Course in
Pathology and Laboratory Medicine

Schedule, Assignments & Slides
Fall Semester
2004 - 2005

Department of Pathology and Laboratory Medicine
Robert Wood Johnson Medical School &
Robert Wood Johnson University Hospital

in collaboration with pathology faculty from the following medical centers:

Jersey Shore
J.F. Kennedy
Muhlenberg
Raritan Bay
Somerset
St. Peter’s

UMDNJ
University of Medicine &
Dentistry of New Jersey
TEACHING PERSONNEL

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COURSE DIRECTOR
Dr. David Weissmann

COURSE COORDINATOR
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COMPUTER EDUCATION
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PATHTALK AND CASE BASED STUDY SMALL GROUPS

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Dr. Billie Fyfe
Dr. Robert Trelstad
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Dr. Frederick Stone
Dr. Parisa Javidian/Dr. Edita Bancila

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Dr. Luminita Marinescu
Dr. Janice Johnson
Dr. Evan Cadoff
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Dr. Silvia DeParalta

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Dr. Marina Chekmareva
Dr. Malik Deen
Dr. Lauri Goodell
Dr. David Heydt
Dr. Yong Ke
Dr. Mercy Kuriyan
Dr. Basim Mohammed
Dr. David Weissmann

SUMMARY PRESENTATIONS/GROSS PRESENTATIONS

Dr. Peter Amenta
Dr. Nicola Barnard
Dr. Hae Sook Kim
Dr. Arnold Rabson
Dr. Amrik Sahota
Dr. Yong Ke
Dr. Brian Stanford
Dr. N. Mikhail
Dr. John Farber
Dr. Peter Yurchenco
Dr. Tetsuo Shimamura
Dr. Anthony D’Aguillo
Dr. Parisa Javidian
Dr. Susan Shen-Schwarz

GUEST LECTURERS

U. S. Health Care Landscape
Mr. John Gantner, Chief Financial Officer, Robert Wood Johnson University Hospital

Pathology Of Oral Cavity And Related Structures
Dr. Arnold Rosenheck, Asst. Dean of Hospital Affairs, New Jersey Dental School

CONSULTANTS

Educational
Dr. Norma Saks  235-4129
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Library
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Computer Education Advisor
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OTHER PARTICIPATING FACULTY
Members of the Departments of Pathology and Medicine of affiliated hospitals
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Introduction
Introduction

COURSE OBJECTIVES

Pathology is the study of disease. The Course in Pathology and Laboratory Medicine provides an introduction to the mechanisms of disease and to the morphology and clinical characteristics of a broad spectrum of disease entities. In the Course we will aim to provide a foundation for the understanding of the disease state at the molecular, cellular, tissue, organ, and organismal levels.

By the end of the course, we expect that you will have:

1. Sufficient data about basic disease reactions and organ specific reactions so that you can:
   a. interpret signs and symptoms elicited in a patient’s history and create a differential diagnosis;
   b. interpret laboratory data;
   c. anticipate the natural course of disease;
   d. continue to learn the pathophysiology of disease;
   e. understand possible avenues of medical or surgical therapy.

2. Sufficient knowledge of gross pathology and histopathology so that you can:
   a. interpret findings at surgery;
   b. interpret pathology reports;
   c. intelligently review pathology slides with a consulting pathologist.

3. A basic understanding of diagnostic laboratory evaluation and of the relationship between laboratory and morphological changes in diseases states.

4. An awareness of the role of the autopsy in medicine.

In addition, we expect that the unique format of this course will enable you:

1. to develop skills in self-directed learning, problem solving, critical reasoning, presenting data, and intellectual team work;
2. to relate basic science knowledge to clinical medicine;
3. to read and assess with critical intelligence the current medical literature to facilitate life-long learning.
Introduction

COURSE FORMAT

The Course In Pathology And Laboratory Medicine covers:

- **General pathology:** The emphasis is on illustrating the basic reactions to disturbances which occur in the body.
- **Systemic pathology:** Deals with diseases specific to particular organs or systems.
- **Laboratory medicine:** Throughout the course we introduce and integrate laboratory data which are frequently used in clinical medicine.

The Course is based on small group instruction combined with a strong emphasis on independent learning, using a variety of learning resources and promoting the use of interactive computer programs. Also important are summaries in lecture format that highlight important concepts and facts in each major topic. The course program includes:

**PathTalk sessions:** These small group sessions are designed to establish a close mentor relationship between students and faculty members and are mandatory. A typical session consists of a review of morphology and pathophysiology, including a question and answer period, and of the Journal Club (most of you will have the opportunity to present a relevant recently published article to the rest of the group). You are expected to come prepared for PathTalk, since the format of the session is a guided discussion, and everyone should participate. For additional information, see page 6.

**Case based study (CBS) sessions:** This type of small group exercise consists of the study of clinical cases with the following main objectives:
- to introduce basic laboratory evaluations reflecting the abnormal state, and
- to promote the understanding of relationships between pathophysiology and morphological changes in disease states.

Attendance at these sessions is mandatory, and you are expected to come prepared with written responses to questions. For additional information, see page 7.

**Summaries of Topics in Systemic Pathology:** emphasizing the main points that are important for their own sake and for examinations. Your attendance is required (see schedule).

**Epidemiology/biostatistics consultations:** These are informal sessions, given for almost all topics, designed to assist students with the evaluation of the statistical and epidemiological aspects of assigned Journal Club articles. Faculty members of the Department of Environmental and Community Medicine will conduct these sessions.

**Gross specimen presentations:** This exercise provides direct experience with the pathology of organs and tissues removed at surgery or at autopsy. All specimens will be presented by instructors via closed circuit video. These specimens will be displayed in the laboratory following the video presentation, time permitting. The video will then be available in the Media Library for your use.
Introduction

PathTalk Sessions

Objective
- To review morphology and pathophysiology of the assigned topic.

Format
This is an interactive small group session. It is necessary that you come prepared, since your participation is expected.

- You will discuss basic facts and concepts of the assigned topic.
- You should be ready both to ask and to answer questions related to the topic.
- You should be familiar with assigned images of gross and microscopic lesions and be ready to interpret them.
- You will be asked to interpret some previously unassigned images ("unknown slides").
- Most of you will present a Journal Club article (see page 18), and you will monitor the discussion of your presentation. Unless otherwise noted, the selected articles are from the New England Journal of Medicine. They are listed in each week of the schedule.
Introduction

Case Based Study Sessions

Objective

To introduce basic laboratory evaluation reflecting the abnormal state and to promote the understanding of relationship between laboratory and morphological changes in disease states.

Format

The format of CBS is intended to facilitate learning through active student participation. Students are expected to study the material and conduct a discussion on the various aspects of the case and to arrive at a conclusion as to what ails the patient.

Role of the Instructor:

The principal role of the instructor should be that of a moderator; the instructor is free to intervene in discussions and to supplement available information. These sessions should be, however, predominantly student driven.

The role of the instructor is to encourage the student “in charge” to elicit more discussion of the case, including a differential diagnosis based on findings. The instructor is not expected to provide answers to all questions raised, nor is the student who is “in charge” of the case. These should be answered through participation of the whole group. All students are expected to actively participate in the discussion. Every student should be given an opportunity to express an opinion and contribute to the resolution of the case.

Printed Cases

Each week all students will have been assigned one to two printed cases. These are included in the Assignments in the second half of this book.

1. The students should study the case and provide a written summary of the diagnosis and conclusion from the case material, or some other type of written response at the instructor’s discretion.

2. On the day of the session, one student will be selected to be “in charge” of the case. This student should:

   a. Review the Clinical Summary and prompt discussion of a differential diagnosis based on the demographics of the patient and clinical findings.

   b. Call on other students to give the answer to questions at the end of each case; one student should be responsible for answering one question. The group should correct/supplement/support this student’s view. The instructor should make a final comment on each of these answers. The instructor should guide the group to cover the objectives that are relevant to the case.

   Each instructor and class will have to discover the learning techniques that work best for them. The “student of the week” strategy may be replaced by other strategies as seems appropriate. Different classes have different “personalities”, and the strategy and personality should match.

   c. Project slides pertaining to the case. (These slides will be available on WebCT.) There will be images previously available to students and images students may not seen prior to the session. The student “in charge” should call on other students for slide descriptions and comments. The instructor should correct/support students’ comments, discuss the types of diagnosis that the slide review indicates, and summarize all findings.
Introduction

3. The instructor will provide closing comments with a brief discussion of how the findings and lab values support the final diagnosis.

4. The written case summary or other written response (students’ homework) will be collected and returned at the next session with instructor’s comments.
Introduction

STUDY MATERIAL

We realize that, in this age of an exponential increase in biomedical knowledge, we can provide only a limited coverage of our field. It is vital for every future physician to assimilate and update a large amount of information. Our course can offer only some dimensions of this process. It is important that you independently pursue every means available to gain continuing mastery of the subject. At selected points during the Course we are allowing for unscheduled time to enable you to do so.

The kodachrome slide material for both PathTalk and Case-Based Sessions is available at the Pathology and Laboratory Medicine section on your WebCT.

Required Reading:
- Robbins’ Pathologic Basis Of Disease (6th edition) by Cotran, Kumar, and Collins

Please make sure you get the 6th edition. The 7th edition will be published too late for use in the 2004-2005 school year. Many (though not all) of your required reading assignments are from this text and are listed in each week in the Assignments section. The Pocket Edition Of Robbins should be used by students for reviewing purposes only—it is too brief to serve alone as the basis for your study. For the most recent developments in the field, you should regularly consult the New England Journal of Medicine.

Required Material for Case Based Study:
- Printed cases provided in your Assignments Guide

In addition, Laboratory Medicine Case Book by Raskova and others, 2nd edition, is supposed to be published at some time during the first semester. If it does appear on time, it will be a required textbook for the 2nd semester Cased-Based Study classes.

Required Material for PathTalk Sessions:
- Slide collection (arranged by weekly topics) on WebCT.
- Slides section of course books - contains slide descriptions and other selected material.

Recommended Reading Texts:
- Interpretation Of Diagnostic Tests, by Wallach (Little Brown). (This will be most helpful in connection with the clinical cases discussed in CBS.)
- The Merck Manual, one of the textbooks of internal medicine (Cecil’s or Harrison’s).
- Pathology Secrets, by Ivan Damjanov, M.D., Ph.D. (Hanley and Belfus).

Self-evaluation Material:
We recommend the following:
- Pathologic Basis Of Disease, Self-Assessment And Review by Carolyn C. Compton (Multiple choice questions with answers). Several copies are available in the Media Library.
- Robbins Review Of Pathology by Edward C. Klatt, M.D., and Vinay Kumar, M.D (Multiple choice questions with answers). Several copies are available in the Media Library.
- Web Based Quizzes: (http://pleiad.umdnj.edu/)
  - Pathology and Laboratory Medicine Quiz
  - Image-based Mini-quiz
Introduction

Computer-based Learning Material:

Keyboard Series: (installed on Interlab Computers): a computer program which permits the flexible use of texts, diagrams, & questions.

Texts:
- *Pathologic Basis Of Disease*, by Cotran, Kumar, & Robbins (Pathology TextStacks)
- *Laboratory Medicine* by McClatchey (Laboratory Medicine TextStacks)

Cases
- *Laboratory Medicine Case Set*, by Skvara, Mikhail, Shea, and Raskova (Also see under Required Case Based Material)
- *Lab Medicine Series*, by Skvara, Mikhail, Shea, and Raskova (CD ROM, MedTech USA) (available in the Media Library)

Other Visual and Audiovisual Material:
Video Tapes of gross specimen presentations for this semester, as well as tapes recorded in recent years, are stored in the Media Library.
EXAMS, GRADES, & EVALUATIONS

On the basis of examination results, the student will be awarded grades of Honors (4), High Pass (3), Pass (2), Low Pass (1), or Fail (0). In addition every student must satisfactorily perform in PathTalk sessions and Case Based Study sessions and attend the Summary Sessions. This performance will be evaluated in 2 written descriptions composed separately by each student’s PathTalk and Cased Based Study instructors.

Examinations
There will be three examinations throughout the Course. Two of these will be based on theoretical and practical multiple choice questions provided by faculty members. The third, final examination will be the Pathology section of Step I of the USMLE. Note: The time allotment assigned for an examination is not necessarily the actual length of time for the exam.

Your final grade will be as follows: Your average grade on the three exams will count for 98% of your grade. Your attendance and performance at the integrated cases will count for 2%. More precisely,

\[ \text{Final percentage grade} = \frac{(\text{exam 1} + \text{exam 2} + \text{exam 3})}{3} \times 0.98 + \text{integrated case points}. \]

To pass the course a student must obtain a final grade of at least 65% as calculated above and have a satisfactory attendance record in the small group sessions.

The first two of these examinations are based on questions provided by the faculty; the third (final) examination is the Pathology section of Step I, USMLE. The results of last examination will be reported to you as a percentage grade after the National Board has analyzed the raw scores and converted them to percentage grades (it does this in order to make your grades as fair as possible). Each of the three examinations will carry equal weight.

<table>
<thead>
<tr>
<th>Final Percentage Grade</th>
<th>Final Course Grade</th>
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</thead>
<tbody>
<tr>
<td>0 - 64</td>
<td>0 (Fail)</td>
</tr>
<tr>
<td>65-70</td>
<td>1 (Low Pass)</td>
</tr>
<tr>
<td>71-80</td>
<td>2 (Pass)</td>
</tr>
<tr>
<td>81-86</td>
<td>3 (High Pass)</td>
</tr>
<tr>
<td>87-100</td>
<td>4 (Honors)</td>
</tr>
</tbody>
</table>

A student who receives a grade of FAIL can correct this grade to LOW PASS by passing a make-up examination, which will be composed and graded by the Department of Pathology and Laboratory Medicine. On this examination a student must achieve a score of at least 65%.

Performance In PathTalk Sessions
Each student must attend and meaningfully contribute to the PathTalk sessions. Each student will be required to:

- participate in group discussions
- evaluate morphological findings

In addition, most students will have the opportunity to present to his peers a published article (Journal Club).

Performance In Case Based Study Sessions
Each student must attend the Case Based Study sessions. Students will be evaluated by the individual instructors on their ability:

- to analyze problems
- to provide both written and oral answers and interpretations to questions related to assigned cases
- to participate in group discussions.
Introduction

Evaluations
The assessment of these performances in PathTalk and CBS sessions will be reported in the final written evaluation of each student by the faculty that will be sent to the Dean’s Office to become part of the basis for the Dean’s letter.

In more detail at the end of the course, students will be evaluated on their performances, focusing on:

**Case Based Studies**

<table>
<thead>
<tr>
<th>Knowledge of material</th>
<th>Knowledge of material</th>
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**PathTalk**

<table>
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<th>Interaction and participation in discussions</th>
<th>Interpretative skills in histopathology</th>
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<tr>
<th>Performance as a moderator</th>
<th>Journal Club presentation (in most cases)</th>
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<table>
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<tr>
<th>Ability to analyze cases/answer assigned questions</th>
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Students will also be evaluated by the instructors of both groups on non-cognitive attributes, such as:

- commitment and general attitude
- conscientiousness
- collaboration with peers
- leadership qualities
- respect for other opinions
- self-criticism
- ethical behavior
- honesty and integrity

Each evaluation will be in the form of a short paragraph, to be sent to the registrar for inclusion in student’s transcript. Students will have the opportunity to review the evaluations before they are submitted.

Absences/Performance In Small Groups
An unsatisfactory performance, as determined by your small group instructors, and/or more than two absences from one of your small group sessions will require remedial activity on an individual basis.

Grade Appeal Mechanism
The *Course in Pathology and Laboratory Medicine* allows for and strongly encourages student-faculty interaction. We believe that good communication between student and teacher is important for mutual understanding and that it is essential for learning.

- **Examination Grade:**
  1. After each departmental examination you will receive a preliminary examination grade. The examination booklets, a copy of the master key, and a copy of your answer sheet will be returned to you, and you are given a period of several days for review and discussion of the questions before a final examination grade is determined. During this time you should contact the Course Director with problems, comments, etc. Any adjustment in the examination will be made by the Course Director and will apply to the whole class. The class will be notified of it, as well as of the reasons justifying the adjustment. No additional changes are made after the final grade on each departmental examination is issued.
Introduction

2. The USMLE Pathology section Step 1 Examination is exempt from the above procedure. Your raw score is scaled and returned by the National Board as a percentage, and this grade is not subject to further discussion.

- **Evaluation Of Small Group Performance (PathTalk And Case-Based Studies):** You will be given a copy of your course evaluation, which is based on your performance in small groups. If a serious discrepancy occurs between a student’s perception of his/her performance in the course and the evaluation, the student should appeal in writing to the Course Director, and the case will be reexamined.

- **Final Course Grade** This grade is determined entirely on the basis of examination results and 0-2 percentage points from the integrated cases series, provided attendance is adequate. No adjustment can be made after the grade is awarded unless a clerical error has been made.
Introduction

How to Approach the Textbook

Norma S. Saks, Ed.D

The textbook that has been selected for this course, Pathologic Basis of Disease, 6th Edition (Cotran, Kumar, and Collins) is an essential resource for your independent study. Because the text is comprehensive and detailed, reading effectively and efficiently will be helpful. An additional handout, Strategies for Studying Pathology, can be obtained at the Cognitive Skills Program offices, UBHC, D338.

How to approach the pathology textbook for effective independent study:

Engage in an active (vs. passive) approach to reading as follows:

1. Develop the habit of looking at the whole chapter/section first to see how it is organized. If you know the structure of the material ("the big picture"), it will help you recall it better; it promotes a "cognitive framework" to which you can pin details.

2. Attend to the format of the textbook - Main headings, subheadings, color coding, diagrams, charts, photographs, general physical arrangement. Think about how the format can aid your learning.

3. Some students like to focus study by reading related questions.

4. Read for a purpose and adjust your rate to that purpose. If you come across material that you already know, then read through it quickly. If your purpose is to learn/understand, then slow down your rate. *It is most effective to develop advance questions and then go on a “search” to find answers to your questions.*

5. When you identify unfamiliar vocabulary, note the word(s) and follow up. If the meaning of a word is essential in order to make sense of what you are reading, look it up immediately. (It is best to have a medical dictionary and your Webster’s nearby.) Keep in mind that these same words may appear on an exam later on.

6. Look for relationships, not just a collection of facts. Compare and contrast. This method will aid in your retention of the material.

7. Develop a note-taking system. How will you remember without rereading the text? Decide on a format and how much detail you will include.


9. Assess your concentration at frequent intervals. Stay alert. Avoid reading the text as if it were a novel.

10. Assess your need for additional resources and use these as needed. It is best not to give up on reading the text.

Introduction

Computer Education Program

David Foran, Ph.D.

We first wish to extend a warm welcome to each of you. In order to facilitate your mastery of the subject material the faculty are developing a number of interactive exercises for web-based teaching in pathology. Two web-based tools are now accessible through the Departmental web server at http://pleiad.umdnj.edu/. Once connected to the server you should click on “2nd Year Course in Pathology & Lab Medicine.” You will then be presented with options to engage in an interactive Review of Pathology and Laboratory Medicine or to take an Image-based Mini-Quiz in Pathology.

If you choose the first option, “Review: Pathology & Lab Medicine” you may choose from approximately 26 broad topics. You will subsequently be prompted for your full name. You will be presented with questions which relate to the topic of interest. The program features immediate feedback regarding the answers that you submit as well as a total score for the section. Once the exercises for any given session are completed, the total score and correct answers are displayed. The web-based review also features a random mode, with questions selected at random across all topics. While an extensive “Image-based Quiz” is currently being developed, you might like to have a look at the “Image-based Mini-Quiz,” based on 24 questions.

You may also access this material by connecting directly to the Pathology and Laboratory Medicine Course Website http://pleiad.umdnj.edu/pathology_course/.

We hope that you will enjoy 2nd year course in Pathology & Laboratory Medicine, and we welcome your comments. For comments please contact:

David J. Foran, Ph.D. 732-235- 4858
David Weissman, M.D. 732-418-8047
Nancy Mundie 732-235-4033
Lin Yang 732-235-5680
Introduction

Instructions for Computer Use in the Pathology & Laboratory Medicine Course

Robert L. Trelstad, MD

The facilities for computer-assisted education are distributed throughout the Kessler Teaching Labs. The software available for all medical students includes, but is not limited to:

Textbooks with figures, diagrams, tables, and references:
* Pathologic Basis of Disease by Cotran, Kumar, and Robbins
  W.B. Saunders
* Clinical Laboratory Medicine by Ken McClatchey
  Williams and Wilkins
* Medical Microbiology edited by Ken Ryan
  Appleton & Lange
* Immunology by Ivan Roitt
  Blackwell Science
* The Merck Manual edited by Robert Berkow
  Merck

Cases:
* Laboratory Medicine “Case Set”
  by Skvara, Mikhail, Shea, and Raskova
* Lab Medicine Series
  by Skvara, Mikhail, Shea, and Raskova

Quizzes:
* Laboratory Medicine “Case Set”
  by Skvara, Mikhail, Shea, and Raskova
* Pathology
* Microbiology
* Cell Biology
* Immunology

Videodisc Image Libraries:
* Histology
* Pathology
* Microbiology

Digital Image Libraries:
* Histology
* Pathology
Strategies for Using Computers in Self-Learning

Robert L. Trelstad, MD

The computer resources you have at your disposal are extensive and match or exceed those of most medical schools. Like any new tool, the value of the computer in education is undergoing rapid change.

Computers will never replace print books. You can drop your book, take it to the beach, or sit on it. It never runs out of energy; you do.

Computer based textbooks can be searched very rapidly. Using the Keyboard Publishing, Inc., platform, all of the textbooks, quizzes, and image banks can be searched simultaneously. You should learn to use the search function of this software so that you can read in topics beyond your immediate target. For example, if you search for endocarditis in Robbins, Sherris, and Merck, you’ll get very comprehensive treatment of the subject. If you construct your searches with some restrictions, such as ‘endocarditis’ and ‘strepto*’, where the ‘*’ allows finding of all words starting with strepto, you can limit the results of the search. If you further limit the finding of these words to within 10 to 15 words of each other, you further reduce and focus the information you’ll get.

We have discontinued our “how to use the computer” sessions in that most students not only know how, but own them. If you feel that you aren’t using the computer effectively, please ask for help. Channel your requests through the Teaching Office. At various times during the course, we will give you demonstrations in which we will use the computer resources.

In addition to the local set of software, there is an extensive amount of material available on the Internet. The ‘net’ is moving from CB radio to AM. It is filled with junk and great stuff. So what’s new? Ever been to WalMart? In addition to the material available on the Pathology portion of your WebCT site, the following are web sites worth exploring:

pleiad.umdnj.edu/
Our Pathology Department’s web site.

pleiad.umdnj.edu/pathology_course/
A Pathology and Laboratory Medicine Course web site. The question bank quizzes can be found here.

www-medlib.med.utah.edu/WebPath/webpath.html
The premier pathology education web site. Quizzes, images, information. A local version of this outstanding collection of images is hosted on the Pathology section of WebCT. Look for it there.

www.pathmax.com/main.html
A wonderful collection of every kind of internet pathology resource.

pleiad.umdnj.edu/hemepath/
A lymphoma tutorial.
Medical knowledge is changing fast. The best way for a physician to “keep up” is to keep searching and reading the literature. One must learn to read effectively and critically. This is where the Journal Club comes in: critical presentation of an article to a critical audience.

The idea is to present the substance of a journal article to your colleagues critically and succinctly. It should not take more than fifteen minutes. To get your bearings, after reading the article’s title, read the abstract, especially its punchline, to see what the authors claim to show.

In journals like the *New England Journal of Medicine*, articles are often multi-authored, but in general fall into one of two categories - reports from a single department (e.g. Medicine) on observations based on a limited patient population, or large multi-center studies.

When you describe methods to your fellows, you need not go into great detail, especially in the case of multi-center studies or review articles, which you may have to present in skeleton form.

Present the findings: usually you will find them nicely tabulated.

Present the discussion: here you can afford to be critical. Were the right controls used: are the statistical arguments convincing? Give your opinion, and ask your colleagues for theirs.

It may seem hard, but it is much more effective to make do without consulting notes. The effort to do so forces one to digest the material and discard the dross. If you say it in your “own words,” you will find you understand matters in a new way, and your audience will understand better, too. You can also make effective use of the blackboard in this way; don’t fill it up in advance, but write down salient points “on the fly.”

The audience should be invited to ask questions, and they should do so. Everyone should become involved.

When the club functions this way, all gain, especially in becoming unselfconscious and effective in thinking on their feet, in clarifying their thoughts, and expressing them effectively.

**When To Seek Epi/Bio Consultation**

Many of the articles will involve quantitative data, often with epidemiological features. It is important that you learn to interpret these; not all published conclusions are necessarily correct. We strongly encourage you to take advantage of the Epi/Bio consultation program, offered by the faculty of the Department of Environmental and Community Medicine to our students. See the schedule for time and location.
Introduction

Journal Clubs—Science as Conversation

Joe Wright. B.A.
(From the New England Journal of Medicine 351;1 pp 10-12)

I had forgotten about it amidst the other tasks of medical-student life: exams, patient write-ups, the shirt I needed to iron. But an e-mail from my fellow student John reminded me that it was my turn to lead the journal club for our HIV-AIDS interest group. I had no idea what article I would bring. I bumbled through PubMed in search of a paper, wandering through several topics before landing on an article about the high prevalence of chlamydia in China,¹ along with an editorial² arguing for a particular strategy for preventing a new explosion of human immunodeficiency virus (HIV) infection. I wasn't sure that I could lead a good discussion on this article, but time was up, so I picked it and hoped it would work out. At least in one important sense, it did.

There were only four of us at the session — just barely enough. My fellow journal-club members were puzzled by some of the statistical methods, and I couldn't help much. And I discovered that I'd failed to examine closely the most interesting aspects of the data tables. Nonetheless, I had brought some questions, and I was blessed with thoughtful, talkative colleagues. We talked about infectious disease, social power, and economic development; about whether different factors might drive outbreaks in different regions of the country (thus requiring different intervention strategies); and about how the structure of sexual networks influences the pattern of spread of sexually transmitted diseases. We tried to get through the data ourselves without relying on the interpretations in the abstract or the editorial.

A few days later, Kanu, a journal-club regular, e-mailed us a link to a news article about the Chinese economy, saying, "Thought you guys might be interested, considering our conversation the other day." And it was then that I remembered the genius of journal club: I was interested in reading this rather dry article about Chinese economics and politics, because now I had a context and a purpose for the information.

Moreover, in the process of looking for an article, I had learned still more. For instance, while looking through the literature on sexually transmitted diseases, I had called my friend Dan (who had been in charge of the first journal club I'd attended) to ask him about network theory in research on sexually transmitted diseases. I had read an interesting review article about GB virus C (which would become the topic of another journal-club meeting when a new research article came out³). I had learned a bit about the economic and physical geography of China. I had remembered that Chlamydia trachomatis is an obligate parasite.

None of this knowledge — except the stray fact about C. trachomatis — will help me on any exams. Nor did our group come up with any particularly helpful ideas about AIDS to offer to the Chinese people. We developed no 10-point plan for stopping HIV epidemics. It might appear as if we accomplished nothing. But by struggling through the article together, we became more awake to the world around us and more immersed in the scientific project of exploring it.

When I was younger, I generally encountered science as a set of facts to be drilled — OK if the facts are interesting, but certainly not an awakening. When I finally experienced science as a creative endeavor, it was through conversations in journal clubs.

My first conversations were about epidemiology, when I was working at a community HIV-prevention agency with a staff journal club. My next conversations were about the immune system, in a journal club run by AIDS activists with the help of a graduate student in immunology. It was a perfect example of the way in which certain kinds of AIDS activists and community AIDS workers not only influenced science, but were influenced by it.⁴ We came to science in an atypical order: first through scientific meetings and journal articles and only later, if at all, through formal training. In the face of the urgency and uncertainty of the AIDS epidemic, even nonscientists like me could see science as discussion, debate, a cooperative search through the unknown — and as a creative activity.

As a second-year medical student, I find that my energies and those of my classmates are more often driven by feelings of inadequacy than by the inspiration of science as a journey. We worry about things we don't yet know but that are known by others — especially those who will test us. Spending time on the unknown often seems indulgent.
Introduction

This preclinical period of acquiring the facts of medicine is an inevitable phase of our development as physicians. Certainly, my greatest suffering in medical school comes when I resist that necessity. I can see that my patients will need me to have a good portion of those facts in hand, and patients, after all, are the reason I came to medical school.

Still, some of my sweetest times here have been those when science stopped being facts to drill and became a conversation. Our HIV-AIDS journal club is informal, small, and led by students; it meets on a catch-as-catch-can, not-during-exam-week schedule. Nonetheless, it has survived for a year now. No faculty members are ever present; I doubt that many know it exists. No one is handing out extra-credit points for attendance. But we care about AIDS, and so we value AIDS research.

Voluntary journal clubs require intense sincerity; little else can motivate people to read scientific articles and really engage with their contents. During my time in an immunology laboratory, I used to receive announcements about another journal club, which started with salutations like "Greetings, B-cell fans" or "Hello, Believers!" Not being a B-cell fan in particular (I like them fine, but I'm more of a T-cell loyalist), I never attended. But I loved the greetings because they conjured up visions of a group of enthusiasts. A good journal club must include not only "journal," but also "club."

For this reason, I distinguish journal clubs that are required (as in work settings) or offer tangible rewards (for instance, notice from powerful people) from voluntary associations. The former are a sort of mandatory fun, more "journal meeting" than "journal club." In a journal club, members are having a conversation for its own sake. People show up at a good journal club even when the boss is out of town or the material won't be on the test. At these moments, science is no longer a means to an end but a pleasurable end in itself.

It's not that I oppose journal meetings. Even a journal meeting fosters an appreciation for the primary literature of science, a healthy skepticism about its findings, and the skills to read critically. Journal meetings and journal clubs alike help readers to form conclusions, raise doubts, and ask questions that extend more deeply and widely than those of the abstracts and accompanying editorials. Both prevent us from treating journals as extensions of textbooks — and remind us to question our textbooks.

But only we ourselves can give each other science as conversation. To do so, we have to announce our enthusiasm and actively seek out others who share it. This is not as easy as it sounds: sincerity is a form of vulnerability. Simply put, one risks looking like a geek. But there are worse things, including never loving science yet spending one's career immersed in it.

Journal clubs don't always work, of course, but they've evolved some practices that make success more likely. For example, each meeting should focus on at least one article containing primary data, although review articles can be an illuminating addition. The responsibility for presenting articles should rotate among members, all of whom should be more or less equally comfortable — or ready to dive in fearlessly — in the club's research area. Senior members should not dominate, and everyone should participate. Presentations should be brief, aiming to start and facilitate conversation, give some background, and clarify research methods. Ideally, the responsibility for scheduling sessions, reserving meeting space, and sending out reminders should also rotate. These customs support an underlying proposition: the journal club is a conversation among equals about the work and fruits of science.

Science makes its splashes with new results. Science lives, however, not by results, but by the exchanges of ideas that follow them. And so journal clubs are a way of keeping science alive — even in medical school, and beyond.

Schedule, Assignments, & Slides
## Schedule

**Week 1: August 16-20**  
Cell and Tissue Response to Injury / Environmental Pathology

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monday, August 16</strong></td>
<td>10 AM - Noon</td>
<td>Orientation</td>
<td>Lecture Hall</td>
</tr>
<tr>
<td><strong>Tuesday, August 17</strong></td>
<td>1-2 PM</td>
<td>Guest lecture, Mr. John Gantner: U.S. Healthcare Landscape</td>
<td>West Lecture Hall</td>
</tr>
<tr>
<td></td>
<td>2-4 PM</td>
<td>Case-Based Study</td>
<td>Laboratory</td>
</tr>
<tr>
<td><strong>Thursday, August 19</strong></td>
<td>1-4 PM</td>
<td>PathTalk</td>
<td>Laboratory</td>
</tr>
<tr>
<td><strong>Friday, August 20</strong></td>
<td>10-11 AM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
</tr>
<tr>
<td></td>
<td>11 AM- Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory – Room N12</td>
</tr>
</tbody>
</table>
Week 1: August 16-20
Cell and Tissue Response to Injury / Environmental Pathology

Assignments

Topic 1: Cell and Tissue Reaction to Injury

Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition,
• Cellular Pathology I: Injury and Cellular Death, Chapter 1, pp. 1-28
• Cellular Pathology II: Adaptions, Intracellular Accumulations, and Cell Aging, Chapter 2, pp. 31-48

Topic 2: Environmental Pathology

Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition,
• Environmental Pathology, Chapter 10, pp. 403-436 & Chapter 16, pp. 727-734

Required Study for Small Groups

PathTalk
Assignments:
• Kodachromes on WebCT
• Slide descriptions
• Journal club articles:
  o Journal Clubs—Science as Conversation (See introductory materials of this booklet)
  o Glutathione Peroxidase 1 Activity and Cardiovascular Events in Patients with Coronary Artery Disease, Stefan Blankenberg, M.D., et al. Volume 349:1605-1613 October 23, 2003 Number 17

Case-Based Study
Assignments:
• Printed Case 1 – “32 year-old man found unconscious at the scene of a fire…”
• Printed Case 2 – “A 73-year-old Italian man…”

Case-Based Study
Required reading: Widmann’s Clinical Interpretation of Laboratory Tests

Principles of interpretation of laboratory tests:
• pp. 3-10
Complete blood count:
- pp. 61-67: Red blood cell and hemoglobin concentration
- pp. 82-85: Peripheral blood and granulocytes
- pp. 87-93: Lymphs, monocytes, abnormal white cells
- pp. 102-103: Anemia, definition and classification
- pp. 245-247: Platelet function

Liver function tests:
- pp. 566-570: Bilirubin
- pp. 573-574: Obstructive liver enzymes
- pp. 576-579: Aminotransferases and gamma-glutamyltransferase
Printed Case #1: 32 year-old man found unconscious at the scene of a fire

This 32-year-old white male was brought to the emergency room after having been found in a small storage building in an industrial park. Apparently, he had been drinking and smoking when a fire started in the building. Using available fire extinguishers containing carbon tetrachloride he succeeded in putting out the fire but was overcome by smoke and passed out. He was found unconscious several hours later by his coworkers. A half-empty bottle of whiskey and a trash basket containing partially burnt paper and rags were noted. One of his coworkers who accompanied the rescue squad to the hospital stated that he knew of no major illnesses in the patient but the patient was known to have a drinking problem.

Physical examination on admission revealed a semiconscious, well-developed, mildly obese white male. Oral temperature -98.6°F: Pulse - 95; B/P - 110/65(supine); Respirations - 25. An odor of smoke and chemical fumes was noticeable, but there were no external burn injuries. Auscultation and percussion of the chest was unremarkable, the heart rate was regular without murmurs. The liver and spleen were not palpable and bowel sounds were active. Neurologically he was semiconscious but all reflexes were intact.

Selected Laboratory Data

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Admission</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (g/dL)</td>
<td>14.0 - 17.0</td>
<td>13.8</td>
<td>12.5</td>
<td>12.7</td>
<td>11.9</td>
<td>10.1</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>40.0 - 49.0</td>
<td>42.0</td>
<td>35.2</td>
<td>34.5</td>
<td>31.8</td>
<td>30.7</td>
</tr>
<tr>
<td>WBC (thou/uL)</td>
<td>4.5 - 11.0</td>
<td>12.7</td>
<td>15.1</td>
<td>22.2</td>
<td>19.8</td>
<td>20.2</td>
</tr>
<tr>
<td>Plts (thou/uL)</td>
<td>130 - 400</td>
<td>275</td>
<td>251</td>
<td>163</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>11- 14</td>
<td>12</td>
<td>27</td>
<td>24</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>21-31</td>
<td>24</td>
<td>28</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>7-24</td>
<td>26</td>
<td>27</td>
<td>47</td>
<td>79</td>
<td>126</td>
</tr>
<tr>
<td>Creat. (mg/dL)</td>
<td>0.7 - 1.4</td>
<td>1.3</td>
<td>1.3</td>
<td>2.8</td>
<td>4.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Tot. Bil. (mg/dL)</td>
<td>0.0-1.5</td>
<td>1.5</td>
<td>9.1</td>
<td>13.8</td>
<td>12.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Dir. Bil. (mg/dL)</td>
<td>0.02-0.18</td>
<td>0.1</td>
<td>2.7</td>
<td>4.1</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>0-55</td>
<td>288</td>
<td>1470</td>
<td>2105</td>
<td>1995</td>
<td>1120</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>0-50</td>
<td>135</td>
<td>410</td>
<td>875</td>
<td>824</td>
<td>459</td>
</tr>
<tr>
<td>Alk Phos (U/L)</td>
<td>30 - 120</td>
<td>125</td>
<td>204</td>
<td>295</td>
<td>374</td>
<td>256</td>
</tr>
<tr>
<td>Urine Vol. (mL/d)</td>
<td>600 - 1600</td>
<td>1375</td>
<td>1000</td>
<td>410</td>
<td>300</td>
<td>215</td>
</tr>
</tbody>
</table>

Clinical Course: Several hours later he complained of a headache, became nauseous and vomited. On the 2nd hospital day, he developed jaundice and tender hepatomegaly. His remaining hospital days were
Week 1: August 16-20
Cell and Tissue Response to Injury / Environmental Pathology

characterized by persistent jaundice and increasing respiratory difficulty eventually developing pulmonary edema and expiring on the 8th day after admission. An autopsy was performed.

Images (WebCT):

Fig 1 Liver H&E stain. x30. At autopsy the liver weighed 1325 gms. The capsule was smooth and the cut surface had a yellow honeycombed trabecular pattern with brown foci of hemorrhage. The biliary system was patent. Several portal areas (p) are labelled.

Fig 2 Liver. H&E stain. x73. Notice the difference in the hepatic parenchyma between the central vein (v) and the portal area (p).

Fig 3 Liver H&E stain. X185. The central vein (cv) is located at the top of the image.

Questions
1. Describe the features of the patient’s liver injury. Which ones (if any) could be the result of the patient’s alcoholism? What is cirrhosis of the liver? Is it present? What is steatosis and what causes it?
2. Why has the patient become jaundiced? Is there any possible connection between this finding and the changes in hemoglobin?
3. How do you explain the changes in his renal status?
4. Why are his coagulation studies abnormal?
5. Why is the complete blood count (leukocytes, platelets, hemoglobin) abnormal (take into account not just the mentioned features of the case, but other factors that influence the outcome of many extended, complex hospitalizations)?
6. Did the patient's alcoholism play a role in this illness?
7. What are the possible causes for the patient’s pulmonary edema?
8. Do you think the patient is likely to be hypovolemic as a result of decreased urine output?
9. What is the most likely diagnosis?
Printed Case #2: A 73-year-old Italian man

**CLINICAL SUMMARY:** A 73-year-old Italian man, a retired factory worker from Johns Manville, with past medical history significant for coronary artery disease and congestive heart failure, presents with a recent 20-lb. weight loss and diffuse chest and abdominal pain. Social history is significant for a 30 pack-year smoking history.

### Laboratory Data

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Urinanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong> 7.8 thou/uL (3.4-11)</td>
<td><strong>Color</strong> Amber (clear)</td>
</tr>
<tr>
<td>polys 71% (40-75)</td>
<td><strong>pH</strong> 5.01 (5.0-7.0)</td>
</tr>
<tr>
<td>lymph 15% (13-45)</td>
<td><strong>Protein</strong> Neg (Neg)</td>
</tr>
<tr>
<td>eos 6% (0-6)</td>
<td><strong>Sugar</strong> Neg (Neg)</td>
</tr>
<tr>
<td>mono 7% (0-11)</td>
<td><strong>Ketones</strong> Neg (Neg)</td>
</tr>
<tr>
<td>baso 1% (0-1)</td>
<td><strong>Bile</strong> Neg (Neg)</td>
</tr>
<tr>
<td>RBC 4.10 mill/uL (4.0-5.4)</td>
<td><strong>Blood</strong> Neg (Neg)</td>
</tr>
<tr>
<td>HGB 12.4 gm% (12-18)</td>
<td><strong>Nitrite</strong> Neg (Neg)</td>
</tr>
<tr>
<td>HCT 35.1% (37-47)</td>
<td><strong>Urobilinogen</strong> 0.2 U (&lt; 1 Ehrlich Unit)</td>
</tr>
<tr>
<td>Pits 235 thou/uL (130-400)</td>
<td><strong>S.G.</strong> 1.015 (1.010-1.035)</td>
</tr>
<tr>
<td>PT 12.1 sec (10-9-13.1)</td>
<td><strong>WBC</strong> Neg (0-5)</td>
</tr>
</tbody>
</table>
| PTT 28 sec (27-40) | *

No microscopic exam performed.
### Electrolytes

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>138 mEq/L</td>
<td>(136-146)</td>
</tr>
<tr>
<td>K</td>
<td>3.6 mEq/L</td>
<td>(3.0-5.0)</td>
</tr>
<tr>
<td>Cl</td>
<td>105 mEq/L</td>
<td>(98-108)</td>
</tr>
<tr>
<td>CO₂</td>
<td>27.5 mEq/L</td>
<td>(24-32)</td>
</tr>
</tbody>
</table>

Chest X-ray: Pleural thickening and opacity at the right hilum.
CT Scan Abdomen: Multiple parenchymal lesions of liver and left kidney.

### Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>97 mg%</td>
<td>(65-110)</td>
</tr>
<tr>
<td>BUN</td>
<td>14 mg%</td>
<td>(7-24)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1 mg%</td>
<td>(0.7-1.4)</td>
</tr>
<tr>
<td>Protein, total</td>
<td>6.2 gm%</td>
<td>(6.0-8.0)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2 gm%</td>
<td>(3.5-5.0)</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.6 mg%</td>
<td>(8.5-10.5)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.5 mg%</td>
<td>(2.5-4.5)</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>161 U/L</td>
<td>(30-120)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.6 mg%</td>
<td>(0-1.5)</td>
</tr>
<tr>
<td>SCOT (AST)</td>
<td>111 U/L</td>
<td>(12-45)</td>
</tr>
<tr>
<td>SGPT (ALT)</td>
<td>96 U/L</td>
<td>(3-40)</td>
</tr>
<tr>
<td>GGTP</td>
<td>221 U/L</td>
<td>(15-70)</td>
</tr>
</tbody>
</table>
**Week 1: August 16-20**  
**Cell and Tissue Response to Injury / Environmental Pathology**

**Review images:** available on Case-Based Studies section of Pathology WebCT site.

**Clinical Course:** While undergoing testing, he had a progressively downhill course, developing mental obtundation. Bronchial brushings were obtained. An autopsy was performed when he expired 7 weeks post admission.

**Questions for homework - to be written and brought to class (at instructor’s discretion)**
1. From the information given derive the red blood cell indices. What do they tell you about the patient's erythrocytes?
2. What laboratory tests are commonly used to evaluate hemostasis? How do you interpret their results in terms of the coagulation process?
3. What is the proper method for collection of a routine urinalysis in an adult man and woman?
4. In Figure 4 on WebCT, what is the rod-like (or dumbbell-like) brown object a tiny bit above and to the right of center? What different diseases is it associated with?

**Questions For Discussion - Not Written**
1. What is the most likely diagnosis in this case and how do you support it?
Cell Injury #1  Cellular Swelling

**Kidney, Hematoxylin & eosin stain. Intermediate magnification.** One of the events to occur in hypoxic or ischemic injury is cellular swelling. The decrease of oxygen tension in the cell results in impairment of mitochondrial oxidative phosphorylation and reduced production of adenosine triphosphate (ATP). Since ATP is used to maintain the cellular ion pumps (the ouabain-sensitive Na⁺,K⁺-ATPase), the lack of ATP leads to an influx of sodium and water and an efflux of potassium with a net increase in osmotic load and consequent cellular swelling. In addition inorganic phosphates, lactate, and purine nucleosides accumulate in the cell and contribute to the osmotic load.

Note the marked swelling and vacuolation in the epithelial cells in this photomicrograph of the kidney from a patient with sulfonamide nephrosis.

Cell Injury #2  Coagulative Necrosis

A. **Normal Myocardium. Hematoxylin & eosin stain. X125 [left image].**

B. **Myocardium. Hematoxylin & eosin stain. X125. [right image].** This is an example of coagulative necrosis from a patient who had a fatal myocardial infarction. The basic outline of the myocardial cells are preserved, but the fibers have a “smudgy” appearance with increased eosinophilia and decreased numbers of nuclei. In coagulative necrosis the necrotic process is due mainly to protein denaturation. When hypoxic injury leads to cell death, it often results in coagulative necrosis except in the brain where liquefactive necrosis is characteristically found.

Cell Injury #3  Late Coagulative Necrosis

**Myocardium: hematoxylin and eosin stain.** This image shows the result of a myocardial infarct after some time has passed. What date would you assign to it? Myocardial tissue is no longer recognizable because so many cells have died. Many nuclei have become pyknotic (shrunken and dark) and have then undergone karorrhexis (fragmentation) and karyolysis (dissolution). The cytoplasm and cell borders are not recognizable. Inflammatory cells or degenerated fragments of them are also numerous. What would the next stage of this process look like?
Cell Injury #4  
**Myocardial Infarct**

This cross-section of the apex of the heart shows a recent, pale yellow-gray infarct with a central dark red-brown tract of rupture. Adjacent to this is a white, old myocardial scar. How would you account for all the various colors you see in these lesions?

Cell Injury #5  
**Coagulative Necrosis: Splenic Infarct**

Two large infarcts (areas of coagulative necrosis) are seen in this sectioned spleen. Since the etiology of coagulative necrosis is often ischemia, the infarct occurs in a vascular distribution that is wedge-shaped with a base at the organ capsule.

Cell Injury #6  
**Liquefactive Necrosis: Liver Abscess**

*Hematoxylin and eosin.* Low power. The liver shows a small abscess here filled with many neutrophils, probably the result of bacterial or fungal infection. The infection elicits a marked acute inflammatory response, and proteolytic enzymes from the inflammatory cells digest the tissue. This abscess is an example of localized liquefactive necrosis.

Cell Injury #7  
**Liquefactive Necrosis: Brain, Gross**

Liquefactive necrosis is usually the result of a bacterial or fungal infection, because these processes evoke a massive influx of inflammatory cells. For unclear reasons, a hypoxic insult to the brain also results in liquefactive necrosis. As this infarct in the brain is organizing and being resolved, the liquefactive necrosis leads to resolution with cystic spaces.

Cell Injury #8  
**Liquefactive Necrosis: Brain**

This is liquefactive necrosis in the brain in a patient who suffered a "stroke" with focal loss of blood supply to a portion of cerebrum. This type of infarction is marked by loss of neurons and neuroglial cells and the formation of a clear space at the center left. The proteolytic enzymes responsible for the necrosis come from lysosomes, either from the dead cells or from the invading leukocytes, or from both.

Cell Injury #9  
**Caseous Necrosis: Lung, Gross**

This is the gross appearance of caseous necrosis in a hilar lymph node infected with tuberculosis. The node has a cheesy tan to white appearance. Caseous necrosis is really just a combination of coagulative and liquefactive necrosis that is most characteristic of granulomatous inflammation.
Cell Injury #10  
**Caseous Necrosis: Lung**

_Hematoxylin and eosin stain. Low power._ Often the result of mycobacterial or fungal infection, caseous necrosis is characterized by acellular pink areas of necrosis, as seen here at the upper right. To the left and down it is surrounded by a granulomatous inflammatory reaction composed of palisading "epithelioid" histiocytes, lymphocytes, and other cells. Although not seen here, multinucleated giant cells are also characteristic.

Cell Injury #11  
**Fat Necrosis: Pancreas, Gross**

This is fat necrosis of the pancreas. Cellular injury to the pancreatic acini leads to release of powerful enzymes which damage fat by the production of soaps, and these appear grossly as the soft, chalky white areas seen here on the cut surfaces. Necrosis of the acinar cells of the pancreas releases lipase and other proteases which in turn lead to injury and death of adipose cells. Triglycerides are hydrolyzed to glycerol and fatty acids and the fatty acids are then saponified (converted to soaps) by reacting with calcium, magnesium and sodium. If fat necrosis is extensive, sufficient calcium may be deposited to result in hypocalcemia and in some cases even tetany. Adipose tissue in other areas (breast or thigh, etc.) may also undergo necrosis following trauma.

Cell Injury #12  
**Fat Necrosis Pancreas**

_Hematoxylin and eosin stain. Low magnification._ Microscopically, fat necrosis adjacent to pancreas is seen here. There are some remaining steatocytes at the left which are not necrotic. The necrotic fat cells at the right have vague cellular outlines, have lost their peripheral nuclei, and their cytoplasm has become a pink amorphous mass of necrotic material.

Cell Injury #13  
**Gangrene: “Dry”**

This is gangrene, or necrosis of many tissues in a body part. Though not a distinct pathway of cell death, the term is in common surgical usage. So-called "dry" gangrene is the result of loss of blood supply with coagulative necrosis due to anoxia. In this case, the toes were involved in a frostbite injury.

Cell Injury #14  
**Gangrene: “Wet”**

This is gangrene of the lower extremity. In this case the term "wet" gangrene is more applicable because of the liquefactive component from superimposed infection in addition to the coagulative necrosis from loss of blood supply. This patient had diabetes mellitus. For a literary treatment of gangrene, read _The Snows of Kilimanjaro_ by Ernest Hemingway.
Cell Injury #15  

**Apoptosis: Viral Hepatitis**

**Hematoxylin and eosin stain. Intermediate magnification.** Apoptosis is a more orderly process of cell death in which there is individual cell necrosis, not necrosis of large numbers of cells. In this example, liver cells are dying individually (arrows) from injury by viral hepatitis. The cells are pink and without nuclei.

Cell Injury #16  

**Apoptosis: Thymus**

Hematoxylin and eosin stain. Intermediate magnification. In this fetal thymus there is involution of thymic lymphocytes by the mechanism of apoptosis. Individual cells fragment and are consumed by phagocytes to give the appearance of clear spaces filled with cellular debris. Apoptosis is controlled by many mechanisms. Genes such as Bcl-2 are turned off and Bax genes turned on. Proteolytic enzymes called caspases produce much cellular breakdown.

Cell Injury #17  

**Cytoskeletal Abnormalities: Mallory Bodies**

**Hematoxylin and eosin stain. High magnification.** Cytoplasmic organelle damage leads to a variety of injury patterns, most of which are best seen by electron microscopy. Acute injuries tend to damage an entire cell, so specific organelle damage is beside the point. However, in some cases the damage can be cumulative over many years. Here are **Mallory bodies** (the red globular material) composed of cytoskeletal filaments in liver cells chronically damaged from alcoholism. These are a type of "intermediate" filament between the size of actin (thin) and myosin (thick).

Cell Injury #18  

**Hyperplasia: Prostate, Gross**

This is an example of prostatic hyperplasia. The normal prostate is about 3 to 4 cm in diameter. The number of prostatic glands, as well as the stroma, has increased. The pattern of increase here is not uniform, but nodular. This increase is in response to hormonal changes due to aging.

Cell Injury #19  

**Hyperplasia: Prostate**

**Prostate gland. Hematoxylin & eosin stain. X20 [left image].** The normal adult prostate gland shows compound tubulo-acinar glands lined by pseudostratified columnar and/or cuboidal epithium and separated by a supporting stroma consisting of bundles of smooth muscle cells separated by hands of fibrous tissue. Some of the glands often show papillary epithelial infoldings.
Prostate gland. Hematoxylin & eosin stain. X20 [right image]. Benign prostatic hyperplasia (BPH) or nodular hyperplasia is an extremely common condition seen in men over the age of 50 years. The histologic hallmark of BPH is the expansile nodule, portions of two of which are seen in this photomicrograph. These nodules are the elements. The cause is most likely related to excess stimulation of the prostate gland by testosterone or its metabolite dehydrotestosterone.

Cell Injury #20  Hypertrophy: Heart

This is cardiac hypertrophy involving the left ventricle. The number of myocardial fibers does not increase, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with systemic hypertension.

Cell Injury #21  Atrophy: Muscle Fibers

Trichrome stain. High magnification. There are some muscle fibers here that show atrophy. The number of cells is the same as before the atrophy occurred, but the size of some fibers is reduced. This is a response to injury by “downsizing” to conserve the cell. In this case, innervation of the small fibers in the center was lost.

Cell Injury #22  Intracellular Accumulation of Glycogen

Liver. Hematoxylin & eosin stain. X78. By light microscopy cells containing excess deposition of glycogen appear to have clear or vacuolated cytoplasm. Since this appearance could also be due to the accumulation of water (hydropic swelling) or fat, special stains are usually employed to aid in differentiation. If the glycogen was preserved during histologic processing, it can be demonstrated as a reddish color by the period acid-Schiff (PAS) stain. Reacting the tissue with diastase to digest glycogen serves as a negative control. This is the liver from a patient with Von Gierke’s disease, one of the glycogen storage diseases. These entities will be discussed more fully in the section on genetic disease. Glycogen can also accumulate in the kidney, liver, pancreas, and myocardium of patients with diabetes mellitus.

Cell Injury #23  Intracellular Accumulation of Lipids

Liver. Hematoxylin & eosin stain. X12 [left image]. This is an example of the accumulation of triglycerides (steatosis or fatty change) in hepatocytes and can be result of any of the following conditions:

1. Increased entry of fatty acids into the cells.
2. Reduced oxidation of fatty acids
3. Excess production of fatty acids from acetate.
4. Inadequate lipoprotein release from hepatocytes.
5. Reduced lipoprotein release from hepatocytes.
Steatosis (Fatty Change)

<table>
<thead>
<tr>
<th>Type</th>
<th>Histology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvesicular</td>
<td>Cell enlarged; numerous small fat droplets; no alteration in nuclear morphology or location</td>
<td>Usually due to acute toxic hepatocellular injury; alcohol, tetracycline, aspirin, etc.</td>
</tr>
<tr>
<td>Macrovesicular (large droplet)</td>
<td>Cell enlarged; usually a large single fatty vacuole; cytoplasm and nucleus pushed to periphery</td>
<td>Usually due to chronic injury; malnutrition; chronic alcohol abuse; corticosteroids; methotrexate; organic solvents, etc.</td>
</tr>
</tbody>
</table>

Subcutaneous tissue. Masson trichrome stain. X80. [right image]. Numerous foam cells in the subcutaneous tissue of a 15-year-old male with a total serum cholesterol level of 525 mg/dL. This is an xanthoma and the intracellular lipid is predominantly cholesterol and cholesterol esters.

Cell Injury #24   Intracellular Accumulation of Iron

A Prussian blue reaction is seen in this iron stain of the liver to demonstrate large amounts of hemosiderin that are present in hepatocytes and Kupffer cells. When ferric iron reacts with an acid solution of potassium ferrocyanide, it forms a deep blue compound, ferric ferrocyanide as seen here. This is the Prussian blue reaction.

Cell Injury #25   Intracytoplasmic Accumulation of Melanin

Hematoxylin and eosin stain. High magnification. This is the microscopic appearance of a malignant melanoma. Large polygonal cells (or spindle cells in some cases) have very pleomorphic nuclei which contain prominent nucleoli. The neoplasm is making brown melanin pigment. A Fontana-Masson stain for melanin may help to detect small amounts of cytoplasmic melanin.

Cell Injury #26   Intracellular Accumulation of Bilirubin

Liver. Hematoxylin & eosin stain. X125. This is an example of drug-induced cholestasis. Most of the hepatocytes contain numerous greenish or greenish–brown droplets of conjugated bilirubin. Intracanilicular cholestasis is also present. Free bilirubin is derived from the porphyrin ring of hemoglobin during red blood cell destruction and can result in cell injury by uncoupling oxidative phosphorylation in mitochondria or by causing protein loss through an effect on the plasma membrane.
Cell Injury #27  Anthracosis: Lung

The black streaks seen between lobules of lung beneath the pleural surface are due to anthracotic pigment. This anthracosis of the lung is not harmful and comes from the carbonaceous material breathed in from dirty air typical of industrialized regions of the planet.

Cell Injury #28  Metastatic Calcification: Lung

Here is so-called "metastatic calcification" in the lung of a patient with a very high serum calcium level (hypercalcemia).

Cell Injury #29  Dystrophic Calcification: Stomach

This is dystrophic calcification in the wall of the stomach. At the far left is an artery with calcification in its wall. There are also irregular bluish-purple deposits of calcium in the submucosa. Calcium is more likely to be deposited in tissues that are damaged.

Environmental Pathology

Cell Injury #30  Radiation Injury

Rectum. Hematoxylin & eosin stain. X31. [left image]. This photomicrograph illustrates the chronic effects of radiation injury to the rectum of a woman who has had pelvic irradiation 17 years previously for cervical carcinoma. The rectal wall is thickened by fibroids, the mucosa is ulcerated, and the vessels are ecstatic. A chronic inflammatory infiltrate and scattered abnormal fibroblasts are present.

Rectum. Hematoxylin & eosin stain. X31 [right image]. Similar findings can be seen deeper in the wall, and here one of the vessels also appears hyalinized.

Cell Injury #31  Heroin: Lung

Lung. Hematoxylin & Eosin Stain. X525. The alveolar spaces of the lung from this 24-year-old heroin addict are filled with the pink, homogeneous fluid of pulmonary edema. Most likely this was a hypersensitivity reaction to the drug or one of its adulterants.

Another common finding in the lungs from intravenous drug users is the presence of granulomas secondary to some of the diluents used to “cut” the drug such as talc. Talc is a silicate compound that is mildly fibrogenic and widely used in industry. Besides its use as a diluent for “street drugs”, exposure to talc occurs in miners and millers, among workers in the pharmaceutical and cosmetics industries, and of course among cosmetic users.
**Week 1: August 16-20**
*Cell and Tissue Response to Injury / Environmental Pathology*

**Cell Injury #32**  
**Heroin Nephropathy**

**Hematoxylin and eosin stain. Intermediate magnification.** A glomerulus of the kidney demonstrates focal scarring with heroin nephropathy.

**Cell Injury #33**  
**Alcoholic Hepatitis**

**Liver, Hematoxylin & eosin stain.** Fatty change (steatosis) has a number of etiologies, including hypoxia, toxins, protein malnutrition, and others. It often occurs in the liver because the liver plays a large role in fat metabolism. In alcoholic steatosis the fat droplets are microvesicular at first, but they become macrovesicular with chronic ethanol ingestion. Alcoholic steatosis results from increased lipid synthesis, faulty lipoprotein assembly and secretion, and increased peripheral fat catabolism. In the bottom image there is other evidence of alcoholic hepatitis:
- Hepatocyte necrosis.
- Mallory bodies (eosinophilic clumps of intermediate filaments).
- Small clusters of neutrophils.

**Cell Injury #34**  
**Tobacco: Lung Carcinoma**

This is a large squamous cell carcinoma in which a portion of the tumor demonstrates central cavitation, probably because the tumor outgrew its blood supply. Squamous cell carcinomas are one of the more common primary malignancies of lung and are most often seen in smokers. Besides lung cancer, cigarette smoking also increases the risk of developing cancer of the oral cavity, pharynx, lip, larynx, esophagus, and pancreas.
### Week 2: August 23-27

**Inflammation/Tissue Repair**

#### Schedule

**Tuesday, August 24**  
1-4 PM  
Case-Based Study  
Laboratory

**Thursday, August 26**  
2-5 PM  
Path Talk  
Laboratory

**Friday, August 27**  
10-11AM  
Summary  
West Lecture Hall

11AM-Noon  
Journal club/Epi-Bio Consult  
Laboratory – Room N12
Topic: Reaction to Tissue Injury: Edema, Thrombosis, and Inflammation

Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition,
- Acute and Chronic Inflammation, Chapter 3, pp. 50-87
- Tissue Repair, Chapter 4, pp. 89-111
- Hemodynamic Disorders, Thrombosis, and Shock, Chapter 5, pp. 113-137

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:
  - C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Artery Disease, J. Danesh, Vol. 350: 1387-1397 April 1, 2004
  - C-Reactive Protein Reassessed, A.R.Tall, Vol. 350: 1450 April 1, 2004

Case-Based Study
Assignments:
- Printed Case 1 - “The case of the excessive nosebleeds…”
- Printed Case 2 - “A 67 year old white female was readmitted…”

Case-Based Study
Required reading: Widmann’s Clinical Interpretation of Laboratory Tests

Principles of interpretation of laboratory tests:
- pp. 10-17

Anemia and coagulation:
- pp. 154-155: Extrinsic hemolytic anemias
- pp. 305-310: Thrombocytopenia due to immune destruction of platelets
- pp. 252-256: Coagulation cascade
- pp. 264-265: Coagulation tests
- pp. 93-95: ESR

Clinical microbiology:
- pp: 603-613: Introduction
- pp: 630-638: Culture of infectious agents
Printed Case #1: The Case of the Excessive Nosebleeds
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Patient: 48-year-old female.
Chief Complaint: Patient had been in her usual state of good health until recently when she noted signs and symptoms of an upper respiratory infection. She noted rhinorrhea, congestion, cough, and later developed epistaxis (nose bleeding). The epistaxis progressively worsened and the patient subsequently developed hematuria and petechia on the right thigh. Patient complained of severe headaches and a fever, but denied chills, night sweats, visual changes, shortness of breath, or hematochezia.
Medical History: Unremarkable.
Surgical History: Cholecystectomy and tubal ligation.
Social History: Patient has smoked 2 packs of cigarettes per day for the last 30 years; denied any alcohol or drug abuse.
Family History: Mother died at age 54 from embolic cerebral vascular accident. Father died at age 54 from myocardial infarction. Patient has 2 brothers with hypertension and a sister with lung cancer.

Physical and Neurological Examination: The patient’s temperature was elevated at 100.5 ° F, and she appeared mildly confused. Petechiae were present over the lower extremities.

Principal Laboratory Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient's Result</th>
<th>&quot;Normal&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC Count</td>
<td>9.9</td>
<td>4-10 (x10^3) /µL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.5</td>
<td>12-16 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>30.</td>
<td>9 37%-47%</td>
</tr>
<tr>
<td>RBC Count</td>
<td>3.4</td>
<td>4.2-5.4 (x10^6) /µL</td>
</tr>
<tr>
<td>MCHC</td>
<td>33.9</td>
<td>32-36 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>91</td>
<td>82-99 fl</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>9</td>
<td>150-400 (x10^3) /µL</td>
</tr>
<tr>
<td>MPV</td>
<td>7.3</td>
<td>6.2-10.6 fl</td>
</tr>
<tr>
<td>Differential Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>70</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>22.7</td>
<td>20%-40%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>6.6</td>
<td>2%-12%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.3</td>
<td>0%-4%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.2</td>
<td>0%-2%</td>
</tr>
<tr>
<td>RBC morphology</td>
<td>normocytic/normochromic with schistocytes present</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte</td>
<td>2.4 %</td>
<td>0.5%-2.8%</td>
</tr>
<tr>
<td>Count (corrected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>13.1</td>
<td>11.5-15.0 s</td>
</tr>
<tr>
<td>INR</td>
<td>1.0</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>PTT</td>
<td>27</td>
<td>24-36 s</td>
</tr>
<tr>
<td>LD</td>
<td>968</td>
<td>0-199 U/L</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>9</td>
<td>20-230 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>28</td>
<td>5-24 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.0</td>
<td>0.8-1.2 mg/dL</td>
</tr>
</tbody>
</table>

WBC, white blood cell; RBC, red blood cell; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; MPV, mean platelet volume; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; LD, lactate dehydrogenase; BUN, blood urea nitrogen.
Figure 1 (On Case-Based Study section of WebCT: Patient’s peripheral blood smear illustrating schistocytes (1000x magnification).

**Questions:**
1. What is (are) this patient's most striking laboratory results?
2. How do you explain this patient's most striking findings/laboratory results(s)?
3. What condition(s) does this patient's laboratory and other findings suggest?
4. Which additional laboratory test(s) are appropriate to order on this patient and why?
5. What is the most appropriate treatment for this patient?
Printed Case #2: A 67 year old white female was readmitted

CLINICAL SUMMARY: A 67-year old white female was readmitted with a chief complaint of weakness and increasing dyspnea. She was recently discharged after a three-month hospitalization for respiratory failure secondary to bulbar paralysis. During that hospital stay she required a tracheostomy and assisted respirations but was discharged ambulatory and eating. She is a known diabetic on NPH insulin. Physical examination revealed a cachectic, weak woman who responded to commands and appeared in mild respiratory distress. Her temperature was normal. Her pulse rate was 120. Rhonchi were noted in her chest bilaterally and the abdomen was protuberant with shifting dullness to percussion.

LABORATORY DATA

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 15.8 thou (3.4-11)</td>
<td>Blood glucose 323 mg/dl (65-110)</td>
</tr>
<tr>
<td>polys 63% (40-75)</td>
<td>Total plasma protein 5.4gm/dl (6-8)</td>
</tr>
<tr>
<td>bands 30% (0-7)</td>
<td>Albumin 3.0 gm/dl (3.5-5)</td>
</tr>
<tr>
<td>lymphs 7% (13-45)</td>
<td>Arterial blood gases</td>
</tr>
<tr>
<td>HGB 10.0 gm% (12-18)</td>
<td>pH 7.10 (7.35-7.45)</td>
</tr>
<tr>
<td>HCT 30.8 % (37-47)</td>
<td>pCO2 36 mmHG (32-46)</td>
</tr>
<tr>
<td>MCV 94 fl (81-99)</td>
<td>HCO3 11 mmol/L (18-29)</td>
</tr>
<tr>
<td>MCH 30.6 pg (27-31)</td>
<td>pO2 60 mmHg (74-108)</td>
</tr>
<tr>
<td>Pits 209 thou (130-400)</td>
<td>O2 saturation 89 % (92-96)</td>
</tr>
<tr>
<td>Sodium 137 meq/L (142-151)</td>
<td></td>
</tr>
<tr>
<td>Potassium 4.0 meq/L (3.5-5.0)</td>
<td></td>
</tr>
<tr>
<td>Chloride 99 meq/L (100-112)</td>
<td></td>
</tr>
</tbody>
</table>

Microbiology

Sputum culture (Admission) - *Klebsiella pneumoniae*

Blood culture (Admission) - *Klebsiella pneumoniae*

Review images: Available on Case-Based Studies section of Pathology WebCT site.

CLINICAL COURSE: An admission chest radiograph showed a patchy infiltrate in the right lower lung field with discoid atelectasis in the left lower lung field. Abdominal films showed gaseous distention of the colon. An EKG revealed sinus tachycardia with left ventricular hypertrophy and subendocardial ischemia. The patient's respiratory difficulty increased despite antibiotic therapy, bronchoscopy, and tracheostomy with respiratory care. On the 5th hospital day, sputum cultures grew *Staphylococcus aureus*, coagulase positive and *Pseudomonas aeruginosa*. She expired on the 15th hospital day. An autopsy was performed.

Questions For Homework - To Be Written And Brought To Class (at the instructor’s discretion)

1. What precautions are necessary in culturing blood and determining the significance of any organisms obtained?
2. How is examination of the urine sediment performed and what can it reveal?
Questions For Class Discussion - Not Written
   1. What is the most likely diagnosis in this case and how do you support that diagnosis?
Reactions to Tissue Injury #1

**Exudation**

**Hematoxylin & eosin stain. Medium power.** Seen here is vasodilation with exudation that has led to an outpouring of fluid with fibrin into the alveolar spaces, along with PMN's. The series of events in the process of inflammation are:

1. Vasodilation: leads to greater blood flow to the area of inflammation, resulting in redness and heat.
2. Vascular permeability: endothelial cells become "leaky" from either direct endothelial cell injury or via chemical mediators.
3. Exudation: fluid, proteins, red blood cells, and white blood cells escape from the intravascular space as a result of increased osmotic pressure extravascularly and increased hydrostatic pressure intravascularly.
4. Vascular stasis: slowing of the blood in the bloodstream with vasodilation and fluid exudation to allow chemical mediators and inflammatory cells to collect and respond to the stimulus.

Reactions to Tissue Injury #2

**Neutrophil in Action**

This animation demonstrates the actions of neutrophils in the acute inflammatory process. These series of events in the process of inflammation are mediated by:

- Selectins: molecules on leukocytes (L-selectin) and endothelium (E-selectin, P-selectin) act as receptors to provide loose binding for rolling.
- ICAM-1: intercellular adhesion molecule 1 provides more firm adhesion of the neutrophil, via integrins on neutrophil surfaces, to the endothelium.
- CD31: this cell to cell adhesion molecule aids in diapedesis.
- C5a and LTB4: chemotaxis is aided by the C5a component from complement activation, along with leukotriene B4, a product of the lipo-oxygenase pathway of arachidonic acid metabolism.
- C3b and IgG: opsonins such as the C3b component from complement activation, as well as immunoglobulin G, coat foreign objects such as bacteria to aid in phagocytosis by binding to leukocyte receptors.
- Myeloperoxidase, lysozyme: after engulfment, killing of bacteria occurs via generation of toxic oxygen species (superoxide) converted to hydrogen peroxide and further converted to a hypochlorous radical by myeloperoxidase from neutrophil granules. In the absence of oxidation, lysozyme from neutrophil granules can form holes in microbial membranes.

Reactions to Tissue Injury #3

**Diapedesis**

**Hematoxylin & eosin stain. Medium power.** Neutrophils that are marginated along the dilated venule wall (arrow) are squeezing through the basement membrane (the process of diapedesis) and spilling out into extravascular space.
Reactions to Tissue Injury #4

**Appendix. Hematoxylin & eosin stain. X80.** This is a portion of the wall of the appendix from a young woman who had a fecalith at the appendiceal opening. Note the separation of the fibers in the muscularis by edema fluid and masses of polymorphonuclear leukocytes. This neutrophilic infiltration of the muscularis confirms the diagnosis of acute appendicitis. The increased vascular permeability of the vessels in this area results in the leakage of a protein-rich exudate, the edema fluid, into the interstitium. Through a process known as extravasation, the leukocytes leave the circulation and migrate, under the influence of chemotactic factors, to the site of injury. The major complication of acute appendicitis is perforation with the formation of periappendiceal abscesses and peritonitis.

Reactions to Tissue Injury #5

**Lung. Hematoxylin & eosin stain. X50.** Another example of acute inflammation is seen in this photomicrograph from a patient with bronchopneumonia. The alveoli are filled with neutrophils that have emigrated from the septal vessels, which are markedly dilated.

Reactions to Tissue Injury #6

Cellular interactions with chronic inflammation are diagrammed.

Reactions to Tissue Injury #7

Chronic inflammation can be seen in conjunction with some degree of scarring. Here, chronic inflammation of the bronchi has led to dilation and scarring with increased tan to white collagenous tissue.

Reactions to Tissue Injury #8

**Lung. Hematoxylin & eosin stain. X20.** Sometimes acute inflammation may evolve into chronic inflammation. All the hallmarks of chronic inflammation can be seen in this photomicrograph: a mononuclear cell infiltrate, tissue destruction, and fibrosis. The normal architecture of the lung has been destroyed by masses of inflammatory cells (mainly lymphocytes) and fibrosis. Several cystic spaces lined by cuboidal epithelium and partially filled by inflammatory cells (neutrophils, macrophages, and lymphocytes) are all that remain of the preexisting alveoli.

Reactions to Tissue Injury #9

**Hematoxylin & eosin stain. Medium power.** This is an example of less massive chronic inflammation. Certain etiologic agents such as viruses are more likely to lead to chronic rather than acute inflammation, as seen here in the lung of a patient with influenza A. Note also that the inflammatory infiltrates of chronic inflammation are more likely to be interstitial (within tissues) rather than exudative (above surfaces or in spaces) like acute inflammation.
Reactions to Tissue Injury #10  Granulomas: Low Power

Hematoxylin & eosin. Low power. The focal nature of granulomatous inflammation is demonstrated in this microscopic section of lung in which there are scattered granulomas in the parenchyma. This is why the chest radiograph with tuberculosis or other granulomatous diseases is often described as "reticulonodular". A biopsy could miss such lesions from sampling error, too.

Reactions to Tissue Injury #11  Granulomas: Medium Power

Hematoxylin & eosin. Medium power. Here are two pulmonary granulomas. Granulomatous inflammation typically consists of epithelioid macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts. There may be some neutrophils.

Literary note: If you want to be fancy, for more than one granuloma you can use the Greek plural of granuloma and call them "granulomata".

Reactions to Tissue Injury #12  Granulomas: High Power

Hematoxylin & eosin stains. High power.

Fig 1. Giant cells are a "committee" of epithelioid macrophages. Seen here are two Langhans type giant cells in which the nuclei are lined up around the periphery of the cell. Additional pink epithelioid macrophages compose most of the rest of the granuloma.

Fig 2. These are epithelioid cells around the center of a granuloma. They get their name from the fact that they have lots of pink cytoplasm similar to squamous epithelial cells. Their nuclei tend to be long and stringy.

Reactions to Tissue Injury #13  Fibrinous Pericarditis: Gross

Exudation of a protein-rich fluid into a cavity leads to a transudate. The fibrin in this fluid can form a fibrinous exudate on the surfaces. Here, the pericardial cavity has been opened to reveal a fibrinous pericarditis with strands of stringy pale fibrin between visceral and parietal pericardium.

Reactions to Tissue Injury #14  Fibrinous Pericarditis

Hematoxylin & eosin. Medium power. Microscopically the fibrinous exudate is seen to consist of pink strands of fibrin jutting from the pericardial surface at the upper left. Below this, there are a few scattered inflammatory cells.
Reactions to Tissue Injury #15  
**Abcess: Bronchopneumonia, Gross**

This abscessing bronchopneumonia has numerous areas of raised, lighter tan appearance which are the areas containing the extensive neutrophilic infiltrates.

Reactions to Tissue Injury #16  
**Pulmonary Abcess: Low Power**

**Lung. Hematoxylin & eosin stain. X5.** This is a photomicrograph of an abscess from another patient, actually a young boy with chronic granulomatous disease, and inherited disorder in which oxygen-dependent mechanisms for bacterial killing are deficient. The alveolar tissue in the center of the abscess has been destroyed and replaced by a large mass of necrotic debris and neutrophils. The edge of the abscess contains fibroblasts and a prominent vasculature. Some of the alveoli surrounding the abscess contain an inflammatory exudate.

Reactions to Tissue Injury #17  
**Pulmonary Abcess: Medium Power**

**Hematoxyline & eosin stain. Medium power.** Here is a focal abscess in the lung. The alveoli in this area have been destroyed.

Reactions to Tissue Injury #18  
**Granulation Tissue**

**Stomach. Hematoxylin & eosin stain. X31.** The repair of damaged tissue includes several processes: 1) new blood vessel formation, 2) fibroblast proliferation, 3) deposition of extracellular matrix, and 4) organization. This photomicrograph illustrates granulation tissue formation in a gastric ulcer. The surface of the ulcer is composed of inflammatory cells and fibrin. Beneath this is a rich complex of new blood vessels, fibroblasts and inflammatory cells.

Reactions to Tissue Injury #19  
**Granulation Tissue: High Power**

**Hematoxylin & eosin stain. High Power.** At high magnification, granulation tissue has capillaries, fibroblasts, and a variable amount of inflammatory cells (mostly mononuclear).

Reactions to Tissue Injury #20  
**Keloid**

This is an example of an exuberant scar in a patient who has had abdominal surgery. The excess formation of scar tissue is called "keloid".

Reactions to Tissue Injury #21  
**Skin: Young Scar**

**Skin. Hematoxylin & eosin stain. Low power** One of the outcomes of acute inflammation and the repair process is fibrosis and scarring. This is a skin biopsy from a patient who developed some tenderness at the site of a previous biopsy for a skin tumor. Compare the epidermis and dermis in the center of the specimen with those same areas toward the edges of the biopsy.
Reactions to Tissue Injury #22  

Edema: Gross

Fig 1. This example of a fluid collection, a friction blister of the skin, is an almost trivial example of edema.

Fig 2. This example of edema with inflammation is not trivial at all: there is marked laryngeal edema such that the airway is narrowed. This is life-threatening. Thus, fluid collections can be serious depending upon their location.

Reactions to Tissue Injury #23  

Edema

Hematoxylin & eosin stain. Low power. The alveoli are distended with edema fluid which appears pink and homogeneous in hematoxylin and eosin stains. Note the dilated septal vessels from which the fluid originates. This is an example of pulmonary edema from a patient with longstanding congestive heart failure. The accumulation of the fluid in the lungs is due in part to an increase in the intravascular hydrostatic pressure secondary to decreased cardiac output.

Reactions to Tissue Injury #24  

Liver: Passive Congestion

Here is an example of a "nutmeg" liver seen with chronic passive congestion of the liver. Note the dark red congested regions that represent accumulation of RBC's in centrilobular regions.

Reactions to Tissue Injury #25  

Congestion: Lung

Lung. Hematoxylin & eosin stain. X50. This photomicrograph illustrates a case of acute passive congestion of the lung in a patient with left ventricular failure following a myocardial infarction. The septal capillaries are markedly distended with blood. The intra-alveolar collections of red blood cells and fibrin present are a result of capillary rupture. Acute pulmonary congestion can lead either to full-blown pulmonary edema as seen above or to the accumulation of hemosiderin-laden macrophages and septal fibrosis.

Reactions to Tissue Injury #26  

Coronary Artery Thrombosis: Gross

Here is coronary thrombosis. The thrombus occludes the lumen and produces ischemia and/or infarction of the myocardium.

Reactions to Tissue Injury #27  

Coronary Artery Thrombosis 1

Hematoxylin and eosin stain. Medium power. Here is occlusive coronary atherosclerosis. The coronary at the left is narrowed by 60 to 70%. The coronary at the right is even worse with evidence for previous thrombosis with organization of the thrombus and recanalization such that there are three small lumens remaining.

The formation of the thrombus in this coronary artery was mainly due to two factors: 1) the exposure of subendothelial tissue substances resulting from ulceration of the atheromatous plaque, and 2) disturbances in local blood flow caused by disruption of the endothelial surfaces.
Reactions to Tissue Injury #28

**Coronary Artery Thrombosis 2**

**Hematoxylin and eosin stain. Medium power.** This is an atheromatous plaque in a coronary artery that shows endothelial denudation with disruption and overlying thrombus formation at the right. Note the appearance of the vessel wall at the left margin of the image.

Reactions to Tissue Injury #29

**Mural Thrombus**

A large mural thrombus has formed over a myocardial infarction in the left ventricle of the heart.

Reactions to Tissue Injury #30

**Disseminated Intravascular Coagulation: Lung**

**Hematoxylin & eosin stain. High power.** Disseminated intravascular coagulation (DIC) is a consequence of widespread activation of the coagulation system through endothelial injury and/or release of thromboplastic substances into the circulation. DIC can be seen with severe infections, trauma, neoplasia, and obstetric complications, among others. Small fibrin thrombi can form in small arteries of brain, heart, lungs, kidneys, and other organs to produce ischemic tissue damage.

Reactions to Tissue Injury #31

**Disseminated Intravascular Coagulation: Kidney**

**Hematoxylin & eosin stain. Medium power.** Small fibrin thrombi from widespread activation of the coagulation system with disseminated intravascular coagulopathy (DIC) can be seen in capillary loops in this glomerulus, highlighted by a fibrin stain. Laboratory findings with DIC include decreased platelets, diminished fibrinogen, prolonged prothrombin time, elevated partial thromboplastin time, and elevated D-dimer. Consumption of coagulation factors with generation of fibrin split products, along with platelet consumption, leads to these findings.

Reactions to Tissue Injury #32

**Pulmonary Thromboembolus: Gross**

The main pulmonary trunk and pulmonary arteries to right and left lungs are seen here opened to reveal a large "saddle" pulmonary thromboembolus. This is one of the few causes of nearly instant death.

Reactions to Tissue Injury #33

**Pulmonary Hemorrhagic Infarct: Gross**

Large thromboemboli can cause death. Medium sized thrombemboli (blocking a pulmonary artery to a lobule or set of lobules) can produce the lesion seen here--a hemorrhagic pulmonary infarction, because the patient survives. The infarct is wedge-shaped and based on the pleura. These infarcts are hemorrhagic because, though the pulmonary artery carrying most of the blood and oxygen is cut off, the bronchial arteries from the systemic circulation (supplying about 1% of the blood to the lungs) is not cut off.

Compared to the saddle embolus in the pulmonary arteries in the last slide, what kind of vessel do you think was occluded to produce this lesion? How do you think this patient was affected?
Reactions to Tissue Injury #34 Pulmonary Embolus & Infarction

Lung. Hematoxylin & eosin stain. X4 [left image]. The artery and its embolus can be seen in the upper portion of the image. The lung parenchyma shows extensive hemorrhage which accounts for the gross appearance. While hemorrhagic infarcts are usually found with venous occlusions, they can also occur after arterial occlusion as seen here in the lung.

Lung. Hematoxylin & eosin stain. X50 [right image]. At higher magnification, portions of the infarct showed fibrin strands and necrotic cells in the air spaces. This is ischemic coagulative necrosis; and it is characteristic of all infarcts except for those in the brain, where liquefactive necrosis is the rule.

Reactions to Tissue Injury #35 Hemorrhagic Infarct, Small Intestine: Gross

A sharply demarcated area of hemorrhagic infarction is seen in the small intestine of this elderly woman who had extensive systemic atherosclerosis and a cardiac arrhythmia.

Reactions to Tissue Injury #36 Hemorrhagic Infarct: Small Intestine

Hematoxylin and eosin. Low power. Note that the more superficial mucosa has undergone ischemic coagulative necrosis; no nuclei are visible. The deeper portion of the intestinal wall is viable, but it is conspicuously hyperremic. What caused the hyperremia?

Reactions to Tissue Injury #37 White Infarct

Spleen. Gross photo. A sharply-demarcated, wedge-shaped, yellow-white splenic infarct is shown here. White infarcts are usually seen in solid organs such as the heart, kidneys, and spleen following an arterial occlusion.

Reactions to Tissue Injury #38 Whack-a-Bug

A very motile bacterium is in an alveolar sac of the lung and wants to establish an infection. You are a neutrophil. Try to click on the bacterium with your mouse to phagocytize it.
Week 3: August 30-September 3

Immunity

Schedule

Tuesday, August 31
1-4 PM  Case-Based Study  Laboratory

Thursday, September 2
2-5 PM  Path Talk  Laboratory

Friday, September 3
10-11AM  Summary  West Lecture Hall
11 AM- Noon  Journal club/Epi-Bio Consult  Laboratory-Room N12
Topic: Immunity

Required Reading:

- Diseases of Immunity, Chapter 7, pp. 188-257
- Bronchial Asthma, Chapter 16, pp. 712-716
- Blistering Diseases, Chapter 27, pp. 1201-1205

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:

Case-Based Study
Assignments:
- Printed Case 1 – “Altered mental status in a middle-aged male…”
- Printed Case 2 – “38 year old man with fever, fatigue, malaise…”

Case-Based Study
Required reading: *Widmann’s Clinical Interpretation of Laboratory Tests*

Principles of interpretation of laboratory tests:
- pp. 17-21

Immunology
- pp. 325-336: Principles of immunology and immunology testing
- pp. 355-359: Autoantibodies
- p. 361: Kidney and lung disease
**Week 3: August 30-September 3**

**Immunity**

**Printed Case #1: Altered Mental Status in a Middle-Aged Male**

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**Patient:** 56-year-old African-American male.

**Chief Complaint:** The patient was escorted to the emergency department by the local police because of altered mental status. A urine drug screen and serum ethanol level were ordered.

**History of Present Illness:** Patient was not a good historian. He did complain of periodic joint pain usually lasting several days and recurring in different joints.

**Past Medical History:** Not available.

**Drug History:** Not available.

**Family/Social History:** Not available.

**Physical Examination:** Vital signs: temperature 37.0°C; blood pressure, 160/100 mm Hg; heart rate, 95 bpm; respiration rate, 18 per minute. The patient was although the patient was not oriented to place, he was cooperative and able to respond during the physical exam. Examination of the skin showed an erythematous facial rash most intense over the malar prominences. In sun-exposed areas of his arms there were erythematous raised patches with scaling. Several oral ulcers are present in the nasopharyngeal area, which the patient stated were not painful. In addition to his increased blood pressure, he had elevated jugular venous pressure. On deep inspiration the patient complained of sharp chest pains. Heart and lung sounds were slightly dull. Periodic jerking movements of his left arm and hand were noted. The left knee and ankle are tender to palpation and appear slightly swollen.

**Principal Laboratory Findings:** *(The following labs were not ordered all at once. The studies were requested as the investigation progressed. It would be an interesting problem to speculate about the order in which they were requested.)*

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient's Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinalysis With Microscope</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.015</td>
<td>1.002-1.030</td>
</tr>
<tr>
<td>Color/clarity</td>
<td>Yellow/Clear</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>5.0</td>
<td>5-7</td>
</tr>
<tr>
<td>Protein</td>
<td>500 mg/dL</td>
<td>Neg</td>
</tr>
<tr>
<td>Glucose</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Ketones</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Bile</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Blood</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>0.2</td>
<td>0.1-1.0 EU/dL</td>
</tr>
<tr>
<td>Leukocyte esterase/nitrite</td>
<td>Neg/Neg</td>
<td>Neg/Neg</td>
</tr>
<tr>
<td>RBCs</td>
<td>14</td>
<td>0-3/hpf</td>
</tr>
<tr>
<td>WBCs</td>
<td>None</td>
<td>0-5/hpf</td>
</tr>
<tr>
<td>Hyaline casts</td>
<td>None</td>
<td>0-2/lpf</td>
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### Urine Drug Screen

<table>
<thead>
<tr>
<th>Substance</th>
<th>Neg</th>
<th>Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine metabolite</td>
<td>Positive</td>
<td>Neg</td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Neg, negative; hpf, high power field; lpf, low power field

### Whole Blood

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>5.0</td>
<td>4.1-10.3 x 10^3 cells/mL</td>
</tr>
<tr>
<td>RBC count</td>
<td>3.44</td>
<td>4.3-6.2 x 10^6 cells/mL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.1</td>
<td>13.2-16.2 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>29.6</td>
<td>40-52%</td>
</tr>
<tr>
<td>MCV</td>
<td>85.9</td>
<td>82-105 fL</td>
</tr>
<tr>
<td>MCH</td>
<td>29.5</td>
<td>28-34 pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>34.3</td>
<td>31-35 g/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>180</td>
<td>150-450 x 10^9 cells/L</td>
</tr>
<tr>
<td>RDW</td>
<td>13.2</td>
<td>11.5-14.5%</td>
</tr>
</tbody>
</table>

### Serum

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>46</td>
<td>7-21 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.8</td>
<td>0.6-1.2 mg/dL</td>
</tr>
<tr>
<td>ANA titer</td>
<td>&gt;1:2560*</td>
<td>&lt;1:160</td>
</tr>
<tr>
<td>ANA pattern by IFA</td>
<td>Diffuse</td>
<td>NA</td>
</tr>
<tr>
<td>RF</td>
<td>&lt;20</td>
<td>0-20 IU/mL</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>&gt;1:2560</td>
<td>Neg#</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>1:1280</td>
<td>Neg</td>
</tr>
<tr>
<td>SMA</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>C3</td>
<td>70</td>
<td>88-201 mg/dL</td>
</tr>
<tr>
<td>C4</td>
<td>18</td>
<td>20-59</td>
</tr>
<tr>
<td>LD</td>
<td>658</td>
<td>100-190 U/L</td>
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</table>
### Week 3: August 30-September 3

#### Immunity

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOT</td>
<td>29</td>
<td>8-78 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>65</td>
<td>13-40 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>24</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>HIV-1,2 Abs</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HAV, IgM</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HBeAb</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HBsAb</td>
<td>NR (not immune)</td>
<td>R (if immunized)</td>
</tr>
<tr>
<td>HBsAg</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HCVAb</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

#### Urine

<table>
<thead>
<tr>
<th>Test</th>
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<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour urine protein</td>
<td>4,342</td>
<td>40-150 mg/24 hours</td>
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</tbody>
</table>

#### CSF

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Clear, Colorless</td>
<td>Clear, Colorless</td>
</tr>
<tr>
<td>Nucleated cells</td>
<td>&lt;1/ L</td>
<td>None</td>
</tr>
<tr>
<td>RBCs</td>
<td>30/ L</td>
<td>None</td>
</tr>
<tr>
<td>Glucose</td>
<td>42</td>
<td>40-70 mg/dL</td>
</tr>
<tr>
<td>Total protein</td>
<td>164</td>
<td>15-45 mg/dL</td>
</tr>
</tbody>
</table>

*Diffuse pattern by indirect immunofluorescence assay (IFA) [fig 3].

# When determined by Crithidia lucidiae IFA.

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; BUN, blood urea nitrogen; ANA, anti-nuclear antibodies; IFA, indirect fluorescence assay; RF, rheumatoid factor; dsDNA, double-stranded DNA; Sm, Smith; SMA, smooth muscle antibody; C3 and C4, complement components; LD, lactate dehydrogenase; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; Abs, antibodies; NR, non-reactive; R, reactive; HAV, hepatitis A virus; HBeAb, hepatitis S core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; CSF, cerebrospinal fluid. NA, not applicable

### Images:

<table>
<thead>
<tr>
<th>Protein</th>
<th>%</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb.</td>
<td>49.9</td>
<td>100.30</td>
</tr>
<tr>
<td>alpha 1</td>
<td>12.4</td>
<td>24.92</td>
</tr>
<tr>
<td>alpha 2</td>
<td>7.5</td>
<td>15.08</td>
</tr>
<tr>
<td>beta</td>
<td>5.0</td>
<td>10.05</td>
</tr>
<tr>
<td>gamma</td>
<td>25.2</td>
<td>50.65</td>
</tr>
</tbody>
</table>
Week 3: August 30-September 3

Immunity

Fig 1 Protein electrophoresis of a random urine sample (total protein = 200.9 mg/dL; estimated 24-hour urine total protein = 4,018 mg/24 h) from our patient demonstrating a pattern consistent with nephrotic syndrome.

Fig 2 A Wright's stained cytospin preparation of our patient's pleural effusion demonstrates the presence of cells (arrows) that have phagocytosed the nuclear components of other cells in an antibody (ANA)-mediated process.

Fig 3 The patient's serum was added to HEp-2 [human epithelioid cells with mitotic figures (Immunocconcepts, M)] followed by the addition of a second antibody [goat anti-human IgG (heavy and light chains)] labeled with a fluorescent probe (FITC) and viewed with a fluorescent microscope (400x).

Fig 4 Subdural hemorrhage seen at autopsy. Note the darkened purplish area on the left side of the dura representing extravascular blood below the dura (arrows).

Results of Additional Diagnostic Procedures: A computed tomography (CT) scan of the head demonstrated periventricular white matter disease and a 9 mm lacunar infarct in the pons region. Electroencephalography (EEG) demonstrated a periodic lateralized epileptiform discharge consistent with partial status epilepticus. A CT of the abdomen was performed to look for a possible abscess, and bilateral pleural effusions were found. Thoracentesis was performed and cytologic analysis of the pleural effusion revealed the presence of LE cells (i.e., macrophages or neutrophils that have ingested the antibody-coated nucleus of another cell) [fig2]. A lumbar spinal tap was performed and the results of the cerebrospinal fluid (CSF) analysis are shown in the table above. Protein electrophoresis was performed on a random urine sample and the urine protein electrophoresis pattern (UPEP) obtained is shown in fig 1.

Questions:
1. What is (are) this patient's most striking laboratory result(s)?
2. How do you explain this patient's most striking laboratory result(s)?
3. What condition(s) does this patient's laboratory and other findings suggest?
4. What are the principal complications found in this patient's condition?
5. What is (are) the most likely cause(s) of the principal complications found in this patient's condition?
6. Which laboratory and non-laboratory test(s) are appropriate to order on this patient and why?
7. What is the most appropriate treatment for this patient?
Printed Case #2: 38 year old man with fever, fatigue, malaise, and pain localized over his nose and maxillary sinuses

**HISTORY:** This 38 year old white man was first seen by his family physician two months ago for a chief complaint of fever, fatigue, malaise, and pain localized over his nose and maxillary sinuses. Associated rhinorrhea was apparent at that time and the patient admitted to cough with one episode of hemoptysis. He is a married accountant with two children. His parents and two siblings are all alive and well. He is a rose gardener and has had some exposure to garden chemical sprays. At age 18 he had an appendectomy and at age 20 he had a torn medial meniscus following a skiing accident. He experiences occasional joint pain, particularly around the knees, which he attributes to football injuries. He describes his urine as recently appearing "rusty" or "tea colored".

**PHYSICAL EXAMINATION:** His temperature was 100.8°F, pulse was 90/min., respiration rate was 26/min. and blood pressure was 170/100 mm Hg. Tenderness was elicited upon point pressure over the antra of the maxillary sinuses. The nasal septum presented erythema with an ulcer adjacent to the middle turbinate. Auscultation of the chest presented no rales or rhonchi. The cardiac rhythm was regular with no murmurs audible. The abdomen was non-tender with no palpable masses. A scar was noted on the left knee. The neurologic examination was unremarkable.

**Laboratory Data**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>BUN</td>
</tr>
<tr>
<td>Polys</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Lymphs</td>
<td>Glucose, blood</td>
</tr>
<tr>
<td>Platelets</td>
<td>Protein, total</td>
</tr>
<tr>
<td>Hct</td>
<td>Globulin</td>
</tr>
<tr>
<td>MCV</td>
<td>Calcium</td>
</tr>
<tr>
<td>MCH</td>
<td>Bilirubin, total</td>
</tr>
<tr>
<td>MCHC</td>
<td>Alk. Phosphatase</td>
</tr>
<tr>
<td>Sed rate</td>
<td>AST (SGOT)</td>
</tr>
<tr>
<td></td>
<td>ALT (SGPT)</td>
</tr>
<tr>
<td></td>
<td>GGTP</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Urine Microscopic</th>
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</thead>
<tbody>
<tr>
<td>Color</td>
<td>WBC</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>(neg)</td>
</tr>
<tr>
<td>Protein</td>
<td>(neg)</td>
</tr>
<tr>
<td>PH</td>
<td>(neg)</td>
</tr>
<tr>
<td>Blood</td>
<td>(neg)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>(neg)</td>
</tr>
<tr>
<td>Glucose</td>
<td>(neg)</td>
</tr>
</tbody>
</table>

**CLINICAL COURSE:** A chest radiograph demonstrated bilateral nodular lesions, with one of the nodules suggesting central cavitation. The cardiac silhouette was within normal limits. Radiography of the paranasal sinuses revealed opacification of both maxillary sinuses without wall destruction. A surgical biopsy was obtained of the ulcer adjacent to the middle turbinate (See WebCT).
QUESTIONS FOR DISCUSSION:
1. What is the differential diagnosis of hemoptysis?
2. What is the most likely diagnosis and how do you support it?
3. What is the significance of hematuria and red cell casts?
Diseases of Immunity #1  
Type I Hypersensitivity: Anaphylaxis Gross

The acute laryngeal edema seen here that killed the patient was due to an anaphylactic reaction to penicillin. Such an allergy is a form of type I hypersensitivity reaction in which there is preformed IgE antibody on mast cells that quickly reacts with an antigen. The mast cells release histamine and other mediators that lead to the edema.

Diseases of Immunity #2  
Type I Hypersensitivity: Asthma

Bronchus. Hematoxylin & eosin stain. X125. This photomicrograph illustrates some of the bronchial wall changes in patients with allergic asthma. The basement membrane is markedly thickened and a moderate inflammatory infiltrate is present with noticeable numbers of eosinophils and some lymphocytes. Mast cells are also present, but they are not easily appreciated with the hematoxylin & eosin stain. Because it represents only a very small portion of the bronchial mucosa, this micrograph does not exhibit other characteristic changes such as hypertrophy of the mucus-secreting lining cells and of the bronchial smooth muscle.

Diseases of Immunity #3  
Type II Hypersensitivity: Hemolytic Disease of the Newborn

Liver. Hematoxylin & eosin stain. X78. [left image]. An example of complement-dependent Type II hypersensitivity reaction is erythroblastosis fetalis. Fetal red cells are attacked by maternal IgG antibodies resulting in subsequent complement activation leading either to direct lysis or increased susceptibility to phagocytosis. The resulting destruction of red cells results in severe anemia and marked extramedullary hematopoiesis, especially in the liver, as seen in this image. Groups of erythrocyte precursors are scattered among the hepatocytes. They appear as clusters of inky-dark dots, especially at the upper right corner of the image.

Urine. Unstained. Phase contrast. X200. [right image]. The transfusion of incompatible blood is another example of a complement-dependent Type II hypersensitivity reaction. This patient received an ABO-incompatible blood transfusion with resulting intravascular hemolysis, shock, DIC and renal failure. Patients with acute immune hemolysis often develop hemoglobinuria with red blood cell and hemoglobin casts. With stasis in the nephron, the red blood cell casts often degrade into hemoglobin casts, on of which is seen here. The presence of these casts usually indicate glomerular injury and can be found in a number of glomerular diseases.
Types of Transfusion Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic reaction</td>
<td>Occurs when ABO-incompatible blood is transfused. Preformed recipient IgM antibodies usually bind complement and lyse the transfused cells</td>
<td>May occur immediately or up to several hours after transfusion. Results in intravascular hemolysis, shock, DIC, and renal failure. Symptoms include fever, chills, flushing, low back pain, hypotension, dyspnea, abdominal pain, vomiting, diarrhea, chest pain, and unexpected bleeding. Responsible for about 41% of transfusion fatalities or about 16 patients who die each year.</td>
</tr>
<tr>
<td>Febrile reaction</td>
<td>Caused by recipient plasma antibodies to donor HLA antigens on donor WBCs.</td>
<td>Can be prevented by removing leukocytes from blood components. Occur in about 0.5%-1% of transfusions.</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Usually IgE mediated reaction to plasma proteins in transfused component.</td>
<td>Hives with no other symptoms. Occur in 1%-2% of transfusions. After administration of antihistamine, the transfusion can be resumed.</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Donor IgA plasma given to patients with IgG anti-IgA.</td>
<td>Respiratory distress, laryngeal edema and other anaphylactoid symptoms. Can be prevented by washing donor red cells to remove IgA or using an IgA-deficient donor.</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>Particularly a problem with platelet transfusions because the units are kept at room temperature.</td>
<td>Facial flushing, fever, vomiting, diarrhea.</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury</td>
<td>Transfusion of donor antibodies that react with recipient WBCs.</td>
<td>A severe, acute and sometimes fatal pulmonary reaction.</td>
</tr>
</tbody>
</table>

**Diseases of Immunity #4**  
**Type III Hypersensitivity: Serum Sickness**

Kidney. Hematoxylin & eosin stain. X125. The classic example of systemic immune complex disease is acute serum sickness resulting from the administration of horse serum. The basis of the injury is the deposition of immune complexes in various tissues and activation of the complement system. The histologic findings in serum sickness glomerulonephritis (an example of acute proliferative glomerulonephritis) include glomerular endothelial cell proliferation and glomerular capillary basement membrane thickening. The protein casts in the tubules on the left side of the image are a reflection of the proteinuria secondary to the glomerular damage.

**Diseases of Immunity #5**  
**Type IV Hypersensitivity: Tuberculosis**

The delayed-type hypersensitivity seen in patients with tuberculosis is one of the forms of Type IV hypersensitivity. The resulting granuloma has a core of caseous necrosis surrounded by epithelioid histiocytes, some of which may form a giant cell. The outermost rim of the granuloma consists of lymphocytes.

**Diseases of Immunity #6**  
**Transplant Rejection: Hyperacute And Acute**

Renal homograft. Gross Photos. The kidney in the upper left image shows cortical necrosis with infarction and is an example of hyperacute rejection. The lower left image and the right image show the gross changes of acute rejection: scattered cortical hemorrhagic foci with medullary congestion and hemorrhage. Note the areas of pallor in the kidney on the right.
Week 3: August 30-September 3

Immunity

Diseases of Immunity #7  Transplant Rejection: Acute Cellular Rejection 1

Renal homograft. Hematoxylin & eosin stains. X50. Some of the histologic features of acute cellular rejection can be seen in these two images from a homograft removed 18 days post transplantation. On the left we note vascular dilatation, interstitial edema, tubular constriction, and some inflammatory cells. Seen on the right a portion of the cortex shows a prominent lymphocytic infiltrate and interstitial edema. Lymphocytes have invaded the wall of the vessel near the top of the image, lifting the endothelial surface (this is a little difficult to see clearly).

Diseases of Immunity #8  Transplant Rejection: Acute Cellular Rejection 2

This is a higher magnification image of acute renal transplant rejection which is also known as acute cellular tubulointerstitial rejection because most of the inflammation is in the interstitium. The glomerulus seen here is normal, but the tubules are infiltrated by many lymphocytes at the upper right. This type of rejection can occur at any time following transplantation when immunosuppression is diminished. This is treated by administering cyclosporine and other immunosuppressive agents.

Diseases of Immunity #9  Transplant Rejection: Subacute Vasculitis

Kidney. Hematoxylin & eosin stain. X20. Another feature of acute rejection is subacute vasculitis seen here in a patient several months after transplantation. It is characterized by intimal thickening due to macrophages, fibroblasts, lymphocytes, plasma cells and neutrophils. Again note the surrounding vascular dilatation, interstitial edema and inflammatory infiltrate

Diseases of Immunity #10  Transplant Rejection: Chronic Vascular Rejection

At high magnification, the renal arteries with chronic vascular rejection are markedly thickened and fibrotic. There is interstitial fibrosis and chronic inflammation. Such chronic rejection usually occurs slowly over several months to years following transplantation. This disease, unlike acute rejection, is difficult to treat.

Diseases of Immunity #11  Graft Versus Host Disease: Skin

Microscopically, graft versus host disease is one of the best examples of a process called "apoptosis" or single cell necrosis. There is vacuolization and dissolution of epidermal cells along the basal layer, along with lymphocytes. At the arrow is a rounded pink apoptotic body.

Diseases of Immunity #12  Autoimmune Disease: Antinuclear Antibodies

Antinuclear antibody. Indirect immunofluorescence. X125. The method of choice to be used in screening for the presence of antinuclear antibodies (ANA) in the serum of patients is the indirect fluorescent antibody (IFA) technique. The patient’s serum is added to a glass slide on which a section of rat liver tissue has been previously fixed. If antinuclear antibodies are present, they will adhere to the rat nuclei in the tissue section. After washing, a fluorescent-tagged anti-human gamma-globulin solution is applied to the tissue section. The slide is washed and viewed by fluorescent microscopy. This photomicrograph shows numerous rat nuclei that have taken up the fluorescent tag indicating the presence of antinuclear antibody. This patient had systemic lupus erythematosus (SLE), but antinuclear antibodies are not specific for SLE and can be found in a number of other conditions.
### Diseases of Immunity #13: Lupus: Malar Rash

The young woman has a malar rash, the so-called "butterfly" rash because of the shape across the cheeks (Ignore the pale pink area in the middle forehead--it is just pixellation artifact from scanning the image). Such a rash suggests lupus. Discoid lupus erythematosus (DLE) involves mainly just the skin and is, therefore, relatively benign compared to systemic lupus erythematosus (SLE). In either case, sunlight exposure accentuates this erythematous rash. A small number (5 to 10%) of DLE patients go on to develop SLE (usually the DLE patients with a positive ANA). [Image contributed by Elizabeth Hammond, MD, University of Utah]

### Diseases of Immunity #14: Lupus Nephritis

Here is a glomerulus with thickened pink capillary loops, the so-called "wire loops", in a patient with lupus nephritis. The surrounding renal tubules are unremarkable.

### Diseases of Immunity #15: CREST Syndrome: Raynaud's Phenomenon

A serious consequence of the "R" in the CREST syndrome (limited scleroderma) is seen here. The fingertips are blackened and additional portions of the hand purplish with early gangrenous necrosis from vasospasm with Raynaud's phenomenon.

### Diseases of Immunity #16: Scleroderma: Hyperplastic Arteriolosclerosis

Renal disease suggests diffuse scleroderma in this patient with hyperplastic arteriolosclerosis (seen here in the kidney) and malignant hypertension (blood pressure 300/150 mm Hg). [Image contributed by Elizabeth Hammond, MD, University of Utah]

### Diseases of Immunity #17: Sjogren's Syndrome: Salivary Gland

The mononuclear inflammatory infiltrates, interstitial fibrosis, and acinar atrophy of a minor salivary gland in a biopsy of lip is typical for long-standing Sjogren's syndrome, an autoimmune disease that involves salivary glands (with xerostomia) and lacrimal glands (with xerophthalmia). Most patients are middle-aged women. The autoantibodies SS-A (Ro) and SS-B (La) have more specificity for Sjogren's syndrome than others, though the antinuclear antibody test is positive in over half of cases.

### Diseases of Immunity #18: X-Linked Agammaglobulinemia of Bruton

Terminal ileum. Hematoxylin & eosin stain. X2. [left image]. Bruton’s agammaglobulinemia is a sex-linked primary immunodeficiency disease characterized by absence of serum immunoglobulins, absence of germinal centers form the lymph nodes and spleen and rudimentary development of the lymphoid tissue in tonsils, appendix and terminal ileum. These male infants present with recurrent infections from pyogenic organisms. In this section of ileum from a 16-month-old male with this disease, no Peyer’s patches are present.

Tonsil. Hematoxylin & eosin stain. X2. [right image]. The tonsil from the same patient shows very little lymphoid tissue and no germinal centers.
Week 3: August 30-September 3

Diseases of Immunity #19  X-Linked Agammaglobulinemia of Bruton 2

Thymus gland. Hematoxylin & eosin stain. X2 [left image]. Since this is a B-cell deficiency, we would expect the areas of T-cell development to be essentially normal and indeed that is the case. The thymus gland from the above patient shows a dark blue cortex indicative of large numbers of lymphocytes (thymocytes).

Lymph node. Hematoxylin & eosin stain. X2. [right image]. No germinal centers are present in this lymph node from the same patient. The lymphoid tissue present is confined mainly to the paracortex of the node, where the primary cell type is the small T-lymphocyte.

Diseases of Immunity #20  Severe Combined Immunodeficiency Disease (SCID)

Thymus gland. Hematoxylin & eosin stain. X2. [left image]. This disease is characterized by both T-cell and B-cell defects and shows an almost total absence of lymphoid tissue and plasma cells, a dysplastic thymus gland, a marked decrease in CD2+ and CD3+ T-cell lymphocytes, decreased numbers of B cells, and a severe agammaglobulinemia. Illustrated in this image is a small dysplastic thymus gland devoid of lymphocytes. but containing scattered lobules of undifferentiated epithelial cells, which appear as the irregular, dark-purple structures. Compare this thymus with the relatively unaffected one seen in a different congenital immunodeficiency as in the slide "X-linked agammaglobulinemia of Bruton 2".

Tonsil. Hematoxylin & eosin stain. X2. [right image]. As noted above B-cell immunity is also defective in these patients. To appreciate the full impact of this and the preceding image, you should compare them to normal thymic and tonsillar tissue.

Diseases of Immunity #21  Acquired Immunodeficiency Syndrome: Pneumocystis Carinii

Lung. Hematoxylin & eosin stain. X50. [left image]. One of the hallmark lesions of AIDS, Pneumocystis carinii pneumonia (PCP) had previously been seen only rarely, usually in patients with disseminated lymphoid malignancies undergoing chemotherapy. In the mid 70s a pathologist at Memorial Hospital-Sloan Kettering Cancer Center in New York City might have seen several cases of PCP in such patients. Debilitated by their malignancy and immunosuppressed by their therapy, they became candidates for a variety of infections of which PCP was only one. This photomicrograph illustrates the characteristic foamy, eosinophilic intra-alveolar exudate seen in this infection. Few inflammatory cells are evident.

Lung. Methenamine silver stain. X50. [right image]. With the aid of special stains, numerous cysts about 5 micrometers in diameter are apparent within the foamy exudate mentioned above. Their irregularly thickened walls and helmet-shapes are characteristic of Pneumocystis carinii but not diagnostic. If one used Giemsa stains, the sporozoites within the cysts can also be detected. The organism is related to the ascomycetous fungi.

In 1981, the following two reports, from the Centers of Disease Control, appeared less than one month apart, in their weekly bulletin MMWR (Morbidity and Mortality Weekly Report).

Pneumocystis Pneumonia – Los Angeles

“In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus infection and candidal mucosal infection…”

MMWR June 5, 1981;30: 250-252

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“During the past 30 months, Kaposi’s sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)-all 8 within 24 months after KS was diagnosed…”

“Seven KS patients had serious infections diagnosed after their initial physician visit. Six patients had pneumonia (4 biopsy confirmed as due to Pneumocystis carinii [PC], and one had necrotizing toxoplasmosis of the central nervous system. One of the patients with Pneumocystis pneumonia also experienced severe, recurrent, herpes simplex infection; extensive candidiasis; and cryptococcal meningitis…”

And so it began!

Diseases of Immunity #22  
Acquired Immunodeficiency Syndrome: Mycobacterium Avium- Intracellulare

Duodenum. Hematoxylin & eosin stain. X78. [left image]. This photomicrograph of the duodenal submucosa shows large numbers of distended macrophages separating the resident glands.

Duodenum. Hematoxylin & eosin stain. X78. [right image]. The acid-fast staining technique demonstrates that the macrophages contain numerous acid-fast bacilli within their cytoplasm. On culture the organism was identified as Mycobacterium avium-intracellulare Complex (MAC). The growth characteristics and biochemical reactions of M avium and intracellulare are so similar that they are not usually distinguished in the clinical laboratory and isolation of either organism is reported as MAC. These organisms are ubiquitous in the environment and have been known to cause pulmonary disease in older debilitated individuals. With the era of AIDS they have achieved a new importance and are now the most common cause of systemic bacterial infection in these patients. Disseminated MAC is seen almost exclusively in immunocompromised individuals and indeed is rare in a patient whose CD4+ lymphocyte count is greater than 100/µL. The portal of entry is most likely the gastrointestinal tract and the main symptoms in AIDS patients with MAC are fever, weight loss and diarrhea.

Diseases of Immunity #23  
Acquired Immunodeficiency Syndrome: Cryptococcus & Cytomegalovirus

Lymph node. Mucicarmine stain. X125. [left image]. This photomicrograph shows large numbers of carminophilic, yeast-like fungi that are oval, spherical or elliptical in shape. They vary in size from 5 to 20µm in diameter. The staining pattern and pleomorphism are consistent with Cryptococcus neoformans. The initial form of the disease is usually pulmonary and is acquired by inhalation of the yeast which is ubiquitous in the environment. Disseminated disease in found in individuals with impaired cell-mediated immunity, such as Hodgkin’s disease and AIDS, and it may lead to cerebromeningeal infection. The tissue reaction to the organism varies from a fully developed granulomatous reaction in otherwise healthy individuals to no apparent host response in patients with severely compromised cell-mediated immunity.

Lung. Hematoxylin & eosin stain. X125. [right image]. From the beginning of the AIDS epidemic, infection with cytomegalovirus (CMV) has been a frequent finding in these patients. A large number of different organs may be involved including liver, kidney, pancreas, lung, brain, intestinal tract, skin, etc. and the disease can be life-threatening. CMV retinitis is seen in about one-fifth of AIDS patients and can lead to blindness if
untreated. The histologic findings are enlarged cells (usually epithelial) containing a large intranuclear inclusion with or without granular cytoplasmic inclusions. The organism may also involve endothelial cells leading to a vasculitits which in the intestine can result in ulceration perforation.

**Diseases of Immunity #24**   
**Amyloidosis 1**

*Kidney. Hematoxylin & eosin stain. X50* [left image]. A glomerulus and several vessels are present in the image and all show deposits of smudgy eosinophilic material. The glomerular architecture is completely obliterated.

*Kidney. Congo red stain. X50* [right image]. With this stain the material appears salmon-colored under ordinary

**Diseases of Immunity #25**   
**Amyloidosis 2**

*Lung. Congo red stain. X30.* When Congo red-stained amyloid is viewed under polarized light, it shows an apple green birefringence.
# Week 4: September 6-10

**Neoplasia**

## Schedule

<table>
<thead>
<tr>
<th><strong>Tuesday, September 7</strong></th>
<th>1-2 PM</th>
<th>Lecture: Introduction to the Autopsy</th>
<th>West Lecture Hall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-4 PM</td>
<td>Case-Based Study</td>
<td>Laboratory</td>
</tr>
</tbody>
</table>

| **Thursday, September 9** | 2-5 PM | Path Talk                             | Laboratory       |

<table>
<thead>
<tr>
<th><strong>Friday, September 10</strong></th>
<th>10-11AM</th>
<th>Summary</th>
<th>West Lecture Hall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 AM- Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory – Room N12</td>
</tr>
</tbody>
</table>
Week 4: September 6-10

Neoplasia

Assignments

Topic: Neoplasia

Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition
• Neoplasia, Chapter 8, pp. 260-325

Required Study for Small Groups

PathTalk
Assignments:
• Kodachromes on WebCT
• Slide descriptions
• Journal club articles
  o The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia, John Sudbo, M.D., Volume 350:1405-1413, April 1, 2004

Case-Based Study
Assignments:
• Printed Case 1 – “A 72 year old female presents with a two week history....”
• Printed Case 2 – “A 70-year-old male presented with complaints of easy fatigability...”

Case-Based Study
Required reading: Widmann’s Clinical Interpretation of Laboratory Tests

Principles of interpretation of laboratory tests:
• pp. 21-27

Cancer:
• pp. 1035-1037: Carcinoembryonic antigen
• pp. 352-353: Lymphocyte surface markers
Printed Case #1: A 72 year old female presents with a two-week history of increasing constipation

**CLINICAL SUMMARY:** A 72 year old female presents with a two week history of increasing constipation and ten pound weight loss. She has noted intermittent nausea over this period and has vomited several times over the past 3 days. She denied a change in the character of her stool or the presence of blood. Past medical history is positive for hypertension and diabetes mellitus. On physical examination vital signs were normal, lung fields clear, and heart sounds normal. The abdomen was distended but was nontender and no guarding was present. Bowel sounds were hyperactive and there appeared to be a mass in the left lower quadrant. The rectal exam was negative.

**Laboratory Data**

<table>
<thead>
<tr>
<th>Hematology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 15.3 thou</td>
<td>(3.4-11)</td>
</tr>
<tr>
<td>polys 95%</td>
<td>(44-80)</td>
</tr>
<tr>
<td>lymphs 3%</td>
<td>(12-43)</td>
</tr>
<tr>
<td>monos 2%</td>
<td>(2-11)</td>
</tr>
<tr>
<td>HGB 9.1 gm%</td>
<td>(12-18)</td>
</tr>
<tr>
<td>HCT 30.4%</td>
<td>(37-47)</td>
</tr>
<tr>
<td>MCV 64 fl</td>
<td>(81-99)</td>
</tr>
<tr>
<td>MCH 19.1pg</td>
<td>(27-31)</td>
</tr>
<tr>
<td>MCHC 29.9 g/dl</td>
<td>(32-36)</td>
</tr>
<tr>
<td>Plts 659 thou</td>
<td>(130-400)</td>
</tr>
</tbody>
</table>

Peripheral smear - *WebCT*

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PH 6.0</td>
<td>(5.0-7.5)</td>
</tr>
<tr>
<td>Protein Trace</td>
<td>(neg)</td>
</tr>
<tr>
<td>Glucose neg</td>
<td>(neg)</td>
</tr>
<tr>
<td>Ketones 2+</td>
<td>(neg)</td>
</tr>
<tr>
<td>Bile 1+</td>
<td>(neg)</td>
</tr>
<tr>
<td>Blood neg</td>
<td>(neg)</td>
</tr>
<tr>
<td>Sp.gr. 1.029</td>
<td>(1.010-1.035)</td>
</tr>
<tr>
<td>WBC/hpf 1-3</td>
<td>(0-5)</td>
</tr>
<tr>
<td>RBC/hpf 0</td>
<td>(0-2)</td>
</tr>
</tbody>
</table>
### Week 4: September 6-10

#### Neoplasia

<table>
<thead>
<tr>
<th>Casts</th>
<th>hyaline &amp; fine granular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>amber &amp; hazy</td>
</tr>
</tbody>
</table>

#### Chemistry

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>128 mg%</td>
<td>(65-110)</td>
</tr>
<tr>
<td>BUN</td>
<td>11 mg%</td>
<td>(7-24)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5.7 mg%</td>
<td>(3.0-7.5)</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4 mg%</td>
<td>(8.5-10.5)</td>
</tr>
<tr>
<td>Protein</td>
<td>6.2 gm%</td>
<td>(6-8)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 gm%</td>
<td>(3.5-5)</td>
</tr>
<tr>
<td>Alk. Phosphatase</td>
<td>110 U</td>
<td>(30-120)</td>
</tr>
<tr>
<td>SGOT</td>
<td>43 U</td>
<td>(0-55)</td>
</tr>
<tr>
<td>LDH</td>
<td>465 U</td>
<td>(100-225)</td>
</tr>
<tr>
<td>GGTP</td>
<td>83 U</td>
<td>(0-50)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2.5 mg%</td>
<td>(0-1.5)</td>
</tr>
<tr>
<td>Sodium</td>
<td>141 meq/L</td>
<td>(135-145)</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.7 meq/L</td>
<td>(3.5-5.0)</td>
</tr>
<tr>
<td>Chloride</td>
<td>104 meq/L</td>
<td>(100-112)</td>
</tr>
<tr>
<td>CO2</td>
<td>26 meq/L</td>
<td>(24-35)</td>
</tr>
<tr>
<td>pH venous</td>
<td>7.48</td>
<td>(7.33-7.45)</td>
</tr>
<tr>
<td>CEA</td>
<td>1100 ng/ml</td>
<td>(0-2.5)</td>
</tr>
</tbody>
</table>

Stool - Guaiac - Positive
Review images: Available on the Case-Based Studies section of Pathology WebCT site.

CLINICAL COURSE: Radiographic studies revealed an obstructing lesion in the sigmoid colon and the presence of ascites. At surgery (i.e. an exploratory laparotomy) a large mass was noted in the sigmoid colon with multiple nodules involving the peritoneum, abdominal wall, omentum, and liver.

Questions for Homework - to be written and brought to class (at the discretion of the instructor)
1. How did the anemia develop in this patient?
2. How do you explain the presence of ketones in this patient's urine?
3. Of what value is the CEA test?

Questions For Discussion - not written
1. What is the most likely diagnosis in this case?
2. What is the likely cause of the hematological abnormalities?
3. What is(are) the most likely cause(s) of the abnormal chemistry values?
Printed Case #2: A 70-year-old male presented with complaints of easy fatigability

CLINICAL SUMMARY:

A 70-year-old male presented with complaints of easy fatigability, weight loss (10% of body weight over 2 months), and anorexia. Physical exam showed a slightly pale individual in no apparent distress. The only significant findings were mild to moderate hepatosplenomegaly and moderate diffuse lymphoadenopathy. A kodachrome of a peripheral blood smear can be seen on WebCT. Relevant lab values are given below.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>30,000/mm³</td>
<td>4.100-10,000 /mm³</td>
</tr>
<tr>
<td>RBC</td>
<td>3.05 million/mm³</td>
<td>4.3-6.2 million/mm³</td>
</tr>
<tr>
<td>HGB</td>
<td>gm/dl</td>
<td>13.2-16.2 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>33.8 %</td>
<td>40-5 2%</td>
</tr>
<tr>
<td>MCV</td>
<td>85.9 fL</td>
<td>82-105 fL</td>
</tr>
<tr>
<td>Plts</td>
<td>110 x 10⁹ cells/L</td>
<td>150-450 x 10⁹ cells/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WBC Differential</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>85%</td>
<td>20.5-51.1 %</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>5%</td>
<td>42.2-75.2%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2%</td>
<td>1.7-9.3%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1%</td>
<td>&lt;= 1%</td>
</tr>
<tr>
<td>Basophils</td>
<td>1%</td>
<td>&lt;= 1%</td>
</tr>
<tr>
<td>Atypical lymphs</td>
<td>6%</td>
<td>&lt;=1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Laboratory Values</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Immunoglobulins</td>
<td>650 mg/dL</td>
<td>820-2,200 mg/dL</td>
</tr>
</tbody>
</table>

Description of specimen and procedure:
The specimen labelled "peripheral blood" containing approximately 10ml was received in a EDTA vacutainer. Red cells were lysed and the remaining cells were stained with monoclonal antibodies and submitted for flow cytometry.
This scattergram shows side scatter (SS: vertical axis) versus CD45 (leukocyte common antigen) staining intensity (horizontal axis). Side scatter corresponds to cytoplasmic structural complexity. Each dot represents a pair of measurements made on a single cell as it passes through the analysis chamber of the flow cytometer. The red cells and junk have low side scatter and low CD45; the lymphs have low side scatter and bright CD45; the granulocytes, which have cytoplasmic granules, have high side scatter and bright CD45. Note that a “gate” has been drawn around the lymphs. These are the cells that will be analyzed.

These 3 diagrams show the number of cells that express each of the listed markers (CD5, CD10, CD19) at a spectrum of intensity (vertical axis is number of cells, horizontal axis is intensity of staining.)
This scatter gram shows the staining intensity for CD19 (vertical axis) versus CD5 (horizontal axis). Note that Quadrant 2 contains events (analyzed cells) that stain for both CD19 and CD5.

**Report: Quantitation of B and T Lymphocytes**

<table>
<thead>
<tr>
<th>Lymphocyte Gate</th>
<th>% in Gate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45</td>
<td>99.5</td>
</tr>
<tr>
<td>CD14</td>
<td>0.1</td>
</tr>
<tr>
<td>CD3 (all cells of T lineage)</td>
<td>19.9</td>
</tr>
<tr>
<td>CD5 (usually a T-cell marker)</td>
<td>96.7</td>
</tr>
<tr>
<td>T helper /inducer CD4</td>
<td>13.4</td>
</tr>
<tr>
<td>T suppressor /cytotoxic CD8</td>
<td>3.0</td>
</tr>
<tr>
<td>B-cells CD20</td>
<td>64.3 (dim)</td>
</tr>
<tr>
<td>B-cells CD19</td>
<td>79.3</td>
</tr>
<tr>
<td>CD23</td>
<td>73.2</td>
</tr>
<tr>
<td>Cells expressing HLA-DR antigen</td>
<td>68.3</td>
</tr>
<tr>
<td>CD10</td>
<td>0.0</td>
</tr>
<tr>
<td>Cells-expressing kappa light chain</td>
<td>72.5 (dim)</td>
</tr>
<tr>
<td>Cells expressing lambda light chain</td>
<td>3.2</td>
</tr>
<tr>
<td>Cells co-expressing CD5/CD19</td>
<td>76.3</td>
</tr>
</tbody>
</table>
Interpretation: This is an abnormal pattern. Majority of cells are of mature ??? lineage (positive for CD20, CD19, HLA-DR, SIg+; negative for CD10). They also coexpress CD5 and CD23. They appear to be of ??? clonality. This pattern is suggestive of ???.

Flow Cytometry
Flow cytometry is a technology which measures multiple characteristics of cells in suspension as they flow through a measurement region. The parameters that can be measured by flow cytometry are divided into intrinsic, such as cell size or cytoplasmic granularity, or extrinsic, such as the presence of a surface antigen, for which specific reagents like fluorescent antibodies are needed.

The principle of the method is simple: individual cells pass through a laser beam. Each cell absorbs and scatters light and also, if labelled with fluorescent antibody to some cell surface marker, emits color. These signals are electronically analyzed and interpreted.

Initially the effect of light scatter is used for the determination of cell size, shape, internal structure, etc. On this basis the flow cytometer "separates" cells into "clusters" with similar properties to produce the scattergram. The presence or absence of a fluorescent marker can be then analyzed within the selected "cluster" (gating) and enables us to quantitate "positive" cells within this cluster.

Scattergram
A histogram (or better, "scattergram") of cells included in this case represents the visual separation of calls (WBC) by light side scatter and intensity of CD45 staining. SS stands for light side scatter and means the light scattered at right angles to the laser beam. It correlates generally with cytoplasmic texture or granularity. This initial view of the cells is usually very helpful in separating leukocytes into different clusters or gates, including granulocytes, lymphocytes, monocytes (not shown), blasts (not shown), and objects with very low side scatter and CD45 expression, including junk, unlysed red cells, plasma cells, and others.

Report
The report included gives a quantitative measurement of extrinsic features of different cells within "lymphocytic" cluster only. The cells have been stained with individual (or with a combination of) monoclonal antibodies, and the percentage of cells staining with that antibody is reported.

Recommended reading:
- http://pleiad.umdnj.edu/hemepath/immuno/immuno.html
- Diagnostic Flow Cytometry, Coon, T. and Weinstein, R; Pub. Williams and Wilkins (available in Media Library)

QUESTIONS FOR DISCUSSION
1. What kind of differential diagnosis do the presenting signs and symptoms generate? What additional information would you like to know about the lymph node examination?
2. What abnormalities are present in the CBC and/or WBC differential count? What kind of differential diagnosis) do they generate, and how might you narrow the differential if, for example, you didn’t have access to flow cytometric data?
3. What do the various markers in the flow report signify?
4. By flow cytometry do you see any evidence of restricted clonality (a proliferation of cells originating from a single cell) in either the T or B cell populations?
5. What is the diagnosis and how do you support it? Fill in the “???” parts of the report interpretation.
6. Are this patient's lymphocytes functionally normal and what clinical course do you expect for this patient?
7. What would the gene rearrangement (Southern blot) studies show in this case?
Neoplasia #1  **Left Ventricular Hypertrophy**

Any increase in tissue size is not necessarily neoplasia. Here is an example of left ventricular cardiac hypertrophy in which there has been an increase in the size of the myocardial fibers in response to an increased pressure load from hypertension. With hypertrophy, the cells increase in size, but the cells do not increase in number. Except for being larger, the cells are normal in appearance.

Alterations in cell growth can be physiologic (normal responses to stimuli) or pathologic. These alterations of cell growth are potentially reversible and include:

- **Hypertrophy**: an increase in cell size. Increase in skeletal muscle fiber size is a physiologic response to exercise, but the cardiac hypertrophy shown above is a pathologic response to abnormally elevated blood pressure.

- **Hyperplasia**: an increase in the number of cells. Postpartum breast lobules undergo hyperplasia for lactation, but endometrial hyperplasia in a postmenopausal woman is abnormal.

Neoplasia #2  **Endometrial Hyperplasia**

The large fronds of endometrium seen in this uterus opened to reveal the endometrial cavity are a result of hyperplasia due to increased estrogen. With hyperplasia, there is an increase in cell numbers to produce an increase in tissue size. The cells usually remain normal in appearance. Sometimes, however, hyperplasias are "atypical", and the cells not completely normal. Such conditions can be premalignant.

Neoplasia #3  **Esophagus with Columnar Metaplasia**

The left side of this biopsy of the lower esophagus in a patient with chronic gastroesophageal reflux disease shows columnar metaplasia with goblet cells resembling intestinal epithelium (Barrett's esophagus). Squamous epithelium typical of the normal esophagus appears at the right. While metaplasia need not be a harbinger of malignancy, this metaplasia in particular does convey an increased risk of esophageal adenocarcinoma. Patients who have it should be closely followed by surveillance biopsies to detect any trend toward more malignant appearances.

Neoplasia #4  **Cervix with Dysplasia, Low Power**

Dysplasia is the next step toward neoplasia. Here there is normal cervical squamous epithelium at the left, but dysplastic squamous epithelium at the right. Dysplasia is a
disorderly growth of epithelium with a milder version of some of the features seen in malignancy. Stromal invasion is never present, and dysplasia is still reversible.

Neoplasia #5  Cervix with Dysplasia, High Power

Seen here at higher magnification, the normal cervical squamous epithelium at the left merges into the dysplastic squamous epithelium at the right. The dysplastic cells are more disorderly and crowded and have larger, more darkly staining nuclei.

Neoplasia #6  Cervix with Dysplasia, Pap Smear

Some epithelia, such as in the cervix, are accessible so that the cells can be screened for cancer by scraping them with a small spatula and smearing them onto a slide. Here is a cervical Pap smear in which dysplastic cells are present. These cells have much larger and darker nuclei than the normal squamous cells with small nuclei and large amounts of cytoplasm. Pathologists are quick to attend to increases in the nuclear to cytoplasmic ratio, which for short is called the "N/C ratio".

Neoplasia #7  Cervical Carcinoma-in-Situ

When the entire epithelium is dysplastic and no normal epithelial cells are left, the process has surpassed dysplasia and is considered to be malignant neoplasia. If the basement membrane is still intact, as shown here, then the process is called "carcinoma in situ" because the carcinoma is still confined to the epithelium. This confinement has tremendous significance. Unlike the underlying lamina propria, the epithelium has no lymphatics or blood vessels; so as long as the malignant growth has not breached the basement membrane and reached the lamina propria, metastasis is not possible.

Neoplasia #8  Cervical Carcinoma, Gross

This is a malignant neoplasm: squamous cell carcinoma of the cervix. The light tan tissue is the squamous mucosa of the ectocervix and the narrow, surrounding margin of vaginal cuff. In the middle is the fungating malignant growth, which has almost obliterated the cervical os. The brown tissue seen in the background is the external surface of the uterus, which has been excised to treat the cancer.

One feature of neoplasia is uncontrolled new growth. Note the mass of abnormal tissue on the surface of the cervix. The term "tumor" is often used synonymously with neoplasm, but a "tumor" can mean any mass effect, whether it is inflammatory, hemodynamic, or neoplastic in origin. Once a neoplasm has started, it is usually not reversible.

Neoplasia #9  Invasive Squamous Cell Carcinoma of the Cervix

Here the malignant squamous cells have transgressed the basement membrane and are coursing through the subjacent stroma. The cells are growing in large, disorderly nests
with pink keratin in the centers. The stroma usually reacts to the presence of malignant cells. Here it is floridly inflamed. The stroma may also exhibit a cellular fibrous response called "desmoplasia".

The process of invasion is complicated and depends in part on the ability of the tumor cells to secrete compounds (proteases, collagensases, etc.) that attack portions of the basement membrane and extracellular matrix.

**Neoplasia #10  “Scirrhous” Breast Carcinoma**

This gross image illustrates another type of stromal response to invasive cancer. Here an infiltrating ductal carcinoma of the breast is invading the surrounding stroma. The central white area is very hard and gritty because the neoplasm is causing a desmoplastic stromal reaction, a cuff of cellular fibrous tissue with abundant collagen. This kind of induration is sometimes called "scirrhous". There is also focal dystrophic calcification that contributes to the gritty areas.

**Neoplasia #11  Lipoma: Small Intestine, Gross**

Of course neoplasms can be benign as well as malignant, though it is not always easy to tell how a neoplasm will act. Here is a benign lipoma dangling from the serosal surface of the small intestine. It has the characteristics of a benign neoplasm: it is well circumscribed, slow growing, and resembles the tissue of origin (fat). The degree of resemblance to the tissue of origin determines whether a malignancy is considered well or poorly differentiated.

**Neoplasia #12  Lipoma: Small Intestine**

At low power magnification, a lipoma of the stomach is seen to be well demarcated from the mucosa at the lower center-right. This neoplasm is so well-differentiated that, except for its appearance as a localized mass, it is impossible to distinguish from normal adipose tissue. Note that a thin fibrous capsule surrounds it. This capsule is produced as the benign neoplasm slowly expands and compresses the surrounding stroma. Malignant neoplasms usually don't have capsules because they tend to invade rather than compress the surrounding stroma.

Pathologists may be able to distinguish benign from malignant neoplasms morphologically based on routine histologic stains. This is possible because in many cases benign and malignant neoplasms differ as described in the table below. Please remember that these criteria are not absolute. Neoplasms with some of the malignant features noted below may behave benignly, while other neoplasms that appear benign will behave aggressively. Pathologists train for four years to learn to make such distinctions.
### Neoplasia #13  Uterine Leiomyomas, Gross

Benign neoplasms can be multiple, as is shown in this uterus with leiomyomas of varying size, but all benign and well-circumscribed firm white masses. Remember that the most common neoplasm is a benign nevus (pigmented mole) of the skin, and most people have several. As a general rule, benign neoplasms do not give rise to malignant neoplasms.

### Neoplasia #14  Uterine Leiomyoma

Here is the microscopic appearance of a benign leiomyoma. Normal myometrium is at the left, and the neoplasm is well-differentiated so that the leiomyoma at the right hardly appears different. Bundles of smooth muscle are interlacing in the tumor mass.

### Neoplasia #15  Uterine Leiomyosarcoma, Gross

In contrast to the benign leiomyoma, this is a malignant leiomyosarcoma protruding from the myometrium into the endometrial cavity of this uterus, which has been opened laterally so that the halves of the cervix appear at the right and left. Fallopian tubes and ovaries project from top and bottom. The irregular nature of this mass suggests that is not just an ordinary leiomyoma. Leiomyomas and leiomyosarcomas are both neoplasms deriving from smooth muscle. The former is benign; the latter is malignant.

### Neoplasia #16  Uterine Leiomyosarcoma

Here is the microscopic appearance of a leiomyosarcoma. It is much more cellular than the benign leiomyoma, and the cells are much more pleomorphic and hyperchromatic. An irregular mitosis is seen in the center.

---

### Neoplasia

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Local growth</td>
<td>Expansive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Encapsulation</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Destruction of tissues</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Vessel invasion</td>
<td>None</td>
<td>Frequent</td>
</tr>
<tr>
<td>Metastases</td>
<td>None</td>
<td>Frequent</td>
</tr>
<tr>
<td>Effect on host</td>
<td>Often insignificant</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Adapted from Anderson’s Pathology, 10th Ed., 1996, Mosby.
**Neoplasia #17**  
**Skin Nevi**

Remember that the most common neoplasm is a benign nevus (pigmented mole) of the skin, and most people have several, as seen here over the skin of the chest. As a general rule, benign neoplasms do not give rise to malignant neoplasms.

**Neoplasia #18**  
**Skin Melanoma**

This excision of skin demonstrates a malignant melanoma, which is much larger and more irregular than a benign nevus. The most important indications that a pigmented lesion may be a malignant melanoma are:

- Enlargement of a preexistent mole.
- Adult acquisition of a new pigmented lesion.
- Irregularity of color within a pigmented lesion.
- Irregularity of borders of a pigmented lesion.
- Pain or itching sensation in a preexisting mole.

**Neoplasia #19**  
**Well-Differentiated Squamous Cell Carcinoma**

This and the next 4 slides illustrate the important concept of differentiation. This term refers to the extent to which neoplastic cells resemble comparable normal cells both morphologically and functionally. The biologic behavior of tumors is often reflected in their degree of differentiation.

Well-differentiated tumors are usually less aggressive than poorly-differentiated ones. Most benign tumors are well-differentiated and, as expected, are not aggressive. Malignant tumors may show a spectrum of differentiation and can be characterized by using prefixes such as well-, moderate, or poorly-differentiated. Numerical grading systems based on nuclear characteristics and overall tumor appearance are used in certain situations where they help to quantify the degree of a tumor's differentiation.

In this slide normal squamous epithelium at the left merges into the squamous cell carcinoma at the right, which is infiltrating downward. The neoplastic squamous cells are still similar to the normal squamous cells, but are less orderly. This is a well-differentiated squamous cell carcinoma.

**Neoplasia #20**  
**Moderately-Differentiated Squamous Cell Carcinoma 1**

Here is a moderately differentiated squamous cell carcinoma in which some, but not all, of the neoplastic cells in nests contain abundant, pink keratin. The ability of the malignant cells to make keratin means that they still bear some functional resemblance to normal squamous cells.
Neoplasia #21  Moderately-Differentiated Squamous Cell Carcinoma 2

At high magnification, this squamous cell carcinoma demonstrates enough differentiation so that the cells can be identified as squamous in origin. The cells are pink and polygonal in shape with intercellular bridges (seen as desmosomes or "tight junctions" by electron microscopy). However, the neoplastic cells show pleomorphism, with hyperchromatic nuclei. A mitotic figure is present near the center.

Neoplasia #22  Poorly-Differentiated Squamous Cell Carcinoma

This neoplasm is so poorly differentiated that it is difficult to tell what the cell of origin is. It is probably a carcinoma because of the shape and nuclear features of the cells and their barely perceptible tendency to form vague clusters. Note that nucleoli are numerous and large in this neoplasm. Neoplasms with no differentiation are sometimes said to be anaplastic. Some pathologists, however, reserve the term "anaplastic" for malignant cells that are extremely bizarre in appearance in addition to lacking identifying characteristics.

Neoplasia #23  Adenomatous Polyp of the Colon

The concept of differentiation is demonstrated by this small adenomatous polyp of the colon. Note the difference in staining quality between the epithelial cells of the adenoma at the top and the normal glandular epithelium of the colonic mucosa below.

Adenomatous polyps are premalignant lesions. If they are discovered on routine colonoscopy performed on middle-aged individuals, the patient will have to undergo more frequent surveillance colonoscopies to monitor the polyps for possible progression.

Neoplasia #24  Adenomatous Polyp of the Colon, High Power

At high magnification, the normal colonic epithelium at the left contrasts with the atypical epithelium of the adenomatous polyp (tubular adenoma) at the right. Nuclei are darker, more irregularly sized, and closer together in the adenomatous polyp than in the normal mucosa. The overall difference between them, however, is not great. This benign (but possibly pre-malignant) neoplasm mimics the normal tissue quite well, and so it may be termed well-differentiated.

Neoplasia #25  Liver Metastases

Both benign and malignant tumors may cause some harm by local growth. It is the ability to spread widely in the body via metastases, however, that makes malignant tumors so much more deadly than benign ones. Metastases, in fact, are the surest indication that a tumor is malignant (though even here there are exceptions). In order to metastasize, malignant cells have to have receptors and secrete chemicals that allow them to enter and
then leave blood or lymphatic vessels to thrive at a distant site. In general carcinomas spread via lymphatics and involve regional lymph nodes, while sarcomas spread mainly through blood vessels and rarely involve regional lymph nodes. Also, certain malignancies tend to metastasize to certain sites.

This is an example of metastases to the liver. Note that the tan-white masses are multiple and irregularly sized. Like many large metastatic lesions, there is central necrosis. A primary neoplasm is more likely to be a solitary mass. The presence of metastases are the best indication that a neoplasm is malignant.

**Neoplasia #26**

Lung Metastasis

Both lymphatic and hematogenous spread of malignant neoplasms is possible to distant sites. Here, a breast carcinoma has spread to a lymphatic in the lung.

**Neoplasia #27**

Epicardial Metastasis with Angiogenesis

In this small focus of metastatic carcinoma to the epicardium can be seen a key feature of neoplasms—angiogenesis. Note the proliferation of many small capillaries adjacent to the neoplastic cells. A number of different tumor cells and macrophages are capable of secreting angiogenic factors (e.g. fibroblast growth factor, transforming growth factor and vascular endothelial growth factor) that stimulate capillary ingrowth and fibroblastic proliferation. Malignancies are thus assured of the vascular and stromal support they require to sustain uncontrolled growth.

**Neoplasia #28**

Perineural Invasion

Branches of peripheral nerve are invaded by nests of malignant cells. This is often why pain associated with cancers is unrelenting.

**Neoplasia #29**

Abnormal Mitosis

The arrow on the right points to an abnormal tripolar mitotic figure. The other 2 arrows point to mitotic figures that are not definitively abnormal. Increased mitoses indicate only rapid cell division and are not by themselves indicators of malignancy. In fact, the lymphoid cells in a benign, reactive germinal center have a mitotic rate higher than all but the most rapidly growing malignancies. Mitoses are, however, suspicious in tissue that usually is quiescent, and abnormal mitoses are highly indicative of malignancy. The marked pleomorphism and hyperchromatism of surrounding cells also favors malignancy.

**Neoplasia #30**

Her2/Neu Immunoperoxidase Staining

Here is an example of positivity for the oncogene her2/neu (also known as c-erb-B2) in a breast carcinoma. This oncogene acts via multiplication of the normal proto-oncogene hundreds of times, leading to production of a protein product that drives unregulated cell growth.
growth. This is detected here by immunoperoxidase staining with the brown reaction product concentrated in a perimembranous pattern around the cells.

**Neoplasia #31**  
**Bcl-2 Immunoperoxidase Staining**

This is an example of bcl-2 positivity in a follicular lymphoma. Malignant follicles express the bcl-2 gene, but benign germinal centers do not. Thus the stain is used to distinguish between them. The over-expression of this oncogene results in an inhibition of apoptosis and increased longevity of lymphocytes. The immunoperoxidase stain here highlights the lymphocytes in lymphoid follicles and interfollicular areas.
<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuesday, September 14</td>
<td>1-4 PM</td>
<td>Case-Based Study</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Thursday, September 16</td>
<td>2-5 PM</td>
<td>PathTalk</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Friday, September 17</td>
<td>10-11 AM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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<td></td>
<td>11-12 Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory – Room N12</td>
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Week 5: September 13-17
Genetics/Pediatric & Developmental Pathology

Assignments

Topic 1: Genetics

Required Reading:

Robbins: Pathologic Basis of Disease, 6th Edition,
- Genetic Disorders, Chapter 6 pp. 139-187

Topic 2: Pediatric and Developmental Pathology

Required Reading:

Robbins: Pathologic Basis of Disease, 6th Edition
- Diseases of Infancy and Childhood, Chapter 11, pp. 459-489
- Female Genital Tract; Section on Gestational and Placental Disorders, Chapter 24, pp. 1079-1089
- Supplemental Material (Attached): Developmental Anomalies

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:
  - Discordant Sexual Identity in Some Genetic Males with Cloacal Exstrophy Assigned to Female Sex at Birth, William G. Reiner, M.D., Volume 350:333-341, January 22, 2004
  - Three Facets of Sexual Differentiation, Daniel D. Federman, M.D., Volume 350:323-324 January 22, 2004

Case-Based Study
Assignments:
- Printed Case 1: - “A 64 year-old female with sudden onset of hip pain…”
- Printed Case 2: - “A two-month-old white male was admitted …”

Case-Based Study
Required reading:

Widmann’s Clinical Interpretation of Laboratory Tests

Genetics:
- p. 862: Inborn errors of metabolism
Pediatric pathology:
p. 363: Evaluation of immunodeficiency states
Developmental Defects (Anomalies)

Major anomalies differ from minor anomalies in that they produce significant functional or cosmetic impairment. The incidence of major anomalies is 3% of live births, and is higher in abortuses, stillborns, prematurity, and multiple gestation. Developmental defects are an important cause of pregnancy losses, neonatal mortality and morbidity, pediatric hospital admissions and long term disabilities. A minor developmental anomaly by itself may have no serious medical consequences to the patient, however, it indicates a flaw in development and can be a clue for internal major anomalies or a specific syndrome.

Pathogenetic Mechanisms

From the standpoint of developmental pathogenesis, a structural defect can be assigned into one of three categories: malformation, deformation and disruption. Whereas malformations occur early during embryonic organogenesis, deformations and disruptions occur at variable periods throughout gestation. The clinical importance of this distinction relates to prognosis and recurrence risk counseling. If a child's anomaly can be determined as disruptive in nature, parents can be given a negligible recurrence risk. If a child's anomaly can be determined to represent a late gestational deformation defect, an excellent prognosis can be given for spontaneous or postural correction.

Malformation: a morphologic defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.

Examples: Absent primordium: agenesis
Incomplete closure: cleft lip and palate, neural tube defects
Incomplete separation: syndactyly
Incomplete septation: tracheoesophageal fistula, ventricular septal defect, truncus arteriosus
Persistence of early forms: Meckel's diverticulum

Deformation: an abnormal form, shape, or position of a part of the body caused by mechanical forces.

Examples: Club feet, Hip dislocation, Scoliosis, Arthrogryposis, Hypoplastic lungs

Causes of deformation: Oligohydramnios, Twins, Uterine leiomyomas, Bicornuate uterus
Disruption: a morphologic defect of an organ, part of an organ, or a larger region of the body resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process.

Examples: Small bowel atresia, Gastrochisis
          Congenital amputation

Dysplasia: an abnormal organization of cells into tissue and its morphologic result.
           (dyshistogenesis)

Examples: Hemangioma, Hamartoma, Renal dysplasia

Classification Of Multiple Defects

In an individual with multiple anomalies, the approach toward making a morphologic diagnosis consists of 4 stages.
1. to determine the pathogenetic mechanism for each anomaly.
2. to decide which is the earliest defect in morphogenesis.
3. to analyze relationship between defects.
4. to classify the multiple anomalies into the following:

Sequence: a pattern of multiple anomalies derived from a single anomaly or pathogenetic mechanism.
Examples: Deformation: Oligohydramnios
          Disruption: Amniotic bands sequence
          Malformation: Micrognathia sequence

Syndrome: a pattern of multiple anomalies that are pathogenetically related and not known to represent a single sequence.
Examples: Malformation: Down syndrome
          Dysmetabolic: Hurler syndrome
          Meckel syndrome
          Fetal hydantoin syndrome

Association: a nonrandom occurrence in two or more individuals of multiple anomalies not known to be a sequence or syndrome.
Examples: VATER association
           CHARGE association

Interrelationships between Malformation, Deformation and Disruption

The distinction between the three mechanisms of anomalies is useful for clinical purposes, however, they are interrelated and may overlap during embryonic and fetal development. In multiple anomalies, it is important to classify individual anomalies and
analyze their interrelationships, so that a sequence could be developed to explain some, if not all of the anomalies.

Amniotic Band Disruption Complex (Sequence) is an example in which all three mechanisms may interact depending on the stage of embryonic/fetal development.

1. Bands cause disruptions by tearing and strangulation:
   - Amputation of limbs and fingers (pseudosyndactyly)
   - Constriction bands
   - Facial cleft
   - Encephalocele, and anencephaly
2. Bands cause deformations by tethering and crowding:
   - Club feet
   - Scoliosis
3. Bands cause malformations by interrupting morphogenesis:
   - Omphalocele
   - Cleft lip and palate
   - Choanal atresia

Teratogenesis and Modifying Factors

Teratogens are chemical, physical and biological agents that cause developmental defects. However, exposure to a known teratogen does not invariably result in a defect, the factors that determine the expression of a developmental defect (teratogenesis) are:

1. Fetal and maternal genotypes.
2. Timing, in relation to developmental stage.
4. Dose of teratogen.
5. Interactions and secondary effects.

Causes of Developmental Defects

See pages 466-470 in Robbins Pathologic Basis of Disease (6th edition)
Printed Case #1: A 64 year-old female with sudden onset of hip pain

**Clinical summary:** The patient is a 64 year-old female who presents with sudden onset of severe right-sided hip pain. She has also complained for years of a sensation of abdominal fullness and intermittent bouts of multifocal bone pain accompanied by a mild fever. Multiple moderately enlarged lymph nodes can be palpated. Relevant history includes the facts that the patient is Jewish and grandparents on both sides were immigrants from Russia. Physical exam reveals a markedly enlarged spleen and liver.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin g/dL</td>
<td>10</td>
<td>12-15</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>331</td>
<td>37-47</td>
</tr>
<tr>
<td>MCV fL</td>
<td>82</td>
<td>80-100</td>
</tr>
<tr>
<td>WBC $10^9$/µL</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Platelets $10^5$/µL</td>
<td>80</td>
<td>150-400</td>
</tr>
<tr>
<td>AST U/L</td>
<td>200</td>
<td>5-30</td>
</tr>
<tr>
<td>ALT U/L</td>
<td>210</td>
<td>5-35</td>
</tr>
<tr>
<td>Acid Phosphatase SI U/L</td>
<td>50</td>
<td>2.2-10.5</td>
</tr>
</tbody>
</table>

By mistake, the ordering physician checked the box for angiotensin converting enzyme levels, and was serendipitously surprised when the test showed an elevated result.

**Imaging studies:** showed multiple bony abnormalities including features suggestive of avascular necrosis of the right femoral head. In addition, marked hepatosplenomegaly was seen.

At this point the patient underwent right total hip replacement, and the femoral head and proximal femur were sent to pathology.

At this point, what might the differential diagnosis include?

After an inordinately long wait, the pathology report confirmed that avascular necrosis was present. It also noted an expansion of the femoral medullary space, and partial replacement of the hematopoietic marrow, by sheets of large cells with a low nuclear-cytoplasmic ratio and cytoplasmic inclusions resembling crumpled tissue paper.

**Questions**
1. What does the differential diagnosis now include? What test(s) should be ordered to distinguish the correct diagnosis? What is the underlying defect? How common is it?
2. How do the patient’s lab values correlate with the physical and radiologic findings? What are the different kinds of acid phosphatase, and in what circumstances can they be elevated?

3. Is there a direct, clear-cut genetic basis for this disease? If so, what is it?

4. Clearly the patient has a form of the disease with an adult onset. Are there other forms?

5. What are the other diseases in the same family as this one? Do they have clear-cut underlying genetic defects?

6. Is the patient’s ethnic background significant? Are there any genetic diseases that correlate with ethnic background?

7. When the pathologist saw that the marrow had been partly replaced by abnormal cells, why wasn’t he worried about a neoplastic process? What is the significance of a low nuclear-cytoplasmic ratio?
Printed Case #2: A two-month old white male was admitted

Clinical History: A two-month-old white male was admitted to the hospital for the second time with pneumonia and respiratory distress. Two weeks prior to this admission he had been seen in the Emergency Department for wheezing, and on chest X-ray examination he was found to have pneumonia. He was hospitalized for 48 hours and was sent home on oral antibiotics. A week after discharge he again presented with respiratory distress, prompting the current admission. His past history included a systolic murmur heard soon after birth and believed to be secondary to aortic stenosis.

Physical Findings: On admission, the patient was pale and in moderate distress. The respiratory rate was increased to 35/min, and there was marked tachycardia. He had subcostal and intercostal retractions, and bilateral wheezes were noted. A harsh III/IV systolic ejection murmur was heard along the left lower sternal border. Examination of the abdomen and central nervous system was normal. His body weight of 10 lb (4.5 kg) was only 26 oz (0.75 kg) over birth weight. A chest X-ray examination showed marked hyperinflation with infiltrates in the right middle and right lower lobes.

Admission Laboratory Data

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value: Conventional Units</th>
<th>Reference Range: Conventional Units</th>
<th>Value: SI Units</th>
<th>Reference Range: SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count (B)</td>
<td>9.1 x 10^3/μL</td>
<td>5.0-19.5</td>
<td>9.1 x 10^9/L</td>
<td>5.0-19.5</td>
</tr>
<tr>
<td>Erythrocyte count (B)</td>
<td>2.45 x 10^6/μL</td>
<td>3.8-5.5</td>
<td>2.45 x 10^{12}/L</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Hemoglobin (B)</td>
<td>8.1 g/dL</td>
<td>10-15</td>
<td>5.03 mmol/L</td>
<td>6.21-9.31</td>
</tr>
<tr>
<td>Hematocrit (B)</td>
<td>24%</td>
<td>30-40</td>
<td>0.24</td>
<td>0.30-0.40</td>
</tr>
<tr>
<td>MCV (B)</td>
<td>95 flL</td>
<td>80-94</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>MCH (B)</td>
<td>33 pg</td>
<td>27-31</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>MCHC (BErcs)</td>
<td>33.7 g Hb/dL</td>
<td>33-37</td>
<td>21 mmol Hb/L</td>
<td>20-23</td>
</tr>
<tr>
<td>Platelet count (B)</td>
<td>390 x 10^3/μL</td>
<td>150-450</td>
<td>390 x 1 0^9/L</td>
<td>150-450</td>
</tr>
</tbody>
</table>

Differential count (B)

<p>| Segment neutrophils      | 37%                       | 41-71                               | 0.37            | 0.41-0.71                 |
| Band neutrophils         | 3%                        | 5-10                                | 0.03            | 0.05-0.10                 |
| Lymphocytes              | 50%                       | 24-44                               | 0.50            | 0.24-0.44                 |
| Monocytes                | 8%                        | 3-7                                 | 0.08            | 0.03-0.07                 |
| Eosinophils              | 2%                        | 1-3                                 | 0.02            | 0.01-0.03                 |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte count (B)</td>
<td>2.2 %</td>
<td>0.5-3.0</td>
<td>0.022</td>
<td>0.005-0.030</td>
</tr>
<tr>
<td>Urinalysis (U)</td>
<td>Within normal limits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes (S)</td>
<td>Within normal limits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, total (S)</td>
<td>6.1 g/dL</td>
<td>6.2-8.0</td>
<td>61 g/L</td>
<td>62-80</td>
</tr>
<tr>
<td>Albumin (S)</td>
<td>3.4 g/dL</td>
<td>3.8-5.4</td>
<td>34g/L</td>
<td>38-54</td>
</tr>
<tr>
<td>Urate (S)</td>
<td>4.1 mg/dL</td>
<td>2.0-5.5</td>
<td>244 nmol/L</td>
<td>119-327</td>
</tr>
<tr>
<td>Cholesterol (S)</td>
<td>60 mg/dL</td>
<td>70-175</td>
<td>1.55 mmol/L</td>
<td>1.81-4.53</td>
</tr>
<tr>
<td>Liver function tests (S)</td>
<td>Within normal limits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate (S)</td>
<td>&gt;20 ng/mL</td>
<td>1.5-9.0</td>
<td>&gt;45 nmol/L</td>
<td>3-20</td>
</tr>
</tbody>
</table>
The laboratory tests showed a normochromic anemia, hypoalbuminemia, and hypocholesterolemia. The leukocyte count was normal with a slight lymphocytosis, thus suggesting a viral illness. Cultures and fluorescent antibodies (FA) for viruses, *Chlamydia*, and *pertussis* were negative. The sputum culture results may represent bacterial colonization secondary to antibiotic therapy. During the hospitalization, the nurses reported that the patient's bowel movements were poorly formed and greasy and had a pungent odor.

**No images are available for this case.**

Questions for classroom discussion:

1) What are the most important findings either from the history, physical exam, or the lab studies?
2) Although they may be broad, what kind of differential diagnoses can you think of for an infant with recurrent serious respiratory infections? For an infant that fails to thrive with this infant’s particular findings? Is there any way to relate the GI and respiratory problems? What about the heart problems? Are any of these “red herrings”?
3) What diagnosis do you favor and why?
Genetics #1       Down Syndrome

Trisomy 21 (Down Syndrome) phenotype: flat face, low nasal bridle, upward slanting palpebral fissures.

Genetics #2       Trisomy 13

Trisomy 13 phenotype: cleft lip and palate, low-set ears, hypotelorism.

Genetics #3       Trisomy 18

Trisomy 18 phenotype: crowded facial features, low-ears, micrognathia, prominent occiput, abnormal hand posture (clenched fist with 2\textsuperscript{nd} finger overlapping 3\textsuperscript{rd} and 4\textsuperscript{th}), rocker-bottom feet.

Genetics #4       Monosomy X 1

Monosomy X phenotype in the fetus: bilateral cystic hygromas and hydrops fetalis.

Genetics #5       Monosomy X 2

Monosomy X phenotype in adolescent: short stature, cubitus valgus, broad chest, minimal breast development, scant axillary and pubic hair.

Genetics #6       Infantile polycystic kidney disease

Abdomen of a neonate with infantile polycystic disease of the kidney. The abdomen is filled by the markedly enlarged kidneys, the bladder and ureters are atretic. The infant had features of oligohydramnios sequence: hypoplastic lungs, club feet, low-set ears, micrognathia, prominent epicanthal folds.

Genetics #7       Infantile polycystic kidney disease

Cut sections of the kidneys: the kidneys are symmetrically enlarged with a smooth cortex and maintain their “kidney-shaped”. It is sponge-like with linear channels at right angle to the cortical surface. The medulla and papillae is recognizable. The renal pelvis, ureters (and bladder) are atretic, indicating no excretion of urine. Microscopically, the cortex showed cylindrical dilatation of tubules without involvement of the glomeruli. The liver invariably show bile ductular proliferation with cystic dilatations and portal fibrosis. The changes in the kidney and liver are known as “dysplasia” of genetic origin. Infantile polycystic disease of the kidney is an autosomal recessive disorder, while adult polycystic disease of the kidney is an autosomal dominant disorder.
Week 5: September 13-17
Genetics/Pediatric & Developmental Pathology

**Genetics #8  Tangier’s Disease**

Tonsil. Hematoxylin & eosin stain. X78. This photomicrograph is from the tonsil of a 6-year-old boy who presented with enlarged, orange-yellow tonsils and hepatosplenomegaly. Scattered among the lymphocytes are a large number of foamy macrophages with pale eosinophilic cytoplasm and small nuclei. Chemical analysis showed that the intracellular lipid was predominantly cholesterol and cholesterol esters.

Tangier’s disease (an-alphalipoproteinemia) is one of the group of disorders of the reverse cholesterol transport pathway. Plasma high density lipoprotein (HDL) levels are markedly reduced presumably because of increased HDL catabolism. Very low density lipoproteins (chylomicron remnants) accumulate and are taken up by the reticuloendothelial cells where they are stored as cholesterol esters. Clinical manifestations include enlarged tonsils, hepatosplenomegaly, and relapsing polyneuropathy. Premature atherosclerosis is not usual in this disease, but it may occur.

<table>
<thead>
<tr>
<th>Selected Laboratory Findings in Tangier’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein A-1 (Apo A-1)</td>
</tr>
<tr>
<td>Apolipoprotein B (Apo B)</td>
</tr>
<tr>
<td>Serum triglycerides</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (LDL-C)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (HDL-C)</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
</tr>
</tbody>
</table>

**Genetics # 9  Von Gierke’s Disease**

Liver. Hematoxylin & eosin stain. X78 (A). The architecture of the liver from a 2-year-old girl, as seen in this photomicrograph is essentially normal, but the hepatocytes appear devoid of cytoplasm. The normally eosinophilic cytoplasm has been displaced to the edges of the cells by the intracellular accumulation of a large amount of glycogen.

Kidney. Hematoxylin & eosin stain. X78 (B). Note the irregular luminal borders in the dilated proximal convoluted tubules from one of the kidneys of the above mentioned patient. The cytoplasm of the epithelial lining cells of these tubules I abundant and pale-staining, reflecting the increased cytoplasmic glycogen. The glomerulus is essentially normal.

Von Gierke’s disease (glycogen storage disease Type I) is due, in the case of this young girl, to a deficiency of glucose-6-phosphatase, a hydrolytic enzyme which catalyzes the removal of the phosphate group in glucose-6-phosphate to yield glucose. The enzyme is bound to the endoplasmic reticulum (ER) membrane, and glucose-6-phosphate must be
transported from the cytosol to the ER lumen in order for the enzyme to act. Deficiencies in the transport system that affects this are also known and can lead to Von Gierke’s disease. Glucose-6-phosphatase is predominantly found in the liver and kidneys and it is these two organs that show the effects of the deficiency.

1) The Roman numeral classification system of the glycogen storage diseases was devised by Gerta T. Cori in 1957 (I-Von Gierke’s disease; II-Pompe’s disease; III-Cori’s disease; IV-Andersen’s disease; V-McArdle’s disease; VI-Hers’ disease). In 1947, Gerta Cori and her husband, Carl F. Cori were jointly awarded the Nobel prize in medicine for their studies on the metabolism of carbohydrates, especially glycogen metabolism.

2) This was discovered by the Coris in 1952.

| SELECTED LABORATORY FINDINGS IN VON GIERKE’S DISEASE |
|-----------------|-----------------|
| **Blood glucose, non-fasting** | Slight to moderate decrease |
| **Blood glucose, fasting** | Severe decrease |
| **Serum triglycerides & Serum cholesterol** | Increased |
| | (due to increased dependence on fat metabolism) |
| **Whole blood pyruvate & L-lactate** | Increased |
| | (due to compensatory increase in glycolysis) |
| **Serum uric acid** | Increased |
| **Plasma glucose response to intramuscular glucagon** | Glucose levels do not rise, but lactate increases |

**Genetics #10**

**Heart. Hematoxylin & eosin stain. X78.** Both longitudinal and tangential sections of myocardium are seen in this image form a 11-month-old female with Pompe’s disease (glycogen storage disease – type II). The “holes” in the cardiac fibers are due to the intracellular deposition of large amounts of glycogen which has pushed the sarcoplasm of the cells peripherally where it stains prominently with eosin. The glycogen accumulates in lysosomes because of the deficiency of alpha-1,4-glucosidase (acid maltase), a hydrolytic enzyme found only in lysosomes. Glycogen accumulation occurs in all tissues but is especially prominent in the heart and usually leads to death by 2 years of age from cardiorespiratory failure. This patient died of bronchopneumonia complication chronic congestive heart failure. A milder adult form exists with chronic myopathy as the main finding.
Selected Laboratory Findings in Pompe’s Disease

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase, acid form-optimum pH-4</td>
<td>Markedly low or absent activity</td>
</tr>
<tr>
<td>1. From amniotic fluid cell culture (prenatal Dx.)</td>
<td></td>
</tr>
<tr>
<td>2. From skin fibroblast cultures or fresh urine</td>
<td></td>
</tr>
<tr>
<td>Periodic Acid-Schiff (PAS) stain</td>
<td>Large numbers of PAS-positive granules in leukocytes (Non-specific finding)</td>
</tr>
<tr>
<td>1. Whole blood or bone marrow</td>
<td></td>
</tr>
<tr>
<td>Plasma glucose response to intramuscular glucagon</td>
<td>Normal (Normal response = 60-80 mg/dL rise within 30 minutes with no rise in lactate)</td>
</tr>
</tbody>
</table>

**Genetics #11  Tay-Sachs Disease**

**Spinal cord. PASD stain. X31.** This photomicrograph illustrates the changes in the anterior horn neurons in Tay-Sachs disease (GM2 gangliosidosis; hexosaminidase α-subunit deficiency) and is from a 7-year-old boy who died following a series of seizures. The normal Nissl substance of the anterior horn cells is diminished and has been displaced by eosinophilic granular material which is the cytoplasmic lysosomes distended with accumulated GM2-gangliosides.

Gangliosides (carbohydrate-rich sphingolipids with sialic acids) account for about 6% of the lipid content of gray mater and are degraded inside lysosomes by removal, in sequence, of their terminal sugars. Deficiency of hexosaminidase A (also known as N-acetyl-β-D-glucosaminidase) leads to a marked increase in the ganglioside content of the brain in patients with Tay-Sachs disease.

**Enzyme Assays for the Diagnosis of Tay-Sachs Disease**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Serum Hexosaminidase A</th>
<th>Serum Hexosaminidase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygote carriers for Tay-Sachs disease</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Homozygotes for Tay-Sachs disease</td>
<td>Virtually absent</td>
<td>Marked increase</td>
</tr>
</tbody>
</table>

1 Normally decreases during pregnancy and in women taking oral contraceptives. To reduce the risk of a false-positive result, it is recommended that in these two populations, the assay be performed with leukocytes as the leukocyte hexosaminidase A levels do not change during pregnancy and with oral contraceptive agents.

2 Prenatal diagnosis is performed by assaying enzyme activity in cultured cells from amniotic fluid or chorionic villus sampling.

Note: A DNA test based on amplification of genomic DNA by the polymerase chain reaction is now available to detect carriers.

**Genetics #12  Niemann-Pick Disease**

**Spleen. Hematoxylin & eosin stain. X78.** This image is from the spleen of a 6-month-old girl who was noted to have progressive enlargement of her abdomen beginning at the age of 2 months. She died at 6 months of age and an autopsy revealed both an enlarged liver and spleen. A number of large macrophages with pale, foamy, eosinophilic
cytoplasm and unremarkable nuclei are present in effect crowding out the normal lymphoid tissue.

Niemann-Pick disease results in the accumulation of sphingomyelin (a phosphorylcholine-containing sphingolipid) and cholesterol in the lysosomes of a number of different cells, but especially those of the reticuloendothelial system. The majority of cases (type A) are due to a deficiency of sphingomyelinase (also known as sphingomyelin phosphodiesterase), a lysosomal enzyme necessary for the degradation of sphingomyelin which is an important component of cellular membranes. In this form of the disease, besides the visceral accumulation of sphingomyelin, there is diffuse involvement of the neurons leading to cell death and patients rarely survive beyond 4 years of age. The diagnosis is made by enzyme assay on serum, leukocytes, or tissue samples. Some forms of Niemann-Pick disease can be prenatally diagnosed from amniotic fluid or chorionic villous cell cultures.

### Genetics #13

**Gaucher’s Disease**

**Spleen. Hematoxylin & eosin stain. X100.** A splenectomy was performed in a 3-year-old boy with hepatosplenomegaly, microcytic anemia and thrombocytopenia. The splenic sinusoids are distended by groups of cell with pale, eosinophilic cytoplasm and moderately large, eccentrically placed nuclei. Numerous fine strands can be seen within the abundant cytoplasm giving it a wrinkled appearance. This is the typical appearance of Gaucher’s histiocytes which can also be found in liver, bone marrow, lymph nodes, thymus, tonsil, gastrointestinal tract, and the lungs. In some forms of the disease, these cells can be found in the cerebrum. By electron microscopy, the cytoplasmic striations apparent in the light microscope are in fact lysosomes distended with accumulated glucocerebrosides.

The various forms of Gaucher’s disease are mainly separated by the age of presentation and whether or not cerebral involvement is present. The basic defect is a deficiency in β-glucocerebrosidase, a lysosomal enzyme that removes the glucose group from the terminal hydroxy group of glucocerebroside resulting in ceramide (N-acyl sphingosine). The diagnosis is made by finding Gaucher’s cells in the bone marrow, liver, or spleen.

#### Selected Laboratory Findings in Gaucher’s Disease

<table>
<thead>
<tr>
<th>Hypersplenism (usually pancytopenia)</th>
<th>Due to infiltration of spleen by Gaucher’s cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum acid phosphatase</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

### Genetics #14

**Hurler’s Syndrome**

**Cerebral cortex. Hematoxylin & eosin stain. X100.** This photomicrograph is from the cerebral cortex of a 5-year-old boy with progressive mental and physical retardation, initially noticed several months after birth. He died of bronchopneumonia. The neurons in this image show several abnormalities: 1) most are round in appearance; 2) the Nissl substance is markedly decreased in amount (actually it has been displaced peripherally);
3) many of the nuclei are pyknotic and eccentrically located; 4) the cytoplasm contains numerous fine, eosinophilic granules and vacuolations.

Hurler’s syndrome is one of the mucopolysaccharidoses (MPS), another group of diseases relating to deficiencies of certain lysosomal enzymes, which in this series of disorders results in the accumulation of glycosaminoglycans (mucopolysaccharides) in the lysosomes of various tissues and organs. alpha-L-iduronidase is the deficient enzyme in Hurler’s syndrome and dermatan sulfate and heparan sulfate are the glycosaminoglycans that accumulate in the various tissues. Diagnosis of the various MPS is made by the clinical presentation, radiologic findings, and the types of mucopolysaccharides present in urine. Confirmation of the enzyme defect is possible by white blood cell or fibroblast culture.

**Developmental Pathology / Perinatal and Pediatric Pathology**

**Pediatrics #1**

**Nephroblastoma (Wilms’ Tumor)**

**Kidney. Hematoxylin & eosin stain. X50.** The most prominent histologic feature in this photomicrograph of a Wilms’ tumor is epithelial differentiation in the form of abortive glomeruli and tubules. The stromal component is mainly myxoid while blastemal tissue is minimal, perhaps a small area on the right side of the image. These tumors, which arise from nephrogenic rests, are large, well-circumscribed and often show a variegated gross appearance with solid gray areas alternation with areas of hemorrhage and cyst formation. They account for 75% of childhood renal tumors, usually occur between the ages of 2 to 4 years and are unilateral in the great majority of cases. Genetic abnormalities on chromosome 11 play an important role in the development of this tumor.

**Pediatrics #2**

**Neuroblastoma 1**

**Adrenal gland & kidney. Gross photo.** A large, multinodular mass of grayish-white and tan tissue has obliterated the adrenal gland and partially surrounded the hilum of the kidney. Areas of necrosis are evident.

**Pediatrics #3**

**Neuroblastoma 2**

**Adrenal gland. Hematoxylin & eosin. X78.** The tumor is composed of nests of small cells with dense nuclei, very little cytoplasm, and ill-defined cell borders. Cells with larger, vesicular nuclei and increased amounts of cytoplasm can also be identified indicating an attempt at differentiation. Note the rich vascular network. The irregular pale fibrilar areas on the right side of the image, while not classical in appearance, are Homer-Wright pseudorosettes. As the tumor differentiates, the cells become more neuronal or ganglion-like in appearance. This is the most common malignancy in
children under 1 year of age, most are found in the abdomen, and about two thirds of children with this tumor will have metastatic disease at presentation.

**Pediatrics #4  Retinoblastoma**

**Retina. Hematoxylin & eosin stain. X5.** An 18-month-old girl was noted to have esotropia of the left eye, a mass in the vitreous cavity, and elevated intraocular pressure. The right eye was enucleated and contained a large pale mass filling the vitreous body. This photomicrograph shows a portion of the vitreous body and optic nerve replaced by a large mass of small, dark blue cells consistent with a retinoblastoma. These tumors arise for the retina and may, as in this case, fill the eye and destroy the normal architecture. Most of these tumors develop sporadically and 90% present before 2 years of age. About 60% are sporadic and 40% are inherited as an autosomal recessive trait.

**Pediatrics #5  Congenital Syphilis**

**Liver. Hematoxylin & eosin stain. X78.** The most striking feature in this photomicrograph from the liver of a 4-month-old male infant is the extensive widening of the sinusoids and portal area by fibrous tissue, Kupffer cells and lymphocytes. Occasional plasma cells are also evident. Many of the hepatocytes appear atrophied with indistinct cell borders, and in some areas nuclei from several of these cells cluster together forming small syncytia. Cholestasis is present. Besides diffuse hepatic fibrosis as seen here, other manifestations of congenital syphilis in young infants include cutaneous lesions, osteochondritis, periostitis, pulmonary fibrosis, Hutchinson’s teeth, and meningovasculitis.

**Comment:** The causative organism of syphilis, *Treponema pallidum*, infects the fetus by hematogenous transmission across the placenta mainly in the 2nd and 3rd trimesters and may lead to stillbirth, spontaneous abortion, or congenital syphilis. Syphilis is now one of the two main causes of known chronic intrauterine infection in young women and has led to an increase in the incidence of congenital syphilis.

**Pediatrics #6  Normal Placenta**

**Placental membranes. Hematoxylin & eosin stain. X31 [left image].** The amnion is composed of a single layer of epithelial cells attached to a basement membrane. Immediately beneath this is a compact acellular layer with an underlying thin fibrovascular band containing macrophages. A spongy layer is also present in this image separating the amnion from the chorion.

**Placental villi. Hematoxylin & eosin stain. X78 [right image].** Normal term placenta showing both cytotrophoblast and syncytiotrophoblast.
Pediatrics #7

Acute Chorioamnionitis

Placental membranes. Hematoxylin & eosin stain. X78. This is an example of acute chorioamnionitis caused by *Escherichia coli*. Grossly the fetal surface of the placenta would be opaque and yellow green. Microscopically, note the polymorphonuclear leukocytes in the chorion and at its junction with the amnion. Acute chorioamnionitis is infection of the amniotic cavity and fetus usually via the vagina and cervix (ascending infection) in the majority of cases. *Group B Streptococcus, E. coli, Mycoplasma* and *Candida albicans* are the more common pathogens. In transplacental (hematogenous) transmission, the infectious agent invades the placenta via the fetal-maternal bloodstream; it may be acquired any time during gestation. Finally a transabdominal (trans-uterine) mode of infection may occur with diagnostic/therapeutic procedures such as amniocentesis, percutaneous umbilical blood sampling, intrauterine exchange transfusions, fetal surgery, etc. Clinical presentations include maternal fever, premature rupture of membranes and fetal distress. Neonatal complications are sepsis and prematurity.

Perinatal Infections

<table>
<thead>
<tr>
<th>Placental Pathology</th>
<th>Pathogenesis</th>
<th>Selected Organisms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis; Funisitis; leukocytes migrating toward amniotic cavity</td>
<td>Organisms enter via internal cervical os (ascending infections) during gestation or at delivery; leads to infection of amniotic cavity &amp; membranes;</td>
<td>Most bacterial infections; <em>Fusobacterium; E. coli; Haemophilus influenzae; Bacteroides species; Gp B Streptococcus; Staphylococcal aureus; Listeria monocytogenes Candida albicans; Herpes simplex; Chlamydia trachomatis</em></td>
<td>Chorioamnionitis is the most important cause of perinatal morbidity &amp; mortality and can lead to premature labor; stillbirth; spontaneous abortion; fetal pneumonia, sepsis, meningitis; maternal infections</td>
</tr>
<tr>
<td>Villitis (leukocytes around and within fetal villi)</td>
<td>Transplacental (hematogenous) transmission; infectious agent invades the placenta via the fetal-maternal bloodstream; acquired any time during gestation</td>
<td>Most viruses &amp; parasites; <em>Cytomegalovirus; Rubella (now rare); Treponema pallidum; E. coli; staphylococcus aureus; H. influenzae; Mycobacteria; Listeria monocytogenes; Campylobacter; Toxoplasma gondii; Herpes</em></td>
<td>Fetal growth retardation, congenital malformation organomegaly</td>
</tr>
<tr>
<td>Placental inflammation usually absent or minimal</td>
<td>Maternal-to-fetal transfusions at delivery; contaminated vaginal mucus</td>
<td>HIV; Hepatitis B</td>
<td>Immune disturbance; growth retardation; hepatitis; chronic lever disease</td>
</tr>
<tr>
<td></td>
<td>Transplacental (hematogenous) transmission or ascending infection</td>
<td><em>Group B Streptococcus; Herpes simplex; Parvovirus B1</em></td>
<td>Stillbirth; spontaneous abortion; hydrops fetalis; fetal anemia (B19)</td>
</tr>
</tbody>
</table>
1. The pathological findings are not exclusive of one another for it is not uncommon to find evidence of both chorioamnionitis and villitis.
2. Certain organisms may produce more than one form of placental pathology reflecting in part the time of the infection and its severity.

**Pediatrics #8**

**Cystic Fibrosis 1**

*Pancreas. Hematoxylin & eosin stain. X31. (#8).* This photomicrograph of the pancreas of a 3-year-old boy with late stage cystic fibrosis shows generalized atrophy of acinar tissue and marked fibrosis. The remaining ducts and acini are distorted by the fibrosis and contain inspissated material within their lumens. A number of islets of Langerhans are seen in this image, again reflecting the atrophy of the intervening acinar tissue.

**Pediatrics #9**

**Cystic Fibrosis 2**

*Hematoxylin & eosin stain. X12.* This a section of the lung from the above patient and shows some of the common pulmonary findings in this disease. Emphysema is present as well as focal atelectasis and intraalveolar edema fluid. Not the markedly widened bronchi filled with inflammatory cells and inspissated mucus. The bronchial epithelium is hyperplastic and focally ulcerated (left side of image) and the large mass of mucus in this area probably represents the site of former mucus glands. An intense inflammatory infiltrate surrounds the bronchi.

The *Sweat Test in the Diagnosis of Cystic Fibrosis*

**Principle:** In cystic fibrosis sweat glands and some salivary glands produce excess amounts of sodium and chloride.

**Method:** Sweating is induced in the patient by the introduction of pilocarpine into the skin (via iontophoresis) and then either measuring the amount of sweat C1 directly with ion-selective electrodes, or by determining the \([C1]\) after the sweat is weighed. As an internal quality control check, the \([Na^+]\) should also be measured as these values should lie within 10 mmol/L of each other.

**Results:** A \([C1]\) greater than 60 mmol/L in infants (70 mmol/L in adults) confirms the diagnosis of cystic fibrosis in the right clinical setting or with a positive family history. (Normal reference range = 5 – 45 mmol/L)

**Limitations:** It may be difficult to obtain an adequate amount of sweat before 3 to 5 weeks of age, even though the test is valid after the first 24 hours of life. It may be falsely negative in cystic fibrosis patients with salt depletion, and it can be falsely positive in persons with skin lesions or rashes. There are a number of other disorders that can result in elevated sweat \([C1]\) but they are either very rare or the clinical presentation is quite different from cystic fibrosis (untreated adrenal insufficiency, hypothyroidism, alcoholic pancreatitis, G6PD deficiency, etc.)
Pediatrics #10  

Autosomal Recessive Polycystic Kidney Disease

Kidney. Hematoxylin & eosin stain. X31. A five-week-old boy died from renal failure and congestive heart failure and at autopsy both kidneys were enlarged with multiple 1-2 cm cysts scattered evenly throughout the renal parenchyma. Multiple cysts were also present in the liver. This photomicrograph, from one of the kidneys, shows that the cysts noted grossly are markedly dilated collecting tubules lined by a single layer of cuboidal epithelium and surrounded by some fibrous connective tissue containing scattered, small islands of hematopoietic tissue. The glomeruli show varying stages of development and rather severe congestion.

This disease usually presents in the neonatal period distention due to enlarged kidneys and with oliguria. Potter’s facies (small chin, beaked nose, abnormal ears) and oligohydramnios are usually present. When it presents in older children, signs of liver disease are more prominent (hepatosplenomegaly, esophageal varices, portal hypertension) as hepatic fibrosis is usually significant.

Pediatrics #11

Neonatal Respiratory Distress Syndrome

Lung. Hematoxylin & eosin stain. X12. This image is from the lung of a preterm female infant who died at birth. It contains several dilated alveolar ducts lined by a focally granular eosinophilic membrane which is composed of fibrinogen, fibrin, and cellular debris. Many of the surrounding alveoli relating to these ducts are collapsed (atelectatic) and their septa appear congested.

The neonatal respiratory distress syndrome (RDS) also known as hyaline membrane disease (HMD) is a significant cause of mortality in preterm infants and is related to immature lungs and a deficiency of pulmonary surfactant which is produced by Type II alveolar pneumocytes in adequate amounts after the 35th week of gestation. An assessment of fetal pulmonary maturation is therefore important in evaluation the risk of development of hyaline membrane disease.

Pulmonary Surfactant

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Amount</th>
<th>Gestational age when present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desaturated dipalmityl phosphatidyl choline (lecithin)</td>
<td>75%</td>
<td>35 weeks</td>
</tr>
<tr>
<td>Phosphatidyl glycerol (PG)</td>
<td>10%</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Sphingomyelin (S)</td>
<td>2%</td>
<td>Constant during 3rd trimester (used as internal standard)</td>
</tr>
<tr>
<td>Miscellaneous lipids, proteins, and carbohydrates (some of these may be very important)</td>
<td>13%</td>
<td>3rd trimester</td>
</tr>
</tbody>
</table>
Laboratory Measurement of Pulmonary Surfactant

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical density of amniotic fluid</td>
<td>Mature amniotic fluid is turbid due to lamellar bodies containing surfactant. Test is affected by pigments.</td>
</tr>
<tr>
<td>Microviscosity of amniotic fluid</td>
<td>Viscosity decreases as surfactant increases. Viscosity measurements should not be run on pigmented amniotic fluid as blood and meconium increase viscosity</td>
</tr>
<tr>
<td>Foam stability assay of amniotic fluid</td>
<td>Surfactant lowers surface tension and stabilized foam. Blood interferes with the test</td>
</tr>
<tr>
<td>Lecithin/Sphingomyelin (L/S) ratio test</td>
<td>Although not well standardized, it is the standard for the determination of lung maturity. In non-diabetic mothers: L/S &gt; 2.0 = absence of severe RDS in over 95% of cases L/S &lt; 2.0 = significant RDS in 25% of cases L/S = 1.5 indicates borderline lung maturity</td>
</tr>
</tbody>
</table>

**Pediatrics #12**

**Erythroblastosis fetalis**

*Liver. Hematoxylin & eosin stain. X100.* This photomicrograph is from the liver of a female infant delivered vaginally at 32 weeks gestation following an episode of profuse vaginal bleeding in the mother. The infant had hydrops fetalis, generalized petechiae and hepatosplenomegaly. She died shortly after birth. The sinusoids are distended with hematopoietic cells (extramedullary hematopoiesis) in all stages of development (erythroblasts and normoblasts are easily seen). The hepatocytes contain abundant hemosiderin pigmentation and bile stasis is present in the bile canaliculi, but it is hard to separate from the hemosiderin in this hematoxylin & eosin stained section. Extramedullary hematopoiesis was also found in the patient’s lymph nodes, spleen, adrenal glands, and kidneys.

**Pediatrics #13**

**Retroplacental hematoma**

Sections of placenta showing a large blood clot on the maternal surface (retroplacental hematoma). The underlying placenta is compressed and ischemic (recent infarct). The three pale nodules are old infarcts. Clinical presentations of the mother include antepartum hemorrhage, abdominal pain and tenderness, premature separation of placenta (abruptio placenta) and pre-eclampsia. A large retroplacental hematoma (30% to 40% of the maternal surface) will compromise fetal maternal exchange, resulting in fetal hypoxia and fetal demise. Neonatal complications include low Apgar scores (low heart rate, depressed respiration, decreased muscle tone, poor cry & cyanosis), intrauterine growth retardation and prematurity.
Week 6: September 20-24
Hematopoietic System/Lymph Nodes and Spleen

Schedule

**Monday, September 20**
10-12 Noon  Integrated Case-Leukemia  TBA

**Thursday, September 23**
2-5 PM  Path Talk  Laboratory

**Friday, September 24**
11-12 Noon  Summary  West Lecture Hall
Week 6: September 20-24
Hematopoietic System/Lymph Nodes and Spleen

Topic: Hematopoietic System / Lymph Nodes and Spleen

Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition,
- White Cells, Lymph Nodes, and Spleen, Chapter 15, pp. 645-675; 688-693
- Leukemias, pp. 675-688 – for review only.
- Red Cells and Bleeding Disorders, Chapter 14, pp. 601-642
  (This material covered in the Hematology Course; please review only)

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:

Case-Based Study
Assignments:
- No printed cases. Prepare for Integrated Course Case in Hematology

Case-Based Study
Required reading: Widmann’s Clinical Interpretation of Laboratory Tests.

Laboratory evaluation of the bone marrow and peripheral blood in acute leukemias:
- pp. 184-192: Acute myeloid leukemia
- pp. 205-209: Acute lymphoblastic leukemia
Hematopoietic System/Lymph Nodes and Spleen

Kodachrome Slides

Hematopathology

An accurate determination of the status of the erythrocytes on a peripheral smear requires a well-made and well-stained slide in which the cells are evenly distributed, pink in color, and free of artifacts. Blood films that are too thick or too thin and variations in the staining process (i.e., washing, staining, drying, etc.) can result in cells that are overstained, understained or contain artifacts (vacuoles, stain precipitates, etc.) that can lead to difficulty in interpretation of the smear. Microscopic examination often reveals cells of different sizes, shapes, and hemoglobinization, and the examiner must be able to determine if the observed variations are within the normal physiologic range or if a pathologic state is present. Most modern clinical laboratories are now using automated hematology analyzers which have the capability to analyze thousands of cells a second and can, through a combination of actual numeric determinations, cytograms, and histograms, provide a wealth of hematology data. Combining the information obtained from these machines with a microscopic examination of a well-prepared peripheral blood smear by a skilled microscopist results in a more accurate picture of a patient's hematological status.

Illustrated in association with the next several slides are the red blood cell volume distribution histograms and the hemoglobin concentration histograms obtained from an automated hematology analyzer in which the red cell analyses are based on flow cytometry and the simultaneous scattering of light at different angles. This results in measuring both volume (size) and optical density (hemoglobin concentration) for each red cell that passes the sensor. A computer converts the signals into a cytogram and two histograms allowing one to obtain several pieces of information:

1. The mean of the red cell volumes measured = MCV (mean corpuscular volume) [Normal range = see next page] Also obtained by the following formula:

   \[
   MCV = \frac{\text{Hct} (\%)}{\text{RBC (millions per microL)}} \times 10
   \]

2. The coefficient of variation (CV) of the red cell volume distribution = RDW (red cell distribution width which reflects the degree of anisocytosis) [Normal range = 11.5% to 14.5%].

3. The mean of the cellular hemoglobin concentrations = MCHC [Normal range = 33.0 to 37.0 g/dL].

4. The standard deviation (SD) of the hemoglobin concentration histogram = HDW (hemoglobin distribution width which reflects the degree of anisochromia) [Normal range = 2.20 to 3.20].

5. The hematocrit (Hct), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) are not measured directly, but are calculated from the measured hemoglobin, red blood cell count and mean corpuscular volume (MCV).
Notes:

1. The normal ranges seen here reflect a particular hospital's population and may vary slightly from the ranges seen in data from other institutions.

3. Remember that indices are mean values and may not identify different cell populations. Microscopic examination of the peripheral blood film and analysis of the histograms are important aids in recognizing more than one red cell population.

Hematology #1

Peripheral blood smear. Wright/Giemsa stain. X252. In this photomicrograph, the majority of the red cells appear round and fairly uniform in size and shape. An area of central pallor occupies about one third of the diameter of most of the cells. The erythrocytes in this image are essentially normal in appearance. Several platelets are also present. In the red cell volume histogram and the hemoglobin concentration histogram illustrated below, the peaks of the curves lie approximately midway between the flags and all values are essentially contained within the flags (i.e. the curves are fairly narrow). These results indicate a single red cell population of normal size and hemoglobinization with little anisocytosis or anisochromia present.

Reference Ranges

<table>
<thead>
<tr>
<th>Test</th>
<th>Adult Female</th>
<th>Adult Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>4.5 – 11.0 thousand/µL</td>
<td>4.5 – 11.0 thousand/µL</td>
</tr>
<tr>
<td>RBC</td>
<td>3.9 – 5.0 million/µL</td>
<td>4.4 – 5.8 million/µL</td>
</tr>
<tr>
<td>HGB</td>
<td>12.0 – 15.0 g/dL</td>
<td>14.0 – 17.0 g/dL</td>
</tr>
</tbody>
</table>
Hematology #2

Peripheral blood smear. Wright/Giemsa stain. X252. A 33-year-old female presents with a chief complaint of being chronically tired, weak and experiencing excessive menstrual bleeding. On physical examination she was pale with a rapid pulse and low-normal blood pressure. Many of the red cells are small (microcytic) with enlarged areas of central pallor (hypochromic). Note the variation in size (anisocytosis) and shape (poikilocytosis). This is an example of a microcytic, hypochromic anemia due to iron loss secondary to excessive menstrual bleeding. Notice that most of the red cell volume distribution curve lies mainly to the left of the low volume flag indicating that there are a lot of small red cells present (MCV = 53.8 fL). The red cell distribution width is elevated at 17.7% reflecting the variability in the cell size that we see in the photomicrograph. Approximately half of the hemoglobin concentration distribution curve lies to the left of the low hemoglobin concentration flag (hypochromia) and it is also wider than the normal curve seen above (increased HDW or anisochromia).
Selected Laboratory Findings in Microcytic Hypochromic Anemias

<table>
<thead>
<tr>
<th></th>
<th>Serum Iron</th>
<th>TIBC</th>
<th>%Saturation</th>
<th>Marrow Iron</th>
<th>Marrow Sideroblasts</th>
<th>HgA2</th>
<th>FEP(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>N-↓</td>
<td>N-↓</td>
<td>↑</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>↑-N</td>
<td>↓-N</td>
<td>↑-N</td>
<td>↑-N</td>
<td>N-↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sideroblastic anemias(^3)</td>
<td>↑</td>
<td>↓-N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Anemia of chronic disease(^4)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
</tr>
</tbody>
</table>

1. FEP = free erythrocyte porphyrins
2. Beta thalassemias only
3. Microcytic hypochromic cells often mixed with normochromic cells
4. Usually normocytic and normochromic, but may be microcytic, hypochromic

**Hematology #3**

**Peripheral blood smear. Wright/Giemsa stain. X252.** A 78 year-old man presents with fever, cough, fatigue and recent weight loss. Bronchopneumonia was diagnosed and on his peripheral blood smear he was noted to have an abnormal white blood cell differential count, platelet abnormalities and a macrocytic anemia. Many of the red cells are large (macrocytic) with reduced areas of central pallor (hyperchromic) and some of them are oval in shape (oval macrocytes), an important finding as it is commonly seen in megaloblastic anemias. There is a significant anisocytosis and slight poikilocytosis. Other abnormal red cells present in the image include target cells and siderocytes (red cells containing non-heme iron particles (Pappenheimer bodies). Notice the marked variation in the size of the platelets. The red cell volume distribution histogram in this patient is broad and shifted to the right reflecting both macrocytosis (MCV =110.6fL) and marked anisocytosis (RDW = 26.9%). The hemoglobin concentration histogram shows some skewing to the left and the MCH is only slightly elevated a bone marrow was consistent with refractory anemia with ringed sideroblasts (RARS), one of the myelodysplastic syndromes.
**Hematopoietic System/Lymph Nodes and Spleen**

**Macrocytic Anemias**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Selected Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (occult)</td>
<td>Increased reticulocyte count; anemia may be normocytic</td>
</tr>
<tr>
<td>Coombs’ positive hemolytic anemia (autoimmune hemolysis)</td>
<td>Increased reticulocyte count; spherocytes on peripheral smear; positive Coombs’ test</td>
</tr>
<tr>
<td>Coombs’ negative hemolytic anemia (DIC, TTP, lead poisoning, G6PD deficiency, PNH)</td>
<td>Increased reticulocyte count; negative Coombs’ test: schistocytes in DIC &amp; TTP; basophilic stippling in lead poisoning</td>
</tr>
<tr>
<td>Macrocytic anemia 2(^{nd}) to drugs, toxins, liver or thyroid disease; aplastic anemia; myelodysplasias</td>
<td>Normal reticulocyte count; round macrocytes on smear; non-megaloblastic bone marrow (myelodysplasias may show megaloblastoid changes in smears and bone marrow)</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Normal reticulocyte count; oval macrocytes; hypersegmented PMNs; megaloblastic bone marrow</td>
</tr>
</tbody>
</table>

**Hematology #4**

**Normocytic anemia**

Peripheral blood smear. Wright/Giemsa stain. X252. This smear is from a 55-year-old female with severe rheumatoid arthritis. Anisocytosis is present but there is very little difference in shape. The area of central pallor in many of the cells is about one third of the cell’s diameter. The red cell volume distribution histogram is widened (RDW = 21.1) but it is mostly within the flags indicating that while there is increased red cell heterogeneity, the size of most of the cells lies within the normal range. The peak and most of the hemoglobin concentration distribution histogram appears centered between the flags reflecting the fact that the hemoglobin concentration of most of the cells lies within the normal range (normochromic).
Use of the Red Cell distribution width (RDW) and Mean Corpuscular Volume (MCV) 
In the Classification of Anemia

<table>
<thead>
<tr>
<th>Anemia</th>
<th>MCV</th>
<th>RDW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early or mixed nutritional deficiency anemia (iron, folate, vitamin B₁₂)</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Normal or Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Thalassemia (trait)</td>
<td>Low</td>
<td>Normal or High</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Anemia due to SS or SC</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Anemia due to hemorrhage</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Normal</td>
<td>High</td>
</tr>
</tbody>
</table>


**Hematology #5**

**Peripheral blood smear.** Wright/Giemsa stain. X252. Several segmented neutrophils are present in this image from a 49-year-old man admitted with an acute myocardial infarction. Notice that the nuclear chromatin is coarsely clumped and some of the lobes are separated by thin strands. The cytoplasm contains numerous granules. This is a thicker part of the smear and it is somewhat overstained. The automated hematology analyzers mentioned above also measure the white blood cells and platelets in the peripheral blood. Again using flow cytometry, thousands of white cells move past a pair of detectors where they are characterized by size and peroxidase activity. A scattergram is produced in which 5 groups of leukocytes can be defined (neutrophils (n), lymphocytes (1), monocytes (m), eosinophils (e), and “large, unstained cells” (u). The intensity of the different groups of cells depends on the number of dots (i.e., cells) within that group in the peroxidase histogram from this patient, seen below on the left, the pattern of distribution is normal, but the intensity is slightly increased reflecting a slightly elevated white blood cell count, in this case mainly due to neutrophils.
Leukocytosis Secondary to Granulocytosis

<table>
<thead>
<tr>
<th>Level</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 20,000/µL</td>
<td>Consistent with inflammation (infection, tissue necrosis) or physiologic causes (exercise, postprandial, pregnancy, emotional excitement, depression, nausea, vomiting, cold, heat)</td>
</tr>
<tr>
<td>WBC 20,000/µL to 100,000/µL</td>
<td>Leukemoid reaction (leukocyte alkaline phosphatase score $&gt; 100$; $&gt; 95%$ segmented neutrophils with usually no cells earlier than myelocytic stage) vs chronic myelogenous leukemia (leukocyte alkaline phosphatase score $&lt; 10$; progranulocytes or blasts can usually be found)</td>
</tr>
<tr>
<td>WBC $&gt; 100,000/µL$</td>
<td>Consistent with chronic myelogenous leukemia</td>
</tr>
</tbody>
</table>

Hematology #6

**Lymph node. Hematoxylin & eosin stain X4.** Numerous secondary follicles are present within the cortex and even extend into the medulla. The follicles vary in size, are surrounded by a mantle of small lymphocytes, and contain several “holes” which are the site of histiocytes with phagocytized debris. Notice how the follicles, with their covering of small lymphocytes are bulging against the subcapsular sinus and capsule. This is a good example of follicular hyperplasia.
**Week 6: September 20-24**

**Hematopoietic System/Lymph Nodes and Spleen**

**Lymph node. Hematoxylin & eosin stain. X4.** For comparison, this is a minimally stimulated lymph node. Many of the follicles are primary with no germinal center formation and are confined to the cortex. The germinal centers that are present are mostly small.

**Hematology #7**

**Chronic Nonspecific Lymphadenitis 2**

**Lymph node. Hematoxylin & eosin stain. X31.** A closer view of follicular hyperplasia shows a large reactive germinal center (secondary follicle) capped by a dense mantle of small lymphocytes which has compressed the subcapsular sinus. The paracortical T-cell zone contains normal appearing small lymphocytes. Other patterns of chronic lymphadenitis include paracortical lymphoid hyperplasia and sinus histiocytosis.

**Hematology #8**

**Infectious Mononucleosis 1**

**Lymph node. Hematoxylin & eosin stain. X31.** The diagnosis of infectious mononucleosis is usually made on the basis of the peripheral blood findings and serologic testing for evidence of the Epstein-Barr virus. Lymph node biopsies are usually not performed as they are generally not necessary. The most characteristic histologic finding in the lymph nodes of patients with infectious mononucleosis is the expansion of the paracortex by the proliferation of large transformed cells (immunoblasts), plasma cells, plasmacytoid lymphocytes, and post-capillary venules. The immunoblasts are large with fairly abundant cytoplasm and can easily be seen scattered among the small predominantly t-lymphocytes of the paracortex. This photomicrograph shows an expanded paracortex on one side, with numerous immunoblasts and venules, and a germinal center on the other side with somewhat irregular borders. The mottled appearance of the paracortex seen here is not specific for infectious mononucleosis and can be seen in other viral disorders. Compare with Hematology slide 7.

**Hematology #9**

**Infectious Mononucleosis 2**

**Lymph node. Hematoxylin & eosin stain. X125.** The image is from the paracortex of the lymph node seen above. Scattered among the small lymphocytes are the large atypical reactive lymphocytes (immunoblasts) with vesicular nuclei, prominent nucleoli, and fairly abundant cytoplasm. These cells correspond to the atypical lymphocytes seen in the peripheral smear. Mitotic figures are present and plasma cells can also be seen. Notice the small venule with its prominent endothelial lining.

**Peripheral blood smear. Wright/Giemsa stain. X197.** The characteristic finding in infectious mononucleosis is the presence of atypical lymphocytes in the peripheral blood smear. Several of these cells with abundant pale, bluish-gray cytoplasm and moderately large nuclei can be seen in this image. The nuclear chromatin is granular and two of the
cells show nuclear indentations. Also seen is red cell clumping (red cell autoagglutination) due to anti-I antibody, a not uncommon finding in this disease.

Hematology #10  
Non-Hodgkin’s Lymphoma: B-Cell Follicular Lymphoma

**Lymph node. Hematoxylin & eosin stain. X12.** At low magnification, several closely-packed nodules are present with minimal interfollicular areas and essentially no mantle zones.

**Lymph node. Hematoxylin & eosin stain. X100.** Most of the cells are small cleaved cells having irregular nuclear membranes, indistinct nucleoli, and coarse chromatin. Also seen are scattered larger lymphoid cells with a rim of amphophilic cytoplasm and vesicular, rounded nuclei with one or more nucleoli. It is one of the low-grade non-Hodgkin’s lymphomas.

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency¹</th>
<th>Clinical findings</th>
<th>Pathology²,³,⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly small cleaved cell (low-grade)</td>
<td>65%</td>
<td>65% patients are stage IV at presentation (bone marrow, spleen and liver involvement); mean age – 55 yrs. (rare in childhood); indolent course but nearly half transform to higher grade lymphoma</td>
<td>As above</td>
</tr>
<tr>
<td>Mixed small cleaved and large cell (low-grade)</td>
<td>25%</td>
<td>Large cells (cleaved and non-cleaved) 25–75% of cell population</td>
<td></td>
</tr>
<tr>
<td>Predominantly large cell (intermediate grade)</td>
<td>10%</td>
<td>Large Cells &gt; 75% of cell population</td>
<td></td>
</tr>
</tbody>
</table>

1. Refers to percentage of follicular lymphomas.
2. > 90% - surface immunoglobulin with light chain restriction
3. Usually CD10⁺, and almost always CD5⁻, CD43⁻
4. Bcl-2 positive (80-90%) and t(14;18)(q32;q21) in 80-90%

Hematology #11  
Non-Hodgkin’s Lymphomas: Diffuse Large B-Cell Lymphoma

**Lymph node. Masson trichrome stain. X30.** This medium power photomicrograph is an example of a diffuse large cell lymphoma, a lymphoma of intermediate grade. Nodules are not apparent and the cells are larger than those seen above. Many of these lymphomas exhibit fibrosis, either in the form of broad bands or as a diffuse sclerosis surrounding individual cells. This image shows a little of both. This is an intermediate grade lymphoma.
### Hematopoietic System/Lymph Nodes and Spleen

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Findings</th>
<th>Pathology</th>
</tr>
</thead>
</table>
| Mixed small cleaved and large cell lymphoma (intermediate grade) | • Most common in adults (median age – 55 yrs) but seen in all age groups including children (25% to 35% of NHL in children)  
   • usually presents as rapidly growing single mass, nodal or extranodal (GI tract, Waldeyer’s ring, skin) | Large lymphoid cells (large round or multilobed vesicular nuclei and scant or moderate amounts of cytoplasm) admixed with significant numbers of small lymphocytes (cleaved or round); necrosis or sclerosis may be present |
| Large cell lymphoma (intermediate grade)           | • 50% are stage III or IV (liver, spleen involvement)                                                | Large cells predominate: necrosis or sclerosis may be present                              |
| Large cell immunoblastic (B cell) lymphoma (high grade ?) | • bone marrow involvement; <15%  
   • respond well to aggressive therapy with overall survival rate of about 60% | Immunoblasts (large round or oval nuclei with prominent central nucleolus and abundant cytoplasm); sclerosis less common |

1. >95% are CD45+  
6. 65% of cases express surface immunoglobulins, and nearly all cases have clonal immunoglobulin heavy and light chain gene rearrangements.  
7. 25% of cases exhibit a bcl-6 rearrangements  
8. 30% of cases show a t(14:18) – usually seen when there was a previous follicular lymphoma

#### Hematology #12  
**Hodgkin’s Disease (Nodular sclerosis type)** 1

**Lymph node. Hematoxylin & eosin stain. X12.** At low magnification, large bands of collagen can be seen surrounding several cellular nodules. Notice the large cells with clear halos (lacunar cells) which are variants of Reed-Sternberg cells.

**Lymph node. Hematoxylin & eosin stain. X100.** The nodules have admixed cell population consisting of lymphocytes, eosinophils, histiocytes, and lacunar cells (multilobed nucleus, prominent nucleoli, and a surrounding clear space). Plasma cells and neutrophils may also be seen in the nodular sclerosis form of Hodgkin’s disease, but they are not prominent in this image.

#### Hematology #13  
**Hodgkin’s Disease (Nodular sclerosis type)** 2

**Spleen.** Multiple tumor nodules diffusely infiltrate the spleen in a case of nodular sclerosing Hodgkin’s disease. Hodgkin’s disease appears to spread, from its original site, mainly through lymphatic channels to adjacent lymphoid structures. Involvement of the spleen is thought to facilitate hematogenous dissemination.
Hematology #14 Hodgkin’s Disease (Mixed cellularity type)

Lymph node. Hematoxylin & eosin stain. X12. A mixed cellular background with minimal fibrosis can be seen in this photomicrograph.

Lymph node. Hematoxylin & eosin stain. X100. The mixed cell population consists of lymphocytes, eosinophils, histiocytes, plasma cells, & Reed-Sternberg cells (both the diagnostic type and mononuclear variants). This is the most common type of Hodgkin’s disease seen in AIDS patients.

Hematology #15 Cutaneous T-cell Lymphoma (mycosis fungoides)

Skin. Hematoxylin & eosin stain. X20. A mononuclear cell infiltrate has widened the papillary dermis and extends into the reticular dermis mainly around the vessels. A small microabscess is present in the overlying epidermis which also exhibits epidermal hyperplasia.

Skin. Hematoxylin & eosin stain. X125. The cells in the microabscess show hyperchromatic nuclei and prominent nuclear folding. Known as Sezary-Lutzner cells they are T-helper cells and this collection in the epidermis is called a Pautrier’s microabscess.

Comment: This is one of the forms of peripheral t-cell lymphoma (PTCL) which are malignant lymphomas derived from T lymphocytes. PTCL accounts for less than 15% of diffuse lymphomas in the United States but it is more common in areas where HTLV-1 infection is present (southern Japan, Caribbean, southeastern United States, etc.). Clinical presentation includes lymphadenopathy, skin involvement is common, and most patients are stage III or IV when diagnosed due to bone marrow (many patients are anemic), spleen, liver, or other visceral organ involvement. These are intermediate to high grade lymphomas. The cells usually express T-cell markers CD2, CD3, CD5 and CD4 but not CD7 or CD8. Most will show T-beta receptor gene rearrangements.

Hematology #16 Multiple Myeloma 1

Peripheral blood smear. Wright/Giemsa stain. X252. The increased circulating paraprotein seen in this disease results in the red blood cell clumping (rouleaux formation) apparent in this image.

Bone marrow biopsy. Hematoxylin & eosin stain. X20. The bone marrow is focally hypercellular (decreased fat cells) and there appears to be a mononuclear cell infiltrate.

Bone marrow aspiration. Wright/Giemsa stain. X252. This image of a portion of the patient’s bone marrow shows a single cell population of plasma cells, including a binucleated plasma cell.
Skull X-ray. The skull shows multiple round, sharply defined lytic defects.

Vertebral column. This is a cross-section of several vertebral bodies and the intervening intervertebral discs. Several dark red gelatinous nodules are present, representing the site of the lytic defects seen radiographically.

Comment: although most patients with multiple myeloma have hypergammaglobulinemia with evidence of a monoclonal protein, approximately 20% of patients are hypogammaglobulinemic and the monoclonal protein is present only in urine as free light chains (Bence-Jones protein). The differentiation of polyclonal gammaglobulinemia from a monoclonal gammopathy is usually determined by serum protein electrophoresis (SPE), where a sharp peak in the beta, pregamma, or gamma region suggests the presence of a monoclonal protein. If the SPE pattern is suggestive of a monoclonal protein, immunoelectrophoresis (IEP) or immunofixation (IEF) is performed allowing actual identification of the heavy and light chain components.
without a germinal center. This is from a lacerated spleen removed following a motor vehicle accident. The sinusoids in the red pulp are open, slightly congested, lined by endothelial cells and some contain white blood cells. Several penicilliary arterioles with their surrounding cuffs of lymphocytes are present.

**Hematology #19**  
**Congestive Splenomegaly**

**Spleen. Hematoxylin & eosin stain. X125.** This is a fairly early stage of congestive splenomegaly showing large numbers of red cells in the red pulp and only minimal widening of the sinusoidal walls.

**Hematology #20**  
**Idiopathic Thrombocytopenic Purpura (ITP)**

**Spleen. Hematoxylin & eosin stain. X12.** This low power photomicrograph shows widening of the white pulp by large germinal centers within which are tingible body macrophages (i.e. the “holes” apparent at this power). Both of these secondary follicles also show expansion of the marginal zones which lie immediately peripheral to the mantle zones.

**Hematology #21**  
**Hairy Cell Leukemia 1**

**Peripheral blood smear. Wright/Giemsa stain. X252.** In order to illustrate several of the characteristic cells of this disease, this image is taken from a thicker part of the smear. Two hairy cells can be seen, one with a round nucleus and one with a indented nucleus, and both with moderately abundant, pale gray cytoplasm having distinct projections.

**Bone marrow biopsy. Hematoxylin & eosin stain. X100.** The bone marrow is loosely, but diffusely infiltrated by a mononuclear cell population (medium-sized lymphoid cells). Normal hematopoietic cells are nearly absent. Although not easily seen in this image, reticulin and collagen fibers are increased in number, and in many cases are markedly so leading to a “dry tap” when one attempts a bone marrow aspiration.

**Hematology #22**  
**Hairy Cell Leukemia 2**

**Spleen. Hematoxylin & eosin stain. X31.** More than any other leukemic disorder involving the spleen, hairy cell leukemia results in a characteristic histologic picture. The normal white pulp around the trabecular vessel near one edge of the image has been replaced for the most part by hairy cells with only a few residual darker-staining lymphocytes apparent. The leukemic cells diffusely infiltrate the red pulp often resulting in venous lakes (pseudosinuses) because of the replacement of the normal splenic sinus lining cells by hairy cells.

**Spleen. Hematoxylin & eosin stain. X100.** At higher magnification, the leukemic cells infiltrating the cords and sinuses are seen as fairly uniform in size with moderately abundant cytoplasm and oval or convoluted nuclei having indistinct nucleoli. The
pseudosinuses mentioned above can also be seen in the image. Mitotic activity is almost never seen in this disease.

**Comment:** Hairy cell leukemia is a B-cell disease of adults (median age 50 years) with a male:female ratio of 5:1. The presenting complaints are weakness and fatigue with the clinical findings including splenomegaly in almost all cases (often massive), and one or more cytopenias (thrombocytopenia (50% of cases), neutropenia (80% of cases), normocytic, normochromic anemia (most cases)) due to bone marrow and splenic involvement. The clinical course is complicated by recurrent infections, many due to Gram-negative organisms. Infections with fungal organisms and atypical mycobacteria are not uncommon. The hairy cells express CD19, CD20, PCA-1 (plasma cell associated antigen), and usually CD11c (monocyte-associated antigen) as well as CD25 (IL-2 receptor). It has been also shown that most hairy cells contain surface membrane immunoglobulin with a single light chain and the cells contain a tartrate-resistant isozyme of acid phosphatase, which is the basis for a laboratory test (i.e. TRAP stain).

**Hematology #23**

**AIDS**

**Lymph node. Hematoxylin & eosin stain. X31.** This photomicrograph illustrates the changes seen in the later stages of AIDS. The node is hypocellular with marked depletion of lymphocytes not only in the mantle zone and paracortex, but also in the germinal centers (one of which here shows partial hyalinization). Vasculature is increased and usually associated with immunoblasts and plasma cells. This picture is in marked contrast to the lymph nodes earlier in the course of this disease when lymphadenopathy is usually present because of marked follicular and paracortical hyperplasia.
Week 9
Monday, October 11
1-4 PM Independent Study

Tuesday, October 12
1-2 PM Journal Club/Epi/Bio Consult Laboratory-Room N12

Friday, October 15
1-4 PM Path Talk Laboratory

Week 11
Friday, October 29
9-10 AM Gross Presentation West Lecture Hall
10-11:15 AM Summary West Lecture Hall
11:15-12 Noon Journal club/Epi-Bio Consult Laboratory-Room N12
Week 9-11: October 11-29
Cardiovascular System

Assignments

Topic: The Cardiovascular System

Required Reading:

*Robbins’ Pathologic Basis of Disease, 6th Edition,*
- Blood Vessels: Chapter 12, pp. 493-540
- The Heart: Chapter 13, pp. 543-598

Required Study for Small Groups

**PathTalk**
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club article:
  - *Understanding Diastolic Heart Failure,* Margaret M. Redfield, M.D., Volume 350: 1930-1931, May 6, 2004

**Case-Based Study**
Assignments:
- No printed cases. Prepare for Integrated Course Case in Hematology.

**Case-Based Study**
Required reading:

Laboratory evaluation of acute myocardial infarction:
- pp. 535-545: Indicators of cardiac injury

Renal function:
- pp. 453-456: Urea and creatinine

Lipids:
- pp. 468-472: Metabolism
- pp. 478-480: Clinical considerations
Cardiovascular Diseases #1  Fatty Streak

**Aorta. Hematoxylin & eosin stain. X31.** This is a cross-section of a raised yellow area in the aorta of a young woman. In the elevated area on the left of the image, a pale band with indistinct cells and amorphous material is apparent between the intimal surface at the top and the tunica media below. This is the tunica intima that has been widened by lipid-containing smooth muscle cells and interstitial lipid.

Cardiovascular Diseases #2  Normal Coronary Artery

**Coronary artery. Hematoxylin & eosin stain. X12.** This is a cross-section of a normal coronary artery from a young girl. The coronary artery is an example one of the larger muscular arteries of the body. The tunica intima consists of the endothelial cell layer, the subendothelial connective tissue lying between the basal lamina of the endothelial cells and the internal elastic lamina. The tunica media consists of smooth muscle cells, a glycoprotein interstitium, and collagenous and elastic fibers. Between the media and the tunica adventitia (loose connective tissue containing nerves, vasa vasorum and again collagenous and elastic fibers) is a poorly defined external elastic lamina.

Cardiovascular Diseases #3  Atherosclerosis

**Coronary artery. Hematoxylin & eosin. X8.** The histologic features of an atherosclerotic plaque are illustrated in this photomicrograph of a coronary artery. The lumen of the artery is markedly narrowed by a well-formed plaque containing a prominent fibrous cap and central lipid core. Note the thinning of the medial wall of the artery beneath the plaque.

Cardiovascular Diseases #4  Atherosclerosis 2

**Coronary artery. Hematoxylin & eosin stain . X31. [left image].** This is another view of the same artery as seen in the previous image. In the central lipid core, foam cells and areas of calcification are present, and immediately exterior to this is an area of fibrosis with leukocytes and macrophages.

**Coronary artery. Elastic stain. X31. [right image].** The elastic stain shows the destruction of the internal elastic lamina and thinning of the media by the overlying plaque. In this section of the artery, leukocytes and macrophages are more abundant.

Cardiovascular Diseases #5  Arteriosclerosis

**Splenic arteriole. Hematoxylin & eosin stain. X78. [left image].** The normal arteriole consists of tunica intima with a layer of flattened endothelial cells, a tunica media with one to three layers of smooth muscle cells and a tunica adventitia containing fibroblasts admixed with collagen and elastic fibers.
Splenic arteriole. Hematoxylin & eosin stain. X31. [right image]. Hyaline arteriosclerosis is shown in this photomicrograph. Histologically, the wall of the arteriole is thickened by a homogeneous, glassy pink band in the subendothelium. It is composed in part of plasma proteins (complement components, etc.), thickened and duplicated endothelial basement membrane and increased extracellular material. Hyaline arteriosclerosis can be seen as a normal physiologic feature of aging, in hypertensive disease and is commonly found in patients with diabetes mellitus.

Cardiovascular Diseases #6  Hypertensive Arteriosclerosis

Soft tissue. Hematoxylin & eosin stain. X78. This is an example of hypertensive arteriosclerosis in a small artery showing hyperplastic (proliferative) changes and fibrinoid necrosis. The intima is thickened by a loose collection of cells (modified smooth muscle cells) and extracellular material (probably proteoglycans). The fibrinoid necrosis is seen here as the amorphous eosinophilic material containing some red blood cells and cellular debris in the center of the vessel. It can be found in small arteries and arterioles in addition to the hyperplastic or hyaline changes described above and often results in further narrowing the lumen. Medial hypertrophy is also present. The pathogenesis is most likely endothelial injury with plasma components entering the intima and stimulating a response that includes migration of smooth muscle cells from the media and fibrosis. While in large and medium-sized arteries medial hypertrophy is the classic finding of hypertension, in smaller arteries and arterioles intimal thickening is the predominant finding (hyaline or hyperplastic change).

Cardiovascular Diseases #7  Giant Cell Arteritis

Artery. Hematoxylin & eosin stain. X32. A 78-year-old woman presented with severe headaches and bitemporal subcutaneous nodules. A biopsy reveals intense inflammation of the arterial wall mainly by lymphocytes and macrophages. There is partial disruption of the internal elastic lamina and focal fibrinoid necrosis is present. Note the giant cell. This is granulomatous arteritis that affects the aorta and its major branches, is found after the age of 50, and over one-half of the patients develop polymyalgia rheumatica (stiffness and aching of the neck, shoulder and hips).

Cardiovascular Diseases #8  Takayasu’s Arteritis

Artery. Hematoxylin & eosin stain. X20. A 27-year-old female presented with hypertension, congestive heart failure, and visual defects. Nine years previously she had a systemic illness characterized by fever, anorexia, malaise, weight loss, arthralgias, pleuritic pain and tenderness over her radial arteries. Physical examination showed early cataract formation and diminished radial pulses. This is a case of Takayasu’s arteritis (pulseless disease or aortic arch syndrome), an inflammatory disorder of the aortic arch and its major branches that almost always occurs in patients under the age of 50. Illustrated is a portion of a large artery showing luminal narrowing from medial fibrosis and intimal thickening. The internal elastic lamina is easily seen and helps to identify the thickened tunica intima.
Week 9-11: October 11-29
Cardiovascular System

Cardiovascular Diseases #9    Polyarteritis nodosa

Artery. Hematoxylin & eosin stain. X50. This is a portion of the mesenteric artery in an adult man who presented with fever and abdominal pain. Necrotizing transmural inflammation is present along with fibrin deposition. The predominant cell is the neutrophil and there is considerable nuclear debris from neutrophil karyorrhexis.

Cardiovascular Disease #10    Thromboangiitis obliterans

Artery. Hematoxylin & eosin stain. X50. During the winter a 30-year-old male smoker complained of pain in his right instep following exercise with discoloration of his toes and fingers. The characteristic lesion of Berger’s disease is segmental thrombotic occlusion, with neutrophilic microabscesses, in the medium-sized arteries, and sometimes veins, of the upper and lower extremities. As the lesion ages, mononuclear cells replace the neutrophils. The thrombus undergoes organization, fibroblasts proliferate in the intima and in the thrombus, and proliferating blood vessels fill the lumen as seen here.

Cardiovascular Diseases #11    Wegener’s Granulomatosis

Lung. Hematoxylin & eosin stain. X31. The hallmark of Wegener’s granulomatosis (WG) is necrotizing granulomatous inflammation as seen here in the lung. Scattered multinucleated giant cells and a loose collection of neutrophils and mononuclear cells are present. Organizing fibrosis can also be seen in this disease.

Antinuclear Cytoplasmic Antibodies (ANCA) and Vasculitis

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigenic specificity</th>
<th>Associated Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoplasmic ANCA (c-ANCA)</td>
<td>Proteinase 3 (PR-3) a neutral serine protease found in the 10th granules of neutrophils and monocyte lysosomes</td>
<td>Found in 90% of patients with active (WG); microscopic polyangiitis1;</td>
</tr>
<tr>
<td>Perinuclear ANCA (p-ANCA)</td>
<td>Myeloperoxidase; other neutrophil cytoplasmic enzymes (elastase, cathepsin G, etc.)</td>
<td>Found in &lt; 5% of patients with WG; microscopic polyangiitis1; active Churg-Strauss syndrome; polyarteritis nodosa (when patients with small vessel disease are included)</td>
</tr>
</tbody>
</table>

1. More than 80% of patients with microscopic polyangiitis have c-ANCA or p-ANCA

Cardiovascular Diseases #12    Normal Aorta

Aorta. Hematoxylin & eosin stain. X12. This is an essentially normal aorta. The tunica intima does not appear to be thickened, the tunica media is broad and the tunica adventitia contains collagen (bright red in image) and the vasa vasorum.
Cardiovascular Diseases #13  Aortic Dissection

Aorta. Elastic stain. X8. Note the rich elastic network of the inner and middle thirds of the aorta. As one approaches the tunica adventitia, the elastic fibers appear disorganized and even absent in some areas. The elastic stain allows us to clearly see the widened tunica intima.

Cardiovascular Diseases #14  Hemangioma

Soft tissue, Hematoxylin & eosin stain. X5. [left image]. A four-month-old male was noted to have a slowly enlarging mass in the left neck. Scattered throughout the soft tissue are irregular spaces filled with cellular nodules.

Soft tissue. Hematoxylin & eosin stain. X78. [right image]. The nodules are composed of numerous small capillaries some of which are filled with blood. This is and example of a capillary hemangioma.

Cardiovascular Diseases #15  Kaposi’s Sarcoma

Skin. Hematoxylin & eosin stain. X50. [top image]. This is a case of Kaposi’s sarcoma in a homosexual AIDS patient. The tumor fills the dermis and contains numerous slit-like spaces and extravasated red blood cells. Scattered mononuclear inflammatory cells are present, mainly near the edge of the tumor.

Skin. Hematoxylin & eosin stain. X125. [bottom image]. The spindle cell nature of the cells and the extravasated erythrocytes are clearly seen in this photomicrograph. Note the mitotic figure.

Cardiovascular Diseases #16  Myocardial Infarction/Mural Thrombus

Heart. Gross photo. [top image]. You are looking at the wall of the interventricular septum which has been divided and laid open. The mottled yellow and red appearance of the myocardium is indicative of a recent myocardial infarction. Myocardial infarcts usually become yellow by the 3rd day following the infarction.

Heart. Gross photo. [bottom image]. This photograph shows the opened left ventricle. Several large, blackish-red thrombi are adhering to the endocardial surface over the areas of infarction.

Cardiovascular Diseases #17  Myocardial Infarction 1

Myocardium. Hematoxylin & eosin stain. X78. [left image]. This patient died 3 days following an acute thrombosis of the left anterior descending coronary artery. In this image the myocardial fibers appear smudgy with loss of cross-striations and focal hypereosinophilia. These changes which were found in a portion of his infarct can be seen about 24 hours after the infarction.
Myocardium. Hematoxylin & eosin stain. X78, [right image]. Another area of the myocardium from the above individual shows a heavy neutrophilic infiltrate with partial dissolution of the fibers. Neutrophilic infiltration is usually heaviest at 2 to 3 days after the infarction.

Cardiovascular Diseases #18  Myocardial Infarction 2

Myocardium. Hematoxylin & eosin stain. X78. [left image]. In another patient who died 1 day following a myocardial infarction, the myocardial fibers again show coagulative necrosis, but appear thinned and “wavy” Neutrophils and edema fluid are present in the interstitium.

Myocardium. Hematoxylin & eosin stain. X78. [right image]. This patient died about 1 week following the infarction. The necrotic myocytes are now being removed by phagocytosis.

Cardiovascular Diseases #19  Myocardial Infarction 3

Myocardium. Hematoxylin & eosin stain. X50. This is a well-healed myocardial infarction of at least 7 weeks of age. Dense fibrosis has replaced the necrotic myocytes.

Cardiovascular diseases #20  Valvulitis

Aortic valve. Gross photo [left image]. This is an example of degenerative calcific aortic valve stenosis with calcified nodules in the sinuses of Valsalva. The valve cusps are not fused but are somewhat thickened.

Mitral valve. Gross photo [right image]. In a patient with rheumatic heart disease the mitral valve cusps are markedly thickened by fibrosis and deposits of dystrophic calcification. Note the “fishmouth” appearance. Rheumatic fever was the most common cause of mitral valve stenosis.

Cardiovascular Diseases #21  Rheumatic Myocarditis

Myocardium. Hematoxylin & eosin stain. [left image]. In active rheumatic myocarditis, focal perivascular collections of inflammatory cells can be found in the interstitium. Known as Aschoff bodies they are composed of lymphocytes, macrophages, plasma cells and Anitschkow cells (“caterpillar cells”) arranged around an area of fibrinoid necrosis.

Myocardium. Hematoxylin & eosin. X125. [right image]. Antischkow cells (Aschoff cells) are histocytes in which the chromatin forms a thin, sometimes wavy line in the nucleus. One of these “caterpillar cells” can be seen in this image.
Cardiovascular Diseases #22

Endocarditis 1

Aortic Valve. Gross photo [left image]. Reddish-tan nodules are present on the cusps of the aortic valve. This is an example of nonbacterial, thrombotic endocarditis which is found in patients with cachexia and chronic diseases (this patient died of disseminated colon carcinoma). It can involve all four valves although the mitral valve is involved the most. Complications include embolization with distant infarctions and the secondary infection of the vegetations.

Mitral valve. Gross photo [right image]. A large, friable vegetation is present on one of the leaflets of the mitral valve.

Cardiovascular Diseases #23

Endocarditis 2

Mitral valve. Hematoxylin & eosin stain. X12. A portion of one of the vegetations is seen here. It is composed of fibrin, platelets, neutrophils, and Gram-positive bacilli. On culture the organism was identified as Staphylococcus aureus. Note in inflammation of the endocardium. Major complications of infective endocarditis include septic embolization leading to lung, cerebral, and other organ abscesses, septicemia, arterial occlusions and infarcts, and direct damage to the heart.

Cardiovascular Diseases #24

Bacterial Myocarditis

Myocardium. Hematoxylin & eosin stain. X 125. Not many normal cardiac muscle fibers are seen in this image. The photomicrograph shows fatty infiltration of myocytes, myocyte necrosis and a mixed inflammatory cell infiltrate. The myocardial damage seen here was due to a protein synthesis inhibiting toxin released from a bacillus, Corynebacterium diphtheriae. Myocarditis occurs in about 20% of diphtheria cases and is the most common cause of death in this disease.

Cardiovascular Diseases #25

Viral Myocarditis

Myocardium. Hematoxylin & eosin stain. X125. This photomicrograph shows a mixed inflammatory cell infiltrate (predominantly mononuclear cells) in the myocardium with focal myocyte necrosis. This is an example of myocarditis due to Coxsackie B virus (an enterovirus (Family Picornaviridae – single stranded RNA Viruses)). While most infections caused by this organism are benign and self-limited, myocarditis due to Coxsackie virus that occurs in the neonate can be fatal. Coxsackie A virus may also produce myocarditis, but not a frequently.

Cardiovascular Diseases #26

Cardiac Myxoma

Myocardium. Hematoxylin & eosin stain. X50. The most common primary cardiac tumor found in adults is the cardiac myxoma usually found in the atria. Within a background of abundant, pale, eosinophilic myxoid material (rich in acid mucopolysaccharide) we can see a number of polygonal, and sometimes stellate, myxoma cells. By electron microscopy, these myxoma cells share features with
multipotential mesenchymal cells. Macrophages and lymphocytes are also present. Systemic symptoms such as headache, syncope, fever, and dysarthria are sometimes seen along with elevated serum levels of C-reactive protein, gammaglobulins and interleukin-6 (IL-6) a cytokine involved in lymphocyte growth and immunoglobulin synthesis.
Week 13-14: November 8-19
Respiratory System

Schedule

Week 13
Monday, November 8
1-4 PM PathTalk Laboratory

Thursday, November 11
10:30-12 Noon Integrated Case: Cardiovascular TBA

Friday, November 12
1-4 PM Independent Study

Monday, November 15
1-2 PM Gross Presentation West Lecture Hall
2-4 PM Summary West Lecture Hall
Topic: The Respiratory System

Required Reading:

*Robbins’ Pathologic Basis of Disease, 6th Edition,*
- The Lung, Chapter 16, pp. 697–753
- Respiratory Distress Syndrome in Newborn (for review only), Chapter 11: pp. 471-473

Required Study for Small Groups

**PathTalk**
**Assignments:**
- Kodachromes on WebCt
- Slide descriptions
- Journal club article:
  - *A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis,* G. Raghu, M.D. and Others Volume 350: 125-133, January 8, 2004

**Case-Based Study**
**Assignments:**
- No printed case. Prepare for Integrated Course Case in pulmonary medicine.

**Case-Based Study**
**Required reading:** *Widmann’s Clinical Interpretation of Laboratory Tests*

Asthma:
- pp. 339-340: Allergy/hypersensitivity
- pp. 362-363: Allergy testing
Pulmonary Pathology

Pulmonary #1 Normal Lung

Lung. Hematoxylin & eosin stain. X50. The normal lung shows delicate alveolar septa and empty alveoli. The cellular composition of the septa is not easily apparent in hematoxylin & eosin stained sections of paraffin-embedded lung tissue. Note the alveolar capillaries within the septal walls.

Pulmonary #2 Pulmonary Edema

Lung. Hematoxylin & eosin stain. X20. This photomicrograph illustrates a portion of the lung from a patient with left-sided congestive heart failure. The main factor in the development of edema in this patient was increased hydrostatic pressure in the pulmonary capillary bed due to a sudden elevation in the pulmonary venous pressure because of left ventricular failure. Grossly the lungs were heavy, wet and exuded large amounts of frothy fluid during sectioning. The alveolar blood vessels are relatively inconspicuous but the alveoli are filled with pale-staining eosinophilic fluid containing fibrin strands and scattered erythrocytes. The interlobular septa seen in the upper left corner of the image is widened, containing several lymphatics distended with fluid. It is the widened interlobular septa that are responsible for Kerley’s lines seen in radiographs of the chest in patients with pulmonary edema.

Pulmonary #3 Diffuse Alveolar Damage

Lung. Hematoxylin & eosin stain. X32. This is a young adult male who developed acute respiratory distress following an upper respiratory viral illness. Several days after the onset of respiratory distress, a lung biopsy was performed and is illustrated with this photomicrograph. Most apparent are the widened alveolar septa due to an influx of fibroblasts and extracellular matrix (fibronectin, collagen fibrils, etc.) and various inflammatory cells such as neutrophils and monocytes. Hyaline membranes and intra-alveolar fibrin deposits are present and represent the remnants of the edema fluid that was initially present and the sloughed necrotic epithelial lining cells of the alveolar walls. Indeed some cellular debris can still be seen in some of the alveoli. Type II pneumocytes are focally prominent as they spread over the denuded alveolar walls.

Comment: Diffuse alveolar damage results from damage to the alveolar capillary endothelium and epithelium and has a number of etiologies. It is the histologic manifestation of the adult respiratory distress syndrome (ARDS), a condition clinically manifest as shortness of breath, tachypnea, cyanosis, hypoxemia, normal pulmonary artery wedge pressure and diffuse lung infiltrates on a chest radiograph. About one-half of the patients with ARDS will subsequently die of the condition, but the initiating cause and the underlying health of the patient will influence this figure.
**Pulmonary #4**  
**Pulmonary Embolus /Infarction 1**

*Lung. Gross photo.* This cross-section of the right lower lobe of lung shows an embolus in a branch of the pulmonary artery and a wedge-shaped area of infarction in the lung parenchyma. The patient was a 58-year-old male who had a recent myocardial infarction and developed large mural thrombi in the right atrium and left ventricle which resulted in multiple pulmonary emboli. Only about 15% of pulmonary emboli result in pulmonary infarction with the major risk factors being multiple emboli, general debilitation and heart failure.

**Pulmonary #5**  
**Pulmonary Embolus/Infarction 2**

*Lung. Hematoxylin & eosin stain. X2.* This photomicrograph is from the same patient as seen above and shows a portion of thrombosed vessel surrounded by alveoli filled with blood.

**Pulmonary #6**  
**Pulmonary Embolus/Infarction 3**

*Lung. Hematoxylin & eosin stain. X3.* This is from another patient and shows a later stage of a pulmonary infarction. The paleness of the erythrocytes in the alveoli reflects their loss of hemoglobin, the septa are homogeneous and lack detail because of the loss of nuclei, and the periphery of infarction is now well-defined due to the accumulation of fibroblasts. Note the pleural surface and the organization of the embolus in the vessel.

**General Blood Gas Patterns in Various Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arterial Po₂</th>
<th>Acid-Base Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolus</td>
<td>Hypoxemia</td>
<td>Respiratory alkalosis from hyperventilation (Pco₂ usually normal)</td>
</tr>
<tr>
<td>ARDS</td>
<td>Hypoxemia</td>
<td>Respiratory alkalosis eventually leading to metabolic acidosis and then respiratory acidosis (Pco₂ increased)</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>Usually normal; Hypoxemia if pneumonia severe</td>
<td>Acid-base disorder not usually found; respiratory acidosis with CO₂ retention if pneumonia severe</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>Hypoxemia</td>
<td>May lead to metabolic acidosis; with CO₂ retention may get respiratory acidosis as well</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Hypoxemia</td>
<td>Pink-puffer syndrome (panacinar emphysema); respiratory alkalosis due to tachypnea – can lead to respiratory acidosis. Blue-bloater syndrome (centriacinar emphysema); CO₂ retention and respiratory acidosis; eventually metabolic acidosis develops.</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Hypoxemia</td>
<td>Metabolic acidosis (Pco₂ usually normal)</td>
</tr>
</tbody>
</table>

1. Wide variations in acid-base findings are often found in these conditions.
**Pulmonary #7**  Chronic Obstructive Pulmonary Disease

**Lung. Unstained thin section [left image].** This is an example of centriacinar emphysema, a form of emphysema which initially involves the respiratory bronchioles and is seen in patients with chronic bronchitis and in smokers. Note that many of the holes are separated from the perilobular septa by a band of normal tissue.

**Lung. Unstained thin section [right image].** The main feature of this section is the subpleural bullae seen as the cystic areas near the top of the image. They may be associated with any of the forms of emphysema or may be found in otherwise normal lungs. They may lead to spontaneous pneumothorax (especially in young adults with otherwise normal lungs) or if very extensive can compress the remaining lung. This patient’s emphysema is too severe to be sure as to its type. In fact it is not unusual to find more than one type of emphysema in a particular lung or to be unable to classify the emphysema as to whether it is centriacinar or panacinar. In such cases, one usually calls it mixed or unclassified emphysema.

**Pulmonary #8**  Bacterial Pneumonia

**Lung. Hematoxylin & eosin stain. X20. [left image].** Large areas of the lungs were similar to this image with congested alveolar capillaries and alveoli filled with neutrophils.

**Lung. Gram stain. X197. [right image].** In some parts of the lungs, groups of Gram-positive cocci were present that were subsequently identified by culture as *Staphylococcus aureus*.

**Pulmonary #9**  Pulmonary Abscess

**Lung. Hematoxylin & eosin stain. X5.** This is a photomicrograph of an abscess from another patient, actually a young boy with chronic granulomatous disease, and inherited disorder in which oxygen-dependent mechanism for bacterial killing are deficient. The alveolar tissue in the center of the abscess has been destroyed and replaced by a large mass of necrotic debris and neutrophils. The edge of the abscess contains fibroblasts and a prominent vasculature. Some of the alveoli surrounding the abscess contain an inflammatory exudate.
Selected Comments on Certain Bacterial Pneumonias

<table>
<thead>
<tr>
<th>Organism</th>
<th>Route of Infection</th>
<th>Pathology</th>
<th>Clinical Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Aspiration from upper airway colonization.</td>
<td>Lobar or bronchopneumonia Necrosis not usually found (except for type 3); usually resolves.</td>
<td>A common cause of community-acquired pneumonia. High-risk groups: alcoholics, HIV patients, the very young or old, splenectomized patients, etc.</td>
</tr>
<tr>
<td>Pseudomonas Aeruginosa</td>
<td>Aspiration or hematogenous.</td>
<td>Confluent bronchopneumonia in aspiration. Foci of coagulative necrosis (due to bacterial toxins).</td>
<td>High risk groups; Aspiration: ventilator patients; mortality near 50%. Hematogenous: patients with leukopenia or burns; mortality approaches 100%.</td>
</tr>
</tbody>
</table>

Pulmonary #10

Adenovirus Pneumonia

**Lung. Hematoxylin & eosin stain. X125.** An interstitial pneumonitis is present with hemorrhage and widened septa containing various inflammatory cells, including neutrophils. Eosinophilic “smudge” cells with indistinct nuclear-cytoplasmic separation line portions of the alveoli. Several nuclei show an intranuclear inclusion in a vacuolated nucleoplasm. Other areas of the lung showed a necrotizing bronchiolitis and peribronchiolitis.

**Comment:** The adenovirus family of double-stranded DNA viruses are the causative agents of a number of illnesses including upper respiratory infections, Pneumonia, conjunctivitis, hemorrhagic cystitis, meningo-encephalitis, and enteritis. The great majority of respiratory infections due to adenovirus are self-limited with severe pneumonia usually being seen in neonates or immunocompromised hosts. Up to 25% of respiratory illnesses in children are due to adenovirus.
Pulmonary #11  Pulmonary Tuberculosis

Lung. Hematoxylin & eosin stain. X20. In the typical granuloma of tuberculosis (tubercle), one finds a core of caseous necrosis and a thick rim of lymphocytes and epithelioid histiocytes often containing multinucleated giant cells. The tubercle is surrounded by fibroblasts. Formation of this lesion is dependent on the immunocompetence of the host.

Pulmonary #12  Pulmonary Aspergillosis

Lung. Gross photo [left image]. Multiple grayish-yellow nodules, some of which are unbilicated, are present on the pleural surface of this lung.

Lung. Gomori’s methenamine silver (GMS) stain. X5 [right image]. Scattered throughout the pulmonary parenchyma were numerous necrotic nodules showing radiating masses of fungal hyphae. The nodules are surrounded by areas of pulmonary hemorrhage. This is a case of pulmonary aspergillosis due to *Aspergillus fumigatus*, and is from a patient being treated with chemotherapy for widespread non-Hodgkin’s lymphoma. *Aspergillus* species, which are found throughout the world, cause a wide spectrum of diseases including indolent superficial infections of the skin, allergic bronchopulmonary disease, systemic disseminated aspergillosis, etc. Host immunocompetence plays a major role in the expression of the disease.

Pulmonary #13  Pulmonary Fibrosis

Lung. Masson trichrome stain. X5. This is an example of late stage diffuse interstitial lung disease showing extensive areas of architectural destruction due to markedly thickened alveolar walls and loss of alveoli. The term for this histologic picture is honeycomb lung. At higher magnification we would see that the widened septa contains fibroblasts, collagen and some inflammatory cells. Also observed would be bronchiolar metaplasia and focal hyperplasia of alveolar lining cells.

Comment: The cause of the fibrosis in this patient was unknown, as it is in a number of patients with this disease, but diffuse interstitial lung disease has been associated with a number of conditions in which a specific agent can be implicated: various drugs, infections, and occupational and environmental agents.

Pulmonary #14  Chronic Silicosis

Lung. Hematoxylin & eosin stain. X32. This is a silicotic nodule from a coal miner. It contains a central core of dense collagen having a whorled pattern, an intermediate area of concentrically arranged collagen fibers, and at the periphery a collection of carbon-laden macrophages and lymphocytes. Carbon pigment is also scattered throughout the nodule.
**Comment:** Pneumoconiosis is the reaction of the lung (non-neoplastic) to the accumulation of inhaled dust, principally mineral dusts. Pathogenic mineral dusts include asbestos, silicon dioxide, mica, talc, kaolinite, etc. Carbon, by itself, is non-fibrogenic, but coal is a complex structure and contains a number of inorganic and organic compounds some of which are fibrogenic. In addition to the fibrogenic compounds within coal, deposits of silica are often found along with coal and thus miners are also routinely exposed to silicon dioxide, which as noted above is highly fibrogenic.

**Pulmonary #15**  
**Asbestosis 1**

*Lung. Hematoxylin & eosin stain. X125.* These two images illustrate a number of asbestos bodies and pigmented macrophages. The segmented bodies, which can be seen within macrophages and multinucleated giant cells, most probably have a central amphibole asbestos fiber (chrysotile asbestos fibers do not usually form asbestos bodies) covered with a ferroprotein coat. Besides the fibers in asbestos bodies, other uncoated fibers can be found following lung digestion.

**Pulmonary #16**  
**Asbestosis 2**

*Lung. Hematoxylin & eosin stain. X20.* Continued exposure to asbestos can result in massive pulmonary fibrosis as seen here is this photomicrograph from the lower lobe of a patient who previously was a worker in an asbestos factory.

**Pulmonary #17**  
**Asbestos-Pleural Plaques**

*Pleural surface. Gross photo [left image].* Clearly seen are several well-defined, irregular whitish plaques with numerous surface nodules.

*Pleural plaque. Hematoxylin & eosin stain. X50 [right image].* They are made up of dense fibrous tissue with scattered lymphocytes. Asbestos fibers have only occasionally been recovered from these plaques.

**Pulmonary #18**  
**Asbestos-Malignant Mesothelioma**

*Pleura. Hematoxylin & eosin stain. X50.* The histologic pattern of malignant mesothelioma can vary from a purely epithelial tumor resembling adenocarcinoma to a sarcomatous pattern mimicking a soft tissue sarcoma. The most common pattern includes elements of both as seen in this photomicrograph. On the left papillary epithelial structures are present while on the right the spindled cells of the sarcomatous pattern are evident. In over half of the cases of malignant mesothelioma, exposure to asbestos has been documented, usually to commercial amphibole asbestos, which is mined mainly in South Africa but which is no longer commercially imported into the United Stated. The disease has a latency period of at least 20 years and is invariably fatal.
Comment: Besides the above conditions, asbestos exposure has also been associated with benign pleural effusions and with an increased incidence of bronchogenic carcinoma in individuals with asbestosis who also smoke.

Pulmonary #19  Sarcoidosis

Lung. Hematoxylin & eosin stain. X50. Illustrated are several noncaseating granulomas in a lung biopsy from a young man with sarcoidosis. The granulomas are composed of epithelioid histiocytes with occasional lymphocytes and monocytes. Fusion of epithelioid cells results in giant cells (foreign-body or Langhans type) which are common in this disease. As the granulomas heal, they are replaced by fibrous tissue and as large numbers of the granulomas become scarred, interstitial fibrosis may result. Thoracic disease usually presents a bilateral hilar lymphadenopathy and in approximately two-thirds to three-fourths of these patients, the disease will regress without therapy.

Pulmonary #20  Squamous Cell Carcinoma of the Lung 1

Lung. Gross Photo [left image]. An exophytic whitish tumor mass can be seen in the cross-section of the bronchus. It has destroyed the bronchial cartilage and extends into the adjacent lung.

Lung. Hematoxylin & eosin stain. X2.5 [right image]. The intraluminal growth of the tumor is clearly seen in this low-power photomicrograph.

Pulmonary #21  Squamous Cell Carcinoma of the Lung 2

Lung. Hematoxylin & eosin stain. X20. While most of the tumor was poorly differentiated, there were areas such as illustrated here, where the tumor was more differentiated and included the presence of well-developed epidermoid pearls. Squamous cell carcinomas of the lung, which are mostly central in location, account for approximately one-third of all lung tumors and are associated with tobacco smoke.

Pulmonary #22  Adenocarcinoma of the Lung 1

Lung. Hematoxylin & eosin stain. X50. This example of an adenocarcinoma of the lung shows glandular acini as well as some solid areas. Adenocarcinomas comprise about one-third of all lung tumors, are mainly peripheral in location and most patients with these tumors are smokers. However, it is the most common type of bronchogenic carcinoma seen in nonsmokers.

Pulmonary #23  Adenocarcinoma of the Lung 2

Lung. Hematoxylin & eosin stain. X50. A distinct subtype of pulmonary adenocarcinoma is bronchioloalveolar carcinoma of the lung. The alveolar walls and
ducks are lined by malignant cells which can vary from cuboidal to columnar in character.

**Pulmonary #24**  
**Bronchial Carcinoid Tumor**

*Lung. Hematoxylin & eosin stain. X50. [left image].* The tumor is composed of trabeculae of uniform cells with clearly defined cytoplasm, small amounts of stroma and little or no necrosis.

*Lung. Hematoxylin & eosin stain. X125. [right image].* The tumor is composed of trabeculae of uniform cells with clearly defined cytoplasm, small amounts of stroma and little or no necrosis.

**Pulmonary #25**  
**Small Cell Carcinoma of the Lung 1**

*Lung. Gross photo.* A small tannish-white nodule has destroyed a portion of the wall of one of the opened bronchi. Even with this small primary tumor, this patient had metastatic disease to his bone marrow and brain.

**Pulmonary #26**  
**Small Cell Carcinoma of the Lung 2**

*Lung. Hematoxylin & eosin stain. X20. [left image].* Masses of small bluish-stained cells are divided into lobules by a vascular stroma.

*Lung. Hematoxylin & eosin stain. X125. [right image].* The tumor cells show little cytoplasm and exhibit coarsely clumped nuclear chromatin.
## Week 17-18: December 6-17
Gastrointestinal Tract/Hepatobiliary Pathology/Nutrition/Oral Cavity and Related Structures

### Schedule

**Week 17**
**Monday, December 6**
1-2 PM  
Gross Presentation  
West Lecture Hall
2-4 PM  
PathTalk  
Laboratory

**Tuesday, December 7**
1-4 PM  
Independent Study

**Week 18**
**Thursday, December 16**
1-2:30 PM  
Lecture: Oral Cavity & Related Structures  
West Lecture Hall
2:30-3:15 PM  
Summary  
West Lecture Hall
3:15-4:00 PM  
Journal Club/Epi-Bio Consult  
Laboratory-Room N12

**Friday, December 17**
10:30-12 Noon  
Integrated Case: Asthma  
TBA
Week 17-18: December 6-17
Gastrointestinal Tract/Hepatobiliary Pathology/Nutrition/Oral Cavity and Related Structures

Assignments

Topic 1: Gastrointestinal Tract
Required Reading:

Robbins: Pathologic Basis of Disease, 6th Edition,
- Chapter 18, pp. 775-842

Topic 2: Hepatobiliary Pathology
Required Reading:

Robbins: Pathologic Basis of Disease, 6th Edition,
- The Liver: Chapter 19, pp. 845-890
- The Biliary System: Chapter 19, pp. 890-900
- The Exocrine Pancreas: Chapter 20, pp. 902-911

Topic 3: Nutrition
Required Reading:

Robbins: Pathologic Basis of Disease, 6th Edition,
- Chapter 10, pp. 436-456

Topic 4: Pathology of the Oral Cavity and Related Structures
Required Reading:

Robbins’ Pathologic Basis of Disease, 6th Edition
- Head and Neck: Chapter 17, pgs. 756-773

Supplemental Reading:
Schaffer, Hine, Levy: A Textbook of Oral Pathology

Required Study for Small Groups
PathTalk
Assignments:
- Kodachromes on WebCt

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Week 17-18: December 6-17
Gastrointestinal Tract/Hepatobiliary Pathology/Nutrition/Oral Cavity and Related Structures

- Slide descriptions
- Journal club articles:
  - *Closing Fistulas in Crohn's Disease — Should the Accent Be on Maintenance or Safety?*, Claudio Fiocchi, M.D., Volume 350:934-936, February 26, 2004

**Case-Based Study**
Assignments:
- No printed cases. Prepare for Integrated Course Case in gastrointestinal medicine.

**Case-Based Study**
Required reading: *Widmann’s Clinical Interpretation of Laboratory Tests*

Viral hepatitis:
- pp. 419-420: Transfusion associated hepatitis
- pp. 594-595: Hepatitis B and C
- pp. 732-733: Serologic diagnosis
- pp. 563-586: Liver function tests
GI/Liver/Nutrition/Oral Cavity #1    Barrett’s Esophagitis

**Esophagus. Hematoxylin & eosin stain. X32.** This is a biopsy from the lower esophagus of an adult woman with a long history of gastroesophageal reflux. The normal squamous epithelial lining of the esophagus has been replaced by tall columnar cells interspersed with goblet cells. Complications of this disease include esophageal ulceration and stricture and, in about 7% of patients with Barrett’s, the development of esophageal adenocarcinoma.

GI/Liver/Nutrition/Oral Cavity #2    Squamous Cell Carcinoma of the Esophagus

**Esophagus. Hematoxylin & eosin stain. X50.** Most squamous cell carcinomas of the esophagus arise in the middle third of the esophagus and are often polypoid with areas of ulceration and infiltration. This biopsy demonstrates an invasive moderately differentiated tumor from an adult male with a 7-month history of dysphagia. The strongest association for the development of this tumor is with smoking, although alcohol consumption, carcinogens in food, lack of vitamins, etc. have also been mentioned as possible risk factors.

GI/Liver/Nutrition/Oral Cavity #3    Helicobacter Gastritis

**Stomach. Silver stain. X100 [top image].** This photomicrograph demonstrates abundant organisms on the gastric surface and in the gastric pit. Most are in the overlying mucus but some can be seen between some of the mucus cells.

**Stomach. Hematoxylin & eosin stain. [bottom image].** In this example, neutrophils are rare, lymphocytes and plasma cells are predominant and mucosal hemorrhage is present.

GI/Liver/Nutrition/Oral Cavity #4    Esophageal Varices/Gastric Ulcer

**Esophagus & Stomach. Gross photo.** A 53-year-old man with known micronodular cirrhosis due to alcoholism presented with severe gastrointestinal bleeding which was determined to be the result of esophageal varices. This photograph shows a probe in the source of the bleeding: an esophageal varix that had ruptured into the esophageal lumen. Esophageal varices are due to increased portal vein pressure, in this case because the patient’s cirrhosis, which shunts the blood through the gastric coronary veins into the submucosal venous plexuses of the esophagus. It then returns to the heart by way of the azygous vein and the superior vena cava. About one-half of the deaths in patients with cirrhosis are due to ruptured esophageal varices. Also seen in the photograph is a large...
gastric ulcer near the lesser curvature of the stomach. It has sharp, clean edges and the surrounding gastric mucosa is atrophic.

**GI/Liver/Nutrition/Oral Cavity #5 Peptic Ulcer Disease**

**Stomach. Hematoxylin & eosin stain. X2. [left image]**. Although peptic ulcers may occur in any portion of the gastrointestinal tract, over 90% occur in the duodenum and stomach. This is a solitary gastric ulcer showing a base denuded of epithelium and the typical rolled edges at is periphery.

**Duodenum. Hematoxylin & eosin stain. X12. [right image]**. The base of an ulcer, whether it be from the stomach or duodenum, usually shows a mix of fibrin, necrotic debris and inflammatory cells. Depending on the age of the lesion, fibrosis may be present, and one commonly finds inflammation of the underlying vessels.

**Comment:** Infection by *Helicobacter pylori* is a major cause of peptic ulcer disease in patients who are not long-term users of non-steroidal anti-inflammatory drugs. Complications of peptic ulcers include hemorrhage by erosion of an underlying blood vessel, perforation through the bowel wall leading to peritonitis, and pyloric obstruction from edema and fibrosis.

**GI/Liver/Nutrition/Oral Cavity #6 Adenocarcinoma of the Stomach**

**Stomach. Gross photo [left image]**. The stomach has been opened to reveal an atrophic gastric mucosa and a partially necrotic, fungating tumor mass near the lesser curvature.

**Stomach. Gross photo [right image]**. The edge of the mucosal tumor mass can be seen at the top of the photograph. The muscular wall of the stomach is thickened due to its infiltration by tumor.

**GI/Liver/Nutrition/Oral Cavity #7 Adenocarcinoma of the Stomach 2**

**Stomach. Hematoxylin & eosin stain. X20. [top image]**. Several histologic patterns of gastric adenocarcinoma have been described. The papillary pattern seen in this image represents one of the more differentiated types that can be seen and as one would expect is associated with a grossly papillary tumor.

**Stomach. Hematoxylin & eosin stain. X50. [bottom image]**. One of the patterns of poorly differentiated gastric adenocarcinoma is seen in this photomicrograph: the “signet-ring” cell carcinomas. They tend to widely infiltrate the wall of the stomach and the regional lymph nodes. There is increasing evidence for a causal relationship between *Helicobacter pylori* infection, chronic atrophic gastritis, and gastric adenocarcinoma.
**Gi/Liver/Nutrition/Oral Cavity #8**  
**Meckel’s Diverticulum**

**Ileum. Gross photo.** The enterovitelline duct links the yolk sac to the midgut in early human development. In the second trimester, the yolk sac involutes and the duct undergoes atresia. The blind pouch seen here is a remnant of the enterovitelline duct and is known as Meckel’s diverticulum. It is symptomatic in 2% of the cases with the symptoms being similar to those of appendicitis except that the left lower abdominal quadrant is involved instead of the right lower quadrant. The diverticulum may contain ectopic gastric mucosa which can undergo peptic ulceration.

**Gi/Liver/Nutrition/Oral Cavity #9**  
**Pseudomembranous Colitis**

**Colon. Gross photo [left image].** Grossly the plaques appear as cream-colored or greenish flat lesions that are fairly adherent to the mucosal surface.

**Colon. Hematoxylin & eosin stain. X31. [right image].** The plaque is a mixture of fibrin, mucin and neutrophils and arises from the crypts and the intervening surface epithelium. In time the entire mucosa may become destroyed.

**Gi/Liver/Nutrition/Oral Cavity #10**  
**Ulcerative Colitis**

**Colon, Gross photos.** These two photographs illustrate two of the gross appearances of ulcerative colitis, one of the inflammatory bowel diseases (IBD). In the upper image, the mucosa is hemorrhagic and granular with numerous small ulcerations. Note that the entire mucosa is involved. In the lower photograph, extensive inflammatory polyp formation has occurred.

**Gi/Liver/Nutrition/Oral Cavity #11**  
**Ulcerative Colitis 2**

**Colon. Hematoxylin & eosin stain. X50.** In active ulcerative colitis the lamina propria is widened by inflammatory cells containing plasma cells, lymphocytes, macrophages, neutrophils and eosinophils. Infiltration of the crypts and crypt abscess formation, as seen here, is reliable indicator of active disease and expansion of these abscesses leads to destruction of the mucosa and ulceration. During quiescent periods of the disease neutrophils disappear and mononuclear inflammatory cells decrease in amount. Ulcerative colitis is an idiopathic inflammatory disorder affecting the rectum and colon with the disease being continuous in the involved portion of the bowel. The inflammatory infiltrate is usually confined to the mucosa and infrequently penetrates the muscularis mucosa.

**Gi/Liver/Nutrition/Oral Cavity #12**  
**Crohn’s Disease**

**Colon. Gross photo.** Another entity included in the term inflammatory bowel disease is Crohn’s disease, a chronic inflammatory disease involving the terminal ileum and colon and characterized by discontinuous involvement of the affected bowel. Grossly one finds linear ulcerations sometimes in combination with transverse ulcers. The inflammation in this disorder is transmural with lymphoid follicles, often found beneath the ulcers, and granulomas in any layer of the bowel wall. The extensive inflammation of the wall leads to strictures and fistulas.
Diverticular Disease

Colon, Gross photo [top image]. Diverticula are outpouchings of colonic mucosa through the muscularis propria, usually where it is penetrated by arteries which represent an area of weakness in the wall. In this photograph two diverticula penetrate the muscular wall (thick white band in image) of the bowel.

Colon. Gross photo. [bottom image]. The openings of the diverticula are sometimes difficult to appreciate, but several can be seen in this photograph. It is not unusual for them to contain fecal material, become inflamed (diverticulitis) and eventually perforate forming small pericolonic abscesses. Colonic diverticula are more commonly found in the descending and sigmoid colon, although no part of the colon is spared.

Tubulovillous Adenoma/Carcinoma of the Colon

Colon. Hematoxylin & eosin stain. X2. This is a pedunculated tubulovillous adenoma which has developed adenocarcinoma. Note that the stalk is lined by normal epithelium. Adenomas are benign tumors that develop from the epithelium and can be pedunculated, sessile or flat with tubular, villous, or tubulovillous microscopic architecture. The incidence of adenomas of the colon increases with age and by age 75, they can be found in 50% of the population in this country. The larger the adenoma; the greater chance that it contains areas of malignancy. Most evidence suggests that colonic adenocarcinomas arise either in adenomas or areas of dysplasia.

Familial Adenomatous Polyposis

Colon. Gross photo. Multiple sessile polyps can be seen in this photograph of a portion of the large bowel from a young man with familial adenomatous polyposis (FAP). Several of these lesions contained carcinoma and the patient eventually underwent a total colectomy. By 40 years of age nearly all of these patients develop colonic cancer. This is an autosomal dominant disease and is usually associated with neoplasms in other parts of the gastrointestinal tract. Patients with Gardner’s syndrome have FAP as well as extra-intestinal lesions (osteomas, desmoids, epidermal cysts, etc.).

Adenocarcinoma of the Colon

Colon. Hematoxylin & eosin stain. X40. Most colonic adenocarcinomas are moderately or well-differentiated tumors consisting of glands of various sized and shapes. The cells are cuboidal or columnar with a variable mitotic rate. Although not seen here, many colonic adenocarcinomas have a mucinous component, which when it represents over 50% of the tumor indicates a worse prognosis.
Hemorrhoids

Anus. Hematoxylin & eosin. X16. The anal mucosa is seen in the upper right hand portion of the image. At the bottom of the photomicrograph are portions of two dilated veins with evidence of thrombosis. This is an example of external hemorrhoids (those that occur below the dentate line) in which there was an episode of previous bleeding.

Hepatobiliary Pathology

Cholestasis

Liver. Hematoxylin & eosin stain. X125. This is an example of drug-induced cholestasis and cholangiolitis. Besides the presence of bile in many of the hepatocytes, inspissated bile can be seen in several of the bile canaliculi as elongated greenish-brown plugs. The dilated sinusoids contain scattered inflammatory cells. Cholestasis is usually due to one of two major causes: hepatocellular damage or obstruction of biliary flow, either intrahepatic or extrahepatic. It is important to identify extrahepatic obstruction as it may be correctable by surgery. In the jaundiced patient, analysis of the serum enzymes and the forms of plasma bilirubin that are present can often determine the cause of the hyperbilirubinemia.

Hepatic Necrosis

Liver. Hematoxylin & eosin stain. X6. This is a case of submassive zone 3 hepatic necrosis due to halothane anesthesia in a 64-year-old man. It is characterized histologically by necrosis of the centrilobular regions with a minimal inflammatory response. The response to halothane may be acute hepatocellular degeneration with little necrosis, submassive necrosis as seen here or massive necrosis of all acinar zones in large portions of the liver. The list of drugs and toxins that can cause hepatic necrosis is a long one and the host reaction to any one agent may vary from individual to individual.

Acinar Zones of the Liver

<table>
<thead>
<tr>
<th>Designation</th>
<th>Anatomic Location</th>
<th>Function¹</th>
<th>Main Site of Injury in²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1</td>
<td>Area closest to arterial blood supply (most oxygenated); peripheral (“periportal”)</td>
<td>Glycogen synthesis and glycogenolysis; protein formation</td>
<td>Phosphorous poisoning, cocaine, mushrooms, severe viral hepatitis A, etc.</td>
</tr>
<tr>
<td>Zone 2</td>
<td>Reasonably food oxygenated blood supply; area between peripheral and central zone</td>
<td>Similar functions to zones 1 &amp; 3</td>
<td>Yellow fever, acute peritonitis, etc.</td>
</tr>
<tr>
<td>Zone 3</td>
<td>Poorest supply of oxygenated blood; area around central veins; contiguous from one acinus to another</td>
<td>Glycogen storage; lipid and pigment formation; drug and chemical metabolism</td>
<td>Hypoxia, chlorinated hydrocarbons, isoniazid, acetaminophen, diethylene glycol, mushrooms, severe viral hepatitis B, etc.</td>
</tr>
</tbody>
</table>
GI/Liver/Nutrition/Oral Cavity #20  Acute Viral Hepatitis

Liver. Hematoxylin & eosin stain. X125. Ballooned hepatocytes are swollen, have indistinct cell membranes, show clumping of cytoplasmic remnants around the nucleus and many contain intracellular bile stasis. Collections of inflammatory cells and Kupffer cells are present in areas where hepatocytes have undergone lysis and “dropped out”.

GI/Liver/Nutrition/Oral Cavity #21  Chronic Active Hepatitis

Liver. Hematoxylin & eosin stain. X78. Some areas of the limiting plate are poorly defined and scattered hepatocytes are being surrounded by inflammatory cells (“piecemeal necrosis”). Lymphocytes, plasma cells, and some neutrophils are present. Inflammatory cells and necrosis of hepatocytes continues into the lobule and is replaced by fibrosis.

GI/Liver/Nutrition/Oral Cavity #22  Macronodular Cirrhosis

Liver. Hematoxylin & eosin stain. X3. In macronodular cirrhosis, the nodules are large (of ten greater than 3mm in diameter) and usually vary markedly is size. Broad bands of fibrosis can be found. Although this form of cirrhosis is the most common type found in viral hepatitis, drug-induced hepatitis, α1-antitrypsin deficiency, and Wilson’s disease, it can also be mixed with micronodular cirrhosis in the above conditions as well as in alcoholic liver disease.

GI/Liver/Nutrition/Oral Cavity #23  Alcoholic Liver Disease

Liver. Masson trichrome stain. X20. A 57-year-old retired merchant marine seaman with a long history of alcohol abuse presents now with weight loss, abdominal swelling, peripheral edema and fatigue. Examination showed jaundice, spider angiomata and ascites. One of the characteristic histologic findings in alcoholic liver disease is steatosis-the intracellular accumulation of fat. As we have seen in previous images, this not specific for alcohol as it can be found in a wide variety of conditions. In this photomicrograph fatty change is prominent but there is also a micronodular cirrhosis with a moderate portal inflammation. Micronodular cirrhosis can be seen in a number of other conditions including primary biliary cirrhosis, cardiac cirrhosis, glycogenosis (type IV), etc.

GI/Liver/Nutrition/Oral Cavity #24  Hepatic Hemochromatosis

Liver. Hematoxylin & eosin stains. X50 & X125. These photomicrographs show the accumulation of iron in hepatocytes and Kupffer cells in a case of hereditary hemochromatosis. This patient also had diabetes mellitus and skin pigmentation. For the distinction between hemosiderosis and hemochromatosis, please refer to the table on iron accumulation that was provided in the cell injury section of this teaching set.
**Gastrointestinal Tract/Hepatobiliary Pathology/Nutrition/Oral Cavity and Related Structures**

**GI/Liver/Nutrition/Oral Cavity #25  Hepatic Wilson’s Disease**

Liver. Hematoxylin & eosin stain. X5 [upper left]. The tissue damage seen in Wilson’s disease (hepatolenticular degeneration) is due to the accumulation of copper. Unless detected early and treatment with penicillamine instituted, it progresses to chronic hepatitis and macronodular cirrhosis.

Liver. Copper stain. X50. [lower left]. The copper stain reveals large amounts of copper in hepatocytes.

Liver. Hematoxylin & eosin stain. X20. [right image]. A dense inflammatory infiltrate of lymphocytes and plasma cells with evidence of piecemeal necrosis and fibrosis is present. These three images are from a 7-year-old girl with Wilson’s disease. Her hepatic copper content was 130µg/100 g liver tissue (normal -3µg/100 g).

Comment: In the early stages of this disease, the patients usually have Kayser-Fleischer rings by slit-lamp examination, decreased serum ceruloplasmin levels, increased urinary copper excretion and as noted above increased hepatic copper content.

**GI/Liver/Nutrition/Oral Cavity #26  Hepatocellular Carcinoma**

Liver. Gross photo. A 45-year-old man with a long history of alcohol abuse and postnecrotic cirrhosis diagnosed 15 years ago, now presents with massive gastrointestinal hemorrhage secondary to esophageal varices. The gross photograph of the cut surface of his liver shows an irregular grayish-white mass set in a background of macronodular cirrhosis. A multiloculated cystic area is also present.

**GI/Liver/Nutrition/Oral Cavity #27  Tumors Metastatic to the Liver**

Liver. Gross photo. Multiple metastatic nodules of ovarian carcinoma can be seen in this image.

Comment: The liver is a common site of metastasis for a number of malignancies, but particularly for cancers of the gastrointestinal tract, lung and breast.

**GI/Liver/Nutrition/Oral Cavity #28  Obstructive Liver Disease**

Liver. Hematoxylin & eosin stain. X78. If the obstruction continues, bile accumulates in the bile ducts, ductules and even in the parenchyma. The large brownish-orange masses seen in this photomicrograph represent the parenchymal accumulation of bile and are known as “bile lakes”. In this and the previous image, the cause of the obstruction was a carcinoma of the head of the pancreas, but choledocholelithisis, common bile duct tumors, chronic pancreatitis, and scarring from previous surgery can also lead to similar liver pathology.
Gallbladder, Hematoxylin & eosin stain. X12. The normal gallbladder wall is quite thin and contains a mucosa consisting of a single layer of tall columnar epithelium and a lamina propria of vascularized loose connective tissue. The mucosa sits on a thin muscular layer which in turn is surrounded by dense connective tissue except in those portions of the gallbladder covered by peritoneum where the connective tissue is much looser in nature.

Gall Bladder: Acute Cholecystitis

Gallbladder. Hematoxylin & eosin stain. X12. This is a case of acute calculous cholecystitis in which a stone had occluded the neck of the gallbladder. The gallbladder was enlarged with an edematous, hemorrhagic and focally necrotic wall. Note that there is essentially no viable tissue for a large portion of the wall in this image. One of the complications of this condition is perforation with abscess formation and occasionally septic peritonitis.

Gall Bladder: Cholelithiasis

Gallbladder. Gross photo. An opened gallbladder shows a number of cholesterol stones. Cholesterol gallstones are the predominant type found in the United States where they are seen in 10% of the adult population and are twice as common in women as in men.

<table>
<thead>
<tr>
<th>Gallstones</th>
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<tbody>
<tr>
<td>Types</td>
</tr>
<tr>
<td>Cholesterol gallstones</td>
</tr>
<tr>
<td>Black pigment gallstones</td>
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<tr>
<td>Brown pigment gallstones</td>
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</table>

Adenocarcinoma of the Gallbladder

Gallbladder. Hematoxylin & eosin stain. X20, [top image]. In this tumor various sized glands infiltrated the fibrotic wall of the gallbladder.
Gallbladder. Hematoxylin & eosin stain. X125. [bottom image]. This is another example of adenocarcinoma of the gallbladder, one in which the predominant form of growth was papillary.

Comment: Carcinoma of the gallbladder has a strong association of cholelithiasis and is more common in women than in men.

GI/Liver/Nutrition/Oral Cavity #33  Acute Pancreatitis 1

Pancreas. Gross photo. This is the cut surface of the pancreas from a 57-year-old man with acute hemorrhagic pancreatitis. The photograph shows focal areas of hemorrhage and extensive fat necrosis. Although this patient did not survive, the complications in patients that do survive include the development of pseudocysts with infection, abscess formation and possible rupture into the peritoneum (chemical peritonitis) or erosion into a vessel (hemorrhage).

GI/Liver/Nutrition/Oral Cavity #34  Acute Pancreatitis 2

Pancreas. Hematoxylin & eosin stain. X32. The remaining acini are disrupted and undergoing liquefactive necrosis. Because of the high cellular content of digestive enzymes, the destruction of acinar tissue takes place in a matter of hours.

GI/Liver/Nutrition/Oral Cavity #35  Adenocarcinoma of the Pancreas

Pancreas. Hematoxylin & eosin stain. X50. [left image]. The tumor is composed of irregular glands, containing cells with pale cytoplasm, set in a dense fibrous stroma.

Pancreas. Mucicarmine stain. X50. [right image]. The clear cytoplasm noted above contains mucin, but mucin production in pancreatic carcinomas is variable and is much less in higher grade tumors. Many pancreatic carcinomas are found in the head of the pancreas where they can cause obstruction resulting in pancreatitis or jaundice.

Nutritional Diseases

GI/Liver/Nutrition/Oral Cavity #36  Celiac Disease

Small intestine. Hematoxylin & eosin stain. X20 [left image]. The histologic findings in celiac disease are villous atrophy with lengthening of the crypts of Lieberkuhn. The surface appears flat and lacks the normal prominent villi seen in the small intestine.

Small intestine. Hematoxylin & eosin stain. X125. [right image]. At higher magnification, the lamina propria is hypercellular containing plasma cells, eosinophils, lymphocytes, and macrophages. Note that some of the lymphocytes are infiltrating the surface epithelium.

Comment: Celiac disease (gluten-sensitive enteropathy) is one of a number of conditions that can lead to malabsorption and malnutrition as the damaged epithelial cells present a
Week 17-18: December 6-17  
Gastrointestinal Tract/Hepatobiliary Pathology/Nutrition/Oral Cavity and Related Structures

Reduced absorptive surface. Many patients present with diarrhea but can also exhibit iron or folate deficiency anemia, amenorrhea, weight loss and weakness. The pathogenesis of this disease is uncertain but we do know the ingestion of wheat gluten (with glutamine and prolamin containing gliadin polypeptides) is a precipitating factor.

**GI/Liver/Nutrition/Oral Cavity #37 Whipple’s Disease**

**Colon. Periodic acid-Schiff stain. X78.** Another cause of malabsorption and malnutrition, albeit a rare one, is Whipple’s disease also known as intestinal lipodystrophy. This biopsy is from an adult male with a 10-month history of diarrhea and fatty stools. In this photomicrograph, PAS-positive macrophages and lymphocytes are present in the lamina propria of the colon, although they are usually more commonly seen in the jejunum and ileum. The causative agent of this disease is a bacillus, *Tropheryma whippelii*, which can be demonstrated in these macrophages by electron microscopy. Note the dilated lacteals (lymph vessels into which chylomicrons pass on their way to the thoracic duct and the blood stream) at the tip of the lamina propria. Fat deposits can be found in the intestinal mucosa and mesenteric lymph nodes and are most likely due to lymphatic obstruction. Besides malabsorption and lymphadenopathy, these patients often have skin hyperpigmentation and arthralgias.

**GI/Liver/Nutrition/Oral Cavity #38 Niacin Deficiency**

**Skin. Hematoxylin & eosin stain. X40.** The histologic changes in the skin due to niacin deficiency seen in this photomicrograph are nonspecific and include extensive compact and basketweave hyperkeratosis, basal vacuolation and dilatation of the dermal capillaries. The full-flown syndrome of niacin deficiency is known as pellagra and includes: 1) dermatitis (scaly, foul-smelling, painful rash on the back of the hands and around the neck), 2) diarrhea, and 3) dementia (anxiety, disorientation, delusions). Niacin is part of the oxidation-reduction coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) which are necessary for energy production and the metabolism of carbohydrates, lipids and proteins.

**Oral Cavity and Associated Structures**

**GI/Liver/Nutrition/Oral Cavity #39 Oral Herpes Simplex Gingivostomatitis**

**Gingival scraping. Hematoxylin & eosin stain. X125.** This patient presented with numerous vesicular and ulcerative lesions on the gingiva and oropharyngeal mucosa, cervical lymphadenopathy, malaise and fever. A scraping of the gingival lesions shows numerous epithelial cells exhibiting intracellular edema and nuclei containing large eosinophilic, intranuclear viral inclusions. Several multinucleated giant cells with crowded nuclei are also present. This is an example of a Herpes simplex virus type 1 (HSV-1) infection.

**GI/Liver/Nutrition/Oral Cavity #40 Oral Leukoplakia**

**Buccal mucosa. Hematoxylin & eosin stain. X20.** A 41-year-old male presents with several whitish plaques on the hard palate adjacent to a small ulcer. This
photomicrograph of one of the plaques shows a central area of surface keratinization with hyperorthokeratosis and acanthosis. There is essentially no dysplasia in this image and it is correctly diagnosed as hyperkeratosis without dysplasia. The ulcerative area described above showed squamous cell carcinoma.

Comment: Leukoplakia is a clinical term used to describe white lesions in the oral cavity and does not indicate the histology of the lesion. It is considered pre-malignant since a small percentage will show carcinoma on biopsy.

GI/Liver/Nutrition/Oral Cavity #41  Oral Squamous Cell Carcinoma

Tongue. Gross photo. This 53-year-old male with a long history of cigarette smoking presented with a firm mass at the base of the tongue. A biopsy showed infiltrating squamous cell carcinoma and the patient underwent a hemiglossectomy and hemimandibulectomy with a radical neck resection. The specimen is illustrated in this image. Histologically, the tumor involved the periosteum of the mandible and had metastasized to several of the regional lymph nodes.

GI/Liver/Nutrition/Oral Cavity #42  Oral Squamous Cell Carcinoma

Tongue. Hematoxylin & eosin stain. X20. A portion of the tumor from the above case showed an exophytic growth pattern with little keratinization. In other areas the tumor was deeply infiltrative involving the tongue, underlying soft tissue and periostium of the mandible. Squamous cell carcinoma is the most common type of oral cancer and has been linked to all forms of tobacco use as well as alcohol consumption.

GI/Liver/Nutrition/Oral Cavity #43  Warthin’s Tumor

Parotid gland. Hematoxylin & eosin. X20. The histologic features of Warthin’s tumor (papillary cystadenoma lymphomatosum) consist of glandular spaces that are lined by two layers of eosinophilic, granular cells and are set in a lymphoid stroma. The tumor is benign, found mainly in men and most commonly involves the parotid gland.
Master Schedule  
Fall Semester

**Monday, August 16, 10 AM-Noon**  
Orientation  
Lecture Hall

**Cell & Tissue Response to Injury**

**Tuesday, August 17**  
1-2 PM  
Guest lecture, Mr. John Gantner: U.S. Healthcare Landscape  
West Lecture Hall

2-4 PM  
Case-Based Study  
Laboratory

**Thursday, August 19**  
1-4 PM  
Path Talk  
Laboratory

**Friday, August 20**  
10-11 AM  
Summary  
West Lecture Hall

11 AM- Noon  
Journal club/Epi-Bio Consult  
Lab – Room N12

**Inflammation/Tissue Repair**

**Tuesday, August 24**  
1-4 PM  
Case-Based Study  
Laboratory

**Thursday, August 26**  
2-5 PM  
Path Talk  
Laboratory

**Friday, August 27**  
10-11 AM  
Summary  
West Lecture Hall

11 AM- Noon  
Journal club/Epi-Bio Consult  
Lab – Room N12

**Immunity**

**Tuesday, August 31**  
1-4 PM  
Case-Based Study  
Laboratory

**Thursday, September 2**  
2-5 PM  
Path Talk  
Laboratory

**Friday, September 3**  
10-11 AM  
Summary  
West Lecture Hall

11 AM- Noon  
Journal club/Epi-Bio Consult  
Lab – Room N12
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<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>Tuesday, Sept 7</td>
<td>1-2 PM</td>
<td>Lecture: Introduction to the Autopsy</td>
<td>West Lecture Hall</td>
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<td></td>
<td>2-4 PM</td>
<td>Case-Based Study</td>
<td>Laboratory</td>
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<td>Thursday, Sept 9</td>
<td>2-5 PM</td>
<td>Path Talk</td>
<td>Laboratory</td>
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<tr>
<td>Friday, Sept 10</td>
<td>10-11 AM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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<td>11 AM- Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Lab – Room N12</td>
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<tr>
<td>Tuesday, Sept 14</td>
<td>1-4 PM</td>
<td>Case-Based Study</td>
<td>Laboratory</td>
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<tr>
<td>Thursday, Sept 16</td>
<td>2-5 PM</td>
<td>Path Talk</td>
<td>Laboratory</td>
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<tr>
<td>Friday, Sept 17</td>
<td>10-11 AM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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<td></td>
<td>11-12 Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Lab – Room N12</td>
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<tr>
<td>Monday, Sept 20</td>
<td>10-12 Noon</td>
<td>Integrated Case: Leukemia</td>
<td>TBA</td>
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<tr>
<td>Thursday, Sept 23</td>
<td>2-5 PM</td>
<td>Path Talk</td>
<td>Laboratory</td>
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<tr>
<td>Friday, Sept 24</td>
<td>11-12 Noon</td>
<td>Summary</td>
<td>West Lecture Hall</td>
</tr>
<tr>
<td>Wednesday, Oct 6</td>
<td>9-12 Noon</td>
<td>EXAMINATION</td>
<td>Lecture Halls</td>
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<tr>
<td>Monday, Oct 11</td>
<td>1-4 PM</td>
<td>Independent Study</td>
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<tr>
<td>Tuesday, Oct 12</td>
<td>1-2 PM</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Lab – Room N12</td>
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<tr>
<td>Friday, Oct 15</td>
<td>1-4 PM</td>
<td>Path Talk</td>
<td>Laboratory</td>
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<td>Friday, Oct 29</td>
<td>9-10 AM</td>
<td>Gross Presentation</td>
<td>West Lecture Hall</td>
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<td>10-11:15 AM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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<tr>
<td></td>
<td>11:15-12 Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Lab – Room N12</td>
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# Master Schedule
## Fall Semester

### Respiratory Pathology

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<th>Date</th>
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<tbody>
<tr>
<td>Monday, November 8</td>
<td>1-4 PM</td>
<td>PathTalk Laboratory</td>
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<tr>
<td>Thursday, November 11</td>
<td>10:30-12 Noon</td>
<td>Integrated Case: Cardiovascular</td>
<td>TBA</td>
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<tr>
<td>Friday, November 12</td>
<td>1-4 PM</td>
<td>Independent Study</td>
<td></td>
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<tr>
<td>Monday, November 15</td>
<td>1-2 PM</td>
<td>Gross Presentation</td>
<td>West Lecture Hall</td>
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<tr>
<td></td>
<td>2-4 PM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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### GI etc. Pathology

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<tbody>
<tr>
<td>Monday, December 6</td>
<td>1-2 PM</td>
<td>Gross Presentation</td>
<td>West Lecture Hall</td>
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<tr>
<td></td>
<td>2-4 PM</td>
<td>PathTalk Laboratory</td>
<td>Laboratory</td>
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<tr>
<td>Tuesday, December 7</td>
<td>1-4 PM</td>
<td>Independent Study</td>
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<td>Thursday, December 16</td>
<td>1-2:30 PM</td>
<td>Lecture: Oral Cavity &amp; Related Structures</td>
<td>West Lecture Hall</td>
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<td>2:30-3:15 PM</td>
<td>Summary</td>
<td>West Lecture Hall</td>
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<tr>
<td></td>
<td>3:15-4:00 PM</td>
<td>Journal club/Epi-Bio Consult Lab – Room N12</td>
<td></td>
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<tr>
<td>Friday, December 17</td>
<td>10:30-12 Noon</td>
<td>Integrated Case: Asthma</td>
<td>TBA</td>
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