Pathology C 601
Infectious Diseases

Assignment page

Reading:

Robbins: Chapter 8

Wheater, Chapter 4

Clinical Lab Source:

- HIV
- Candida
- Strep antibodies
- Chlamydia
- Clostridium difficile
- WBC differential

Laboratory assignment:

- C601/C602 Histopathology manual, Infectious Diseases unit.
- Pay special attention to the following slides: 1, 16, 76, 77, 78, 131, 165, 166, 173

On-line assignment, there are two:

1. Infectious disease tutorial, on your CD and the web.

2. Case 1, Mr. Martin's fever, on your CD or through the web if you chose. It's the same both places.

I'm sure by now you know the drill. You must take the **on-line quiz** at the end. As with all of the cases, you will see there are two quizzes. One is for you to practice with and the other is for the grade. To do the graded quiz, you must **connect to the Quizsite Server** through the Internet.

Infectious Diseases

I. What's really the big story here?

A. What's an infectious disease in the first place?

B. Basic elements and factors determining if a "disease" will develop

1. Host

2. Bug

3. Environment

C. Types or groups of organisms

D. Mechanisms of injury (much more involved than you might think)

E. Specific diseases

II. Koch's postulates still applied today but with a few modifications

A. Linkage of bug with disease; the original recipe

1. Bug is regularly found with lesion
2. Can grow bug in isolated colonies
3. Inoculation results in disease
4. Recovery of bug from experimental inoculation that produced the disease

B. New and improved Koch

1. Phenotypic trait isolated with virulent strains of bug
2. Inactivation of gene responsible for virulence results in no disease
3. Replacement of gene results in disease

III. What's new?

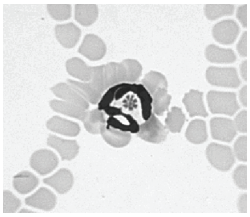
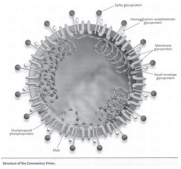


TABLE 8–3 Some Recently Recognized Infectious Agents and Manifestations

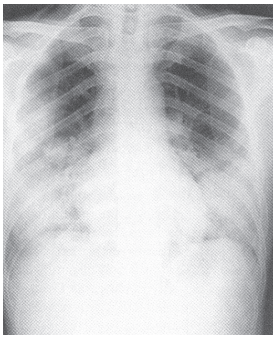
Date Recognized	Infectious Agent	Manifestations
1977	Ebola virus Hantaan virus *Legionella pneumophila* *Campylobacter jejuni*	Epidemic Ebola hemorrhagic fever Hemorrhagic fever with renal syndrome Legionnaires disease Enteritis
1980	HTLV-I	T-cell lymphoma or leukemia, HTLV-associated myelopathy
1981	*Staphylococcus aureus*	Toxic shock syndrome
1982	*Escherichia coli* O157:H7 *Borrelia burgdorferi*	Hemorrhagic colitis, hemolytic-uremic syndrome Lyme disease
1983	HIV *Helicobacter pylori*	AIDS Gastric ulcers
1988	Hepatitis E	Enterically transmitted hepatitis
1989	Hepatitis C	Hepatitis C
1992	*Vibrio cholerae* O139 *Bartonella henselae*	New epidemic cholera strain Cat-scratch disease
1995	KSHV (HHV-8)	Kaposi sarcoma in AIDS
1999	West Nile virus	West Nile fever, neuroinvasive disease
2003	SARS coronavirus	Severe acute respiratory syndrome

- West Nile

- Severe Acute Respiratory Syndrome (SARS)
  - Coronavirus
  - Diffuse alveolar damage
  - Immune mediated



- Palm civet, dogs, badgers and raccoons
- 11/2002, Guangdong Province of China
- International attention in 2/2003



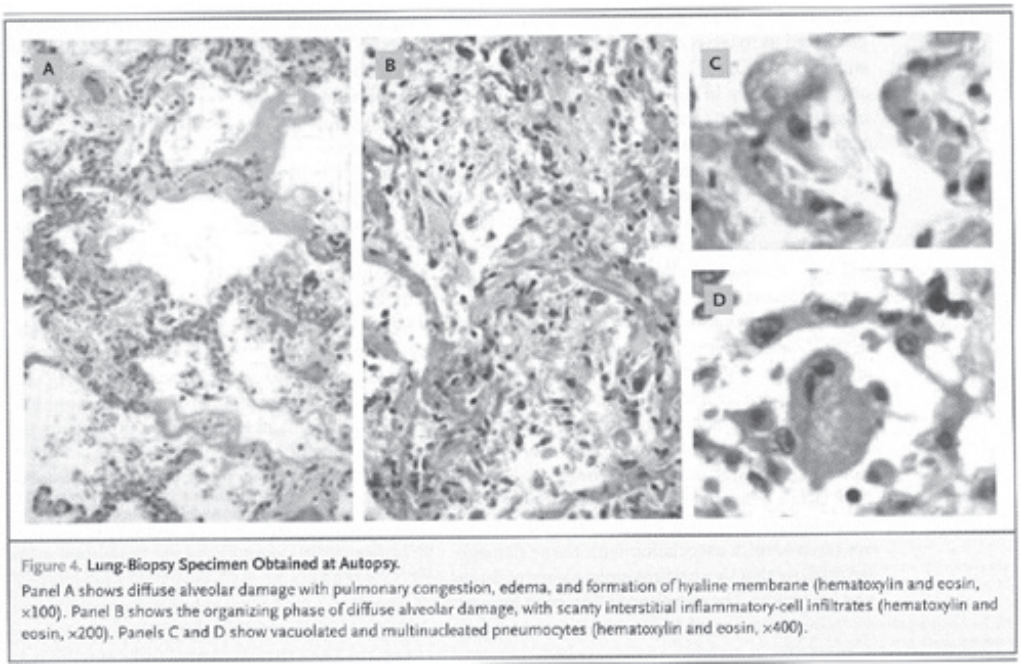
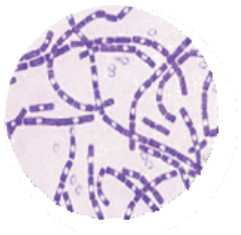


Figure 4. **Lung-Biopsy Specimen Obtained at Autopsy.**
Panel A shows diffuse alveolar damage with pulmonary congestion, edema, and formation of hyaline membrane (hematoxylin and eosin, ×100). Panel B shows the organizing phase of diffuse alveolar damage, with scanty interstitial inflammatory-cell infiltrates (hematoxylin and eosin, ×200). Panels C and D show vacuolated and multinucleated pneumocytes (hematoxylin and eosin, ×400).

IV. Bioterrorism CDC groups



Category A: highest risk

- readily spread
- high mortality
- major public health impact
- Smallpox, plague, anthrax, hemorrhagic fevers, botulism toxin

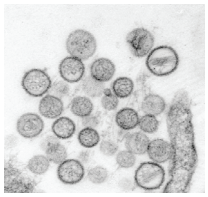
Category B

- moderately easy to spread and moderate mortality
- Brucella, pathogenic strains of E. coli, typhus, cholera

Category C

- Emerging infectious diseases that can be modified for mass distribution.

- Hantavirus



V. Types or categories of infectious agents

A. Prions

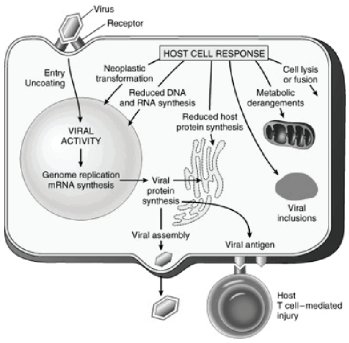
B. Bacteriophages, plasmids and transposons

1. “mobile” genetic elements that can transform a bug
   - antibiotic resistance
   - adhesive proteins
   - etc....

C. Viruses

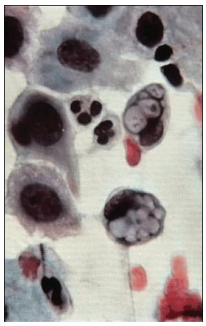
1. Too numerous to count - the most frequent cause of illness and probably death.
2. Highly specific “target” organ

3. Direct killing of host cell
4. Expression of viral proteins with activation of host immune response
5. Tumor transformation
6. Delayed action of some
7. Vector +/-



D. Chlamydia, Rickettsiae and Mycoplasmas

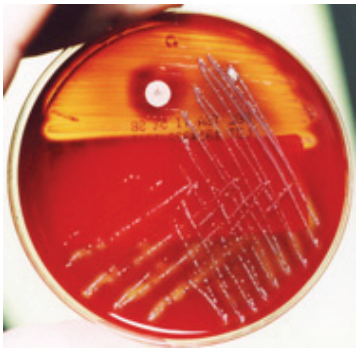
1. Intracellular
2. Specificity
3. Vector frequently
4. Wide variety of types of injury



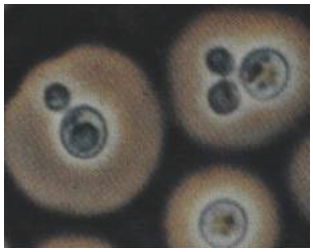
E. Bacteria

1. Prokaryotes - no nuclear membrane and no ER
2. Wall structure varies
3. Some general pathogens and some have target specificity
4. Direct killing
5. Toxin
6. Immune activation
7. Modification of bodily material to cause reaction

   - zits



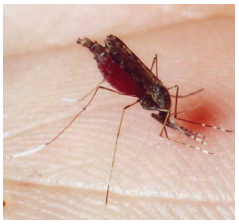
F. Fungi



1. Complex wall
2. Some have sexual reproduction
3. More of a challenge for our immune systems

G. Protozoa

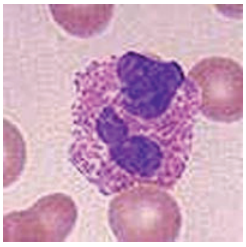
1. Complex life form, some with ingenious reproductive strategies
2. Gastrointestinal
3. Systemic (know malarial life cycle)
4. Different types of hosts
    - definitive
    - indefinitive
    - reservoir



H. Helminths and “ectoparasites (you know, worms and “cooties”)

1. As complex as us on a cellular basis
2. Multicellular
3. Systemic vs. Gastrointestinal
4. Complex life cycles
5. Grouped by appearance
    - nematodes (round)
    - cestodes (flat)
    - trematodes (flukes)

6. Host response
    - eosinophils

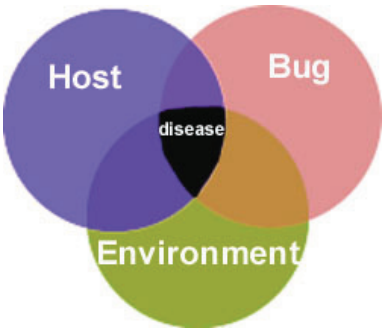


VI. Host factors designed to keep your genes in the gene pool

A. Barriers

1. Skin and membranes

2. Mucous



B. Removal of bug

1. Ciliary action

2. Cough

C. Normal flora

D. Agents we release into the local environment

1. Lysozyme

2. Soaps

3. IgA

E. Immune system with memory

- peripheral blood pattern can be quite helpful in diagnosis as measured in CBC

VII. Bug factors

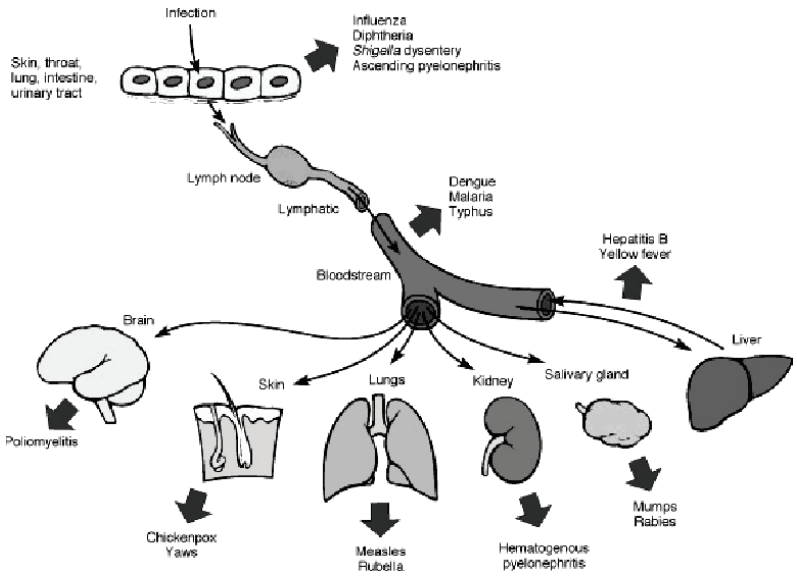
A. Mother nature loves all her creations

B. Bugs can get around virtually all the host factors

- rapid growth
- adhesive proteins
- encysted or dormant portion of life cycle
    - TB
    - sporulation - C. Dificile
- look like the host
    - intracellular
    - host proteins

C. Methods of spread

- droplet, how long will it survive?
- direct contact
- complex and multiple steps, just consider some of the parasites
- cell borne, HIV



Ref: Robbins, Pathologic Basis of Disease

VIII. How do they cause disease?

- kill the host cell directly
- toxins and enzymes that cause cellular injury
- host immunity goes wild

A. Direct cell death - virus is easiest to understand

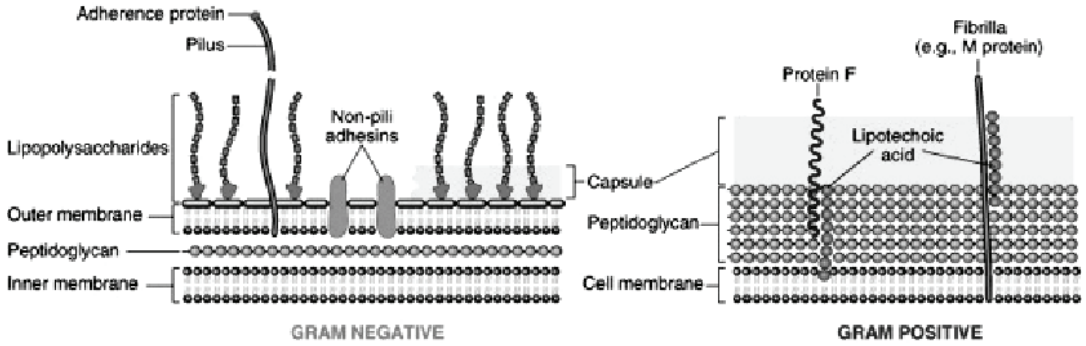
1. replication and cell rupture

B. Toxins and other proteins

1. Adhesins

- selective binding for bug

- Strep M protein

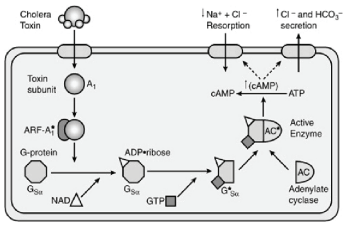


Ref: Robbins, Pathologic Basis of Disease

2. Toxins

- endotoxin - wall fragments and bug parts - LPS

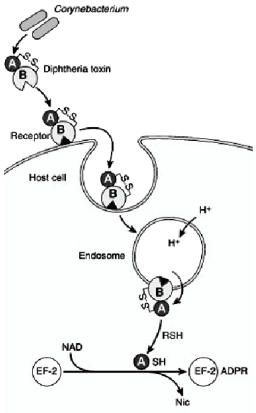
- exotoxins - made and released by living bug - bug poop



- diphtheria

- clostridium

- cholera and enteropathogenic E. coli

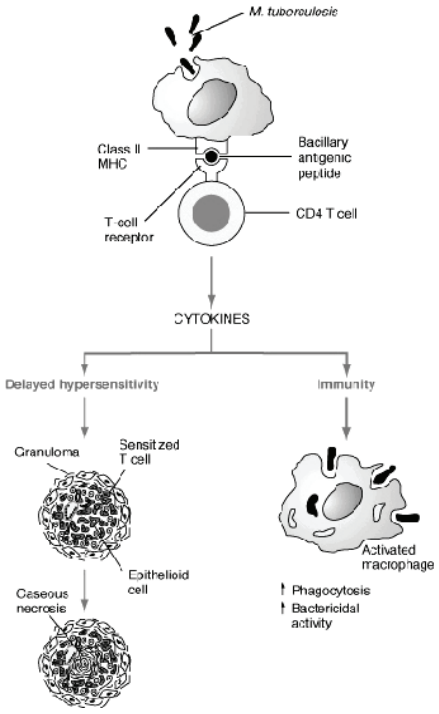


C. Immune injury and/or evasion by bug

1. Cellular

- TB (type IV)

- virus - hepatitis B



Ref: Robbins, Pathologic Basis of Disease

2. Antibody mediated

- direct cross reaction - Goodpastures Disease, post strep cardiac

- immune complexes - Post Strep kidney disease

3. Immune evasion by bugs

- they hide - intracellular

- destroy complement before it goes to work

- shed or modify antigens

- direct immune suppression

IX. How do you diagnose an infection and how do you feel?

A. **HISTORY AND PHYSICAL**

1. Look and listen
2. Specific signs
    - local
    - systemic

B. Go for the bug

1. Culture

2. Tissue biopsy and special stains to demonstrate the bug, not all can be cultured
    - pneumocystis
    - blood smear for malaria

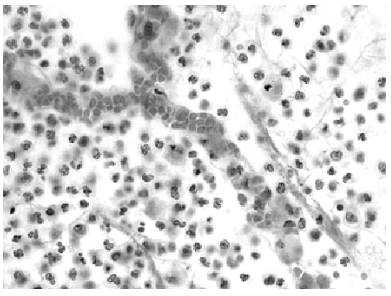
C. Serological conversion - OK, this is much after the fact - Why use it?

1. acute and convalescent antibody levels

2. specific or unique antibodies

D. "Diagnostic" enzyme pattern

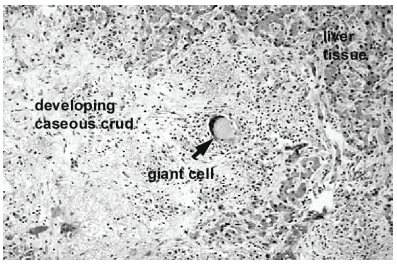
1. hepatitis
2. myocarditis



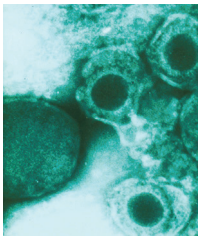
E. Specific and/or helpful **histological** patterns: you need to know these and what each looks like microscopically.

1. Suppurative

2. Granulomatous



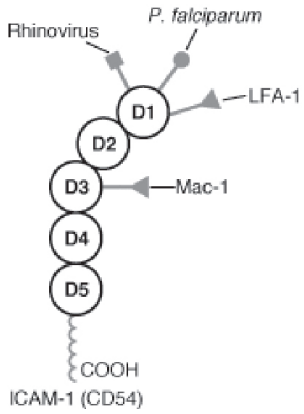
3. Cytopathic



4. Necrotizing

5. Chronic inflammatory pattern with scar tissue formation

X. Viral Infections, acute and transient



A. Rhinoviruses

- "canyon" that protects attachment site
  - ICAM-1 binding site
- upper airway
- bradykinin causes excess mucous production

B. Influenza

- RNA 'chromosomes'

- type A - antigenic shift - new vaccine called for - 1918

- types B and C - stable. Once you have antibodies you are OK

- upper and lower airway (Ducks and pigs)

- sometimes there are odd and disastrous complications

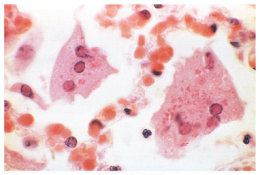
    - Reye's syndrome

C. Measles

- respiratory

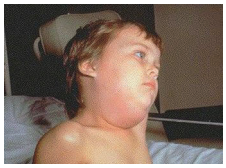
    - "rash"

- serous in adults



- Warthin-Finkeldey giant cells

D. Mumps - epidemic parotitis



- pancreas too

- testis

E. Polio

- world wide still a heck of a problem

- enteric

- motor neurons - ICAM-1 receptors on neurons

F. Enteric viruses - "The squirts"

- Rotavirus in kids

- Enteric adeno and Norwalk agent

- Coronavirses like SARS

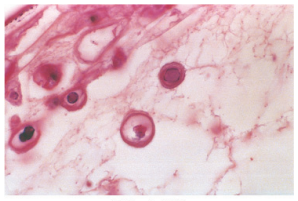
G. West Nile

H. Hemorrhagic fevers

XI. Chronic and/or latent viral infections

A. - Herpesvirus

- HSV-1



- oral

- fever blister

- gingivostomatitis

- ocular

- conjunctival

- CNS

- Skin

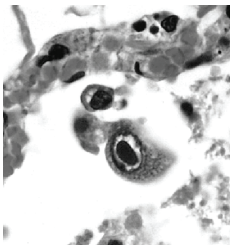
- Kaposi's varicelliform eruption

- HSV-2

- genital

B. CMV

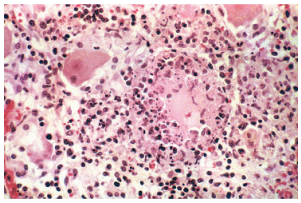
- adult infections



- neonatal (urine sediment)

- Any and every organ

C. Varicella zoster (chicken pox and "shingles" in adults)



- sites of infection
  - skin
  - mucous membranes
  - neurons (dorsal root ganglia)

- childhood

- shingles - long dormant period - adult or aged
  - what else is going on with the patient?
  - painful and sometimes hemorrhagic

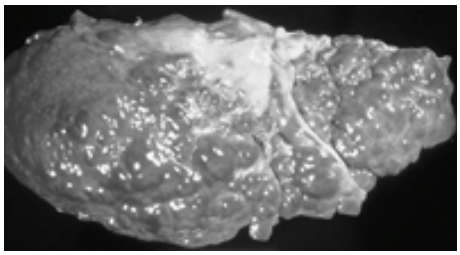
XII. Chronic Productive viral infections

Hepatitis B "serum hepatitis"

- This virus does it all
  1. Acute hepatitis
  2. Chronic
  3. Fulminant necrosis with liver failure and death

4. Seemingly stable, asymptomatic carrier state (infectious!)

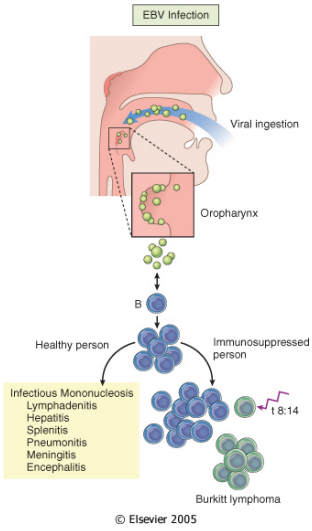
- Geographical variations in incidence
    - Asia
- Incubation of 4-26 weeks
- Mechanism
    - **immunological damage**
        - expressed antigens on infected hepatocytes
        - cytotoxic T cells



XIII. Transforming viral infections

A. Epstein-Barr - mononucleosis (herpes virus actually)

- life cycle

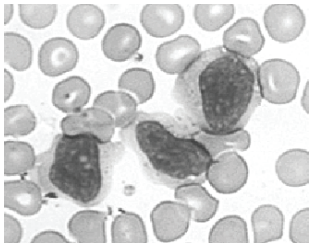


- pharyngeal epithelium cells

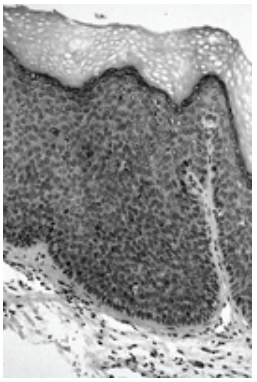
- peripheral blood - B cells - "atypical" lymphocytes
- other organs
- nodes
- liver
- spleen

- bad complications

- oral pharyngeal cancer



- Burkitt's lymphoma, t8:14



B. Human papilloma virus (HPV)

- skin and mucous membranes

- dangerous serotypes:

- epithelial tumors, some with malignant transformation

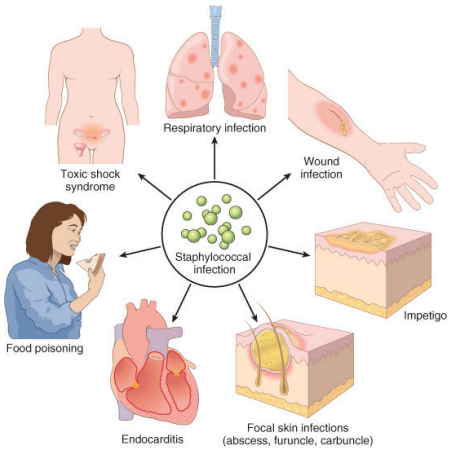
XIV. Bacterial Infections

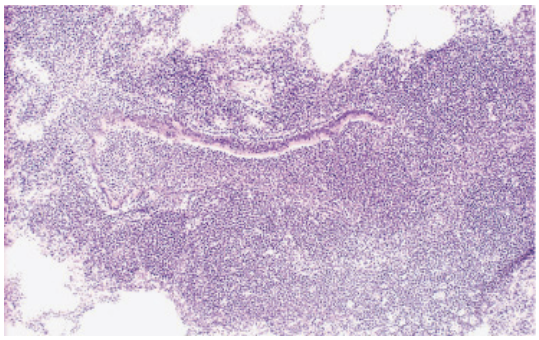
A. Gram Positive (pyogenic bacterial infections, staph and strep)

1. Staphylococcus:

- one in the group of the so-called **gram positive pyogenic organisms**

- pus forming: pyogenic





- actually causes injury by all three methods
    - kills cells directly or directly infects many different tissues
        - abscess formation
    - toxic and enzymatic injury
        - enterotoxin
        - exfoliative toxin
        - toxic shock syndrome
        - immunological
- two major divisions based on **coagulase test**
    - staph epidermidis is coag -
    - staph aureus is coag +

- sometimes works in conjunction with streptococcus - real bad

2. Streptococcus: Gram +, many, many serotypes and many, many disease patterns

- skin, mucous membranes and "deep" infections
    - erysipelas (bugs in skin)
    - scarlet fever (toxic injury of skin)

- two basic patterns of infection
    - localized
    - disseminated

- methods of injury - like staph - everything
    - local injury and cell death

- toxic injury

- **STREP INDUCED IMMUNOLOGICAL DAMAGE**
    - delayed
    - chronic
    - antibodies
        - cross reaction with host antigens
        - immune complex disease
    - long-term serious consequences
        - heart damage
        - kidney

- sometimes teams up with staph in skin - serious problem!

- **Classification of subgroups**
    - hemolytic reaction on **SHEEP** blood agar

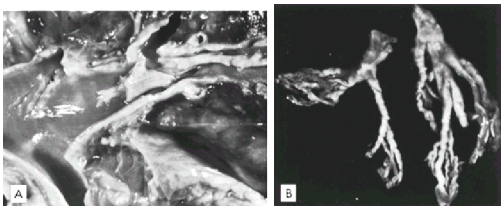
    - growth requirements

    - **SEROTYPING**

    - example: Group A, beta hemolytic, serotype 12

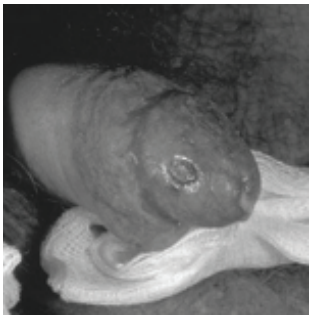
- Strep pneumoniae a special situation
    - pneumonia
    - meningitis

- joints and heart valves rarely



3. Corynebacterium diphtheria

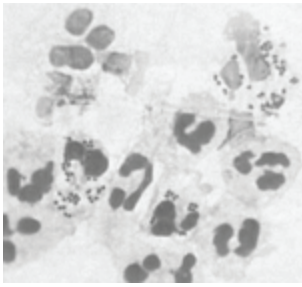
- still a problem
- bronchi
- toxic injury of heart



B. Gram negative (pyogenic forms are gc and meningititus)

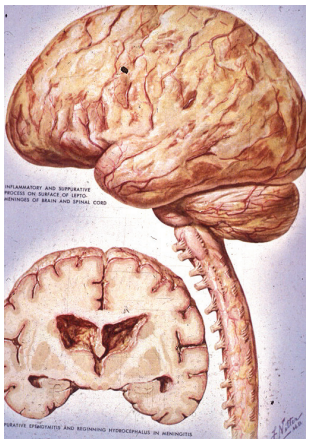
1. Neisseria gonohoreae

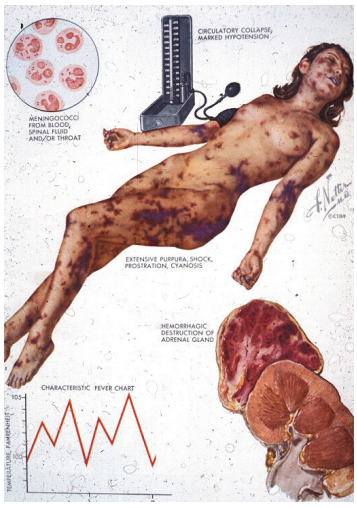
- encapsulated
- shares DNA with neighbors
- mucous membranes
- systemic or wide spread infections
  - joints
  - heart valves
  - rarely meninges



2. Neisseria meningititus

- endothelial cell is target
- meninges are secondarily involved
  - "sporadic" and "epidemic" strains
  - Waterhouse-Friderichsen Syndrome





3. Haemophilus influenza: gram -

- the bug of childhood bacteriology
    - encapsulated (5%)
    - unencapsulated (95%)
- upper airway first
    - laryngitis and epiglottis
    - lower airway - cough but good
        - bronchitis and pneumonia
    - meninges - encapsulated bug

4. Bordetella Pertussis

- Whooping cough
- Lives in ciliated border
- Several toxins, one acts like cholera toxin

5. Shigella - bacillary dysentery

- colon
- plasmid may confer virulence
- superficial invader of mucosa
- toxin

6. Campylobacter

- dysentery symptoms
- much more common than we think
- bloody diarrhea
- injures in various ways
    - toxin

- direct superficial invasion with cell death

- possibly spreads to local nodes - marked fever

7. Salmonella

- upper GI

- systemic form

- reticuloendothelial system is target

- harbored in gallbladder

- funky symptoms and signs of Salmonella infection

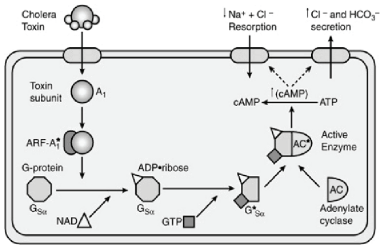
- HIGH fever

- bradycardia

- low WBC's in peripheral blood

8. cholera and enteropathogenic E. coli

- rice-water stools

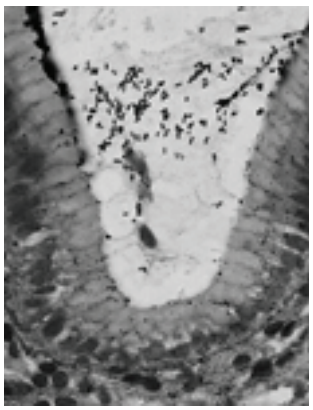


9. Helicobacter

- upper GI

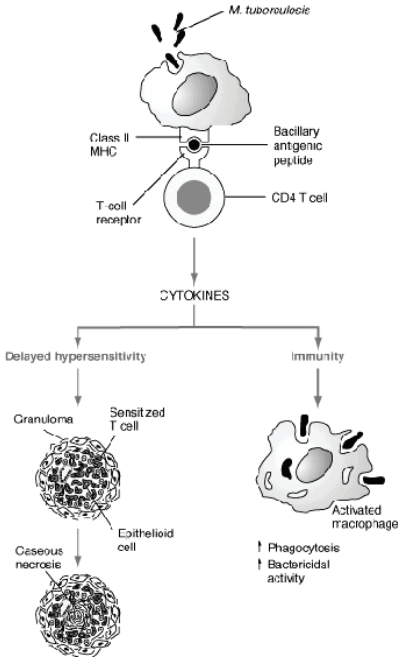
- ulcer and possible some link to cancer

- destroys mucous protective layer



C. Mycobacterium tuberculosis: no gram reaction: **acid fast**

- **KNOW THIS BUG and ESPECIALLY HOW IT CAUSES CELLULAR INJURY**



- **Host reaction to bug wall elements**

- Primary infection - pulmonary, less likely GI
  - Apex of lung
  - acute cells can't do it
  - macrophages
    - **epithelioid histiocytes**
    - granuloma
    - possible hematogenous spread over the entire body
    - miliary (not military)
  - skin reaction
    - How do read it?
    - you can lose it

- Secondary or reactivation infection
  - implications
  - timing
- Atypical mycobacteria
- Mycobacterium lepra - host reaction to bug wall
  - leprosy
  - skin and perineural
    - cooler areas

- pattern depends on degree of host response

- lepromatous - nodular and very deforming (no granulomas)

- tuberculoid - macular (flat) lesions (granulomas)

D. Spirochetes

Treponemal disease

- No cultures

- Serological or direct visualization of bug

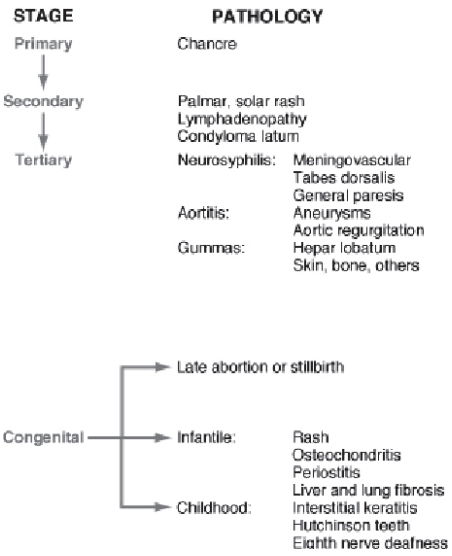
- VDRL

- specific antibodies

- Many organisms (actually this type of bug is really quite common in nature)

- Treponema pallidum

- Syphilis:



- primary

- secondary

- tertiary

- infantile

- bone deformities

- "Hutchinson's" teeth

- interstial keratitis

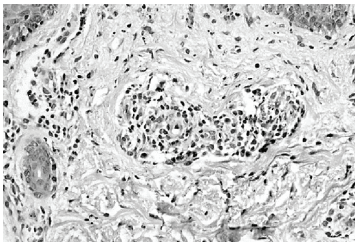
- eighth nerve deafness

- meningiovascular involvement

- lungs and liver

- Pathology

- **OBLITERATIVE ENDARTERITIS**



- gumma

- aortic aneurysm - thoracic

- How does this happen?

- GPI

- menigovascular

- direct involvement of cerebral micro vessels

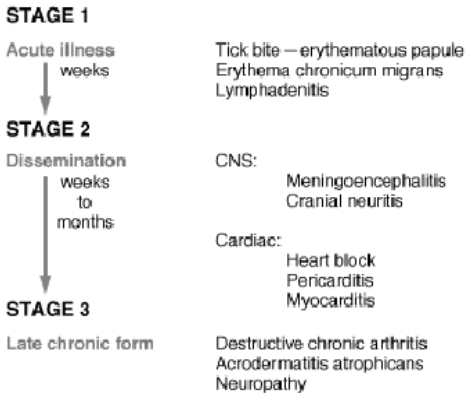
2. Borrelia burgadorferi - Lyme disease

- arthritis

- Ixodes ticks

- deer

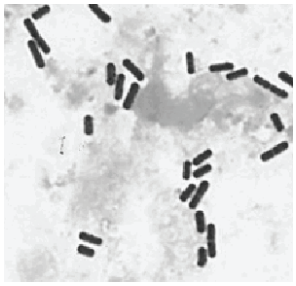
- mouse



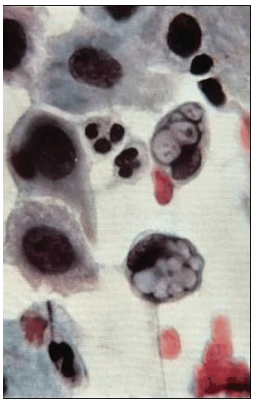
E. Anaerobic Bacteria

1. Clostridial organisms: Gram positive, spore forming rods

- toxic and enzymatic injury
- spores
- special situations to establish an infection
- many organ systems are involved
- types
  - C. perfringens..
  - C. tetani
  - C. botulinum
  - C. difficile
    - iatrogenic



F. Obligate intracellular bacteria



1. Chlamydia and "almost" bacteria
   - Chlamydia trachomatis
     - intracellular bug
     - people and birds
     - genital and newborn
       - LGV
     - blindness
     - isolated urthritis and probably pelvic inflammatory disease.
     - *Reiter's syndrome*
       - conjunctivitis
       - polyarthritis
       - urethritis

2. Rickettsia

- small vessel vasculitis

- Typhus

- Rocky Mountain Spotted Fever

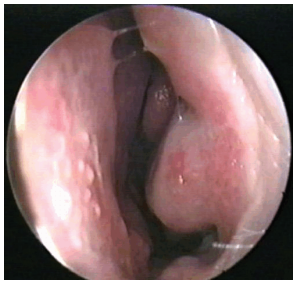
- Typhus (this is not ‘typhoid fever)

- Short hair cuts

XV. Fungal infections

A. Yeasts

Fungi we divide these into “cutaneous” and “systemic” types, although under the right circumstances, just about any fungus can produce a systemic infection.



- cutaneous:

- systemic:

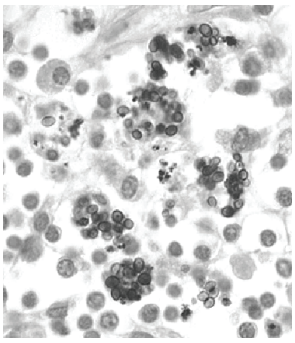
- some result in granuloma formation, some do not

- some have specific geographic distributions

- Dimorphic yeasts: What does this mean?

- Histoplasma capsulatum

- Coccidioides immitis



- Cryptococcus neoformens

- Blastomycosis

B. Molds

Allergic reactions

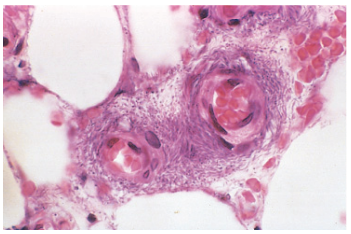
Infections in compromised folks

- immuno
- malnourished (coming below)

XVI. Opportunistic infections

- Opportunistic bacteria
  - gram negative for the most part, but there are a few gram positive ones
  - come as a consequence of something else
  - infections of a burn site
  - tracheostomy opening
  - post-operative wound infection
  - immunosupressed
- Best bug to use as an example is *Pseudomonas aeruginosa*

- gram negative
- “grapy odor” on culture plate
- “swarming”
- highly resistant to antibiotics
- **infected burns !!!!**



- Best example of a gram positive would be the *Strep viridans* (also called group ‘D’ streps) and *Staph epidermitis* group.
  - post-operative wound
  - resistant to cephalosporin antibiotics (Group D streps anyway)
  - colonizes artificial heart valves and damaged valves due to rheumatic fever
  - very common bug on your skin and in your gut

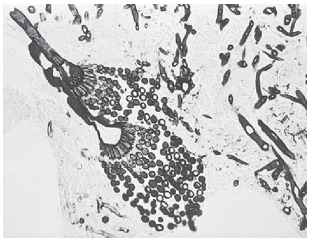
- Legionella pneumphila
  - actually no gram stain to speak of (maybe weakly gram negative).
    - resistant to chlorine in cleaning solutions
    - interesting outbreaks
    - seroconversion
    - bug shots off killing system and grow to lyse the inflammatory cell.
    - sputum has lots of acute inflammatory cells, but no bugs that you can see or culture.
    - pleural effusion and lots of pain
  - Candid species (part of flora)
    - proteins that facilitate binding to host proteins
      - fibrin, laminin and fibronectin
    - lectin facilitating binding to epithelial cells
    - Cutaneous and disseminated forms

- esophageal is very painful, leads to malnutrition

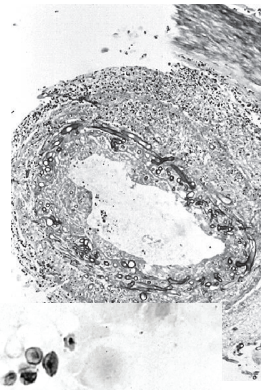
- hyphal and yeast growth phases

- Cryptococcus, skin, CNS and just about everywhere

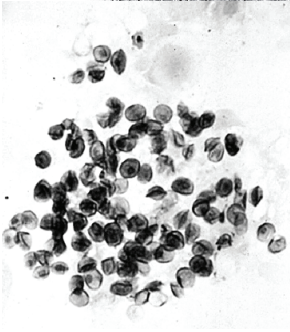
- Aspergillus



- Mucormycosis



- Pneumocystis cainii



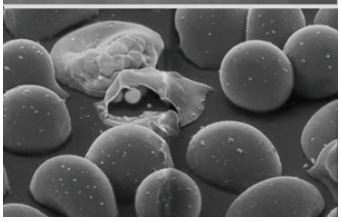
- now classed as fungus

- AIDS

- immune suppression with cancer therapy and some tumors themselves

XVII. Parasitic Disease

A. Malaria - four types



- Plasmodium falciparum

- P. vivax

- P. ovale

- P. malaria

- Know basics of life cycle

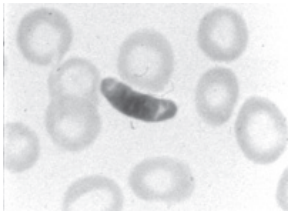
- mosquito is definitive host (what does this mean?)

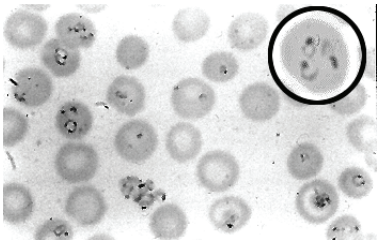
- liver

- RBC's

- Spleen for chronic

- Organs and basic pathology





- spleen

- liver

- CNS

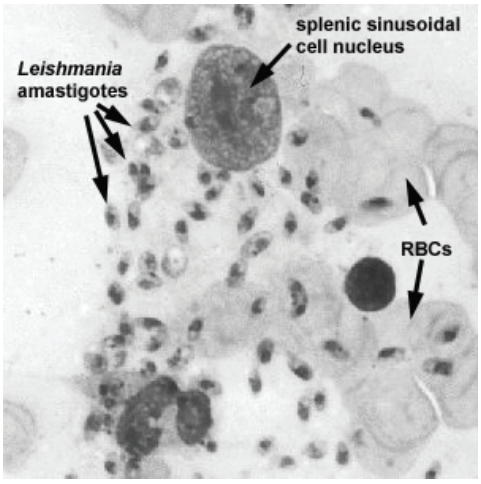
- "Black Water" episode of malaria

- Babesiosis

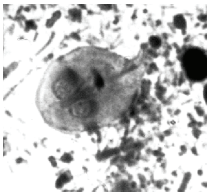
- Leishmaniasis

- Sand fly

- cutaneous and visceral
    - reticuloendothelial system is target in visceral

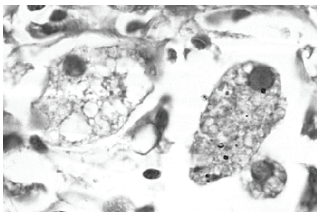


- typanasomes
    - Old World
        - T. rhodesiense
        - T. gambiense
        - sleeping sickness
    - New World
        - T. cruzi
        - Chaga's disease
            - heart
            - esophagus
    - Unicellular gut parasites
        - giardia



- amoeba of various kinds

- may also be systemic



- Trichinella spiralis

- pigs

- encyst in heart, brain, lungs and skeletal muscle

- asymptomatic

- rarely fatal

- periorbital edema

- Tape worms (cestodes)

- T. solium - cysticercosis in disseminated form

- encysts in brain and about everywhere else

- seizure disorder

- T. saginatum

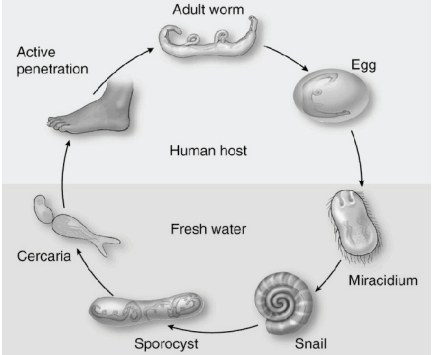
gut

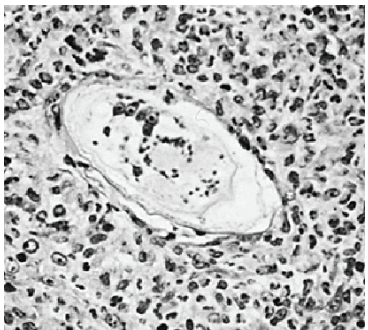
- Schistosomiasis

- very complex reproductive cycle

- Invades vascular walls of various organs

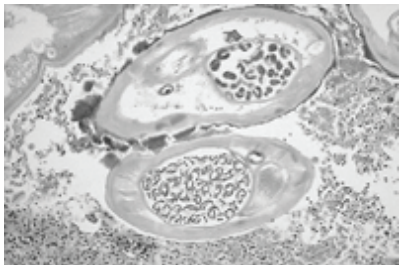
- Bladder cancer in Middle East





- Filariasis
    - Wuchereria bancrofti - worms in nodes
        - look for ‘children’ in blood smear
        - elephantiasis

- Onchocerciasis
    - Black fly
    - filarial nematode
    - mate in dermis and chambers of eye
    - major cause of blindness in equatorial Africa



Infectious Disease Cases

Case 1:

HISTORY: This 33-year-old housewife was admitted to the hospital in a state of prostration and extreme debilitation. She had been ill for two years with low-grade fever, nightsweats, progressive weakness, continuing weight loss and a gradually worsening productive cough.

PHYSICAL FINDINGS: The patient was acutely ill and emaciated; temperature was 38C.

LABORATORY RESULTS: chest radiography-extremely large cardiac shadow, multiple areas of increased density in both lung fields with cavitary lesions in the left upper lobe

CLINICAL COURSE: There was no change in her condition during the first week in the hospital.

In addition to sputum cultures, what other test might be helpful in helping with a diagnosis?
The most likely cause of the enlarged cardiac shadow is?
Gross and microscopic features of the lung lesions would MOST LIKELY be characterized by?

In addition to sputum cultures, what other test would very helpful in making a diagnosis?
The most likely cause of the enlarged cardiac shadow is?
Gross and microscopic appearance of the lung lesions would MOST LIKELY be characterized by?

Case 2:

HISTORY: This 4-year-old child was admitted to the hospital with nuchal rigidity, left facial paralysis, right internal strabismus and continuous jerking movement of the extremities. She had been well until two days before admission when she developed a fever and complained of bright lights hurting her eyes. The family had recently returned from a trip to New York City.

PHYSICAL FINDINGS: BP-100/60 mm Hg; pulse-100/min; respirations-26/min; temperature (rectal)-40C.

LABORATORY RESULTS:
- hemoglobin-12 g/dl
- WBC-13,600/mm3
- urinalysis-negative
- spinal fluid- 3,000 cells/mm3 (90% lymphocytes 10% neutrophils)(N=0-5 mononuclear cells/mm3)

spinal fluid protein (lumbar)-65 mg/dl (Normal-15 to 45 mg/dl)
spinal fluid culture-negative at seven days

CLINICAL COURSE: Despite treatment her condition steadily worsened and she died on the 12th hospital day.

The MOST LIKELY causative agent of this patient's illness is?
Histologically the lesions in the central nervous system are most probably to be characterized by?
The most likely mode of transmission of the agent of this disease is?

Case 3:

One day after receiving a small wound on his leg from a chisel, a carpenter develops a sore with red streaks on the leg, tender inguinal lymph nodes and high fever.

The most likely causative organism is?
What is the significance of the enlarged lymph nodes?
What do the red streaks up his leg indicate?