrin resulting in fibrin split products which cause vascular permeability. Plasmin can also activate factor XII.

D. Arachidonic acid pathway (eicosanoids)

1. **Cyclooxygenase pathway:** mediated by COX1 and COX2 - leads to formation of prostaglandins. This pathway can result in a variety of mediators:

   a. Prostaglandins: PGD2 causes vasodilation, PGE2 causes pain and fever

   b. Prostacyclin (PGI2) is formed in vascular endothelium to cause vasodilation and inhibit platelet aggregation

   c. Thromboxane (TXA2) is formed in platelets to cause vasoconstriction and promote platelet aggregation

The Cyclooxygenase path is blocked by Non-steroidal anti-inflammatory drugs (NSAIDS). The entire pathway is blocked by steroids at the cell membrane by up regulation of lipocortin-1 that inhibits the release of AA from membrane phospholipids.

2. **Lipoxygenase path** - leads to the formation of Leukotrienes which cause chemotaxis, vasoconstriction, bronchospasm, & increased vascular permeability.

3. **Lipoxins** - are formed by platelets with LTA4 from leukocytes. It inhibits neutrophil chemotaxis and adhesion, stimulates monocyte adhesion, stimulates vasodilation and attenuates action of LTC4 (vasoconstriction). It may be a negative regulator of the leukotrienes.

E. Substances preformed in cells:

1. Histamine in mast cell, basophils and platelets - powerful vasodilator and increases vascular permeability (gaps).

2. Serotonin in platelets - released during aggregation - a vasodilator not important in most inflammatory processes

3. Platelet activating factor (PAF) in most inflammatory cells - causes leukocyte and platelet adhesion activation, vasoconstriction and broncho-constriction.

F. Cytokines

Produced mainly by lymphocytes and macrophages after stimulation by toxins, injury or inflammatory mediators. They include: lymphokines, monokines, chemokines, colony stimulating factors, interleukins, & growth factors. They are categorized by their **actions**:

1. autocrine - acts on the cell that produce it

2. paracrine - acts on adjacent cells - activation of neutrophils and fibroblasts

3. endocrine - acts systemically (Acute Phase Reactions) including: production of fever, fatigue, decreased appetite and increased WBC.

They are categorized by their **functions**:

1. regulate lymphocytes - IL 2, 4, 10 and TGF-b

2. natural immunity - TNF-a, IL1b, IL6, IFNg and IFNb

3. activate macrophages - IFNg, TNF a&b, IL5, 10, 12

4. chemokines - IL8 (leukocytes), lymphotaxin, eotaxin

5. stimulate hematopoiesis - IL3, 7 c-kit, CSF and stem cell factor

The two most important cytokines in inflammation are:

1. **Interleukin-1** produced by many cell types

2. **Tumor necrosis factor** TNFa from macrophages, TNFb from T-cells

   Both of these cause endothelial cell activation, induce acute phase responses, stimulate fibroblasts and stimulate leukocytes to secrete cytokines.

G. Nitric oxide (NO) synthesized in cells containing nitric oxide synthase (NOS)

1. Endothelial cells, neurons and macrophages can produce NO

2. Actions of NO, which are short lived, depend on the concentration:

   a. Small amounts produced by endothelial cells result in smooth muscle relaxation and vasodilation and are anti-thrombogenic to platelets.

   b. Small amounts produced by neurons may act as a neurotransmitter.

   c. Large amounts produced by macrophages may act as a cytotoxic free radical and kill bacteria and tumor cells.

   d. Inappropriate release of NO by macrophages in sepsis may cause shock.

III. Outcomes of Acute Inflammation:

A. Resolution - the tissues are restored to normal, this is seen when the process is limited in tissues that are capable of regeneration.

B. Scarring - the tissue is repaired by fibrosis, this is seen when the process is extensive or in tissues unable to regenerate.

C. Abscess formation - this is seen when the organism can not be completely eradicated or drained, and an accumulation of pus occurs.

D. Progression to chronic inflammation - this is seen if the irritating agent persists and there is a evolution to a mononuclear infiltrate.

CHRONIC INFLAMMATION

Definition: Chronic inflammation is an ongoing process of mononuclear inflammatory infiltration, repair and angiogenesis. Causes of chronic inflammation include:

A. Persistent infection - TB, T pallidum, fungi these organisms may live within cells and avoid neutrophilic destruction. They may also lead to delayed hypersensitivity reactions.

B. Prolonged exposure to nondegradable material such as silica may not be removed by the host immune system.

C. Autoimmune diseases are directed at host tissues and persist indefinitely.

D. Repeated acute inflammation.

Mediators of chronic inflammation:

A. Lymphocytes:

Lymphocytes are activated by antigens and cytokines from macrophages, lymphocytes produce gamma interferon which stimulates macrophages. They produce lymphokines and growth factors which act on other inflammatory cells.

B. Plasma cells:

These are activated B lymphocytes that produce immunoglobulins

C. **Monocytes** in the blood stream become macrophages in the tissues:

1. These produce proteases, collagenases, plasminogen activator, they also store and release plasma proteins including: tissue factor, growth factors, cytokines, clotting factors, complement, O2 metabolites, AA metabolites, PAF and NO.

2. Monocytes secrete the cytokines IL-1 & TNF which can attract neutrophils and cause fever.

3. Monocytes elaborate Growth Factors which stimulate fibroblasts and angiogenesis.

4. Macrophages can proliferate in tissues (atheromas).

5. They can be immobilized in tissue by MIF and oxidized lipids.

6. They can induce extensive tissue destruction.

D. **Fibroblasts** make collagen, fibronectin & others matrix proteins, and are involved in the repair process and walling off of areas of inflammation which are not resolving.

E. **Eosinophils** respond to IgE or parasites, contain major basic protein which is toxic to parasites and host cells.

Examples of chronic inflammation:

A. Chronic interstitial pneumonia - there is widening of the alveolar walls with fibrosis and lymphocytic infiltration. This is commonly seen in viral infections.

B. Chronic gastritis - Helicobacter pylori inflammation of the stomach results in a chronic inflammatory infiltrate of lymphocytes and macrophages. Ulcers may be seen focally in this disease with reactive and reparative changes of the epithelium.

C. Granulation tissue - in the healing stage of inflammation, fibroblasts and capillaries grow into the inflamed area, particularly in areas of damage as in a gastric ulcer. The fibroblasts lay down collagen and capillaries grow by sprouting into the new matrix (angiogenesis).

D. Chronic inflammation heals by forming connective tissue, fibrosis and scarring.

Granulomatous Inflammation

A. Hallmark is the granuloma (plural granulomata):

1. A granuloma is an aggregation of **epithelioid histiocytes** (large macrophages with abundant pink cytoplasm) with a **collar of lymphocytes**, with or without plasmacytes. It is a persistent, localized area of inflammation frequently surrounded by fibrosis and may calcify over time.

2. **INF-g** produced by T lymphocytes transforms macrophages into epithelioid cells and giant cells. It is part of the T-cell immune reactions (cellular immunity).

3. **Giant Cells** may be seen in the granuloma or at its periphery:

   Foreign body - nuclei are scattered in the cytoplasm

   Langhans - nuclei are lined up around one edge of the cell

B. Types of granulomata:

1. Foreign body granulomata may be caused by suture or other irritants such as inorganic dusts like silica, talc and asbestos.
2. Infectious granulomata are seen with:

   TB - Caseating granuloma

   Fungi - Cryptococcosis, histoplasmosis, coccidiomycosis

   Sarcoid - An unknown agent causes non-caseating granulomata throughout the tissues.

C. Resolution of granulomatous disease:

1. In a healthy person granulomata may eventually reduce in size and disappear or leave a small calcified scar.

2. Loss of immunity may lead to loss of containment and spread of the infection after many years.

3. The response to organic and inorganic agents varies widely between individuals.

TISSUE REPAIR AND CELL GROWTH

Wound healing

A. Healing depends on the agent involved, the host immune response, blood supply and nutritional status, and the length of time of the insult. It may proceed by regeneration of parenchymal cells or replacement by connective tissue.

B. The type of cells involved in the process determine if they can totally resolve the injury:

1. Labile cells - cells that normally proliferate (bone marrow, epithelia and lymphocytes)

2. Stable cells do not normally proliferate but can if injured (fibroblasts, osteoblasts, smooth muscle and hepatocytes)

3. Permanent cells no longer replicate because they are highly specialized and differentiated beyond the capacity for regeneration (neurons, neuroendocrine cells and heart). All these tissues heal by scarring (fibrosis).

Molecular events in Cell Growth

A. **Cell surface receptors**

1. Receptors with intrinsic tyrosine kinase activity (dimers)

Binding results in autophosphorylation and is linked to 3 transduction pathways (ras, PI-3 & PKC).

Examples: EGF, FGF, PDGF

2. Receptors with intrinsic catalytic activity (Single transmembrane portion)

Binding results in activation of a cytosolic protein tyrosine kinase and is linked to the JAK/STAT transduction path.

Examples: cytokines

3. G protein linked receptors (7 membrane loops)

Binding results in activation of signal transducing G protein complex and is linked to the cAMP transduction path.

Examples: chemokines, epinephrine, glucagon

B. **Signal transduction**

1. Mitogen activated protein kinase pathway (MAP kinase). Autophosphorylation of receptor leads to activation of the ras protein and eventually activates gene expression.

2. Phosphoinositide-3-kinase pathway (PI-3) generates membrane associated lipid mediators as second messengers. Response is associated with cell survival and increased glycogen synthesis.

3. Inositol lipid pathway (IP3) serves tyrosine kinase or G-protein receptors and activation results in the release of calcium in the cytoplasm.

4. Cyclic adenosine monophosphate pathway (cAMP) serves the G-protein receptor and activation results in stimulation of target genes.

5. JAK/STAT pathway serves the receptors without intrinsic tyrosine kinase activity (cytokines) and activation results in functional responses (not proliferative).

C. **Transcription factors**

1. Regulate gene transcription up or down.

2. Bind to DNA, their affinity is determined by phosphorylation

3. Many protooncogenes in this group (c-myc and p53

Cell Cycle and Division

A. **Cyclins** control progression of cell through the cycle

1. Cyclins A, B & E act on cyclin dependent kinases (CDK's)

2. After action they are rapidly degraded by ubiquitin proteasome pathway

3. CDK's also are regulated by inhibitors (p21, p27)

B. **Checkpoints**

1. p53 (tumor suppressor gene) is activated in response to DNA damage. It inhibits cell cycle by increasing the CDK inhibitor p21.

2. Loss of check points results in genomic instability (IE: hereditary cancers).

C. **Growth inhibition**

1. Contact inhibition - mechanical (cell culture)

2. Growth suppression - size limit (liver regeneration)

3. TGF-b has negative effects on transcription factors and increases CDK inhibitors resulting in the inhibition of progression of the cell to S phase.

Growth factors - Chemical mediators of repair

A. **Epidermal Growth Factor** (EGF) mitogenic (means it causes proliferation) to epithelial cells, fibroblasts, hepatocytes. Binds receptor c-erbB1.

B. **Platelet derived growth factor** (PDGF) stored in platelet a-granules & released on activation (also produced by endothelium, macrophages, smooth muscle & tumors).

Causes migration and proliferation of fibroblasts, smooth muscle & monocytes.

PDGF applied to wounds enhances healing.

C. **Fibroblast growth factor** (FGF) has the ability to induce all steps of angiogenesis. It is also involved in wound repair stimulating migration of fibroblasts, macrophages and endothelial cells and skeletal muscle development and lung maturation.

D. **Transforming growth factors**:

1. TGF-alpha has homology to EGF & binds the EGF receptor, it is mitogenic to epithelia and fibroblasts.

2. TGF-beta is a growth inhibitor to most epithelial cells and is chemotactic to fibroblasts while also stimulating collagen production, it therefore favors fibrogenesis. It is produced by many cell types (platelets, endothelium, lymphs and macrophages) and is involved in chronic inflammatory processes (granulation tissue).

E. **Vascular endothelial growth factor** (VEGF) stimulates angiogenesis, the receptor is found only on endothelial cells. It is seen in cancer, inflammation and healing wounds.

F. **Cytokines** have growth promoting activities

IL-1, TNF - fibrogenic

TNF - angiogenic

Extracellular matrix

A. **Structural proteins**

1. Collagen is a triple helix of 3 polypeptide alpha chains

I, II, III are interstitial fibrillar types

IV, V, VI are amorphous interstitial and BM

Crosslinking stabilizes and gives strength

2. Elastin and fibrillin

Central core of elastin surrounded by fibrillin microfibers

Found in blood vessels, lung, uterus, skin and ligaments

Crosslinks regulate elasticity

B. **Adhesive glycoproteins and integrins** link the ECM components together and to cells

1. Fibronectin attaches cells to ECM by cell receptor for RGD on molecule (arg-glyc-asp) allows cells to attach, spread and migrate in/on ECM.

2. Laminin attaches cells to BM and assists in endothelial formation of tubules.

3. Integrins are cell surface receptors that mediate attachment to the ECM (bind fibronectin and laminin). They are involved in cell to cell attachment, platelet aggregation and leukocyte extravasation.

   They are linked to the intracellular cytoskeleton which also has a "signaling system" and may convert a mechanical signal to a biochemical one.

C. **Matricellular proteins**

Non-structural proteins that interact with matrix proteins and cell receptors and may disrupt them.

1. SPARC (secreted protein acidic and rich in cysteine) also known as osteonectin is an inhibitor of angiogenesis.

2. Thrombospondins also may inhibit angiogenesis

3. Osteopontin regulates calcification, and mediates leukocyte migration.

4. Tenacin modulates cell adhesion.

D. **Proteoglycans and Hyaluronan**

1. Proteoglycans in ECM: Heparan sulfate, chondroitin sulfate, dermatan sulfate regulate connective tissue structure and permeability.

2. Proteoglycan in cell membrane, syndecan, attaches to ECM and links to intracellular cytoskeleton. It modulates activity of growth factors and maintains epithelioid sheets.

3. Hyaluronan binds water and create a viscous gel type matrix. It binds collagen and cells (CD44) and provides resilience and lubrication of cartilage and joints. It also facilitates cell migration and can inhibit cell-cell adhesion.

Repair by connective tissue

A. **Events:**

1. Angiogenesis (TNF, FGF, VEGF)

2. Migration and proliferation of fibroblasts (fibroplasia) and deposition of ECM (TGFb, PDGF, EGF, FGF, IL-1, TNFa)

3. Maturation and organization of fibrous tissue (remodeling) involves metalloproteinases that break down ECM. These require zinc for activity. They are inhibited by tissue inhibitors of metalloproteinases (TIMP's). Results in debridement and remodeling of connective tissue.

B. Formation of a scar: The descriptions below apply primarily to external wounds and to surgical sites.

1. Primary union or healing by first intention is seen in small, clean injuries or surgical incisions. The epithelial surface heals over within one week. When sutures are removed at 7-10 days the wound strength is at 10% of the original tissues. The wound strength returns to 70% of normal in one to three months. The small gap is initially illed with blood clot, and then granulation tissue grows into the space and fibroblasts cross the gap with parallel rows of collagen forming a small scar. A minimal scar is formed.

2. Secondary union or healing by second intention is seen in larger defects with granulation tissue filling in the defect. Wound contraction occurs to close the gap and the granulation tissue supports the regrowth of epithelium over its surface. This process is longer and more irregular, with a resultant large scar remaining.

3. Role of fibroblasts in repair is to lay down collagen and extracellular matrix.

   a. Early in granulation tissue type III (embryonic)collagen is made, it is then replaced with type I collagen.

   b. Fibronectin & Laminin promote cellular migration, organization and attachment of epithelial cells.

Pathology in wound repair

A. Host factors in inflammatory response:

1. Nutrition - low protein & low vitamin C levels in the host inhibit collagen synthesis.

2. Glucocorticoids - steroids decrease the inflammatory response by decreasing mediators.

3. Infections cause delay in healing.

4. Wound dehiscence - high pressures on wound from infection, edema or expansion of organs causes the wound to break down mechanically.

5. Poor venous drainage or blood supply slows healing.

6. Foreign bodies impede healing by stimulating the inflammatory mediators.

B. Aberrations of Growth

1. A keloid is an excessive deposition of collagen within a scar (hypertrophic scar).

2. Exuberant granulations also called pyogenic granulomata are formed by excessive granulation tissue which precludes the epithelium from reconnecting over its surface.

3. Desmoids are aggressive fibromatoses (low grade tumors) usually seen at previous sites of surgery.

C. Disease states

1. Rheumatoid arthritis, lung fibrosis & hepatic cirrhosis are seen when there is persistence of the initial stimuli for fibroplasia .

2. Autoimmune reactions which maintain lymphocyte-monocyte interactions result in the continued production of growth factors & cytokines resulting in self perpetuating inflammatory responses.

3. Excessive collagenase results in joint destruction in rheumatoid arthritis.

Thrombosis and Hemostasis
Edward C. Klatt, MD

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 119-143)

LEARNING OBJECTIVES: At the end of this lecture and reading assignment, the student will be able to:

1. Describe the sequence of events leading to thrombosis
2. Describe the gross and microscopic appearances of thrombi
3. Outline the sequence of events in coagulation and indicate what laboratory tests can be used to determine abnormalities of coagulation
4. List underlying conditions leading to arterial and to venous thrombosis
5. Describe the process of embolization and when it occurs
6. Describe etiologies, appearances, and consequences of infarction
7. Describe the cause and appearances of tissue congestion

THROMBOSIS AND HEMOSTASIS

A. Definitions associated with blood clotting:

Thrombus:	A mass of clotted blood within the vascular system (artery, vein, capillary)
Thrombosis:	The process of forming a thrombus
Coagulation:	The process of forming a blood clot
Anticoagulant:	A natural or pharmacologic agent that inhibits the process of thrombosis
Blood clot:	A simple coagulum of blood formed only with the coagulation sequence and using only elements of the blood
Embolus:	An abnormal collection of material on the move in the bloodstream
Thromboembolus:	A thrombus on the move. Arterial thrombi move more peripherally. Venous thrombi tend to move toward the lungs.

B. Definitions associated with lack of hemostasis:

Hematoma: An blood clot outside of the vascular system

Petechiae: Minute areas of hemorrhage

Purpura: Larger areas of hemorrhage (up to 1 cm)

Ecchymoses: Large, blotchy areas of hemorrhage

C. Definitions associated with stasis of blood flow:

Hyperemia: Arterial vasodilation and opened capillary beds (part of inflammation) - also called erythema

Congestion: Venous stasis of blood in an organ or tissue

Edema: Extracellular fluid accumulation

D. Sequence of events in hemostasis and thrombosis

1. Factors favoring thrombosis

a. Damage to the endothelium with:

trauma

inflammation

b. altered blood flow leading to endothelial injury or platelet activation

venous stasis

arterial turbulence

c. hypercoagulable states from decreased anticoagulant activity or increased procoagulant activity:

increased age

smoking

some malignant neoplasms

congenital anticoagulant deficiencies

birth control pills

2. Arteriolar vasoconstriction (vasospasm) - transient process, but it may potentiate serious ischemic injury (coronary arteries and myocardial infarction, cerebral arteries and stroke)

3. Platelets are activated by exposure to highly thrombogenic subendothelial materials such as collagen when normal endothelium is damaged.

Platelet activation is called "primary" hemostasis because it is the first response of the coagulation system and occurs in minutes.

Clinical measurement of the "bleeding time" assesses this function, but is not commonly performed.

The sequence of events in platelet activation include:

a. Adhesion and shape change

attachment (adhesion) to exposed collagen

von Willebrand factor (VWF) needed for adhesion

round platelets elongate to cover the exposed collagen

b. Release

alpha granules release platelet factor 4 with anti-heparin activity

dense granules release ADP and calcium

release generates phospholipid complex (platelet factor 3) that promotes coagulation

c. Aggregation

released ADP promotes initial aggregation into a "primary plug"

thromboxane is synthesized and promotes additional aggregation and, along with thrombin, formation of a more stable "secondary plug"

4. Coagulation sequence

   a. Intrinsic pathway - stimulated by platelets and by endothelial damage

   b. Extrinsic pathway - stimulated by tissue damage with release of tissue thromboplastin

   c. End result --> formation of thrombin that converts fibrinogen to fibrin

   d. Pathways are NOT independent and do not substitute for one another, and a loss of a single factor may lead to a bleeding disorder

E. Anticoagulant mechanisms

1. Endothelial cell defenses

   a. endothelium is naturally resistant to clotting

   b. synthesis of anticoagulants:

      Protein S

      prostacyclin: vasodilator and inhibitor of platelet aggregation

      plasminogen activators

   c. binding of anticoagulants to surface:

      thrombomodulin

      heparin-like molecules

   d. activation of anticoagulants

      Protein C

      conversion of adenosine diphosphate (ADP) to platelet inhibitors

2. Inhibitors of coagulation

a. Fibrinolytic system: plasminogen is converted to plasmin by tissue and plasma plasminogen activators

b. Antithrombin III

c. Protein C and Protein S

F. Morphologic appearances of thrombi

1. Gross: concentric layering of red cells, white cells and platelets gives characteristic "lines of Zahn", particularly in faster flowing arteries.

In slower flowing veins, the thrombus resembles a blood clot.

Thrombi tend to adhere to vessel walls.

2. Microscopic: lines of Zahn appear as laminations of red cells, white cells and platelets that are enmeshed in fibrin.

G. Locations for thrombosis - arterial

1. Heart

a. on damaged valves (endocarditis)

b. over damaged myocardium (mural thrombus)

c. within aneurysms or dilated heart chambers (mural thrombus)

d. on an abnormal surface (mechanical valve prosthesis)

2. Aorta (mural thrombus)

a. on ulcerated atheromatous plaques

b. within aneurysms

3. Smaller arteries

a. in areas of trauma

b. in areas of inflammation

H. Locations for thrombosis - venous

1. appear most frequently in deep veins (particular lower extremities and pelvis) and are called phlebothrombosis; rare in upper extremities (that's why you want to put IV's in upper extremities)

2. occur with stasis or inflammation and is given the name thrombophlebitis

I. Events following thrombosis

1. Propagation: the thrombus continues to grow

2. Lysis: removal by fibrinolytic system

3. Embolization: the thrombus moves on

4. Organization: granulation tissue is formed and resolves with recanalization of the vascular lumen (perhaps with fibrosis or degrees of occlusion by connective tissue)

J. Thromboembolization: Movement of a thrombus from its origin to another site via bloodstream

1. Arterial

   a. Most often come from heart (endocarditis or mural thrombus)

   b. Follow systemic circulation

   c. Can result in infarction from arterial occlusion

2. Venous

   a. Most often come from leg veins of immobilized patients in hospital

   b. Follow vena cava to right side of heart and then to pulmonary artery

   c. Can result in pulmonary embolism

      if massive, sudden death results

if medium sized, pulmonary infarction results

if small, multiple, and chronic, pulmonary hypertension results

HYPERCOAGULABILITY SYNDROMES

A. Hypercoagulability is the tendency to have thrombosis. Pregnant women with these conditions may have an increased risk for stillbirth. These syndromes can be due to both inherited and acquired abnormalities of the coagulation system.

B. The most common causes for hypercoagulability syndromes include:

1. Antiphospholipid antibody syndrome: there are circulating antibodies that bind plasma proteins with an affinity for phospholipid surfaces and cause thrombosis. This syndrome is most often acquired in adulthood, either from underlying disease or as an idiopathic condition. The two subsets of this syndrome, as defined by laboratory testing, are:

   a. Lupus anticoagulant (may or may not be seen with SLE)

   b. Anti-cardiolipin antibody

2. Factor V Leiden mutation: this is the most common inherited form of hypercoagulability. The mutation is present in 5% of Caucasians but is rare in persons of African and Asian ancestry. A point mutation leads to impaired inactivation of factor V by activated protein C. Venous thrombosis occurs.

3. Prothrombin mutation: the prothrombin G20210A mutation increases the level and activity of prothrombin that mildly increases the risk for arterial and venous thrombosis. The mutation occurs more often in persons of southern European ancestry.

4. Elevated factor VIII: this is as common as factor V Leiden. There may be genetic and

environmental factors causing it. Oral contraceptive use increases factor VIII levels. The result is deep venous thrombosis.

5. Malignancy: tumors may elaborate factor, such as a thromboplastin-like substance, that increase the risk for thrombosis. This is one form of paraneoplastic syndrome, with the name Trousseau's syndrome.

6. Protein C, Protein S, antithrombin III deficiencies: these conditions are autosomal dominant and lead to venous thrombosis.

7. Homocystinemia: persons with elevated plasma homocysteine levels not only have increased problems with atherosclerosis, but also thrombosis.

TESTS OF THE COAGULATION SYSTEM

A. Tests to determine risk for bleeding:

1. Prothrombin time (PT): measures factors in the "extrinsic" pathway of coagulation, affected mainly by liver disease, Coumadin therapy

2. Partial thromboplastin time (PTT): measures factors in the "intrinsic" pathway of coagulation, affected by a variety of diseases including inherited factor deficiencies such as hemophilia, and Coumadin therapy

3. CBC with platelet count: measures the number of circulating platelets

For pre-operative workup, a PT, PTT, and platelet count are typically ordered

4. Factor deficiencies: ordered only in specific circumstances to determine if an acquired or inherited factor deficiency is present. Example: measure Factor VIII-VWF to determine the presence of von Willebrand disease

B. Tests to determine risk for thrombosis:

The diseases producing thrombosis are much less common than those that produce bleeding, but should be tested for when patients with thrombosis (usually venous thrombosis) are young, have recurrent thrombosis, or have unexplained thrombosis.

1. Factor V Leiden mutation

2. Protein C or S

3. Prothrombin mutation

4. Antithrombin III

5. Anti-phospholipid antibody: lupus anticoagulant, anticardiolipin antibody

6. Plasma homocysteine

7. Factor VIII level

C. Disseminated intravascular coagulation (DIC)

1. Occurs when the coagulation-anticoagulation system is activated on a wide scale--with severe organ damage, sepsis, shock, etc.

2. There can be both thrombosis and bleeding.

3. Diagnosed with an elevated D-Dimer test

INFARCTION

A. An infarct is an area of ischemic necrosis resulting from:

1. Arterial occlusion (99% of all infarctions, such as coronary artery and MI)

2. Venous occlusion (such as cerebral venous thrombosis) - rare

B. Gross appearances

1. Distribution: depends on vascular supply, collateral blood flow, metabolic demand

2. Morphology: localized, wedge-shaped; pale in most parenchymal organs because of loss of blood supply

Red in lung (from the dual blood supply) or if due to venous occlusion

C. Age

1. Acute (recent): hours to days old; the cells have died

   Often diagnosed clinically by measurement of enzymes are being released (CPK, LDH)

2. Intermediate (subacute): days to weeks; the infarct is undergoing organization, resolution, healing

3. Remote (old): months to years; the infarct has organized leaving a scar or a cavity

HEMORRHAGE

A. Failure of the hemostasis mechanism leads to hemorrhage.

   A blood clot formed outside a vessel is a hematoma

B. Loss of a unit of blood (about 500 cc) is usually not accompanied by serious difficulties; loss of 1000 cc or more can produce shock

C. Hemorrhage into a body cavity or tissue

   1. No loss of iron

   2. May compress vital structures

D. Hemorrhage into viscus or tract

   1. Loss of iron

   2. Physical diagnostic signs: melena, hematuria, hematochezia, etc.

CONGESTION

A. Passive congestion is due to stasis of blood, particularly on the venous side of the circulatory system, and usually due to congestive heart failure (CHF)

   Can be acute or chronic

B. Passive congestion of visceral organs

   1. Increased weight

2. Appearances: dark red; blue (cyanosis); brown (from red cell breakdown to hemosiderin)

2. Liver: gives classic "nutmeg" appearance and may be accompanied by centrilobular necrosis

EDEMA

Extracellular fluid accumulation

1. Interstitial (tissue swelling)

2. Body cavities (effusions)

   Peritoneal (ascites)

   Pleural

   Pericardial

   Joint

Mechanisms for edema formation

1. Inflammation: Vessel permeability leads to leakage of fluid

2. Increased intravascular hydrostatic pressure:

   a. impaired venous return due to obstruction or heart failure

   b. venous stasis due to gravity or inactivity

3. Decreased intravascular oncotic pressure:

   a. loss of protein due to nephrotic syndrome, poor nutrition or protein losing enteropathy

   b. decreased production of protein due to liver disease

4. Lymphatic obstruction: due to inflammation, surgical trauma or tumors

5. Sodium retention:

   a. hormonal in pregnancy and with menstrual cycles

   b. cardiac failure

   c. renal failure

Patterns of edema

1. Dependent - depends on position of patient, lower extremities if ambulatory, sacral if bedridden

2. Anasarca - total body edema seen in severe thyroid deficiency and DIC

3. Periorbital edema - seen in thyroid deficiency and renal failure

4. Pulmonary edema - seen in heart failure as "backwards failure" causes shortness of breath

PATHOLOGY 6601, FALL 2006
Vascular Diseases
Edward Klatt, MD

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 515-530)

LEARNING OBJECTIVES: At the end of this reading assignment and lecture, the student will be able to:

1. Assess the risk factors, both reversible and irreversible, for development of atherosclerosis in your patient.

2. Define the role of lipids and lipoprotein transport in development of atherosclerosis.

3. Describe how and why an atheroma forms in an artery.

4. List complications that occur within arteries at the site of atheromatous plaques.

5. Describe major organ system sequelae of atherosclerosis.

6. Describe three forms of arteriolosclerosis and what their significance is.

7. List ways that atherosclerosis can be prevented.

RISK FACTORS FOR ATHEROSCLEROSIS

1. Irreversible, uncontrollable factors

    a. Age: older people have a greater risk

    b. Sex: males are at greater risk; physiologic estrogen levels are protective

    c. Genetics: there is a familial predisposition that can include inherited disorders of lipid metabolism. There are a variety of these, often having complex modes of inheritance, but most of these conditions are also markedly influenced by diet. The most important are:

        i. familial hypercholesterolemia

        ii. abnormal apoproteins (rare)

        iii. history of coronary artery disease in a first degree relative (age <55 male; <65 female)

2. Reversible, correctable factors

    a. Hyperlipidemia: hypercholesterolemia with LDL is worst, but hypertriglyceridemia with VLDL is also a risk. Risk rises significantly with total serum cholesterol >200 mg/dl. Dietary factors include:

        i. high total dietary fat increases risk

        ii. high saturated fat content increases risk

        iii. high cholesterol content increases risk

        iv. fish oils decrease risk (Eskimos)

    b. Hypertension

        i. increases angiotensin II to promote arterial smooth muscle proliferation

        ii. promotes formation of oxidized LDL and free radicals

    c. Smoking - promote free radical formation

d. Diabetes mellitus - promotes formation of oxidized LDL and free radicals

3. "Soft" risk factors with less definable risk

a. Obesity

b. Decreased physical exercise

c. Stressful lifestyle

d. Use of oral contraceptives

4. Laboratory parameters that have been used to determine risk for atherosclerosis include:

a. Total cholesterol

b. LDL cholesterol

c. HDL cholesterol

d. homocysteine

e. C-reactive protein

f. fibrinogen

5. Lipoprotein transport

a. Exogenous pathway: lipids absorbed in the small intestine form chylomicrons with blood transport apoproteins. Endothelial lipoprotein lipase splits off fatty acids that go to adipose tissue and muscle. Cholesterol-rich remnants go to liver.

b. Endogenous pathway: VLDL from liver are transformed in adipose tissue and muscle to LDL which are then taken up by a variety of cells with LDL receptors that need cholesterol for membrane synthesis. About a third of LDL is degraded to a form that can be taken up by macrophages and cells with modified LDL receptors (arterial walls).

COMPONENTS OF ARTERIES

1. Intima: composed of endothelium - single layer of flattened cells (fenestrated in the glomerulus) and supported by a thin underlying layer of connective tissue under which is the internal elastic lamina. Endothelial cells contain Weibel-Palade bodies by EM.

2. Media: composed of smooth muscle cells that can proliferate, migrate, and phagocytose. Elastic fibers are interspersed (and most prominent in the aorta). Outer limit is marked by the external elastic lamina.

3. Adventitia: Connective tissue layer. In larger vessels, may contain nerves. In aorta, also contains the vasa vasorum (small arteries that supply the aorta itself).

THEORIES OF ATHEROMA FORMATION

1. Vascular injury with thrombus formation are key events. The injury has three phases:

   a. Type 1 - functional endothelial cell alteration, but no morphologic changes to endothelium. Blood monocytes become macrophages and accumulate lipids (foam cells), creating a so-called "lipid lesion".

   b. Type II - denudation of endothelium with intimal damage. Platelets adhere. Macrophages migrate in. Growth factors, such as PDGF, are released that stimulate smooth muscle cell migration and proliferation, leading to a "fibrointimal lesion" alone or on top (a "cap") of the lipid lesion. May also contain T-lymphocytes.

   c. Type III - endothelial denudation with damage to both intima and media. Disruption leads to thrombus formation which can organize and become part of the atheroma or occlude the lumen. Macrophage release of proteases contributes to this.

   The first gross evidence for an atheroma is the "fatty streak" which can be seen in the aorta even in children. This lesion is benign, but may be the precursor to more serious atheromatous plaques.

2. Injury to endothelium is promoted by vascular turbulence, so atheromas have a predilection to occur at arterial branch points or in tortuous arteries:

   a. Abdominal portion of aorta

   b. Bifurcation of carotids

   c. First few centimeters of coronaries

3. Atheroma formation is potentiated by hypercholesterolemia:

a. LDL cholesterol - brings cholesterol to the arterial wall

b. HDL cholesterol - prevents deposition of cholesterol

4. Atheroma formation is accelerated (initial appearance of type II or III lesions) following angioplasty, bypass grafts, and heart transplants.

5. Over time, atheromatous plaques may become “complicated”. The initial event is the formation of fissures in the plaques which lead to thrombus formation, either as one event or as several events.

Anticoagulant or platelet inhibitor therapy (aspirin) may help to reduce the risk of thrombosis.

a. Thrombosis in coronary arteries may lead to:

i. myocardial infarction

ii. unstable angina

iii. sudden death

b. Thromboses leading to these acute syndromes are more likely to occur with mild to moderate stenosis in lipid-rich plaques that are more easily disrupted.

c. Vasoconstriction may accompany type II or III injury, from platelet activating factor (PAF) and/or thromboxane release from platelets, leading to further narrowing. The endothelium can counteract this by releasing prostacyclin.

d. Additional complications include:

i. ulceration

ii. calcification

iii. aneurysmal dilation

iv. hemorrhage into plaque

6. Stenosis: lesions over time occlude more and more of the arterial lumen (but they can never occlude the aorta). Fibrosis and organized thrombus produce progressive narrowing.

If this is gradual, the heart adapts by generating collateral circulation. There are experimental

therapies for ischemic heart disease using drugs designed to promote angiogenesis.

SEQUELAE OF ATHEROSCLEROSIS

These are all variations on a theme of decreased blood flow with varying degrees of ischemia to infarction, depending upon the acuteness and severity of the arterial occlusion:

1. Heart: coronary artery atherosclerosis
    a. Sudden death with arrhythmia
    b. Myocardial infarction
    c. Chronic ischemia with fibrosis, cardiomegaly

2. Brain: cerebral artery atherosclerosis
    a. Stroke (infarction)
    b. Transient ischemic attacks
    c. Atrophy, multi-infarct dementia

3. Aorta
    a. Atherosclerotic aneurysms (abdominal) with mural thrombosis
    b. Atheromatous (cholesterol) emboli - rarely symptomatic

4. Kidney
    a. Arterial and arteriolar nephrosclerosis
    b. Hypertension
    c. Chronic renal failure

5. Extremities (usually legs)
    a. Claudication (pain)

b. Ischemia, infarction with gangrene

6. Intestines

a. Ischemia with pain (abdominal angina)

b. Infarction

Note: The extensive anastomoses between the arterial supplies to the bowel mean that severe atherosclerosis must affect all branches for sequelae to occur.

The severity of ischemic tissue damage from atherosclerotic complications depends upon the:

a. degree of vascular occlusion

b. length of time of occlusion

c. amount of collateral circulation

d. metabolic demand of the tissue

Therefore, restoration of blood flow as soon as possible is important. For example, more rapid and complete restoration of coronary blood flow with tissue plasminogen activator (t-PA) after coronary thrombosis with myocardial infarction results in improved ventricular performance and lower mortality. The idea is to not get beyond the point of reversible injury to cells.

APPROACHES TO PREVENTION OF ATHEROSCLEROSIS

1. Decrease cholesterol (and total fat intake)

a. Reduce LDL while maintaining HDL levels

b. Regression of lipid-rich plaques is of key importance in preventing acute events

2. Increase exercise: even light exercise has major benefits

3. Drugs: there are several classes of drugs that affect lipoprotein metabolism, typically by reducing LDL and increasing HDL cholesterol

a. Statins: such as lovastatin and pravastatin; they inhibit HMG-CoA reductase in the pathway of endogenous cholesterol synthesis

b. Bile acid sequestrants: such as cholestyramine and colestipol; they lower cholesterol by a mechanism of increased bile acid excretion

c. Nicotinic acid (niacin): a potent anti lipolytic agent, limiting the free fatty acids available for the synthesis of triglyceride and cholesterol

d. Fibric acids: such as gemfibrozil and bezafibrate; work by activation of peroxisome proliferator-activated receptor-alpha 1 in the liver, with the net effect of improving the plasma transport rates of several lipoproteins

e. Ezetimibe: inhibits absorption of cholesterol at the brush border of intestinal enterocytes; the decreased absorption aids the cholesterol lowering function of statins.

OTHER FORMS OF ARTERIOSCLEROSIS

1. Arteriolosclerosis

a. Hyaline arteriolosclerosis occurs in the small arterioles of the kidney in persons with hypertension and/or diabetes mellitus. It is sometimes seen in very elderly patients who are normotensive.

There is concentric hyaline thickening of the media.

It is associated with benign nephrosclerosis of the kidneys.

b. Hyperplastic arteriolosclerosis occurs with malignant hypertension.

It is characterized by concentric hyaline thickening with more severe narrowing. If severe, there can be necrotizing arteriolitis. The kidney is usually affected the most, but the process may be widespread.

2. Mönckeberg's arteriolosclerosis (medial calcific sclerosis)

This is a process that does not lead to significant vascular problems. It is really just an incidental finding in the elderly. Medium to small arteries (often in neck, extremities, and pelvis) show ring-like medial calcification. It may make arteries appear bright on radiographs.

This study guide is based upon material contained within the following reference sources:

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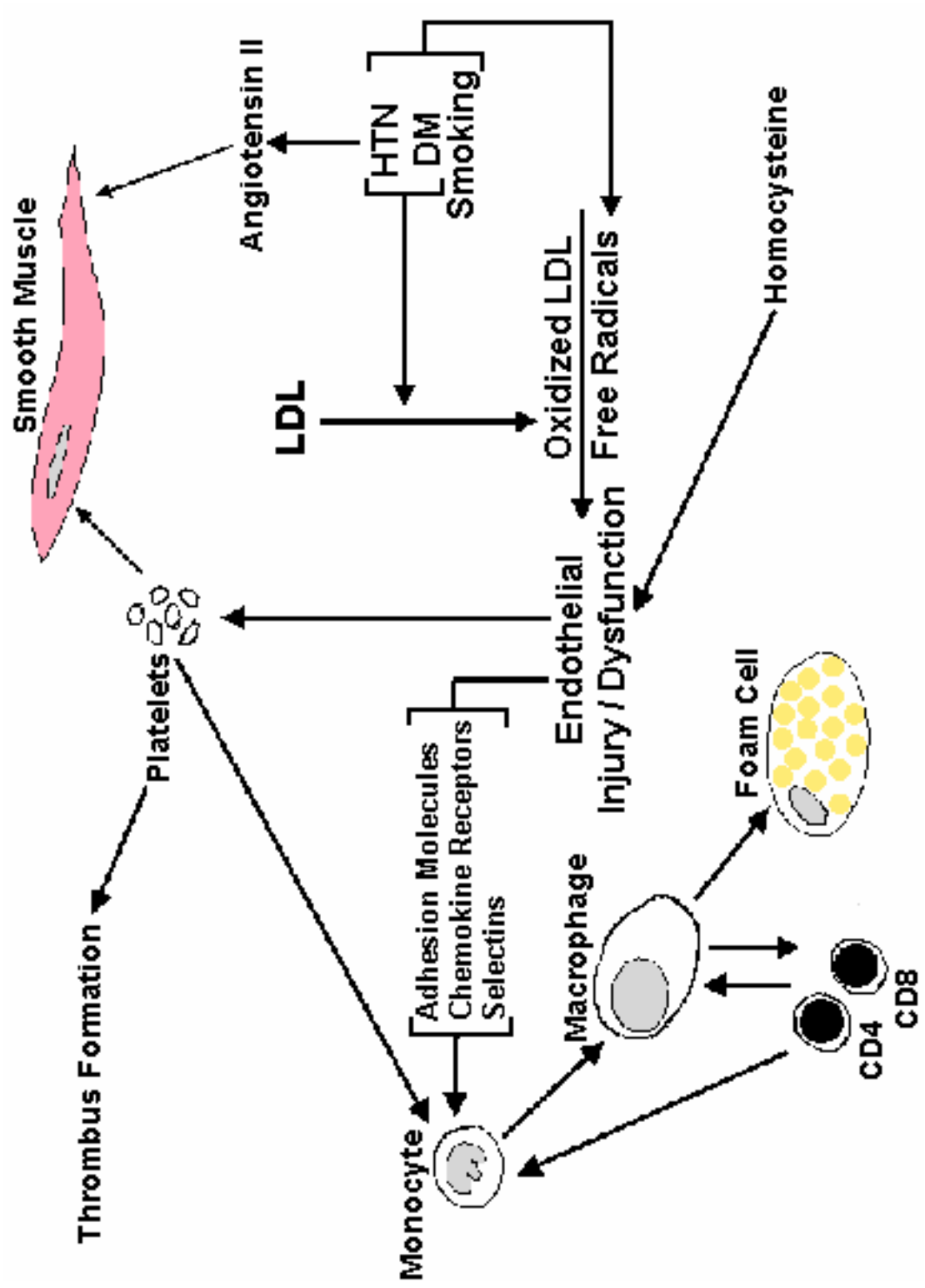

Smooth Muscle
Angiotensin II
HTN
DM
Smoking
LDL
Oxidized LDL
Free Radicals
Homocysteine
Platelets
Endothelial
Injury / Dysfunction
Thrombus Formation
Adhesion Molecules
Chemokine Receptors
Selectins
Foam Cell
Macrophage
Monocyte
CD4
CD8

CASE STUDIES IN ARTERIOSCLEROSIS

CASE 1

History: A 54 year old male has had increasing chest pain which is associated with exercise. You find that he is 5' 6" tall and weighs 195 lb. He says that he continues to smoke about a half a pack of cigarettes per day, because when he tried quitting, he gained weight. He works as a commodities broker for a financial institution that is being investigated by the securities exchange commission. He is worried about the chest pain because his father and one brother died from heart attacks.

Questions for discussion:

1.1: What risk factors are involved in the pathogenesis of atherosclerosis? Which are present in this case?

1.2: What laboratory tests would be helpful in this case?

1.3: What is causing this man's symptoms? What are potential sequelae?

1.4: What is the significance of the family history?

CASE 2

History: A 45 year old male is playing racquetball. After the second game, he says he doesn't feel well. He says he feels some chest pain and some numbness in the left arm. He then collapses to the floor and his playing partner calls the paramedics and initiates CPR. However, when the paramedics arrive, he is without a pulse. He cannot be revived.

Questions for discussion:

2.1: Review the theories of atheroma formation

2.2: What factors potentiate atheroma formation

2.3: What are the complications of atheromatous plaques?

2.4: What do you suspect as the cause of death in this case?

CASE 3

History: A 61 year old male is brought to the emergency room after he complains of abdominal pain. Physical examination reveals that bowel sounds are present and the abdomen is mildly tender. A midline pulsatile mass is palpated. After this initial assessment, he is admitted.

However, on the way to the ward, he suffers an episode of severe abdominal pain associated with sudden drop in blood pressure and loss of consciousness. He is taken to surgery.

Questions for discussion:

3.1: What is the pathogenesis of this man's problem?

3.2: Describe what the lesion would look like both grossly and microscopically.

3.3: Describe the locations where such lesions can occur and what the complications would be.

CASE 4

History: A 63 year old woman says she has had episodes of feeling "light-headed" or faint over the past couple of years. Rarely, she will pass out, but regain consciousness within a couple of minutes. Her total serum cholesterol is found to be 255, with an HDL component of 38.

Questions for discussion:

4.1: Discuss the pathways of lipoprotein transport and lipid metabolism.

4.2: Describe the places where atheromas form and why.

4.3: What advice could you give to her about treating her problem.

CASE 5

History: A 73 year old male has noted that his left leg, particularly in the lower portion, seems cold and numb at times over the past several months. He also experiences pain in this extremity when he tries walking more than 100 meters. His past history is significant for a myocardial infarction at age 59. On physical examination, dorsalis pedis, posterior tibial, and popliteal pulses are not palpable. His legs are not tender to palpation.

Questions for discussion:

5.1: Where do you think the major pathologic problem is in this man?

5.2: What is the reason for his symptoms?

5.3: What is the significance of the past history of MI?

CASE 6

History: A 69 year old male who is overweight has had diabetes mellitus for the past 12 years. His blood pressure has gradually increased over that time and is now 155/95. An abdominal radiograph shows calcification of periprostatic vessels.

Questions for discussion:

6.1: What arterial lesion is present in the kidney?

6.2: If his blood pressure were 220/150 what lesions could be present?

6.3: What is the significance of the calcified periprostatic vessels?

ARTERIOSCLEROSIS CASES
DISCUSSION POINTS

CASE 1

Questions for discussion:

1.1: What risk factors are involved in the pathogenesis of atherosclerosis? Which are present in this case? Male sex, smoking, stressful lifestyle, family history, obesity.

1.2: What laboratory tests would be helpful in this case? Total cholesterol and HDL cholesterol.

1.3: What is causing this man's symptoms? Probable angina from narrowed coronary arteries with atheromatous plaques. What are potential sequelae? Continued and worsening chest pain, myocardial infarction, congestive heart failure, stroke.

1.4: What is the significance of the family history? It suggests a similar disease process in relatives. Perhaps there is a familial hypercholesterolemia or perhaps diabetes mellitus.

CASE 2

Questions for discussion:

2.1: Review the theories of atheroma formation. Endothelial injury with thrombosis. Smooth muscle proliferation has also been suggested as one possibility.

2.2: What factors potentiate atheroma formation? Vascular turbulence and hypercholesterolemia. Unfortunately, people who have been treated with a new heart or new vessels or angioplasty tend to gum up the new vessels even faster with atherosclerosis.

2.3: What are the complications of atheromatous plaques? The complications depend upon the location of the atheromatous lesions: stroke, myocardial infarction, renal failure, gangrene, etc.

2.4: What do you suspect as the cause of death in this case? Coronary artery thrombosis.

CASE 3

Questions for discussion:

3.1: What is the pathogenesis of this man's problem? Atherosclerotic aortic aneurysm.

3.2: Describe what the lesion would look like both grossly and microscopically.

Slides of the lesion are shown

3.3: Describe the locations where such lesions can occur and what the complications would be. Most of these occur in the aorta below the renal arteries. The complications include leakage and rupture. Mural thrombus within them may embolize.

CASE 4

Questions for discussion:

4.1: Discuss the pathways of lipoprotein transport and lipid metabolism.

a. Exogenous pathway: lipids absorbed in the small intestine form chylomicrons with blood transport apoproteins. Endothelial lipoprotein lipase splits off fatty acids that go to adipose tissue and muscle. Cholesterol-rich remnants go to liver.

b. Endogenous pathway: VLDL from liver are transformed in adipose tissue and muscle to LDL which are then taken up by a variety of cells with LDL receptors that need cholesterol for membrane synthesis. About a third of LDL is degraded to a form that can be taken up by macrophages and cells with modified LDL receptors (arterial walls).

4.2: Describe the places where atheromas form and why. They often form in muscular arteries, particularly at bifurcations.

4.3: What advice could you give to her about treating her problem. Lower the serum cholesterol through diet and exercise. Drug therapy is a next resort. Surgical therapy to remove atheromatous plaque is possible, but an operation carries a risk of morbidity and mortality.

CASE 5

Questions for discussion:

5.1: Where do you think the major pathologic problem is in this man? Peripheral vascular atherosclerosis involving the iliac arteries or their major branches. Deep venous thrombosis is unlikely in this setting.

5.2: What is the reason for his symptoms? Occlusion of blood flow to the lower extremities.

5.3: What is the significance of the past history of MI? Further evidence for severe atherosclerosis.

CASE 6

Questions for discussion:

6.1: What arterial lesion is present in the kidney? Hyaline arteriolosclerosis.

6.2: If his blood pressure were 220/150 what lesions could be present? Hyperplastic arteriolosclerosis.

6.3: What is the significance of the calcified periprostatic vessels? None. This is probably Mönckeberg's medial calcific sclerosis.

DIABETES MELLITUS

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 1189-1205)

LEARNING OBJECTIVES: At the end of the lecture and upon completion of the reading assignment, the student will be able to:

1. How would you diagnose diabetes mellitus in your patient?

2. If you were an insulin molecule, what would you do?

3. Describe the features of Type 1 and Type II diabetes mellitus in regard to:

    a. age of onset
    b. body weight
    c. pathologic appearances of the islets of Langerhans
    d. laboratory features
    e. etiologies
    f. complications

4. Describe the long term complications of diabetes mellitus with regard to:

    a. pathogenesis
    b. major organ system pathology (heart, kidney, brain, eye, soft tissues)

5. How does diabetes mellitus affect pregnancy?

DEFINITION OF DIABETES MELLITUS

A. Diabetes mellitus is a relative or absolute deficiency of insulin leading to glucose intolerance.

B. Glucose intolerance is measured by detection of hyperglycemia. This is determined in the laboratory by measurement of serum glucose. A random blood glucose, not determined in relation to meals or fasting is normally between 70 and 110 mg/dl.

C. Definition of diabetes mellitus:

    1. A fasting blood glucose (no caloric intake for eight or more hours) exceeds 126 mg/dL.

    2. The 75 gm glucose tolerance test is more than 200 mg/dL after 2 hours.

    3. Older definition: Diabetes mellitus is diagnosed when the fasting blood glucose is > or = 140 mg/dL on two occasions.

    4. Typical symptoms of polydipsia, polyuria, and unexplained weight loss are present along with any blood glucose measurement >200 mg/dL.

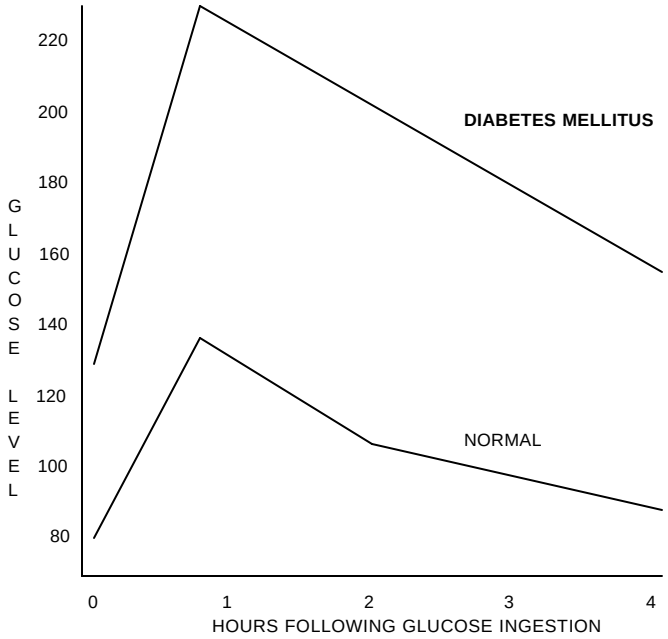
D. Glucose measurements:

1. Many diabetes patients nowadays measure their own blood glucose with a fingerstick from which a drop of blood is placed on a reagent test strip that can be read by a simple device (glucometer).

2. An older method that you may read about or see that is a simple, rough measure of control of blood sugar is measurement of urine glucose with a "Clinitest" tablet put into an aliquot of urine and the color change recorded to give a semiquantitative measure of the amount of glucose being spilled into the urine.

3. Glucose tolerance test: this test is not done that much anymore. After an overnight fast, the patient is given a measured quantity of glucose (usually a bottle of Glucola containing 75 gm of glucose) and then blood glucose levels are determined at baseline, 1 hour, 2 hours (and occasionally up to 6 hours) later.

   Ordinarily, the glucose will rise and then fall with a normal insulin response. With diabetes mellitus, the glucose will rise higher and not fall as fast.



PHYSIOLOGIC FUNCTIONS OF INSULIN

A. Under the influence of the blood glucose level, beta cells of the pancreatic islets of Langerhans secrete proinsulin which is cleaved to C-peptide and biologically active insulin. Normally, C-peptide and insulin are secreted into portal venous blood in a 1:1 ratio, but C-peptide is cleared more slowly, so the ratio of insulin to C-peptide should be <1

B. Insulin promotes transport of glucose and amino acids through cell membranes. The lack of insulin leads to:

Hyperglycemia

Glycosuria (spilling of glucose in the urine)

Polyuria (osmotic diuresis leading to...)

Polydipsia (increased water consumption)

Polyphagia (increased appetite)

1. Important cells (which make up 2/3 of body weight) which require insulin for glucose uptake include:

   a. skeletal, smooth, and cardiac muscle

   b. steatocytes

   c. fibroblasts

2. Important cells which do not need insulin for glucose uptake include:

   a. neurons

   b. red blood cells

   c. kidney

   d. retina

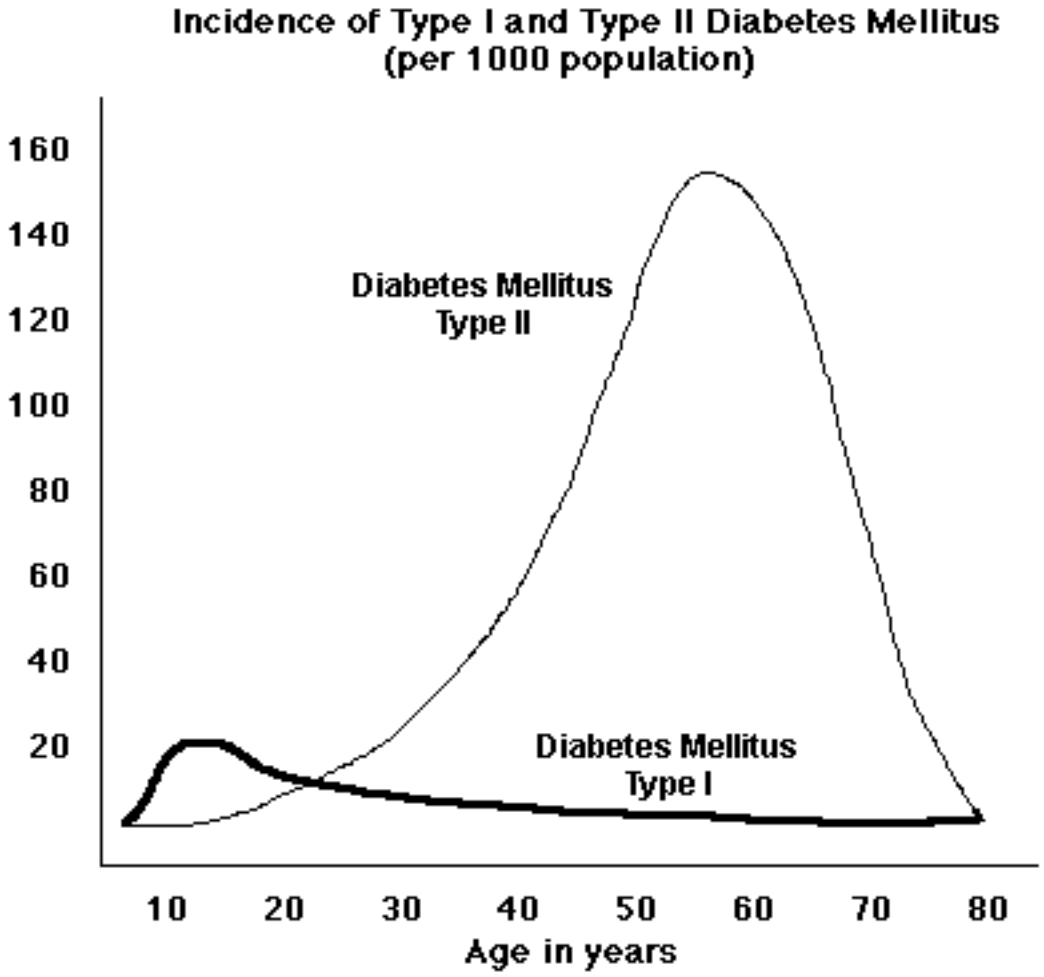
   e. lens

C. Inulin promotes the conversion of glucose to triglycerides and adipose tissue; if insulin is lacking, there is increased use of fatty acids with generation of ketone bodies leading to a metabolic acidosis.

D. Insulin promotes glucose conversion to glycogen (glycogenesis in the liver and skeletal muscle). A lack of insulin leads to glycogenolysis and gluconeogenesis in the liver.

E. Insulin promotes increased protein synthesis (anabolic effect). The lack of insulin leads to increased protein catabolism, particularly of muscle and adipose tissue.

INCIDENCE OF DIABETES MELLITUS



There are about 15 million Americans with diabetes mellitus; about half are undiagnosed.

TYPE I DIABETES MELLITUS

A. There is an absolute lack of insulin because there is a lack of beta cells in the islets of Langerhans. Hence, plasma insulin levels will be low. Hence, the synonym for this condition: insulin dependent diabetes mellitus (IDDM).

B. Etiologies that have been proposed include:

1. A genetic susceptibility. This is suggested by the tendency for diabetes mellitus to run in families. It is also suggested by the increased appearance of HLA DR3 and HLA DR4 in diabetics.

2. Environmental causes. Chemical toxins might be involved (pentamidine). Viral infection of the pancreas with inflammation may precede diabetes mellitus.

3. Autoimmunity. The beta cells are attacked by the immune system. The infiltration of the islets by T-lymphocytes suggests that autoimmunity may play a role.

C. Histologic examination of the islets of Langerhans may reveal an "insulitis" with lymphocytes (this occurs before the clinical onset of disease). Later, when the disease is overt, there may be hardly any islets remaining.

D. The age of onset is usually under 20, hence, the name of "juvenile onset diabetes mellitus" but type I diabetes mellitus can sometimes occur at an older age.

E. Body habitus: usually thin because of glucosuria with loss of glucose and increased protein catabolism.

F. Major metabolic complication is ketoacidosis.

1. The absolute insulin lack, coupled with glucagon increase, results in the use of fatty acids in metabolism. This leads to the elaboration of ketone bodies (acetone, acetoacetic acid, beta hydroxybutyric acid) which lead to metabolic acidosis.

   The ketone bodies are expired (can be detected on the breath of the patient) and excreted in the urine (where they can be detected with a urine dipstick).

2. Typical laboratory findings with type I diabetes mellitus include:

	Patient	Normal

Glucose	500 mg/dl	<110
Sodium	152 mEq/L	135-147
Potassium	5.0 mEq/L	3.5-5.0
Bicarbonate	8 mEq/L	22-28
Urine Ketones	4+	negative
Osmolarity	320 mosm/L	275-295

3. Physical findings include:

    a. dehydration

    b. Kussmaul respirations

4. Clinical symptoms include:

    a. anorexia

    b. nausea

    c. vomiting

    d. abdominal pain

    e. coma

TYPE II DIABETES MELLITUS

A. There is a relative lack of insulin. Plasma insulin levels may be normal to decreased. The problem is increased resistance of cells to insulin, leading to a decreased or blunted insulin response with hyperglycemia. Adipocytes secrete a signaling molecule called resistin which is increased in obesity and diminishes insulin action. The synonym for this condition: non-insulin dependent diabetes mellitus (NIDDM).

B. Etiologies proposed include:

1. Insulin resistance. Too many fat cells, or malfunction of glucose receptors and transport units with increased resistin levels.

2. Beta cell hypofunction. The beta cells do not respond normally and the response to hyperglycemia is blunted. There is a lack of insulin relative to the demand for it.

3. A genetic susceptibility is suggested by the fact that 60% of type II diabetics have a close relative with diabetes.

C. Histologic examination of the pancreas reveals normal numbers of islets of Langerhans that may appear normal or that have deposition of amyloid.

D. The age of onset is usually over 30, hence the name "adult onset diabetes mellitus" but some cases may appear in younger persons.

E. Body habitus: usually obese (in about 80 to 90% of cases). Diet and exercise alone could control blood glucose in 10 to 20% of type II diabetics.

F. Major metabolic complication is hyperosmolar coma (non-ketotic diabetic coma): there is enough insulin to prevent burning of fatty acids, but not enough to keep the glucose from rising. Usually, there is dehydration from lack of adequate fluid intake coupled with an osmotic diuresis. The result is a markedly elevated blood glucose.

G. Typical laboratory findings with type II diabetes mellitus:

	Patient	Normal
Glucose	1000 mg/dl	<110
Sodium	144 mEq/L	135-147
Potassium	5.0 mEq/L	3.5-5.0
Bicarbonate	22 mEq/L	22-28
Urine Ketones	negative	negative
Osmolarity	380 mosm/L	275-295

H. Clinical findings of type II diabetes mellitus:

a. dehydration
b. clouded sensorium or coma
c. seizures

PREGNANCY AND DIABETES MELLITUS

A. The stress of pregnancy may lead to development of diabetes mellitus in mothers who have a predisposition toward diabetes, or mother may already be a diabetic. About 2.5% of live births are accompanied by maternal diabetes (5% for Native Americans).

B. The major problem is accelerated aging of the placenta, leading to placental insufficiency.

1. This risk increases as the pregnancy progresses, but is especially high >36 weeks gestation.

2. The problem: get the pregnancy out far enough to avoid complications of prematurity (such as hyaline membrane disease) while not waiting too long and risking intrauterine fetal demise.

C. Infant of a diabetic mother.

1. Baby tends to be large (macrosomia) due to the growth-enhancing effects of insulin.

2. After birth, baby may develop hypoglycemia because the baby's islets are increased in number and size from being in the maternal hyperglycemic environment.

3. There is a slightly increased risk for fetal malformation.

LONG TERM COMPLICATIONS OF DIABETES MELLITUS

A. The biochemical basis for complications is partially explained by:

1. Non-enzymatic glycosylation of proteins with hyperglycemia

a. advanced glycosylation end products accumulate, attach to arterial walls, link LDL cholesterol, and accelerate atherosclerosis. Macrophages may be stimulated to secrete TNF and IL-1.

b. this can be measured with hemoglobin A1C. HgbA1C gives an indication of diabetic control over a longer time than a single blood glucose measurement (because RBC's last for about 4 months).

2. Increase in sorbitol in cells of tissues not requiring insulin for glucose uptake. Hyperglycemia leads to increased glucose in such cells (e.g., retina, nerve, lens), conversion of glucose to sorbitol, and subsequent osmotic cell injury.

Aldose reductase acts on the first step of the polyol metabolic pathway to catalyze the reduction of glucose to sorbitol. Hyperactivity of the pathway in individuals with high blood glucose level is closely related to the onset or progression of diabetic complications. This may partially explain the neuropathy, retinopathy, and cataracts that appear with diabetes mellitus.

Aldose reductase inhibitors, such as fidarestat, may be a way of lessening the damage done via the polyol pathway.

B. Microangiopathy: thickening of the vascular basement membranes. Capillaries become more permeable. Hyaline arteriolosclerosis develops in renal arterioles. May or may not be accompanied by hypertension.

C. Accelerated atherosclerosis is present with the following features:

1. Earlier, more advanced, and more severe lesions than in non-diabetics

2. Hyperlipidemia is more frequent

3. HDL is degraded faster because it becomes glycosylated

4. LDL cholesterol attaches more readily to vessels, as do platelets

D. Infection is more frequent: hyperglycemia reduces leukocyte function; also, poorly perfused tissues are more prone to injury and poor healing.

ORGAN SYSTEM COMPLICATIONS OF DIABETES MELLITUS

Note: most of these organ system changes appear decades after onset of diabetes mellitus.

A. Heart: coronary atherosclerosis with myocardial ischemia and infarction are common. The most common cause of death in diabetics is acute myocardial infarction.

B. Kidney: chronic renal failure is a common complication

1. Glomerulosclerosis
2. Nephrosclerosis
3. Pyelonephritis and papillary necrosis

C. Brain: cerebral atherosclerosis contributes to the appearance of a “stroke”. This may also be a complication of cardiac disease.

D. Eye: ocular disease in diabetics often includes diabetic retinopathy, which is a common form of blindness; cataracts of the crystalline lens may appear; glaucoma (increased intra-ocular pressure) may appear.

About 90% of diabetic eye problems could be prevented by diagnosis and treatment of diabetes mellitus. 25,000 Americans go blind each year from complications of diabetes.

E. Peripheral nerve

1. Both sensory and motor peripheral nerves are affected, but the loss of pain sensation and touch is more significant.

2. Autonomic nerve dysfunction leads to:

a. abnormal gastrointestinal tract motility
b. hypotonic bladder and obstructive uropathy
c. impotence through failure of erection and ejaculation

F. Skin and soft tissues ("diabetic foot")

1. Extremities are more easily traumatized due to peripheral neuropathy

2. Tissues are slower to heal because of peripheral atherosclerotic vascular disease

3. Injured tissues are more prone to infection

4. Simple inspection of the feet for minor injuries could prevent about half of the 50,000+ amputations performed each year on diabetics.

FUTURE OF TREATMENT FOR DIABETES MELLITUS

A. The gene for human insulin synthesis has been utilized via recombinant DNA technology to manufacture pure, non-immunogenic human insulin in large quantity.

B. Efforts are underway to perfect the technique of islet cell transplantation.

CASE 1

History: The mother of a 15 year old girl schedules an office visit for her daughter with you. The mother is concerned because her daughter is consuming a large amount of food and yet does not appear to gain weight. Her daughter has also developed the habit of drinking a whole six-pack of diet Coke in an evening.

Question 1: Which of the following laboratory findings would you expect in this setting:

A. Increased plasma insulin

B. Decreased plasma glucagon
C. Urine ketones 4+
D. Serum osmolarity of 360 mosm
E. Decreased plasma hydrogen ion (alkalosis)

Question 2: She is at most risk in the coming year for:

A. Hyperosmolar coma
B. Acute myocardial infarction
C. Renal failure
D. Blindness
E. Ketoacidosis

CASE 2

History: A 57 year old man is 5'7" and weighs 264 lb. He has an ulcer on his foot that hasn't healed in 3 months following a 5 mile hike (his first attempt at exercise in years). A urinalysis shows 1+ protein and 3+ glucose.

Question 1: Which of the following best fits with this history:

A. Islet cell antibodies
B. Insulitis at some point in the past
C. Propensity for ketoacidosis
D. Normal or decreased blood insulin
E. Increased HDL cholesterol

Question 2: Which of the following renal lesions is LEAST likely to occur in this man:

A. Interstitial nephritis
B. Nodular glomerulosclerosis
C. Renal papillary necrosis
D. Renal arteriolosclerosis
E. Pyelonephritis

Question 3: Persons with diabetes mellitus for several decades are most prone to develop:

A. Chronic viral infections
B. Malabsorption
C. Dementia
D. Pulmonary fibrosis

E. Myocardial infarction

CASE 3

History: A 25 year old male diabetic has been on regular injections of insulin for the past 14 years. One morning, he does not show up at his scheduled time for work. Co-workers have an idea what may have happened, because of the fight with his girlfriend he described yesterday, at which time he was feeling fine. One co-worker grabs something from a desk drawer and heads to his house, where the young diabetic is found on the floor in a stuporous condition.

Question 1: What is the complication that occurred:

A. Acute myocardial infarction
B. Hypoglycemic shock
C. Ketoacidosis
D. Acute renal failure
E. Hyperosmolar coma

Question 2: What is the best laboratory test to indicate whether or not he has been in good control of his diabetes mellitus (on the prescribed diet and taking insulin on schedule):

A. Fasting blood glucose
B. Serum osmolarity
C. HgbA1C
D. Urinalysis
E. Serum C-peptide

Question 3: What did the co-worker take out of the desk drawer:

A. Insulin injection
B. Bottle of Glucola
C. Epinephrine injection
D. Bottle of Gatorade
E. Pamphlet with phone number for prior approval for hospitalization in his HMO

CASE 4

History: A 40 year old nurse has recently begun working an evening shift on 3 North. After about a week, she is suddenly and without warning found down in the supplies room a few minutes after eating lunch. The co-worker noted that she had been fine only a few minutes before when she had been eating lunch. She is admitted and found to have the following laboratory findings: serum glucose 32, sodium 135, potassium 4.5, bicarbonate 26, and osmolarity 285. Urine ketones are negative. She is given D50 and revives in a few minutes. She gives a history of frequent attacks of hypoglycemia. Her physician suspects that he can explain these findings with one laboratory test.

Question 1: What is the laboratory test the physician ordered:

A. Glucose tolerance test
B. HgbA1C
C. Plasma insulin
D. Serum C-peptide
E. HDL cholesterol

Question 2: Which of the following would not explain hypoglycemia:

A. Islet cell adenoma
B. Chronic pancreatitis
C. Factitious insulin administration
D. Prolonged fasting
E. Liver failure

CASE 5

History: A 71 year old female with NIDDM is found comatose by her nephew. She had phoned him just yesterday and stated, "I'm always alone and nobody ever visits me." He found out that she had not been feeling well for several days and had not been drinking much water and had been eating only some cookies.

Question 1: Which of the following is most likely to be present:

A. Markedly increased serum osmolarity
B. Insulitis
C. Serum glucose of 20 mg/dl
D. Increased HDL cholesterol
E. 4+ urine ketones

Key:

CASE 1:

1. C; this patient has IDDM; the plasma insulin should be decreased, the glucagon increased, the serum osmolarity slightly increased because of an increased serum glucose, and she should have acidosis because of the use of fatty acids in metabolism, leading to acidosis and urine ketones.

2. E; the complications of myocardial infarction, blindness, and renal failure take years to occur; hyperosmolar coma is a feature of NIDDM.

CASE 2

1. D; this patient has NIDDM (type II).

2. A; interstitial nephritis is not a feature of DM.

3. E; the MI would result from atherosclerosis of coronary arteries.

CASE 3

1. B; this describes a former colleague of mine who, following a fight with his girlfriend, would act out by not eating--but he would continue his regular insulin injections. This would lead to hypoglycemia. The other complications listed would be unlikely if he had been fine the day before. Heart disease would probably be seen at a later age. Given the age of onset of his disease, he probably has IDDM.

2. C; the HgbA1C measures the degree of glycosylation of RBC's; since RBC's survive an average 4 months, this gives a good indication of how much hyperglycemia has been present over time.

3. B; if he didn't show up to work by 10:00 we would send someone over to his house with a bottle of Glucola. Insulin must be refrigerated.

CASE 4

1. D; she did not give a history of diabetes mellitus; she does not have hyperosmolar coma or ketoacidosis; she has severe hypoglycemia but it is not for lack of food; if the hypoglycemia is due to increased endogenous insulin, then C-peptide should be present, but if the hypoglycemia is factitious, then C-peptide will be absent. Normally, the insulin to C-peptide ratio should be <1

2. B; chronic pancreatitis has the potential for wiping out islets as well as acini if the inflammation is severe enough. This would lead to IDDM.

CASE 5

1. A; she has hyperosmolar coma. The glucose can reach 800 mg/dl or more.

PATHOLOGY 6601, FALL 2006
NEOPLASIA
Morton H. Levitt, MD
Robert Oldham, MD

READING ASSIGNMENT: Pathologic Basis of Disease, (7th ed: 270-339)

LEARNING OBJECTIVES: At the end of the lectures , lab and small group, and reading assignment, the student will be able to:

1. Define what a neoplasm is and describe ways to determine if it is benign or malignant.

2. Describe the sequence of events from metaplasia to dysplasia to carcinoma and what controls them.

3. Outline and use a nomenclature for naming of neoplasms.

4. Describe what differentiation is and how it applies to grading of neoplasms.

5. Describe how neoplasms spread and how this applies to staging of neoplasms.

6. Describe how the following techniques are used to characterize neoplasms pathologically:

    light microscopy
    electron microscopy
    immunohistochemistry
    tumor markers (antigens)
    gene rearrangements
    flow cytometry
    microarrays

7. Describe the biology of:

    tumor origin (carcinogenesis and the factors that increase it)
    tumor growth
    spread of tumors

8. Define what an oncogene is and how oncogenes function in neoplasia.

9. Describe karyotypic (chromosomal) abnormalities in neoplasia.

10. Define paraneoplastic syndrome and describe clinical and pathologic findings that may occur with them.

11. Describe the major epidemiologic features of malignant neoplasms in terms of frequency, death rates, and changes in incidence over time.

12. Outline methods for treatment of neoplasia and why they work (or not).

DEFINITIONS AND BASIC CONCEPTS:

1. Normal growth and differentiation. Cells grow in an orderly manner. They go through the cell cycle which has been divided into several events

    In G1, mRNA is made for the proteins which will be used to synthesize DNA

    In S-phase, the cells DNA is made

In G2, mRNA is made which codes for the proteins necessary for cell division

In M-Phase (mitosis), cells divide.

2. Growth Alterations.

A. **Hypertrophy.** This refers to an increase in the size of cells which is reflected in an increase in the size of an organ. This is caused by increased workload or stimulation. It is not a neoplastic process.

B. **Hyperplasia.** This refers to an increase in the number of cells. This can only occur in tissues that have the ability to divide such as bone marrow.

Sometimes the increase in the size of an organ is due to both hyperplasia and hypertrophy such as occurs in the uterus during pregnancy.

Atypical hyperplasia can be a precursor to cancer.

C. **Metaplasia.** This refers to the phenomenon in which one mature cell type is replaced by another mature cell type.

The most common is the change from columnar epithelium to squamous epithelium. This commonly occurs in the uterine cervix and the lung and is probably an adaptive event since it generally follows chronic irritation. Functional deficits may result. For example, the lack of cilia and mucus production associated with squamous metaplasia in bronchi may predispose to pulmonary infections.

Metaplasia can be the first step toward neoplasia, when followed by dysplasia.

D. **Dysplasia.** This refers to an abnormality of differentiation and maturation with disorderly growth of cells in epithelial linings. Dysplastic cells have nuclear abnormalities, cytoplasmic abnormalities, increased rate of cell multiplication and show a disordered maturation sequence.

Dysplasia is generally felt to be a **pre-malignant** process. It is associated with a high risk of invasive cancer. Consequently, if dysplastic epithelium is removed, your patients risk of subsequently developing cancer is decreased.

E. **Neoplasia.** The term is from Greek (Neo=new and plasia=growth). Neoplasms are commonly recognized by the formation of abnormal tissue masses called tumors, although the term "tumor" can be applied to any swelling.

Whereas all of the above growth disturbances have some type of defined stimuli controlling them, neoplasms grow independently and are uncontrolled by normal physiologic processes.

There are many different kinds of neoplasms and it is necessary to distinguish all of these types for reasons of establishing prognosis and selecting therapy.

There are two main categories of neoplasms; those that are **benign** and those that are **malignant**.

In general, benign neoplasms are slower growing, remain localized, will not invade underlying tissue, will not metastasize, and can often be completely removed by surgical excision.

Malignant neoplasms tend to be faster growing, irregular in shape, will invade and destroy underlying and surrounding tissues, will metastasize (spread throughout the body) and may be difficult to control. Malignant neoplasms will kill your patient if they are not adequately controlled.

There is a semi-consistent nomenclature used to refer to neoplasms:

Benign neoplasms are indicated by the suffix "oma".

Malignant neoplasms of epithelial tissues are referred to as **carcinomas**

Malignant neoplasms of mesenchymal (stromal) tissues are referred to as **sarcomas**

There are exceptions:

Teratomas arise from totipotential germ cells and can differentiate into tissues of the embryo. They are usually benign in the ovary but malignant in the testis.

Blastomas are neoplasms of primitive embryonic cells usually found in infants and children.

Melanomas are malignant tumors of melanocytes.

Lymphomas are malignant tumors of lymphoid cells.

Hepatomas are malignant tumors of hepatocytes and should probably be

referred to as hepatocellular carcinomas.

Gliomas (e.g., astrocytoma) are malignant tumors of the glial supporting cells of the central nervous system.

THE NATURE OF NEOPLASIA

I. MORPHOLOGIC FEATURES:

A. **Differentiation**. Differentiation refers to the degree that a neoplasm resembles its cell of origin.

Well differentiated means the neoplasm has a close resemblance to its normal counterpart, the cell of origin. A lipoma looks just like mature adipose tissue.

Poorly differentiated means there is only a distant resemblance and it might not even be possible to determine by light microscopy the cell of origin. Malignant tumors tend to have less differentiation.

All benign neoplasms are well differentiated. Malignant neoplasms may be well differentiated but also may be moderately differentiated or poorly differentiated.

The term anaplasia is sometimes used for a malignant neoplasm that is so poorly differentiated that it is hard to tell what the cell of origin is. Such tumors tend to be very aggressive.

B. **Cytologic features of malignant neoplasms.** Malignant cells tend to be pleomorphic. They vary in size and shape. The nuclei of malignant cells also have a pronounced tendency to show variation in size and shape.

Malignant cells may show a high nuclear to cytoplasmic (N/C) ratio. Many times the chromatin in a malignant cell is irregular and appears clumped. the high DNA content also makes the nuclei stain darker, and they are called hyperchromatic.

Malignant cells also may have prominent nucleoli and mitotic figures may be quite abundant.

These cytologic features are clues that aid pathologists in diagnosing malignancy.

C. **Architectural features of malignant neoplasms.** The cells in a malignant neoplasm show loss of normal orientation. They grow without well defined boundaries. This can result in a disorganized mass of tissue.

D. **Ultrastructural features of malignant neoplasms.** There are no diagnostic clues from electron microscopy as to whether a neoplasm is benign or malignant.

Ultrastructural analysis of a neoplasm can help determine lineage (the cell of origin). For example, if a poorly differentiated neoplasm is found to have some melanosomes by electron microscopy, this might indicate the neoplasm is a melanoma. Separation of a melanoma from other malignant neoplasms is important for clinical management.

E. **Stroma.** The stroma surrounding a neoplasm can vary greatly from very little to abundant dense connective tissue. It is thought that some neoplasms induce normal fibroblasts via growth factors to produce abundant collagen, called desmoplasia.

This yields a dense connective tissue stroma in which the malignant cells grow. This is referred to as a **desmoplastic response**. Breast cancers commonly do this. Such cancers are sometimes described as "scirrhous". This makes the neoplasm feel hard on palpation.

SPECIALIZED DIAGNOSTIC TECHNIQUES:

In order to determine the cell of origin of a neoplasm to help determine appropriate therapy, a variety of techniques can be applied. Formost among these is immunohistochemistry, which involves using specific antibodies to cellular components of tissues obtained cytologically, on biopsy, or in resected specimens from surgical procedures. The results are viewed by light microscopy.

A. **Intermediate filaments.** These represent a class of cytoskeletal proteins that show lineage restrictions.

Cytokeratins are a group of cytoskeletal proteins found in epithelial cells. They generally are not found in cells of mesenchymal origin.

Antibodies against cytokeratins can be used to stain human tissues. If a poorly differentiated neoplasm shows reactivity towards the cytokeratins, this suggests that the neoplasm is of epithelial origin (carcinoma).

Alternatively, vimentin is an intermediate filament common to mesenchymal tissues. A tumor showing reactivity towards vimentin may be of mesenchymal origin (sarcoma).

B. **Tissue specific antigens.** Many tissues and cells express specific antigens.

Lymphocytes express a surface glycoprotein referred to as leukocyte common antigen (LCA).

Prostate tissue expresses prostate specific antigen (PSA) and prostate specific acid phosphatase (PAP).

Thyroid expresses thyroglobulin.

Cells of neural origin may express S-100 or neuron specific enolase (NSE).

Melanomas may express HMB-45 or Melan-A.

Cells of glial origin may express glial fibrillary acidic protein (GFAP).

Sometimes cancers derived from a specific tissue will still express the tissue specific antigen, even when poorly differentiated or when metastatic. For example, prostate cancers many times will still express PSA.

Unfortunately, the antibodies are not completely specific for a particular tumor type, and the cells may not express the antigen. Panels of antibodies can be performed to try and determine the cell of origin.

C. **Gene rearrangements.** Molecular biology is now finding its way into diagnostic pathology. This is most noticeable in the diagnosis of the lymphomas. Many lymphomas recapitulate the normal process whereby a lymphocyte rearranges its immunoglobulin genes or T-cell receptor genes in order to generate the diversity found in response to many antigens.

Since lymphomas are clonal, all tumor cells show the same gene rearrangement. This rearrangement can be detected by Southern blot analysis and yields data both on the lineage of a particular neoplasm as well as indicating clonality.

D. **Flow cytometry.** Flow cytometric analysis of neoplasms analyzes DNA content. This yields information on the fraction of cells in S-phase as well as the chromosome content.

Neoplasms which have a high S-phase value and/or an odd number of chromosomes (aneuploidy) tend to be more aggressive and may require more aggressive therapy. This information is now routinely being obtained on breast carcinomas as well as other neoplasms.

E. **Microarray technology.** A microarray is a slide which contains thousands of DNA sequences of known genes. Messenger RNA from a tumor is isolated and copied into cDNA. The cDNA is then applied to the microarray slide and hybridized.

The genes which are expressed in the tumor, and therefore copied into cDNA, can be determined by seeing which microarray sequences the tumor cDNA hybridizes to. In this way, the expression of thousands of genes in a tumor can be studied.

Microarray technology is being used to classify human cancers based on gene expression.

GROWTH AND SPREAD OF NEOPLASMS:

A. **Clonal origin.** Neoplasms probably are derived from a single cell. This is true both of benign and malignant tumors. Evidence for this includes:

Multiple myeloma: Patients with multiple myeloma, a malignancy of plasma cells, excrete a single immunoglobulin in their urine.

Uterine leiomyomas in women who are heterozygous for different alleles of glucose-6-phosphate deydrogenase (G6PD) express either one or the other allele, but not both.

Lymphoma: As discussed above, many lymphomas show a single rearranged immunoglobulin or T-cell receptor gene.

B. **Growth rate.** In general, benign neoplasms grow slowly and malignant ones grow fast although there are many exceptions. Fibroadenomas of the breast, for example, may increase rapidly in size during pregnancy.

The more poorly differentiated a cancer is, usually the faster it grows.

C. **Style of growth.** Benign neoplasms expand and many are surrounded by a fibrous capsule or compressed normal tissue ("pseudocapsule"). They tend to be well demarcated and freely mobile (not attached to surrounding structures). This can be appreciated during palpation on physical exam.

Malignant neoplasms invade surrounding or underlying tissue. Their borders are not well defined and they can be difficult to demarcate on physical exam. Their invasiveness means that they are not freely mobile (they tend to be fixed to surrounding structures).

TUMOR INVASION AND METASTASIS:

A. **Tumor cell attachment.** To invade tissues, cancers must first be able to attach to the basement membrane. Laminin is a basement membrane glycoprotein.

Some cancers have increased laminin receptors on their cell surfaces. This may allow them to attach more readily to basement membranes.

B. **Matrix degradation.** In order for cancers to penetrate and move into underlying stroma, they must degrade it. It is becoming apparent that highly invasive and aggressive cancers secrete a variety of degradative enzymes which destroy tissue.

Some of these enzymes may turn out to be diagnostically useful. For example, cancers producing high levels of cathepsin may be more aggressive than those that do not and these cancers might need to be treated more aggressively.

C. **Tumor cell locomotion.** Obviously tumor cells must be able to move in host tissue if they are invasive. Little is known as to what controls this. Perhaps chemotactic factors may be important.

D. **Metastatic spread.** Metastasis is a highly selective process. It may be that only one cancer cell out of many is endowed with metastatic potential. Such a cell must be able to penetrate microvasculature and attach to vascular endothelium.

Once in the metastatic site, the cancer cell must penetrate the stroma of the foreign organ and then grow as an independent colony in an environment quite different from that in the tissue of origin.

ONCOGENES AND NEOPLASIA

There are many genes involved with the process of cellular proliferation. Many of these genes were active in embryonic life as cellular division, differentiation, and growth occurred. Some of these genes continue to function in some capacity throughout life. If such genes are inappropriately turned on or are not suppressed, or if abnormal growth genes are introduced into the genome, then there is loss of growth control. In such situations, a neoplasm can occur.

RETROVIRUSES:

A retrovirus has an RNA molecule as its genome. As part of its life cycle, the RNA gets converted to DNA by the action of reverse transcriptase. The DNA can then get incorporated into the host chromosome.

Retroviruses can cause tumors in many animals. The question as to how a retrovirus can cause cancer in an animal is fundamental to our understanding of carcinogenesis. In studies with cells in culture, it was found that retroviruses generally transform a cell (cause it to become malignant) over a period of several months. However, occasionally a retrovirus was found that can transform a cell in a matter of days.

These latter viruses were found to contain a single, novel gene that when expressed in a animal cell, caused the cell to become malignant. This gene was therefore referred to as an oncogene.

Much effort has been put into the study of how oncogenes work and although RNA viruses probably play only a minor role in human malignancies, what we have learned from viral oncogenes has revolutionized our understanding of human malignancies.

II. SRC ONCOGENE AND THE THEORY OF ONCOGENESIS:

This is the oncogene of the Rous Sarcoma Virus (RSV) and was the first oncogene to be amenable to scientific experimentation. The src oncogene codes for a protein kinase. A kinase is an enzyme which attaches phosphate to proteins.

The src protein is a tyrosine kinase which makes it somewhat different than other kinases found in cells.

When cells are transformed by RSV, the level of phosphotyrosine goes up 10-fold which is an indicator of src activity. It now appears that one target of the src kinase is vinculin which is found

in cellular adhesion plaques. These are areas in which cells are anchored to surfaces.

By phosphorylating vinculin, adhesion plaques are disrupted and cells can now grow without anchorage to solid supports. Anchorage independent growth is a hallmark of malignant cells.

Where did the src gene come from? The oncogene hypothesis, first expounded by Huebner and Todaro in 1972, states that oncogenes are in fact derived from normal cellular genes. These genes may be activated or changed, but all oncogenes have a normal counterpart in non-transformed cells.

During evolution, retroviruses have apparently incorporated these cellular genes into the viral genome. When in the virus, the src gene is referred to as v-src. Its counterpart in normal cells is referred to as c-src. In normal cells, c-src is made in small amounts and is non-transforming, however, when carried on a viral genome during infection, v-src is made in high amounts and is able to transform cells.

If the oncogene hypothesis is true, then DNA isolated from normal, non-malignant cells should contain the src gene. With the new techniques of molecular biology it has now been possible to answer this question. It turns out that DNA isolated from non-malignant cells does indeed contain the src oncogene, which suggests the oncogene hypothesis is true.

This suggests that we probably all carry genes, that if inappropriately turned on or mutated, can cause cancer. This was a major insight into our understanding of the nature of the malignant cell.

RAS ONCOGENE:

Some human cancers have been found to contain oncogenes. If DNA from normal, non-transformed cells is incubated with mouse fibroblasts, the mouse cells take up the DNA but nothing abnormal happens to the cells. If, on the other hand, mouse fibroblasts are incubated with DNA derived from certain human cancers, the mouse cells take up the DNA but become malignant.

This says that the DNA isolated from some human cancers contains a gene that when introduced into a normal mouse cell, causes that cell to become cancerous. For human bladder cancers, that gene is related to the oncogene of the rat sarcoma virus (RAS).

The normal ras gene product is a GTP binding membrane protein. It probably has something to do with transmitting signals from the outside of the cell to the inside. In performing this function, it hydrolyzes GTP; it is a GTPase.

When ras becomes oncogenic, it appears to have acquired certain mutations that prevent the protein from hydrolyzing GTP. This keeps the cell in a "turned on" or transformed state. This is an example how a single mutation can activate a normal cellular gene and cause it to become an oncogene.

CHROMOSOMAL TRANSLOCATIONS AND ONCOGENE ACTIVATION:

For a long time it has been known that many human cancers are associated with chromosome translocations in which a portion of one chromosome is transferred to another. Only recently has the significance of some of these translocations become clear.

Burkitt's lymphoma is a common lymphoma in Africa. This tumor is characterized by a specific chromosomal translocation.

A portion of 8 joins up to 14 and a portion of 14 joins up with 8. This is a balanced translocation. As scientists were beginning to understand what oncogenes were, they became interested in Burkitts lymphoma because a particular oncogene, c-myc, is located on the portion of chromosome 8 that gets translocated to chromosome 14.

C-myc codes for a nuclear protein that probably has something to do with DNA synthesis. Normally it is made in very small amounts but when translocated to chromosome 14 it comes under an active promoter and its expression is greatly elevated.

Only when c-myc is expressed in high amounts, does it become oncogenic. This is reminiscent of the src gene.

Another chromosomal translocation that was known for a long time is the 9 to 22 translocation that characterizes chronic myelogenous leukemia (CML).

This is sometimes referred to as the Philadelphia chromosome. In this case, an oncogene, c-abl, is translocated from its normal position on chromosome 9 to chromosome 22.

When spliced to genetic material on chromosome 22, it now codes for a protein which is

about 60,000 daltons higher in molecular weight. Interestingly, this hybrid protein now has an active tyrosine kinase which the normal, unspliced c-abl did not have.

ONCOGENES AND ANTI-ONCOGENES:

In recent years data have been accumulating which indicates that some cellular genes function by keeping cell growth under control. As long as these genes are functional, cells grow normally. These genes have been called anti-oncogenes or tumor suppressors.

Thus if a cell loses a tumor suppressor gene either by mutation or deletion, the cells growth will no longer be held in check and a cancer results. Retinoblastoma gene product is an example of a tumor suppressor gene. Retinoblastoma results when this gene is inactivated. Since there are two alleles, both normal copies must be lost.

Another example is the **p53** protein. This protein is a 53 kilodalton molecule which functions in the nucleus of a cell as a tumor suppressor. Mutations in this protein are one of the most common genetic alterations found in human cancers.

One of the most fascinating aspects of the tumor suppressor story is how some virsuses are able to transform cells. The oncogenes so far discussed are mainly limited to the RNA tumor viruses.

There also exist in nature DNA tumor viruses. These viruses also contain oncogenes but these genes function in a different manner than do the oncogenes of the RNA tumor viruses.

From biochemical studies, it was found that the oncogenes of the several DNA tumor viruses function by binding the p53 protein and/or the retinoblastoma gene product. This effectively removes these tumor suppressor molecules from the cell resulting in a malignant phenotype.

The human papilloma virus (HPV), which is associated with cervical cancers and dysplasias, is a DNA virus which uses this mechanism of transformation.

CLINICAL ASPECTS OF NEOPLASTIC DISEASE

TUMOR PROGRESSION:

Tumors are clonal. However, by the time they have grown to be clinically evident, the mass of tumor cells is quite heterogeneous. There has been plenty of time for additional mutations to develop and additional clones with different characteristics to arise. As an example, by the time a breast cancer can be felt by palpation, about 1 cm in size, it may have been present 7 years and there are billions of cancer cells present.

You can appreciate this easily if you look at a neoplasm under the microscope. The neoplasm is not homogeneous even though the cells all had the same parent. Some areas of the tumor may be well-differentiated while other areas of the tumor may be poorly differentiated.

Since microenvironments differ, the tumor cells, although all derived from a single clone, undergo the process of natural selection.

The end result is a very heterogeneous population of malignant cells.

This process of natural selection occurring in cancers can be illustrated by considering the case of a kind of lymphoma known as a follicular lymphoma (because it has cells similar to those in lymph node follicles):

> All of these lymphomas have a basic underlying defect which is a translocation of the Bcl-2 oncogene from chromosome 18 to chromosome 14. Bcl-2 is an oncogene, which when activated, prevents cell death.
>
> Generally, follicular lymphomas with just the Bcl-2 activation are low-grade tumors. However, with increasing accumulations of genetic defects, the initial low-grade follicular lymphomas become intermediate to high grade in their clinical aggressiveness. Even the high grade tumors, however, which can sometimes no longer be recognized as a follicular lymphoma, still retain the initial Bcl-2 translocation.

PARANEOPLASTIC SYNDROMES:

This refers to distinct symptom complexes that occur in cancer patients. They may appear in 10-15% of patients with neoplastic disease. The effects of paraneoplastic syndromes are sometimes apparent even before the malignancy is.

The most common and best understood paraneoplastic effects are the endocrine abnormalities that result from the production of a hormone or hormone-like substance by tumor cells. This is sometimes referred to as ectopic hormone production.

> One of the most common types of ectopic hormone production is seen in patients with lung cancers. Many times lung cancers will produce ACTH like hormones which can

result in adrenal hyperplasia, excessive corticosteroid production, and Cushings syndrome. Therefore, if you are seeing a patient who has Cushings syndrome, remember that one possible mechanism for this is ectopic hormone production by a cancer.

Hypercalcemia is another clinical finding that can be seen in patients with malignant disease. Sometimes it is due to bone destruction by metastatic disease, but sometimes it is due to ectopic hormone production by a neoplasm. Lung cancers, kidney cancers, and breast cancers sometimes do this.

Carcinoid syndrome is characterized clinically by flushing of the skin, intestinal hypermotility resulting in vomiting and diarrhea, and bronchoconstrictive attacks. These clinical symptoms are secondary to peptide hormone production by carcinoid tumors. Carcinoid tumors are malignant tumors that arise from neuroendocrine cells that populate the lung and gastrointestinal tract.

TUMOR RESISTANCE TO CHEMOTHERAPY:

Although many types of cancers are intially sensitive to drug therapy, a recurring problem is that eventually the tumors cells become drug resistant. This led to the idea of combination chemotherapy in which patients are treated with multiple drugs at the same time. The idea was that the chance of a tumor cell becoming resistant to multiple drugs at the same time should approach zero.

Although some cancers are curable with drug therapy, many others eventually develop resistance to all of the drugs. The basis for this resistance has been studied with cell culture techniques. Surprisingly, it was found that if a malignant cell develops resistance to drug A, it may also be resistant to drugs B, C, and D even though the cell had never been exposed to these latter drugs.

What may be happening is that a membrane protein, called P-glycoprotein, becomes elevated in the resistant cell. P-glycoprotein acts as a pump to pump toxic compounds out of the cell. It is somewhat nonspecific and will pump a variety of drugs out of the cell. This would explain why a tumor cell which becomes resistant to one drug by elevating its level of P-glycoprotein, may also demonstrate resistance to another drug that it had never been exposed to. Current research is now focusing on overcoming P-glycoprotein resistance.

There is another class of drugs that cells show resistance to which are now known to target the enzyme DNA topoisomerase II. This is a nuclear enzyme which untangles DNA at the end of mitosis. The drugs that target topoisomerase II freeze the enzyme as it is cutting DNA strands. This leads to DNA strand breakage and cell death. Resistant cells in culture show alterations in the topoisomerase II protein. It is not yet clear what role this enzyme plays in the resistance seen in the clinic.

TELOMERES, TELOMERASE, AND CANCER

Telomeres are repetitive DNA sequences at the ends of chromosomes. They probably serve to protect the chromosomes from being degraded or from undergoing illegitimate recombination. The extreme ends of a chromosome (the telomers) can not be entirely replicated by DNA polymerase because this enzyme requires an RNA primer for DNA synthesis. The RNA primer at the chomosomal ends is never replaced. This leads to progressive chromosomal shortening with each cell division. It has been suggested that progresssive chromsomal shortening represents a type of biologic clock. A cell can undergo only a limited number of divisions before the telomeric ends of the chromosome are gone, with catastrophic consequences for the cell.

Telomerase is a ribonucleotide protein that synthesizes telomeric chromosomal ends. It can, therefore, replenish telomeric ends that have become shortened with each cell division. Telomerase activity has been observed in many different types of human cancers, but not in normal cells or tissues. This suggests that the "immortality" of a cancer cell may be related to the presence of telomerase. It also suggests potential novel types of anticancer therapy.

GRADING AND STAGING OF NEOPLASMS:

For oncologists treating patients, it is useful to semi-quantitate the extent of neoplastic disease. This allows a way of predicting outcome and arriving at an appropriate therapy.

Tumor grade and tumor stage are two different terms.

Grade refers to how differentiated the tumor is and is many times indicated by:

grade 1 (well differentiated)

grade 2 (moderately differentiated)

grade 3 (poorly differentiated)

In general, grade 3 cancers have a worse prognosis than grade 1 cancers.

Stage refers to how large and extensive the malignancy is. A common way to stage cancers is with the **T** (tumor) **M** (metastasis) **N** (node) system. This varies somewhat from cancer to cancer but in general:

T goes from T1 to T4 with increasing size

N goes from N0 to N3 depending on whether lymph nodes are involved and how close they are to the primary site

M goes from M0 to M1 depending on whether metastases are present.

The treatment of a cancer may be different depending on the stage of the disease.

In the future, oncogenes and anti-oncogenes may also be included in the evaluation of a cancer patient. These proteins may yield important information concerning therapy. For neuroblastoma, the number of copies that the tumor has of the oncogene N-myc is the best indicator of clinical response.

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STUDY HANDOUT
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Oncology I - Colon Cancer

Colon Cancer Incidence

- 150,000 cases per year (USA)
- 55,000 deaths
- 1/20 persons affected sometime in their lifetime
- Third most common cause of death from cancer

Worldwide incidence

- Varies by region: In North America:

  44.3 cases/100,000 for males

  32.8 cases/100,000 for females

1930-1995 Age-adjusted death rate

- Has not changed significantly over several decades
- 20 to 25/100,000 for males

Risk factors for Colon Cancer:

- General - Age > or = 40

- Genetic
  - -Familial adenomatous polyposis (FAP)
  - -Gardner, Oldfield, or Turcot syndrome
  - -Peutz-Jehgers syndrome
  - -Hereditary non-polyposis colorectal cancer (HNPCC)
    - Lynch 1 syndrome
    - Lynch 2 syndrome

- Pre-existing
  - -Inflammatory bowel disease
  - -Colorectal cancer
  - -Pelvic cancer after irradiation
  - -Neoplastic colorectal polyps

Risk factors for Colon Cancer

- Familial adenomatous polyposis (FAP):
  - – Several syndromes described (Gardner, Turcot, etc.)
  - – All caused by mutations in the adenomatous polyposis coli (APC) gene
  - – Thousands of adenomatous polyps (tubular adenomas) develop during first decade of life.
  - – Invasive cancer develops in second to fourth decade

- Hereditary Non-Polyposis Colon Cancer (HNPCC):
  - – Other names : familial cancer (Lynch) syndrome
  - – Multiple cancers at multiple sites, including colon

- Onset in second to fourth decades
- Modest increase in the number of colon polyps
- Caused by mutations in 4 different DNA repair genes: MSH2, MLH1, PMS1, PMS2 (?)

Role of Prostaglandins

- Prostaglandins: metabolites of long-chain fatty acids (arachadonic acid)
- Synthesis controlled by cyclo-oxygenases:
  - two forms: COX1, COX2, both inhibited by ASA
  - COX1 is expressed constitutively
  - COX2 expression increases in tumors
- Selective COX2 inhibitors inhibit polyp formation in APC animals

Colon Cancer: Prevention

- Non-selective COX1/2 inhibitors:
  - Low-dose ASA prevents coronary artery disease (antiplatelet action)
  - Low-dose ASA has no detectable effect on colon cancer risk (Physician's Health Study)
  - NSAIDs reduce polyp number in APC patients
- Selective COX2 inhibitors
  - No antiplatelet effects
  - Clinical trials testing effectiveness in colon cancer prevention in general population are in progress

Role of Prostaglandins: Model Systems

- Sulindac in APC patients
- Selective COX2 inhibitors inhibit polyp formation in APC animals:
  - Oshima et al. Cell 1996 87:803-809
  - APC +/-, COX2 +/+ : 652 polyps at 10 weeks

– APC +/-, COX2 +/- : 224 polyps at 10 weeks

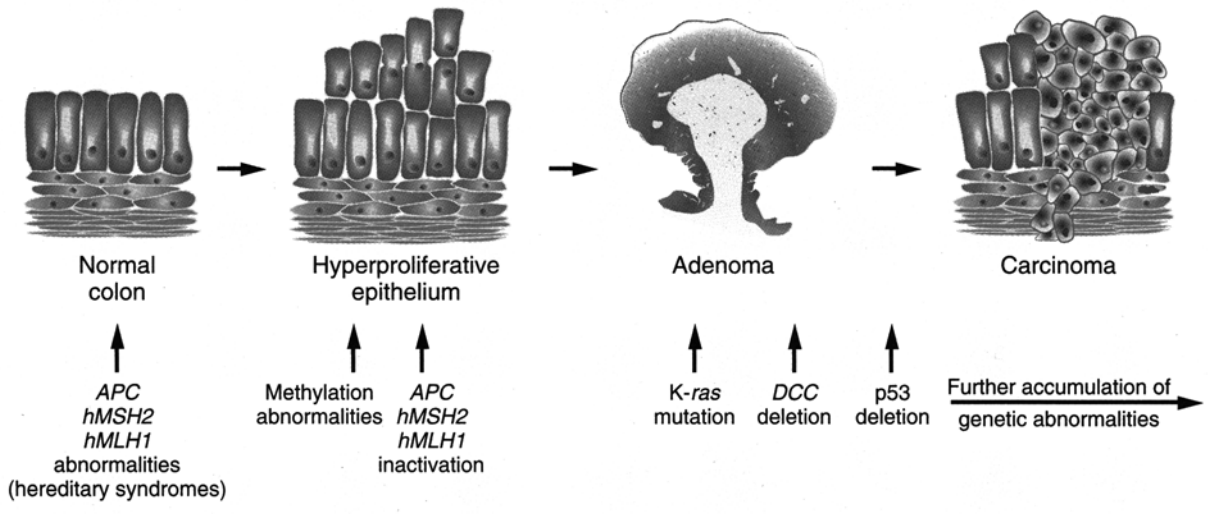
– APC +/-, COX2 -/- : 93 polyps at 10 weeks

– APC +/-; COX2 inhibitor: 161 polyps at 10 weeks

Colon Cancer - Tumor Progression

- Hereditary syndromes
  - "First hit" is germline; others acquired
- Non-hereditary syndromes
  - All "hits" acquired
- Sequence:
  - Normal epithelium; Pre-neoplastic epithelium; Adenomatous polyp; Carcinoma in situ; Invasive carcinoma; Metastatic carcinoma

Colon Cancer Progression



Colon Cancer Progression - Rationale for early diagnosis

- The earlier the stage at detection, the better the outcome:

- Fewer tumor cells
- Fewer genetic changes in the tumor cells
- Tumor cells remain in a localized area

Colon Cancer Screening

- Endoscopy:
  - Look for early cancers, or cancer precursors
  - Many are visible on flexible sigmoidoscopy 40-50 cm from rectum
- Fecal occult blood testing:
  - Testing of stool samples for blood
  - Guaiac test

Why do tumors bleed?

- Tumor neovascularization
  - Fundamental property of all invasive cancers
  - Cancer cells produce angiogenic factors
    - Basic fibroblast growth factor (bFGF)
    - Vascular endothelial growth factor (VEGF), etc.
  - New vessels are more friable or more numerous than normal blood vessels, and therefore more likely to bleed

Randomized Trials of Screening I: The Minnesota Trial

- Mandel et al., NEJM 1993 328:1365-1371
  - 46,551 volunteers, 50-80 years of age;
- 5 years intervention; 13 years total follow-up
  - Hemoccult slides, with hydration
  - 90% of subjects completed at least one screening
- 59.7% completed all screening

- 12,246 colonoscopies were performed (38%)
- 33% reduction in colorectal cancer mortality

Randomized Trials of Screening II: The Danish Trial

- Kronberg et al., Lancet 1996 348:1467-1471
  - 61,933 subjects; population-based; 45-75 years
- 10 years intervention and follow-up
  - Hemoccult II slides; no rehydration
  - 67% of subjects completed at least one screening
- 46% completed all screening
  - 892 colonoscopies were performed (4.3%)
  - 18% reduction in colorectal cancer mortality

Screening Sigmoidoscopy

- Widely used
- Several randomized trials show increased detection of tumors at curable stages
  - All trials to date in Europe
- Several randomized trials in progress to determine the effect on mortality from colon cancer

Residual Controversies

- Frequency of FOB screening: ?two years
- Age; other morbid conditions
  - < 75 years; life expectancy > 3-5 years
- Cost:
  - $10,000 - 20,000 per year of life
  - $200,000 per prevented death
- Newer screening tools:
  - "Viritual colonoscopy"

Screening (average risk at age ≥50, no known risk factors)

- DRE with fecal occult blood testing every year
- One of the following:
  - Sigmoidoscopy every 5 years
  - Double-contrast barium enema every 5 to 10 years
  - Colonoscopy every 10 years

Colon Cancer: Staging

- TNM Staging
- Tumor
  - T1: Submucosa
  - T2: Muscularis
  - T3: Surrounding fat
  - T4: Peritoneal cavity or adjacent organs
- Nodes: N0, N1 (1-3), N2 (>3), N3 (central)
- Metastases: M0, M1

Disease Stage at Time of Diagnosis

● Stage I	15%
● Stage II	20 - 30%
● Stage III	30 - 40%
● Stage IV	20 - 25%

Prognostic Factors

- Stage
- Invasion of blood / lymphatic vessels
- Number of involved local lymph nodes
- Tumor has penetrated or perforated bowel wall

Unfavorable Prognostic Factors for Colon Cancer

- Obstruction of large bowel or rectum
- Pelvic / abdominal lymph node involvement
- Invasion of veins / lymphatics of bowel
- Tumor cells poorly differentiated
- Abnormal chromosome pattern of tumor cells
- Higher serum carcinoembryonic antigen (CEA) levels post-operatively
- Tumor cell DNA abnormality
- Tumor has invaded or adhered to other parts of the pelvis or adjacent tissues
- Tumor is deeply ulcerated
- Tumor encircles the rectal wall
- Tumor is > 6 cm in size

Colon Cancer: Therapy

- Local therapies:
  - Affect disease in the colon and ?surrounding lymph nodes
  - Colonoscopic resection: very early disease
  - Surgery: wide excision, when possible
  - Radiation therapy: rectal disease
- Systemic therapy:
  - Affects disease both within and outside the local treatment field
  - Chemotherapy

Sites and frequency of distant metastases

Liver	38-60%
Abdominal lymph nodes	39%
Lung	38%
Peritoneum	28%

Ovary		18%
Adrenal glands	14%	
Pleura		11%
Bone		10%
Brain		8%

Colon Cancer: Summary I

- Hereditary colon cancer provides clues to genetic changes occurring in sporadic colon cancer
- Modulation of colonic epithelium by diet or COX2 inhibitors may be useful in prevention

Colon Cancer: Summary II

- Tumors undergo genetic progression as they grow:
  - Importance of early detection
- Tumors bleed more easily because of neovascularization:
  - Usefulness in FOB screening
- Progress in colon cancer occurs by the interaction between basic science concepts and clinical trials

PATHOLOGY 6601, FALL 2006
Oncology II - Lung Cancer

Lung Cancer: Incidence

Most common cause of death from cancer in both males and females

Male death rate: 80/100,000/year

– Rate of increase has leveled and may be declining

Female death rate: 35/100,000/year

– Rate of increase continues to climb

Lung Cancer-Epidemiology I

Almost all cases occur in **smokers**

Other causes usually superimposed on a history of heavy smoking

– Uranium mining: Radon daughters

– Asbestos exposure

Mining, shipbuilding, construction

Air pollution: No role in causation

Lung Cancer: Genetics

No clear Mendelian pre-neoplastic syndrome(s)

Populations studies show familial segregation

– ? Environmental

– ? Genetic

Association between lung cancer and COPD in sibships - ?mechanism unclear

Lung Cancer: Epidemiology II

Evidence for the causative role of smoking is primarily statistical and there are five epidemiological criteria:

– **Consistency** of the association

– **Strength** of the association

– **Specificity** of the association

– **Temporal** association

– **Coherence** of the association

Consistency of the association

– Presence in various populations, at different times

– 1. Different populations with a low incidence of smoking all show low cancer rates:

Ethnic groups: Asians, Pacific Islanders, American natives (historically)

Religious groups

– 2. Different populations with a high incidence of smoking all show high cancer rates:

US men, latter half of the 20th century

– 3. As smoking rates in population increase (or decrease) over time, cancer rates increase (decrease) over time

Strength of the association

– Dose-response curve

– Duration of exposure (years)

– Intensity of the exposure (packs/day)

– "Pack-year" statistic

Specificity of the association:

– Association with a specific set of exposures:

Only smoking (and a small list of additional carcinogens) causes lung cancer

– Association with a specific set of cancers

Temporal relationship of the exposure

– Prolonged exposure (years) is required.

– Incidence is reduced in former smokers

– Incidence in increases in recent former smokers (< 1 year)

– Incidence never falls to level observed in lifetime non-smokers

Lung Cancer: Carcinogenesis

Smoking-related cancers provide a model for chemical carcinogenesis in general.

Model:

– Chemicals in smoke cause mutations in lung epithelial cell DNA.

– Mutation rate is dose-dependent.

– Mutations are irreversible.

– Mutations that affect genes involved in cellular growth control produce a selective growth advantage.

Chemical Carcinogenesis I

Multiple carcinogens are present in tobacco smoke

– Polycyclic hydrocarbons

e.g., Benzo(a)pyrene

– Polycyclic amines (nitrosamines)

e.g., o-aminoazotoluene

e.g., 2-napthylamine

– Other factors

– Nicotine has minimal carcinogenic properties

Chemical Carcinogenesis II

Carcinogens must be activated

– Locally: in epithelial cells

– By hepatic metabolism

Cytochrome p450 system

Activation/inhibition by diet/drugs/age/environment

Polymorphisms influence activity

– ethnic, inter-individual variation

Activation produces chemically active intermediates

– "ultimate carcinogen"

Chemical Carcinogenesis III

Carcinogen metabolites affect DNA

1. Base-pair adducts

– e.g., Benzo(a)pyrene - deoxyguanosine adducts

2. Methylation

– e.g., N-nitrosamine produces methylation of deoxyguanosine at the O6 position.

3. Deamination

– e.g., 5-methylcytosine deamination

Others

Lung Cancer: K-RAS oncogene

One of 4 oncogenic RAS genes

GTPase

Oncogenic mutations destroy GTPase activity: Codons 12, 13, 61

Mutated in 30-50% of lung cancers

Most common mutation: ^{12}Gly ^{12}Val codon: GGN to GTN

Typical of mutations induced by nitrosamines

Lung Cancer: TP53 mutations

p53 is a DNA-binding protein with transcriptional activation activity

Mutated in 50% of lung cancers

Approximately 2/3 of mutations occur at the C of CpG

– Hotspot: codon 273

– Methylation of C is a normal event

G:C to T:A transversions are common in lung cancer (but not colon cancer)

Mechanism: **deoxyguanosine adduct formation**

Typical of mutations induced by benzo(a)pyrene

Colon Cancer: TP53 mutations

Approximately 50% of colon cancers

Most mutations at C of CpG

– Hot spots: codons 175, 248, 272, 282

G:C to A:T transitions are common

Mechanism: deamination of 5-methylcytosine

– requires methylation as a precursor for mutation

Exact carcinogen unclear

Skin Cancer: TP53 mutations

G:C to A:T transitions

Reflect the production of **pyrimidine dimers**

– Adjacent TT, TC, CT, CC bases

– UV induced

– Seen only in UV-induced cancers

Lung Cancer: New tumor suppressors

FHIT gene

– Located at 3p

– Fragile Histidine Triad

– Straddles a fragile site

– Deletions extremely common

almost universal in small cell cancer

– Encodes a dinucleoside 5',5'"- P1, P3-triphosphate hydrolase

– Alterations of FHIT also common in cervical cancer, leukemias and other malignancies

Lung Cancer: Prevention

"The most preventable cause of death"

Affects both cancer and cardiovascular disease

Public health measures can include advertising regulation

Role of the physician

– Advocate

– Smoking cessation

Nicotine addiction

Nicotine is highly addictive

– Moderately euphoric effects

– Short half-life, rapid onset of action

mucosal delivery

Physical withdrawal symptoms

– flushing, diaphoresis

– headaches

Psychological withdrawal symptoms

– "craving"

Smoking cessation strategies

Nicotine replacement

– gum

– transdermal patch

– nasal spray

Antidepressants

– Bupropion (Zyban)

All effective when administered as **part of a comprehensive program of smoking cessation**

Smoking Cessation Therapies (Randomized study (Jorenby et al., 1999 NEJM 340:685-91)

% Quit at 12 months:

– Placebo: 15.6%

– Nicotine patch: 16.4%

– Bupropion: 30.3%

– Nicotine patch and bupropion: 35.5%

Lung Cancer: Histologic types

Non-small cell lung cancer

– Squamous carcinomas

– Adenocarcinomas

– Large cell cancers

Small cell lung cancer

Lung Cancer: Small cell cancer

Neuroendocrine origin

– Stains with neuroendocrine markers

– May share a common cell of origin with carcinoid tumors

Specific oncogenes: FHIT

Aggressive behavior: small primary but early metastatic behavior

Lung Cancer: Therapy

Small cell lung cancer

Surgery has no role

– ? coin lesion

Combination chemotherapy

– prolongs median survival from 1-2 mo. to 12-18 mo.

Radiation

5-year survival: 5-10% limited; 0% extensive

Lung Cancer: Therapy

Non-small cell lung cancer

Surgery for T1-3, N1-2, M0 disease

Radiation for pain palliation

Chemotherapy has no proven survival value at any stage

Lung Cancer: Conclusions

Lung cancer provides a model for **epidemiological inference**

Lung cancer provides a model for **chemical carcinogenesis**

Physicians can play a major role in **smoking cessation**

Therapy of clinical disease is generally unsatisfactory

PATHOLOGY 6601, FALL 2006
Oncology III - Breast Cancer

Breast Cancer: Incidence

- 186,000 cases/year (USA)
- 45,000 deaths/year
- 1/9 women develop the disease in their lifetime
- Tied with lung cancer as the most common cause of death from cancer in women

Worldwide incidence in females

- 86.3 cases/100,000 in North America
- 28.6 cases/100,000 in Japan

Age-specific incidence (per 100,000)

- Increases with age, particularly in countries with the highest incidence

Breast Cancer: Risk Factors

- Major risk factor: Family history
- Lifetime risk with affected first degree relatives:
  (NEJM 342:564-571 (Feb 24, 2000)
  - One relative < 50 years: 13-21%
  - One relative >50 years: 9-11%
  - Two relatives <50 years: 30-48%
  - Two relatives >50 years: 11-30%

Breast Cancer: Risk Factors

- Endocrine risk factors:
  - Age at first pregnancy
  - Number of pregnancies
  - Age at menarche
  - Age at menopause
  - Hormone replacement therapy
- Demonstrate hormonal influence on pre-neoplastic cells
  - Important in explaining pathogenesis

- Modest clinical value

Breast Cancer: Susceptibility Genes

- Most of the important susceptibility genes have yet to be identified !
- Two genes important in pre-menopausal cases:
  - BRCA1
  - BRCA2
  - Together, germline BRCA1 and BRCA2 mutations are seen in 1-3% of patients with pre-menopausal breast cancer

Mutations in BRCA1

- Germline mutations predispose to breast and ovarian cancer
- Autosomal dominant
- 80% lifetime breast cancer risk
  - Possible allelic variation v. risk
- Median onset of breast cancer < 45 years
- 30-40% chance of ovarian cancer
- ? Other tumors

Mutations in BRCA2

- Germline mutations predispose to breast and ovarian cancer
- Autosomal dominant
- 80% lifetime breast cancer risk
- Median onset < 50 years
- 25% risk of ovarian cancer
- 5% of MALE carriers develop breast cancer

HER2/Neu Gene

- A transmembrane protein tyrosine kinase
- Relatives: EGFR, etc.

- Binds a ligand, heregulin, which acts as a growth factor
- Tumor expression may predict prognosis
- Antibodies to HER2 have therapeutic benefit in patients

Breast Cancer: Steroid Hormone Receptors I

- Nuclear proteins
- Bind estrogens and progestins
- Bind specific DNA sequences
  - Steroid response elements
- Transcriptional activators

Breast Cancer: Steroid hormone receptors II

- Most pre-menopausal breast cancers are receptor-negative
- Most post-menopausal breast cancers are receptor-positive
- Administration of estrogens promotes cell growth
- Administration of anti-estrogens (e.g.,Tamoxifen), causes cell death

Breast Cancer: Prevention with hormones

- SERMs: Selective Estrogen Receptor Modulators
- NSABP study: Tamoxifen reduces invasive breast cancer by 49%
- MORE study: Raloxifene reduces breast cancer 76%
- Benefits limited to ER positive tumors
- SERMs also have non-tumor-related beneficial effects
  - Reduction of heart disease
  - Prevention of osteoporosis
- Some increase in endometrial cancer

Breast Cancer: The STAR trial

- Study of Tamoxifen And Raloxifene
- Randomized comparison of the two SERMs

- Endpoints:
  - Breast cancer mortality
  - Endometrial cancer
  - Heart disease
  - Other vascular effects (thrombosis)
  - Osteoporosis

Goals of mammography screening

- Earlier diagnosis in asymptomatic individuals
- Reduction of mortality due to detection at earlier stage

Age	Mortality Reduction (%)	
40 - 49	17%	15 years post-screening
50 - 69	25 - 30%	10 - 12 years post-screening
70+	insufficient data	

Screening (high-risk)

- Annual mammogram, beginning 5 yrs before age of youngest affected relative at time of diagnosis
  - High familial risk
  - BRCA 1 or 2 positive

Screening mammography

- Reduces mortality by 26% in women aged 50-74
- Supports view that early diagnosis and treatment can prevent metastasis
- ACS recommends
  - 1st screening mammography by age 40
  - Mammography every 1 to 2 years between the ages of 40 and 49
  - Mammography annually thereafter

Signs and symptoms at presentation

- Mass or pain in the axilla
- Palpable mass, thickening or pain in breast
- Nipple discharge or retraction
- Edema or erythema of the overlying skin

Breast Cancer: Staging

- TNM system
- Tumor:
  - T1: <2 cm
  - T2: 2-5 cm
  - T3: >5 cm
  - T4: Extension to skin/chest wall
- Nodes: Number of nodes
- Metastases: M0, M1

Natural history

- Highly variable in different patients
- Relatively slow growth rate
- Median survival without treatment: 2.8 yrs
- Generally present several years by time of diagnosis
- Long preclinical period enables early detection

Commonly assessed prognostic factors

- Number of positive axillary nodes (5-year survival decreases as a function of the number of positive axillary lymph nodes)
- Tumor size
- Lymphatic and vascular invasion
- Histologic tumor type

- Nuclear grade
- Estrogen / Progesterone receptor status
- HER2 overexpression

Breast Cancer: Therapy

- Local therapies:
  - Treat disease in the breast and surrounding tissues (axillary nodes, chest wall)
  - Surgery and XRT, usually in combination
  - Combination therapy allows organ preservation
- Systemic therapy:
  - Treats disease both within and outside of the local treatment field
  - Chemotherapy and hormonal therapy

Adjuvant therapy

- Definition: Treatment of clinically inapparent disease after definitive local therapy.
  Goal: Increase survival
- Treats "Micrometasases"
- Adjuvant chemotherapy: Premenopausal women
- Adjuvant hormonal therapy: Postmenopausal women, ER + tumors

Breast Cancer - Summary

- Family history is the single most important risk factor for breast cancer
- Screening mammography prevents deaths from breast cancer
- Hormones are important in pathogenesis and therapy
- Both anti-estrogens and chemotherapy work by inducing apoptosis

PATHOLOGY 6601, FALL 2006
ONCOLOGY IV

CHRONIC MYELOGENOUS LEUKEMIA

Case Presentation:

A 38-year-old previously healthy man presents with fatigue, weight loss, early satiety and left upper quadrant pain. The physical exam is remarkable for a spleen felt 25 centimeters below the costal margin

laboratory studies

WBC: 150,000/ml
Hgb: 12g/dL
Plts: 500,000/ml
LDH: 900 U/L

Blood smear: tailed poikilocytes, leukocytosis with left shift in the myeloid series

Differential: 5% promyelocytes,
12% myeolocytes,
20% metamyelocytes,
25%, bands,
25% granulocytes,
4% eosinophils,
4% basophils,
1% monocytes,
4% lymphocytes

Bone Marrow: Myeloid hyperplasia. 4% myeloblasts, 7% promyelocytes,
10% myelocytes, 22% metamyelocytes, 25% bands, 27% granu

Bone Marrow: karyotype with t (9:22) in 20/20 examined metaphases

Treatment: Hydroxyurea to bring WBC to 50,000/microliter, followed by Interferon-a. Search for a matching bone marrow donor.

II. Epidemiology:

20% of all leukemias

incidence of 1/100,000

M:F = 1.4:1

peak in the 5th and 6th decade of life

III. Clinical features:

weakness, fatigue, weight loss

splenomegaly (95% of cases)

leukocytosis, thrombocytosis, basophilia, eosinophilia

elevated LDH, decreased leukocyte alkaline phosphatase score

3 phases of the disease: chronic, accelerated, blastic (75% myeloid, 25% lymphoid)

5 year survival 50-60%

- poor prognostic factors: older, weight loss, poor performance status, African-American race, hepatomegaly, splenomegaly, anemia, thrombocytosis or thrombocytopenia, basophilia, marrow fibrosis

IV. Biology:

t(9:22) (q34:q11) found in 95% of patients at presentation (BCR-ABL gene product detected by PCR in another 5%)

balanced translocation from the distal long arms of chromosome 9 and 22. c-ABL proto-oncogene transposed from its normal location on the long arm of chromosome 9 to the breakpoint cluster region (bcr) on chromosome 22.

the new hybrid gene (*BCR-ABL* oncogene) yields an abnormal fusion protein that has increased tyrosine kinase activity.

several major signaling pathways are activated by BCR-ABL. These include: RAS, MYC, JUN, STAT, PI-3K, NF-*k*B

as the disease evolves into the accelerated and blast phase, leukemia cells acquire new cytogenetic anomalies (often including a second Ph chromosome) and become growth factor independent.

V. Treatment:

Goals: hematologic remission, cytogenetic remission, cure.

Hydroxyurea: 80% hematologic response in the chronic phase. No cytogenetic remission.

IFN-alpha: 80% cytogenetic response (minor in 40-60% of patients, major in 20-30% of patients). Patients who achieve a complete cytogenetic remission have a longer

survival than patients who achieve a partial or minor cytogenetic remission.

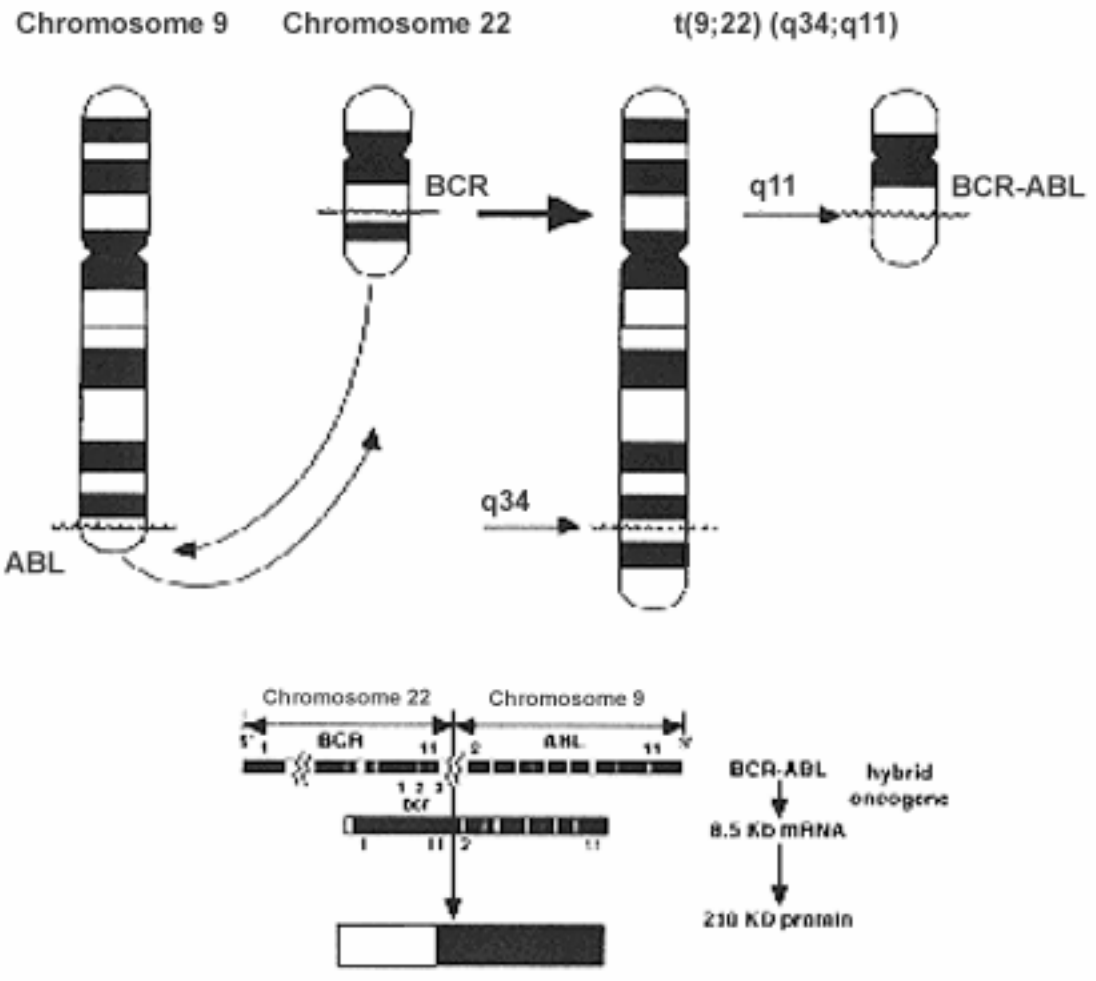
IFN-alpha and Ara-C combination yields better remission and survival rates than IFN-alpha alone.

Remissions with IFN-alpha therapy take longer to achieve than with hydroxyurea.

Allogeneic bone marrow transplantation is the only known curative modality. Best results when performed in the chronic phase in within 1 year of diagnosis.

PCR studies for BCR-ABL are positive in almost all patients with cytogenetic remission.

Among patients who have received allogeneic BMT more than 75% have persistant *BCR-ABL* by PCR within the first 12 months after transplant. 40-50% will be positive after 12 months. The prognostic significance of this finding is not clear.



PATHOLOGY 6601, FALL 2006
Genetic Diseases
Edward C. Klatt, MD

READING ASSIGNMENT: Pathologic Basis of Disease, (7th ed: 146-191;487-495)

LEARNING OBJECTIVES: At the end of the lecture and upon completion of the reading assignment, the student will be able to:

1. Describe the processes of mitosis and meiosis and the cell cycle.

2. Outline problems related to abnormalities of chromosome number, mosaicism, translocation, deletion, and uniparental disomy.

3. Describe the types and consequences of single gene mutations.

4. Draw a Punnett square for genetic analysis.

5. Recognize from a pedigree the differences among inheritance patterns:

autosomal dominant	co-dominance
autosomal recessive	dosage sensitivity
X-linked recessive	mitochondrial inheritance
X-linked dominant	multifactorial inheritance
germline mutation	

6. Describe abnormalities associated with DNA repair, specifically xeroderma pigmentosa.

7. Describe features of teratogenicity, specifically in relation to fetal alcohol syndrome, fetal hydantoin syndrome, and fetal valproate syndrome.

8. Use the above principles to counsel patients with care and concern regarding genetic diseases.

9. Describe inheritance patterns and pathologic features of the following diseases:

cystic fibrosis	familial hypercholesterolemia
hemophilia A	Tay-Sachs disease
osteogenesis imperfecta	Von Gierke disease
Marfan syndrome	McArdle disease
achondroplasia	Pompe disease

Gaucher disease
NF-1
Huntington disease
Niemann-Pick disease
Fragile X syndrome

10. Apply care and concern when counseling parents and families regarding genetic diseases.

Problems with chromosomes:

Cells with a multiple of 23 chromosomes are euploid. Germ cells (spermatozoa, ova) are haploid with 23. A polyploid cell has a multiple of 23. Normal somatic cells are diploid with a complement of 46 chromosomes. Abnormal euploid numbers seen in humans include triploidy (69 chromosomes) and tetraploidy (92 chromosomes).

Aneuploidy refers to an abnormal number of chromosomes that is not a multiple of 23. There is either monosomy (one less chromosome of a pair), or trisomy (one extra chromosome). In general, either extra genetic material, or less, is detrimental. Most cases of aneuploidy result in fetal loss. In general, abnormalities of sex chromosomes are better tolerated than abnormalities of autosomes. Thus, aneuploidy can involve:

Autosomes (chromosome pairs 1 – 22)
Sex chromosomes (X or Y)

These abnormalities often occur because of nondisjunctional events in meiosis.

An example of autosomal aneuploidy is Down syndrome, or trisomy 21. In this condition, there is an extra chromosome 21. Some cases are liveborn, and survival is possible, but multiple congenital anomalies are present, some of which can be severe, such as heart defects.

An example of a sex chromosome aneuploidy is monosomy X, or Turner syndrome, with a 45, X karyotype. There is marked fetal hydrops (edema) along with a variety of congenital anomalies. Some cases are liveborn.

Survival may be more likely in some cases in which the aneuploidy does not involve all cells or does not involve the entire chromosome. Examples include:

Mosaicism

Confined placental mosaicism

Partial aneuploidy

A "mosaic" is a person with a combination of two cell lines with different karyotypes (normal and abnormal). When karyotyping is performed, multiple cells are analyzed to rule out this possibility. An example would be a Turner's mosaic, with a 45,X/46,XX karyotype, with some cells having the abnormal karyotype and some cells having a normal karyotype. The mosaic condition is not as severe as the completely abnormal karyotype, and the features may not be as marked, and livebirths may be possible. "Somatic mosaicism" occurs if the chromosomal anomaly or mutation arises during embryogenesis (after fertilization) and only some cells are affected.

Sometimes the mosaicism is confined to the placenta ("confined placental mosaicism"). The placenta is a fetal structure. A placenta with an abnormal karyotype may lead to stillbirth, even though the fetus has a normal karyotype; conversely, a placenta with a normal karyotype may allow longer survival for a fetus with a chromosomal abnormality.

Rarely, a translocation of part of one chromosome to another in the parent will be passed on to the child as a partial trisomy (such as 6p+ or 16p+) which may not be as severe as a complete trisomy.

Deletions of part of a chromosome result in the loss of genetic material. An example is the loss of a portion of the long arm of chromosome 22 (22q-) that is associated with the DiGeorge anomaly in which there is an abnormal formation of structures arising from the 3rd and 4th pharyngeal pouches, particularly the thymus, resulting in immunodeficiency.

Translocations involve the shift of a part of a chromosome to another chromosome. Translocations can be balanced (portions of two chromosomes exchange places) or unbalanced (some chromosomal portion is lost in the process). A good example of a translocation is the "Philadelphia chromosome" that is seen with chronic myelogenous leukemia (CML).

The t(9:22)(q34;q11) is a balanced translocation from the distal long arms of chromosome 9 and 22. The c-ABL proto-oncogene is transposed from its normal location on the long arm of chromosome 9 to the breakpoint cluster region (bcr) on chromosome 22. The new hybrid gene (*BCR-ABL* oncogene) yields an abnormal fusion protein that has increased tyrosine kinase activity that drives cellular proliferation.

Robertsonian translocation: A special type of translocation is called "centric fusion" or "Robertsonian translocation" when two acrocentric chromosomes (with very short "p" arms) have break points very close to the centromere. There is subsequent fusion of the long arms. The fused short arms are often lost, but contain so little genetic material that the consequences are not severe. The carrier of such a "Robertsonian" translocation will appear normal, though only 45 chromosomes are present, but fertilization with gametes from such a carrier will result in half of all zygotes being non-viable

In the case of Down syndrome where chromosomes 14 and 21 are involved, fertilization with a normal gamete

and a "Robertsonian" gamete will potentially yield non-viable monosomy 14, trisomy 14, and monosomy 21. Potential viable fertilized eggs may be normal, be balanced carriers, or have trisomy 21.

Microdeletions involve only small parts of chromosomes, but the missing segment may have important genes. An example of a microdeletion syndrome is the Prader-Willi syndrome characterized by decreased mental function, speech problems, and excessive eating.

Uniparental disomy is a rare phenomenon in which each of a pair of chromosomes came from one parent. This can occur when trisomy is followed by loss of one extra chromosome or when monosomy is followed by nondisjunction. Some cases of Prader-Willi syndrome result from uniparental disomy.

Genes

A gene is a unit of DNA that codes for a specific protein. The location of a gene on the chromosome is called the locus. Genes consist of exons and introns. The exons contain the DNA code for the protein, while intervening introns, which make up most of the size of a gene, have an unknown function. The introns must be cut out and the exons spliced together in the mRNA before it leaves the nucleus.

The DNA sequence of a gene may vary among persons. Each variation is called an allele. If both alleles are the same, then the person is homozygous for the gene. If the alleles are different, then the person is a heterozygote.

If gene frequencies of alleles exceed 1% of persons in a population, then such alleles are called polymorphisms. For example, the major human blood grouping system, the ABO system, is determined by a single gene with three alleles—A, B, and O. Persons with type O are homozygotes (OO) because the presence of A or B determines the presence of A or B antigens on the red blood cells. Persons with blood group A can be either AA or AO and those with type B are either BB or BO. The rarest type is AB, in which case both antigens are present. This is an example of codominance. The frequency of these alleles varies around the world (the majority of Europeans are type A, Asians are mostly type B, while Mayans are exclusively type O).

The relationship between gene frequency and genotype is determined by the Hardy-Weinberg principle, which assumes that the genotype does not have an influence on marriage. Using this principle, one can roughly estimate the carrier rate. The rate of homozygotes should be the square of the gene frequency. Thus, for a disease such as cystic fibrosis, with 1 in 2500 Caucasians affected, the square root gives a gene frequency of 1 in 50, and a carrier rate double that, or 1 in 25.

The theory of natural selection is based upon selective advantage of genetic mutation introduced into a population, with advantageous genes increasing survival because of a selective advantage. Genes without

selective advantage may become less frequent with time. The rapid increase in antibiotic resistant strains of micro-organisms is a good example of this phenomenon accelerated by modern medicine.

Differences in allelic frequencies in populations may be due to “founder effect” and to “genetic drift” over time. An example of the founder effect is the disease porphyria seen in the Afrikaner population of South Africa. The Afrikaans community started with a small number of "founders" when the Dutch East India Company established a refreshment station at the Cape of Good Hope in 1652. The defective gene is believed to have been brought to South Africa in 1688 by Dutch orphan Ariaantje Adriaansse who was sent to the Cape to marry one of the early settlers, Gerrit Janz van Deventer. In a small, isolated population, the effect of random variation can become more pronounced, with genetic drift.

The alleles that are present represent the genotype of a person. The expression of the genotype leads to the phenotype—what is clinically apparent in the person. Genetic heterogeneity refers to the appearance of a common phenotype for several genotypes. Pleiotropy refers to the appearance of multiple effects from one gene. The increase or decrease of gene function with various alleles is called dosage sensitivity.

Transcriptional genes, such as those of the HOX and PAX group, often act on other genes to activate or repress them. Mutations in the transcriptional genes may result in abnormalities that appear in multiple body sites.

Single gene mutations

Mutations can occur in many forms:

Missense	Change in a single amino acid
Nonsense	Change in a stop codon
Deletion	Loss of a single base pair, with frameshift
Insertion	Gain of a single base pair, with frameshift
Duplication	An extra gene with more protein production
Splice site	Abnormalities at the intron-exon boundary
Triple repeats	Increased tandem repeats

Mutation “hot spots” occur in places where there is a methylated CG dinucleotide sequence that can easily lose the methyl group on the cytosine base, converting it to thymine. Mutation rates are higher in genes where this sequence is present.

Genetic mutations can involve autosomes or the X chromosome.

For autosomal recessive conditions, the standard recurrence risk for parents having further children is 25%. For autosomal dominant conditions, the recurrence risk is 50%. Bear in mind that about 3% of all births have some sort of birth defect, from a variety of causes, not all of which can be diagnosed completely. Thus, the recurrence risk for any pregnancy is 3%.

Pedigree and Punnett square analysis:

Brown / blue eyes	Brown	blue
Brown	BB	Bb
blue	Bb	bb

Brown / blue eyes	blue	blue
Brown	Bb	Bb
blue	bb	bb

Cystic fibrosis	?F508	normal
?F508	?F508 ?F508	?F508 normal
normal	?F508 normal	normal normal

Gene frequency:

Cystic fibrosis appears in 1 per 2500 Caucasians. The gene frequency of ?F508 is the square root of 1/2500, or 1/50. The heterozygous carrier rate would be double that frequency, or 1/25.

Autosomal Recessive Inheritance

In general, a mutation involving a gene coding for an enzyme appears as a recessive trait because, in the heterozygote, one gene copy is present and enough enzyme is made to provide for sufficient metabolic function.

Recessive traits tend to result from “loss of function” of a protein. Thus, mutations involving genes coding for enzymes involving autosomes typically lead to autosomal recessive conditions.

The mutation leads to loss of enzyme function, typically in a biochemical pathway. A critical product may not be made, or an intermediate metabolite may increase in quantity.

```
                ENZYME 1                    ENZYME 2                    ENZYME 3
SUBSTRATE  ---------->  INTERMED 1  ---------->  INTERMED 2  ---------->  PRODUCT
                                            |
                                        ALTERNATE
                                        PRODUCT
```

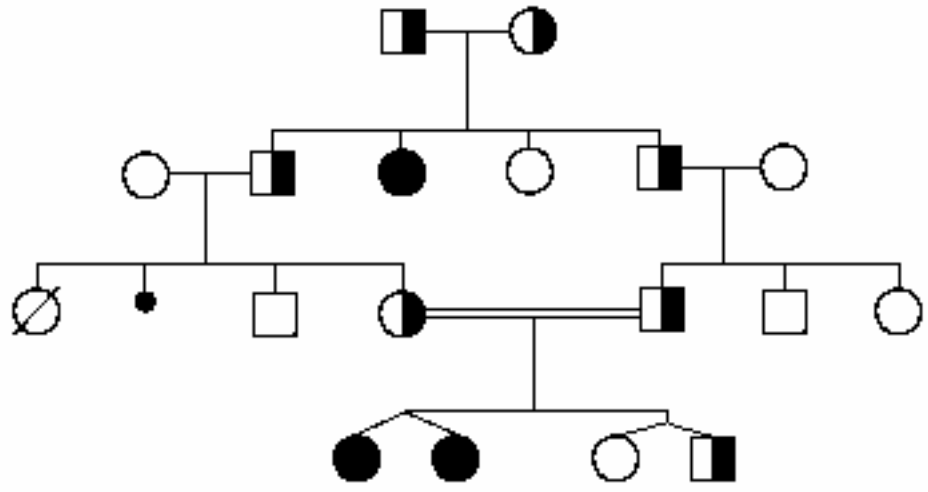
These conditions are typically apparent early in life.

New mutations involving these genes are rare, but the rarity of these traits also makes tracking a family history difficult.

Cystic fibrosis

An example of a single gene that can have multiple different mutations (alleles) resulting in a similar phenotype is cystic fibrosis. Mutations occur in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. The gene codes for a chloride channel protein that controls chloride ion movement across epithelial cells. CFTR mutations lead to production of abnormally viscid mucoid secretions that lead to organ abnormalities, particularly in the lungs. Since multiple organs are involved, the CFTR gene exhibits pleiotropy.

CFTR is also an example of how many different mutations can appear clinically similar and confound screening strategies. There are over 700 known CFTR mutations. The ?F508 mutation accounts for two-thirds of all mutations. About 12 mutations account for 90%. Thus, you can't just apply a single genetic screening test. Also, even though this is one of the most common inherited abnormalities (1 in 25 Caucasians carries this gene), general population screening is more likely to yield false positives. The standard strategy is to screen only when a family history is present or a new case is diagnosed in a family.



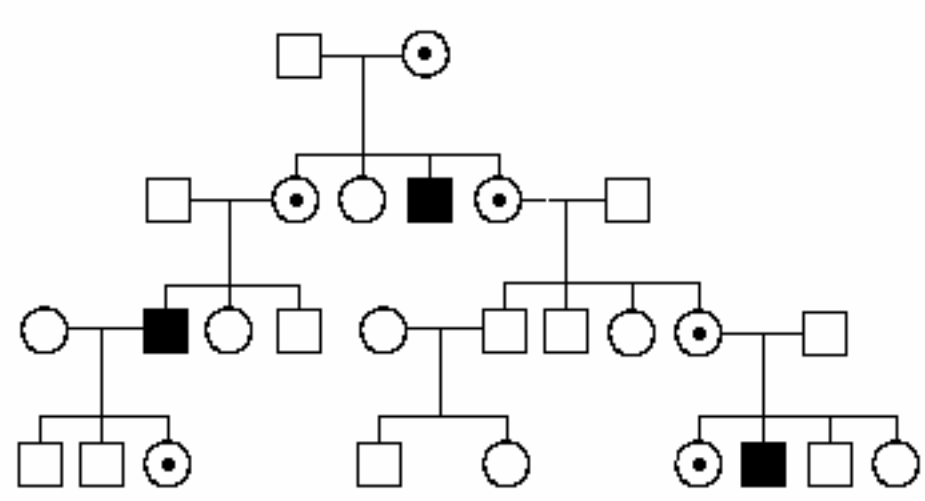
The metabolic defect is an abnormally low permeability to Cl^- in the membrane of secretory cells at the base of glands and/or (depending upon the organ) absorptive cells lining ducts. This is probably due to the absence of a secondary messenger which normally upregulates Cl^- or HCO_3^- secretion and resorption via these channels.

Different CFTR mutations account for different clinical courses.

X-linked Recessive Inheritance

If the mutation involves the X chromosome, and the trait is recessive, then the outcome depends upon whether you are male or female. If you are female, then you have two X chromosomes. One of them becomes inactivated (appears as a Barr body), but this is random, so in general, with a defective gene, you will have at least 25% enzyme activity. If you are a male, you are out of luck, and the trait appears. This is known as an X-linked recessive trait. In a pedigree, such a trait appears to involve only males (rare females unlucky enough to inherit two bad X chromosomes could be affected).

Hemophilia A: An example of an X-linked recessive condition is the blood clotting disorder known as hemophilia A. In this condition, there is a mutation in the gene coding for the production of blood clotting factor VIII. This disease illustrates the fact that the amount of product made can vary somewhat, and factor VIII activity determines the severity of the disease, so the phenotype varies from mild to severe, a phenomenon called variable expression. Females are typically carriers. Fathers with the disease cannot transmit the disease to sons, but may give the trait to daughters who become carriers. Thus, the disease often shows a pattern of skipping a generation. In females, one X chromosome is typically inactivated, and this is random, so female carriers are usually left with adequate factor VIII activity.



Autosomal Dominant Inheritance

In general, a mutation involving a gene coding for a structural protein appears as a dominant trait, because one copy of the abnormal gene leads to formation of an abnormal protein that interferes with formation of tissues. Structural genes tend to be large, so spontaneous new mutations are likely to occur, and a family history need not be present. Such genes can display locus heterogeneity, where different mutations in the same large gene can lead to similar phenotypic expression.

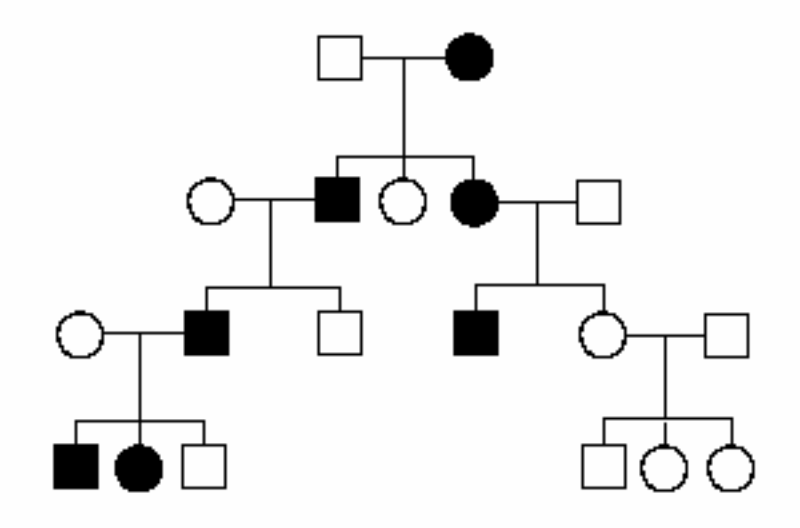
Osteogenesis imperfecta

An example of a mutation involving a gene encoding for a structural protein is osteogenesis imperfecta (OI). Structural genes tend to be quite large (many kilobases) and so mutations can occur at a variety of places, and a variety of mutations can involve the same gene. This explains variations in the expression of the mutation. Thus, because the OI gene is large (over 50 exons) mutations can occur in a variety of places, and the result is different expressions of the disease.

Since big genes are more prone to mutation, this also explains why mutations involving structural genes are more likely to arise de novo than be inherited. OI is a disorder based upon abnormal collagen formation, leading to abnormal bone matrix production and abnormal bone that fractures easily. Collagen is a large, complex molecule that requires multiple steps for production.

OI mutations are in a gene encoding for type I collagen. Since even in heterozygotes abnormal protein is made and incorporated into collagenous structures, there is expression of the abnormality. Thus, mutations in structural genes tend to be expressed in a dominant fashion.

OI is an example of a “dominant negative” mutation in which the loss of function disturbs the product of other normal genes encoding for the multimeric protein.



Marfan syndrome

Marfan syndrome is another example of an autosomal dominant condition involving a structural gene, in this case the fibrillin gene, which encodes for a protein that is a component of microfibrils that form connective tissues, particularly in the aorta, eye, and skeletal system. Affected persons are tall, with long fingers (arachnodactyly), loose joints, ocular problems, and a propensity for the aorta to rupture. Thus, the fibrillin gene leads to pleiotropism.

Structural genetic diseases are often good examples of a "gain of function" mutation because heterozygotes and homozygotes express the disease similarly. The gene product is overexpressed or inappropriately expressed in development. The result is the appearance of a dominant trait.

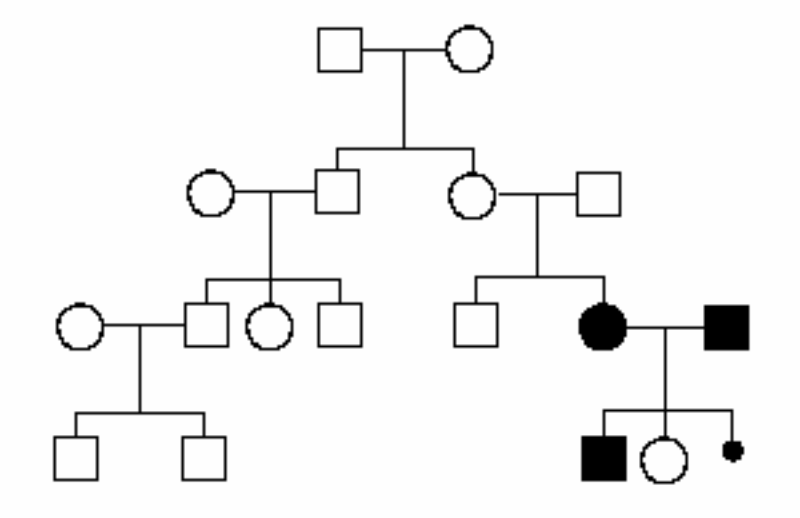
The frequency is 1 in 50,000, with 15-30% of cases due to spontaneous mutations in paternal germ line. Mutation is usually mapped to 15q21.1 by in situ hybridization.

Marked clinical variation is seen in patients with FBN1 mutations.

Achondroplasia

This is a form of short-limbed dwarfism in which height is reduced from long bone shortening. Affected persons are of normal intelligence and function normally—they are just short. Like many disorders involving structural genes, it is autosomal dominant. However, since most cases occur when parents are of normal height, it is apparent that most cases of achondroplasia are due to spontaneous new mutations in the fibroblast growth factor receptor 3 (FGFR3) gene.

If two persons with achondroplasia marry (another combination is unlikely) then 3/4 of their children can be expected to have achondroplasia—but 1/4 will die in utero, because the homozygous condition is lethal.



The pattern of transmission can be confounded by reduced penetrance and by variable expression. Reduced

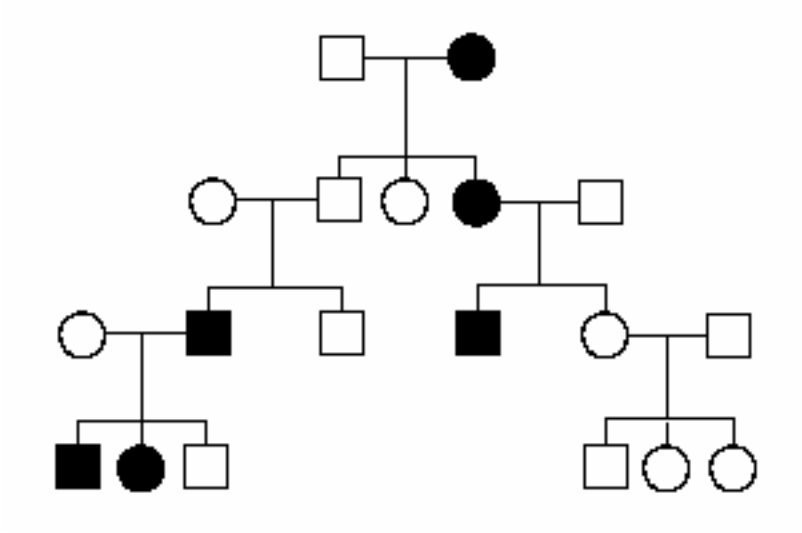
penetrance means that the gene is present and can be transmitted to offspring but does not produce the phenotype in the parent, leading to a “skipped” generation in a pedigree.

More complex yet is variable expression, where the disease is present (complete penetrance) but the severity of gene expression varies from mild to severe. Modifier genes or allelic heterogeneity (different mutations of the gene) may explain variable expression.

Huntington disease

Huntington disease occurs from a mutation in the huntingtin gene encoding for a protein in the central nervous system. The presence of the abnormal protein causes a movement disorder. Since the onset of the disease occurs in middle age (40’s), it is easy to pass the condition on to children without knowing it.

This phenomenon of apparent lack of phenotypic expression for a time is called delayed onset. The specific abnormality is what is known as a “triple repeat” in which there are increased numbers of a particular sequence of DNA (tandem repeats). In this case, there are multiple CAG repeats. Unaffected persons have 11 to 35 copies, while affected persons have 36 to 100 copies. Incomplete penetrance is seen at 36 to 38 copies. In general, the number of repeats increases with successive generations, leading to worse symptoms and earlier appearance.

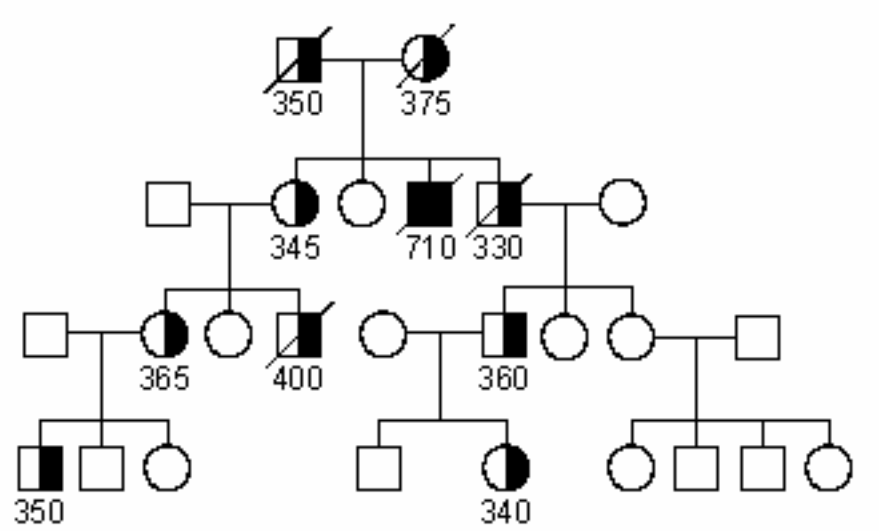


This disease exhibits the phenomenon of penetrance—not all persons with the genetic disorder (genotype) express manifestations of the disease (phenotype). Such persons are said to have reduced penetrance of the disease. This confounds family history taking, since the carrier may be missed.

Inheritance with Dosage Sensitivity

Familial hypercholesterolemia

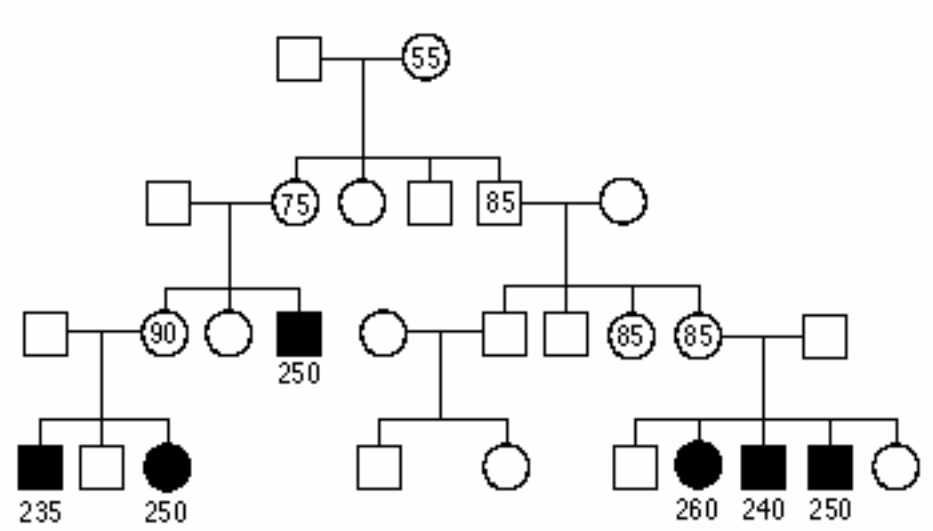
This is an example of a mutation which leads to dosage sensitivity. The gene codes for a protein that forms the LDL cholesterol receptor in arteries. Persons with the normal allele have normal numbers of LDL receptors and normal cholesterol levels <200 mg/dL. Persons heterozygous with an abnormal gene have 50% fewer LDL receptors and cholesterol levels around 300 to 400 mg/dL. Homozygotes have virtually no LDL receptors and cholesterol levels can exceed 600 mg/dL.



X-linked Dominant Inheritance

Fragile X syndrome: This disorder illustrates an unusual inheritance pattern that depends upon differences in male and female transmission. Fragile X syndrome is an X-linked dominant disorder, but is another example of a tandem repeat (triple repeat) disorder involving a gene that codes for a protein in the CNS. It leads to mental retardation. Normally, there are fewer than 50 repeats. Persons with 50 to 230 repeats transmit the disease, but do not express the disease.

Even though it is dominant, twice as many males as females are affected. This is due in part to X inactivation which reduces penetrance and expression in females. It is also because the risk for the disease increases if you are a male born to a woman who is a carrier. In females passing the trait, the number of repeats expands. The more repeats that are present, the more likely the expansion in female transmission will exceed 230 repeats. Thus, the number of affected males increases in successive generations. Males with fewer than 230 repeats will pass the same number of repeats to all their daughters, but those daughters will pass expanded repeats to their offspring. More recent generations are more severely affected, a phenomenon called anticipation.

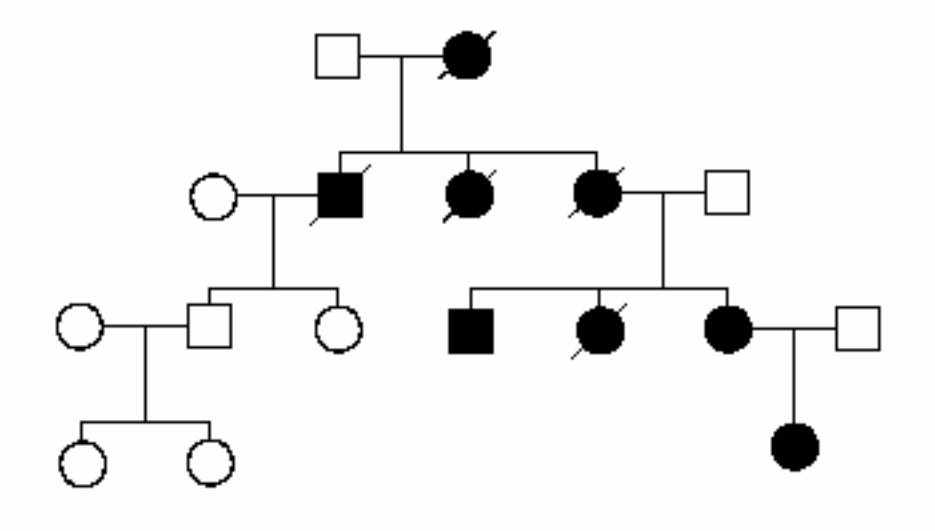


Genomic imprinting

For a small number of disorders, phenotypic expression of a trait depends upon whether inheritance was from father or mother. This results from differences in activation of genes. Methylation of DNA prevents its transcription. A gene may be active only on a chromosome from the father, or vice versa. A mutation will only produce an effect if it involves the active gene. The best example of this is Prader-Willi syndrome (mutation inherited from father) versus Angelman syndrome (mutation inherited from mother). In Beckwith-Wiedemann syndrome, uniparental disomy can give a child two paternal active abnormal alleles, where normally at least one inactive maternal copy is present.

Mitochondrial inheritance

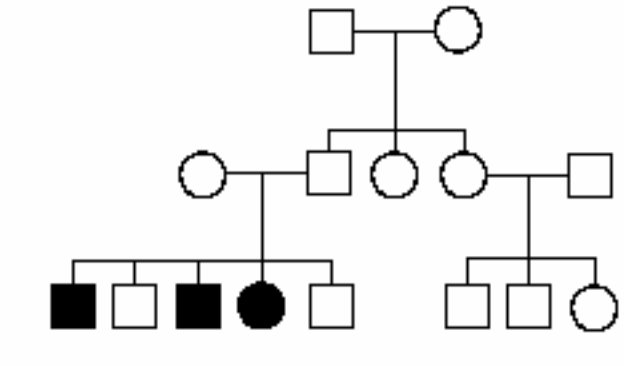
Mitochondria have their own set of genes in a piece of circular double stranded DNA encoding for proteins involved in oxidative phosphorylation. These genes are transmitted through the mother, not the father. Some CNS, muscle, and hearing disorders have mutations in mitochondrial genes. Affected males never transmit these disorders.



Germline mosaicism

This pattern of inheritance is most often suspected if multiple children are affected by a disorder, and the parents and relatives are not affected. One parent must have had a mutation, but it was confined to the germ cells early in embryogenesis, so that somatic cells did not have the mutation, and the parent is phenotypically normal, but able to transmit the mutation to offspring.

Some cases of achondroplasia, hemophilia A, and neurofibromatosis I, among others, may be transmitted in this fashion.



Multifactorial Inheritance

Some conditions do not appear to be linked to a single gene defect, but are more complex, perhaps representing the effects of more than one gene and also interaction with environmental influences or embryogenesis. Two such disorders are cleft lip and diabetes mellitus. Both conditions occur more frequently when there is a family history, but without a clear pattern of inheritance.

Of babies born with congenital anomalies, many (perhaps 40 to 50%) fall into a category of "multiple congenital anomalies" without a defined syndrome or without an identifiable genetic or chromosomal defect. Many syndromes still do not have a defined genetic basis.

Research continues to turn up new genes linked to disorders, so in the future more congenital anomalies may be explained by specific defects. Be aware that a normal karyotype or the absence of a family history of a genetic disease does not reduce the risk of birth defects to 0.

The recurrence risk for such conditions is probably above the standard 3% risk, but is not as high as the 25% risk for autosomal recessive conditions. The often quoted recurrence risk for anomalies of unknown cause is 5-8%, indicating that there is an increased risk, but not a greatly increased risk.

A condition, though multifactorial, may have a "threshold of liability" above which the disease is manifested—more genetic risks are present. The disease pyloric stenosis, which causes bowel obstruction with vomiting in babies about 1 month old, exhibits this pattern. The incidence in males is 1/200 and in females 1/1000, reflecting the fact that more risks must be present in females for the disease to occur. Estimating the recurrence risk when there is a sex ratio difference is counter-intuitive. If males are more likely to have the disease, then the risk is increased if a female child is born with the condition. This is because more risks must be present in the family in order for a girl to have the disease, and thus the threshold of liability will be exceeded more easily for males born into such a family.

Twin studies

Twin studies are another way of demonstrating relative influences of genetic and environmental factors on phenotype.

Monozygous (identical) twins share the same genome and (presumably) the same environment, unless they are raised apart, in which case environmental influences should account for any differences.

Dizygous (non-identical) twins are the same as siblings and have variable genetic differences, but may be raised in the same environment. Thus for dizygous twins raised in the same environment, genetic differences should account for the phenotype. Twins that share a trait are called concordant, while those that do not share a trait are discordant.

The concordance rates for diabetes mellitus, autism, bipolar disorder (manic-depressive illness), and epilepsy in monozygous twins are much higher than for dizygous twins, raised in the same environment, suggesting that there are genetic factors at work.

Teratogenicity

Maternal exposure to drugs, toxins, and other environmental insults may have an effect upon the developing embryo and fetus. Some associations are well known, such as the drug thalidomide and risk for phocomelia (short limbs). Other exposures may result in sporadic appearance of birth defects. The most common teratogen is alcohol.

Fetal Alcohol Syndrome

Fetal alcohol syndrome (FAS) may affect at least one out of every 750 live births. Thirty to forty percent of babies whose mothers drink heavily throughout pregnancy develop FAS. There is no threshold amount of alcohol consumption by the mother to produce the disease--no amount is safe. The probability of having a child with FAS increases with the amount and frequency of alcohol consumed. Whenever a pregnant woman stops drinking, she reduces the risk of having a baby with FAS. Damage to the fetus from FAS cannot be reversed.

The most common deformity with FAS is moderate to severe growth retardation. Anomalies include microcephaly, frontal bossing, long and narrow forehead, hypotelorism, maxillary and mandibular hypoplasia, narrow palpebral fissures, thin elongated philtrum and vermillion border of the upper lip, temporomandibular joint disorders, and dental malocclusion, wide roof of the nose, saddle nose, tooth enamel hypoplasia, and uvular hypoplasia. Ocular problems include microphthalmia, corneal clouding, coloboma, nystagmus, strabismus, and ptosis. Internal anomalies include congenital heart disease, particularly ventricular septal defect. Vertebral abnormalities including scoliosis can be present. The liver can have fatty metamorphosis with hepatomegaly and elevated serum transaminases. The physical anomalies tend to become less apparent as the child ages.

The effect of FAS on the brain results in varying degrees of mental retardation and behavioral problems. Adverse psychosocial, behavioral, physical, and intellectual consequences of prenatal alcohol exposure continue into adulthood.

Anti-convulsant Drug Teratogenicity

Several anticonvulsant drugs, including phenytoin, carbamazepine, and phenobarbital, are metabolized by the liver through the arene oxide pathway that leads to increased epoxide intermediate metabolites that may have teratogenicity. Fetuses of mothers who require such medications can be at risk for malformations. The risk of

birth defects can be up to 10%.

The best known of these is the fetal hydantoin syndrome with use of phenytoin. Features of this syndrome may include facial dysmorphology with epicanthal folds, hypertelorism, upturned nose, and flat nasal bridge, along with distal digital hypoplasia, growth retardation, and mental retardation.

Fetal valproate (valproic acid) syndrome has a facial appearance characterized by a small broad nose, small ears, flat philtrum, a long upper lip with shallow philtrum, and micro/retrognathia. In addition, there can be musculoskeletal abnormalities, minor skin defects, cardiovascular abnormalities, genital abnormalities, pulmonary abnormalities, and neural tube defects. Fetal loss may occur in 12% of cases, and 29% of survivors have developmental deficits and/or mental retardation. Growth retardation occurs in one-sixth of cases.

Maternal use of other anticonvulsant drugs, including phenobarbital, primidone (which is metabolized to phenobarbital), carbamazepine, and valproic acid, has been associated with a variety of birth defects, but the findings vary in published studies.

What causes birth defects?

Cause	%
Unknown	43
Multifactorial	23
Familial	15
Chromosomal abnormalities	10
Single gene disorder	3
Teratogen	3
Uterine problems	3
Twinning problems	<1

Observation: Why do so many genetic disorders result in decreased mental function or neurologic problems? Because a third of the genome is devoted to the nervous system.

Different Approaches (told by a parent) (adapted from p 296 from Jorde et al, Medical Genetics)

Late in my pregnancy I had an ultrasound that showed several problems with the baby. During delivery, the baby's heart rate dropped dramatically. We were given the option of a C-section and without hesitation chose that option. A drape was hung so that I could not see, and I only knew that the baby was born when the pediatrician ran out of the room with something in his arms. My husband quickly followed, and then I waited for what seemed an eternity.

Later…as my husband and I sat in awe over our new baby girl, a physician entered the room. He pointed out several characteristics and concluded that she had trisomy 18. Of the grim things he rattled off, the only thing I remembered was that he said she would be a vegetable and that she would most likely die within the next couple of days. He then walked away, and we sat there, stunned.

On the day of her birth, a pediatrician came forward, put his arms around us, and told us he thought she was beautiful and to love her for as long as she could be with us. He turned her into a human being with a life to be highly valued.

Prader-Willi syndrome (told by a parent) (p. 81 in Jorde et al, Medical Genetics)

We have a 3 1/2 year old son, John, who has Prader-Willi syndrome (PWS). Months before John was born, we were concerned about his well-being because he wasn't as active in utero compared to his older siblings. At the first sight of John, the doctors suspected that things "weren't quite right." John opened his eyes but made no other movements. He couldn't adequately suck, required supplemental oxygen, and he was "puffy." He remained hospitalized for nearly 3 weeks. The following 3 years were filled with visits to occupational therapists, physical therapists, home health care aids, early childhood service providers, and speech therapists.

From the day John was born, we searched diligently for a diagnosis. His father insisted that we need only love and help him. However, I wanted specifics on how to help him and knowledge from other parents who might have traveled a similar path. After extensive testing and three "chromosome checks," John was diagnosed with Prader-Willi syndrome. We were glad to be provided with some direction and decided we would deal with further challenges as they came upon us. We used what we learned about PWS to get started helping John reach his potential. We were not going to worry about all the potential problems John could have because of his PWS.

John attends a special education preschool at the local elementary school 4 days a week. The bus ride takes about 5 minutes, but is long enough for John to very much anticipate it each day. If he is ill, we have to tell him that the bus is broken. He attends a Sunday school class with children of a similar age. He misbehaves by saying "hi" and "bye" very loudly to each participant. He receives speech therapy once a week, and I spend at least 30 minutes each day with John, practicing speech, cognitive, and play skills. John has not yet experienced the feeding difficulties commonly observed in children with PWS. However, excessive eating and weight gain are more common in older children with PWS.

Compared with other 3-year old children, John struggles with speech and motor developmental milestones. Yet, he loves to play with his siblings and their friends and to look at books. In fact, we struggle to keep people from doing too many things for John because they might prevent him from attaining the same goal independently. We feel very privileged to have him in our family.
Our expectations for John are that he achieves everything that is possible for him plus a little bit more. Indeed, some of his care providers are already impressed with his capabilities. I hope that his success is partly because of the care and support that we have given to him. Moreover, I hope that John continues to overcome the daily challenges that face him.

Key points about the parent(s) perspective:

1. I know something is not quite right.

2. I want an exact answer (or, I don't want to know if I gave it to him).

3. I need help.

4. I want to believe that what I am doing is making a difference.

PATHOLOGY 6601, FALL 2006
PLACENTA/PERINATAL/PEDS
Dr. Morton H. Levitt

DISEASES OF INFANCY AND CHILDHOOD: PART 1

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 469-487)

LEARNING OBJECTIVES: At the end of this lecture and upon completion of the reading assignment and laboratory, the student will be able to:

1. Use in context definitional terms that describe fetal events and complications.

2. Describe diagnostic techniques that are available for prenatal diagnosis and at what gestational age.

3. Describe the pathophysiology of problems of prematurity: intraventricular hemorrhage, kernicterus, necrotizing enterocolitis, and respiratory distress syndrome.

4. Explain how erythroblastosis fetalis occurs and what the consequences are.

5. Define the types of birth injuries, especially those involving the head and nervous system (extracranial hemorrhage, intracranial hemorrhage, skull fractures, spinal cord and brachial plexus injuries).

6. Understand the routes of perinatal infection; outline the organisms that cause the TORCH infections; describe the effects of perinatal infection.

Definitions:

Embryo	Up to 8 to 12 weeks gestation (first trimester)
Fetus	After 8 to 12 weeks and up to delivery
Abortion	Pregnancy loss up to 20 weeks gestation
Stillbirth	Pregnancy loss after 20 weeks gestation
Perinatal period	28th week of gestation to 7th day of life
Neonatal period	Birth to 28th day of life
Infancy	First year of life

Term pregnancy	38 to 42 weeks gestation
Trimester	Division of pregnancy into three equal segments (first trimester, second trimester, third trimester)

Diagnostic Studies

Ultrasound	Radiologic procedure to bounce sound waves off of internal structures to create a 2 dimensional image; gestational sac first seen at 6 to 8 weeks gestation. Best imaging of the fetus (extremities and internal organs) to detect congenital anomalies is obtained between 15 and 20 weeks gestation. Can use transabdominal or transvaginal approach. Ultrasound machines for doctor's offices are good for screening, but those in hospitals have better resolution and are operated by a trained technician in radiology or OB.
CVS	Chorionic villus sampling is done under ultrasound guidance, usually between 9 and 11 weeks gestation, to obtain a small biopsy of placental tissue for karyotyping or genetic studies. Can be contaminated by maternal cells.
Amniocentesis	Under ultrasound guidance, a needle is inserted into the amniotic fluid around the fetus to obtain material for biochemical testing, karyotyping, or genetic studies. Fetal amniocytes collected are desquamated epithelial cells. Can be contaminated by maternal cells. Performed safely after 15 weeks, when enough amniotic fluid is present.
PUBS	Periumbilical blood sampling is a technique in which a needle under ultrasound guidance is inserted into the umbilical cord to obtain fetal circulating cells for analysis.

Maternal serum Biochemical analysis of maternal blood can be done to reflect fetal problems.

The classic test is the "triple screen" for alpha-fetoprotein (MSAFP), beta-HCG, and estriol.

Maternal blood Sampling of maternal blood takes advantage of the fact that fetal cells do cross the placenta into maternal circulation. Harvessting of such cells could avoid the complications of CVS or amniocentesis.

However, they are few in number, making their use in testing difficult.

Maturity and Birth Weight

Gestational age Age in weeks after conception

Prematurity	Birth at less than 38 weeks gestation (37 in some series)
Term	Birth between 38 and 42 weeks gestation
Postmaturity	Birth after 42 weeks gestation
Birth weight	Weight of baby at time of delivery, normally between 2500 and 4000 grams
Low birth weight	Weight < 2,500 gms at birth (40 X increased risk of death compared with infants > 2,500 gms)
Very low birth weight	Weight < 1,500 gms (200 X increased chance of death)
SGA	Small for gestational age is < 10th percentile weight for age
LGA	Large for gestational age is > 90th percentile weight for age--think

macrosomia in infants of diabetic mothers (related to fetal hyperinsulinemia), hydrops fetalis, other causes.

IUGR

Intrauterine growth retardation is lack of normal increase in size of the developing fetus in proportion to gestational age. It can be detected antenatally using ultrasound (biparietal diameter, head circumference, abdominal circumference).

Proportionate IUGR reflects the limited ability of the fetus to grow and results in symmetric growth retardation. It is seen in chromosomal disorders, congenital anomalies and congenital infections.

Disproportionate IUGR occurs when uteroplacental insufficiency leads to decreased nutrient supplies but results in relative sparing of the brain. IUGR is associated with higher perinatal mortality and a higher incidence of perinatal complications. Placental findings in uteroplacental ischemia: acute--abruption; chronic--decreased weight, increased knotting, infarction.

Maternal diseases associated with IUGR include toxemia, chronic hypertension, nutritional status. Additional risk factors are narcotics, alcohol, and cigarette smoking.

Assessement of the Baby at Birth

Apgar scores allow a rapid means of evaluating the condition of the infant and are useful in predicting perinatal morbidity. (Named for a real person – Virginia Apgar.) They are usually done at 1 and 5 minutes after birth and are assessed by giving 0, 1, or 2 points for each of the following mnemonic (CHRMS):

C = color
H = heart rate
R = respiratory effort
M = muscle tone
S = stimulus = response to catheter in nostril

A good score is 8 to 10

Low score at 1 minute: Suggests asphyxia.

Low score at 5 minutes: Associated with a poor outcome,

50% mortality within first month of life

Uteroplacental Insufficiency

This term describes a phenomenon with many causes. There are a variety of reasons why a failure of exchange of oxygen and nutrients across the placenta from maternal to fetal circulation might occur. Causes could include:

Placental implantation in a poor location (lower uterine segment)

Placental abruption (premature separation of the placenta)

Vascular problems

Infection

Hypertension (pregnancy induced hypertension, or PIH)

Chromosomal abnormalities (remember that the placenta is a fetal structure)

Uteroplacental insufficiency can lead to neonatal asphyxia, which leads to the following complications in the fetus: myocardial failure, pulmonary hypertension, necrotizing enterocolitis, renal failure, CNS hemorrhage and damage, meconium aspiration, and death (8-34% of stillbirths, 1 to 3.5/1,000 births).

Placental findings in acute asphyxia include fresh meconium on placental membranes, fetus, and in fetal respiratory tract. Chronic asphyxia results in meconium in macrophages. (Meconium is the intestinal content of the fetus and it is a green, bile stained material--usually not discharged before 34 weeks gestation. Meconium aspiration is seen near term).

Perinatal infections.

There are two primary routes of perinatal infection:

Ascending or transcervical

Hematologic or transplacental

Ascending infections may be caused by bacteria (Group B Strep), or viruses (herpes simplex virus, or HSV). There are several outcomes:

Chorioamnionitis/funisitis: infection of the fetal membranes is called chorioamnionitis. Infection of the umbilical cord is called funisitis. Inflammation in either suggests infection has entered the amniotic cavity, which is ordinarily sterile.

Fetal pneumonia, from micro-organisms attracting neutrophils in the lung due to aspiration of infected amniotic fluid.

Hematologic or transplacental infections.

In reality, it is often difficult to tell just how an intrauterine infection started.

Infections that occur in utero can be called "congenital infections" because they occurred before birth.

Congenital infections can be categorized by etiology. The mnemonic "TORCHES" helps in remembering these causes:

Toxoplasmosis
Other: Parvovirus B19, group B strep, Listeria
Rubella
Cytomegalovirus
Herpes simplex virus, HIV
E. coli
Syphilis

The clinical presentation of TORCH infections includes multisystemic effects:

fever pneumonitis hepatosplenomegaly

encephalitis	myocarditis	skin lesions
chorioretinitis	hemolytic anemia	

If the infection occurs early in gestation, it can lead to other consequences, including:

growth and mental retardation	congenital cardiac anomalies
cataracts	bone defects

Perinatal viral infection with herpes simplex virus can affect the fetus in utero, intrapartum, or postnatally. If this infection occurs in utero, there is LBW in most cases, with extensive neurologic damage because HSV is neurotropic.

Perinatal infection with HIV can have a variety of outcomes. Some infants are seemingly unaffected, with a slower course. Some may have AIDS soon after birth. Most progress faster to AIDS than infected adults. Transplacental infection can be reduced by giving antiretroviral thrapy (zidovudine) to mothers. A few cases result from transmission by breast milk.

Problems of Prematurity

Pulmonary Immaturity. The premature lung has three goals as it matures:

Increase surface area

Produce surfactant

Decrease alveolar wall thickness

Respiratory distress syndrome (RDS) in the newborn is caused by a deficiency of surfactant.

Pathophysiology. In premature infants, the synthesis, storage, and release of surfactant is decreased due to lack of and immaturity of type II alveolar cells. This leads to increased surface tension and difficulties with ventilation (hypoxemia and CO_2 retention). Damage to capillary endothelium and alveolar epithelium results in the formation of hyaline membranes, which consist of fibrin and cellular debris.

The pathology of classic respiratory distress syndrome includes distended, airless, dark red, heavy lungs with atelectasis (collapse of alveoli) alternating with dilated alveoli and

air spaces filled with fluid and lined by hyaline membranes.

The clinical course depends on the birth weight, with infants < 1,000 gms having a much higher morbidity and mortality.

Bronchopulmonary dysplasia is an outcome of RDS. It is diagnosed clinically by the presence of persistently increased densities in the chest radiograph and oxygen dependency > 27 days of life following mechanical ventilation during the first week of life. Pathologic evidence of bronchopulmonary dysplasia can be seen within 5 days of life. It is characterized by acute, reparative, and healed stages of pulmonary acinar injury.

Central Nervous System Problems

Intraventricular hemorrhage

In premature infants it usually arises in the germinal matrix, especially in the capillaries overlying the head of the caudate.

The greatest risk is at 22-31 weeks gestation.

Risk factors include stress from hypoxia and changes in blood pressure in the premature neonate.

Kernicterus

This is a neonatal metabolic encephalopathy characterized by the accumulation of unconjugated bilirubin in the brain, especially the basal ganglia.

The immature liver with its low levels of glucuronyl transferase cannot handle elevated bilirubin and the poorly developed blood brain barrier permits the passage and deposition of bilirubin.

Neonatal Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis is an acute, necrotizing inflammation of the small and large intestines.

Clinically this is characterized by the presentation of an infant at 2-4 days of life with bloody stools, diarrhea, and abdominal distension. Radiographs may include pneumatosis intestinalis (air bubbles in the bowel wall).

It is thought to have a multifactorial etiology, including mucosal ischemia, oral feedings, and bacterial infection.

Risk factors include LBW and premature infants.

The pathology of NEC includes coagulative and hemorrhagic necrosis and inflammation of portions of the small and large intestine. The terminal ileum, cecum, and the right colon are the most severely affected.

Erythroblastosis fetalis--hemolytic disease of the newborn.

Hydrops fetalis is a term used to describe increased subcutaneous and interstitial tissue fluid and serous cavity effusions in the fetus in utero and at birth.

There are numerous causes of hydrops fetalis: hematologic, cardiac, intrathoracic, vascular, musculoskeletal, urogenital, gastrointestinal, tumors, genetic metabolic disease, chromosome anomalies, infection, and maternal disorders.

Erythroblastosis fetalis is a hemolytic disease in the newborn (HDN) which is caused by blood group incompatibility between mother and child. It occurs when:

Maternal IgG antibodies cross the placenta and attach to fetal red blood cells.

Fetal RBCs undergo accelerated destruction.

HDN may be caused by incompatibility in Rh antigens (mother is Rh negative and fetal cells which are Rh positive cross the placenta to sensitize the mother, who develops antibodies that cross the placenta). In general, the titer of antibodies is not high in the first pregnancy when sensitization occurs, but increases in subsequent pregnancies. The mother may also have been sensitized from a prior blood transfusion.

HDN can be due to other blood group antigens.

HDN due to ABO incompatibilities tends to be less severe (most of these antibodies are of the IgM type that does not cross the placenta). It will occur when the baby is Group A or Group B and the mother is Group O.

Clinical features of erythroblastosis fetalis include:

Accelerated RBC destruction with anemia, with increased numbers of nucleated RBCs in peripheral blood, and subsequent…

High output cardiac failure with generalized edema (hydrops fetalis)

Jaundice (unconjugated hyperbilirubinemia) from hemolysis, possibly with kernicterus.

Hepatosplenomegaly due to increased extramedullary hematopoiesis (EMH).

Birth injuries.

Birth injuries are not common with modern obstetrical practice.

Birth injuries may involve the head, skeletal system (fractures of the humerus or clavicle), liver, and peripheral nerves.

Injuries of the head and nervous system frequently have the most serious consequences. They occur as a result of mechanical factors and fall into the following categories:

Extracranial hemorrhage can occur either into the subcutaneous tissue or the subperiosteum. When it involves the subcutaneous tissue, it is termed caput succedaneum and occurs as a result of prominent head molding during vaginal delivery. It crosses suture lines and resolves in 1-2 days.

Extracranial hemorrhage into the subperiosteum is termed cephalohematoma and is associated with forceps delivery. It can continue to increase after birth, resolves in weeks to months, does not cross suture lines, and is usually seen in the parietal bone. In 25% of cases it is associated with an underlying skull fracture.

Intracranial hemorrhage is related to cranial trauma at delivery and is most commonly subdural and subarachnoid. This location differs from hemorrhage seen in immature brains.

Skull fractures occur due to direct compression, are accompanied by either intracranial or extracranial hemorrhage, and are usually localized to the parietal bone.

The spinal cord may be injured by severe traction or rotation.

Damage to the brachial plexus is more common than spinal cord damage and occurs when nerve roots are stretched during delivery. It can involve either the shoulder (C5, C6; Erb's palsy) or wrist and fingers (C8, T1, Klumpke's paralysis).

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PLACENTA/PERINATAL/PEDS
Dr. Morton Levitt

PLACENTAL PATHOLOGY & GESTATIONAL TROPHOBLASTIC DISEASE

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 1104-1114)

LEARNING OBJECTIVES: At the end of these lectures and upon completion of the reading assignment and laboratory, the student will be able to:

1. Determine which placentas need pathologic examination and why.

2. Evaluate the normal placenta and describe the features (vessels, villi, membranes, umbilical cord, maternal surface, fetal surface).

3. Recognize and interpret the significance of abnormal findings in the placenta (including: single umbilical artery, meconium staining, amnion nodosum, chorioamnionitis, abnormal shapes and sizes).

4. Define the difference between:

   Monozygotic and dizygotic twins
   Dichorionic, diamnionic placentation
   Monochorionic diamnionic placentation
   Monochorionic monoamnionic placentation

5. Describe the pathophysiology of complications of twinning (including: conjoined twins and twin-twin transfusion syndrome).

6. Define molar pregnancy and discuss the significance of complete versus partial molar pregnancy.

Placental Function

The placenta is a fetal organ, derived initially from cells of the developing blastocyst soon after fertilization occurs. In fact, there are initially more fetal cells devoted to placental formation than other fetal organs, for the blood supply that sustains the fetus through pregnancy must be established.

The developing placental tissue invades the endometrium to establish an interface with the maternal circulation. The placenta enlarges. At 15 weeks, the fetal:placental weight ratio is about 2:1, at 20 weeks 3:1, and at term about 5 or 6:1.

Placental Evaluation

Examination of the placenta following delivery can help clarify the pathophysiology of an adverse fetal or maternal outcome, evaluate recurrence risk, and evaluate zygosity of twins. It is also important documentation for medicolegal purposes.

The placentas that need pathologic evaluation are typically those which come from: multiple gestations (e.g., twins), stillbirths, premature births, neonates with medical problems, and mothers with medical problems. Any placenta that looks odd should have a pathologic examination. In general, this scheme results in examination of about 10% of placentas.

Placental Structure

There are three major placental components:

- Fetal membranes
- Umbilical cord
- Placental disk, with a:
  - Fetal surface
  - Maternal surface

Placental membranes (and fetal surface of placental disc)

Normal membranes

gross exam: thin, glossy, and translucent

microscopic exam: what appears as a single thin membrane is composed of two layers—a chorion and an amnion. The amnion faces the inside of the amniotic cavity.

- amnion--epithelium and connective tissue
- chorion--connective tissue, fetal blood vessels, involuting villi (at margin)
- decidua--modified endometrium (maternal component at interface with the chorion)

Acute chorioamnionitis

Acute chorioamnionitis is an acute inflammatory process in which neutrophils are seen in the fetal membranes and often in the chorionic plate and umbilical cord (funisitis).

The fetal membranes may appear less translucent and thicker because of the presence of the inflammatory cells.

Most common pathogenesis - ascending bacterial infection.

Associated with premature labor and fetal infection.

Meconium staining

Meconium is the substance in the fetal colon that is a thick, mucoid, dark green substance.

Meconium is normally not passed until after birth. If meconium is released under conditions of fetal stress, generally toward the end of the third trimester, then the meconium is released into the amniotic cavity where it can:

Stain the fetus and placenta (meconium staining)

Go into the lungs and produce a pneumonitis (meconium aspiration)

If the fetus survives the episode in utero, then the meconium is taken up into macrophages.

Evidence for meconium staining at birth should make you suspect possible aspiration, and a lung lavage can be done to wash out the meconium.

Amnion nodosum

Fetal squamous epithelial cells from skin, along with the paste-like protective vernix caseosa are normally present. Small nodular deposits of this material can form on the membranes of the placental fetal surface and umbilical cord.

It occurs when the amount of amniotic fluid is reduced (oligohydramnios). Lack of amnionic fluid prevents the fetal skin cells from being washed off the membranes. Grossly, they can be scraped off.

Common underlying conditions: malformations that prevent urine from entering the amnionic sac and chronic loss of amniotic fluid.

Amnion disruption

The amnionic band syndrome is characterized by fibrous bands extending from placenta to fetus, between fetal parts, and amputation/cleavage of fetal parts. It can be part of the "limb-body wall complex" with vertebral column curvature (scoliosis), abdominal wall defect (gastroschisis), and limb abnormalities. This is a sporadic condition (not a genetically determined process) that is a disruption of normal embryogenesis.

Umbilical cord

Length: umbilical cord length is primarily determined by stretching due to fetal movement.

Normal: mean length of the cord at term is 55-60 cm (range 25 – 75 cm).

A short cord indicates either fetal hypoactivity or intrauterine abnormality leading to compression.

A long cord may be due to fetal hyperactivity and is associated with increased incidence of cord prolapse, true knot and coiling around fetal parts.

The normal insertion of the cord is central or eccentric.

Marginal insertions at the edge of the placental disk occur in 5-7% of cases, and are more susceptible to vessel rupture.

Velamentous insertions are seen when vessels run unprotected by Wharton's jelly within the fetal membranes before reaching the placental disk; occur in 1-2% of cases, and are susceptible to compression and rupture.

The normal number of umbilical vessels is three: two arteries and one vein.

A single umbilical artery is seen in 1% of term pregnancies, results from either agenesis or

degeneration during development and is associated with 50% incidence of fetal anomalies and 25% incidence of IUGR. Fetal anomalies may involve any organ system.

Mechanical lesions

True knot: rarely tighten before labor and are associated with an increased perinatal mortality rate. Knots rarely cause marked constriction because the umbilical cord is like a rubber band.

False knot (pseudoknot): focal nodular collection of dilated vessels and increased Wharton's jelly. It has no significance, other than being able to recognize it and distinguish it from pathologic processes.

Prolapse: the cord extends out through the cervical canal prior to or during delivery, which can compromise blood flow.

Nuchal cord: the cord wraps around the neck (or another body part). This has the potential to compromise the blood supply, but not that often.

These "cord accidents" such as true knots, prolapse, and nuchal cord are more likely to occur with a long cord.

Infections

Ascending infections can involve the umbilical cord. Inflammation of the cord is known as funisitis.

Placental disk

Weight

The normal weight varies with gestational age and race.

A small for gestational age (SGA) placenta suggests uteroplacental insufficiency.

A large for gestational age (LGA) placenta suggests maternal diabetes mellitus, fetal hydrops, or congenital infections such as congenital syphilis.

Maternal surface of normal placenta:

Are the lobules or cotyledons (usually there are 10 to 40 of them) intact?

Fragmentation suggests retention

A hematoma with depression of the surface suggests abruption

A pale, firm area suggests infarction

Appearance:

90% of placentas are discoid, flat, round to oval

Abnormal invasiveness of the placenta into the uterine wall, without an intervening decidual plate, with placental villi interdigitating directly with myometrium, can lead to:

Placenta accreta: villi are adherent to myometrium rather than decidua

Placenta increta: villi interdigitate with myometrium

Placenta percreta: villi extend through uterine wall into serosa; associated with hemorrhage, uterine rupture, 10% fetal and maternal mortality

This abnormal invasiveness means that the placenta does not separate from the uterus normally following delivery. This can require a hysterectomy to control bleeding.

Abruption:

Abruptio placenta (placental abruption) occurs when there is sudden separation of a normally implanted placenta prior to labor.

Pathologically, a retroplacental hematoma is seen, with or without compression of the villi.

Clinical findings with abruption are classically the sudden onset of severe lower abdominal pain accompanied by vaginal bleeding. Findings are variable. Ultrasound can

be done for diagnostic confirmation.

Abnormal location:

Normally, the blastocyst implants on a lateral wall of the uterine fundus. Placenta previa is a condition in which the placenta is implanted over the internal os and is a significant cause of third trimester bleeding.

Placental parenchyma:

The normal intervillous space is bathed in maternal blood.

The normal placental villi are composed of fetal vessels, connective tissue cells, and surrounding trophoblasts (cytotrophoblast, syncytiotrophoblast).

As pregnancy proceeds, the villi become smaller and more vascular to aid the increased need for diffusion of oxygen and nutrients across the placenta to support the growing baby.

Inflammation

Acute villitis is typically due to bacteria, with neutrophilic infiltrates. This is far less common than chorioamnionitis or funisitis.

Chronic villitis (mononuclear inflammation) is more likely to be seen with the congenital TORCH organisms. It is frequently not possible to culture a specific agent (villitis of unknown etiology). It is seen more frequently in stillborns (3X) and in SGA infants.

Twins

Dizygotic twins (fraternal twins) occur when there is fertilization of two ova by two different sperm.

As the two babies grow, their placental disks often fuse and appear as one placenta.

It is more common than monozygotic twinning and is associated with increased maternal age.

Monozygotic twins (identical twins) occur when there is fertilization of one egg by one sperm followed by early separation of the early embryo into two individuals.

There is no association with maternal age.
The formation of membranes and placentas depends on when division of the embryoblast occurs.

TWINS AND TWINNING*	Dizygous	Monozygous
incidence	1:30-150	1:200-330
# of placental disks	1 or 2	1 or 2
dividing membranes	DCDA (72%)	MCDA (25%) DCDA (3%) MCMA (<1%)

DCDA = dichorionic diamnionic
MCDA = monochorionic diamnionic
MCMA = monochorionic monoamnionic)

*These figures are rough estimates and marked interracial variation occurs.

Complications of monozygous or dizygous twins:

There is an increased incidence of deformations

There is an increased incidence of velamentous insertion (7X)

There is an increased incidence of a single umbilical artery (3-4X).

Complications seen primarily in monozygous twins:

There is increased incidence of developmental abnormalities, malformations and vascular disruptions.

MCMA: high fetal mortality (30-50%): fratricidal knots and entangled cords.

MCDA: perinatal mortality (7-25%).

Conjoined twins- incompletely separated monozygous twins of approximately equal size.

Twin transfusion syndrome

Present in 15-30% of MCDA placentas.

There is unequal shunting of blood from one twin to another.

Anastomoses: Artery-Vein, Artery-Artery, Vein-Vein.

Donor twin appears anemic; placenta is growth retarded, and there is oligohydramnios.

Recipient twin appears plethoric; the placenta is large and congested; there is polyhydramnios.

If the blood flow to one monozygous twin is markedly reduced from early in gestation, it may not completely develop all body parts. This results in the so-called "acardiac" twin which may be lacking a heart, other internal organs, a head, or extremities.

Gestational Trophoblastic Disease (Molar Pregnancy)

Hydatidiform mole:

Complete

Partial

Invasive hydatidiform mole

Choriocarcinoma

Placental site trophoblastic tumor (rare)

Complete Hydatidiform Mole

Karyotype is usually 46 XX, with paternal chromosomes only (fertilization with loss of maternal component)

= 0.1% of pregnancies in USA; more common in Asia

Placental tissue develops, but not a fetus. There is rapid placental growth, so the pregnancy appears large for dates

The serum beta-hCG is markedly elevated

In 10 to 20% of cases, persistent trophoblastic disease occurs (invasive mole, choriocarcinoma).

The gross pathologic appearance is that of "grape-like" villi--transparent vesicles 1-2 cm in diameter; there is absence of fetal parts.

The microscopic appearance of the villi is marked by edematous enlargement (hydropic villi) with little or no blood vessels in the villi. The trophoblastic cells are proliferated.

Partial Hydatidiform Mole

There is a triploid-karyotype (e.g., 69,XXY)—with an extra set of haploid chromosomes (fertilization of an ovum by two sperm, diploid sperm, or persistence of polar body in ovum). Flow cytometry will demonstrate a triploid population of cells.

Since maternal chromosomes are present, a fetus is present, but the fetus is small and malformed. Stillbirth typically occurs, and livebirths are rare.

The serum beta-hCG elevated (though not as high as with complete mole)

Persistent trophoblastic disease is less common than for a complete mole.

Hydropic “grape-like” villi are present in some cases but not as large (<1 cm) than with a complete mole.

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Dr. Morton Levitt

DEVELOPMENTAL ABNORMALITIES, COMMON CYTOGENETIC DISORDERS, AND NEWBORN SCREENING

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 469-487)

LEARNING OBJECTIVES: At the end of these lectures and upon completion of the reading assignment and laboratory, the student will be able to:

1. Define the following terms:

abortion	stillbirth	syndrome	association
malformation	deformation	hereditary	congenital
disruption	dysplasia	euploid	aneuploid
monosomy	trisomy	sequence	

2. Indicate the most likely consequences of sublethal injury during the following periods of gestation:

0 to 3 weeks 3 to 9 weeks 10 weeks to birth

3. Indicate the relative importance of chromosome abnormalities as causes of an early abortion, stillbirth and neonatal death.

4. List 3 categories of genetic factors and 3 of environmental factors that may cause developmental abnormalities.

5. Describe one characteristic external feature and one common internal feature for each of the following:

monosomy X trisomy 18 trisomy 13 trisomy 21

6. List six techniques which are used for the prenatal diagnosis of genetic diseases and malformation.

7. Discuss the metabolic diseases which are part of the newborn screening program in Utah.

DEVELOPMENTAL ABNORMALITIES

Congenital vs. Hereditary

1. **Congenital disorder:** A disorder manifest at birth which may or may not be caused by abnormal genes and which may or may not be transmissible.

2. **Hereditary disorder:** A disorder caused by abnormal genes that can be transmitted to offspring, but may or may not be manifest at birth.

Classification of errors in morphogenesis

1. **malformation:**

   a. Intrinsically abnormally formed structure due to incomplete or aberrant (dysplastic) morphogenesis (the term dysplasia in pediatric pathology refers to disordered development, not a pre-neoplastic process).

   b. Occur relatively early during development

   c. Example - Multicystic dysplastic kidney

2. **disruption:**

   a. Extrinsic breakdown of previously normal tissue

   b. Example - Amniotic band syndrome (limb-body wall complex)

3. **deformation:**

   a. Altered mechanical forces on previously normal tissue, often due to intrauterine constraint

   b. Occur relatively late during development

   c. Example – Equinovarus (varus) deformity of foot from constriction in utero with oligohydramnios

Classification of multiple lesions

1. **sequence:**

   a. Multiple anomalies derived from a single, localized known or presumed anomaly. This initiating event leads to secondary effects on other organs ("cascade")

   b. Example - Oligohydramnios sequence

2. **syndrome:**

   a. A pattern of multiple anomalies thought to be pathogenetically related but not a sequence

   b. Example - Short rib-polydactyly syndrome

3. **association:**

   a. Non-random occurrence of multiple anomalies not one of the above

   b. Example - VATER association (vertebral problems, anal atresia, tracheo-esophageal fistula/atresia, renal anomalies)

The target of the insult- molecular mechanisms of congenital malformations

Molecular mechanisms of malformation include perturbation of:

differentiation of different cell types (WT-1)

growth or proliferation of each cell type (TGF-beta)

pattern formation - the arrangement of cell types in space (Hox, PAX)

cell adhesion (fibronectin)

programmed cell death / apoptosis (bcl-2)

The timing of the insult

1. The coding system(s) that control these processes may act at several different times during morphogenesis (for example, during initial dorsal-ventral-left-right organization of the embryo and then later during similar organization of the limb buds).

2. **Critical periods**

   a. **0 to 3 weeks - fertilization and implantation**

      i. insult will either have **no effect or cause death**

      ii. chromosomal abnormalities predominate (>70%)

   b. **3 to 9 weeks - organogenesis**

      i. insult may cause **malformation(s) or death**

      ii. chromosomal abnormalities still predominate

   c. **10 weeks to birth - histogenesis**

      i. insult may cause **growth retardaation, growth injury, inflamation, or death**

      ii. maternal-placental factors, blood group dyscrasias, and infection predominate after approximately 20 weeks EGA

      iii. chromosomal abnormalites in 5% of stillborn fetuses/early neonatal deaths and 0.5 - 1% of live births

COMMON CYTOGENETIC DISORDERS (abnormal karyotype)

Chromosomal abnormalities seen in abortuses

Trisomies (13, 16, 18, 21)

Monosomy X

Polyploidies (69 chromosomes = triploidy; 92 chromosomes = tetraploidy)

Chromosomal abnormalities that may be seen in newborns

Trisomies (13, 18, 21)

XXY (Klinefelter syndrome)

XYY

XXX

Monosomy X

Numerical abnormalities of chromosomes (Genome mutations)

euploid - exact multiples of the haploid number (23) -- diploid (normal), triploid, tetraploid, etc.

aneuploid - a chromosome number that is not an exact multiple of 23 -- monosomy, trisomy, or higher order additions.

Autosomal monosomy – embryonic or fetal death (more or less sex chromosomes are tolerated more)

Autosomal trisomy

1. often fatal
2. some better tolerated (trisomies 21, 18, 13)
   a. associated with advanced maternal age, particularly Down syndrome
   b. recurrence risk depends on mechanism
   c. abnormal differentiation (multiple congenital anomalies)
   d. disturbed growth (intrauterine growth retardation, mental retardation)
   e.. screening tests include:
      i. History (family history, maternal age)
      ii. Maternal serum triple screen -

          alpha-fetoprotein (AFP)
          human chorionic gonadotropin (HCG)
          unconjugated estriol (uE3)

          for trisomy 21 and 18

iii. Ultrasonography

iv. Karyotype or fluorescence in situ hybridization (FISH) on a sample obtained by chorionic villus sampling (CVS), amniocentesis

Trisomy 21 (Down syndrome)

1. Incidence is 1 per 1000 live births and stillbirths

2. Constellation of malformations: hypotonia, flat face (90%), slanted palpebral fissure (80%), simian crease (50%), congenital heart disease (40%), duodenal atresia (30%).

3. Mental retardation.

4. Abnormal immunity, increased risk for leukemia in late childhood.

5. If survival occurs to middle age, then Alzheimer's disease develops.

Trisomy 18 (Edward's Syndrome)

1. Prevalence 1 in 5000 live births and stillbirths.

2. Constellation of malformations: overlapping fingers, prominent occiput, micrognathia, omphalocele, cardiac (90%) and renal (75%) anomalies.

3. Severe mental retardation and poor prognosis; few livebirths survive more than 4 months.

Trisomy 13 (Patau's Syndrome)

1. Prevalence 1 in 8000 live births and stillbirths.

2. Constellation of malformations: microcephaly, midline facial defects, polydactyly, cardiac anomalies (80%), bicornuate uterus (80%).

3. Severe mental retardation and poor prognosis.

Monosomy X (Turner syndrome)

1. Fetus: fetal hydrops (80%), webbed neck (50%).

2. Adult (survivors are typically mosaics): short stature, webbed neck, wide-spaced nipples, cubitus valgus, amenorrhea (ovarian dysgenesis).

NEWBORN SCREENING

Criteria for genetic screening:

1. Early intervention can prevent or ameliorate the disease.

2. A sensitive and specific test can be done on a small volume of fluid or tissue.

3. The benefit of detection outweighs the cost of testing and treatment.

Diseases screened for in Florida:

(http://www.savebabies.org/states/florida.htm)

1. **Congenital Hypothyroidism**

   a. incidence: 1:4000

   b. inadequate production of thyroid hormone due to a number of causes (thyroid dygenesis, genetic disorders of thyroid hormonogenesis, iodine deficiency, hypopituitarism, etc).

   c. difficult to diagnose clinically at birth.

   d. delay in treatment results in mental retardation (mean IQ=80), growth failure, deafness and hypometabolic state.

   e. adequate treatment with levothyroxine results in normal growth and development.

2. **Phenylketonuria**

a: incidence: 1:12,000, Northern European predilection.

b: autosomal recessive disorder of phenylalanine metabolism.

c. symptoms typically not apparent at birth but by 6 months of age mental retardation (IQ<50) is irreversible. Seizures, hyperactivity and eczema are common.

d. lifelong avoidance of phenylalanine (especially important during childbearing to avoid microcephaly and congenital heart disease in the fetus) results in normal early growth and development, but school problems are common.

3. **Galactosemia**

a. Incidence: 1:40,000, no racial predilection.

b. Autosomal recessive disorder of galactose metabolism.

c. Symptoms develop after exposure to galactose (in milk); and include failure to thrive, vomiting and diarrhea, hepatomegaly, jaundice, cataracts and mental retardation. Untreated, the disease is lethal with the cause of death frequently being E. coli sepsis.

d. With avoidance of galactose there should be normal growth and development, but learning disabilities and ovarian failure are not uncommon.

4. **Congenital Adrenal Hyperplasia (CAH)**

a. Incidence: 1:600 in Pacific Northwest natives.

b. Autosomal recessive disorder of adrenal steroid hormone synthesis.

c. Signs and symptoms develop in childhood, with precocious sexual development, hypertension.

5. **Sickle cell disease and hemoglobinopathies**

a. incidence of Hgb S gene is 1:10 in African-American population. Hgb

SS, SC and S-thalassemia affect about 1:400 African-American newborns, but are also seen in other populations.

b. autosomal recessive disorders of globin chain synthesis.

c. Children have anemia, increased risk for infections, and organ damage from crises with thrombosis.

6. Newborns in the State of Florida must also have hearing screening.

7. A major advance in newborn screening is use of tandem mass spectrometry, beginning in the early 1990's with continuing development. More than 20 disorders of body chemistry can be detected in a single analysis of a small blood sample that is collected on a special paper during the first few days of life.

D. Diseases screened for in other states or countries:

1. Tay-Sachs disease (1:3000 in Ashkenazi Jews)

2. Biotinidase deficiency (1:60,000)

3. Tyrosinemia (1:1850 in French Canadians from Saguenay – Saint Jean region)

4. Other amino acid and organic acid disorders (1:8000 - 1:200,000)

5. Cystic fibrosis (1:2500 in Caucasians)

6. Neuroblastoma (1:10,000, more common in Japan)

The use of a test method known as tandem mass spectrometry can detect up to 30 inborn errors of metabolism (all rare)

Technique	Earliest use (wks)	Risk (sab)	Utility in		
			Single Gene Eefect	Chromosomal Abnormality	Developmental Abnormality
History	Any	None	Consanguinity Ethnicity	Previously Affected Child Mother >35 y.o.	Exposure Race

Maternal serum (AFP,HCG, estriol)	15	None	--	Trisomy 21 & 18	Neural tube defects
Ultrasound	10	None	Demonstration of morphologic lesion		
Chorionic villus sampling	9	1-2%	Enzyme/DNA	Karyotype/FISH	DNA/FISH
Amniocentesis	15	0.5%	Enzyme/DNA	Karyotype/FISH	DNA/FISH
Umbilical blood sampling	18	1-2%	Enzyme/DNA	Karyotype/FISH	DNA/FISH
Fetal cells in maternal blood	?	None	Enzyme/DNA	Karyotype/FISH	DNA/FISH

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DISEASES OF INFANCY AND CHILDHOOD: PART 2
PEDIATRIC NEOPLASIA

READING ASSIGNMENT: Pathologic Basis of Disease, (7th ed: 487-506)

LEARNING OBJECTIVES: At the end of this lecture and upon completion of the reading assignments and laboratory, the student will be able to:

1. List the ten most common general categories and the ten most common histologic types of childhood cancer.

2. Understand the concept of histologic-prognostic subtypes of solid tumors of childhood.

3. Define the main clinical, pathologic, cytogenetic/molecular genetic, and prognostic features of these solid tumors of childhood.

    a. Wilms' tumor (also called nephroblastoma).
    b. Neuroblastoma.
    c. Rhabdomyosarcoma.

Overview of childhood cancer.

Childhood cancer, though rare, is the leading cause of death from disease in children 1 to 15 years old.

Most cancers in children are malignant solid tumors, and about 4,000 new cases are diagnosed each year in the U.S. Table 1 lists the most common childhood cancers by general category (anatomic axis) and by histologic type. Different tumors predominate at different ages, as shown in Table 2. Benign neoplasms are much more common in children than malignancies.

In the past 30 years, there have been tremendous advances in the understanding and treatment of solid malignancies of childhood.

1. Cure rates have increased by as much as 50%.

2. Histologic subtypes with prognostic significance have been identified and grading systems developed.

3. Clinical staging systems have been developed, with improved precision because of advances in medical imaging.

4. Chromosomal and molecular genetic abnormalities have been identified for specific types of tumors.

5. Treatment has been refined to match risk status.

6. Late effects of treatment have been identified.

7. Manifestations of cancer family syndromes in pediatric patients are being increasingly recognized.

Most Common Childhood Cancers

General Category by Anatomic Axis	Distribution (%)
1. Leukemias (acute lymphoblastic leukemia)	31.4
2. Central nervous system (medulloblastoma)	17.6
3. Lymphomas	12.4
4. Sympathetic nervous system	8.1
5. Soft tissue sarcomas (rhabdomyosarcoma)	7.1
6. Renal tumors (Wilms tumor)	6.4
7. Malignant bone tumors (Ewings tumor, osteosarcoma)	5.0
8. Carcinoma and other epithelial malignancies	4.0
9. Germ cell, trophoblastic, and other gonadal neoplasms	3.2
10. Hepatic tumors (hepatoblastoma)	1.3

Neuroblastoma is a "small round blue cell tumor" that originates in neural crest cells of the sympathetic nervous system.

Clinical features.

1. Abdominal or mediastinal mass.

2. Median age at diagnosis is 2 years.

a. Most common malignancy in first year of life.

b. Can be congenital.

3. Imaging: retroperitoneal mass with calcification and necrosis.

4. Signs/symptoms.

a. Related to location, presence of metastases.

b. Associations with other diseases: cardiovascular malformations, von Recklinghausen's neurofibromatosis, Hirschsprung's disease.

Genetic aspects.

1. Abnormalities of chromosomal number (ploidy).

2. Deletions of short arm of chromosome 1.

3. In 28%, amplification of proto-oncogene N-myc.

4. Defects in expression or function of nerve growth factors (tyrosine kinase-A [TRK-A] proto-oncogene expression).

5. Occasional familial cases with autosomal dominant pattern.

Prognostic features.

1. Age at diagnosis: < 13 months better.

2. Clinical stage based on size, extension of tumor across midline, and local, regional or distant metastases: low stage better.

3. Extra-adrenal or extra-abdominal primary better.

4. Low urinary homovanillic:vanillylmandelic acid ratio better.

5. DNA aneuploidy better.

6. Absence of chromosome 1p deletion better.

7. Absence of N-myc amplification better.

Survival overall has improved from 25% to 55% in 20 years (1960-1963 to 1980-1985), with selected subgroups having especially good outcome.

1. Localized but unresectable: 90% cured with chemotherapy.

2. Infants have 75% chance of survival with chemotherapy.

Wilms' tumor (nephroblastoma) is the most common intra-abdominal solid malignancy of childhood. It occurs in the kidney and is believed to arise from primitive metanephric blastema. There are several histologic variants.

Clinical features.

1. Abdominal mass arising in kidney, usually asymptomatic.

2. Median age at diagnosis is 3 years.

3. Hypertension due to increased renin activity occurs in 25%.

4. Imaging is useful for staging.

5. Several dysmorphic syndromes are associated with a substantially increased risk of developing Wilms' tumor (Table 4). Sixty percent of bilateral and 4% of unilateral Wilms' tumors are associated with congenital malformations.

   a. WAGR syndrome: Wilms' tumor, aniridia, genital anomalies, retardation.

b. Beckwith-Wiedemann syndrome: macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, embryonal tumors.

c. Denys-Drash syndrome: intersexual disorders, nephropathy, Wilms' tumor.

6. Familial Wilms' tumors have been reported with an autosomal dominant pattern.

Genetic aspects.

1. Specific genetic loci are implicated in Wilms' tumorigenesis.

a. WT1 is a Wilms' tumor-suppressor gene located at chromosome 11p13 that encodes a transcription factor critical to development of normal kidneys and gonads.

b. WT2 at chromosome 11p15 is a putative tumor-suppressor gene, and the 11p15 locus is linked to Beckwith-Wiedemann syndrome.

Survival overall has improved from < 50% in the 1950s to a greater than 80% cure rate with contemporary protocols.

Rhabdomyosarcoma is a soft tissue sarcoma with a striated muscle phenotype and distinctive histologic-prognostic subtypes. It accounts for 50% of childhood soft tissue sarcomas.

Clinical features.

1. Over 50% occur in the first decade of life, but adults may be affected.

2. The most frequent primary sites are the head and neck (40%), genitourinary tract (20%), and extremities (20%).

3. Signs and symptoms are related to primary site and clinical stage.

4. Staging is based on both the surgical extent of disease and the tumor-node-

metastasis concept.

5. Associations with inherited and developmental disorders: Li-Fraumeni cancer family syndrome, Beckwith-Wiedemann syndrome, and von Recklinghausen's neurofibromatosis. Fetal alcohol syndrome and antenatal paternal marijuana use may also predispose to rhabdomyosarcoma.

Genetic aspects: A variety of chromosomal alterations and genetic mutations are seen.

Survival overall has improved since the 1960s from an estimated 25% to greater than 70% with contemporary protocols. Risk-based therapy may improve this.

Other childhood malignancies:

Medulloblastoma occurs in the cerebellar midline

Hepatoblastoma occurs in the liver

Childhood leukemias typically are acute lymphoblastic leukemias (ALL) and over 90% are curable

Benign pediatric neoplasms:

Lymphangioma: can be found in the head and neck region. Often do not have discreet borders, making their removal challenging.

Hemangioma: can be found anywhere. If extensive, may cause a high output congestive heart failure.

Fibromatoses: Can be found in soft tissues in a variety of places. They may interdigitate with normal tissues, making resection challenging. If not completely removed, they may recur.

Summary and conclusions.

Childhood tumors differ in histologic type and prognosis from adult tumors.

Histologic/prognostic and genetic classifications are emerging for specific types of childhood tumors.

Therapeutic strategies will reflect expanding knowledge about risk.

As survival improves, second malignant neoplasms will be a serious complication. The present risk is about 10% within 20 years of treatment. This risk is probably higher in the setting of a familial cancer syndrome.

PATHOLOGY 6601, FALL 2006
Pathology of Trauma
Dr. Edward C. Klatt

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 436-442; 444-446)

LEARNING OBJECTIVES: At the end of this lecture and upon completion of the reading assignment, the student will be able to:

1. Define the incidence of accidental death in the U.S.
2. List the major causes for accidents.
3. Describe the patterns of blunt force injury to head, chest, and abdomen.
4. Describe the classification of burn injuries and factors influencing prognosis.
5. Describe injury patterns from physical agents (heat, cold, pressure changes, electrical, drowning).
6. List the major types of emboli, their etiologies, and their consequences.
7. Describe injury patterns with historical findings that would make you suspect domestic violence/abuse.

ACCIDENTS

The scope of the problem:

A. Accidents kill one person in 20 in the U.S., and are the fifth leading cause of death overall. Accidents are the leading cause of death in both males and females under the age of 35. They are the leading cause of years of potential life lost (YPLL). Leading causes of YPLL before age 65 are:

1. Accidents
2. Malignant neoplasms
3. Suicide/homicide
4. Heart disease
5. AIDS
6. Congenital anomalies
7. Prematurity
8. SIDS
9. Stroke
10. Liver disease (cirrhosis)

B. Non-fatal trauma is extremely common in medical practice and is a leading cause of morbidity.

About 1/3 of injuries to children aged 5 to 17 are sports-related (about 4.5 million total sports-related injuries)

Non-fatal choking incidents in children are most often due to food and coins. Fatal incidents are often due to choking on balloons.

Accidental (non-fatal) Injuries in the U.S. in 1998

Diagnosis	Number of People
Contusion	495,103
Laceration	371,567
Fracture	158,679
Strain/Pain	104,054
Internal injuries	110,319
Puncture	106,051
Foreign body	3,391
Other	244,057
Unknown	14,914

Primary Body Part	Number of People

Head/Neck	864,324
Upper trunk	161,025
Lower trunk	86,311
Arm/Hand	311,065
Leg/Foot	96,369
Other	68,931
Unknown	20,108

Auto accidents

A. About 1 person in 1000 will be involved in a major auto accident each year (fatal or non-fatal). >40% of fatalities are associated with impairment by drugs, of which alcohol is the most common, alone or in combination with others.

Teenagers have one of the highest risks, and the risk increases as the number of persons (typically peers) in the car increases.

Children as passengers are at risk when the driver is drinking, and the risk is worse because they are less likely to be restrained passengers.

B. Trauma is primarily blunt force trauma:

1. Head injuries with skull fractures, hematomas

2. Abdominal trauma including laceration of major organs, hemoperitoneum

3. Chest trauma including steering wheel injuries such as aortic laceration, cardiac contusions. Additional chest trauma such as lung contusions and pneumothorax

4. Extremities: long bone fractures, soft tissue contusions

C. Trauma is worse for persons thrown from car; you are 5 times more likely to die in a crash if you are not wearing a seat belt

D. Airbags can or would save 10,000 lives per year in the U.S.

Falls

A. Worse in older persons. A third of persons over 65 will have a fall each year and 15% will result in serious injuries, half of which are fractures.

Hip and wrist and vertebral fractures are common and debilitating in older women because of accelerated bone loss (osteoporosis)

B. Head trauma with skull fractures is leading cause of death from falls (especially from falls at home in bathroom)

1. Subdural hematoma from tear of bridging veins and gradual accumulation of blood

2. Epidural hematoma from tear of middle meningeal artery; classic "lucid" interval

C. Many infant injuries occur from falls with baby walkers, which do not promote early walking or motor development, but do give a child increased height and mobility and, therefore, increased access to stairs, stoves, electrical cords, pools, etc.

Burns

A. There are about 2 million burn injuries each year in the U.S. Half of these involve children. Burn injuries are more common in the elderly, minorities, and in low-income housing. About 4,000 fatal burn injuries occur per year. Injuries may occur from:

1. Fires, hot gases

2. Scalding injuries (water, oils)

3. Chemical burns (acids, alkali)

B. Deaths caused by fires are often due to inhalation of the smoke containing toxic gases (carbon monoxide, hydrogen cyanide, etc.) and not the flames, particularly in closed spaces with combustion of synthetic materials.

C. Factors making burn injuries more severe:

1. greater total body surface area (TBSA)

2. head & neck area involvement

3. greater skin depth of burn

4. inhalation injury (breathing in hot gases)

5. greater age of patient

D. Classification of burns

1. Partial thickness - not all of epidermis and dermal appendages destroyed, allowing regeneration

2. Full thickness - entire epidermis and upper dermis destroyed, requires grafting

E. Complications

1. Survival with >90% TBSA burn is rare

2. Immediate problem is shock

3. Long-term problem is sepsis (lack of skin barrier to infection)

Hypothermia

A. Exposure to cold environment, core temperature $<35^{o}$ C (95^{o} F)

B. Systemic hypothermia made worse by underlying disease:

1. Liver disease (impaired gluconeogenesis)

2. Anemia

3. CNS disease (impaired judgment)

C. Frostbite - localized hypothermia - a form of gangrene

Hyperthermia

A. Exposure to a hot environment. Injuries due to heat are most prevalent in the first days of a heat wave, before acclimatization occurs.

B. Heat injury exacerbated by high humidity and decreased fluid intake. Dehydration can be suspected by physical examination with decreased skin turgor. Laboratory findings of increased analytes are found, such as elevated serum sodium (hypernatremia). The urea nitrogen and creatinine may be mildly increased in the absence of renal failure. Likewise, the hemoglobin and hematocrit appear artificially higher with hemoconcentration as free water is lost.

C. Heat injuries include:

1. Heat cramps: brief and intermittent muscle cramps from strenuous exercise and electrolyte depletion

2. Heat exhaustion: sudden, brief collapse preceded by weakness, headache, nausea. Due to cardiovascular collapse with hypotension and tachycardia

3. Heat stroke: potentially fatal, as core body temperature rises above 40.6 C (105 F) and there is inadequate or absent perspiration. Cardiovascular collapse with renal failure, rhabdomyolysis, and lactic acidosis

D. Other causes of malignant hyperthermia - cocaine, thyrotoxicosis, succinyl choline

Pressure injuries

A. Decompression injury - from diving accidents - nitrogen bubbles form in blood vessels

B. Blast injury: shock wave may be transmitted to lung or abdominal organs

C. Altitude sickness - pulmonary and cerebral edema can be life-threatening and persons affected must be taken immediately to a lower altitude

Electrical injuries

A. Factors involved:

1. AC worse than DC

2. Greater voltage and amperage make injury worse

3. Resistance - skin is a good insulator, but this is reduced by water, electrolytes

4. Path of current - worse across torso (heart) or head (brain)

B. Morbidity from heat injuries in tissues; mortality from interruption of nerve impulses or cardiac conduction

C. Lightning - high voltage direct current; avoid standing under a tall object, such as a tree; lightning can even be conducted inside a house via telephone or utility wires

82 deaths per year (more than hurricanes and tornadoes) mostly in young males; neurologic and cardiac injuries

1/3 of persons struck by lightning die soon after injury

Drowning

A. Does not require immersion in water

B. Laryngospasm may prevent water from entering lungs

C. Death from hypoxia.

Poisoning

A. Children are most often affected; these are accidental ingestions of products or pills found in the home. Children can grab and drink or swallow a toxic substance in just a few seconds.

B. Example: over the counter vitamins with iron contain 325 mg of ferrous sulfate and a lethal dose is 300 mg/kg, so only 10 tablets will kill an infant. Most containers have 100 tablets.

Emboli

A. Air emboli - air enters veins or arteries and occludes vasculature - complication of surgical procedures or presence of access lines, stab wounds; >100 cc needed on venous side for death.

B. Fat emboli - produced by trauma (long bone fractures or soft tissue) with release of lipids that block pulmonary or cerebral circulation.

C. Amniotic fluid emboli - rare but very lethal complication of pregnancy, usually seen during labor; symptoms resemble pulmonary embolus; debris from amniotic fluid occludes small pulmonary arteries.

D. Pulmonary emboli - can follow accidental trauma when patient is immobile

PATHOLOGY 6601, FALL 2006
Environmental Pathology
Dr. Edward C. Klatt

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 417-436)

LEARNING OBJECTIVES: At the end of the reading assignment and lecture, the student will be able to:

1. Detail the extent of environmentally caused disease in the U.S.

2. List the major constituents of air pollution and what illnesses they can cause.

3. List the major pneumoconioses, in whom they occur, and what pathologic appearances are produced.

4. Describe the pathologic findings with inhalation of organic dusts.

5. Describe the difference between farmer's lung and silo-filler's disease.

6. Describe the scope and the pathologic consequences of smoking-related diseases.

7. Describe the significance of radon gas exposure.

8. Describe the scope, effects, and legal definition of ethanol intoxication.

9. Describe the pathologic effects of the following poisonings and ingestions: carbon monoxide, methanol, lead, chlorinated hydrocarbons, organophosphates

10. List major environmental carcinogens and the neoplasms they produce.

11. List the types, patterns, and features of radiation injury.

INTRODUCTION

A. >400,000 non-traumatic occupationally-related illnesses in the U.S. each year with >40,000 deaths causally related to occupational exposures.

B. "Sentinel health event (occupational)" defined as any unnecessary disease, disability, or untimely death which is occupationally related helps the physician to recognize causal relationships.

C. Take an occupational, geographic, and drug history from patients because environmental diseases often mimic diseases from other causes.

EXTERNAL IRRITANTS

Though numerous substances can produce a contact dermatitis or conjunctivitis which is rarely serious, this may be the first sign of a more significant problem.

AIR POLLUTION AND INHALED TOXINS

A. **Toxic fumes or vapors**: NO_x, ozone, SO_2, chlorine, hydrocarbons (toluene), cyanates, ammonia, cadmium, or mercury can cause:

1. Acute pneumonitis, ranging from mild to severe, or

2. Contribute to obstructive pulmonary diseases: bronchitis, asthma, emphysema.

Persons with underlying lung disease or who are in poor health are at greatest risk.

B. **Pneumoconioses**: Produced by inhalation of inorganic dusts or aerosols in mining, shipbuilding, construction industries, some farming occupations, and persons living in close proximity to the above activities.

Development of disease depends upon:

1. concentration of the pollutant and the amount retained in lungs and airways

2. size & shape of contaminant: 1 to 5 micron diameter particles are worst

3. solubility+reactivity: >solubility = more acute disease; insoluble dusts collect and gradually produce fibrosis. Macrophages mediate the process.

"Coal workers pneumoconiosis" (CWP) or "black lung disease" from inhalation of coal dust in large amounts to produce "coal macules" which, if numerous, can produce fibrosis. (Simple anthracosis is not fibrogenic).

Silicosis caused by minerals with silicates such as quartz or talc produces silicotic nodules throughout the lung. There is a slight increase in risk for lung cancer (1.5 times average) with silicosis.

Asbestosis produces diffuse interstitial fibrosis over a period of decades; pleural plaques are

common. Mesothelioma is a rare neoplasm seen only with asbestos exposure. Asbestosis increases the risk for lung carcinomas, particularly in persons who smoke.
Berylliosis is manifested either chronically as multiple granulomas that resemble sarcoidosis or more acutely as a hypersensitivity pneumonitis. Very rare.

C. **Organic dusts** (moldy hay, bagasse, bird droppings) produce an extrinsic allergic alveolitis (rarely fibrosis) from allergens contained in them.

D. **Fibers, foams, dyes**: Asthma is associated with inhalation of cotton fibers (byssinosis), wood dusts, workers using polyurethane (isocyanates, formaldehyde), and plastic dyes.

E. **Smoking**: Contributes to the deaths of over 400,000 Americans per year--the single most important factor contributing to premature mortality, primarily from coronary atherosclerosis, lung cancer, and emphysema.

To a lesser extent, cigarette smoking increases cancer of the oral cavity, esophagus, and bladder, and contributes to gastritis and peptic ulcers. Cancer of the oral cavity is increased among "smokeless tobacco" users.

Morbidity & mortality from smoking is linearly correlated to numbers of cigarettes per day and years of use or "pack years" (1 pack/day x 20 years = 20 pack years). Risks diminish after quitting.

Passive smoking contributes to a slightly increased incidence of heart disease and minimally increased incidence of lung cancer in non-smokers.

F. **Radon gas**: Second most common cause of lung cancer. Radon seeps from soils in many areas of the U.S., collecting in houses and other buildings. Accounts for about 22,000 of 175,000 lung cancer deaths per year in the U.S. (but <10% of these 22,000 are in non-smokers).

G. **Carbon monoxide**: Poisoning occurs from auto exhaust and from poorly ventilated furnaces.

1. 10% CO level can occur on a crowded freeway, can cause drowsiness.

2. 20 to 30% CO level causes hypoxia and mental impairment.

3. Death occurs at 60 to 70%.

CO poisoning in the U.S. is most common in the Southeast, typically from use of unvented

kerosene heaters used in homes.

	Male		Female	
Disease Category (ICD-9 code)	**Total Deaths**	**Smoking Associated Deaths**	**Total Deaths**	**Smoking Associated Deaths**
Neoplasms				
Lip, Oral Cavity, pharynx (140-149)	5,180	3,873	2,645	1,264
Esophagus (150)	8,627	6,280	3,778	1,613
Pancreas (157)	13,429	3,065	14,339	3,415
Larynx (161)	3,031	2,525	816	602
Trachea, lung, bronchus (162)	91,295	80,571	61,593	44,242
Cervix uteri (180)	~~~	~~~	4,138	552
Urinary Bladder (188)	7,778	3,699	3,772	1,057
Kidney, other Urinary (189)	7,066	2,799	4,537	236
Total	136,406	102,812	94,618	52,949
Cardiovascular diseases				
Hypertension (401-404)	17,575	3,320	25,182	2,740
Ischemic heart disease (410-414)				
Aged 35-64	52,977	22,059	19,381	7,069
Aged 65 +	191,172	29,312	217,962	23,536
Other heart diseases	98,088	18,822	117,645	10,546
Cerebrovascular disease (430-438)				
Aged 35-64	9,726	3,898	8,103	3,586
Aged 65 +	51,369	4,697	88,452	5,264
Atherosclerosis (440)	6,008	1,644	10,050	883
Aortic aneurysm (441)	9,971	6,489	6,201	3,135
Other Arterial disease (442-448)	4,716	665	6,183	940
Total	441,602	90,906	499,159	57,699
Respiratory diseases				
Pneumonia, influenza (480-487)	38,295	8,802	47,420	6,774
Bronchitis, emphysema (490-492)	10,935	9,944	9,585	7,752
Chronic airways obstruction (496)	42,765	34,919	39,727	29,816
Total	91,996	53,665	96,731	44,342
Perinatal diseases				
Short gestation/ low birthweight (765)	2,198	227	1,768	175
Respiratory distress syndrome (769)	931	85	639	24
Other respiratory - newborn (770)	912	84	645	33
SIDS (798.0)	1,766	202	1,197	175
Total	5,808	599	4,249	408
Secondhand smoke deaths				
Lung cancer	~~~	1,110	~~~	1,890
Ischemic heart disease	~~~	14,407	~~~	20,646
Overall total	~~~	264,087	~~~	178,311

CHEMICALS AND DRUGS WITH SYSTEMIC EFFECTS

A. **Ethyl alcohol**: Acute alcoholism is the commonest form of drug overdose, is associated with 50% of vehicular accident fatalities; contributes to many other accidents. Chronic alcoholism leads to over 50,000 deaths per year from liver disease and gastrointestinal hemorrhage.

Legal limit for intoxication in many states is now 0.08% blood level; severe impairment occurs at 0.2%; coma and death occur at 0.4 to 0.5% from CNS depression.

B. **Methyl alcohol**: Toxicity from ingesting as little as 20 ml and occurs when it is metabolized to formic acid and formaldehyde. Principal targets are the retina and brainstem, leading to blindness and coma. Fomepizole, an alcohol dehydrogenase inhibitor, can be used to treat poisoning.

C. **Drugs of abuse**: 5,000-10,000 deaths/yr from overdosage. Chronic effects of most drugs of abuse are minimal. Cocaine: ischemic heart disease (from coronary arterial vasoconstriction, thrombosis, or accelerated atherosclerosis) or malignant hyperthermia

Most diseases resulting from drugs of abuse stem from infections (bacterial sepsis, hepatitis, AIDS) from non-sterile intravenous injection, from concomitant chronic alcoholism, and from mental impairment leading to accidents.

D. **Lead**: Found in plumbing pipes, paint (in old houses), poorly glazed pottery, and the atmosphere from industry and leaded gasoline. Ingested or inhaled lead accumulates in bone, blood, and soft tissues, but toxic effects are primarily neurologic impairment from demyelinating injury to neurons, especially in children.

Other heavy metals (As, Hg) also can cause neuropathy.

E. **Insecticides**:

1. Chlorinated hydrocarbons (e.g., DDT) are minimally toxic to humans, but they accumulate in the food chain, are ingested by humans, and can lead to CNS depression.

2. The organophosphates (e.g., parathion, malathion) are acetyl-cholinesterase inhibitors that do not persist in the environment but are capable of producing more acute disease including paralysis, arrhythmia, and respiratory failure.

F. **Carcinogens**: Many substances have been suspected of causing malignancies, but the following list includes the best known:

Asbestos	Mesothelioma, Bronchogenic carcinoma, GI carcinoma
Nickel	Nasopharyngeal and Lung carcinomas
Arsenic	Carcinomas of skin, lung, and liver
Hydrocarbons (benzene)	Bladder carcinoma, Leukemia
Nitrites	Gastric carcinoma
Vinyl chloride	Hepatic angiosarcoma

RADIATION INJURY

A. Ionizing radiation comes in two forms:

1. electromagnetic waves (X-rays, gamma rays) that penetrate tissues deeply but pass through without hitting many cells

2. charged particles (alpha, beta) that penetrate poorly but hit many cells.

B. Radioactive isotopes are characterized by their half-life: U-238 is 4.5 billion years, I-125 is 58 days.

High levels of long-lived isotopes in the environment are dangerous and can get into the food chain (Strontium-90 gets into cow's milk and into the bones of humans).

C. Tissues are damaged with radiation either by:

1. direct hits on genetic material (DNA) to produce mutations with cell death, birth defects, or carcinogenesis as a result, typical of nuclear accidents (Chernobyl)

2. production of free radicals that destroy cells, typical of therapeutic radiation (hospital).

D. Cellular radiosensitivity is most closely related to mitotic activity: germ cells in testis and ovary, bone marrow, and GI tract lining are most sensitive; muscle, bone, and nerve are least sensitive. This may partially determine which tumors are radiosensitive.

E. Morphologic changes to tissues consist of cytologic alterations (nuclear swelling, pyknosis, karyorrhexis), cytoplasmic vacuolization, and chromosomal damage with disorderly mitoses;

F. Morphologic vascular changes to tissues are time dependent:

1. early - vascular dilation, endothelial swelling, focal necrosis of vessel wall, occasionally with hemorrhage and thrombosis.

2. late - medial fibrosis, hyalinization, endothelial proliferation, sclerosis of contiguous connective tissue with tissue atrophy and fibrosis.

Radiation-induced injury patterns include:

Bone marrow failure from total body radiation - as little as 200-300 rads may be lethal.

Gastrointestinal syndrome - begins with mild GI symptoms at doses of 50-100 rads but more apparent at 300-1000 rads.

Cerebral syndrome - convulsions, coma, and death; usually appears only above 5000 rads.

Late sequelae of nuclear accident survivors include leukemias, lymphomas, and carcinomas (breast, thyroid, stomach, esophagus, lung, bone).

Therapeutic radiation is given in carefully divided dosages to a set maximum to specific areas. Radiation-induced fibrosis and necrosis may still occur.

PATHOLOGY 6601, FALL 2006
Forensic Pathology I
Dr. Edward Klatt

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 442-444)

LEARNING OBJECTIVES: At the end of this lecture and reading assignment, the student will be able to:

1. Describe what a medical examiner does.

2. Outline which deaths must be reported to the medical examiner.

3. Describe how a death certificate should be properly filled out.

4. Define what is meant by "mechanism of death" as compared to "cause of death" and the difference between intermediate, intervening, and underlying causes of death.

ROLE OF THE MEDICAL EXAMINER

I. INTRODUCTION

Description of the duties of the Medical Examiner

1. Under the direction of a board certified forensic pathologist.

2. Personnel and training.

II. MEDICAL EXAMINER JURISDICTION

A) Statute governing medical examiners in the State of Florida (Section 406)

B) What the average physician needs to know

III. DEATH CERTIFICATION

A) Define “Cause of death”

- Immediate cause

- Intervening causes

- Underlying cause

B) Define “Mechanism of death”

The physiology of dying. This is not something which should be recorded on the death certificate.

C) Define “Manner of death”

Natural vs. Non-natural

If non-natural, is it:

- Accident

- Suicide

- Homicide
- Undetermined

PATHOLOGY 6601, FALL 2006
Forensic Pathology II
Dr. Edward Klatt

LEARNING OBJECTIVES: At the end of this lecture and the small group session, the student will be able to:

1. Describe the differences between an entrance and an exit gunshot wound.

2. Describe the differences between a close range (contact) and intermediate and distant range gunshot wound.

3. List factors that determine the type of wound path and injury pattern with bullet tracks.

4. Describe the basic features of a shotgun wound.

5. Define and use in context the following terms:

   - Stab wound
   - Incised wound
   - Abrasion
   - Patterned abrasion
   - Contusion
   - Laceration

6. Define and compare asphyxial deaths due to:

   - Strangulation
   - Suffocation/smothering
   - Hanging

MECHANISMS OF INJURY

I. INTRODUCTION

This lecture will focus on various types of injuries and the mechanisms. We will also discuss the forensic implications of injuries and their medicolegal significance.

The investigation and certification of any injury or injury related death requires correlation between the physical findings on the body and a reconstruction of the circumstances surrounding the injury event. Physical findings alone can give an indication of how the injury or death came about, but are almost never sufficient to accurately explain what happened. Careful observation and documentation of associated findings and historical information is crucial to understanding the

injury and putting the physical findings into context.

II. MECHANISMS OF INJURY AND THEIR FORENSIC CONSEQUENCES

A. Injuries due to gunfire

Gunshot injuries are responsible for over 30,000 deaths per year in the U.S.. No matter what specialty or area of medicine you pursue in your career, you will probably deal with these types of injuries or their consequences to the patient and/or their family. This discussion will focus on the physical findings of gunshot wounds.

1) **Entrance Wounds:** The features of an entrance wound depend on the range of fire and location on the body.

Contact range - The wound can be of variable size depending on the type of weapon and the tightness of the contact with the skin surface.

- Soot and powder in and around the wound
- Singing and searing of wound margins.
- Carboxymyoglobin formation.
- Blow-back effects (variable degree of laceration depending on weapon and wound location).
- Muzzle imprint - abrasion of surrounding tissue with patterned injury.

Intermediate range - Gunpowder stippling or "tattooing" the sine qua non of this type of entrance wound.

- Fragments of burning and unburned gunpowder strike and penetrate the skin and become embedded in the epidermis. These embedded fragments can not be washed away (unlike soot). Distribution and density depends on type of weapon, type of ammunition and range of fire.
- Defect in skin of variable shape and size. You can not accurately estimate caliber of weapon from entrance defect size.
- Marginal abrasion about defect due to scraping and deformation of skin prior to actual perforation by projectile. Shape depends on angle of entry. Soot is present in some intermediate range wounds depending on

range and type of weapon.

"Distant" range - Indeterminate a better term. Only findings are those of an entrance wound without specific findings allowing for range estimation. Intermediary targets can affect appearance of wound.

2) **Exit Wounds:** These can have a extremely variable appearance. In most cases, there will be no marginal abrasion.

Shored exit wounds can occur when the skin is supported as the projectile exits. This results in an exit wound with marginal abrasion.

3) **Wound path and injury:** Track through the body which causes injury to internal structures. Wounding potential is a function of projectile velocity and design characteristics. Formation of a temporary cavity becomes important in high velocity wounds (rifles as opposed to most handguns).

- Secondary missile (fragments of bone and other objects carried into wound may cause additional damage.

- Directionality of track can be determined by path of secondary missiles and appearance of damaged bone (bevelling).

- Recovery of projectile. Ballistic information from projectile crucial in identifying weapon used. Proper handling required so that this evidence is preserved.

4) **Shotgun wounds:** Basic description of shotgun features, mechanics and cartridge construction.

- Contact or near contact range

  Large round entrance defect with marginal abrasion and variable amounts of soot.

- Intermediate range

  "Cookie cutter" appearance to entrance wound.

  Wad marks.

  Stippling from gunpowder and/or filler materials.

- Indeterminate range.

  Variable pattern of shot dispersion depending on range, choke, gauge and pellets.

  Billiard ball effect. Pattern of dispersion of pellets in the body does not allow one to estimate range.

B. Sharp force injuries

1) **Stab wounds:** Stab wounds are sharp force injuries that are deeper than they are long.

   - Depth of penetration loosely correlated to blade length of weapon used.
   - Appearance of entrance wound has features which can help identify the type of weapon used.
   - Single vs. double edged. Presence of a sharp or blunted margin. (Serrated blade will not have any specific features unless there is dragging with insertion or withdrawal).
   - Width of blade. Variably correlated to size of wound. Langer's lines will have marked effect on wound appearance. Thickness of blade can be approximated only after edges have been opposed.
   - Twisting of blade can produce irregular wound with altered features.
   - Hilt mark or "quillon".
   - Taper of blade or shape can be estimated by size of wound at different depths of penetration.

2) **Incised wounds:** Sharp force injuries that are longer than they are deep.

   - Defensive wounds. These are incised wounds of the extremities suffered in trying to ward off attack.
   - Hesitation marks. Superficial incised wounds seen in suicidal sharp force injuries.

C. Blunt force injuries

1) **Abrasion:** Scraping away of superficial layer of epidermis. Tissue tags at one end may indicate direction of force.

   Patterned abrasions are extremely helpful in identifying object that caused the injury.

2) **Contusion:** Rupture and crushing of underlying vessels and tissue without breakage of skin. Can be patterned. External findings can be much less striking that underlying tissue damage would lead you to expect.

3) **Laceration:** Rupture of skin and tearing of underlying tissues. Marginal abrasion and tissue bridges usually seen. Undermining can indicate direction of force.

Dating of blunt force injuries. Based on appearance of injury (drying, scab formation, color changes, etc.) and microscopic examination of injury.

D. Asphyxial Injuries

1) **Strangulation:** Compression of the vessels of the neck with alteration of cerebral blood flow. Airway occlusion rarely a significant factor in strangulation deaths.

   - **External findings variable.** Contusions and abrasions of neck. Petechiae of face, sclera, conjunctivae and mucosal surfaces.

   - **Internal findings.** Hemorrhage of neck musculature. May see tracheal cartilage fractures and breakage of hyoid bone.

2) **Suffocation/smothering:** May be impossible to diagnose on basis of physical examination alone. May see petechiae, but this is variable and they are often absent.

3) **Hanging and ligature strangulation:** Ligature abrasion usually seen unless wide, soft material used. May see patterning which corresponds with material used.

- In hangings, ligature abrasion will show definite point of suspension.
- In strangulation, ligature abrasion usually horizontal.
- Internal injuries are rare or absent in ligature asphyxial deaths. CNS will have evidence of hypoxic injury if there is some period of survival.

III. CONCLUSION

Injuries have medicolegal significance (either civil or criminal). Their appearance and features are important in allowing a reconstruction of what happened to the injured individual. Careful observation and documentation of any injury is essential, especially if lifesaving or other therapeutic procedures alter the injury.

U.S. Deaths Related to Injuries - 1998

All injury deaths	146,941
Motor vehicle related	42,337
Firearms	30,708
Poisoning	18,392
Falls	13,301
Suffocation	11,095
Drowning	5,096
Burns	3,813
Sharp force injury	2,693
Blunt force injury	1,467
Machinery	1,018

By mode of death:

Accidents	94,331	
	Motor vehicle	42,191
	Fall	12,595

	Poisoning	10,801
	Other	8,802
	Suffocation	4,585
	Drowning	4,406
	Burns	3,363
	Blunt force	1,059
	Machinery	1,018
	Firearms	866
	Sharp force	121
Suicide		30,575
	Firearms	17,424
	Suffocation	5,726
	Poisoning	5,072
	Fall	621
	Sharp force	476
	Drowning	375
	Burns	161
	Motor vehicle	133
Homicide		17,893
	Firearms	11,798
	Other	2,570
	Sharp force	2,087
	Suffocation	661
	Blunt force	399
	Burns	197
	Poisoning	86
	Drowning	66
	Fall	29
Undetermined		4,142

PATHOLOGY 6601, FALL 2006
Nutritional Diseases
Dr. Edward Klatt

READING ASSIGNMENT: Pathologic Basis of Disease, (7^{th} ed: 408-428)

LEARNING OBJECTIVES: At the end of this reading assignment and lecture, the student will be able to:

1. List the causes for and major pathologic appearances of malnutrition.
2. Define obesity in terms of body mass index.
3. Describe health problems related to obesity.
4. List the major dietary sources of vitamins and minerals.
5. Describe the pathologic disorders associated with deficiencies of fat soluble vitamins.
6. Describe the pathologic disorders associated with deficiencies of water soluble vitamins.
7. Describe the pathologic disorders associated with mineral deficiencies.
8. Outline relationships between diet and cancer.

MALNUTRITION

A. Malnutrition affects 10 to 15% of the earth's population, mostly children, mostly in developing nations. It occurs less commonly in developed nations among the disadvantaged and among

drug users (especially alcoholics).

B. Etiologies for malnutrition include:

1. Inadequate total dietary intake

2. Dietary imbalance:

   a. often from alcoholism

   b. also from ignorance, as in Ronald Reagan's famous quote, "Ketchup is a vegetable" or in the excerpt from a bulletin announcing a seminar for teenagers: "An expert will speak this evening on the importance of a proper diet. Pizza will be served"

3. Malabsorption - from gastrointestinal, pancreatic, biliary tract, or liver disease

4. Debilitating disease - cancer and cancer treatment

5. Iatrogenic

   a. Dieting - depends upon the completeness and balance (Weight Watchers is a good one; your patients will ask your advice about diets)

      Note: the less you eat, the more important it is to eat a variety of foods to obtain essential nutrients

   b. Anorexia - basis in psychiatric disorder

   c. Total parenteral nutrition (TPN) - an attempt to replace diet in long-term care of obtunded patients or in persons who have lost considerable bowel from surgery; nowadays it works well, but is expensive; may lead to portal fibrosis and fatty change in liver in infants

   d. Surgical procedures (jejunoilial bypass, stomach stapling) - have fallen out of favor and have associated health risks (operative complications, malnutrition)

C. Pathologic appearances in malnutrition

1. Kwashiorkor: primarily a protein calorie deficiency, leading to fatty liver, ascites, edema (from failure of lipoprotein transport and protein metabolism)

2. Marasmus: total calorie deprivation (proteins, carbohydrates, fats) with severe wasting (<60% of ideal body weight for age)

D. Malnutrition assessment

1. Laboratory measures of nutritional status can include albumin and prealbumin. Albumin has a month half-life and prealbumin 2 days. Thus, long term and short term nutritional status can be assessed.

2. Prealbumin is decreased when inflammation is present, regardless of nutritional status. Albumin can be low with liver diseases (decreased synthesis) or with renal diseases (albuminuria).

OBESITY

A. Intake of calories exceeds metabolic rate of use; common problem in the U.S., even in children. A third of persons over age 20 in the U.S. are overweight.

Obesity can be defined by the body mass index (BMI). The BMI can be measured by testing impedence from a small electrical current passed through the body (fat has less water than muscle and provides more resistance). The BMI can be estimated as:

$$\text{BMI} = \text{weight in kilograms} \div (\text{height in meters})^2$$

The ranges for BMI in regard to health risks are as follows:

20 - 24	Ideal
25 - 29	Increased health risk
30+	Greatly increased health risk

Obese persons have a >50% risk for a total serum cholesterol >25 mg/dL

Moderately obese persons have a five-fold risk for diabetes mellitus; for severe obesity the risk is ten-fold.

B. Caloric Intake - How many calories do you need?

For an adult, 10 calories per day per pound is needed to maintain weight with normal daily activities. Thus, a 150 lb person needs about 1500 calories.

Exercise can increase calorie use.

Growing children and teenagers need more.

Increased activity has a "carryover" effect with increased metabolism

Exercise can burn calories (average for a standard 70 kg person) as follows:

Activity (moderate)	kcal/minute
walking	3
cycling	4
dancing	5
ice skating	6
swimming	6
jogging	10
shovelling	15

A good aerobic exercise with cardiovascular benefit is to climb 10 flights of stairs once a day.

Young adults can generally eat more and not gain weight, but metabolism tends to slow in the mid-30's (and middle-aged people become more inactive), so that is when many adults begin to gradually gain weight. (Tip for health care workers: don't join the Department of Cafeteria Medicine)

Glycemic Index: this is a measure of the ability of foods to raise the blood sugar. Many factors together, including carbohydrate type, fiber, protein, fat, food form and method of preparation, determine the GI of a particular food.

B. Complications of obesity: truncal obesity (mostly in men) is worse than fat distribution to hips and extremities (mostly in women) because of greater association with

1. Diabetes mellitus

2. Hypertension

3. Coronary artery atherosclerosis.

C. Other problems associated with obesity:

1. Gallstones

2. Degenerative joint disease

3. Decreased HDL cholesterol with risk for atherosclerosis

4. Endometrial carcinoma in women, renal cell carcinoma in men, colon carcinoma (but probably not breast carcinoma)

D. Surgical therapies

Stomach stapling and jejunoileal bypass have fallen out of favor--they only provide a benefit in very selected cases. Liposuction is NOT weight reduction surgery; it is for body contouring.

E. Diets

If you diet, your body adapts to the lower caloric intake and becomes more efficient at utilizing and storing as fat calories taken in. Thus, if you go off the diet, you gain weight even faster than before. The best diet is the one your patient can stick with.

Americans are enfatuated with "quick fixes", fads, and pill-popping, so a popular adjunct to weight loss is the infamous "diet pill".

1. Amphetamines ("uppers") were first used for this purpose, but fell out of favor with their increasing use as drugs of abuse.

2. "fen-phen" - a combination of dexfenfluramine and phentermine (a noradrenergic agent). Dexfenfluramine increases serotonergic activity by stimulating serotonin into brain synapses. On the basis of the serotonin hypothesis of appetite control, this would be expected to reduce appetite.

   It worked, and diabetics on it had good control too, however, the uncommon but potentially fatal side effects of d-fenfluramine of pulmonary hypertension and cardiac valvular sclerosis led to its removal from the market. More common side effects were psychiatric, including depression.

   The newest antidepressant-antiobesity drug is sibutramine, which produces its effects by norepinephrine, serotonin, and dopamine reuptake inhibition.

3. Orlistat - an inhibitor of pancreatic and gastric lipase when taken with meals, thus inhibiting the hydrolysis of triglycerides so that absorption of fats is reduced, by about 30% at the most. It does not appear to affect the absorption of other nutrients or drugs.

4. A host of diet "fads" come and go, with numerous books, promotional tapes, videos, and

seminars devoted to diet and weight loss. As a physician, you will be asked by your patients about diets they are considering (e.g, "Is the grapefruit diet for me?").

Legitimate weight loss programs incorporate life-style changes, including exercise, that have more longer-lasting effects.

Also, some diet programs require physician approval (to avoid potential complications from underlying diseases).

Weight loss should be gradual (1 pound per week). Diets should incorporate a variety of foods that are readily available. Beware of diet programs selling supplements or diet pills.

The "Atkins diet" like many scams, does have a shred of reality behind it, based upon "specific dynamic action" (SDA) of foods. More complex proteins and fats require more energy to process, while simple carbohydrates do not. However, the differences in SDA are not marked. If total calories are reduced, lipolysis and ketosis with acidosis occurs.

F. Special Diets

For specific disease states, diet may play an important role, as in following examples:

1. Diabetes mellitus: Diabetics, particularly those with type II, try to enhance glucose control and weight through diet.

2. Gout: persons with symptomatic hyperuricemia may benefit from a diet that reduces purine metabolism to uric acid (no red wine, asparagus, fish).

3. Phenylketonuria (PKU): This rare genetic disorder results from an inborn error of metabolism leaving victims unable to utilize phenylalanine. The most devastating effect is mental retardation. A phenylalanine-free diet is the treatment.

   However, a mother with PKU must be on the diet BEFORE pregnancy begins to be most effective, and stay on the diet during pregnancy.

   The affected baby must then be placed on the diet, which is maintained during early childhood.

NUTRITIONAL DEFICIENCIES - FAT SOLUBLE VITAMINS

A. General features

1. Fat soluble vitamins have fairly common dietary sources and two (D and K) can be made endogenously. They can be stored in liver or fat.

2. Require adequate digestion and absorption of fats. Conditions decreasing absorption include:

    a. malabsorption in small intestine
    b. pancreatic disease (decreased lipase)
    c. biliary tract disease (especially obstruction)
    d. liver disease (especially affects vitamin K)

B. Vitamin A

1. Dietary sources in vegetables (such as carrots) with carotenes. Stored in the liver

    Functions in maintaining epithelia (skin, cornea, mucus membranes)

2. Deficiency leads to: xerophthalmia, keratomalacia, and corneal scarring; increase in infections

3. Excess acutely causes headache; long term causes hyperkeratosis, increased teratogenicity in pregnant women

C. Vitamin D

1. Manufactured in skin with exposure to sunlight; major source in diet is fortified milk, also salt water fish and some grains

2. Functions to promote mineralization of bone and maintain serum ionized calcium level (preventing tetany)

3. Serum calcium levels are regulated by parathormone from the parathyroid glands. The body's bone mass provides a large calcium reserve.

4. Causes of decreased calcium include:

    a. decreased dietary intake (of calcium or vitamin D)
    b. malabsorption (of calcium or vitamin D)
    c. decreased sunlight exposure (diminished endogenous vitamin D)
    d. phosphate binding aluminum hydroxide antacids (Maalox) - calcium loss

5. Deficiency states:

   a. rickets: occurs in growing children; osteoid seams and epiphyses are widened, leading to skeletal deformities

   b. osteomalacia: occurs in adults; bone is not properly mineralized and is osteopenic and resembles osteoporosis

D. Vitamin E

1. A deficiency state is extremely rare.

2. Vitamin E has been touted as having anti-carcinogenic and anti-aging properties from an anti-oxidant effect, but this has not been proven to play a major role in increasing the longevity of the population.

E. Vitamin K

1. Found in many vegetables and plant oils; also a small amount is generated by intestinal bacteria; some is recycled; about 30 days' supply stored in liver

2. Functions in generation of clotting factors II, VII, IX, and X in the extrinsic pathway; also helps to generate anticoagulant proteins C and S

3. Deficiency (from malabsorption, dietary lack, chronic liver disease) leads to bleeding. Newborns are given vitamin K to prevent hemorrhagic disease of newborns.

NUTRITIONAL DEFICIENCIES - WATER SOLUBLE VITAMINS

A. General features

1. Are widely distributed in many foods

2. Deficiencies can occur quickly because most of them are not stored in the body, particularly in babies dependent upon milk as a major food source

B. Thiamine (B_1)

1. Source in bran or hulls of cereal grains; refined flour and sugar lack it

2. Functions in generation of ATP and in maintaining peripheral nerve conduction

3. Deficiency states:

   a. "wet" beri-beri: dilated cardiomyopathy with congestive heart failure

   b. "dry" beri-beri: peripheral neuropathy

   c. Wernicke's or Korsakoff's syndromes (in alcoholics)

C. Riboflavin (B_2)

1. Found in meats, milk, and vegetables

2. Functions in basic metabolic pathways, but deficiency does not produce any characteristic finding.

3. Deficiency may produce: cheilosis, glossitis, ocular interstitial keratitis, scaling dermatitis

D. Niacin (B_3)

1. Found in grains, beans, sunflower seeds; can also be endogenously synthesized from tryptophan (which is blocked by leucine)

2. Functions in a variety of metabolic pathways for fats, proteins, and carbohydrates (especially glucose)

3. Pharmacologic doses in the range of 3 g/day have been used to treat hyperlipidemia in persons with diabetes and peripheral vascular disease for whom the "statin" drugs are not effective

4. Deficiency state is called pellagra, and is characterized by:

   a. dermatitis (on sun-exposed areas)
   b. dementia
   c. diarrhea

E. Pyridoxine (B_6)

1. Found widely in foods

2. Functions in a variety of metabolic pathways, required for synthesis of neurotransmitter GABA.

3. Deficiency state similar to riboflavin, plus peripheral neuropathy

F. Folic acid (folate)

1. Found in green and yellow leafy vegetables

2. Functions in synthesis of purines and methionine

3. Deficiency (common in alcoholics) leads to megaloblastic anemia

4. Adequate (0.4 mg/day) intake by pregnant women helps to lower risk for neural tube defects in fetuses. Since January, 1998, folic acid has been added to all enriched grain products by order of the U.S. Food and Drug Administration; accordingly, the incidence of folic acid deficiency has fallen markedly.

G. Cobalamin (B_{12})

1. Found in animal products (ultimate source is bacteria) and lacking in a strict vegetarian diet; however, enough can be stored in the liver to last for years

2. Functions in formation of methionine from homocysteine and in conversion of methylmalonyl coenzyme A to succinyl coenzyme A

3. Deficiency leads to pernicious anemia (megaloblastic anemia, along with dorsal and lateral tract degeneration of spinal cord). Causes include:

   a. atrophic gastritis (lack of intrinsic factor, IF)
   b. loss of terminal ileum (lack of absorption)

H. Ascorbic acid (C)

1. Found in fruits and vegetables, milk, and liver

2. Functions in hydroxylation of proline in collagen synthesis

3. The body's use of C increases with stress, but a severe prolonged deficiency leads to scurvy characterized by:

   a. purpura from leaky blood vessels

   b. hyperkeratotic rash

   c. delayed wound healing

   d. anemia

   e. failure of osteoid formation

MINERALS

A. Iron

1. Found in animal products (as heme), some in vegetables (as inorganic iron)

2. Functions in manufacture of heme in hemoglobin

3. Deficiency of iron is the most common nutritional deficiency worldwide (after chocolate deficiency) and can result from:

   a. poor diet

   b. impaired duodenal absorption

   c. increased requirement in pregancy or childhood

   d. blood loss

      i. menstruation
      ii. gastrointestinal hemorrhage

4. Deficiency leads to hypochromic, microcytic anemia

B. Calcium

1. Found in milk, bread; a lot of calcium in the diet causes constipation

2. Required for bone formation, maintenance of serum ionized calcium

3. Hypocalcemia leads to tetany, hypercalcemia leads to cardiac arrhythmia

C. Magnesium

1. Found in many foods; a lot in the diet leads to diarrhea

2. Required for regulation of ATP stores

3. Levels of magnesium are linked to calcium, potassium and phosphorus

4. Deficiency leads to symptoms of hypocalcemia

D. Sodium

1. Normal diet has plenty of sodium; the problem is avoiding it. Sodium chloride makes a good preservative and adds flavor, so packaged and canned foods have lots of sodium. The average can of soup may have nearly a gram of sodium.

2. Increased sodium intake is associated with hypertension.

E. Trace elements

1. Zinc: a host of enzymes require it; a deficiency is rare but there are many non-specific manifestations. Wound healing requires zinc.

2. Copper: needed for heme synthesis and neurotransmitter synthesis; there is too much copper storage in Wilson's disease (an inherited disorder of copper metabolism).

3. Selenium: functions as a component of glutathione reductase (an antioxidant); a deficiency leads to myopathy

F. Fiber: increased dietary fiber reduces the incidence of diverticulosis of the colon and is also felt to decrease the risk for colon cancer. Increased fiber aids gastrointestinal motility in older adults prone to constipation.

G. Comparison of selected dietary constituents, ancient and modern:

	Ancient Man	Modern U.S.
% of calories from fat	21	42
Polyunsaturated/Saturated fat ratio	1.4	0.4
Fiber (in gram)	100-150	20
Sodium (in mg)	690	2300-6900
Calcium (in mg)	1500-2000	740
Ascorbic acid (in mg)	440	90

H. Fluoride and Dental Caries

Flourine is typically complexed with sodium and available in water and food as sodium fluoride. Flouride is attracted to and incorporated into hydroxyapatite crystal that forms the enamel covering of teeth. The surface of a tooth is undergoing constant remodelling, and when fluoride is available, it is incorporated into hydroxyapatite crystal. In fact, fluoride is more readily taken up into damaged, demineralized enamel than into normal enamel. Dental plaque contains calcium, phosphorus, food material, and salivary material. The plaque is strongly adherent to the enamel surface.

Fluoride provides more protection against tooth decay (dental caries) because fluoride replaces carbonate, which is more readily disolved by acid generated from bacteria in overlying plaque.

Tooth decay results when a buildup of dental plaque allows cariogenic bacteria such as Streptococcus mutans to increase in number and when foods high in sugars such as glucose provide a substrate for

enhanced bacterial growth. The acids produced by the bacteria damage the enamel.

Most of the fluoride is available in water and beverages consumed. Fluoride is available also in toothpaste and mouthwashes. Additional forms are available to apply topically. Dietary fluoride supplements are available. Saliva helps to concentrate any ingested fluoride. The most cost effective method for reducing the risk for dental caries in a population is supplementing the public water supply with flouride to the level of 1 ppm (1 mg/L).

Too much fluoride can lead to hypomineralization of enamel in a process known as fluorosis. Virtually all cases are of the "mild" variety with no visible changes, and water fluoridation has not led to increased cases of moderate to severe fluorosis. Children under the age of 6 are at most risk for fluorosis, and having small children use toothpaste without a high concentration of fluoride, or using less toothpaste, can be encouraged.

TOXINS AND ADDITIVES

Poor food storage conditions can result in growth of microorganisms (particularly fungi) that can elaborate toxins which are then ingested. Examples include:

Aflatoxin on moldy peanuts (induces liver cancer)

Ochratoxin on moldy grain (a nephrotoxin).

A thousand years ago in Europe, ergot poisoning from moldy rye was a serious problem.

Some food addititves, such as monosodium glutamate (MSG), cause severe reactions in some people.

NUTRITIONAL STRATEGIES TO REDUCE CANCER RISK

Maintain desirable body weight; eat a varied diet

Include 3-5 servings of vegetables and 2-4 servings of fruits (especially green and yellow vegetables rich in vitamin A and citrus fruits high in vitamin C)

Eat more high fiber foods such as whole grain cereals, legumes, vegetables and fruits to attain 20-30 g/day of fiber

Aim for no more than 30% total calories from fat (and no more than 10% of calories from saturated fat)

Limit consumption of alcohol; and limit consumption of salt-cured, smoked, or nitrite-preserved foods

Vitamin A may help reduce the risk for breast cancer.

NUTRITIONAL STRATEGIES TO REDUCE HYPERTENSION

Increase the amount of fruits and vegetables in the diet

Increase intake of low-fat dairy foods

Reduce intake of total fat and saturated fat

Reduce intake of sodium

EATING WITH YOUR HEALTH IN MIND:

The most important elements of healthful eating are:

To eat a daily diet that helps you either lose weight or keep your weight in the range that is considered "healthy" or "ideal" for your height and sex.

To choose a diet that is low in saturated fat and cholesterol, and moderate in total fat intake.

To eat foods high in fiber.

To reduce the number of calories in your diet that come from processed sugars.

To choose and prepare foods with less salt.

To drink the daily recommended amount ofwater: 8 to 10 cups (64 to 80 ounces) of water a day.

If you drink alcoholic beverages, drink them in moderation (no more than 1 drink per day for women and no more than 2 drinks per day for men).

REDUCING FAT IN THE DIET:

Less than 30 percent of your daily calories should come from fat.

Broil, roast, bake, boil, steam, or microwave food; avoid fried foods.

Season vegetables and meats with herbs and spices rather than using fatty sauces, butter, or margarine.

Choose low-fat or skim milk, rather than whole milk.

Substitute plain low-fat yogurt or low-fat cottage cheese whipped in a blender for sour cream or mayonnaise.

Substitute egg whites for whole eggs when baking (substitute 2 eggs without yolks for every whole egg).

Limit the number of egg yolks when scrambling eggs.

Choose lean cuts of meat and trim off any visible fat.

Remove the skin from poultry.

REDUCING SUGAR IN YOUR DIET:

Read the label; look for any of the following types of sugar listed as the first or second ingredient (the most abundant ingredient in the product): corn syrup, sucrose, fructose, glucose, dextrose, maltose, lactose, maltodextrin, mannitol, sorbitol, malt syrup, honey molasses, or maple syrup.

Substitute water or unsweetened beverages for sugared soft drinks.

Snack on fresh fruits and vegetables or dried fruits rather than sugary snacks such as candies, cookies, cakes, and pies.

ADDING MORE FIBER TO YOUR DIET:

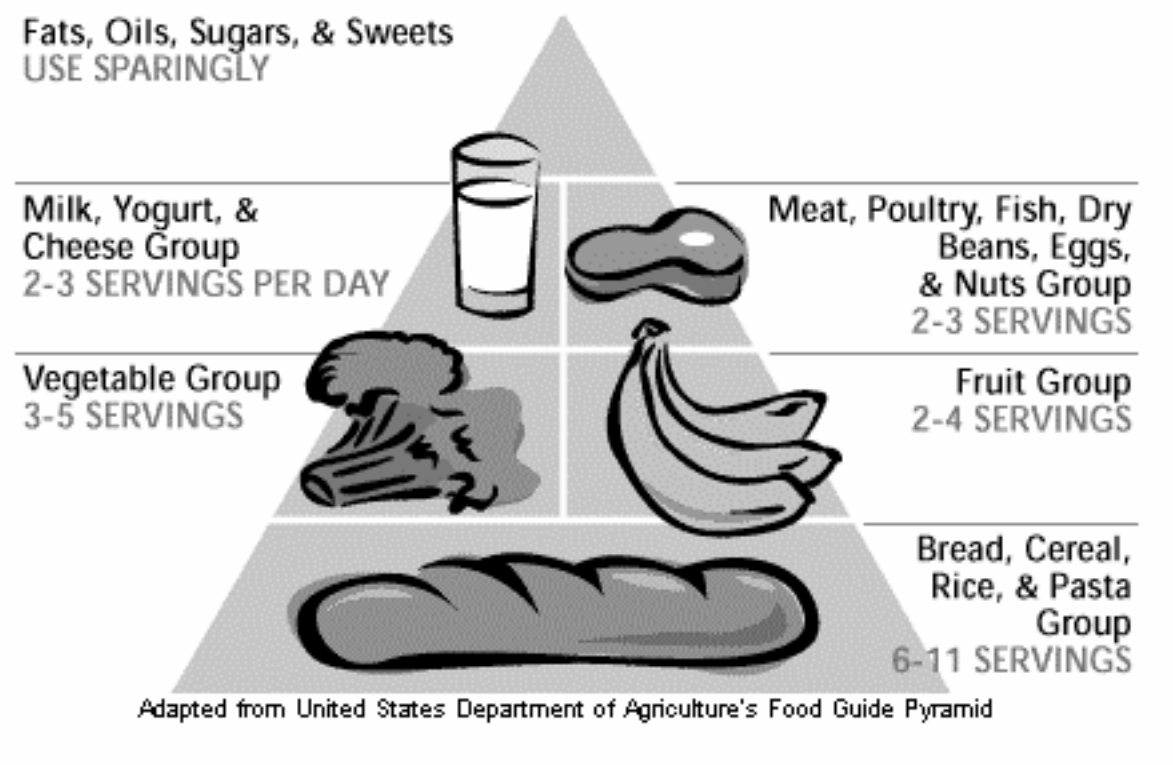
Eat whole-grain cereals and breads.

Eat vegetables uncooked; if you cook them, steam only until they are just tender.

Avoid peeling fruits and vegetables; when appropriate leave the skins on--the skins are high in fiber.

Add beans to soups and salads.

Snack on fresh fruits and vegetables or dried fruits (such as raisins or figs).



WHAT GOES ON YOUR PLATE DETERMINES YOUR FATE

PATHOLOGY 6601, FALL 2006
AGING
Dr. Morton Levitt

READING ASSIGNMENT: Pathologic Basis of Disease, (7th ed.: 42-44)

LEARNING OBJECTIVES: At the end of this reading assignment, small group exercises and lecture, the student will be able to:

1. Describe the demographics of aging in the U.S.

2. List general theories for aging.

3. Describe organ system changes in aging with particular regard to: heart, kidney, lung, and musculoskeletal system.

4. List general systemic changes with aging.

AGING

A. Demographics of aging in the U.S.

   1. Birth rate is falling in the U.S. - about 15/1000; Death rate has also been slowly falling - about 9/1000; overall growth rate is about 0.9% (compared to Kenya 4.2% and Sweden 0.1%))

   2. Longevity has increased: life expectancy in U.S. in 1900 was 47 years but now for males is 72 years, for females 79 (compared to Japan 76 for males and 82 for females or Ethiopia 50 for males and 53 for females)

   3. Population in the U.S. is aging and geriatric medicine will become much more important in the next century

B. Aging and health

   1. Aging is NOT a disease, but the changes that occur with aging make aged persons more susceptible to disease

2. Theoretical maximum is 120 years and is not increasing; ideal maximum is currently about 85 years

3. 80% of causes of premature deaths have been eliminated, and changes in lifestyle may further decrease or postpone chronic illness

   a. acute illness (infections) has been prevented (vaccination) or controlled (antibiotics); surgically amenable diseases such as appendicitis are easily treated

   b. chronic illness (heart disease, cancer, stroke) now accounts for most deaths

4. Ideal for mortality: compress incidence of death into a narrow range in old age

5. Many expensive medical treatments do not necessarily increase longevity (coronary bypass). The amount of time Medicare patients spent in hospital in the last 6 months of life ranges from 4.4 days to 22.9 and is directly proportional to levels of reimbursement.

6. Policy decisions in the future must determine how best to utilize resources (preventive medicine vs. acute care vs chronic care)

THEORIES OF AGING

A. Cell organelles wear out

1. Free radical damage to DNA and proteins (perhaps due to lack of antioxidants)

2. Protein degradation through cross-linking of amino acids (same as formaldehyde) and glycosylation (as in cataracts)

3. Cellular “garbage” in the form of lipochrome collects (as in brown atrophy of the heart)

B. Genetic programming and malfunction

1. Limited cellular division: fibroblasts can divide about 50 times, then stop; other cells may act similarly; the number of divisions is not increased by the time that passes between divisions

2. Errors in DNA replication and repair occur: mutations or transcription errors

3. Telomerase activity declines, telomeres shorten, and ability of chromosomes to replicate is lost

4. Programmed cell death (apoptosis): part of a sequence of cell maturation

C. Loss of homeostasis

1. Loss of "organ reserve" capacity, which is normally 4 to 10 times that needed to sustain life (e.g., you can live with just half of one normal kidney); organ reserve diminishes linearly with time after age 30.

2. Loss of "complexity" as evidenced by reduced branching of neuronal dendrites, by less variability of heart rate, and by loss of pulsatile hormonal release.

3. The result is an inability of the body to cope with or adapt to stress or changes in the environment, trauma, or disease states, even if minor

D. Environmental stress

1. Stress-induced increases in glucocorticoids over time dampen the feedback response of neuronal steroid receptors in the brain, leading to hypersecretion of corticosteroids

2. Increased corticosteroids contributes to immune suppression, osteoporosis, and impaired cognition; T lymphocyte function declines

E. Neuroendocrine dysfunction

1. Hypothalamic-pituitary-adrenal axis regulates much of development and involution of the reproductive functions

2. Dehydroepiandroterone (DHEA), growth hormone, and secondary sex steroids decrease with age

F. Nutrition

1. The one sure way to increase the lifespan of laboratory animals (rodents) is to restrict caloric intake

2. Proposed mechanisms include: increased free radical production with high caloric intake and decreased mutation rate with decreased caloric intake

G. Progeria: a disease model of aging

1. Rare disease seen in children

2. Morphologic features of aging are manifest in early childhood

3. Etiology unclear

ORGAN SYSTEMS IN AGING

A. The decreases in organ function could be due to any or all of the following:

1. Physiologic deterioration

2. Disease processes (something to be prevented or treated by you as a physician)

3. Environment (pollution, trauma, sun exposure)

4. Lifestyle (diet, drug use, work habits)

B. Central nervous system

1. Brain function

a. "Senile" dementia - loss of neurons (which cannot divide), small infarcts

b. Presenile dementia – Alzheimer's disease

3. Eye: cataracts form in lens; lens becomes less distensible (presbyopia) so bifocals are needed for close vision

4. Ear: hearing loss from otosclerosis, nerve dysfunction, loss of cochlear structure (from exposure to loud noises); ability to hear high-pitched sounds goes first

C. Cardiovascular

1. Increased atherosclerosis, arterial intimal thickening

2. Cardiac valvular calcification (aortic leaflets, mitral annulus)

3. Senile cardiac amyloid deposition

4. Maximal heart rate and cardiac output decrease

5. Compensatory mechanisms to support circulation are delayed or deficient, leading to syncope

D. Renal

1. Decreased glomerular filtration rate (GFR)

2. Reserve is so great that renal failure is uncommon in aging without specific underlying renal disease

3. More urinary tract infections in women; urinary incontinence with uterine descensus

E. Pulmonary

1. Mild “senile” emphysema from loss of alveoli

2. Anthracosis (not significant)

F. Musculoskeletal

1. Muscle fibers are gradually replaced by fat and fibrous tissue.

2. Hyaline cartilage wears out, resulting in osteoarthritis and chronic pain, mostly of larger weight-bearing joints first

3. Bone mass decreases more pronounced in women past menopause, (however, an abnormal accelerated form of bone loss is called osteoporosis)

G. Genital

1. Women: menopause - programmed atrophy of ovaries, uterus, breasts; epithelium of vagina and vulva thinner

2. Men: decreased spermatogenesis (but not necessarily infertility); prostatic hyperplasia and carcinoma are more frequent

H. Dermatologic

1. Loss of skin elasticity (accelerated by solar damage from ultraviolet light) leads to wrinkles

2. Squamous epithelium becomes thinner and more easily traumatized (which you will experience first hand putting in IV’s in the elderly)

3. "Age spots" on skin are areas of lentigo senilis

I. Hematopoietic and lymphatic

1. Marrow mass decreases (limited to ribs, sternum, and vertebrae in elderly), so the reserve capacity is reduced when fighting infections or responding to blood loss

2. Lymphoid tissues decrease in size (but major functional capacity remains)

J. Summary of Major Health Problems in the Elderly

Condition	% of Aged Persons Affected
Hypertension	43
Heart-related conditions	39
Arthritis	35
Gastrointestinal problems	31
Anemia	23
Eye problems	19
Urinary tract problems	18
Previous cancers	15
Gallbladder problems	15
Emphysema (COPD)	15
Diabetes	13
Fracture	11

J. Neoplasia

1. Both incidence and prevalence of cancer increases with age

2. Over the age of 75, lung, prostate, breast, and colon cancers become more frequent

3. Accumulation of more mutational ‘hits” in oncogenes and tumor suppressor genes

4. Cancers in the elderly

Type of Cancer	% in Persons Aged 65 years or more
Prostate	81
Colon	74
Pancreas	72
Bladder	70
Stomach	69
Lung	63
All Cancers	60

A. Resistance to infection decreases

B. Increased problems from pharmacologic therapy

1. Tolerance to drugs and toxins is diminished, pharmacodynamics altered (partly from diminished renal and hepatic function);

2. "Polypharmacy" or the use of multiple drugs. Increases the risk for a greater number of adverse drug reactions and drug interactions, as well as decreased compliance

C. Healing or recovery from injury or illness is prolonged

D. Response to therapy is diminished or prolonged

PREVENTION OF AGING

A. Use of antioxidants such as vitamin E (not proven to be effective)

B. Special vitamin and mineral supplements (including trace elements such as zinc and selenium) are probably not as important as just an overall good diet

C. Physical activity - exercise (use it or lose it)

D. Continued mental activity

E. Lifestyle - avoidance of behaviors that are detrimental to health

REFERENCES

Ershler WB, Longo DL. The Biology of Aging. Cancer. 1998;80:1284-1291

Yancik R. Cancer Burden in the Aged. Cancer. 1998;80:1273-1283.

Flier JS, Underhill LH. Caloric Intake and Aging. N Engl J Med. 1998;337:986-994.

EXAMPLE OF POLYPHARMACY IN A 72 YEAR OLD WOMAN:
From an actual medical record in a University Hospital
(as a challenge, can you match each medication with a problem on the list?)

Active Problem

Glaucoma
Nausea
DNR
Bronchitis, acute
Oral candidiasis
Chronic renal failure
Sinusitis, chronic
Hypoglycemia
Low B12 level
Anemia
Polymyalgia Rheumatica
Low back, buttock, and hamstring pain
Aortic and mitral valve sclerosis
History of CHF
GERD
Gout
Coronary artery disease
Diabetes Mellitus
COPD
Hypertension

Active Medication

Bumex 5 mg 1 po bid
Levoquin 500 mg 1 po qd
Quinine Sulfate 325 Mg Cap 1 po q hs for muscle cramps
Paxil 10 mg 1 po q am
Restoril 15 mg 1 po q hs prn insomnia
Axid 150mg Cap 1 po qd
Prednisone 5mg Tab 1 po q am
Imdur 60mg Tab 1 po qd
Insulin Regular 20 u q am; 5 u before dinner
Insulin Humulin NPH 90 units q am
Lisinopril 20mg Tab 1/2 po qd
Atrovent Inhaler 2 puffs qid
Xalatan (ophth) 0.005% 1 gt OU q hs
Centrum 1 po qd
Allopurinol 300mg Tab 1/2 p QOD
Ventolin inhaler 2 puffs qid
Aspirin 81mg Tab 1 po qd

Azmacort 100mcg Inh 2 puffs tid
Mycelex troches suck on one 5X/day
Ocuvite 1 every afternoon

Immunology Module

Session	Topic	Abbas & Lichtman Chapter
1	Components of the immune system	1
2	Innate immune responses	2
3	Cell mediated immunity I	3, 4
4	Cell mediated immunity II	5, 6
5	Humoral immunity I	7, 8
6	Humoral immunity II	7, 8
7	Tumor immunology	9, 10
8	Tissue transplantation	9, 10
9	Primary Immunodeficiencies I	12
10	Primary immunodeficiencies II	12
11	Autoimmunity	9
12	Hypersensitivity	11
13	AIDS PBL	12, Robbins 245-258
14	Immunopathology	Robbins 194-245, 258-264