Course in
Pathology and Laboratory Medicine

Schedule, Assignments & Slides
Fall Semester
2005 - 2006

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
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SUMMARY PRESENTATIONS/GROSS PRESENTATIONS

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

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

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Dr. Robert LeBeau  235-4129

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Mrs. Zana Etter  235-4460

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Dr. Robert Trelstad

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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 that 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 that 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 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:** These summaries are a valuable guide to what the faculty considers most important in each unit. This can help to organize your studying by emphasizing material that is likely to be covered by the exams. Your attendance is required (see schedule).

**Epidemiology/biostatistics consultations:** These are informal sessions, given for almost all journal articles, 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. Usually only the one student in each section assigned to present the article will attend the consultation.

**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 lead 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, to 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 leading the discussion to elicit full responses the case, including a differential diagnosis based on the findings. The instructor is not expected to provide answers to all questions raised, nor is the lead student. 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 one to two printed cases will be assigned. These are included in the Assignments sections in the second half of this book.

1. Each student should study the case and provide either 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 lead the discussion. 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 answer the questions at the end of each case. Individual students should be responsible for answering each question, and the group as a whole should correct/supplement/support this student’s view. The instructor should guide the discussion to cover the objectives that are relevant to the case and offer a final comment on each of the answers
   c. View the slides on WebCT pertaining to the case. The lead student 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.

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

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

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

STUDY MATERIAL

We realize that in this age of exponential increase in biomedical knowledge we can provide only a limited exposition of our field. It is vital that future physicians assimilate and update a large amount of information, to which our course can offer only an introduction. 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 site.

Required Textbook:

- Robbins and Cotran Pathologic Basis of Disease, 7th Edition (the complete edition)

Please make sure you get the 7th edition. 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 for the seventh edition will not be available until an unknown date in the 2005-6 school year. Students who feel a need for a more condensed text to supplement (and not replace!!) the complete edition should consider the current, 7th edition of Basic Robbins, which is about half the size. Examination questions will be based on the complete edition, however, and there is no guarantee that relying on the Basic edition will suffice for students to do well in the course.

For the most recent developments in the field, you should regularly consult the New England Journal of Medicine and other journals.

Required Material for PathTalk Sessions:

- Slide collection (arranged by weekly topics) on WebCT
- Slides section of the course book - contains slide descriptions and other selected material

Required Material for Case Based Study:

- Printed cases provided in the Assignments sections
- Case-Based Pathology and Laboratory Medicine, 2005, by Mihail, Raskova, and She (Blackwell Publications). Note that this is an up-dated version of Laboratory Medicine Case Book by Raskova and others.

Recommended Reading Texts:

- Netter’s Illustrated Human Pathology, by Buja and Krueger. This is the most significant recommended text. The “Netter” in the title is the same Netter who produced the magnificent CIBA anatomy atlases. It is not required reading, and exams will not cover material present solely in it although the contents of the Robbins and Netter’s almost completely overlap. It is an excellent means of visually reinforcing the facts and concepts from Robbins and might introduce some welcome variation into your studying.

Other recommended books include:

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

Self-evaluation Material:
We recommend the following:

- *Robbins and Cotran Review Of Pathology* by Edward C. Klatt, M.D., and Vinay Kumar, M.D., 2nd Edition (Multiple choice questions with answers). This edition is brand new, and the questions reflect the format you are likely to find on the Boards. Several copies are available in the Media Library.

- *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. The questions are worthwhile; but the book is somewhat old, and the questions no longer reflect the style of the Boards examinations.

- Web Based Quizzes: (http://pleiad.umdnj.edu/)
  - Pathology and Laboratory Medicine Quiz
  - Image-based Mini-quiz

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. The first two of these will consist of both image- and text-based multiple-choice questions provided by faculty members and will cover material from the previous third of the year.

The third and final exam covering the entire year will be a copy of the Pathology section of Step I of the USMLE. This is just a copy and not the actual USMLE examination itself. The results of the last exam will be reported to you as a percentage grade after the National Board has analyzed the raw scores and converted them to percentage grades in order to make your grades as fair as possible.

Note: The time allotment assigned for an examination is not necessarily the actual length of time for the exam. It includes time both before and after the examination for administrative tasks.

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

\[
\text{Final percentage grade} = \frac{(\text{exam 1} + \text{exam 2} + \text{exam 3})}{3} \times 0.98 + 0-2 \text{ integrated case points.}
\]

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.

<table>
<thead>
<tr>
<th>Final Percentage Grade</th>
<th>Final Course Grade</th>
</tr>
</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%.

You may not memorize questions or make notes about questions in order to record them for your own or others' future use. Because portions of the exam may be used again in the future, any attempt to do so is an honor violation. As a reminder, in regard to this and to your performance on the exam itself, the following honor code is in effect:

“I hereby affirm that I have neither given nor received unauthorized assistance during this examination. I acknowledge that the Code of Professional Conduct of UMDNJ-Robert Wood Johnson Medical School stipulates that students may not cheat, plagiarize or assist others in the commission of these acts. I also acknowledge that the Code of Professional Conduct provides that students have a duty to report any breach of these ethics through appropriate channels.”
Introduction

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 their 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.

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:

<table>
<thead>
<tr>
<th>Case Based Studies</th>
<th>PathTalk</th>
</tr>
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<tbody>
<tr>
<td>Knowledge of material</td>
<td>Knowledge of material</td>
</tr>
<tr>
<td>Interaction and participation in discussions</td>
<td>Interaction and participation in discussions</td>
</tr>
<tr>
<td>Performance as a moderator</td>
<td>Interpretative skills in histopathology</td>
</tr>
<tr>
<td>Ability to analyze cases/answer assigned questions</td>
<td>Journal Club presentation (in most cases)</td>
</tr>
</tbody>
</table>

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 or more than two absences from one of your small group sessions will require remedial activity on an individual basis.
Introduction

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 of the 2 departmental examinations, both the question booklets and answer sheets will be collected. Over the course of the next few days, you will have the opportunity to review both the questions and your answers in a supervised setting. After your review you may leave any written challenges to the questions with the supervisor, and the books/answer sheets will again be collected. The course director and the faculty will then review the challenges. The class will be notified of any adjustments, which will apply to every student’s grade. No additional changes are made after the final grade for each departmental examination is issued.

    **As mentioned above, you may not memorize questions or make notes about questions in order to record them for your own or others future use.**

  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:** As described above, 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, Robbins and Cotran Pathologic Basis of Disease, 7th Edition, is a primary resource for your independent study. Because the text is comprehensive and detailed, reading effectively and efficiently is essential. A 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. (Check out the outline that begins every chapter.) If you know the structure of the material (“the big picture”), it will help you recall it better; as 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. 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. Some students like to focus study by reading related questions. (Be sure to take a look at the Robbins companion question book.)

4. 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.

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

6. Develop a note-taking system. How will you remember without rereading the text? Decide on a format and how much detail you will include. Creating your own charts and annotating charts/figures in the text can work well.

7. Assess your comprehension at frequent intervals. Summarize after a meaningful chunk. Paraphrase (restate in your own words).

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

9. Assess your need for additional resources and use these strategically. If you are having trouble keeping up with the textbook reading, it is best to use the abridged resource as an adjunct source, not as a complete substitution for the text.

* For individual consultation about effective & efficient strategies for reading & more durable learning, please call the Cognitive Skills Program offices at 732-235-4129 (Dr. Robert Lebeau; Ms. Maris Cutting; Dr. Norma Saks).
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 that 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 Weissmann, M.D. 732-418-8047
Nancy Mundie 732-235-4033
Lin Yang 732-235-5680
Introduction

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.

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.
Introduction

Journal Club Guidelines: How To Present An Article

Stephen M. Shea, M.D.

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, along with an editorial 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 out). 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. 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.

Introduction
Schedule, Assignments, & Slides
## Week 1: August 15-19

**Cell and Tissue Response to Injury / Environmental Pathology**

### Schedule

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monday, August 15</strong></td>
<td></td>
<td>Orientation</td>
<td>Lecture Hall</td>
</tr>
<tr>
<td></td>
<td>10 AM - Noon</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tuesday, August 16</strong></td>
<td></td>
<td>Lecture: Apoptosis and Necrosis</td>
<td>West Lecture Hall</td>
</tr>
<tr>
<td></td>
<td>1-2 PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-4 PM</td>
<td>Case-Based Study: Cell Injury &amp; Environmental Pathology</td>
<td>Laboratory</td>
</tr>
<tr>
<td><strong>Thursday, August 18</strong></td>
<td></td>
<td>PathTalk: Cell Injury &amp; Environmental Pathology</td>
<td>Laboratory</td>
</tr>
<tr>
<td></td>
<td>1-4 PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Friday, August 19</strong></td>
<td></td>
<td>Summary: Inflammation/Tissue Repair</td>
<td>West Lecture Hall</td>
</tr>
<tr>
<td></td>
<td>10-11 AM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 AM- Noon</td>
<td>Journal club/Epi-Bio Consult: Inflammation/Tissue Repair</td>
<td>Laboratory – Room C207</td>
</tr>
</tbody>
</table>
Topics 1: Cell and Tissue Reaction to Injury

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Cellular Adaptations, Cell Injury, and Cell Death, Chapter 1, pp. 3-46

Recommended Reading
Netter's Illustrated Human Pathology
- Chapter 1: General Reaction Patterns

Topic 2: Environmental Pathology

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Environmental Pathology, Chapter 9, pp. 415-446

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:
  - Journal Clubs—Science as Conversation (See introductory materials of this booklet)
  - Telomerase Mutations in Aplastic Anemia, William E. Fibbe, M.D., Ph.D. Volume 352:1481-1483 April 7, 2005 Number 14

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
Week 1: August 15-19
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Printed Cases

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 15-19
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</td>
<td>Color Amber (clear)</td>
</tr>
<tr>
<td>polys 71% (40-75)</td>
<td>pH 5.01 (5.0-7.0)</td>
</tr>
<tr>
<td>lymph 15% (13-45)</td>
<td>Protein Neg (Neg)</td>
</tr>
<tr>
<td>eos 6% (0-6)</td>
<td>Sugar Neg (Neg)</td>
</tr>
<tr>
<td>mono 7% (0-11)</td>
<td>Ketones Neg (Neg)</td>
</tr>
<tr>
<td>baso 1% (0-1)</td>
<td>Bile Neg (Neg)</td>
</tr>
<tr>
<td><strong>RBC</strong> 4.10 mill/uL</td>
<td>Blood Neg (Neg)</td>
</tr>
<tr>
<td><strong>HGB</strong> 12.4 gm%</td>
<td>Nitrite Neg (Neg)</td>
</tr>
<tr>
<td><strong>HCT</strong> 35.1%</td>
<td>Urobilinogen 0.2 U</td>
</tr>
<tr>
<td>Pits 235 thou/uL</td>
<td>S.G. 1.015 (1.010-1.035)</td>
</tr>
<tr>
<td>PT 12.1 sec</td>
<td>WBC Neg (0-5)</td>
</tr>
<tr>
<td>PTT 28 sec</td>
<td>No microscopic exam performed.</td>
</tr>
</tbody>
</table>
# Week 1: August 15-19

Cell and Tissue Response to Injury / Environmental Pathology

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na</strong></td>
<td>Glucose</td>
</tr>
<tr>
<td>138 mEq/L</td>
<td>97mg%</td>
</tr>
<tr>
<td>(136-146)</td>
<td>(65-110)</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>BUN</td>
</tr>
<tr>
<td>3.6 mEq/L</td>
<td>14mg%</td>
</tr>
<tr>
<td>(3.0-5.0)</td>
<td>(7-24)</td>
</tr>
<tr>
<td><strong>Cl</strong></td>
<td>Creatinine</td>
</tr>
<tr>
<td>105 mEq/L</td>
<td>1.1 mg%</td>
</tr>
<tr>
<td>(98-108)</td>
<td>(0.7-1.4)</td>
</tr>
<tr>
<td><strong>CO₂</strong></td>
<td>Protein, total</td>
</tr>
<tr>
<td>27.5 mEq/L</td>
<td>6.2gm%</td>
</tr>
<tr>
<td>(24-32)</td>
<td>(6.0-8.0)</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.

<table>
<thead>
<tr>
<th>Chemistry</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>97mg% (65-110)</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>14mg% (7-24)</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>1.1 mg% (0.7-1.4)</td>
</tr>
<tr>
<td><strong>Protein, total</strong></td>
<td>6.2gm% (6.0-8.0)</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>3.2gm% (3.5-5.0)</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>8.6 mg% (8.5-10.5)</td>
</tr>
<tr>
<td><strong>Phosphorus</strong></td>
<td>3.5 mg% (2.5-4.5)</td>
</tr>
<tr>
<td><strong>Alk Phos</strong></td>
<td>161 U/L (30-120)</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>0.6 mg% (0-1.5)</td>
</tr>
<tr>
<td><strong>SCOT (AST)</strong></td>
<td>111 U/L (12-45)</td>
</tr>
<tr>
<td><strong>SGPT (ALT)</strong></td>
<td>96 U/L (3-40)</td>
</tr>
<tr>
<td><strong>GGTP</strong></td>
<td>221 U/L (15-70)</td>
</tr>
</tbody>
</table>
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?

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Cell Injury

Cell Injury #1  Cellular Swelling

**Kidney, Hematoxylin & eosin stain. Intermediate magnification.** One of the events that occurs 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?
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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, which release various degradative enzymes. For unclear reasons, a hypoxic insult to the brain (as opposed to most other organs) results in liquefactive necrosis. As this infarct in the brain becomes organized and 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 that 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 proteases that 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 are important in the chain of intracellular events that lead to apoptosis.

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 epithelium and separated by a supporting stroma consisting of bundles of smooth muscle cells separated by bands 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. Either the glands, the stroma, or both may undergo hyperplasia. The cause is most likely related to excess stimulation of the prostate gland by testosterone or its metabolite dehydrotestosterone.

Cell Injury #20
Heart: Hypertrophy

This is cardiac hypertrophy involving the left ventricle (the chamber on seen here on the left). 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. Intracanicular 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.
Week 1: August 15-19
Cell and Tissue Response to Injury / Environmental Pathology

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). Crunchy alveoli.

Cell Injury #29  Dystrophic Calcification: Stomach

This is dystrophic calcification in the wall of the stomach. At the bottom of the image 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 fibrosis, the mucosa is ulcerated, and the vessels are ectatic. 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.
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 22-26
Inflammation/Tissue Repair

Schedule

Tuesday, August 23
1-2 PM  Lecture: General Laboratory Medicine  West Lecture Hall
2-4 PM  Case-Based Study: Inflammation  Laboratory

Thursday, August 25
2-5 PM  Path Talk: Inflammation  Laboratory

Friday, August 26
10-11AM  Summary: Immunity  West Lecture Hall
11AM-Noon  Journal Club/Epi-Bio Consult: Immunity  Laboratory – Room C207
Week 2: August 22-26
Inflammation/Tissue Repair

Assignments

Topic: Reaction to Tissue Injury: Edema, Thrombosis, and Inflammation

Required Reading:
*Robbins and Cotran Pathologic Basis of Disease, 7th Edition,*
- Acute and Chronic Inflammation, Chapter 2, pp. 47-86
- Tissue Renewal and Repair, Chapter 3, pp. 87-118
- Hemodynamic Disorders, Thrombembolic Disease, and Shock, Chapter 4, pp. 119-144

Required Study for Small Groups

**PathTalk**
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:
  - December 16, 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 Pathology and Laboratory Medicine, Case 17 – “A 70 year-old gardener…”*

**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.

<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 Count</td>
<td>2.4 %</td>
<td>0.5%-2.8%</td>
</tr>
<tr>
<td>(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>
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<tr>
<td>PTT</td>
<td>27</td>
<td>24-36 s</td>
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<tr>
<td>LD</td>
<td>968</td>
<td>0-199 U/L</td>
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<tr>
<td>Haptoglobin</td>
<td>9</td>
<td>20-230 mg/dL</td>
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<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</td>
<td>Blood glucose 323 mg/dl (65-110)</td>
</tr>
<tr>
<td>polys 63%</td>
<td>Total plasma protein 5.4 gm/dl (6-8)</td>
</tr>
<tr>
<td>bands 30%</td>
<td>Albumin 3.0 gm/dl (3.5-5)</td>
</tr>
<tr>
<td>lymphs 7%</td>
<td>Arterial blood gases</td>
</tr>
<tr>
<td>HGB 10.0 gm%</td>
<td>pH 7.10 (7.35-7.45)</td>
</tr>
<tr>
<td>HCT 30.8 %</td>
<td>pCO2 36 mmHg (32-46)</td>
</tr>
<tr>
<td>MCV 94 fl</td>
<td>HCO3 11 mmol/L (18-29)</td>
</tr>
<tr>
<td>MCH 30.6 pg</td>
<td>pO2 60 mmHg (74-108)</td>
</tr>
<tr>
<td>Pits 209 thou</td>
<td>O2 saturation 89 % (92-96)</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.
Week 2: August 22-26
Inflammation/Tissue Repair

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  

**Hematoxylin & eosin stain. Medium power. Lung.**  

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  

**Acute Inflammation**

**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  

**Acute Inflammation 2**

**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  

**Chronic Inflammation: Diagram**

Cellular interactions with chronic inflammation are diagrammed.

Reactions to Tissue Injury #7  

**Chronic Inflammation: Lung**

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  

**Chronic Inflammation**

**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  

**Chronic Inflammation: Alveolar Walls**

**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) as in 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

Seepage of a protein-rich fluid into a cavity leads to an exudate. 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, an 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

Hematoxyling & 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. A coronary artery buried in the epicardial fat has been longitudinally sectioned to reveal a pale, pink-brown thrombus. 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, 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 (magenta arrow) and pulmonary arteries to right and left lungs (green arrows) 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 thromboembolii 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 has survived, there is time for the tissue to form a distinct reaction. 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, so tissue outlines are preserved. Coagulative necrosis 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 2: August 22-26
Inflammation/Tissue Repair
Week 3: August 29-September 2

Immunity

Schedule

Tuesday, August 30
1-2 PM  
Lecture: “What Do Pathologists Do?”  
West Lecture Hall

2-4 PM  
Case Based Study: Immunity Laboratory

Thursday, September 1
2-5 PM  
Path Talk: Immunity Laboratory

Friday, September 2
10-11 AM  
Summary: Neoplasia  
West Lecture Hall

11 AM- Noon  
Journal club/Epi-Bio Consult: Neoplasia  
Laboratory-Room C207
Week 3: August 29-September 2

Immunity

Assignments

Topic: Immunity

Required Reading:

Robbins and Cotran Pathologic Basis of Disease, 7th Edition

- Diseases of Immunity, Chapter 6, pp. 193-268
- Bronchial Asthma, Chapter 15, pp. 723-727
- Blistering Diseases, Chapter 25, pp. 1259-1263

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 Pathology and Laboratory Medicine, Case 11- “A 78 year-old pale woman…”

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
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>
</tr>
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### Week 3: August 29-September 2

#### Immunity

**Urine Drug Screen**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Neg</th>
<th>Neg</th>
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<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>Range</th>
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</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>
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</table>

**Serum**

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<tr>
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<th>Range</th>
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</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>
</tr>
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Week 3: August 29-September 2

Immunity

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<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>HBcAb</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

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>24 hour urine</td>
<td>4,342</td>
<td>40-150 mg/24 hours</td>
</tr>
</tbody>
</table>

CSF

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></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/microL</td>
<td>None</td>
</tr>
<tr>
<td>RBCs</td>
<td>30/microL</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 Crithida lucidae 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; HBcAb, 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>
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</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 29-September 2

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 (Immunoconcepts, 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 (ie, 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></th>
<th>Hematology</th>
<th>Chemistry</th>
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<tbody>
<tr>
<td>WBC</td>
<td>12.2 thou</td>
<td>BUN</td>
</tr>
<tr>
<td>(3.4-11)</td>
<td></td>
<td>40 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7-24)</td>
</tr>
<tr>
<td>Polys</td>
<td>85 %</td>
<td>Creatinine</td>
</tr>
<tr>
<td>(40-75)</td>
<td></td>
<td>2.0 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.7-1.4)</td>
</tr>
<tr>
<td>Lymphs</td>
<td>15 %</td>
<td>Glucose, blood</td>
</tr>
<tr>
<td>(13-43)</td>
<td></td>
<td>80 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(65-110)</td>
</tr>
<tr>
<td>Platelets</td>
<td>360 thou</td>
<td>Protein, total</td>
</tr>
<tr>
<td>(130-400)</td>
<td></td>
<td>7.5 g/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.0-8.1)</td>
</tr>
<tr>
<td>Hgb</td>
<td>8.0 gm/dl</td>
<td>Albumin</td>
</tr>
<tr>
<td>(12-18)</td>
<td></td>
<td>4.2 g/dl</td>
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<td></td>
<td></td>
<td>(3.0-4.9)</td>
</tr>
<tr>
<td>Hct</td>
<td>30 %</td>
<td>Globulin</td>
</tr>
<tr>
<td>(37-47)</td>
<td></td>
<td>3.3 g/dl</td>
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<tr>
<td></td>
<td></td>
<td>(2.3-3.5)</td>
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<tr>
<td>MCV</td>
<td>94 fl</td>
<td>Calcium</td>
</tr>
<tr>
<td>(81-99)</td>
<td></td>
<td>9.2 mg/dl</td>
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<td></td>
<td></td>
<td>(8.5-10.2)</td>
</tr>
<tr>
<td>MCH</td>
<td>25 pg</td>
<td>Bilirubin, total</td>
</tr>
<tr>
<td>(27-31)</td>
<td></td>
<td>1.2 g/dl</td>
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<td>(0.4-1.4)</td>
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<td>MCHC</td>
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<tr>
<td>(32-36)</td>
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<td>80 IU/L</td>
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<td></td>
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<td>(36-92)</td>
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<tr>
<td>Sed rate</td>
<td>80 mm/hr</td>
<td>AST (SGOT)</td>
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**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?
**Week 3: August 29-September 2**

**Kodachrome Slides**

**Immunology**

**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

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<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>
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<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>
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<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>
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<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>
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<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>
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<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>
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</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: Acute, Gross

**Renal homograft. Gross Photo.** The kidney in this image has been sectioned. There is extensive hemorrhage and necrosis. One form of acute rejection has been called "cell mediated", with involvement of both CD4+ helper and CD8+ cytotoxic T cells. The pathology is mainly a tubulitis, so the inflammatory changes are confined to the interstitium. Another form of acute rejection has been called "humoral", but a more appropriate term would be "acute vascular rejection" because both cellular and humoral mechanisms are at play.
Diseases of Immunity #7 Transplant Rejection: Acute Cellular (Interstitial) Rejection

This is an 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 relatively 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 #8 Transplant Rejection: Acute and Subacute Vasculitis

Kidney. Hematoxylin & eosin stain. X20. This form of rejection is the result of both humoral and cell-mediated processes. Although there is some degree of inflammatory changes in the tubules and interstitium, the most significant effects are vascular. Intimal arteritis is present with variable numbers of mononuclear inflammatory cells in the subendothelial space. In the most severe cases there is also fibrinoid necrosis of the arterial wall.

Diseases of Immunity #9 Transplant Rejection: Chronic Vascular Rejection

Currently chronic rejection is the most common cause of graft failure. At high magnification, the renal arteries with chronic vascular rejection show prominent thickening of the intima. Such obliterative arteritis is the most salient characteristic of chronic rejection. There is also tubulointerstitial fibrosis and chronic inflammation and glomerular pathology, both probably from ischemia due to the arteritis. 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 #10 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 #11 Autoimmune Disease: Antinuclear Antibodies

Antinuclear antibody. Indirect immunofluorescence. X125. In the work-up of suspected autoimmune disease, the method of choice to be used in screening for the presence of antinuclear antibodies (ANA) 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 #12**  
**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 primarily 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 #13**  
**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 #14**  
**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 #15**  
**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 #16**  
**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 other auto-antibodies.

**Diseases of Immunity #17**  
**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.
Diseases of Immunity #18  
**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 #19  
**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 agammablobulinemia 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 #20  
**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

**Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men-New York City and California**

“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…”

MMWR July 3, 1981;30: 305-308

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**Diseases of Immunity #21 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 residual 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 advent of the AIDS era, 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/microL. 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.

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**Diseases of Immunity #22 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 20 microns 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 is found in individuals with impaired cell-mediated immunity, such as patients with 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 vasculitis, which in the intestine can result in ulceration perforation.

**Diseases of Immunity #23**  
* 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 #24**  
* Amyloidosis 2

**Lung. Congo red stain. X30.** When Congo red-stained amyloid is viewed under polarized light, it shows an apple green birefringence.
Week 3: August 29-September 2

Immunity
Week 4: September 5-9
Neoplasia

Schedule

Tuesday, September 6
2-4 PM  Case-Based Study: Neoplasia Laboratory

Thursday, September 8
2-5 PM  Path Talk: Neoplasia Laboratory

Friday, September 9
10-11 AM  Summary: Genetics/Pediatric & Developmental Pathology West Lecture Hall
11 AM- Noon  Journal club/Epi-Bio Consult: Laboratory – Room C207 Genetics/Pediatric & Developmental Pathology
Week 4: September 5-9
Neoplasia

Assignments

Topic: Neoplasia

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition
• Neoplasia, Chapter 7, pp. 269-342

Required Study for Small Groups

PathTalk
Assignments:
• Kodachromes on WebCT
• Slide descriptions
• Journal club articles
  o Lymphoma-specific Genetic Aberrations in Microvascular Endothelial Cells in B-cell Lymphomas, Berthold Streubel, M.D., Volume 351:250-259, July 15, 2004 Number 3
  o Neoplastic Angiogenesis – Not All Blood Vessels are Created Equal, Isaiah J. Fidler, D.V. M., Ph.D. et al., Volume 351:215-216, July 15, 2004 Number 3

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 Pathology and Laboratory Medicine, Case 9 – “A 75 year-old man who fell…”

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

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Peripheral smear - WebCT

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### Chemistry

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</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>C02</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 - Guiac - 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>11.2 g/dl</td>
<td>13.2-16.2 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>33.8 %</td>
<td>40-5 %</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 cells (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 cluster 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  \hspace{1cm} 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  \hspace{1cm} 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  \hspace{1cm} 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, collagenases, 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 as residents for four years (and often afterwards study for a year or 2 as fellows) to learn to make such distinctions.
<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 #13**

Uterine Leiomyomas, Gross

Benign neoplasms can be multiple, as is shown in this uterus with leiomyomas of varying size; but all of them are 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 #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 little or 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 were discovered and biopsied on routine colonoscopy performed on middle-aged individuals, the patient would have to undergo more frequent surveillance colonoscopies. It would be important to biopsy any additional, future polyps to rule out malignant changes.

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.

**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 happens because the infiltrating malignant cells seek paths of least resistance, and the tissue plane between the nerve and the surrounding fibrous tissue is one such plane. This is often why pain associated with cancers is sometimes 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.
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. This is detected here by immunoperoxidase staining with the brown reaction product concentrated in a perimembranous pattern around the cells.

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.
### Schedule

**Tuesday, September 13**
- 1-2 PM: Lecture: Introduction to the Autopsy  
  West Lecture Hall
- 2-4 PM: Case-Based Study: Genetics/Pediatric & Dev. Pathology  
  Laboratory

**Thursday, September 15**
- 2-5 PM: PathTalk: Genetics/Pediatric & Dev. Pathology  
  Laboratory

**Friday, September 16**
- 10-11 AM: Summary: Hemopoietic System, Lymph Nodes and Spleen  
  West Lecture Hall
- 11-12 Noon: Journal club/Epi-Bio Consult: Hematopoietic System, Lymph Nodes  
  Laboratory – Room C207
Week 5: September 12-16
Genetics/Pediatric & Developmental Pathology

Assignments

Topic 1: Genetics

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Genetic Disorders, Chapter 5 pp. 145-192

Topic 2: Pediatric and Developmental Pathology

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Diseases of Infancy and Childhood, Chapter 10, pp. 469-510
- Female Genital Tract; Section on Gestational and Placental Disorders, Chapter 22, pp. 1104-1114
- Supplemental Material (Attached): Developmental Anomalies

Recommended Reading:
Netter's Illustrated Human Pathology
- Pregnancy and Its Diseases, pp. 310-321

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club articles:
  - Should Parents Speak eith a Dying Child about Impending Death?, Lawrence Wolfe, M.D., Volume 351:1251-1253 September 16, 2004 Number 12

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 Pathology and Laboratory Medicine, Case 10 – “A 5 year-old boy with a swollen right ankle”

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

Genetics/Pediatric Pathology:
  • pp. 862-864: Inborn errors of metabolism
Week 5: September 12-16  
Genetics/Pediatric & Developmental Pathology

Developmental Pathology  
Perinatal And Pediatric Pathology

Dr. Susan Shen-Schwarz

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 loses, 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 stand point 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 lager 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, Gastroschisis
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 472-476 in Robbins and Cotran Pathologic Basis of Disease, 7th Edition
Printed Cases

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 $10^3$ cells/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 x10³/micro L</td>
<td>5.0-19.5</td>
<td>9.1 x 10⁹/L</td>
<td>5.0-19.5</td>
</tr>
<tr>
<td>Erythrocyte count (B)</td>
<td>2.45x10⁶/micro L</td>
<td>3.8-5.5</td>
<td>2.45x10¹²/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 fL</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 (B/Ercs)</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 10³/nL</td>
<td>150-450</td>
<td>390 x 1 1⁹/L</td>
<td>150-450</td>
</tr>
</tbody>
</table>

Differential count (B)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Value</th>
<th>Reference Range</th>
<th></th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmented neutrophils</td>
<td>37%</td>
<td>41-71</td>
<td>0.37</td>
<td>0.41-0.71</td>
<td></td>
</tr>
<tr>
<td>Band neutrophils</td>
<td>3%</td>
<td>5-10</td>
<td>0.03</td>
<td>0.05-0.10</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>50%</td>
<td>24-44</td>
<td>0.50</td>
<td>0.24-0.44</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>8%</td>
<td>3-7</td>
<td>0.08</td>
<td>0.03-0.07</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2%</td>
<td>1-3</td>
<td>0.02</td>
<td>0.01-0.03</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Value</td>
<td>Normal Range</td>
<td>Unit 1</td>
<td>Unit 2</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>-----------------------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>2.2%</td>
<td>0.5-3.0</td>
<td>0.022</td>
<td>0.005-0.030</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Within</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Within</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, total</td>
<td>6.1 g/dL</td>
<td>6.2-8.0</td>
<td>61 g/L</td>
<td>62-80</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4 g/dL</td>
<td>3.8-5.4</td>
<td>34 g/L</td>
<td>38-54</td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td>4.1 mg/dL</td>
<td>2.0-5.5</td>
<td>244 nmol/L</td>
<td>119-327</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>60 mg/dL</td>
<td>70-175</td>
<td>1.55 mmol/L</td>
<td>1.81-4.53</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Within</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>&gt;20 ng/mL</td>
<td>1.5-9.0</td>
<td>&gt;45 nmol/L</td>
<td>3-20</td>
<td></td>
</tr>
</tbody>
</table>
**Week 5: September 12-16**  
Genetics/Pediatric & Developmental Pathology

<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>Vitamin 61 2 (S)</td>
<td>1393 pg/mL</td>
<td>160-1300</td>
<td>1028 pmol/L</td>
<td>118-959</td>
</tr>
<tr>
<td>Ferritin (S)</td>
<td>269 ng/mL</td>
<td>50-200</td>
<td>269 microg/L</td>
<td>50-200</td>
</tr>
<tr>
<td>Chlamydiazyme</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia culture</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus, direct fluorescent antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV culture</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral respiratory battery: influenza, parainfluenza, adenovirus)</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis fluorescent antibodies</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Streptococcus pneumoniae, Corynebacterium species</td>
<td></td>
<td></td>
<td></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?
**Week 5: September 12-16**  
Genetics/Pediatric & Developmental Pathology  

Kodachrome Slides  

*Genetics*

**Genetics #1 **  
Trisomy 21, Gross  
Trisomy 21 (Down Syndrome) phenotype: flat face, low nasal bridge, upward slanting palpebral fissures.

**Genetics #2 **  
Trisomy 21, Palmar Crease  
There is an abnormal *transverse crease* across the palm of each hand seen here. Together with the *single flexion crease* on the 5th digit, this is quite typical for trisomy 21 (e.g., 47, XX, +21).

**Genetics #3 **  
Trisomy 13, Gross  
This baby with trisomy 13 has cyclopia (single eye) with a proboscis (the projecting tissue just above the eye). [Image contributed by John Nicholls, MD, Hong Kong University].

**Genetics #4 **  
Trisomy 18, Gross  
*Upper Image:* These are clenched hands resulting from camptodactyly (fingers bent over) and clinodactyly (fingers inclined to one side or the other). This particular appearance is very suggestive of trisomy 18.

*Lower Image:* This is the appearance of a "rocker bottom" foot with a prominent calcaneus and rounded bottom. Such an anomaly may suggest a chromosomal abnormality such as trisomy 18.

**Genetics #5 **  
Monosomy X, Cystic Hygroma, Gross  
One very characteristic feature of a fetus with monosomy X is the "cystic hygroma" of the neck. This is not a true neoplasm, but represents failure of lymphatics to form and drain properly. It is this structure that eventually forms the "web neck" feature of women with Turner's syndrome. Note the grey coloration from prolonged intrauterine demise.

**Genetics #6 **  
Monosomy X, Gross  
Monosomy X phenotype in adolescent: short stature, cubitus valgus, broad chest, minimal breast development, scant axillary and pubic hair.
**Week 5: September 12-16**
Genetics/Pediatric & Developmental Pathology

**Genetics #7**

**Autosomal Recessive Polycystic Kidney Disease**

Kidney. Hematoxylin & eosin stain. X31. A five-week-old boy died from renal failure and congestive heart failure. 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. They are surrounded by some fibrous connective tissue containing scattered, small islands of hematopoietic tissue. The glomeruli show varying stages of development and rather severe congestion.

**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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein A-1 (Apo A-1)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Apolipoprotein B (Apo B)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>Normal or moderately increased</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (LDL-C)</td>
<td>Decreased</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (HDL-C)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

**Genetics #9**

**Von Gierke's Disease**

Liver. Hematoxylin & eosin stain. X78 (A). As seen in this photomicrograph from the liver from a 2-year-old girl, the architecture 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 same patient. The cytoplasm of the epithelial lining cells of these tubules is abundant and pale-staining, reflecting the increased cytoplasmic glycogen. The glomerulus is essentially normal.

Von Gierke's disease (glycogen storage disease Type II) 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 effects 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.

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.

<table>
<thead>
<tr>
<th>Selected Laboratory Findings in Von Gierke's Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose, non-fasting</td>
</tr>
<tr>
<td>Blood glucose, fasting</td>
</tr>
<tr>
<td>Serum triglycerides &amp; Serum cholesterol</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Whole blood pyruvate &amp; L-lactate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum uric acid</td>
</tr>
<tr>
<td>Plasma glucose response to intramuscular glucagon</td>
</tr>
</tbody>
</table>
**Genetics #10**  
**Pompe’s Disease**

**Upper Image: Heart, Gross:** In Pompe's disease (glycogen storage disease – type II) there is accumulation of glycogen in many organs, but it is especially notable in the heart. It usually leads to death by 2 years of age from cardiorespiratory failure. This image shows a heart with the left ventricle opened to reveal a massively thickened ventricular wall.

**Lower Image: Heart, Hematoxylin & eosin stain. X78.** Both longitudinal and tangential sections of myocardium are seen in this image. 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. A significant laboratory finding is plasma glucose response to intramuscular glucagon, which is normal as opposed to other glycogenoses (normal response = 60-80 mg/dL rise within 30 minutes with no rise in lactate). A milder adult form exists with chronic myopathy as the main finding.

**Genetics #11**  
**Tay-Sachs Disease**

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

<table>
<thead>
<tr>
<th>Enzyme Assays for the Diagnosis of Tay-Sachs Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
</tr>
<tr>
<td>Serum Hexosaminidase A_1,2</td>
</tr>
<tr>
<td>Serum Hexosaminidase B</td>
</tr>
<tr>
<td>Heterozygote carriers for Tay-Sachs disease</td>
</tr>
<tr>
<td>Decreased</td>
</tr>
<tr>
<td>Increased</td>
</tr>
<tr>
<td>Homozygotes for Tay-Sachs disease</td>
</tr>
<tr>
<td>Virtually absent</td>
</tr>
<tr>
<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 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 or "tissue-paper" 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 with 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.
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 appears markedly decreased in amount (actually it has been displaced peripherally);

Hurler’s syndrome is one of the mucopolysaccharidoses (MPS), another group of diseases caused by deficiencies of certain lysosomal enzymes that result 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 MPSs 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 (Wilm’s 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, present perhaps in 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 alternating 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

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, and most are found in the abdomen. About two thirds of children with this tumor will have metastatic disease at presentation.
Pediatrics #3  

**Retinoblastoma**

**Retina. Hematoxylin & eosin stain. X5.**  An 18-month-old girl was noted to have esotropia of the right 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 (red arrow) 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 in children before 2 years of age. About 60% are sporadic, while 40% are inherited as an autosomal recessive trait.

Pediatrics #4  

**Congenital Syphilis**

**Upper Image:** This image shows some of the classical findings of full-blown congenital syphilis in a maturing male. These findings include short stubby teeth (Hutchinson's teeth), missing upper incisors, a large cleft palate, and abnormal nostrils.

**Lower Image: 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 #5  

**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.
Placenta Percreta

Placenta percreta is a severe form of placenta accreta. In placenta percreta, the vascular processes of the chorion (the chorionic villi) may invade the full thickness of the myometrium. This can cause an incomplete rupture of the uterus. Even more drastically, the chorionic villi can go right on through both the myometrium and the outside covering of the uterus (serosa), causing complete and catastrophic rupture of the uterus. They may even extend to nearby organs, such as the bladder.

Retroplacenta Hematoma

These sections of placenta show 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 placentae) and pre-eclampsia. A large retroplacental hematoma (30% to 40% of the maternal surface) will compromise fetal maternal exchange, resulting in fetal hypoxia and demise. Neonatal complications include low Apgar scores (low heart rate, depressed respiration, decreased muscle tone, poor cry & cyanosis), intrauterine growth retardation and prematurity.

Acute Chorioamnionitis Placenta, Gross

The fetal surface of the placenta is opaque and yellow green. Microscopic examination will show dense infiltrates of acute inflammatory cells in the amnion and chorion. Acute chorioamnionitis is an infection of the amniotic cavity and fetus usually via the vagina and cervix (ascending infection). 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. Group B Streptococcus, E. coli, Mycoplasma and Candida albicans are the more common pathogens. Clinical presentations include maternal fever, premature rupture of membranes, and fetal distress. Neonatal complications are sepsis and prematurity.

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. 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.
## 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, leading to infection of amniotic cavity &amp; membranes.</td>
<td>Most bacterial infections: <em>Fusobacterium</em>, <em>E. coli</em>, <em>Haemophilus influenzae</em>, <em>Bacteroides species</em>, <em>Gp B Streptococcus</em>, <em>Staphylococcal aureus</em>, <em>Listeria monocytogenes Candida albicans</em>, <em>Herpes simplex</em>, <em>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, and maternal infections and fetal pneumonia, sepsis, and meningitis.</td>
</tr>
<tr>
<td>Villitis (leukocytes around and within fetal villi).</td>
<td>Transplacental (hematogenous) transmission. The infectious agent invades the placenta via the fetal-maternal bloodstream. It is acquired at any time during gestation.</td>
<td>Most viruses &amp; parasites: <em>Cytomegalovirus</em>, <em>Rubella</em> (now rare), <em>Treponema pallidum</em>, <em>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, transplacental (hematogenous) transmission or ascending infection.</td>
<td><em>HIV, Hepatitis B, Group B Streptococcus, Herpes simplex, Parvovirus B19</em>.</td>
<td>Immune disturbance, growth retardation, hepatitis, chronic liver disease, stillbirth, spontaneous abortion, hydrops fetalis, fetal anemia.</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 #10  Complete Hydatidiform Mole**

Histologically, the hydatidiform mole has large avascular villi and areas of trophoblastic proliferation. Usually ultrasound has confirmed the diagnosis before curettage is done to evacuate the tissue seen here.

**Pediatrics #11  Cystic Fibrosis, Pancreas**

**Pancreas. Hematoxylin & eosin stain. X31.** 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, reflecting the atrophy of the intervening acinar tissue.

**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 the amount of sweat chloride is either measured directly with ion-selective electrodes or is determined by the concentration of chloride after the sweat is weighed. As an internal quality control check, the sodium concentration should also be measured, as these values should lie within 10 mmol/L of each other.

**Results:** A [Cl⁻] 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 an infant is 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 [Cl⁻] 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 #12  Cystic Fibrosis, Lung**

**Lung. Hematoxylin & eosin stain. X12.** This is a section of the lung from the same patient and shows some of the common pulmonary findings in this disease. Emphysema is present as well as focal atelectasis and intraalveolar edema fluid. Note 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.
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 (hyaline membrane) 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 is a significant cause of mortality in preterm infants and is related to immature lungs and a deficiency of pulmonary surfactant. Surfactant 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.

<table>
<thead>
<tr>
<th>Pulmonary Surfactant</th>
<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>
<td></td>
</tr>
<tr>
<td>Phosphatidyl glycerol.</td>
<td>10%</td>
<td>36 weeks.</td>
<td></td>
</tr>
<tr>
<td>Sphingomyelin.</td>
<td>2%</td>
<td>Constant during 3rd trimester (used as internal standard).</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous lipids, proteins, and carbohydrates (some of these may be very important).</td>
<td>13%</td>
<td>3rd trimester.</td>
<td></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. The 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>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 #14  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 #15  Kernicterus, Gross

The yellow staining in the brain of a neonate is known as kernicterus. There is a coronal section of medulla on the left and cerebral hemisphere on the right demonstrating kernicterus in deep grey matter of hemisphere and brain stem. Increased unconjugated bilirubin, which accounts for the kernicterus, is toxic to the brain tissue. Kernicterus is more likely to occur with prematurity, low birth weight, and increased bilirubin levels. [Image contributed by Jeannette J. Townsend, MD, University of Utah]
## Schedule

**Monday, September 19**  
10-12 Noon  
Integrated Case-Leukemia  
TBA

**Thursday, September 22**  
1-4 PM  
Path Talk: Hematopoietic System/Lymph Nodes & Spleen  
Laboratory
Week 5: September 12-16
Genetics/Pediatric & Developmental Pathology

Topic: Hematopoietic System / Lymph Nodes and Spleen

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
• White Cells, Lymph Nodes, and Spleen, Chapter14, pp. 661-690; 702-709
• Myeloid Neoplasms, pp.690-702 – for review only.
• Red Cells and Bleeding Disorders, Chapter 13, pp. 619-660 – for review only

Recommended Reading:
Netter's Illustrated Human Pathology
• Chapter 10, Hematopoietic and Lymphatic Tissues

Required Study for Small Groups

PathTalk
Assignments:
• Kodachromes on WebCT
• Slide descriptions
• Journal club articles:
  o Prediction of Survival in Follicular Lymphoma Based on Molecular Features of Tumor-Infiltrating Immune Cells, Dave S. Sandeep, M.D., et al., Volume 351:2159-2165, November 18, 2004 Number 21
  o Prognosis in Follicular Lymphoma, It’s in the Microenvironment, Ralf Kuppers, Ph.D., Volume 351:2152-2153, November 18, 2004 Number 21

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
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:

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

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.

<table>
<thead>
<tr>
<th>CBC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7.10</td>
<td>×10^3/µL WBC</td>
</tr>
<tr>
<td>4.14</td>
<td>×10^3/µL RBC</td>
</tr>
<tr>
<td>13.4</td>
<td>g/dL HGB</td>
</tr>
<tr>
<td>33.1</td>
<td>% HCT</td>
</tr>
<tr>
<td>94.3</td>
<td>fL NCV</td>
</tr>
<tr>
<td>32.4</td>
<td>pg MCH</td>
</tr>
<tr>
<td>34.3</td>
<td>g/dL MCHC</td>
</tr>
<tr>
<td>13.5</td>
<td>% RDW</td>
</tr>
<tr>
<td>2.50</td>
<td>g/dL MCV</td>
</tr>
<tr>
<td>152</td>
<td>×10^6/µL PLT</td>
</tr>
<tr>
<td>8.7</td>
<td>fL MPV</td>
</tr>
<tr>
<td>50.7</td>
<td>% PDW</td>
</tr>
<tr>
<td>13.3</td>
<td>% PCT</td>
</tr>
</tbody>
</table>

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>
<tr>
<td>HCT</td>
<td>36.0 – 44.0 %</td>
<td>40.0 – 49.0 %</td>
</tr>
</tbody>
</table>
**Hematology #2**

**Iron Deficiency Anemia**

*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: 53.8fL). 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 in the normal blood smear (increased HDW or anisochromia).

**Hematology #3**

**Macrocytic Anemia**

*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 called "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 = 110.6 fL) 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 biopsy revealed findings consistent with refractory anemia with ringed sideroblasts (RARS), one of the myelodysplastic syndromes.

### 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 due 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 the cells fall mostly within the flags. This indicates 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 Slightly High</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Slightly 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**

**Leukocytosis**

*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.

Automated hematology analyzers measure the white blood cells and platelets in the peripheral blood. In flow cytometric analysis, 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 (l), monocytes (m), eosinophils (e), and “large, unstained cells” (u)). The density 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 density is slightly increased, reflecting a slightly elevated white blood cell count, in this case mainly due to neutrophils.

**Hematology #6**

**Normal Node**

*Lymph node:* In the *Upper Image*, numerous primary follicles, which by definition lack germinal centers, are present within the cortex. Notice how the follicles are bulging against the subcapsular sinus and capsule. A secondary follicle containing a germinal center surrounded by a mantle zone is also present. Both primary and secondary follicles along with their mantle zones are B-cell areas. This is illustrated in the *Lower Image*, which shows how several reactive follicles stain with the pan-B cell marker CD20. The intervening paracortex is a T-cell zone.

**Hematology #7**

**Reactive Follicles**

Here you see reactive follicles including germinal centers and mantle zones at increasing magnification. In the *Low Power* image, the lymph node capsule is at the top. Note how the mantle zone is thicker toward this capsule and thinner to the point of non-existence toward the middle of the node. Although it is hard to perceive at this magnification, the germinal center is divided into a dark zone at the bottom (composed of large, rapidly proliferating centroblasts) and a lighter zone toward the top (composed of smaller, less proliferative centrocytes). This phenomenon, called "polarization", is an excellent clue that the follicle is benign.

The *High Power* image shows mostly the darker zone of a germinal center with its rapidly proliferating centroblasts. Those centroblasts whose immunoglobulin receptors do not fit snugly with the stimulating antigen undergo programmed cell death, also called "apoptosis". The so-called "tingible-body" macrophages, which make debris-filled gaps in the dark zone, are summoned to mop up the remnants of these miserable centroblasts.
Hematology #8  Toxoplasmosis

Not all patients with lymphadenopathy have malignant disease. Lymph nodes are often enlarged due to numerous infectious or inflammatory conditions. Malignant nodes tend to be hard or rubbery, non-tender, and fixed in position due to fibrosis. Infected or inflamed nodes tend to be soft or fluctuant, tender, and mobile to the palpating hand unless the reaction is severe enough to stimulate fibrosis.

The node illustrated above is infected with *Toxoplasma gondii*, which in immunocompetent patients causes only lymphadenopathy, often cervical. This protozoa has the cat as its definitive host, and humans are infected by contact with feces from an infected animal. The inflammatory response in the node is characterized by a monocytoid B-cell hyperplasia (green arrow), follicular hyperplasia (red arrow), and clusters of epithelioid histocytes (yellow arrow), which tend to encroach upon the hyperplastic follicles.

Hematology #9  AIDS

Persistent generalized lymphadenopathy is an early symptom in HIV+ individuals and is accompanied by headaches, weight loss, fever, and malaise. Persistent generalized lymphadenopathy is defined by extrainguinal lymphadenopathy lasting for at least 3 months and present in at least 2 noncontiguous groups of nodes. In the early stage of HIV infection, the basic finding is marked follicular hyperplasia, with the enlarged follicles often assuming bizarre shapes and containing revved-up, stimulated germinal centers. Much later in the course of the disease, the follicles are decreased in number and appear "burnt-out", often containing residual dendritic cells and only a small number of lymphocytes. The interfollicular region is also depleted of its lymphoid population, which is replaced by plasma cells, vessels, and fibrosis.

Hematology #10  Small Lymphocytic Lymphoma

Small lymphocytic lymphoma is a low-grade, indolent B-cell lymphoma that affects older adults. Though the disease is incurable, patients frequently survive for 8-10 years. At low magnification the lymphoma cells are seen to be a diffuse infiltrate that effaces normal nodal structures such as follicles and may spill into the surrounding soft tissue. At high magnification the individual malignant cells are seen as small cells with scant cytoplasm. They are said to appear "mature" because their chromatin is coarsely clumped, unlike the fine, velvety chromatin seen in immature lymphoblasts. In isolation, they would be very difficult to distinguish from normal, small, resting lymphocytes.

Because the cells are "well-differentiated", they retain the ability of normal lymphocytes to circulate, so they are often seen in the peripheral blood and bone marrow. In fact in most cases their presence in blood and marrow is their predominant manifestation, with only relatively minor lymph node involvement. The disease is then called *chronic lymphocytic leukemia*. Chronic lymphocytic leukemia is the most common adult leukemia in the Western world, whereas small lymphocytic lymphoma constitutes only 4% of non-Hodgkin lymphoma cases.
Follicular lymphoma, which affects mainly older adults, is one of the 2 most common lymphomas in the United States (the other being diffuse large cell lymphoma). It is generally a low-grade, indolent disease. The malignant cells are well-differentiated, so they retain their ability to form follicles. Compared to normal follicles, however, malignant ones are closely packed, poorly defined, lack crisp mantle zones, and contain a comparatively homogeneous cell population with a lower rate of mitosis. Thus they are an example of a rare phenomenon: malignant tissue with a lower proliferation rate than its normal counterpart.

At low magnification, several closely-packed nodules are present with minimal interfollicular areas and essentially no mantle zones. At high magnification, most of the cells are small cleaved cells having irregular nuclear membranes, indistinct nucleoli, and coarse chromatin. Scattered larger malignant lymphoid cells with a rim of amphophilic cytoplasm and vesicular, rounded nuclei with one or more nucleoli are admixed. These lymphomas are graded as 1, 2, and 3, according to the frequency with which the large cells are found.

More than 90% of the cases express monoclonal surface immunoglobulin proteins. The cells are also positive for B-cell markers such as CD20 and usually coexpress CD10. They are almost always negative for CD5. Eighty to 90% are positive for the protein product of the BCL2 gene, and the same percentage are positive for a t(14;18) translocation, which juxtaposes the BCL2 gene on chromosome 18 and the immunoglobulin gene promoter region on chromosome 14.

<table>
<thead>
<tr>
<th>Follicular B-cell Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Predominantly small cleaved cell (Grade 1 of 3).</td>
</tr>
<tr>
<td>Mixed small cleaved and large cell (Grade 2 of 3).</td>
</tr>
<tr>
<td>Predominantly large cell (Grade 3 of 3).</td>
</tr>
</tbody>
</table>

1. Refers to percentage of follicular lymphomas.
**Hematology #12** Non-Hodgkin’s Lymphoma
B-cell Diffuse Large Cell Lymphoma

DLBCL is an aggressive lymphoma with a diffuse growth pattern. It is seen at all ages but is particularly common in adults. The malignant cells are large lymphoid cells (large round or multilobed vesicular nuclei and scant or moderate amounts of cytoplasm) admixed with variable numbers of smaller cells. 25% of cases exhibit a BCL6 gene rearrangement. 30% of cases show a t(14:18) translocation, usually in the setting of a previous follicular lymphoma that transformed. Sometimes the predominant cells are immunoblasts (large round or oval nuclei with prominent central nucleolus and abundant cytoplasm). It is often found as an extra-nodal lymphoma. The bottom image shows a gastric DLBCL, with 3 gastric glands denoted by black arrows toward the top of the image.

- M DLBCLs are most common in adults (median age is 55 yrs) but seen in all age groups including children (5% of NHL in children).
- A DLBCL usually presents as rapidly growing single mass, nodal or extranodal (30% in the GI tract, Waldeyer's ring, skin and other sites).
- 50% are stage III or IV (liver, spleen, bone marrow involvement).
- May respond well to aggressive therapy with overall survival rate of about 50%

**Hematology #13** Multiple Myeloma

Multiple myeloma is a malignant proliferation of plasma cells, which are terminally differentiated B-cells that secrete immunoglobulin. As the name of the disease implies, among the diagnostic criteria is the requirement that multiple sites in the body are involved, usually as lytic bone lesions. The malignant cells proliferate in the marrow, where they form clusters and eventually solid sheets that displace the normal hematopoietic precursors and the fat cells. Although some myelomas are composed of mature-appearing plasma cells that would be difficult to distinguish from benign ones, some more aggressive myelomas feature immature, blastic plasma cells that occasionally cause the disease to be misdiagnosed as acute leukemia.

The upper image shows a low power view of sheets of plasma cells in the marrow, with the insets showing the cells at higher power (left inset) and the cells as they might appear on a marrow smear (right inset). The lower image is a high magnification view of a cytologic smear. Can you detect the nucleoli present in some of the forms, which is an atypical feature for a plasma cell?

**Hematology #14** Hairy Cell Leukemia

This collage of cells on peripheral blood smears depicts abnormal lymphocytes with indistinct cytoplasmic borders and projections, giving the cells a "hairy" appearance. At the lower right can be seen one of these cells with red cytoplasmic staining indicative of tartrate resistant acid phosphatase (TRAP) positivity. This is hairy cell leukemia, an
uncommon B cell proliferation seen mostly in older males and marked by marrow involvement, pancytopenia, and splenomegaly.

**Hematology #15**

**Cutaneous T-cell Lymphoma**

*(Mycosis fungoides)*

**Skin. Hematoxylin & eosin stain. X20.* Malignant T-cells have expanded the dermis as a band-like infiltrate. Several microabscesses are present in the overlying epidermis. The cells in both the microabscesses and the dermis show hyperchromatic nuclei and prominent nuclear folding, which is best appreciated at higher magnification. The malignant forms are CD4+ T-helper cells that often fail to express the pan-T-cell surface antigen CD7. As here they may collect in the epidermis to form a so-called "Pautrier’s microabscess".

**Hematology #16**

**Hodgkin’s Disease (Nodular Sclerosis Type)**

Hodgkin lymphoma is a vast subject unto itself. Until 5-10 years ago, it was called Hodgkin's disease, because the cell of origin was unknown. More recently molecular investigations have shown that the vast majority of cases are clonal proliferations of B-cells that begun their roguish careers by undergoing germinal center mutations that block their further development as B-cells. Additional mutations then render them malignant. The most striking difference from non-Hodgkin lymphoma is the fact that in Hodgkin lymphoma far less than 1% of the cells of involved lymph nodes are malignant. Most of the cells are heterogeneous inflammatory cells that are present as a result of cytokine release directly or indirectly from the malignant cells. The characteristic cell of Hodgkin lymphoma is the "Reed-Sternberg cell" a large, binucleated cell often likened to owl eyes. Mononuclear variants of this cell also exist.

Hodgkin lymphoma is divided into several subtypes. Illustrated here is the *nodular sclerosis* subtype, in which the nodal infiltrate is divided into nodules by broad bands of collagen. Nodular sclerosis Hodgkin lymphoma is the most common subtype and the only one that is more common in females. Affecting cervical and mediastinal lymph nodes, it has an excellent prognosis with contemporary treatment modalities.

**Hematology #17**

**Hodgkin's Disease (Nodular Sclerosis Type), Gross**

**Spleen** Multiple tumor nodules infiltrate the spleen as innumerable nodules in a case of nodular sclerosis Hodgkin lymphoma. Hodgkin lymphoma appears to spread from its original site mainly through lymphatic channels to adjacent lymphoid structures. Involvement of the spleen is thought to reflect hematogenous dissemination and places the disease at a higher stage.
Hematology #18 Normal Spleen

This is the normal histologic appearance of the spleen. Note the small lymphocytes centered around the splenic arteriole at the center, forming the white pulp. Although this follicle does not have a germinal center, germinal centers may be present in the spleen in reactive conditions. Surrounding the white pulp is the red pulp comprising many splenic sinusoids. The spleen acts as a filter, removing old red blood cells and RBC inclusions. The spleen also acts as a storage area for platelets.

Hematology #19 Splenomegaly from Portal Hypertension

Note how immense this spleen is; the ruler is 4.5 cm long. One of the most common causes for splenomegaly is portal hypertension with cirrhosis of the liver. Micronodular cirrhosis from chronic alcoholism is more common in the U.S. than macro nodular cirrhosis following hepatitis B or C infection. This spleen also shows irregular tan-white fibrous plaques over the purple surface. This "sugar icing" has the name hyaline perisplenitis.

Hematology #20 Splenic Infarcts

Here are splenic infarcts in a patient with infective endocarditis. Portions of the vegetations have embolized to the spleen. These infarcts are typical of ischemic infarcts: they are based on the capsule, pale, and wedge-shaped. The remaining splenic parenchyma appears dark red. Why do you think one infarct is white and the other is greyish pink?

Hematology #21 Thymoma

Although the function of the thymus is the education and differentiation of the immature T-cells that reside within it, thymomas are clonal proliferations of the smaller number of thymic epithelial cells. Included in the midst of the neoplastic epithelial cells are a variable proportion of polyclonal T-cells, which are like faithful dogs that remain obedient to their masters even after their masters have turned to crime. Thymomas have some surprising associations, such as myasthenia gravis and pure red cell aplasia.

The image above shows a typical lobulated thymoma. Many thymomas are benign and require no additional treatment after surgical removal. Malignant thymomas include both invasive thymomas that, while cytologically banal, have transgressed their capsules and invaded adjacent structures, and thymic carcinomas, which appear and behave as frank malignancies.
Week 5: September 12-16
Genetics/Pediatric & Developmental Pathology

Schedule

**Monday, October 10**
1-2:30 PM  
Summary: Cardiovascular  
West Lecture Hall

2:30-4 PM  
Gross Presentation: Cardiovascular System  
West Lecture Hall

**Tuesday, October 11**
11-Noon  
Journal Club/Epi/Bio Consult: Cardiovascular System  
Laboratory-Room C207

**Friday, October 14**
1-4 PM  
Path Talk: Cardiovascular System  
Laboratory
Week 5: September 12-16
Genetics/Pediatric & Developmental Pathology

Assignments

Topic: The Cardiovascular System

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Blood Vessels: Chapter 11, pp.511-554
- The Heart: Chapter 12, pp. 555-618

Recommended Reading:
Netter's Illustrated Human Pathology
- Chapter 2, Cardiovascular System

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCT
- Slide descriptions
- Journal club article:
  - Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress, Ilan S. Wittstein, M.D., Volume 352:539-548, February 10, 2005, Number 6

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

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 #2

Aorta with Fatty Streaks, Gross

This is about as normal as an adult aorta in America gets. The faint reddish staining is from hemoglobin that leaked from RBC's following death. The surface is quite smooth, with only occasional faint small yellow lipid streaks visible.

Cardiovascular Diseases #3

Aorta: Fatty Streak

These are 2 images of an aortic fatty streak. The left image is an H & E stained section that shows a collection of foam cells immediately subjacent to the endothelial cells on the intimal surface. The right image shows a section from the same lesion that has been stained with Oil Red O, a process that stains lipid red.

Cardiovascular Diseases #4

Aorta, Ulcerated Plaques, Gross

This is a portion of an aorta with severe atherosclerotic disease. Note the many diffuse, complicated plaques, and compare the surface of this aorta to the aorta in a previous slide that showed only mild fatty streaks.

Cardiovascular Diseases #5

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 of 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 #6  Atherosclerosis

**Coronary artery. Hematoxylin & eosin. X8.** There are several types of arteriosclerosis ("hardening of the arteries").

- Atherosclerosis
- Arteriolosclerosis
  - Hyaline arteriolosclerosis
  - Hypertensive arteriolosclerosis
- Monckeberg medial calcific sclerosis

This slide illustrates an atherosclerotic plaque in 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 #7  Atheromatous Plaque

This high magnification of the atheroma shows numerous foam cells and an occasional cholesterol cleft. A few dark blue inflammatory cells are scattered within the atheroma. What do you think the band of pink material at the bottom of the image toward the left is?

Cardiovascular Diseases #8  Arteriolosclerosis

**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 arteriolosclerosis 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.), a thickened and duplicated endothelial basement membrane, and increased extracellular material. Hyaline arteriolosclerosis can be seen as a normal physiologic feature of aging, in hypertensive disease, and is commonly found in patients with diabetes mellitus.

Cardiovascular Diseases #9  Hypertensive Arteriolosclerosis

**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 #10  
Monckeberg’s Medial Calcific Sclerosis

Monckeberg's medial calcific sclerosis is seen in this artery to the right of thyroid tissue. Dark-purple staining calcium deposits collect in the media of muscular arteries. This finding occurs most often in the elderly and does not typically have serious pathologic consequences because the arterial lumen is not compromised. Small muscular arteries in the pelvis, neck, and breast regions can be affected. Medial calcific sclerosis can also be seen involving the extremities in association with autonomic neuropathy in diabetes mellitus. The calcified arteries may be visualized on radiographs.

Cardiovascular Diseases #11  
Giant Cell Arteritis (Temporal Arteritis)

Artery. Hematoxylin & eosin stain. X32. A 78-year-old woman presented with severe headaches and bitemporal subcutaneous nodules. A biopsy reveals inflammation of the arterial wall mainly by lymphocytes and macrophages. Although it cannot be discerned at this low magnification, there is partial disruption of the internal elastic lamina and focal fibrinoid necrosis. Note the several prominent granulomas containing giant cells. This granulomatous arteritis is found in patients after the age of 50, and over one-half of the them develop polymyalgia rheumatica (stiffness and aching of the neck, shoulder and hips).

Temporal arteritis is one manifestation of giant cell arteritis, which can affect mainly branches of external carotid artery, but sometimes also the great vessels at the aortic arch and coronaries. There is focal granulomatous inflammation of the media.

Cardiovascular Diseases #12  
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 (red arrow) is easily seen and helps to identify the thickened tunica intima.

**Cardiovascular Diseases #13**  
**Polyarteritis Nodosa**

This muscular artery seen at low and high magnification demonstrates a severe vasculitis with acute and chronic inflammatory cell infiltrates, along with necrosis of the vascular wall. This is a case of polyarteritis nodosa (PAN), a form of vasculitis involving mainly small to medium-sized arteries anywhere in the body, but more often renal and mesenteric arteries. The anti-neutrophil cytoplasmic autoantibody (ANCA) test is often positive.

**Cardiovascular Diseases #14**  
**Thromboangiitis Obliterans**

The hallmark of Wegener’s granulomatosis is necrotizing granulomatous inflammation as seen here in the lung at low power (upper image). Scattered multinucleated giant cells and a loose collection of neutrophils and mononuclear cells are present. Organizing fibrosis can also be seen in this disease.

At high power (lower image), the vasculitis is seen to involve a pulmonary artery branch. In this case, the C-ANCA serology was positive and a diagnosis of Wegener's granulomatosis was made.

**Cardiovascular Diseases #15**  
**Wegener's Granulomatosis**

The hallmark of Wegener’s granulomatosis is necrotizing granulomatous inflammation as seen here in the lung at low power (upper image). Scattered multinucleated giant cells and a loose collection of neutrophils and mononuclear cells are present. Organizing fibrosis can also be seen in this disease.

At high power (lower image), the vasculitis is seen to involve a pulmonary artery branch. In this case, the C-ANCA serology was positive and a diagnosis of Wegener's granulomatosis was made.

**Cardiovascular Diseases #16**  
**Aortic Dissection, Gross**

This aorta has been opened longitudinally to reveal an area of fairly limited dissection that is organizing. The red-brown thrombus can be seen in on both sides of the section as it extends around the aorta. The intimal tear would have been at the left. This creates a "double lumen" to the aorta. This aorta shows severe atherosclerosis which, along with cystic medial necrosis and hypertension, is a risk factor for dissection.
Cardiovascular Diseases #17  Aortic Dissection

In this image the dissection is seen within the muscular wall of an artery. An aortic dissection is an extreme emergency and can lead to death in a matter of minutes. The blood can dissect up or down the aorta. Blood dissecting up around the great vessels can close off the carotids. Blood can dissect into the coronaries and shut them off as well.

Cardiovascular Diseases #18  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 an example of a capillary hemangioma.

Cardiovascular Diseases #19  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.

Cardiovascular Diseases #20  Transmural Myocardial Infarct, Gross

This cross section through the heart demonstrates the left ventricle on the right. Extending from the anterior portion at the top of the image and into the septum to its left is a large recent myocardial infarction. The center is tan with surrounding hyperemia. The infarct is "transmural" in that it extends through the full thickness of the wall. What is the difference between an "infarction" and an "infarct"?

Cardiovascular Diseases #21  Myocardial Infarction

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 damaged myocardium shows myocardial fibers that appear smudgy with loss of cross-striations and focal hypereosinophilia. These changes 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 #22 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 #23 Myocardial Infarction, Remote

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 #24 Aortic Valve w/Senile Calcifications, Gross

In this distal view of a previously normal tricuspid aortic valve, we see nodular, white deposits in sinus of Valsalva. This degenerative change is the outcome of wear and tear due to the 40 million cardiac cycles per year. It is found in patients in their seventies and eighties and causes aortic stenosis. With abnormal, congenitally bicuspid aortic valves, similar changes are found in the patients’ sixties.

Note the relatively thin and delicate free edges of the valve. If the degenerative changes had been due to an inflammatory process such as rheumatic fever, most likely the leaflets would be fused and the free edges thickened and distorted.

Cardiovascular Diseases #25 Acute Rheumatic Carditis

Figure 1. Microscopically, acute rheumatic carditis is marked by a peculiar form of granulomatous inflammation with so-called “Aschoff nodules” seen best in myocardium. These are centered in interstitium around vessels as shown here. The myocarditis may be severe enough to cause congestive heart failure.

Figure 2. Here is an Aschoff nodule at high magnification. The most characteristic component is the Aschoff giant cell. Several appear here as large cells with two or more nuclei that have prominent nucleoli. Scattered inflammatory cells accompany them and can be mononuclears or occasionally neutrophils.
Cardiovascular Diseases #26  Non-Bacterial Thrombotic Endocarditis, Gross

The small pink vegetation on the rightmost cusp margin represents the typical finding with non-bacterial thrombotic endocarditis (or so-called "marantic endocarditis"). This is non-infective. It tends to occur in persons with a hypercoagulable state (Trousseau's syndrome, a paraneoplastic syndrome associated with malignancies) and in very ill persons.

Cardiovascular Diseases #27  Aorta: Infective Endocarditis, Gross

The more virulent bacteria causing the acute bacterial form of infective endocarditis can lead to serious destruction, as shown here in the aortic valve. Irregular reddish tan vegetations overlie valve cusps that are being destroyed. Portions of the vegetation can break off and become septic emboli.

Cardiovascular Diseases #28  Infective Endocarditis

Here is a valve with infective endocarditis. The blue bacterial colonies on the lower left are extending into the pink connective tissue of the valve. Valves are relatively avascular, so high dose antibiotic therapy is needed to eradicate the infection.

Cardiovascular Diseases #29  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 #30  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, a 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 as frequently.
Cardiovascular Diseases #31  Cardiac Myxoma

The left atrium and ventricle have been cut open to expose a large, tan-grey mass in the atrium.

The most common primary cardiac tumor in adults is the cardiac myxoma, usually found in the atrium. Against a background of abundant, pale, eosinophilic myxoid material rich in acid mucopolysaccharide, we see a relatively small 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, a cytokine involved in lymphocyte growth and immunoglobulin synthesis.

Cardiovascular Diseases #32  Cardiac Transplant Rejection

This inflammation is mostly mononuclear and perivascular in a patient with a heart transplant. Necrotic myocytes are not seen.
Week 5: September 12-16  
Genetics/Pediatric & Developmental Pathology

Schedule

Week 11

Friday, October 28
9-11 AM  Summary: Pulmonary  West Lecture Hall
11- Noon  Journal Club Epi/Bio Consult: Pulmonary  Laboratory Room C207

Week 13
Monday, November 7
1-4 PM  PathTalk: Pulmonary & Nutrition  Laboratory

Thursday, November 10
10:30 AM - Noon  Integrated Case  TBA

Friday, November 11
1-4 PM  Case Based Study: Pulmonary & Nutrition  Laboratory

Week 14
Monday, November 14
1-4 PM  Gross Presentation: Pulmonary  West Lecture Hall
Topic 1: The Respiratory System

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- The Lung, Chapter 15, pp. 711-772
- Neonatal Respiratory Distress Syndrome (for review only), Chapter 10: pp. 481-483

Recommended Reading:
Netter's Illustrated Human Pathology
- Chapter 3, Respiratory System

Topic 2: Nutrition

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
- Nutrition, Chapter 9, pp. 446-468

Required Study for Small Groups

PathTalk
Assignments:
- Kodachromes on WebCt
- Slide descriptions
- Journal club article:
  - Small Airways in COPD, Peter J. Barnes, D.M., D.Sc., Volume 350:2535-2637, June 24, 2004 Number 26

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

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

Pulmonary #1  Normal Lung, Gross
This is a cross-section of normal lung with only minimal posterior congestion at the lower right due to passive settling of blood during the autopsy. The hilar lymph nodes are small and appear grayish-black due to anthracotic pigment from dusts in the air breathed in, scavenged by pulmonary macrophages, transferred to lymphatics, and collected in lymph nodes.

Pulmonary #2  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 #3  Pulmonary Edema
At high magnification, the alveoli in this lung are filled with a smooth to slightly floccular pink material characteristic of pulmonary edema. Note also that the capillaries in the alveolar walls are congested with many red blood cells. Congestion and edema of the lungs is common in patients with heart failure and in areas of inflammation of the lung.

Pulmonary #4  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 epithelium and capillary endothelium 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 #5**

**Pulmonary Embolus, Gross**

Seen in the pulmonary artery of the left lung on cut section is a large pulmonary thromboembolus. Such thromboemboli typically originate in the leg veins or pelvic veins of persons who are immobilized. Other contributing factors include trauma to the extremities, hypercoagulable states (Trousseau's syndrome in patients with carcinomas; protein C or S deficiency; use of oral contraceptives), heart failure, pregnancy, and older age.

**Pulmonary #6**

**Pulmonary 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 that 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.

**Pulmonary #7**

**Pulmonary Embolus-Infarction**

**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. An arrow points to the organization of the embolus in the vessel, although it is hard to perceive at this magnification.

| **General Blood Gas Patterns in Various Conditions** |
|-----------------|------------|-----------------|
| **Condition**   | **Arterial Po₂** | **Acid-Base Status** |
| Pulmonary embolus | Hypoxemia | Respiratory alkalosis from hyperventilation (Pco₂ usually normal) |
| ARDS            | Hypoxemia | Respiratory alkalosis eventually leading to metabolic acidosis and then respiratory acidosis (Pco₂ increased) |
| Bronchopneumonia Lobar pneumonia | Usually normal; Hypoxemia if pneumonia severe | Acid-base disorder not usually found; respiratory acidosis with CO₂ retention if pneumonia severe |
| Pulmonary edema | Hypoxemia | May lead to metabolic acidosis; with CO₂ retention may get respiratory acidosis as well |
| Chronic obstructive pulmonary disease | Hypoxemia | Pink-puffer syndrome (panacinar emphysema); respiratory alkalosis due to tachypnea – can |
lead to respiratory acidosis.

Blue-bloater syndrome (centriacinar emphysema in association with chronic bronchitis); CO₂ retention and respiratory acidosis; eventually metabolic acidosis develops.

| Myocardial infarction | Hypoxemia | Metabolic acidosis (Pco₂ usually normal) |

1. Wide variations in acid-base findings are often found in these conditions.

**Pulmonary #8  Chronic Obstructive Pulmonary Disease**

This lung shows the ravages of chronic obstructive pulmonary disease with superimposed pneumonia. Chronic bronchitis does not have characteristic pathologic findings, but is defined clinically as a persistent productive cough for at least three consecutive months in at least two consecutive years. Most patients are smokers. Often, there are features of emphysema as well.

**Pulmonary #9  Bronchopneumonia, Gross**

The pattern of patchy distribution of a bronchopneumonia is seen in this lung. The consolidated areas here very closely match the pattern of lung lobules (hence the term "lobular" pneumonia). Pneumonias may also involve an entire lobe or a major portion of one, in which case they may be called "lobar". Pneumonias may be acquired either in the community or in the hospital. The major bacterial agents (there are also viral and mycoplasmal agents) of community-acquired disease are *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *S. aureus*, and *Klebsiella pneumoniae*. Bacterial causes of hospital acquired pneumonia include gram-negative rods and *S. aureus*.

**Pulmonary #10  Pulmonary Abscess**

*Lung. Hematoxylin & eosin stain. X5.* This is a photomicrograph of an abscess from a young boy with chronic granulomatous disease, an 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 border of the abscess contains fibroblasts and 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><em>Streptococcus</em></td>
<td>Aspiration from</td>
<td>Lobar</td>
<td>A common cause of</td>
</tr>
</tbody>
</table>
### **Week 5: September 12-16**
**Genetics/Pediatric & Developmental Pathology**

<table>
<thead>
<tr>
<th>Pneumoniae</th>
<th>Upper Airway Colonization</th>
<th>Bronchopneumonia; Necrosis Not Usually Found (Except for Type 3); Usually Resolves</th>
<th>Community-Acquired Pneumonia. High-Risk Groups: Alcoholics, HIV Patients, the Very Young or Old, Splenectomized Patients, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Aspiration from Nasopharynx Colonization; Hematogenous Spread</td>
<td>Bronchopneumonia; Necrotizing Bronchitis; Septic Infarcts; Abscesses.</td>
<td>Patients with Soft Tissue Staph Infections, IV Lines, IV Drug Users, Endotracheal Intubation. High-Risk Groups: Similar to Above.</td>
</tr>
<tr>
<td><em>Pseudomonas Aeruginosa</em></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 #11

**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 #12  Pulmonary Tuberculosis, Gross

On closer inspection, the granulomas have areas of caseous necrosis. This is very extensive granulomatous disease. This pattern of multiple caseating granulomas primarily in the upper lobe is most characteristic of secondary (reactivation) tuberculosis. However, fungal granulomas (histoplasmosis, cryptococcosis, coccidiodomycosis) can mimic this pattern as well.

Pulmonary #13  Pulmonary Tuberculosis

The edge of a pulmonary granuloma is shown here at medium power magnification. Amorphous pink caseous material is present toward the upper right, composed of the necrotic elements of the granuloma as well as the infectious organisms. This area is ringed by the inflammatory component with epithelioid cells lymphocytes, and fibroblasts. A Langhans multi-nucleated giant cell is seen as well.

Pulmonary #14  Pulmonary Aspergillosis, Gross

This is a fungal granuloma produced by Aspergillus. It has an irregular, red margin and a firm, tan-orange center. If you couldn't tell (or weren't told) that this is a granuloma, what feature lets you know that this is very likely an infective process instead of a neoplastic or vascular process??

Pulmonary #15  Pulmonary Aspergillosis

The hyphae of Aspergillus are seen clearly here. Aspergillus has a propensity to invade into blood vessels.

Pulmonary #16  Pulmonary Fibrosis

Lung. Masson trichrome stain. X5. This is an example of late stage diffuse interstitial lung disease showing extensive areas of architectural destruction. Alveoli are lost and others have markedly thickened walls. The term for this histologic picture is "honeycomb lung". At higher magnification we would see that the widened septa contain 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 #17  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 nonfibrogenic, 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 #18  Asbestosis Body

This is the causative agent for asbestosis. This long, thin object is an asbestos fiber. This photomicrograph was taken from a cytology aspirate smear rather than a tissue section, so around the fiber you can see whole cells. Some houses, business locations, and ships still contain building products with asbestos, particularly insulation materials, so care must be taken when doing remodelling or reconstruction.

Pulmonary #19  Asbestosis

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 #20  Plaques-Lung, Gross

Another gross lesion typical for pneumoconioses, and asbestosis in particular, is a fibrous pleural plaque. Seen here on the superior pleural side of the diaphragmatic leaves are several tan-white pleural plaques.

Pulmonary #21  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. This is mined mainly in South Africa but 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 #22**  **Sarcoidosis**  
**Lung, Hematoxylin & eosin stain. X50.** Illustrated are several noncaseating granulomas (if you want to be hoity-toity, you can use the true Greek plural and call them "granulomata") in a lung biopsy from a young man with sarcoidosis. The granulomas are composed of epithelioid histiocytes (so-called because they have so much cytoplasm they resemble epithelial cells) 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 #23**  **Squamous Cell Carcinoma of the Lung, Gross**
This is a squamous cell carcinoma of the lung that is arising centrally in the lung (as most squamous cell carcinomas do). It is obstructing the right main bronchus. The neoplasm is very firm and has a pale white to tan cut surface.

**Pulmonary #24**  **Squamous Cell Carcinoma of the Lung**
This is the microscopic appearance of squamous cell carcinoma with nests of polygonal cells with pink cytoplasm and distinct cell borders. The nuclei are hyperchromatic and angular.

**Pulmonary #25**  **Adenocarcinoma of the Lung 1**
This is the microscopic appearance of squamous cell carcinoma with nests of polygonal cells with pink cytoplasm and distinct cell borders. The nuclei are hyperchromatic and angular.

**Pulmonary #26**  **Adenocarcinoma of the Lung 1**  
**Lung, Hematoxylin & eosin stain. X50.** A distinct subtype of pulmonary adenocarcinoma is bronchioloalveolar carcinoma of the lung. The alveolar walls and ducts are lined by malignant cells that can vary from cuboidal to columnar in character.
**Pulmonary #27**  
**Small Cell Carcinoma of the Lung, Gross**

Here is an oat cell carcinoma which is spreading along the bronchi. The speckled black rounded areas represent hilar lymph nodes with metastatic carcinoma. These neoplasms are more amenable to chemotherapy than radiation therapy or surgery, but the prognosis is still poor. Oat cell carcinomas occur almost exclusively in smokers.

**Pulmonary #28**  
**Small Cell Carcinoma of the Lung**

This is the microscopic pattern of a small cell anaplastic (oat cell) carcinoma in which small dark blue cells with minimal cytoplasm are packed together in sheets. The cells have dark, dusty chromatin and inapparent nucleoli. The cells are fragile and are often subject to crush artifact from the process of performing the biopsy or cutting a tissue section.

Oat cell carcinomas, which are a highly malignant form of neuroendocrine tumor, are often associated with paraneoplastic syndromes from hormonal effects. The ectopic ACTH syndrome and the syndrome of inappropriate ADH are two such syndromes.

**Pulmonary #29**  
**Bronchial Carcinoid Tumor, Lung**

Here is a well circumscribed mass arising from the bronchial wall and composed of uniform small blue cells in sheets and nests. It is growing within the endobronchial space (the black arrows indicate the bronchial lining epithelium, with the bronchial lumen above). This a carcinoid tumor, considered possibly the benign counterpart of the small cell carcinoma. These tumors usually reach 1 to 2 cm in size before producing symptoms related to obstruction and bleeding.
### Week 16 - November 28-December 4

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<th>Event Description</th>
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<tr>
<td>Friday, Dec 2</td>
<td>1-3 PM</td>
<td>Summary: GI/ Hepatobiliary/ Oral Cavity</td>
<td>West Lecture Hall</td>
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### Week 17 - November 5-8

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<tr>
<td>Monday, Dec 5</td>
<td>1-4 PM</td>
<td>PathTalk: GI/ Hepatobiliary/ Oral Cavity</td>
<td>Laboratory</td>
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<tr>
<td>Tuesday, Dec 6</td>
<td>1-3 PM</td>
<td>Gross Presentation: GI/ Hepatobiliary/Oral Cavity</td>
<td>West Lecture Hall</td>
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### Week 18 - November 13-16

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<tr>
<td>Tuesday, Dec 13</td>
<td>9:30-11 AM</td>
<td>Integrated Case: Asthma</td>
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<td>Thursday, Dec 15</td>
<td>1-3 PM</td>
<td>Lecture: Oral Cavity &amp; Related Structures</td>
<td>West Lecture Hall</td>
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<tr>
<td></td>
<td>3-4 PM</td>
<td>Journal Club/Epi-Bio Consult: Renal</td>
<td>Laboratory C207</td>
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Week 16-18: November 28-December 16
Gastrointestinal Tract/Hepatobiliary Pathology//Oral Cavity and Related Structures

Assignments

Topic 1: Gastrointestinal Tract

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
• The Gastrointestinal Tract, Chapter 17, pp.797-876

Recommended Reading:
Netter's Illustrated Human Pathology
• Chapter 4, Gastrointestinal System

Topic 2: Hepatobiliary Pathology

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
• The Liver and Biliary Tract, Chapter 18, pp. 877-938
• The Pancreas (Exocrine), Chapter 19, pp. 939-954

Recommended Reading
Netter's Illustrated Human Pathology
• Chapter 5, Liver, Gallbladder and Pancreas

Topic 3: Pathology of the Oral Cavity and Related Structures

Required Reading:
Robbins and Cotran Pathologic Basis of Disease, 7th Edition,
• Head and Neck: Chapter 16, pp. 773-796

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

Required Study for Small Groups

PathTalk
Assignments:
• Kodachromes on WebCt
• Slide descriptions
• Journal club articles:
  No journal club articles this week
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 Esophagus**

**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 Pylori in the Stomach**

**Top Image:** This is an example of chronic gastritis. There is a dense chronic inflammatory cell infiltrate in the lamina propria. Focally some of the glands show occasional goblet cells indicative of intestinal metaplasia. The red arrow points to such a focus, but the goblet cell is difficult to resolve at this magnification. There may be a subtle component of acute gastritis in the form of neutrophils, but we would need greater magnification to see it.

**Bottom Image:** Chronic gastritis and peptic ulcer disease are often accompanied by infection with *Helicobacter pylori*. This small curved to spiral rod-shaped bacterium is found in the surface epithelial mucus of most patients with active gastritis. The rods are seen here with a methylene blue stain.

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 (dimly
seen at the right) inserted into 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 of the patient’s cirrhosis. This shunts the blood from the portal vein 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. The black arrow points to the esophageal-gastric junction.

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

**Stomach: Peptic Ulcer** 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. Note that the edges are ragged and rolled, but they are not significantly heaped up compared to the surrounding epithelium. Heaped up borders are more characteristic of malignancy ulcers.

The base of an ulcer, whether it be from the stomach or duodenum, usually shows a mix of fibrin, necrotic debris and inflammatory cells, and may be quite smooth due to peptic digestion of its surface. 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 the group of patients who are not long-term users of non-steroidal anti-inflammatory drugs (which are themselves a major cause of ulcers). 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.** This image shows an excavated gastric adenocarcinoma surrounded by relatively normal gastric rugae. The shaggy, hemorrhagic base of the malignancy is seen in the middle of its heaped-up margin.

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

**Stomach. Hematoxylin & eosin stain. [top image].** Several histologic patterns of gastric adenocarcinoma have been described. This is an example of the intestinal type, although it is not well-differentiated and lacks the mucin-containing goblet cells of colonic glands. Nonetheless it is sufficiently differentiated so that its glandular differentiation is obvious. These intestinal-type carcinomas tend to grow along broad, cohesive fronts in an expansive growth pattern.
Week 16-18: November 28-December 16
Gastrointestinal Tract/Hepatobiliary Pathology/Oral Cavity and Related Structures

**Stomach. Hematoxylin & eosin stain. [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 to produce a diffuse thickening termed "linitis plastica". The inset shows a high magnification picture of the malignant cells. In many of them the droplet of mucin in the cytoplasm pushes aside the nucleus to create the signet-ring appearance.

**GI/Liver/Nutrition/Oral Cavity #8** Meckel’s Diverticulum

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 Enterocolitis

**Top Image** This is an example of pseudomembranous enterocolitis. The mucosal surface of the colon seen here is hyperemic and is partially covered by a yellow-green exudate. The mucosa itself is not eroded. Broad spectrum antibiotic usage (such as clindamycin) and/or immunosuppression allows overgrowth of bacteria such as Clostridium difficile or S. aureus or fungi such as Candida to cause this appearance. The colonoscopic appearance is seen below.

**Bottom Image** Microscopically, the pseudomembrane (in the upper half of the image) is seen to be composed of inflammatory cells, necrotic epithelium, and mucus in which the overgrowth of microorganisms takes place. The underlying mucosa (in the bottom half of the image) shows congested vessels, but is still intact.

Please see the endoscopic image of this lesion.

**GI/Liver/Nutrition/Oral Cavity #10** Ulcerative Colitis, Gross

**Top Image** This gross appearance is characteristic for ulcerative colitis. The most intense inflammation begins at the lower right in the sigmoid colon and extends upward and around to the ascending colon. At the lower left is the ileocecal valve with a portion of terminal ileum that is not involved. Inflammation with ulcerative colitis tends to be continuous along the mucosal surface and tends to begin in the rectum. The mucosa becomes eroded, as in this photograph, which shows only remaining islands of mucosa called "pseudopolyps".

**Bottom Image** At higher magnification, the pseudopolyps can be seen clearly as raised red islands of inflamed mucosa. Between the pseudopolyps is only remaining muscularis.
However, the process is primarily mucosal, without transmural inflammation and without fistula formation.

**GI/Liver/Nutrition/ Oral Cavity #11  Ulcerative Colitis**

**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, indicates active disease, although a similar picture can be seen in other diseases. 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.

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

**Top Image** This portion of terminal ileum demonstrates the gross findings with Crohn's disease. Though any portion of the gastrointestinal tract may be involved with Crohn's disease, the small intestine--and the terminal ileum in particular--is most likely to be involved. The middle portion of bowel seen here has a thickened wall, and the mucosa has lost the regular folds. The serosal surface demonstrates reddish, indurated adipose tissue that creeps over the surface. Serosal inflammation leads to adhesions. The areas of inflammation tend to be discontinuous throughout the bowel.

**Bottom Image** Microscopically, Crohn's disease is characterized by transmural inflammation. Here, inflammatory cells (the bluish infiltrates) extend from mucosa through submucosa and muscularis and appear as nodular infiltrates on the serosal surface with pale granulomatous centers.

The endoscopic appearance with colonoscopy, demonstrating mucosal erythema and erosion, is seen below.

**GI/Liver/Nutrition/ Oral Cavity #13  Diverticular Disease**

Diverticula are outpouchings of colonic mucosa through the muscularis propria where it is penetrated by arteries. Such foci represent an area of weakness in the wall. The openings of the diverticula are sometimes difficult to appreciate, but they are well visualized here on cross-section (the specimen has been fixed in formalin). 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.
GI/Liver/Nutrition/ Oral Cavity #14  Adenomatous Polyp, Gross

This adenomatous polyp has a hemorrhagic surface (which is why they may first be detected with stool occult blood screening) and a long narrow stalk. The size of this polyp--above 2 cm--makes the possibility of malignancy more likely, but this polyp proved to be benign. In the endoscopic view on colonoscopy seen below, there is a large pedunculated polyp on a long stalk.

GI/Liver/Nutrition/ Oral Cavity #15  Adenomatous Polyp

This small adenomatous polyp (tubular adenoma) is much smaller than the large, pedunculated specimen in the previous gross photograph. At the end of a small stalk, it is seen microscopically to have more crowded, disorganized glands than the normal underlying colonic mucosa. Goblet cells are less numerous and the cells lining the glands of the polyp have hyperchromatic nuclei. However, it is still well-differentiated and circumscribed, without invasion of the stalk, and is benign.

GI/Liver/Nutrition/ Oral Cavity #16  Adenocarcinoma of the Colon

Colon. Hematoxylin & eosin stain. X40. Most colonic adenocarcinomas are moderately or well-differentiated tumors consisting of glands of various sizes 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 indicates a worse prognosis when it represents over 50% of the tumor.

GI/Liver/Nutrition/ Oral Cavity #17  Colon, Familial

This is familial polyposis coli. The mucosal surface of the colon is essentially a carpet of small adenomatous polyps. Even though the polyps are small now, there is a 100% risk over time for development of adenocarcinoma. A total colectomy is indicated, generally before the patient is 20. Patients with this disorder inherit a faulty adenomatous polyposis coli (APC) gene.

GI/Liver/Nutrition/ Oral Cavity #18  Prolapsed Hemorrhoids

Seen here is the anus and perianal region with prominent prolapsed true (internal) hemorrhoids. Hemorrhoids consist of dilated submucosal veins which may thrombose and rupture with hematoma formation. External hemorrhoids form beyond the intersphincteric groove to produce an "acute pile" at the anal verge. Chronic constipation, chronic diarrhea, pregnancy, and portal hypertension enhance hemorrhoid formation. Hemorrhoids can itch and bleed (usually bright red blood, during defecation). Seen on colonoscopy are views of hemorrhoids at the anorectal junction.
GI/Liver/Nutrition/ Oral Cavity #19  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.

GI/Liver/Nutrition/ Oral Cavity #20  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.

GI/Liver/Nutrition/ Oral Cavity #21  Acute Viral Hepatitis

Individual hepatocytes are affected by viral hepatitis. Viral hepatitis A rarely leads to significant necrosis, but hepatitis B can produce a fulminant hepatitis with extensive necrosis. A large pink cell undergoing "ballooning degeneration" is seen below the right arrow. At a later stage, a dying hepatocyte is seen shrinking down to form an eosinophilic "councilman body" below the arrow on the left. Other hepatocytes are swollen and have granular pink cytoplasm.

GI/Liver/Nutrition/ Oral Cavity #22  Chronic Active Hepatitis

Liver. Hematoxylin & eosin stain. X78. Some areas of the limiting plate (the border between the portal area and the lobule) 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, which is being replaced by fibrosis. The black arrow points to a bile duct.

GI/Liver/Nutrition/ Oral Cavity #23  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 in 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, alphal-antitrypsin deficiency, and Wilson’s
disease, it can also accompany micronodular cirrhosis in the above conditions as well as in alcoholic liver disease.

**GI/Liver/Nutrition/ Oral Cavity #24 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 shows jaundice, spider angioma and ascites. One of the characteristic histologic findings in alcoholic liver disease is steatosis—the intracellular accumulation of fat. This is 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 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 #25 Hemachromatosis**

**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, a combination sometimes called "bronzed" diabetes.

**GI/Liver/Nutrition/ Oral Cavity #26 Wilson's Disease**

The red-brown granular material seen here is excessive lysosomal copper in a patient with the rare autosomal recessive disorder of Wilson's disease. The ceruloplasmin that transports serum copper is quite low in Wilson's disease, leading to excessive copper accumulation in brain, eye, and liver. CNS disease is most marked by neuronal degeneration of the basal ganglia, especially the putamen. Kayser-Fleischer rings are seen on slit-lamp examination of the cornea. Hepatic copper accumulation results in fatty change (seen here with cholestasis as well), acute hepatitis, chronic hepatitis, and eventual cirrhosis. Urinary copper excretion is increased.

**GI/Liver/Nutrition/ Oral Cavity #27 Hepatocellular Carcinoma**

Here is an hepatocellular carcinoma. 85% of such cases occur in parts of the world with high rates of chronic hepatitis B viral infection. In the West HBV is less common, and most liver cancers arise in the setting of cirrhosis. In the U.S., chronic alcoholism is the most common cause. The neoplasm is large and bulky and has a greenish cast because it contains bile. To the right of the main mass are smaller satellite nodules. The color of the tissue is greyish because it has been fixed.
GI/Liver/Nutrition/ Oral Cavity #28  Metastatic Tumors

Note the numerous mass lesions that are of variable size. Some of the larger ones demonstrate central necrosis. The masses are metastases to the liver. The obstruction from such masses generally elevates alkaline phosphatase, but not all bile ducts are obstructed, so hyperbilirubinemia is typically not present. Also, the transaminases are usually not greatly elevated.

GI/Liver/Nutrition/ Oral Cavity #29  Obstructive Liver Disease

Liver. Hematoxylin & eosin stain. X78. If the obstruction continues, bile accumulates in the bile ducts, ductules and even 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 case the cause of the obstruction was a carcinoma of the head of the pancreas, but choledocholithiasis, common bile duct tumors, chronic pancreatitis, and scarring from previous surgery can also lead to similar liver pathology.

GI/Liver/Nutrition/ Oral Cavity #30  Normal Gallbladder

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. A good trivia question is, "What is the only part of the GI tract with only a single muscularis layer (i.e. there are no distinct mucosa and submucosa)?"

GI/Liver/Nutrition/ Oral Cavity #31  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. The black arrow points to residual epithelium.

GI/Liver/Nutrition/ Oral Cavity #32  Cholelithiasis

Multiple yellow-tan faceted gallstones are seen in the opened gallbladder pictured here. It is possible for a stone to exit the gallbladder via the cystic duct. It may then produce obstruction of cystic duct, or it may get into the common bile duct and obstruct that. It may obstruct at the ampulla of Vater and produce a pancreatitis. Biliary tract obstruction leads to jaundice with increased total and direct bilirubin in serum.
GI/Liver/Nutrition/ Oral Cavity #33  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.

GI/Liver/Nutrition/ Oral Cavity #34  Acute Pancreatitis

Upper Image: Yellow-tan foci of fat necrosis are visible throughout the pancreas seen here which has been sectioned in half. There is some edema, but no hemorrhage in this case of mild acute pancreatitis.

Lower Image: This image is from a different, more severe case. Microscopically, acute pancreatitis has necrosis of pancreatic parenchyma (lower left) with acute inflammation and fat necrosis (right and upper part of photograph). Fat necrosis appears grossly as tan-yellow flecks of soft material within and on the surface of pancreas as well as on mesentery.

GI/Liver/Nutrition/ Oral Cavity #35  Adenocarcinoma of the Pancreas

At high magnification, the microscopic appearance of an adenocarcinoma of the pancreas is seen. At the left (black arrow) can be seen normal pancreatic acini, but the neoplasm is composed of small irregular glands.

GI/Liver/Nutrition/ Oral Cavity #36  Celiac Disease

Normal small intestinal mucosa is seen at the left, and mucosa involved by celiac sprue at the right. There is blunting and flattening of villi with celiac disease, and in severe cases a loss of villi with flattening of the mucosa as seen here. Celiac sprue has a prevalence of about 1:2000 Caucasians, but is rarely seen in other races. Over 95% of affected patients will express the DQw2 histocompatibility antigen, which suggests a genetic basis.

GI/Liver/Nutrition/ Oral Cavity #37  Whipple’s Disease

Another cause of malabsorption and malnutrition, albeit a rare one, is Whipple’s disease. This biopsy is from an adult male with a 10-month history of diarrhea and fatty stools. In this photomicrograph, macrophages and lymphocytes (seen at higher magnification in the inset) are present in the lamina propria of the intestine. 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-blown 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 2oxidation-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.

**GI/Liver/Nutrition/ Oral Cavity #39 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 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  Squamous Cell Carcinoma

The normal respiratory tract pseudostratified columnar epithelium has been replaced by the metaplastic squamous epithelium as seen at the left. Arising at the center and right is a well-differentiated squamous cell carcinoma that infiltrates downward into the submucosa.

GI/Liver/Nutrition/ Oral Cavity #42  Warthin’s Tumor

Pathologists sometimes call a lesion with a very distinctive histologic appearance a "purple cow" or an "Aunt Minny". This is such a lesion, a benign papillary cystadenoma lymphomatosum, or Warthin's tumor, of salivary gland. There are cystic to cleft-like spaces filled with pale pink mucinous to serous secretions. The spaces are lined by a double layer of pink (oncocytic) cuboidal to columnar epithelial cells over papillary fronds. The fronds beneath the epithelium are filled with lymphocytes, sometimes with germinal centers. A rim of compressed normal salivary gland parenchyma is seen at the left.

This is the second most common salivary gland tumor. It is almost always found in the parotid gland, is much more common in males, and in some cases can be multifocal or bilateral.
# Master Schedule
## Fall Semester

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<th>Date</th>
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<th>Event</th>
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<td><strong>Monday, August 15</strong></td>
<td></td>
<td>Orientation</td>
<td>West Lecture Hall</td>
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<tr>
<td>10-Noon</td>
<td></td>
<td><strong>Cell Injury &amp; Environmental Pathology</strong></td>
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<tr>
<td><strong>Tuesday, August 16</strong></td>
<td>1-2 PM</td>
<td>Lecture: Apoptosis and Necrosis</td>
<td>West Lecture Hall</td>
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<td></td>
<td>2-4 PM</td>
<td>Case-Based Study: Cell Injury &amp; Environmental Pathology</td>
<td>Laboratory</td>
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<td><strong>Thursday, August 18</strong></td>
<td>1-4 PM</td>
<td>PathTalk: Cell Injury &amp; Environmental Pathology</td>
<td>Laboratory</td>
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<tr>
<td><strong>Friday, August 19</strong></td>
<td>10-11AM</td>
<td>Summary: Inflammation/Tissue Repair</td>
<td>West Lecture Hall</td>
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<td>11 AM-Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory – Room C207</td>
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<tr>
<td><strong>Tuesday, August 23</strong></td>
<td>1-2 PM</td>
<td>Lecture: General Laboratory Medicine</td>
<td>West Lecture Hall</td>
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<td></td>
<td>2-4 PM</td>
<td>Case-Based Study: Inflammation</td>
<td>Laboratory</td>
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<td><strong>Thursday, August 25</strong></td>
<td>2-5 PM</td>
<td>Path Talk: Inflammation</td>
<td>Laboratory</td>
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<td><strong>Friday, August 26</strong></td>
<td>10-11AM</td>
<td>Summary: Immunity</td>
<td>West Lecture Hall</td>
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<td>11AM-Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory – Room C207</td>
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<tr>
<td><strong>Tuesday, August 30</strong></td>
<td>1-2 PM</td>
<td>Lecture:” What Do Pathologists Do?”</td>
<td>West Lecture Hall</td>
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<td></td>
<td>2-4 PM</td>
<td>Case Based Study: Immunity</td>
<td>Laboratory</td>
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<tr>
<td><strong>Thursday, September 1</strong></td>
<td>2-5 PM</td>
<td>PathTalk: Immunity</td>
<td>Laboratory</td>
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<td><strong>Friday, September 2</strong></td>
<td>10-11 AM</td>
<td>Summary: Neoplasia</td>
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<td>11 AM-Noon</td>
<td>Journal club/Epi-Bio Consult</td>
<td>Laboratory C207</td>
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Master Schedule
Fall Semester

Tuesday, September 6
2-4 PM
Neoplasia
Case-Based Study: Neoplasia Laboratory

Thursday, September 8
2-5 PM
Path Talk: Neoplasia Laboratory

Friday, September 9
10-11AM
Summary: Genetics/Pediatric & Developmental Pathology
West Lecture Hall
11 AM- Noon
Journal club/Epi-Bio Consult Lab – Room C207

Tuesday, September 13
1-2 PM
Lecture: Introduction to the Autopsy West Lecture Hall
2-4 PM
Case-Based Study: Genetics/Pediatric & Developmental Pathology Laboratory

Thursday, September 15
2-5 PM
Path Talk: Genetics/Pediatric & Developmental Pathology Laboratory

Friday, September 16
10-11 AM
Summary: Hemopoietic System/Lymph Nodes and Spleen West Lecture Hall
11-12 Noon
Journal club/Epi-Bio Consult Lab – Room C207

Monday, September 19
10-12 Noon
Integrated Case: Leukemia TBA

Thursday, September 22
1-4 PM
Path Talk: Hemopoietic System/Lymph Nodes & Spleen Laboratory

Tuesday, September 27
1-4 PM
Exam Preparation Week

Wednesday, September 28
9-Noon
Independent Study

Thursday, October 6
9-Noon
Exam Week
Examination Lecture Halls
### Master Schedule  
**Fall Semester**

#### Cardiovascular Pathology

**Monday, October 10**  
1-2:30 PM  
Summary: Cardiovascular  
West Lecture Hall  
2:30-4 PM  
Gross Presentation: Cardiovascular System  
West Lecture Hall

**Tuesday, October 11**  
11-Noon  
Journal club/Epi-Bio Consult: Cardiovascular System  
Lab – Room C207

**Friday, October 14**  
1-4 PM  
Path Talk: Cardiovascular System  
Laboratory

**Friday, October 28**  
9-11 AM  
Summary: Pulmonary  
West Lecture Hall  
11-Noon  
Journal club/Epi-Bio Consult: Pulmonary  
Lab – Room C207

#### Respiratory Pathology

**Monday, November 7**  
1-4 PM  
PathTalk: Pulmonary & Nutrition  
Laboratory

**Thursday, November 10**  
10:30 AM-Noon  
Integrated Case: Cardiovascular  
TBA

**Friday, November 11**  
1-4 PM  
Independent Study  
Laboratory

**Monday, November 14**  
1-4 PM  
Gross Presentation: Pulmonary  
West Lecture Hall

#### GI etc. Pathology

**Friday, December 2**  
1-3 PM  
Summary: GI/Hepatobiliary/Oral  
West Lecture Hall

**Monday, December 5**  
1-4 PM  
PathTalk  
Laboratory

**Tuesday, December 6**  
1-3 PM  
Gross Presentation: GI/Hepatobiliary  
West Lecture Hall

**Tuesday, December 13**  
9:30-11 AM  
Integrated Case: Asthma  
TBA
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<tr>
<td>1-3 PM</td>
<td>Lecture: Oral Cavity &amp; Related Structures</td>
<td>West Lecture Hall</td>
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<tr>
<td>3-4 PM</td>
<td>Journal club/Epi-Bio Consult</td>
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