

# REVIEW OF PATHOGENIC MICROBIOLOGY

The first portion of this section will deal with infectious diseases by various body systems. This will then be followed by descriptions of the major pathogens encountered in each body region, with particular attention being paid to those of major incidence in the United States of America.

## RESPIRATORY TRACT MICROBIOLOGY

The respiratory tract has an enormous normal flora, which extends from the lips to the larynx. The bronchial tree distal to the larynx is usually considered sterile, although microbial agents are continuously impinging upon those surfaces as well. They normally do not colonize, however, and are removed by the mucociliary blanket as it propels upward from the bronchioles. Thus factors that interfere with secretory processes or ciliary action will predispose the host to infections in the lower respiratory tract.

### Normal Flora

Most of **the agents are potential pathogens**. Some only express their pathogenicity in immunological compromised hosts; (for example, *Pneumocystis carinii* in AIDS patients); others cause disease when they gain access to areas of the body more susceptible to their deleterious effects. Examples of the latter include *Neisseria meningitidis*, and *Staphylococcus aureus*. The most commonly encountered microorganisms are enumerated below.

### Microbial Agents Found in the Upper Respiratory Tract

| PROTOZOA            | BACTERIA               | FUNGI          | VIRUSES |
|---------------------|------------------------|----------------|---------|
| <i>Entamoeba</i>    | <i>Streptococcus</i>   | <i>Candida</i> | Adeno   |
| <i>Trichomonas</i>  | <i>Staphylococcus</i>  |                | Herpes  |
| <i>Pneumocystis</i> | <i>Neisseria</i>       |                | Rhino   |
|                     | <i>Corynebacterium</i> |                | Reo     |
|                     | <i>Haemophilus</i>     |                |         |
|                     | <i>Klebsiella</i>      |                |         |
|                     | <i>Pseudomonas</i>     |                |         |
|                     | <i>Mycoplasma</i>      |                |         |

It is perhaps permissible to consider all **normal flora** as agents responsible for **inapparent infections**, as they have colonized the tissues and are multiplying without causing discomfort to their host. In fact in some instances they may be of benefit, as they will limit the growth rate of less desirable inhabitants either through elaboration of products antagonistic to the other microbes or by successful competition for nutrients. Individuals on broad spectrum antibiotic therapy often experience **thrush**, a disease resultant from modification of the flora is caused by *Candida albicans* (*Candida* are resistant to the usually antibiotics).

The **viruses** represent a somewhat different type of inapparent infection in that they grow **within the cells** and may cause some very localized tissue destruction. REO (Respiratory Enteric Orphan) viruses are readily isolated from the upper respiratory tract but have not been convincingly associated with any pathological process. The **adenoviruses** were first isolated from **normal adenoidal tissues**; however, most human serotypes are not associated with disease processes. **Herpesviruses** are sometimes referred to as **latent viruses** in that they persist in the host after an initial infection and recurrent clinical disease may be elicited by various environmental and/or hormonal stimuli.

## Disease Spectrum

Acute respiratory diseases afflict 200 million people in the United States each year. The clinical pictures that are manifested in the respiratory tract are extremely variable. The diseases may be characterized as to clinical course, pathologic process or anatomic location. As a general rule, **upper** respiratory tract infections are acute processes with short incubation periods and relatively rapid clinical courses; whereas **lower** respiratory diseases of microbial etiology may be either acute (e.g., pneumococcal pneumonia) or chronic, such as mycotic infections or tuberculosis. Chronic diseases are characterized by the development of granulomas, in which the predominate cellular response is mononuclear. Polymorphonuclear leukocytes are the cells that are usually found in acute infectious processes. The most common microbial etiologies of respiratory disease are presented below.

### Common Agents of Upper Respiratory Infections

| Clinical Illness            | Bacteria   | Viruses   | Fungi                   |
|-----------------------------|--|---|-------------------------|
| Rhinitis                    |  | <b>Rhinoviruses</b> <sup>1</sup>                                    |                         |
| Stomatitis                  |  | <b>Herpes simplex</b>   | <i>Candida albicans</i> |
| Otitis media and Sinusitis  | <b><i>Streptococcus pneumoniae</i></b><br><i>Haemophilus influenzae</i>        |   |                         |
| Otitis externa              | <b><i>Pseudomonas</i></b>  |   | <i>Aspergillus</i>      |
| Epiglottitis                | <b><i>Haemophilus influenzae</i></b>   |   |                         |
| Pharyngitis and Tonsillitis | <b><i>Streptococcus pyogenes</i></b>   | Adenoviruses  | <i>Candida albicans</i> |
| Laryngotracheitis (croup)   |  | <b>Parainfluenza</b>  |                         |
| Bronchitis                  | <i>Haemophilus influenzae</i><br><i>Bordetella pertussis</i> in young children | <b>Parainfluenza</b><br>Respiratory syncytial virus<br>Adenoviruses |                         |

1. The most common agent in each illness category is in **bold face**

## **Pneumonia**

Pneumonia (pneumonitis) is defined as any inflammation of the lung parenchyma distal to the bronchioles. It may involve the air sacs with exudation into the alveoli or it may be seen as an interstitial lesion, which is the case with most of the viral agents. Bacterial pneumonias are the leading cause of mortality due to infection in the United States, being responsible for over 70,000 deaths per year. Many of the etiologic agents are normal flora of the nasopharynx. *Klebsiella pneumoniae*, for example, is a significant cause of pneumonia in alcoholics although it causes very little clinical disease in individuals with a more intact respiratory apparatus. Many severe diseases result from secondary bacterial invasion following viral infections or whooping cough. The etiology varies with the age of the patient; this is summarized below.

### **Most Common Causes of Pneumonia**

| <b><u>Age</u></b> | <b><u>Microorganism</u></b>             |
|-------------------|---|
| 0 - 1 month       | Group B streptococci and <i>E. coli</i> |
| 1 month - 1 year  | Respiratory Syncytial virus (RSV)       |
| 1 - 5 years       | Parainfluenza virus                     |
| 5 - 30 years      | Mycoplasma (Influenza virus epidemics)  |
| Over 30 years     | <i>Streptococcus pneumoniae</i>         |
| Debilitated       | <i>Klebsiella pneumoniae</i>            |
| AIDS at any age   | <i>Pneumocystis carinii</i>             |

Viral pneumonias usually take a much more benign course; they are often referred to as "walking pneumonia," meaning the patient is still ambulatory. Differences in bacterial and viral pneumonias are summarized below. *Mycoplasma pneumoniae*, *Coxiella burnetii*, and *Chlamydia psittaci* cause a similar mild disease. Many of the differences in symptoms relates to the fact that the viruses and mycoplasma cause an interstitial pneumonitis while most bacterial agents are inhabiting the alveoli and bronchial tree with resultant inflammatory exudation (i.e., sputum) into the airways

### **Clinical Differentiation of Pneumonias**

| <b>Characteristic</b>         | <b>Bacterial</b>  | <b>Viral</b>     |
|-------------------------------|-------------------|------------------|
| Age of Pt.                    | Adult             | Child            |
| Onset                         | Sudden            | Gradual          |
| Fever                         | High              | Moderate         |
| Cough                         | Productive        | Dry              |
| Microbial Site of Replication | Airways           | Interstitial     |
| Sputum                        | Copious; purulent | Moderate; mucoid |
| Elevated WBC                  | Common            | Rare             |
| Chills                        | Common            | Rare             |
| Pleuritis                     | Common            | Rare             |
| Tachypnea                     | Common            | Rare             |
| Tachycardia                   | Common            | Rare             |

## Complications of Bacterial Pneumonia

The organisms may spread contiguously to involve the pleural space causing pleuritis or empyema (bacteria and WBC in the pleural space). If the organisms become hematogenous they can cause septicemia or may localize in various organs and cause disease there (e.g., meningitis, arthritis, etc.)

## Immunity

The major protective immune response is humoral and antibodies act primarily via their opsonic ability. Many of the agents are encapsulated and the IgG and IgM neutralize the anti-phagocytic properties of these carbohydrates. **Pneumovax** is a mixture of capsular carbohydrates from 23 serotypes of *S. pneumoniae*. It is presently recommended for patients particularly susceptible to pneumococcal disease because of age, underlying disease (e.g. sickle cell disease) or immune deficiency.

## Diagnosis of Bacterial Pneumonia

A Gram stain can be valuable as an early guide to therapy. Also the age of the patient should be taken into consideration. Sputum samples should be plated on blood-containing media (blood agar or chocolate agar). A good sputum specimen will contain PMNs and a relatively pure microbial population; samples from the upper respiratory tract (saliva) will have numerous squamous epithelial cells and a variety of microbes present. Antibiotic sensitivity should be done on the microorganism isolated from the sample.

## Therapy for Pneumonias

The patient should be treated with aspirin to help with the fever and discomfort; oxygen and external cooling may also be required. The following are drugs of choice for the agents listed (these same antibiotics could be used for treatment of infections caused by the same organisms in other parts of the body).

|                             |   |
|-----------------------------|---|
| <i>Streptococcus</i>        | Penicillin  |
| <i>Staphylococcus</i>       | Penicillinase-resistant beta lactam antibiotic<br>(EG., Oxacillin, Methicillin;<br>methicillin-resistant <i>S. aureus</i><br>(MRSA) can be treated with<br>Vancomycin |
| <i>Mycoplasma</i>           | Erythromycin  |
| <i>Legionella</i>           | Erythromycin  |
| <i>Chlamydia</i>            | Erythromycin or tetracycline  |
| <i>Escherichia</i>          | 3rd generation cephalosporin  |
| <i>Klebsiella</i>           | 3rd generation cephalosporin plus an aminoglycoside   |
| Respiratory syncytial virus | Ribavirin via aerosol   |
| Influenza virus             | Amantadine  |
| <i>Pneumocystis</i>         | Trimethoprim plus sulfamethoxazole  |

## SEPSIS

The terms bacteremia and septicemia are sometimes used interchangeably. Transient bacteremias occur every day. When it becomes clinically noticeable then it is usually called a septicemia. Septicemia is the 13th leading cause of death in the United States.

### Predisposing Factors

Primary conditions that can lead to septicemia include urinary tract infection, burns, prolonged intravenous therapy and septic abortion. Underlying diseases that predispose to septicemia and shock include AIDS, leukemia, diabetes, cirrhosis, and sickle cell anemia.

### Symptoms

**Fever** may be the only clinical manifestation of septicemia; it is usually associated with chills, malaise, sweating, headache, abdominal pain, myalgia and arthralgia.

**Splenomegaly** is a common presentation. There is a particular syndrome that is associated with **meningococcemia**, i.e. the **Waterhouse-Friderichsen syndrome** (adrenalcortical necrosis). These patients also usually have a petechial rash. Many infectious agents can cause disseminated intravascular coagulopathy (DIC) and septic shock with associated hypotension.

**Hematogenous dissemination** can result in secondary foci of infection in the CNS, cardiovascular, and renal tissues; arthritis may also occur.

### Etiologies of Septicemia

**Group B streptococci** and **E. coli** predominate in the neonatal period. **Pneumococcus** and **Neisseria meningitidis** are among the most common in children. **Staphylococci** and enteric bacteria occur in patients who acquire bacteremia in hospitals.

The most common cause of septicemia in asplenic or sickle cell patients is **Streptococcus pneumoniae**. **Staphylococci** are the main cause of septicemia following a surgical procedure.

**Escherichia coli** is the most common cause of gram negative bacteremia/septicemia; the origin of the microbe is the GI or GU tract. The signs/symptoms include shaking and chills, prostration and hypotension (LPS shock). Gram negative organisms can also be introduced by needle. This is an etiology that might be expected in an IV drug user. The most common agent here is also **Escherichia coli**. Other etiological agents of Gram negative bacteremia include **Klebsiella**, **Pseudomonas**, and **Proteus**. The most common cause of Gram negative septicemia in a burn patient is **Pseudomonas**. If the patient is an army recruit the organism would be **Neisseria meningitidis**. Complications of bacteremia and septic shock include; meningitis, disseminated infection, and endotoxin shock.

## Diagnosis of Bacteremia/Sepsis

**Fever** and **hypotension** are the biggest clues for diagnosing bacteremia. The recommendation is to do repeated blood cultures throughout a 24 hour period at 4 hour intervals. Serial blood cultures of 10-15 ml should be drawn during febrile periods.

## Therapy of Bacteremia/Sepsis

Since this is a rapidly evolving condition, aggressive intervention is needed to avoid having the patient die. Gram stain of purulent exudate may help determine the portal of entry and what the agent might be. Antibiotic susceptibility testing should be done. Use the intravenous route and continue therapy two weeks.

## Endocarditis/Myocarditis

*Staphylococcus aureus* is the most common cause of **acute bacterial endocarditis** in normal heart tissue. The organisms that causes **subacute bacterial endocarditis** (SBE) are **viridans streptococci**. These organisms attack previously damaged heart tissue. This usually infects secondarily to a previous infection. Some of the predisposing factors are Rheumatic Heart Disease, valvular damage or prosthetic valves. Laboratory diagnosis of SBE depends on demonstration of alpha hemolytic streptococci that are not inhibited by **optochin**.

**Coxsackie group B** viruses are the most common viral cause of **myocarditis**. They also cause pleurodynia characterized by fever and severe pleuritic chest pain. Group A Coxsackie viruses are primarily associated with herpangina which is characterized by fever, sore throat, and tender vesicles in the oropharynx.

## Septic Arthritis/Osteomyelitis

The same agents that predominate in neonatal pneumonias and meningitides are also seen in these consequences of septicemia, i.e. **group B streptococci** and **E. coli**. In older infants and children to the age of five **Haemophilus influenzae type b** is found most frequently as a cause of septic arthritis; this will likely decline as the vaccine becomes more widely used. **Staphylococcus aureus** is the most common cause of **septic arthritis and osteomyelitis** in all other age groups with perhaps the exception of **Neisseria gonorrhoeae** arthritis as a serious sequela of gonococcal infections in sexually active individuals.

## PURULENT MENINGITIDES

The presence of large amounts of pus characterize most of the bacterial meningitides, in distinction to those of fungal or viral etiology where the inflammatory response is primarily lymphocytic or granulomatous. Purulent meningitis presents a real medical emergency due to the fulminate nature of the disease which develops. The infection may be limited to the leptomeninges or the brain parenchyma may also be infected (meningoencephalitis). The viral diseases are called **aseptic** because the etiological agent is not recovered from the patient by standard bacteriological techniques, not because the agent is not present in the lesion.

### ETIOLOGY

Bacterial meningitis most commonly results from **hematogenous dissemination** of an organism which is either a member of the normal flora or is causing an infection in another part of the body, usually the lungs. The age of the host and his immunologic status have a major bearing on the type of organism causing the disease. Bacterial meningitis in neonates is usually caused by *E. coli* or group B streptococci. Both are normal inhabitants of the birth canal and may colonize the skin or gastrointestinal tract of the infant.

The **oropharynx** is usually the source of organisms causing bacterial meningitis in children greater than 2 months of age and in adults. The most common etiological agents of acute bacterial meningitis as they are distributed in different age groups is presented below. Fatality rates vary with the agent and the age of the patient but in general are highest in neonates (over 50% ) and the elderly. A 10 to 20 percent mortality is seen in the other age groups.

### Common Causes of Purulent Meningitis

| Age                | Microbial Etiology     | Approximate Incidence <sup>1</sup> |
|--------------------|------------------------|------------------------------------|
| Less than 2 months | Group B streptococci   | 40                                 |
|                    | <i>E. coli</i>         | 30                                 |
| 2 to 60 months     | <i>H. influenzae</i>   | 60 <sup>2</sup>                    |
| 5 to 40            | <i>N. meningitidis</i> | 45                                 |
| over 40            | <i>S. pneumoniae</i>   | 50                                 |

<sup>1</sup>These figures are the number of cases caused by that agent per 100 in that age group.

<sup>2</sup>The introduction of the HIB conjugate vaccine is causing this number to decrease. In the next few years the meningococcus or the pneumococcus will likely take over.

**Brain abscesses** may develop from hematogenous dissemination of organisms but more often are the result of trauma (during birth, accident, or surgery) or by direct extension from contiguous tissue such as the sinuses and mastoids. The causative organisms include peptostreptococci, staphylococci, *Bacteroides spp*, and Group A or D streptococci. ***Staphylococcus aureus*** and ***S epidermidis*** are the leading causes of brain abscesses following trauma (accidental or surgical).

## MANIFESTATIONS OF DISEASE

The most common findings in purulent meningitis are **fever** (often over 105° F, particularly in infants) **headache** and **nuchal rigidity** caused by paraspinal muscle spasms resulting from meningeal irritation. The increased intracranial pressure which develops as a result of the acute inflammatory response may cause bulging of the fontanelle. A list of the major symptoms of meningitis are presented in the Table below. The clinical course is highly variable being dependent upon the agent, and the age and associated immunologic status of the host. However, the disease is usually acute and death can occur within a few hours of the onset of symptoms.

### Clinical Findings Suggestive of Meningitis

| <u>Symptom</u>            | <u>Comment</u>                                   |
|---------------------------|--|
| Fever                     | 100 - 106°F                                      |
| Headache                  | Generalized, persistent and extremely painful    |
| Stiff Neck                | Positive Brudzinski (1) and Kernig (2) signs (3) |
| Decreased mental function | Lethargy, confusion, delirium, coma              |
| Vomiting, anorexia        | Seen in neonates                                 |

(1) Resistance to neck flexion when in a supine position with knees raised

(2) Inability to straighten the leg when supine and thigh is perpendicular to body

(3) These will be absent in neonates

**Post-meningitis sequelae** are uncommon except in the neonatal patient, where approximately 50 percent will exhibit either motor or intellectual impairment. It is important to follow these patients for a few years after their acute disease in order that appropriate rehabilitative action can be taken should any dysfunction surface.

## DIAGNOSIS

### Cerebrospinal Fluid (CSF)

In patients with brain abscesses this examination reveals little and may in fact be contraindicated due to the potential for mechanical injury to the brain as a result of its displacement caused by intracranial and spinal column pressure differentials. In patients with purulent meningitis where a spinal tap is indicated the following abnormalities will be found.

1. The presence of **neutrophils** - 400 to 20,000/mm, the observation of large numbers of lymphocytes would suggest mycobacterial, mycotic or viral meningitis.
2. **Glucose concentrations significantly lower** than that in blood. The glucose is utilized by the phagocytic cells as well as by most of the bacterial organisms causing meningitis. Viral disease does not cause a decrease in glucose.
3. **Elevated protein concentration** - associated with the inflammatory response.
4. **The presence of bacteria** detected by Gram stain.
5. **The presence of bacterial products** - most of the pathogens are encapsulated and the development of sensitive tests (e.g. ELISA) has permitted the identification of capsular antigens in spinal fluid.

### Bacterial cultures

In all cases it is imperative that CSF cultures be performed, and antibiotic sensitivities be determined on the organism isolated. It is common to centrifuge the specimen before inoculating the media. Blood cultures should also be done.

## THERAPY

The fulminating nature of bacterial meningitis precludes any delay in the institution of antimicrobial therapy. The age of the patient is a major guideline in the selection of the appropriate antimicrobial. Ampicillin should be given to the very young (in the case of *H. influenzae* some pediatricians add chloramphenicol to cover the 15-20% of strains that contain a  $\beta$  lactamase encoding plasmid). Penicillin is the drug to give to patients above 5 years of age. Modifications in antibiotic therapy should be considered after culture and sensitivity testing is completed.

The intravenous route of drug administration should be used as the patient's condition often compromises absorption from the gut or intramuscular depot. Large "loading" doses are necessary as very few antibiotics cross the blood-brain barrier readily (an exception is chloramphenicol) and it is imperative to achieve bactericidal concentrations in the CSF rapidly. Treatment should be continued for at least 1 week after symptoms have subsided and for longer periods in neonates.

## ENTERIC DISEASES

Acute gastrointestinal infection ranks as one of the most prevalent of ills which affects mankind, and in its complex interactions with malnutrition, this group of disorders ranks high among the killing diseases of childhood being responsible for 3-5 million deaths per year world wide.

### NORMAL FLORA OF THE GASTROINTESTINAL TRACT

**Composition.** The feces of normal adults contain from  $10^{11}$  to  $10^{12}$  viable bacteria/gram. The majority of these bacteria are found in the colon. The fluid contents of the small intestine contain between  $10^2$  to  $10^3$  bacteria/ml, and in the terminal ileum the count usually does not exceed  $10^7$ . The bacterial flora of the gastrointestinal tract is established within several weeks after birth and remains relatively stable for life. The dominant bacteria in feces are non-sporeforming anaerobic bacilli (*Bacteroides*) although coliforms, such as *Escherichia coli* and other members of the family *Enterobacteriaceae* are also normally present.

Transient organisms are seen in the stomach and upper small intestine, whereas, organisms which adhere to and colonize the mucosal surface are observed in the distal ileum and large bowel. Obligate anaerobes outnumber facultative organisms at least 1000:1. The indigenous flora of the large bowel is diverse in composition although it is predominated by Gram-negative organisms; e.g., *Bacteroides*, *Fusobacterium* and coliforms. Gram-positive cocci and bacilli are also present, including lactobacilli, *Peptostreptococcus*, enterococci, and clostridia.

### Microorganisms Normally Found in The Gastrointestinal Tract

**Stomach and Upper Small Bowel**  
(These transients are found  
throughout the GI tract)

Lactobacilli  
Streptococci  
Bifidobacteria  
Clostridia  
*Veillonella*  
Coliforms  
Yeasts

**Distal ileum**

*Bacteroides*

**Large Bowel and feces**

*Peptostreptococcus*  
*Peptococcus*  
*Propionibacterium*  
*Bacteroides*  
*Fusobacterium*

In addition to bacteria, certain parasites and viruses are classified as enteric agents. Although many of the respiratory viruses may produce gastrointestinal symptoms, two major groups associated with viral gastroenteritis are the Rotaviruses and the Norwalk agent. The parasites *Entamoeba histolytica* and *Giardia lamblia* are primary pathogens of the gastrointestinal tract. Other parasites, including *Trichinella spiralis*, *Balantidium coli*, *Schistosoma* and *Strongyloides stercoralis* may induce enteric disease during certain phases of their infective cycle in man.

## Function

Normal flora may enhance the host defense mechanisms by 1) production of bacteriocins and antibiotics active against potential pathogens; 2) competition for nutrients; 3) occupation of the intestinal mucosal surface, thereby preventing exogenous pathogens from attaching and 4) serving as a constant source of immunogens, continually priming the local and systemic immune systems. Two negative aspects of the gastrointestinal flora are 1) a source of antigens which induce endotoxin tolerance and 2) large numbers of organisms potentially dangerous when bowel perforation occurs or the host become severely immunologically compromised.

An important factor in establishing enteric infection is the ability of the parasite to adhere to host mucosal surfaces. The adherence of bacteria to animal cells is dependent on specific recognition systems. Receptors on the membranes of tissue cells interact with specific ligands on surfaces of bacteria. Lipoteichoic acid (LTA), fimbrial protein, colonizing factor antigen, and other microbial surface proteins are thought to serve as ligands involved in host cell adhesion. Animal strains of *E. coli* possessing K88 and K89 antigens may bind to host cells via galactose or N-acetylgalactosamine moieties, respectively. Human strains of *E. coli* seem to possess a mannose-specific lectin-like substance that binds the organisms via fimbriae to mannose residues on epithelial cells.

## Toxins of Enteric Bacilli

Endotoxin, the LPS moiety of the Gram-negative cell wall, is highly toxic. The biological effects of bacterial endotoxins are myriad (see Table below), although no clearcut molecular-biological basis for their activities is known. Many effects of endotoxin appear to be mediated through host humoral and cellular responses. The morbidity and mortality associated with many infections caused by Gram-negative bacteria are considered related to the endotoxins present in the cell walls of these bacteria.

### Biological Effects Induced by Bacterial Endotoxins

|                            |                               |
|----------------------------|-------------------------------|
| Pyrogenicity               | Mitogenic for B lymphocytes   |
| Lethal shock               | Increases interferon          |
| Adjuvancy                  | production                    |
| Shwartzman phenomenon      | Release of colony-stimulating |
| Tumor necrosis             | factor                        |
| Leukopenia - leukocytosis  | Complement activation         |
| Hypotension                | Hagemann factor activation    |
| Plasminogen activation     | Stimulation of prostaglandin  |
| Enhancement of nonspecific | synthesis                     |
| resistance                 |                               |

**Enterotoxins** are usually protein substances that exert their toxic effect specifically in the small intestine. The **cholera** of *V. cholerae* is the prototype of bacterial enterotoxins. A number of enterics have been shown to produce enterotoxic materials which cause large amounts of fluid and electrolytes to be secreted into the intestinal lumen, without demonstrable gastrointestinal histopathology .

## Spectrum of Enteric Diseases

Diseases that affect the gastrointestinal tract of man are diverse and multifaceted. In a few cases, the pathogenesis is well understood, although most of the syndromes have only recently been studied in experimental animal models. The spectrum of microbial enteric infections is presented below.

### TYPE OF INTESTINAL BACTERIAL INFECTIONS

| Type of Infection  | Microorganisms  | Virulence Factors   | Clinical Features |                     |
|--|---|---|-------------------|---------------------|
|  |   |   | Fever             | Stools<br>water pus |
| Bacteria attach to epithelium of small intestine and cause <b>watery diarrhea</b> by forming an enterotoxin which induces fluid loss from epithelial cells | <i>Vibrio cholerae</i><br><i>E. coli</i>  | Adhesin<br>Enterotoxin ADP ribosylates an adenylylate cyclase regulatory protein, causing an increase in enzyme activity                                    | No<br>No          | Yes                 |
| Microorganism attaches to and penetrates epithelial cells of large intestine or ileum causing <b>bloody diarrhea</b> by killing cells                      | <i>E. coli</i><br><i>Campylobacter jejuni</i><br><i>Yersinia enterocolitica</i><br><i>Shigella spp.*</i><br><i>Salmonella spp.*</i> | Adhesin<br>Hemin binding protein in outer membrane coats cells which are then taken up to enterocytes<br>Cytotoxin kills enterocytes                        | Yes<br>Yes        | No                  |
| Bacteria attach to and penetrate epithelium of small intestine. Invade subepithelial tissues, cause ulceration and spread systemically                     | <i>Salmonella typhi</i><br><i>Salmonella choleraesuis</i>   | Adhesin<br>Vi surface antigen<br>Microbes survives in phagocytes by inhibiting oxidative metabolism and production of toxic oxygen metabolites<br>Endotoxin | Yes<br>No         | No                  |

\* Only these 2 affect large intestine; the rest are pathogens of the small intestine.

## Laboratory Diagnosis

Laboratory diagnostic procedures include microscopic examination, culture, toxin detection, and serologic procedures. The relative value of each is different for the various etiologies.

## Treatment

In most gastrointestinal infections the goal of treatment is relief of symptoms, with particular attention to maintaining fluid and electrolyte balance. The effect of common antidiarrheal medications such as bismuth compounds (Pepto Bismol) or antispasmodics (lomotil) is variable depending on the etiology. In general, they may be helpful for the watery diarrhea caused by enterotoxins, but not for dysentery caused by mucosal invasion, and antispasmodics may be harmful in the latter instance. Antimicrobial agents are usually not indicated for self-limited watery diarrhea, but are required for more severe dysenteric infections. Some enteric infections, such as typhoid fever, are always treated with antimicrobics.

### Antibiotic-induced Gastrointestinal Disease

The prolonged administration of antibiotics, particularly those with an extended spectrum, may alter the existing balance in the normal flora and give minor members of that population (that are resistant to the antibiotic) an opportunity to increase in numbers to such an extent that they will produce disease. Two diseases deserve mention.

**Thrush**, a *Candida albicans* infection of the oral cavity, can occur following the use of broad spectrum antibiotics, particularly via the per os route. This same yeast infection occurs in the very young and in immunocompromised patients of any age. Parenteral antibiotic administration may permit the overgrowth of candida cells in the vaginal tract or in the anal area, with resultant irritation and disease (e.g., candidal vaginitis).

**Pseudomembranous colitis** results from an overproliferation of the obligate anaerobic organism *Clostridium difficile*. This organism may be resistant to several antibiotics that act on other members of the colonic flora, thus giving it a selective advantage. In the presence of antibiotic therapy with, for example, **clindamycin**, the clostridia reproduce and elaborate a potent enterotoxin that produces diarrhea with WBC infiltration and hemorrhagic necrosis of the intestinal mucosa. **Vancomycin** is the drug of choice, although merely withholding the offending antibiotic often is successful.

## Food Poisoning

Many gastrointestinal infections involve food as a vehicle of transmission. The term "food poisoning" however, is usually reserved for instances in which a single meal can be incriminated as the source. This usually arises when multiple cases of the disease develop among persons whose only common experience is a shared meal.

The most common causes of food poisoning are shown in table below. Some are not infections but intoxications caused by ingestion of a toxin produced by bacteria in the food before it was eaten. Intoxications generally have shorter incubation periods than infections and may involve extra-intestinal symptoms (for example, the neurologic damage in botulism). Infectious food poisoning does not differ from endemic diarrheal infections caused by the same species. The length of the incubation period and the severity of the symptoms are generally related to the number of organisms in the infecting dose.

### CLINICAL AND EPIDEMIOLOGIC FEATURES OF FOOD POISONING

| Etiology                      | Incubation Period (hr) | Clinical Findings       | Characteristic Foods                   |
|-------------------------------|------------------------|-------------------------|--|
| <b><u>Intoxications</u></b>   |                        |                         |  |
| <i>Bacillus cereus</i>        | 1-6                    | Vomiting, diarrhea      | Rice                                   |
| <i>Staphylococcus aureus</i>  | 1-6                    | Vomiting                | Meats, custards, salads                |
| <i>Clostridium botulinum</i>  | 12-72                  | Neuromuscular paralysis | Improperly preserved vegetables, meats |
| <b><u>Infections</u></b>      |                        |                         |  |
| <i>Cl. perfringens</i>        | 12-24                  | Watery diarrhea         | Meat, poultry                          |
| <i>Salmonella spp.</i>        | 6-48                   | Gastroenteritis         | Poultry products                       |
| <i>Shigella spp.</i>          | 12-48                  | Dysentery               | Variable                               |
| <i>Vibrio parahemolyticus</i> | 12-24                  | Watery diarrhea         | Shellfish                              |
| <i>Trichinella spiralis</i>   | 3-30 days              | Fever, myalgia          | Pork                                   |
| Hepatitis A                   | 10-50 days             | Hepatitis               | Shellfish                              |

## SEXUALLY TRANSMITTED DISEASES

The incidence of sexually transmitted diseases (STD) has increased alarmingly in the last 2 decades, and has now reached epidemic proportions. The incidence of the major venereal diseases is presented in the table below. The most serious complications of these diseases include infertility, congenital abnormalities, ectopic pregnancy and abortion.

### The Major Pathogens and Their Estimated Frequencies in the United States

| <u>Disease</u>                           | <u>Pathogen</u>              | <u>Annual cases</u> |
|--|------------------------------|---------------------|
| Condylomata acuminata<br>(Genital warts) | Papillomavirus               | 10,000,000          |
| Non-gonococcal urethritis                | <i>Chlamydia trachomatis</i> | 4,000,000           |
| Gonorrhea                                | <i>Neisseria gonorrhoeae</i> | 2,000,000           |
| Genital herpes                           | Herpesvirus type II          | 500,000             |
| Syphilis                                 | <i>Treponema pallidum</i>    | 150,000             |
| Cervical carcinoma                       | Papillomavirus               | 20,000              |

### Epidemiology and Etiology

These diseases are contracted during sexual intercourse. The increase in oral and/or anal sexual contact has changed the method of spread as well as the types of diseases transmitted. Several enteric diseases are now considered STDs among homosexual males. It is not uncommon for a patient to have more than one STD at the same time. A partial list grouped by sexual incidence is tabulated below.

#### Sexually Transmitted Pathogens of Women

| <u>Microbe</u>               | <u>Disease</u>                 |
|------------------------------|--------------------------------|
| <i>Gardnerella vaginalis</i> | Vaginitis                      |
| Group B streptococci         | Neonatal sepsis and meningitis |
| <i>Trichomonas</i>           | Vaginitis                      |
| <i>Candida albicans</i>      | Vulvovaginitis                 |

#### Sexually Transmitted Among Homosexual Men

|                              |                         |
|------------------------------|-------------------------|
| <i>Shigella spp.</i>         | Shigellosis             |
| <i>Campylobacter fetus</i>   | Enteritis and proctitis |
| Herpesvirus hominis, type II | Genital herpes          |
| Hepatitis B                  | Hepatitis               |
| <i>Entamoeba histolytica</i> | Amebiasis               |
| <i>Giardia lamblia</i>       | Giardiasis              |

## Prevention and Control

The condom is the most effective means of **protection** against venereal disease. Unfortunately, individuals who need protection the most (those with multiple sex partners) are the least likely to use them.

**Control** of STD is best accomplished by diagnosis and treatment of patients and their sexual contacts. Prompt reporting of all cases to the appropriate health agency is imperative if a thorough epidemiological survey and partner contact is to be achieved. At least 3 factors are operating to confound attempts at the control of these diseases. First, many patients are reluctant to seek medical assistance due to embarrassment, guilt, fear of complications in their personal lives, etc. Secondly, many cases are asymptomatic, particularly in females. Finally, **treatment must be sufficient to cure** the disease. Whenever possible a single dose therapy should be employed as the patient's continued self-treatment will probably stop when the symptoms moderate, which very likely will not coincide with a bacteriological cure.

## Common Presenting Complaints

**Urethral Discharge** of purulent material is seen in infections with the **gonococcus**, *C. trachomatis*, *C. albicans*, *T. vaginalis* and type II herpes virus. A burning pain is usually associated with urination.

A copious vaginal discharge, characterized by the presence of large numbers of neutrophils and an offensive odor, is seen in women infected with many of the same agents that cause urethritis in males. **Gardnerella vaginalis** also causes a vaginitis; characteristics of the latter include by a fishy odor and the presence of "clue" cells (i.e., sloughed epithelial cells with adherent gram negative rods).

**Skin lesions** may be of 2 types, either as a rash or an ulcer. **Rashes** are seen in candidiasis and in secondary syphilis. **Ulcerative** lesions occur in syphilis, and genital herpes.

## Complications

The serious consequences of STDs are manifold. They may result from;

- 1) **contiguous** spread of the infection to involve the reproductive organs,
- 2) **hematogenous** dissemination of the microorganism to other organ systems,
- 3) **infection of the infant** either during pregnancy or while passing through the birth canal. A list of the more common complications is presented in the table below. **Salpingitis** (inflammation of the fallopian tubes) is probably the most serious manifestation of STD in females. It can lead to infertility (nearly 20% in women with 1 or more cases of salpingitis) and ectopic pregnancies with resultant fetal death and potential maternal mortality.

Infant morbidity and mortality due to *T. pallidum* and the gonococci is quite low in the United States due to the fact that pregnant women are routinely tested and treated for these agents; however, congenital and perinatal diseases caused by **cytomegalovirus**, **herpes virus**, *C. trachomatis* and **Group B streptococci** are of considerable importance.

At least 2 malignancies are thought to be associated with STDs of viral etiology. Cervical carcinoma has been suggested as a sequela of **Papilloma virus** infections. Hepatocellular carcinoma has been linked to **hepatitis type B viral disease**. Acquired Immune Deficiency Syndrome (AIDS) is another human affliction which occurs as a sequela of a sexually transmitted infection caused by the human immunodeficiency virus..

### **Complications of Sexually Transmitted Diseases**

| <b><u>Method of Dissemination</u></b> | <b><u>Disease</u></b>                               |
|---------------------------------------|---|
| Contiguous                            | Salpingitis<br>Epididymitis                         |
| Hematogenous                          | Hepatitis<br>Meningitis<br>Arthritis                |
| Congenital                            | Abortion, birth defects, etc.                       |
| Perinatal infections                  | Conjunctivitis<br>Pneumonia<br>Sepsis<br>Meningitis |

### **Miscellaneous Genitourinary Pathogens**

**Escherichia coli** is the most common cause of uncomplicated urinary tract infections (cystitis and pyelonephritis), causing over 80 %of all disease. **Klebsiella pneumoniae** is #2 at 5-10%. The same two agents predominate in prostatitis. **Adenovirus type 2** causes an **acute hemorrhagic cystitis in young children**. Patients with urinary tract abnormalities that interfere with urine flow are likely to experience chronic and/or recurrent infections. Hospitalized patients are susceptible to nosocomial infections with agents other than E. coli, although this agent still predominates in most urinary catheter-induced cases.

PRINCIPAL MICROORGANISMS INFECTING THE HUMAN FETUS

|          | Microorganisms                    | Effect                                   |
|----------|-----------------------------------|--|
| VIRUSES  | Rubella virus                     | Abortion<br>Still birth<br>Malformations |
|          | Cytomegalovirus                   | Malformations                            |
|          | Human Immuno-<br>deficiency Virus | AIDS                                     |
| BACTERIA | <u>Treponema pallidum</u>         | Stillbirth, malformation                 |
|          | <u>Listeria monocytogenes</u>     | Meningoencephalitis                      |
| PROTOZOA | <u>Toxoplasma gondii</u>          | Stillbirth, CNS disease                  |

The mnemonic for these agents is TORCHES

Toxoplasma  
Rubella  
Cytomegalovirus  
Human Immunodeficiency virus  
Herpes  
Syphilis

# THE GRAM STAIN

The Gram stain aids in the identification of bacteria according to their size, shape and grouping by rendering them more visible. It also helps identify them by dividing the eubacteria into Gram positive or negative organisms. The cell wall composition of Gram negative bacteria differs from that of Gram positive. Since Gram negative bacteria have a high lipid content of their cell walls, one theory holds that the decolorizer (acetone or ethanol) solubilizes the cell wall thus reaching the crystal violet. In the cell wall of Gram positive organisms, the decolorizer is unable to act as a solvent thus the crystal violet remains.

Mycoplasma do not have a cell wall.

Their gram reaction would be

\_\_\_\_\_.

## Step      Reagent

1. Crystal violet (c.v.)
2. Sodium bicarbonate
3. Gram's iodine
4. Acetone
5. Safranin

Appearance of organisms, step by step:

| <u>Gram Positive</u>         | <u>Gram Negative</u>  |
|------------------------------|---|
| 1. purple                    | purple  |
| 2. purple;alkalinized        | purple;alkalinized  |
| 3. purple;fixes c.v. in cell | purple;fixes c.v. in cell   |
| 4. purple                    | colorless; c.v. washes out because cell wall (lipid) soluble in acetone -thus the organisms are unstained again |
| 5. purple                    | red/pink  |

Age can cause conversion from Gram positive to negative. What technical errors in the staining procedure could

do the same?

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

The thick spore coat is resistant to the penetration of dyes. They will appear blue/red/colorless in a Gram stain?

MORPHOLOGY AND GRAM REACTION OF SOME BACTERIA OF MEDICAL IMPORTANCE

Gram +

Gram -

COCCI

Staphylococcus  
Streptococcus

Neisseria  
Veillonella(2)

BACILLI

Bacillus(1)  
Clostridium(1,2)  
Corynebacterium  
Listeria  
Mycobacterium

Escherichia  
Klebsiella  
Proteus  
Pseudomonas  
Salmonella  
Shigella  
Brucella  
Francisella  
Yersinia  
Haemophilus  
Bordetella  
Bacteroides(2)

SPIROCHETES

Borrelia(2)  
Leptospira  
Treponema(2)

1. only sporeforming pathogens
2. only obligate anaerobic pathogens in list

Generalities That Can Be Draw From Gram Reaction Table

Generality

Exceptions

All cocci are Gram positive

Neisseria, Veillonella

All rods are Gram negative

Bacillus, Clostridia, Corynebacteria,  
Listeria, Mycobacteria

All pathogens are facultative  
anaerobes

Clostridia, Bacteroides (obligate  
anaerobes)

Only bacilli have flagella

None

# PROPERTIES OF A- B TOXINS

| Toxin                           | Structure*            | Enzymatic      |   | Biologic Effects   |
|---------------------------------|-----------------------|----------------|---|--|
|                                 |                       | Activity       | Substrate                                 |  |
| Diphtheria toxin                | A-B<br>↓              | NADase<br>↓    | Elongation factor II<br>↓                 | ↓ Stop protein synthesis (ADP-ribosylate EF-2)                         |
| Pseudomonas exotoxin A          | ↓                     | ↓              | ↓   |  |
| Cholera toxin                   | A-B <sub>5</sub><br>↓ | ↓              | Adenylate cyclase-regulatory protein<br>↓ | ↑ Increases adenylate cyclase activity                                 |
| E. coli Heat-labile enterotoxin | ↓                     | ↓              | ↓   |  |
| Pertussis toxin                 | ↓                     | ↓              | ↓   |  |
| Botulinum toxin                 | A-B<br>↓              | Not known<br>↓ | Not known<br>↓                            | ↓ Depresses presynaptic acetylcholine release from peripheral neurons  |
| Tetanus toxin                   | ↓                     | ↓              | ↓   | ↓ Depresses neurotransmitter (glycine) release from inhibitory neurons |
| Shigella toxin                  | A-B <sub>5</sub>      | ↓              | ↓   | ↓ Inhibits protein synthesis   |

\* A is active (toxic) moiety, B is binding protein

# PROPERTIES OF SPECIFIC PATHOGENS

## GRAM POSITIVE COCCI

### STREPTOCOCCUS GENUS

#### I. General Characteristics

- A. Some have capsules (Group A = hyaluronic acid)
- B. Production of hemolysis
  - 1.  $\alpha$ -hemolytic (viridans)
  - 2.  $\beta$ -hemolytic (complete)
  - 3.  $\gamma$ -hemolytic (none)
- C. Catalase negative
- D. Penicillin = Drug of Choice

The drug of choice for most streptococcal infections is \_\_\_\_\_.

### STREPTOCOCCUS PNEUMONIAE

#### I. General Characteristics

- A. bile, optochin, detergents lyse colonies
- B. alpha hemolytic; optochin sensitive
- C. Drug of choice = penicillin

Artificial, actively acquired immunity against pneumococcal pneumonia is readily induced by a vaccine composed of

#### II. Antigenic Structure

- A. Capsular polysaccharide = 75-80 serological types
  - 1. SSS - specific soluble substance = quellung rx (capsule swelling)
  - 2. protective antibody = opsonin
  - 3. Vaccine is composed of SSS from the most prevalent 23 types

\_\_\_\_\_.

#### III. Distribution

- A. Normal flora; common cause of lobar pneumonia in alcoholics, and as secondary invader following viral infections (e.g., influenza) Hematogenous spread may result in meningitis in debilitated adults.

The pneumococcus is alpha/beta/gamma hemolytic.

#### IV. Bacterial Factors Involved in Pathogenicity

- A. Prime virulence factor = Capsule - antiphagocytic - content of vaccine (Pneumovac) - confers opsonic immunity

BETA-HEMOLYTIC STREPTOCOCCI

I. Antigens used for Identification  
(bacterial cell wall antigens)

- A. Group-specific C Antigens
  - 1. carbohydrate
  - 2. divide organisms into groups A-O;  
A is sensitive to bacitracin
- B. Type-specific M Antigens (protein)
  - 1. subdivide group A into 50 + types
  - 2. antiphagocytic - virulence factor
  - 3. immunity is type specific

II. Other Surface Components

- A. Hyaluronic acid capsule = anti-phagocytic CHO; not antigenic
- B. Lipoteichoic acid = important in adherence to epithelial cells

III. Extracellular Products

- A. Erythrogenic toxin (pyrogenic exotoxin) - produced by lysogenic strains of group A
  - 1. erythema and edema
  - 2. three immunological types (A-C)
  - 3. positive Dick test indicates susceptibility to Scarlet fever
- B. Streptolysin O (oxygen labile; sulfhydryl activated)
  - 1. antigenic - used to detect antibody resulting from infection (ASO)
  - 2. leukotoxic - cytolytic
- C. Streptolysin S (oxygen stable; serum required for synthesis)
  - 1. responsible of hemolysis of surface colonies on blood agar
  - 2. non-antigenic
  - 3. leukotoxic
- D. DNase
  - 1. 4 immunologic types (A,B,C,D) - type B used to measure antibody resulting from infection
- E. Streptokinase (Fibrinolysin) - converts plasminogen to plasmin
- F. Hyaluronidase (spreading factor)

Antigens of importance in the serologic identification of beta hemolytic

streptococci include

- A. group specific C carbohydrate
- B. type specific M protein
- C. both
- D. neither

(answer at bottom of page)

Antiphagocytic surface components of group A streptococci include

- A. hyaluronic acid
- B. M protein
- C. both
- D. neither

(answer at bottom of page)

|  |
|--|
| Streptococcal pili contain two important virulence factors:<br>lipoteichoic acid = adherence<br>M protein = anti-phagocytic. |
|--|

(answers to both = C)

IV. Types of Diseases

- A. Group A (S. pyogenes) acute infections
  1. streptococcal pharyngitis (with toxemia = scarlet fever)
  2. pneumonia
  3. puerperal sepsis
  4. erysipelas, impetigo
  
- B. Group A post-infection sequelae
  1. acute glomerulonephritis - associated with skin or upper respiratory tract infections
    - a) one + weeks after infection
    - b) nephritogenic strains (e.g., types 4, 12, 49)
    - c) may be antigen-antibody reaction resulting in binding of complement ("lumpy-bumpy" deposition of Ig in basement membrane)
  2. acute rheumatic fever - associated with upper respiratory tract infection only: strep M protein cross reacts with heart tissue
  
- C. Non-group A Diseases
  1. Caries - plaque caused by adherent dextrans of S. mutans; glucan formed from sucrose by glucosyl transferase; may also predispose to periodontal disease
  2. Subacute endocarditis (oral and enteric strep); alpha hemolytic
  3. Meningitis and septicemia (enteric strep such as S. agalactiae = group B) in neonates

Non-suppurative sequelae of group A streptococcal infections include

- A. Scarlet fever
- B. erysipelas
- C. puerperal fever
- D. caries
- E. Rheumatic fever

(answer at bottom of page, left side)

Rheumatic Fever Symptoms  
 Pericarditis  
 Arthritis  
 Chorea  
 SubQ nodules  
 Elevated ASO

Two streptococcal organisms are commonly associated with meningitis. Complete the table below.

PEPTOCOCCI, PEPTOSTREPTOCOCCI

- I. Obligate anaerobes
- II. Mixed infections
- III. Pulmonary abscesses by aspiration from oral cavity

| <u>Patient group</u>              | <u>Streptococcal species</u> |
|-----------------------------------|------------------------------|
| example - <u>kids with caries</u> | <u>S. mutans</u>             |
| <u>neonates</u>                   | _____                        |
| <u>elder</u>                      | _____                        |

(answer is E)

## STAPHYLOCOCCUS AUREUS

### I. General Characteristics

- A. beta hemolytic, facultative aerobe
- B. golden pigment
- C. coagulase produced
- D. catalase positive

### II. Surface Antigens

- A. capsular antigen - antiphagocytic,
- B. protein A-antiphagocytic, reacts with Fc portion of Ig

### III. Extracellular substances

- A. coagulase
- B. alpha toxin - hemolytic, leukotoxic
- C. enterotoxin - exotoxin
  - 1. resistant to boiling
  - 2. resistant to proteolytic enzymes
  - 3. incubation period 2-4 hrs for symptoms of food poisoning
  - 4. toxin ingested preformed
  - 5. causes nausea, vomiting, diarrhea
- D. penicillinase
- E. pyrogenic exotoxins (toxic shock)
- F. exfoliatin

### IV. Types of Infections

- A. Most common - pimples, boils, carbuncles, furuncles
- B. Most dangerous - septicemia, endocarditis, meningitis, pneumonia, abscesses, osteomyelitis
- C. Other diseases - food poisoning (2-4 hr incubation), nosocomial infections post-surgery, scalded skin syndrome in neonates (exotoxin = exfoliatin), Toxic Shock Syndrome (Pyrogenic toxins A-C)

### V. Diagnosis

- A. Organism isolated on selective media such as Mannitol Salt Agar
- B. Demonstrate beta hemolysis
- C. Test for production of coagulase and/or DNase
- D. If concerned with hospital epidemic, do bacteriophage typing

### VI. Therapy

Because of high incidence of beta lactamase producers (plasmid encoded) start with oxacillin, cefotaxime, or another enzyme-resistant drug

## Major Causes of Skin Infections

|                               |  |
|-------------------------------|--|
| <i>Staphylococcus aureus</i>  | Bullous impetigo<br>Folliculitis(1)<br>Furuncles<br>Carbuncles   |
| <i>Streptococcus pyogenes</i> | Erysipelas<br>Cellulitis<br>Pyoderma<br>(Streptococcal impetigo) |

(1) *Propionibacterium* is associated with acne but the primary etiology is unknown.

Staphylococcal **protein A** acts as an **anti-opsonin** by reacting with antibody molecules at the Fab/Fc portion.

Staphylococci can colonize normal heart valves; alpha streptococci only grow on damaged or prosthetic ones.

### An Intoxicating Story

Staphylococcal food poisoning is due to ingestion of preformed enterotoxin, thus the disease has a short/long incubation period.

Foods commonly incriminated include

- 1. cooked meats like ham = 40%
- 2. potato salad = 20%
- 3. baked foods = 10%
- 4. poultry = 10%

# GRAM NEGATIVE COCCI

## NEISSERIA

### I. General Characteristics of Genus

- A. Most species are normal human flora (NOT gonococcus)
- B. Pathogens occur in vivo inside PMNs
- C. Pathogens (fastidious) - grow on chocolate or Thayer-Martin agar, 37C, 10% CO<sub>2</sub>, produce indophenol oxidase which is useful in identification of colonies. Produce IgA1 protease.
- D. Killed rapidly by drying, sunlight, UV, moist heat at 55 C, phenol
- E. Penicillin sensitive: a few strains have plasmid directed beta lactamase

The drug of choice for neisserial infections is \_\_\_\_\_.

## NEISSERIA MENINGITIDIS

### I. Antigenic Structure

- A. There are 4 serogroup-specific capsular polysaccharides (A-D)
  - 1. Type A majority of epidemics
  - 2. Anti-phagocytic
- B. Endotoxin involved in disease (Waterhouse-Frederichsen syndrome)

The major virulence factors of the meningococcus are

- A. endotoxin
- B. IgA protease
- C. capsular carbohydrate
- D. all of the above
- E. A and C only

### II. Epidemiology

- A. Man is only reservoir - up to 30% carriers
- B. Disease appears sporadically or in epidemics in military personnel

### III. Pathogenesis

- A. gain access to nasopharynx
- B. Pili affect adherence
- C. local inflammatory rx - organism produces IgA1 protease
- D. bacteremia → meningitis or meningococemia
- E. result in metastatic lesions in skin (causes purpuric rash), joints, ears, lungs, adrenals, etc.
- F. fulminating cases - acute adrenal insufficiency (Waterhouse-Frederichsen syndrome) associated with hemorrhagic necrosis of both adrenal glands

(answer at bottom)

Meningococci adhere to host cells by means of pili/capsule.

(answer = D)

## NEISSERIA GONORRHOEAE

### I. Antigenic Structure

- A. K antigen - cell wall polysaccharide lost on subculture: I-IV related to virulence and colony morphology; I and II are virulent, contain pili and are leukocyte associated).
- B. This variability has confounded efforts at vaccine development.

Gonococci adhere to host cells by means of pili/capsules.

### II. Pathogenicity

- A. Enter through mucous membrane of genitourinary tract.
- B. Penetrate between columnar epithelial cell. In subepithelial tissue cause acute inflammatory response resulting in purulent yellow urethral or vaginal discharge.
- C. Pili responsible for adherence to cell membranes and survival within PMNs.
- D. Organisms elaborate a protease which cleaves IgA1 at the hinge region of the H chain.

One of the most serious complications of gonorrhea is PID, which stands for

\_\_\_\_\_.

### III. Symptomatology

- A. Male
  - 1. incubation period - 2-8 days
  - 2. frequent, urgent, painful urination
  - 3. mucopurulent discharge
- B. Female
  - 1. commonly asymptomatic
  - 2. urethritis
  - 3. may involve fallopian tubes; may cause pelvic inflammatory disease, salpingitis.
- C. Culture is required to confirm diagnosis in both males and females

The drug of choice for penicillinase producing *N. gonorrhoeae* is

\_\_\_\_\_.

### IV. Diseases Other Than Gonorrhea

- A. Arthritis via hematogenous route
- B. Ophthalmia neonatorum acquired passing through birth canal

### V. Therapy

- A. Penicillin = drug of choice
- B. Spectinomycin for PPNG (Penicillinase producing Neisseria gonorrhoeae)

# GRAM POSITIVE RODS

## BACILLUS ANTHRACIS

### I. Pathogenicity of Anthrax

- A. Spore is infectious particle
- B. Penicillin = drug of choice
- C. Three routes of infection
  - 1. cutaneous (puncture); disease = malignant pustule
  - 2. ingestion
  - 3. inhalation (wool sorter's disease)
- D. Virulence
  - 1. d-polyglutamic acid capsule (antiphagocytic)
  - 2. Tri-molecular toxin
    - a. Edema factor = adenylate cyclase
    - b. Protective antigen - binds to host cell membrane
    - c. Lethal factor

The antiphagocytic capsule of

B. anthracis is composed of

\_\_\_\_\_.

## CLOSTRIDIUM GENUS

### I. Gas Gangrene: complex infection by anaerobic bacteria

The spore is the infectious particle in all of the following diseases except:

- A. Organisms involved
  - 1. Clostridium perfringens type, A,D,F
  - 2. Clostridium novyi
  - 3. Clostridium septicum
- B. Pathogenicity
  - 1. Any wound contaminated with dirt has potential for gas gangrene infection due to low redox potential of traumatized tissue.
  - 2. Toxins and enzymes
    - a. alpha toxin - lecithinase C
    - b. collagenase, hyaluronidase
    - c. hemolysin
    - d. enterotoxin = food poisoning
- C. Treatment
  - 1. antiserum
  - 2. debridement of wound
  - 3. hypochlorite or H<sub>2</sub>O<sub>2</sub>
  - 4. hyperbaric oxygen
  - 5. penicillin, tetracycline

A. tetanus

B. anthrax

C. gas gangrene

D. botulism

(answer at bottom)

(the best answer to the question above is D, although infant botulism is spore-mediated)

II. Tetanus - organism involved -  
Clostridium tetani

A. Toxin

1. Tetanus toxin - B chain binds to cell; A chain is the toxic moiety.
  - a. acts at synaptic junction of specific interneurons to block inhibitory pathways in anterior horn cells.
2. Toxoid=prophylaxis; antitoxin=therapy; single antigenic type

Tetanus toxin interferes with

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B. Pathogenesis

1. Deep wound and inflammatory response
2. Anaerobic conditions
3. Very limited infection: disease is an intoxication
4. Toxin production locally; spread through body intraaxonally
5. Causes spastic paralysis; opisthotonus.

III. Botulism-organism involved -  
Clostridium botulinum

Botulinum toxin interferes with

A. Pathogenicity

1. Potent neurotoxin-H chain binds to cell; L chain is toxic moiety.
  - a. 8 serologic types-A, B, and E most common in man.
  - b. protein, heat labile, resistant to gastric acidity and proteolysis; ingested as prototoxin.
  - c. mechanism of action - interferes with release of acetylcholine in the efferent autonomic nervous system and prevents the transmission of nerve impulses across the myoneural junction.

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The drug of choice for C. difficile

IV. Pseudomembranous enterocolitis  
Organism involved = Clostridium difficile

enterocolitis is \_\_\_\_\_.

- A. Clindamycin oral therapy is involved as a precipitating factor. It depresses anaerobic gut flora which allows C. difficile to grow.
- B. Vancomycin is the drug of choice.

## CORYNEBACTERIA

I. Diphtheria causative agent -  
Corynebacterium diphtheriae;  
diphtheroids = normal flora

### A. Diphtheria toxin

1. Protein of 65-70,000 daltons
2. Production of toxin
  - a. requires the presence of beta phage, and low iron content
  - b. toxin is a phage-coded protein (lysogenic conversion)
3. Mechanism of action
  - a. Fragment B - attaches to cell membrane
  - b. Fragment A - inhibits protein biosynthesis by inhibiting the transferase II enzyme, Elongation Factor 2, by ADP ribosylation.

Diphtheria toxin inhibits protein  
synthesis by \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_.

B. Disease is due to toxemia. No bacteria are found in the blood, therefore, the therapy of choice is antitoxin, not antibiotics. Prophylactic toxoid stimulates the production of antitoxin.

C. Pseudomembrane that forms in the throat is composed of fibrin, PMNs, dead tissue cells and bacteria. It may break free from the underlying epithelium and close off the airway, causing suffocation.

Therapy of choice for diphtheria is

\_\_\_\_\_  
\_\_\_\_\_.

### D. Diagnosis

1. Observe Gram + pleomorphic rods in palisade arrangement in stain of swab of pseudomembrane.
2. Culture organism on Blood agar, Loeffler's or tellurite agars.
3. Demonstrate metachromatic nature of organism.
4. Prove toxigenicity of organism. This is the definitive step; must use antitoxin as specificity control.

Elongation factor 2 is ADP-ribosylated by diphtheria toxin. The prokaryotic translocation factor EF-G is not. This specificity is due to the presence in eukaryotic EF-2 of a unique residue, **diphthamide**, which is a modified histidine side chain in the protein which is the site of ADP-ribose attachment.

## LISTERIA MONOCYTOGENES

L. monocytogenes - cousin of C. diphtheria - but is motile at 24 C.

- A. Causes 10% of neonatal meningitis (normal vaginal flora).
- B. Cell wall lipid induces monocytosis.

The most common listerial infection in adults is meningitis; endocarditis and septicemia may also occur.

## ACID FAST BACILLI

### I. Mycobacterioses

#### A. Organisms

1. Mycobacterium tuberculosis (facultative intracellular parasite)
2. Mycobacterium leprae (obligate intracellular parasite)
3. Atypical mycobacteria e.g., M. kansasii, M. avium intracellulare
4. BCG = bacille Calmette Guerin;
  - a. attenuated M. tuberculosis (bovine strain)
  - b. vaccine vs. tuberculosis

B. Acid fast due to high lipid content (mycolic acids) of cell wall

C. Growth - most are slow growers (M. tuberculosis = 3-6 weeks); obligate aerobes

D. Toxic product = Cord Factor (trehalose 6,6 dimycolate) and sulfatides; blocks production of toxic oxygen metabolites

E. Cell wall is rich in lipids, (e.g., wax D); resistant to acids, alkali, and chemical disinfectants

#### F. Epidemiology

##### 1. M. tuberculosis

- a. Man to man or animal to man transfer by ingestion, contact, or aerosol

##### 2. Atypical mycobacteria

- a. No man to man transfer
- b. Probable source in soil and water
- c. Portal of entry is upper respiratory tract, or through the skin
- d. M. avium occurs in AIDS patients

##### 3. M. leprae

- a. Man is major host; agent has also been cultured in armadillo
- b. Transmission by prolonged contact

M. tuberculosis is

- A. Acid fast
- B. Gram positive
- C. Both
- D. Neither

(Answer at bottom)

Niacin production is a valuable

laboratory test in the identification of

- A. M. tuberculosis
- B. M. leprae
- C. Both
- D. Neither

(answer at bottom)

#### G. Diagnosis

1. Observe acid fast rods in tissue
2. Culture (except M. leprae)
3. Niacin test - M. tb = positive, atypicals = negative

(answer = C)

(answer = A)

H. Treatment

1. First Line Drugs (atypicals may be resistant)
  - a. Isoniazid (INH) and PAS
  - b. Streptomycin and PAS
  - c. Rifampin and ethambutol
  - d. INH alone for skin test converters
2. Second Line Drugs
  - a. Ethionamide
  - b. Cycloserine
  - c. Pyrazinamide

First line drugs for tuberculosis include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_

Leprosy

1. Etiologic agent: M. leprae (Hansen's bacillus)
2. Two types of disease
  - a. lepromatous (nodular skin lesions with abundant acid fast bacilli; lepromin negative)
  - b. tuberculoid (anaesthetic macular skin lesions with very few acid fast bacilli; lepromin positive)
3. Transmission is by direct contact
4. Skin testing - lepromin - extract of lepromatous nodules
5. Chemotherapy with DAPSONE

Drug of choice for Hansen's bacillus

\_\_\_\_\_.

II. Actinomyces israelii

- A. not acid fast
- B. obligate anaerobe; normal oral flora
- C. lumpy jaw; cervicofacial abscess with "sulfur granule" exudate

Etiologic agent associated with lumpy

jaw is \_\_\_\_\_.

III. Nocardia asteroides

- A. Weakly acid fast
- B. aerobe; soil organism
- C. pulmonary disease in immunodepressed patients; skin and subcutaneous infections via trauma

# GRAM NEGATIVE RODS

## I. Characteristics of interest

- A. Some produce exotoxins
- B. Enterobacteriaceae are oxidase negative
- C. All contain endotoxin
  1. component of cell wall; lipopolysaccharide (lipid A = toxic part)
  2. pyrogenic; induces release of endogenous pyrogen (interleukin 1) which acts on hypothalamus
  3. B cell mitogen; weakly antigenic
  4. activation of alternate pathway of complement
  5. may trigger disseminated intravascular coagulation
- D. Eosin Methylene Blue (EMB) agar is useful in isolating enteric organisms

The outer membrane of Gram negative bacteria contains a potent toxin, LPS, which stands for \_\_\_\_\_.  
The toxic moiety is \_\_\_\_\_.

EMB is a selective/differential/both medium used to purify \_\_\_\_\_ from mixed flora specimens (e.g. feces).

### ESCHERICHIA COLI

## I. Diseases

- A. Most common cause of urinary tract infections (cystitis, pyelonephritis of pregnancy);  $10^3$ /ml in urine suggests etiology of cystitis
- B. Neonatal meningitis: especially during 1st 2 months (with Gp. B strep); ascending infection occurs in utero or organisms are acquired during birth process
- C. Epidemic childhood diarrhea common in developing countries
- D. Traveler's diarrhea

Diseases produced by E. coli include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

## II. Immunologic Considerations

- A. O Antigens - (somatic)
- B. H Antigens - (flagellar)
- C. K Antigens - (capsule)

## III. Products Associated with Disease

- A. Adherence pili
- B. Endotoxin
- C. 2 enterotoxins, 1 is heat stable ( $\uparrow$  guanylate cyclase), the other 1 heat labile, ( $\uparrow$  adenyl cyclase)

Heat labile toxin structure is A-B5:  
A is an enzyme that ADP ribosylates an adenylate cyclase regulatory protein, increasing cAMP in the enterocyte and causing secretory diarrhea; B binds to GM-1 ganglioside in the enterocyte membrane.

## IV. Therapy

- A. Systemic diseases = aminoglycosides
- B. Cystitis = sulfonamides, nalidixic acid
- C. Diarrhea = trimethoprim + sulfamethoxazole

## KLEBSIELLA

### I. Diseases Caused by K. pneumoniae

- A. Normal flora in 5% of population
- B. Important in elderly compromised by major surgical or medical problems and in alcoholics
- C. Pneumonia - bronchitis, bronchiectasis. Necrosis accompanied by cavitation and fibrosis
- D. Virulence factor = anti-phagocytic capsular polysaccharide
- E. Drug of choice = aminoglycosides

## SALMONELLA

### I. General Characteristics

- A. Non-lactose fermenters, Acid and gas from glucose      Septicemia occurs commonly in infection
- B. All motile, several species H<sub>2</sub>S+      with

### II. Immunology

- A. O=somatic antigen and H=flagellar antigen      A. S. typhi
- B. Vi (virulence) antigen--found on S. typhi      B. S. enteritidis
- C. LPS=endotoxin=major virulence factor      C. S. cholerae-suis
- D. Iron binding siderophores (enterochelins) = important for growth      D. All of the above
- E. A and C only

### III. Types of Diseases (Salmonellosis)

(answer at bottom of page)

- A. Enteric fevers
- B. Septicemia --suppurative lesions; prototype = typhoid fever
- C. Gastroenteritis from contaminated food, poultry, poultry products like eggs, etc: an infection, not an intoxication; incubation period = 12-24 hrs
- D. Treatment=chloramphenicol, ampicillin

### IV. Three species = typhi, cholerae-suis and enteritidis

(answer = E)

- A. Typhi is restricted to humans, the others are zoonotic
- B. Just one organism in each of the first two
- C. All of the "old" species are now serotypes of enteritidis

## SHIGELLA

### I. General Characteristics

- A. Non-lactose fermenter
- B. Differentiated from Salmonella by:
  - 1. acid only from carbohydrates
  - 2. no hydrogen sulfide
  - 3. non-motile (no H antigens)
- C. Organisms invade epithelial cells
- D. Disease = high fever, bloody diarrhea; local infection
- E. Treat with trimethoprim/sulfa

### II. Antigenic structure

- A. Grouping is based on major cell wall carbohydrate antigens (O)

### III. Toxic Metabolites

- A. All have endotoxin
- B. Sh. dysenteriae produces an heat labile A-B5 enterotoxin
  - 1. effects the colon, not the ileum
  - 2. inhibits protein synthesis by reaction with 60S ribosome

## VIBRIO CHOLERAE

### I. General Characteristics

- A. Gram negative, comma shaped
- B. Motile
- C. Destroyed by heat and disinfectants

### II. Pathogenicity due to

- A. Enterotoxin (cholerae) stimulates adenyl cyclase and increases intracellular cAMP. Increases the secretion of Cl, HCO<sub>3</sub>, and H<sub>2</sub>O.
  - 1. A subunit ADP-ribosylates a GTPase (ala diphtheria toxin) thereby blocking its control of adenylate cyclase.
  - 2. B subunit binds to GM-1 ganglioside of epithelial cells.
- B. Adherence to the gut epithelium in the jejunum and ileum; local infection.
- C. Motility is related to adherence; motile strains adhere

### III. Related organisms

- A. V. parahemolyticus causes diarrheal disease; source is shellfish
- B. V. vulnificus causes diarrheal disease as well as septicemia and wound infections; source is seawater

## V. cholerae, cont.

### IV. Disease

- A. Found only in man; fecal-oral route of transmission
- B. Nausea, marked dehydration
- C. Rice-water stools and mucus with 20 liters of liquid lost per day
- D. Local infection confined to the small intestine - no bacteremia
- E. Treatment is supportive with fluids and electrolytes

### V. Immunity

- A. Due to antibody to microbial cell wall plus antitoxin against the enterotoxin

Cholera toxin has an A-B5 structure. A is an enzyme that ADP ribosylates an adenylate cyclase regulatory protein, increases cAMP in the cell, and causes watery diarrhea; B binds to a cell membrane GM-1 ganglioside.

## CAMPYLOBACTER JEJUNI

- A. This organism, related to V. cholerae morphologically and physiologically, is probably the most common bacterial cause of pediatric diarrhea in the US
- B. Symptoms = fever, bloody diarrhea and abdominal pain.
- C. Mucosal damage (bloody diarrhea) in small and large intestine.
- D. Produces a cytotoxin.

## HELICOBACTER PYLORI

- A. Cause of peptic ulcers
- B. Presence associated with stomach cancer
- C. Strongly urease positive

**PSEUDOMONAS AERUGINOSA**

I. *P. aeruginosa* produces blue-green pus due to production of water soluble pigments (pyocyanin). It is a non-fermenter. It produces oxidase.

II. Clinical significance (as an opportunist)

- A. Hospital acquired infections
  - 1. Wounds, burns, etc.
  - 2. Urinary tract via catheter
  - 3. Respiratory via nebulizers
  - 4. High rate of multiple drug resistance
  - 5. Treatment = tobramycin + carbenicillin
- B. Causes pneumonia in cystic fibrosis patients
- C. Produces enterotoxin which causes watery diarrhea
- D. Produces exotoxin A similar to diphtheria (i.e., A and B fragments; interferes with protein synthesis by adenosine ribosylating elongation factor II)
- E. The pseudomonas capsule is composed of Ca++ alginate; it acts as an antiphagocytic virulence factor and is responsible for the micro-colonies seen in lungs of patients with cystic fibrosis.

**BACTEROIDES**

- I. Gram negative, non-sporeforming, anaerobic rods
- II. The predominant organism in the bowel
- III. Virulence factors
  - A. Capsule
  - B. Endotoxin is of minor importance
- IV. Diseases = aspiration pneumonia, pulmonary abscesses, septicemia
- V. Treatment = clindamycin

Complete the following table:

|                   | Salmonella | Shigella |
|-------------------|------------|----------|
| acid from lactose | _____      | _____    |
| acid from glucose | _____      | _____    |
| gas from glucose  | _____      | _____    |
| hydrogen sulfide  | _____      | _____    |
| motile            | _____      | _____    |

Cholera toxin causes diarrheal disease

by \_\_\_\_\_.

**Major Causes of Wound Infections**

|           |                                  |
|-----------|----------------------------------|
| Surgical  | <i>Staphylococcus aureus</i> (1) |
| Traumatic | Clostridia                       |
| Umbilical | <i>C. tetani</i>                 |
| Burns     | <i>Pseudomonas</i>               |
| Bites     | <i>Pasteurella multocida</i>     |

(1) *S. aureus* also seen in burns and umbilical infections

**FUSOBACTERIUM**

- I. Gram negative anaerobic rod
- II. Normal flora organism
  - A. found in the gut and mouth
  - B. Observed as cigar-shaped rods
- III. Virulence factors
  - A. Endotoxin
  - B. Synergistic growth with other bacteria
- IV. Diseases = abscesses, synergistic gangrene, periodontitis, Vincent's angina (trench mouth, acute necrotizing ulcerative gingivitis)
- V. Treatment = clindamycin

# GRAM NEGATIVE RESPIRATORY PATHOGENS

## HAEMOPHILUS INFLUENZAE

### I. Growth factors - requires both:

- A. X factor - hematin
- B. V factor - NAD

### II. Virulence factors

- A. Polysaccharide capsule
  - 1. serotypes a-f (b most common; causes 90% of human disease)
  - 2. antiphagocytic
- B. Endotoxin
- C. IgA protease

Most cases of H. influenzae meningitis in young children are due to capsular type \_\_\_\_\_; non-encapsulated strains are associated with \_\_\_\_\_.

### III. Types of infection

- A. Upper respiratory tract-life threatening epiglottitis in infants
- B. Lower respiratory tract - pneumonia
- C. Meningitis in young children (2-60 months)
- D. All of the above are caused by encapsulated strains; non-encapsulated variants produce localized infections such as otitis media.

Cousins of H. influenzae cause;

| <u>Disease</u> | <u>Haemophilus species</u> |
|----------------|----------------------------|
|----------------|----------------------------|

|          |       |
|----------|-------|
| Pink eye | _____ |
|----------|-------|

|              |       |
|--------------|-------|
| Soft chancre | _____ |
|--------------|-------|

### IV. Culture - growth in presence of X and V factors = Satellite phenomenon

### V. Therapy - Chloramphenicol and ampicillin

(answers on next page)

### VI. Prevention - vaccine of type b capsule alone or coupled to carrier proteins such as tetanus toxoid or outer membrane proteins of N. meningitidis

## BORDETELLA PERTUSSIS

### I. Growth

- A. Cultured by cough plate or with pernasal swab
- B. Require Bordet-Gengou medium
- C. Colonize ciliated epithelial cells of respiratory tract; non-invading

The drugs of choice for H. influenzae meningitis include \_\_\_\_\_ and \_\_\_\_\_.

### II. Epidemiology of whooping cough

- A. Highly contagious disease of humans
  - 1. 50% of cases are under 4 years old
  - 2. 67% of deaths are under 1 year
- B. Antibodies to B. pertussis do not cross the placental barrier so newborns are completely unprotected.

### III. Pathogenicity

- A. Three stages of whooping cough
  - 1. Catarrhal stage
  - 2. Spasmodic (Paroxysmal) stage
  - 3. Convalescent stage
- B. Toxic Products
  - 1. Carbohydrate capsule
  - 2. Pilus; adherence organelle
  - 3. Lipopolysaccharide endotoxin
  - 4. Pertussis exotoxin; responsible for lymphocytosis and histamine sensitivity
  - 5. Adenylate cyclase
- C. Localized infection

Answers to "Cousins" question

Pink eye = H. aegyptius

Soft chancre = H. ducreyi

### IV. Immunity

- A. Single antigenic type
- B. Killed cell vaccine available (opsonic immunity)
- C. New acellular vaccine composed of 2 hemagglutinins being developed
  - 1. fimbrial HA (adherence pilus)
  - 2. pertussis toxin HA
- D. Excellent convalescent immunity

Vaccine induced immunity in whooping cough is antitoxic/opsonic.

### LEGIONELLA PNEUMOPHILA

- I. Cause of nosocomial pneumonia acquired from the environment, e.g., water cooled, air conditioning units); not man to man
- II. Fastidious Gram negative rod
- III. Facultative intracellular parasite
- IV. Cell mediated immunity important

MYCOPLASMA PNEUMONIAE

I. Similar to Protoplasts, Spheroplasts and L-forms of Bacteria

- A. Protoplasts and spheroplasts are laboratory-induced forms of bacteria which contain little or no cell wall: induced by penicillin or lysozyme.
- B. Drug of choice = tetracyclines or erythromycin
- C. Pathogenesis = organisms attach to host cell membrane's sialic acid residues via a neuraminidase-like receptor. There is no tissue invasion, but the production of toxic metabolites such as H<sub>2</sub>O<sub>2</sub> cause damage locally.
- D. Highly pleomorphic organisms without a cell wall
- E. Require cholesterol for growth; genus Acholeplasma do not

Mycoplasma, protoplasts and spheroplasts all lack \_\_\_\_\_ and \_\_\_\_\_ are resistant to \_\_\_\_\_ antibiotics.

III. Disease = primary atypical pneumonia (PAP)

IV. Characteristics of PAP

- A. Non-productive cough
- B. Minimal physical findings; may be myalgia, no pleuritic chest pain
- C. Usually normal white blood cell count; few polymorphonuclear leukocytes in sputum
- D. X-ray findings show pulmonary involvement out of proportion to physical findings
- E. Etiologic agents; M. pneumoniae, Chlamydia psittaci, Coxiella burnetti, adenovirus, respiratory syncytical virus, influenza virus, parainfluenza virus
- F. Histopathology is of an interstitial pneumonia with a mononuclear cell infiltrate and very little exudate into the alveolar space
- G. Disease caused by Mycoplasma, psittacosis and Q fever can be treated with tetracycline. Other etiologies of PAP will not respond to antibiotic therapy

Etiologies of primary atypical pneumonia include:

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_

V. Laboratory Diagnosis of M. pneumoniae

A. Cultures

1. Special media required for isolation; colonies are beta hemolytic
2. Growth requires 1-2 weeks

B. Serology

1. Non-specific
  - a. Cold hemagglutinins
  - b. Streptococcus MG agglutinins
2. Specific
  - a. Dye reduction inhibition test
  - b. Immunofluorescence
  - c. Complement fixation

UREAPLASMA

- I. Very similar to mycoplasma, but hydrolyze urea
- II. Produce extremely tiny colonies (less than 20 microns) hence also called T strains (T=tiny) adults
- III. Etiology implicated in non-gonococcal urethritis

| MOST COMMON CAUSES OF PNEUMONIA |  |
|---------------------------------|--|
| <u>Age</u>                      | <u>Microorganism</u>                           |
| 0 - 1 month                     | E. coli<br>Group B streptococci                |
| 1 - 6 months                    | Chlamydia<br>Respiratory Syncytial virus (RSV) |
| 1/2 - 5 years                   | Parainfluenza virus                            |
| 5 - 15 years                    | Mycoplasma<br>Influenza virus                  |
| 16 - 30 years                   | Mycoplasma                                     |
| Over 30 years                   | Streptococcus pneumoniae                       |
| Debilitated                     | Klebsiella pneumoniae                          |

OPPORTUNISTIC PATHOGENS

| <u>Source</u>               | <u>Microorganism</u>  |
|-----------------------------|---|
| Normal Flora <sup>(1)</sup> | Candida<br>Staphylococcus<br>Actinomyces<br>Pneumocystis  |
| Environment                 | Klebsiella<br>Escherichia<br>Enterobacter<br>Serratia<br>Pseudomonas<br>Legionella<br>Aspergillus<br>Phycomyces |

1. Other normal flora may be pathogenic when introduced into normally sterile areas ex. PID with Bacteriodes, aspiration pneumonia with oral flora, peritonitis with gut flora.

# GENERALIZED GRAM NEGATIVE PATHOGENS

ALL 3 ARE: FACULTATIVE INTRACELLULAR  
PARASITES

- : ZOONOSES
- : TREATMENT = STREPTOMYCIN

## YERSINIA PESTIS

### I. Epidemiology of plague

- A. Disease of animals (rodents) transmitted to man by
  1. rat fleas (bubonic plague)
  2. direct contact with infected animals
- B. Man to man transmission by
  1. human fleas (bubonic)
  2. direct contact - droplet infection (pneumonic)
- C. Most cases occur in rural populations in contact with wild animals (sylvatic)

II. V and W antigens - associated with virulence, as is capsular polysaccharide (F I)

### III. Yersinia enterocolitica

- A. Human gastroenteritis with fever, diarrhea and cramps, usually in children
- B. Produces an enterotoxin similar to E. coli heat stable toxin; I quanyl cyclase

## FRANCISELLA TULARENSIS

### I. Epidemiology of tularemia

- A. Disease of rodents (rabbits and squirrels)
- B. Transmitted to man by contact with infected animal, by tick bites, and by ingestion of water

### II. Two types of disease

- A. Ulceroglandular
- B. Typhoidal (must be distinguished from typhoid fever)

(answers = C and E)

Y. pestis is a

- A. facultative intracellular parasite.
- B. zoonotic agent transmitted to may by rat fleas.
- C. both
- D. neither

(answer at bottom, left)

F. tularensis is

- A. transmitted to man by infected ticks.
- B. an obligate intracellular parasite.
- C. susceptible to streptomycin.
- D. all of the above.
- E. A and C only.

(answer at left)

## GARDNERELLA VAGINALIS

- I. normal vaginal flora
- II. causes vaginitis with fishy odoriferous discharge; may be mixed infection
- III. Diagnosis = clue cells; epithelium adherent coccobacilli
- IV. treat = metronidazole (same for trichomonas)

## BRUCELLA

### I. Introduction

#### A. Three species

1. Brucella suis - swine
2. Brucella melitensis - goats, sheep
3. Brucella abortus - cattle

### II. Tissue tropism - B. abortus

#### A. Infection in animals usually limited to placenta due to high concentration of erythritol

1. Abortion
2. Infection of supramammary lymph nodes and spillage of organisms into milk

#### B. In man infection is usually generalized

B. abortus is a cause of abortion in

cattle due to \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_.

### III. Clinical types of Brucella infections

#### A. Intermittent-high fever rising to 101-104 C; night sweats

#### B. Chronic-CNS abnormalities seen

#### C. Undulant-step wise increases in temperature over a period of days

#### D. Malignant - sustained high temperature, extreme hyperpyrexia before death

Treatment of brucellosis involves \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_.

### IV. Pathogenicity

#### A. Organisms are continually phagocytosed by the reticuloendothelial system, then released into the blood stream

#### B. Virulent organisms resist intracellular killing

### V. Treatment

#### A. Combination of streptomycin and tetracycline recommended

#### B. Chronic nature of the infection may necessitate prolonged period of therapy

# SPIROCHETES

## I. Introduction

### A. Organisms

1. Genus Borrelia
2. Genus Leptospira
3. Genus Treponema

### B. Morphology and Growth

| <u>Genus</u>      | <u>Morphology</u>                    | <u>Oxygen Requirements</u> |
|-------------------|--------------------------------------|----------------------------|
| <u>Borrelia</u>   | Long with loose spirals              | micro-aerophilic           |
| <u>Leptospira</u> | Fine, tight spirals with hooked ends | aerobes                    |
| <u>Treponema</u>  | Short with tight spirals             | anaerobes                  |



The organism shown above most likely

- A. can grow in the presence of oxygen.
- B. causes relapsing fever.
- C. causes sexually transmitted diseases.
- D. causes Lyme disease.
- E. causes acute necrotizing ulcerative gingivitis.

(answer below)

### LEPTOSPIRA

- A. Organism involved - L. interrogans
- B. Description of disease process
  1. Fever with jaundice
  2. Infection of kidney and liver; acute hemorrhagic hepatitis
- C. Epidemiology
  1. Parasites of wild and domesticated animals
  2. Infection by contact with urine from infected animals or water contaminated with urine

### BORRELIA

- A. Organisms involved
  1. B. burgdorferi - Lyme disease
  2. B. recurrentis - relapsing fever
- B. Reservoir and Transmission
  1. Organism is perpetuated by tick-animal cycle
  2. Maintained in tick by transovarial transmission
  3. Wound created by tick bite is contaminated with secretions and excretions of tick
  4. Endemic disease
  5. Reservoirs
    - a. Relapsing fever = rodents, humans in epidemics
    - b. Lyme disease = deer
  6. Vectors (ticks)
    - a. Relapsing fever = Ornithodoros spp.
    - b. Lyme disease = Ixodes dammani

(answer = A)

- C. Description of Relapsing Fever
1. abrupt onset with chills, fever (3-10 days), generalized pain, prostration and delirium
  2. free interval of 1-3 weeks followed by several relapses; relapses due to emergence of new antigenic types
- D. Borrelia also seen in Vincent's angina, fuso-spirochetal stomatitis; acute necrotizing ulcerative gingivitis

#### TREPONEMA PALLIDUM

#### Stages of syphilis

1. Primary stage
  - a. lesion usually appears 10-30 days after infection
  - b. Hunterian (hard chancre) - indolent, indurated ulcer, usually single, painless; loaded with spirochetes
2. Secondary stage
  - a. usually occurs 6-12 weeks after chancre
  - b. invasion of skin, eyes, blood stream, cerebrospinal fluid
  - c. ulcerating, necrotic lesions of skin (rash), alopecia, numerous spirochetes
3. Tertiary stage [months - years later]
  - a. gummata of skin, bones, nervous system, no organisms seen
  - b. cardiovascular and neurosyphilis
4. Congenital syphilis
  - a. primary and secondary stages occur in utero
  - b. child has latent stage upon birth

#### Serologic diagnosis of syphilis

1. VDRL and RPR
  - a. antibody measured (reagin) is not specific antibody for T. pallidum
2. FTA-abs (Fluorescent Treponemal Antibody-Absorption Test)
  - a. Serum contains antibody to organism
  - b. Fluorescent labelled antiglobulin reacts with Ab fixed to spirochete

The drug of choice for syphilis is penicillin. Erythromycin is used in cases of penicillin allergy.

#### ERYTHEMA CHRONICUM MIGRANS

Lyme disease is a condition of spirochetal etiology which is characterized by a migrating erythematous rash that is usually followed a few weeks later by migratory polyarthritides. The organism is spread by the bite of ticks. First described as an epidemic in Lyme, Conn. The etiologic agent, Borrelia burgdorferi, has a tissue tropism similar to treponemes (i.e., heart, nerves and bone). Some untreated patients develop cardiac and neurologic manifestations.

Spirochetes are readily demonstrated in primary/secondary/tertiary syphilis.

# BACTERIA, RICKETTSIAE, CHLAMYDIAE AND VIRUSES

## CHARACTERISTICS IN COMPARISON

| Characteristic                              | Bacteria | Rickettsiae<br>& Chlamydiae | Viruses             |
|---|----------|-----------------------------|---------------------|
| 1. Obligate intracellular parasite          | -        | +                           | +                   |
| 2. Growth on lifeless media                 | +        | -                           | -                   |
| 3. Contain both DNA and RNA                 | +        | +                           | -                   |
| 4. Multiple by fission                      | Binary   | Binary<br>&<br>Unequal*     | Subunit<br>Assembly |
| 5. Visible with light microscope            | +        | +                           | -                   |
| 6. Contains muramic acid in cell wall       | +        | +                           | -                   |
| 7. Independent metabolic activity           | +        | +                           | -                   |
| 8. Possess ribosomes                        | +        | +                           | -                   |
| 9. Susceptible to antibacterial antibiotics | +        | +                           | -                   |

\* Reticulate bodies multiply and then disintegrate into elementary bodies.

RICKETTSIAE AND CHLAMYDIAE

Properties of the two groups:

1. Considered to be bacteria rather than viruses because they:
  - a. Contain both DNA and RNA.
  - b. Multiply by binary fission, chlamydia also multiply by unequal fission involving elementary and reticulate bodies.
  - c. Contain some metabolically active enzymes.
  - d. Contain ribosomes.
  - e. Resemble Gram-negative bacteria in that they possess a cell wall with inner and outer membranes.
  - f. Are inhibited by antibiotics, e.g., tetracycline.
  - g. Are obligate intracellular microorganisms, intermediate in size between large viruses and small bacteria.
  - h. Each group has toxic properties associated with the cell. This endotoxin differs from lipopolysaccharide in that it can be detoxified, and is neutralized by type-specific antisera.

2. The two groups differ, in general as follows:

- a. Rickettsiae (R) have an arthropod vector; Chlamydiae (C) do not.
- b. R are transmitted by the bite of the vector; C by droplet or contact.
- c. R diseases involve endothelial lining of blood vessels; C are localized infectious processes (e.g., lungs, eyes)
- d. Tetracycline is the drug of choice for both. Sulfa is contraindicated for R and for psittacosis.
- e. Serodiagnosis of R is by Weil Felix agglutination and C fixation. C diseases are diagnosed by C fixation and neutralization.
- f. R have peptidoglycan in cell wall; C do not.

Bacterial characteristics of Rickettsia include:

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_
6. \_\_\_\_\_
7. \_\_\_\_\_
8. \_\_\_\_\_

Complete the following Table:

| <u>Characteristic</u>         | <u>Rickettsia</u> |
|-------------------------------|-------------------|
| Disease Transmitted by Vector | _____             |
| Tissue Tropism                | _____             |
| Drug of Choice                | _____             |
| Serodiagnosis                 | _____             |

ETIOLOGY AND EPIDEMIOLOGY OF RICKETTSIAL DISEASE

| DISEASES <sup>1</sup>              | AGENTS                   | ARTHROPOD VECTORS <sup>2</sup>  | RESERVOIR           |
|------------------------------------|--------------------------|---|---------------------|
| Epidemic typhus                    | <u>R. prowazekii</u>     | human louse   | Human               |
| Brill's relapsing typhus           | <u>R. prowazekii</u>     | None  | Human               |
| Endemic or murine typhus           | <u>R. typhi</u>          | rat flea  | Rodents             |
| Tsutsugamushi fever (Scrub typhus) | <u>R. tsutsugamushi</u>  | chigger mite  | Rodents             |
| Rocky Mountain Spotted Fever       | <u>R. rickettsii</u>     | tick  | Dogs<br>rodents     |
| <u>Rickettsialpox</u>              | <u>R. akari</u>          | mite  | Mice                |
| <u>Q fever</u>                     | <u>Coxiella burnetii</u> | None; human inhalation of dried infectious material, ingestion of contaminated milk | Cattle, sheep, etc. |

<sup>1</sup> All except *C. burnetii* invade endothelial cells of vasculature; thrombosis = rash; Treatment = tetracyclines, chloramphenicol

<sup>2</sup> All vectors are infected for life; some (louse & flea) die of disease

CHLAMYDIAL AGENTS

| Agent*                       | Disease                               | Mode of Transmission  |
|------------------------------|---------------------------------------|---|
| Group A:                     |                                       |   |
| <u>Chlamydia trachomatis</u> | Trachoma                              | Contact with infected human or fresh fomites  |
|                              | Inclusion conjunctivitis              | Passage out birth canal; contact  |
|                              | Infant pneumonia                      | Passage out birth canal; contact  |
|                              | Urethritis                            | Sex mediated  |
|                              | Lymphogranuloma venereum; salpingitis | Sex mediated  |
| Group B:                     |                                       |   |
| <u>Chlamydia psittaci</u>    | Psittacosis                           | Contact with sick birds and their infectious excreta; inhalation of infectious material from birds. |

\* Treatment: Group A: Sulfonamides and/or tetracyclines  
 Group B: tetracyclines

## MEDICAL MYCOLOGY

| Agent and Disease  | Infectious* Particle        | APPEARANCE   |
|--|-----------------------------|--|
| <u>Cryptococcus neoformans</u> meningitis                                  | yeast                       | encapsulated yeast   |
| <u>Candida albicans</u> vulvovaginitis, thrush                             | yeast; endogenous infection | yeast and pseudohyphae in vivo; add chlamydospores in vitro          |
| <u>Sporothrix schenckii</u> lymphadenitis                                  | microconidia                | hyphae: spores in "daisy" clusters (RT)                              |
| <u>Blastomyces dermatididis</u> lung & skin                                | microconidia                | hyphae: microconidia (RT)<br>yeast; broadbased bud (37)**            |
| <u>Histoplasma capsulatum</u> lung and RES                                 | microconidia                | hyphae: tuberculate macroconidia (RT):<br>intracellular yeast (37)** |
| <u>Coccidioides immitis</u> lung and brain                                 | arthrospores                | hyphae: arthrospores (RT)<br>spherules (37)**                        |
| <u>Mucor &amp; Rhizopus</u> spp.<br>Phycomycosis<br>blood vessels and lung | spores                      | coenocytic hyphae,<br>sporangia                                      |
| <u>Aspergillus</u> spp.<br>lungs and systemic                              | spores                      | septate hyphae and spores  |

\* Only 2 dermatophytes spread from man to man (M. audouini & T. tonsurans), the rest are environmental or normal flora.      \*\*Dimorphic (37C=yeast, 24C=mold)

### ANTIFUNGAL DRUGS

| <u>Drug</u>                                | <u>Agents/Diseases</u>  | <u>Mechanism of action</u>  |
|--|---|---|
| Amphotericin B*                            | Systemic fungi, e.g.<br>Histo, Cocci,<br>Blasto, Crypto,<br>Aspergillosis | Binds to ergosterol in cell membrane;<br>causes pore formation and cytosol<br>leaks out |
| Ketokonazole<br>Clotrimazole<br>Miconazole | Most systemics <u>except</u><br>aspergillosis                             | Similar to amphotericin B   |
| Flucytosine                                | Yeasts, Candidiasis<br>Cryptococcosis                                     | Incorporated into RNA and blocks<br>protein sythesis                                    |
| Potassium iodide                           | Sporotrichosis  | Unknown   |
| Griseofulvin                               | Dermatophytoses   | Interferes with cell division   |
| Tolnaftate                                 | "   | Unknown   |

\* Related polyene, Nystatin, is limited to topical use vs Candida

# MEDICAL PARASITOLOGY

## EPIDEMIOLOGY AND PATHOGENESIS OF PARASITIC INFECTIONS

### TRANSMITTED VIA INGESTION OF OVA

| <u>Parasite</u>                | <u>Pathogenesis</u>  |
|--------------------------------|--|
| <u>Enterobius vermicularis</u> | Adults in rectum and colon; Most common parasite of children; anal pruritis.   |
| <u>Ascaris lumbricoides</u>    | Adults in small intestine; light infections asymptomatic; occasional intestinal obstructions or abnormal migrations of adult in heavy infection. |
| <u>Toxocara canis</u>          | Larvae invade various organs; mark eosinophilia; ↑IgE, hepatosplenomegaly, occasionally retinal granuloma due to larval migration.               |
| <u>Trichuris trichiura</u>     | Adults in colon and rectum; light infections asymptomatic; heavy infections may cause diarrhea, tenesmus and rectal prolapse.                    |
| <u>Taenia solium</u>           | Larvae (cysticercus) in all tissues; CNS damage may be serious.  |
| <u>Echinococcus granulosus</u> | Growth of hydatid cyst damages liver or lung.  |

Complete the Following Table:

| <u>Agent</u>  | <u>Disease</u>                          |
|---------------|---|
| Taenia        |   |
|               | Anal pruritis                           |
| Echinococcus  |   |
|               | Visceral larval migrans                 |
| Toxoplasma    | Disease =<br>Reservoir =                |
|               | Muscle pain, ocular edema, eosinophilia |
| Giardia       |   |
|               | B12 deficiency and macrocytic anemia    |
| Naegleria     |   |
|               | Iron deficiency anemia                  |
| Strongyloides |   |

TRANSMISSION VIA INGESTION OF CYST

Entamoeba histolytica Primary ulcers in large intestine; secondary abscess in liver or other organs.

Giardia lamblia Asymptomatic to protracted diarrhea.

Toxoplasma gondii Usually asymptomatic in adults; serious CNS damage to fetus if mother infected during pregnancy. Obligate intracellular parasite. Cat reservoir.

TRANSMISSION VIA INGESTION OF LARVAE

Trichinella spiralis Adults cause GI disturbances; larvae cause muscle pains, ocular edema, eosinophilia.

Taenia saginata Adult in small intestine may cause vague GI disturbances

Taenia solium Adult in small intestine may cause vague GI disturbances

Diphyllobothrium latum Vague GI disturbances; rarely vitamin B12 deficiency with macrocytic (pernicious) anemia.

TRANSMISSION VIA LARVAL PENETRATION OF SKIN

Necator americanus or Ancylostoma duodenale Adults in small intestines; light infections are asymptomatic; heavy infection plus malnutrition causes hypoalbuminemia and iron deficiency anemia.

Strongyloides stercoralis Adults in small intestinal mucosa; symptoms vary, i.e. asymptomatic, mucoid diarrhea with malabsorption potentially fatal in immunological compromised host (e.g. AIDS) due to autoinfection.

TRANSMISSION VIA CERCARIAL PENETRATION OF SKIN

Schistosoma mansoni or S. japonicum Granulomatous reactions to eggs deposited in intestinal venules or those trapped in liver or other organs.

TRANSMISSION VIA BITE OF ARTHROPOD VECTOR

Plasmodium vivax, etc. [vector = Anopheles mosquito] Fever, musculoskeletal pains, severe headache, diarrhea; capillary occlusions in falciparum are especially dangerous. larvae develop into adult worms in subcutaneous tissue; cause formation of tumor-like nodules. Microfilarial forms migrate through eye and may cause blindness.

Wuchereria bancrofti [vector = Anopheles mosquito] Larva develop into adults in lymphatics. Host's immediate and delayed allergic responses to these causes lymphadenitis which may develop to elephantiasis.

Leishmania [vector = sandflies] Hyperplasia of cells of the RES. May be localized cutaneous ulcer or severe systemic disease.

Trypanosoma T. cruzi = Chagas' disease [vector = reduviid bugs] T. gambiense = African sleeping sickness [vector = tsetse fly]

TRANSMISSION VIA DIRECT CONTACT AND/OR INVASION

Trichomonas vaginalis Local, non-fatal disease; usually symptomatic in females as vaginitis

Naegleria fowleri Travel up olfactory to brain; cause amebic meningoencephalitis.

PARASITE CHEMOTHERAPY

| <u>AGENT</u>  | <u>DRUG</u>  |
|---|--|
| <u>Nematodes (Roundworms)</u>   |  |
| Enterobius vermicularis<br>(pinworm)<br>Ascaris lumbricoides<br>Trichuris trichiura<br>(whipworm)<br>Necator americanus and<br>Ancylostoma duodenale<br>(hookworms) | MEBENDAZOLE  |
| Strongyloides stercoralis   | THIABENDAZOLE  |
| <u>Trematodes (Blood flukes)</u>  |  |
| Schistosoma mansoni<br>Schistosoma japonicum<br>Schistosoma hematobium  | PRAZIQUANTEL   |
| <u>Cestodes (Tapeworms)</u>   |  |
| Taenia saginata<br>Taenia solium<br>Diphyllobothrium latum<br>Hymenolepis nana  | NICLOSAMIDE  |
| <u>Protozoa</u>   |  |
| Entamoeba histolytica<br>Trichomonas vaginalis<br>Giardia lamblia   | METRONIDAZOLE*   |
| Plasmodium  | CHLOROQUINE for vivax<br>malariae<br>falciparum, and<br>ovale<br><br>and add<br>PRIMAQUINE for vivax, and<br>ovale |
| Toxoplasma gondii   | PYRIMETHAMINE** & SULFADIAZINE   |
| Pneumocystis carinii  | TRIMETHOPRIM & SULFAMETHOXAZOLE***   |

\* also useful vs. anaerobes, Gardnerella, quinacrine also used vs. Giardia  
 \*\* Teratogenic - do not use in first trimester  
 \*\*\* Pentamidine is used in patients who find T/S toxic

#### MECHANISMS OF ACTION OF ANTIPARASITIC DRUGS

---

|               |   |
|---------------|---|
| Sulfonamides  | Blocks conversion of PABA to dihydrofolic acid                    |
| Trimethoprim  | Inhibits dihydrofolate reductase                                  |
| Mebendazole   | Blocks glucose uptake   |
| Thiabendazole | Inhibits fumarate reductase                                       |
| Praziquantel  | Induces loss of Ca <sup>++</sup> with muscular spasms in parasite |
| Niclosamide   | Uncouples phosphorylation   |
| Metronidazole | Alkylation of DNA   |
| Quinine drugs | Intercalates into dsDNA of blocks DNA synthesis                   |

# DNA VIRUSES

## HERPES VIRUSES

### Properties of the group

Enveloped dsDNA viruses with cubic symmetry. Multiply in the nucleus

### Herpes simplex serotypes 1 & 2

### Epidemiology

Man is the only host; spread by close contact.

### Clinical features

#### Primary disease

Vesicular lesions of the mouth, lips, etc seen in young children

#### Recurrent disease

The herpes viruses have a great propensity to develop **latent infections** (i.e., the disease disappears but the virus stays hence recrudescence of disease can occur later). Cold sores (**stomatitis**) are vesicular lesions which may be triggered by fever, trauma, menses, stress, etc.

#### Neonatal disease

A rare but highly fatal infection of the neonate characterized high fever, jaundice and encephalitis.

#### Other diseases

The most common are **genital sores** particularly with the **type 2** virus; **keratitis** and **encephalitis** are more serious but less common.

**Herpetic whitlow** is an infection of the end of the finger. It occurs commonly in dental professionals.

### Treatment

**Acyclovir** is a very effective drug; Ara C is also useful as are idoxuridine and trifluorothymidine

### Diagnosis

Culture or **immunofluorescence** stain or Tzanck stain to see multinucleate cells with intranuclear inclusions

### Herpes viruses

1. are DNA/RNA
2. are single/double stranded
3. are naked/enveloped
4. multiply in the nucleus/cytoplasm
5. have helical/cubic symmetry

### Drugs that are effective

against Herpes simplex include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

Most cases of genital herpes are caused by type 1/2.

The herpes infection at the ends of fingers and around nails is called \_\_\_\_\_. It is an \_\_\_\_\_ occupational disease of \_\_\_\_\_.

Varicella (chickenpox or Herpes zoster)

Serotype

There is only one serotype of the varicella-zoster virus

Epidemiology

1. Man is the natural host
2. The overall incidence of infection is very high.
3. Transmission probably follows inhalation of infective aerosols, or direct skin contact

Clinical features

1. The onset is sudden, with a rash progressing from macules to papules to vesicles. Pustules do not develop; there is no scarring
2. The lesions appear in successive crops over 3 to 4 days
3. The lesions are distributed chiefly on the trunk and face

Zoster (Herpes zoster or shingles)

Epidemiology

This disease occurs chiefly in adults, most of whom give a history of having had varicella. Infection is communicable from as early as 5 days before to one week after the rash first appears

Pathogenesis

The virus probably persists in cells of the root ganglia after an attack of varicella, and is activated later with a resultant inflammatory reaction along the nerve followed by destruction of the epithelial cells served by that nerve

Clinical features

1. Erythematous maculopapular lesions develop, and on the trunk these have a band-like distribution
2. A disseminated form of disease is sometimes seen in patients who have received immunosuppressive therapy or radiotherapy

Herpes zoster causes

- A. chicken pox
- B. cold sores
- C. shingles
- D. all of the above
- E. A and C only

(answer at bottom)

Positive heterophile hemagglutinating antibodies are seen in infectious mononucleosis caused by

- A. Cytomegalovirus
- B. Epstein-Barr virus
- C. Both
- D. Neither

[see next page for answer]

[answer = E]

## Infectious mononucleosis

Etiologic agent (Epstein-Barr)  
herpesvirus.

### Epidemiology

1. Man is the natural host
2. Infection is most common in young adults
3. Incidence of infection is high
4. Mode of transmission; inhalation of infective aerosols during close personal association
5. Viruses associated with Burkitt's lymphoma and nasopharyngeal carcinoma

### Serodiagnosis

The heterophile agglutination test detects a IgM hemagglutinin vs sheep RBC

## Cytomegalic inclusion disease

### Etiologic agent

Cytomegalovirus; multiple serotypes are known

### Epidemiology

1. Man is the only known natural host
2. The virus can be transmitted across the placenta and cause congenital infection. The mode of postnatal transmission is unclear, but the virus is excreted in saliva, semen, milk and urine

### Clinical features

1. Intrauterine infections may cause death of the fetus, or result in congenital disease which is frequently fatal. In those who survive, hepatosplenomegaly with jaundice, blood dyscrasias, cerebral calcification, mental retardation, microcephaly and chorioretinitis are common sequelae
2. Postnatal infections are usually symptomless in infants and children, but occasionally hepatitis, pneumonitis or acquired hemolytic anemia develop
3. In patients with malignancies, AIDS, or those receiving immunosuppressive therapy, hepatitis, pneumonitis, infectious mononucleosis-like disease (with negative heterophile), pneumonia, or even generalized disease may develop, possibly resulting from the activation of latent virus

Burkitt's lymphoma occurs in young black males in Central Africa. The disease is the result of the translocation of a piece of chromosome 8 which contains an oncogene (c-myc) to the D-J joining region or an S switch region in the immunoglobulin H chain locus of chromosome 14. Apparently this occurs while pre-B cell is undergoing rearrangement of genes preparatory to production of antibodies. Once the c-myc oncogene is translocated to this genetically active site it gets turned on and its product, a nuclear binding protein that is involved in cell activation, is made in abnormally high amounts driving the cell to repeated replications.

Epstein-Barr virus is associated with what two human malignancies (see Oncogenic Viruses section)?

1. \_\_\_\_\_
2. \_\_\_\_\_

Human Herpes virus 6 causes sixth disease [exanthem subitum]

Parvovirus B19 is the cause of fifth disease [erythema infectiosum]

(answer = B)

## ADENOVIRUSES

### Properties of the group

1. Naked viruses, which have an icosahedral nucleocapsid, contain double-stranded DNA and replicate in the nucleus
2. There are more than 40 human serotypes, some cause tumors in animals

### Diseases caused by adenoviruses

#### A. Pharyngo-conjunctival fever

1. Particularly common in military recruits; in the general population, only about 5% of all respiratory illness is caused by adenoviruses
2. The mode of transmission is via infective aerosols or fresh fomites
3. Bronchitis and pneumonia sometimes occur, the latter usually in infants

#### B. Epidemic keratoconjunctivitis

1. Associated with serotype 8
2. Outbreaks in certain industries are associated with minor ocular trauma resulting from dusty atmosphere

#### C. Exanthem

Adenovirus is possibly responsible for a rubelliform rash

#### D. Hemorrhagic Cystitis

Particularly in children

Adenoviruses are

1. DNA/RNA.
2. single/double stranded.
3. naked/enveloped.
4. multiply in the nucleus/cytoplasm.
5. helical/cubic symmetry.

Diseases caused by Parvoviruses include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

## PARVOVIRUSES

### Properties of the group

1. Naked, single stranded DNA

### Diseases caused by Parvovirus B19

1. Fifth disease (erythema infectiosum)
  - a. primarily a disease of children
  - b. in individuals with chronic hemolytic diseases such as sickle cell disease or thalassemia B19 infections can precipitate an acute, sometimes fatal, anemia.

## PAPOVAVIRUSES

### Properties of the group

Naked viruses, which have an icosahedral nucleocapsid, contain dsDNA, and replicate in the nucleus

### Papilloma virus

Several serotypes affect humans

### Epidemiology

1. Man is the only known host
2. The mode of transmission is presumably by direct contact

### Pathogenesis and pathology

Replication occurs in the epithelial cells of the skin, virus causes a benign neoplasm. Papilloma #16 has a high association with cervical carcinoma

### Clinical features

The common wart - serotypes 1 and 4  
cervical carcinoma - serotypes 16 and 18  
condyloma acuminatum - serotypes 6 and 11

### Polyoma virus

Causes many different malignancies in several animal species

### Vacuolating virus

A simian virus (SV40) causes tumors when inoculated into newborn animals. Also transforms cells in culture

### JC virus

Has been isolated from immunocompromised individuals and from the brains of patients with progressive multifocal leukoencephalopathy. Most humans have specific antibody vs. the JC virus

The papovavirus responsible for the common wart is \_\_\_\_\_.

The papovavirus associated with progressive multifocal leukoencephalopathy is \_\_\_\_\_.

Papilloma virus serotype 16 is associated with \_\_\_\_\_.

## POXVIRUSES

### Properties of the group

Complex ellipsoid viruses, which contain double-stranded DNA, replicate in the cytoplasm; virion contains many enzymes (e.g. DNA-dependent RNA polymerase)

### Smallpox

#### Epidemiology

1. Man is the only natural host; disease has been eradicated from the planet
2. Smallpox is transmitted by inhalation of infective aerosols through personal association, or by contaminated fomites such as bedding

#### Treatment

Methisazone, which is of value prophylactically, is also useful in treating dermal complications following vaccination. It blocks synthesis of certain viral proteins thus inhibiting viral replication

### Artificially-acquired immunity

Active (vaccination)

Immunization is carried out with live vaccinia virus

### Molluscum contagiosum

#### Epidemiology

Infection probably occurs through minor abrasions, and in swimming pools

#### Clinical features

Multiple discrete benign tumors appear on the skin anywhere except on the palms and soles; the lesions last for several months, and then disappear spontaneously

Poxviruses are

1. DNA/RNA.
2. single/double stranded.
3. naked/enveloped.
4. multiply in the cytoplasm/nucleus.
5. helical/cubic/complex symmetry.

A Poxvirus which causes benign skin tumors in humans is

\_\_\_\_\_.

# RNA VIRUSES

## ORTHOMYXOVIRUSES

### Properties of the group

1. Enveloped viruses, helical nucleocapsid, contain 8 distinct segments of single-stranded RNA and replicate in both nucleus and cytoplasm
2. Orthomyxoviruses cause influenza

### Serotypes

1. There are 3 serotypes: A, B and C.
2. Each contains 2 surface antigens (H and N):
  - a. A hemagglutinin (H) which enables the virion to attach to receptors on the cell surface
  - b. A neuraminidase (N) which facilitates the release of progeny virus from infected cells
3. The 2 surface antigens of serotypes A and B undergo frequent antigenic changes (caused by point mutations) resulting in antigenic "drift"
4. Antigen "shift" is a much more drastic change which is caused by reassortment of RNA segments of the viral (human or animal) genome
5. All known pandemics have been caused by serotype A/B/C influenza virus. (answer at bottom, right)

Reye's syndrome (encephalopathy and fatty liver) is associated with type B, and perhaps also with other viruses (e.g. chickenpox). Salicylates may also be involved in the pathogenesis of the disease.

### Serodiagnosis

Using the hemagglutination-inhibition technique, the patient's serum can be tested for antibody against a particular strain of virus.

### Antiviral therapy

Amantadine hydrochloride (Symmetrel) is used as a prophylactic drug before or immediately after exposure to influenza A. It acts by blocking penetration of the virus into cells and also blocks uncoating of the virus.

### Artificially-acquired immunity

Induced by egg-derived viruses inactivated by formalin or by subunit vaccines

Influenza is an ssRNA virus whose genome is in \_\_\_\_\_ segments. It agglutinates RBCs through the action of its \_\_\_\_\_; the enzyme \_\_\_\_\_ facilitates progeny release.

(Pandemics = A)

## PARAMYXOVIRUSES

### Properties of the group

Enveloped viruses, helical nucleocapsid, contain single-stranded RNA, and replicated in the cytoplasm. The measles virus is known to replicate in both nucleus and cytoplasm

### Parainfluenzavirus infections

The viruses cause a variety of upper and lower respiratory tract illnesses; cold-like ills, pharyngitis, bronchitis, bronchiolitis and pneumonia. In young children, the viruses are the commonest cause of acute laryngotracheobronchitis (croup)

### Respiratory Syncytial Virus (RSV) Infection

1. In the infant, severe necrotizing bronchiolitis can occur; bacterial complications are common
2. RSV is the most common cause of viral pneumonia in infants
3. Reinfection occurs commonly, but is usually mild and confined to the upper respiratory tract, frequently resulting in the common cold syndrome
4. Ribavirin is used in therapy in patients likely to have serious disease and sequelae (e.g., patients with a history of coronary heart disease)

### Mumps

1. Sudden onset of swelling of the parotid glands, usually bilateral
2. Submaxillary and sublingual glands may also be involved
3. Inflammation of the testis (orchitis) often occurs in males past puberty, but testicular atrophy or sterility is rare
4. Meningitis is a relatively common complication

Respiratory syncytial virus is the most common cause of \_\_\_\_\_.

Complications of mumps infection include

1. \_\_\_\_\_
2. \_\_\_\_\_

Paramyxovirus infections with agents such as RSV can be treated with \_\_\_\_\_.

This chemotherapeutic is very expensive, hence treatment is limited to patients in which the disease may be life-threatening.

Measles

1. Cytopathic effect = multinucleated giant cells with nonspecific cytoplasmic and nuclear inclusions
2. Prodromal signs are photophobia, fever, cough, coryza, conjunctivitis and appearance of Koplik's spots in the mouth
3. Viremia
4. After 3 days, a rash starts on the head and spreads to chest, trunk and limbs in the next day or two; the rash disappears slowly
5. May have a transient depression of cell mediated immune responses
6. Complications are fairly common, and sometimes severe: These include - otitis media and pneumonia
7. Encephalomyelitis: rare, occurs 1 to 2 weeks after the rash, and is associated with a high mortality rate
8. Subacute sclerosing panencephalitis may be a post-infection sequela
9. May be transient depression of cell mediated immunity during infections

Prodromal signs of measles include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_

Complications of measles include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

ARENNAVIRUSES

Properties of the group

Enveloped RNA viruses  
 Rodent reservoirs: no vector;  
 disease acquired via contact  
 with rodent urine, etc.

Lymphocytic choriomeningitis

A disease usually manifest as "aseptic" meningitis or a mild influenza-like illness, rarely as a severe encephalomyelitis. The natural host of the virus is the mouse

Lassa fever

Hemorrhagic fever with bradycardia, neurologic manifestations and shock

## ARTHROPOD-BORNE VIRAL DISEASES

### Classification

1. The arboviruses encompass a heterogeneous collection of some 400 viruses related only by the epidemiological fact that they are arthropod-borne
2. The so-called 'arboviruses' alternate between an invertebrate vector and a vertebrate reservoir
3. Arboviruses belong to several viral families: Togaviridae, Bunyaviridae, Reoviridae, Flaviviridae and others

### Epidemiology

1. The cycle of transmission of these viruses is from arthropod to vertebrate host and back to arthropod
2. The arthropods involved are commonly mosquitoes, but sometimes ticks, sandflies and gnats act as vectors
3. The natural hosts, which act as reservoirs, include birds, reptiles, mammals and, rarely, man

### BUNYAVIRUSES

Bunyamwera viruses are enveloped, spherical viruses with helical symmetry. They are similar ecologically to the togaviruses and are arthropod-borne (arboviruses). The single-stranded RNA is composed of three segments. The pathogenesis of disease is similar to the togaviruses (encephalitis). One group of this diverse family of viruses which has been associated with encephalitis in humans is California viruses, first found in California and more recently in other parts of the USA

Arthropod-borne viral diseases belong to the following viral families

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

There are four major pathogens in the Parainfluenza group:

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

## TOGAVIRUSES

### Arbovirus encephalitis

Most arboviruses are antigenic groups A or B. They are enveloped ssRNA viruses with (+mRNA) genome

1. These encephalitides in the USA include Venezuelan, Western and Eastern equine viruses
2. The usual reservoir is birds, and the vector is the mosquito
3. Clinical findings include fever, chills, headache, widespread muscular aches, drowsiness, nuchal rigidity, convulsions, paralysis, coma and death. (EEE has 50-70% mortality rate)

## FLAVIVIRUSES

### Yellow fever

1. The natural host is the monkey, and the vector is the Aedes mosquito; two forms of yellow fever, the urban and the jungle (sylvatic), are recognized
2. In the urban type of yellow fever, man is the main reservoir, and the transmission cycle is man-mosquito-man
3. In the jungle type, the monkey is the main reservoir, and the cycle is monkey-mosquito-monkey with man being infected occasionally
4. The outstanding feature in cases of yellow fever is the extent of damage to liver and kidney in severe cases

### Dengue

1. Man is the reservoir for this virus
2. The onset of illness is characterized by fever, chills, headache, conjunctivitis, lymphadenitis, severe pain in the back, muscles and joints ('break-bone fever')
3. Fever often falls, then rises again within a week ("saddleback curve")
4. Dengue hemorrhagic fever is a severe disease with a 10% mortality which occurs in individuals who have passive maternal antibody or have recovered from a previous attack by a different dengue serotype. Virus/antibody complexes form early in the disease; they activate complement with the result of DIC and shock.

Clinical signs of viral encephalitis include

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_
6. \_\_\_\_\_
7. \_\_\_\_\_
8. \_\_\_\_\_
9. \_\_\_\_\_

## ARENAVIRUSES

1. Rodents are the reservoir
2. No arthropod vector
3. Man gets infected by contact, inhalation of infectious animal excreta (LCM)
4. Man-to-man transmission also occurs (Lassa fever)

## RUBELLA VIRUS

### Properties

Enveloped virus, which contains single-stranded RNA, and replicates in the cytoplasm. There is only one serotype. The rubella virus is classified with Togaviruses; however, it is NOT an arthropod-borne disease, but rather is droplet spread

### Clinical feature of postnatal rubella

1. There is enlargement of lymph nodes with conjunctivitis, often followed by a fine macular rash; slight fever may occur
2. The main risk of this infection is that it may occur in a non-immune woman during the first trimester of pregnancy, with serious consequences for the fetus

### Clinical features of prenatal rubella

1. The risk of congenital malformations is greatest when the mother is infected during the first trimester of pregnancy
2. One or more of the following features may be present:
  - a. Blindness
  - b. Deafness
  - c. Congenital heart defects
  - d. Mental retardation (often with microcephaly)

Rubella virus is

1. DNA/RNA.
2. single/double stranded.
3. naked/enveloped.
4. multiplied in the nucleus/cytoplasm.

Replication of Rubella virus occurs in the following stages (see Viral Replication section)

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

## RHABDOVIRUSES

### Properties of the group

1. Bullet-shaped enveloped viruses, which contain single-stranded RNA, have a helical nucleocapsid, replicate in the cytoplasm, and are released by budding.
2. The group includes the virus responsible for rabies

### Rabies

Serotypes: There is only one serotype of rabies virus

### Epidemiology

1. The natural hosts include many kinds of mammals especially bats and skunks
2. The usual mode of transmission is by inoculation (bite). Infection may rarely result from inhalation of infective aerosols from bat secretions

### Pathogenesis

1. Virus spreads along nerves to the CNS.
2. The virus causes destruction of nerve cells and demyelination; the highest concentration is usually found in the hippocampus

### Artificially-acquired immunity

#### Vaccines

1. Virus is grown in human diploid cells and inactivated. Weekly, SubQ injections for 4 to 6 weeks are adequate. Human cell source virus has resulted in significant decrease in neurologic complications of vaccination
2. Passive antibody in the form of rabies immune globulin is also available

### Treatment

1. Wound must be thoroughly cleansed
2. Inject rabies immune globulin (human origin) into the wound and I M
3. Start the vaccine immediately at another site

### Diagnosis

1. Detain animal and observe for signs
2. Examine brain for Negri bodies

|  |
|--|
| THE NEGRI BODY IS THE INCLUSION SEEN IN THE CYTOPLASM OF CELLS IN THE HIPPOCAMPUS AND OTHER CNS AREAS. |
|--|

The replication cycle of the rabies virus includes the following stages  
(see Viral Replication section)

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_

## PICORNAVIRUSES

There are 2 groups of small (pico) RNA viruses, the enteroviruses and the rhinoviruses

### ENTEROVIRUSES

#### Properties of the group

1. Naked viruses, icosahedral nucleocapsid, contain single-stranded RNA, and replicate in the cytoplasm
2. There are 4 subgroups: polioviruses, coxsackieviruses, echoviruses, and hepatitis A

#### Pathology

1. Most infections are subclinical
2. Virus multiplies first in the pharynx, small intestines and local lymph nodes
3. Viremia follows, with spread of virus to the brain and spinal cord

#### Polioviruses

1. A formalin-inactivated viral vaccine (Salk) containing all 3 serotypes is available for injection
2. A live attenuated viral vaccine (Sabin) containing either a single serotype or all 3 are given orally. It induces sIgA in addition to IgG and IgM and imparts immunity of long duration. May be dangerous in immunosuppressed individuals (use Salk vaccine)
3. Clinical diseases
  - a. Most cases are subclinical
  - b. Aseptic meningitis
  - c. Poliomyelitis-an acute disease which causes flaccid paralysis. The virus replicates in many cells in the body. The target cells are the motor neurons in the CNS where destruction causes paralysis

There are 5 virus groups classified as small RNA viruses

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_
4. \_\_\_\_\_
5. \_\_\_\_\_

- A. Salk vaccine
  - B. Sabin vaccine
  - C. Both
  - D. Neither
1. Confers intestinal immunity
  2. Confers immunity to viremic phase of infection
  3. Not recommended for patients with Bruton's disease

(answers on next page)

Coxsackieviruses

These viruses are classified as either A or B depending on their pathogenicity for mice

Clinical features

Infection may be inapparent, or result in illness ranging in severity as far as lethal disease. Several different forms of illness can develop as follows:

- 1. Herpangina (vesicular pharyngitis) is the commonest manifestation of infection by A-serotypes
- 2. "Aseptic" meningitis can be caused by some A-serotypes or any B-serotypes
- 3. Epidemic myalgia is a common manifestation of infection by B-serotypes
- 4. Myocarditis or pericarditis can occur in infants from a B-serotype infection, and B-serotypes occasionally cause a myocardiopathy in children or adults

Match the disease with the Coxsackie virus.

serotype A

serotype B

- \_\_\_\_\_ 4. vesicular pharyngitis
- \_\_\_\_\_ 5. aseptic meningitis
- \_\_\_\_\_ 6. myocarditis
- \_\_\_\_\_ 7. pericarditis

(answers at left, bottom)

Echoviruses

Clinical features

- 1. Meningitis is commonly caused by echoviruses, but permanent paralysis is very rare
- 2. Skin rashes, pharyngitis and fever may occur
- 3. Echoviruses are a cause of a cold-like disease
- 4. Gastroenteritis and infantile diarrhea have been associated with echovirus infection

Hepatitis A is considered to be in this group as well. (cf section on hepatitis viruses for more information on this agent)

|                    |
|--------------------|
| Chemically pure    |
| picornaviral RNA   |
| <u>CAN/CAN NOT</u> |
| produce progeny    |
| when introduced    |
| into host cells.   |

answers

- 1 = B
- 2 = C
- 3 = B
- 4 = A
- 5 = A, B
- 6 = B
- 7 = B

## RHINOVIRUSES

### Properties of the group

Naked icosahedral viruses, contain single-stranded RNA

### Serotypes:

More than 100 serotypes are known

1. These viruses are the commonest cause of the common cold (rhinitis, rhinorrhea)
2. Rhinoviruses usually remain localized in the nasal mucosa

### Artificially-acquired immunity

In view of the number of serotypes, the development of a vaccine is not practicable

## CALICIVIRUSES

RNA virus which is single stranded. Etiologically associated with sporadic acute gastroenteritis in children

## REOVIRUSES

### Properties of the group

1. Naked icosahedral viruses, contain double-stranded RNA
2. Reoviruses can be isolated from feces and respiratory secretions of healthy persons, as well as from patients with a variety of illnesses, e.g., rhinitis
3. Rotaviruses cause gastroenteritis in human infants and lower animals
  - a. most common cause of viral gastroenteritis in the US; cause 70% of diarrheal disease seen by a US pediatrician.
  - b. may cause 5-10% of adult diarrheas
  - c. virus identified by ELISA

## CORONAVIRUSES

Enveloped helical viruses, contain RNA; Coronaviruses are a common cause of a cold-like disease in adults, but they do not seem to be an important cause of acute respiratory illness in children

Match the disease with the virus

- A. Norwalk agent
- B. Reovirus
- C. Rhinovirus
- D. Rotovirus

1. Rhinitis
2. Gastroenteritis in adults
3. Gastroenteritis in infants

(answers at bottom)

Viruses with dsRNA include

1. \_\_\_\_\_
2. \_\_\_\_\_

Answers

1. B, C
2. A
- D. D

## NORWALK AGENT

Cause of diarrheal disease in infants less than two years of age; disease occurs both in epidemics as well as sporadically

## HEPATITIS VIRUSES

### Viral hepatitis types A and B

Three particular forms of viral hepatitis can be distinguished clinically; these are hepatitis type A (infectious hepatitis or short- incubation hepatitis) = RNA virus; hepatitis type B (serum hepatitis or long-incubation hepatitis) = DNA virus and; non A-/non B hepatitis (disease resembles that of type B). There are multiple causes of non A-non B hepatitis including Hepatitis C and E; hepatitis A is now enterovirus 72

#### Incubation period

Type A: 10 to 50 days  
Type B: 50 to 180 days  
Non A, Non B: 50 to 180 days

#### Signs and symptoms

The illness is characterized by malaise, anorexia, nausea, vomiting, diarrhea, fever and also jaundice which may or may not appear between two days and three weeks after onset

Type A: In young children, infection frequently remains inapparent or develops into a mild illness without jaundice; in older age groups, infection often leads to icterus or more severe disease

Type B: The Dane particle is the infectious entity. Infection may remain inapparent. Many cases continue to chronic hepatitis with surface antigen carrier state. Primary hepatocellular carcinoma may develop

Type C: The leading cause of post-transfusion hepatitis. High incidence of chronic liver disease; cirrhosis and hepatocellular carcinoma common. Interferon  $\alpha$  approved for therapy.

Type D: A defective virus that replicates only in Hepatitis B-infected cells. Needs HBsAg for capsid. Delta antigen is unique. Uncommon in US; seen mainly in Italy and the Middle East.

Which of the following agents of viral hepatitis can be transmitted via transfusion?

1. Hepatitis A
2. Hepatitis B
3. Hepatitis C
4. Hepatitis D
5. Hepatitis E

[answer at bottom of page]

Hepatitis D virus is defective; it needs

\_\_\_\_\_ which  
is/are supplied by  
\_\_\_\_\_.

Serious, life threatening complications of hepatitis B and C viral diseases

include \_\_\_\_\_  
and \_\_\_\_\_.

Therapy for chronic hepatitis includes \_\_\_\_\_.

The incubation period for Hepatitis B is \_\_\_\_\_.

[answer = all are possible]

Type E: Enterically transmitted calicivirus (naked ssRNA) disease seen mainly in Far East. Mortality rate of 20% in pregnant women.

The presence of HBsAg in serum means \_\_\_\_\_

Epidemiology

All may be transmitted via blood during viremic stage but HAV and HEV are also spread via fecal/oral route.

\_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_.

Laboratory diagnosis

Serum is examined in a "hepatitis profile" that looks for the following viral markers; anti-HAV IgM, HBsAg, anti-HB IgM and anti-HCV.

The two viral hepatitises that are spread by the

Therapy

Immune serum globulin useful for HAV, HBV and HCV exposures. Interferon used for chronic hepatitis, especially HCV.

Fecal/Oral route are \_\_\_\_\_, and \_\_\_\_\_.

Prophylaxis

Vaccine available for HBV; either purified HBsAg from human plasma or recombinant vaccine using HBsAg gene.

\_\_\_\_\_ is the cause of high mortality in pregnant Asian women.

SIGNIFICANCE OF HEPATITIS B ANTIGENS AND ANTIBODIES IN SERUM

Component Present in Serum

| <u>HBsAg</u> | <u>Anti-HBs</u> | <u>Anti-HBc</u> | <u>Interpretation</u>   |
|--------------|-----------------|-----------------|---|
| +            | -               | -               | Prodromal period or early acute disease. Person is considered infectious.   |
| +            | -               | +               | Acute disease or chronic carrier. Person is considered infectious.  |
| -            | +               | +               | Convalescing from the disease or immune.  |
| -            | +               | -               | Immune via disease or vaccination.  |
| -            | -               | +               | Recovered from disease and lost reactivity. Antibody of IgG class; low level.<br>or<br>Recent disease; serum taken after HBsAg disappeared, before anti-HBs. Anti-HBc should be high. Such people are infectious. |

## SLOW VIRUSES

Diseases caused by viruses and virus-like agents belonging to different taxonomic groups, and linked together by the fact that they are all characterized by spongiform encephalopathy, and a long incubation period. Some of these agents may be PRIONS, small proteinaceous infectious particles

### Subacute sclerosing panencephalitis (SSPE)

Infectious measles virus has been isolated from brain tissue and lymph nodes of affected individuals with a history of measles

### Kuru

The disease seems to have resulted from cannibalism. Kuru has been found only in a single tribe in New Guinea

### Progressive Multifocal leukoencephalopathy

A rare disease of the CNS. Papovavirus JC has been isolated from affected tissues

### Creutzfeldt-Jakob disease

A rare disease of the CNS which has been transmitted to chimpanzees by inoculation of material from the brains of patients

### Multiple sclerosis

A CNS disease suspected to be of viral etiology. There is serological evidence suggesting that measles virus may be involved

Match the virus with the disease

- A. measles
- B. JC papovavirus

1. multiple sclerosis
2. subacute sclerosing panencephalitis
3. progressive multifocal leukoencephalopathy

(answers at bottom of page)

1=A  
2=A  
3=B

# ONCOGENIC VIRUSES

## Properties of oncogenic viruses

1. Among the RNA viruses, only Retroviridae are oncogenic
  - a. the Oncornavirus group causes tumors in diverse animal species; HTLV-I and II are the human pathogens
  - b. the Lentiviruses are in the same family: these are the slow viruses of spongiform encephalopathies; Human immunodeficiency virus is not oncogenic (does not contain an oncogene) but is associated with certain cancers
2. Oncogenic DNA viruses that cause tumors in humans are found in the Papova, Hepadna, and Herpesvirus families
3. It appears that some or all of the genes of some oncogenic viruses may be integrated into host DNA; the RNA viruses being integrated by an RNA-dependent DNA polymerase (reverse transcriptase). Integration is essential for oncogenesis.

## Transformation in vitro

The properties of transformed cells include:

1. Loss of contact inhibition
2. Altered cell morphology
3. The presence of new antigens in the membrane (tumor specific transplantation antigens) and intracellularly
4. The ability to proliferate rapidly with concomitant high energy demand
5. Altered chromosomal morphology and/or number
6. Ability to grow in soft agar and produce tumors when injected into an appropriate host

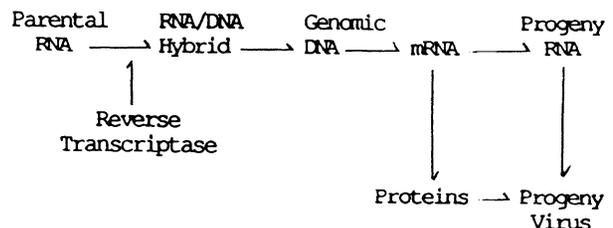
## HEPADNAVIRUS

Hepatitis B virus is associated with hepatocellular carcinoma in humans

## Oncogenesis by DNA Viruses

**Early proteins** produced during viral infection have many functions, including **activation** of cellular biosynthetic processes and **down-regulation** of others. In viral oncogenesis some of these proteins **bind to cellular ANTI-oncogenes and inactivate their growth suppressing functions**, thus permitting uncontrolled proliferation of the infected cell. In most instances the viral replicative cycle is not completed, so that the cells do not have overt evidence of the viral infection. Thus following a viral infection the cell has two paths it might follow - productive infection with release of infectious virus, or transformation to malignancy.

## Replication of Retroviruses



Retroviral reverse transcriptase has four catalytic functions:

1. RNA-dependent DNA polymerase
2. DNA-dependent DNA polymerase
3. RNase which degrades the RNA in the RNA-DNA hybrid
4. Integrase which inserts viral DNA into the host genome

POXVIRUSES

Molluscum contagiosum virus in this group cause benign skin lesions

HERPESVIRUSES

- 1. In lower animals these viruses cause Marek's disease (a neurolymphomatosis) in chickens, renal carcinoma in frogs and other malignancies
- 2. Epstein-Barr virus is associated with Burkitt's lymphoma in young African boys and nasopharyngeal carcinoma in certain ethnics groups in southern China. Consumption of cantonese-style salted fish during childhood appears to be a co-factor

Human DNA viruses are associated with following cancers

- 1. \_\_\_\_\_
- 2. \_\_\_\_\_
- 3. \_\_\_\_\_

PAPOVAVIRUSES

- 1. Papillomaviruses
  - a. These cause benign papillomas (warts) in man and other mammalian species. In man, condyloma acuminatum causes genital wart which are usually benign
  - b. Human papilloma virus # 16 causes cervical carcinoma

RETROVIRUSES

- 1. These enveloped viruses contain single-stranded RNA; the virion also contains reverse transcriptase which, together with certain other enzymes, produces double-stranded DNA homologous to the virion RNA. This goes to the nucleus and becomes integrated into the cellular DNA as a provirus which may be transcribed by a DNA-dependent RNA polymerase to make RNA copies, some of which are viral genome and some act as mRNA
- 2. The oncogene hypothesis proposes that the viral genome consists of at least 2 sets of genes, one of which controls the process of oncogenesis, and the other the production of infectious virus; either, neither or both sets may be evoked by endogenous or exogenous factors
- 3. Retroviruses can activate host genes (e.g., the c-myc gene)

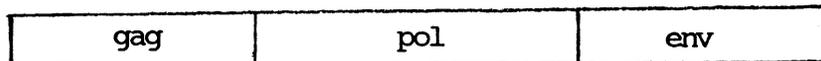
Polyomavirus

It induces the formation of sarcomas and carcinomas in diverse animal species; not in humans

- 3. SV 40 virus and Adenoviruses

In experimental conditions, they induce malignant neoplasms in mice, and causes transformation in vitro of cells of many species.

SAMPLE RETROVIRUS GENOME



The gag gene encodes capsid proteins, which are synthesized as a polyprotein precursor and then split by a protease. The pol gene encodes reverse transcriptase. The env gene encodes glycoprotein spikes in the envelope. Additional genes in the env region include tat which encodes a transactivator that enhances expression of all viral genes, rev which is required for expression of gag, pol, and env, and nef which down regulates HIV genome replication.

## VIRUSES AND HUMAN CANCER

### Burkitt's lymphoma

Specific antigen and nucleic acid of Epstein-Barr (EBNA) herpesvirus is present in cells cultured from cases of Burkitt's B cell lymphoma. This virus also appears to be responsible for infectious mononucleosis. Patients with Burkitt's lymphoma have a high incidence and high titers of antibody against EB virus

### Nasopharyngeal carcinoma

herpesvirus has been detected in cells obtained from cases of nasopharyngeal carcinoma, and patients show high titers of anti-EB herpesvirus antibody

### Carcinoma of the uterine cervix

Papilloma virus, serotype 16, seems to be etiologically associated with cervical cancer

### Hepatocellular Carcinoma

Hepatitis B virus has been associated with primary carcinoma of the liver

### Kaposi's Sarcoma

1. Human Immunodeficiency Virus 1 (HIV), a Retrovirus, is etiologically associated with Kaposi's sarcoma and AIDS. It is antigenically different from all other retroviruses.
2. Individuals with AIDS suffer from infections by opportunists such as Pneumocystis, Candida, Cryptococcus and Cryptosporidium. CMV infections are often activated.
3. There will be inverted CD4:CD8 lymphocyte ratios (due to the CD4 "target" of this virus) and normal to elevated levels of IgG, etc. The disease is particularly common in homosexuals, hemophiliacs, and intravenous drug users. Neonates are involved via transplacental passage of the virus. Heterosexual transmission is common in Africa.

The most common mechanism of viral oncogenesis is insertional activation of the oncogene. In neoplastic cells a new provirus is found in close proximity to the c-myc proto-oncogene. The provirus is usually but always contains one LTR (long terminal repeat) units which are very important in integration of the viral DNA into that of the cell and also serve as an enhancer to activate the c-myc gene and deregulate cell proliferation.

## GENETIC STRUCTURE OF THE RETROVIRUSES

### FOUR MAIN GENES

gag = codes for nucleocapsid proteins  
Pro = codes for protease  
Pol = codes for polymerase enzymes  
reverse transcriptase  
integrase  
Env = codes for envelope proteins

### HUMAN T-CELL LYMPHOTROPIC VIRUSES

A human Retrovirus has been isolated from numerous cases of adult T-cell leukemia and lymphoma. The HTLV agents have a marked affinity for mature T cells. Clusters of HTLV disease have been reported from the Caribbean basin and the southern United States.

## REVIEW STATEMENTS

**These should be used to strengthen and expand your understanding of Pathogenic Microbiology. If you are uncertain about the veracity of a statement, please “check it out.” This will help you strengthen your grasp of the material. You may wish to develop your own list. If you have a spare sheet of paper available, write down the correct statement for every question you miss in going through review exams. This way you can avoid marking on the review exam (so you can use it again) and still have captured that fact for future review.**

The **major virulence** factor of the **pneumococcus** is the **capsular carbohydrate**. It aids in the invasiveness of the agent by virtue of its antiphagocytic action. The vaccine is composed of capsular antigens from the 23 most common types.

*Streptococcus pneumoniae* produces alpha hemolysis on blood agar; the pneumococci are differentiated from the green (viridans) streptococci by their sensitivity to **optochin**.

The antibiotic of choice for pneumococcal pneumonia is **penicillin**.

**Group A** beta hemolytic streptococci are differentiated from other beta hemolytic streptococci by their **sensitivity to bacitracin**.

Two **antiphagocytic** surface components of Group A streptococci are the **M protein** and **hyaluronic acid**; the latter is not antigenic.

**Erythrogenic toxin** is produced only by lysogenic strains of streptococci.

The extracellular product of streptococci which converts plasminogen to plasmin is **streptokinase** (fibrinolysin). It is used to treat heart attack victims.

**Acute glomerulonephritis** is associated with group A streptococcal infections of either skin or upper respiratory tract.

**Staphylococci** are **resistant to penicillin** by virtue of a plasmid-conferred enzyme, **beta lactamase**.

**Staphylococcal carriers** are identified in epidemiologic studies (e.g., hospital nurseries) by bacteriophage sensitivity patterns.

Surface components of the staphylococcus which are **anti-phagocytic** include **capsule** and **protein A**.

*Streptococcus pneumoniae* is the most a common cause of bacterial **pneumonia in adults**.

Aerobic Gram negative diplococci belong to the genus *Neisseria*.

*N. meningitidis* is divided into four **serologic types** on the basis of antigenic difference of the capsular carbohydrate; the **majority of meningococcal epidemics are caused by type A**.

The acute adrenal insufficiency seen in fulminating cases of meningococcemia is called the **Waterhouse-Friderichsen syndrome**.

The surface components of the **meningococcus** which are involved in its pathogenicity include the **capsule** and **endotoxin**. Pili are responsible for the organism's interaction with host cell membranes.

**Pili** are found on the virulent strains of **gonococci**, types I and II.

**Gonorrhea** may be an asymptomatic infection, particularly in females. Gonorrhea can be diagnosed in males (only) by the observation of **Gram negative diplococci inside PMN's**.

In addition to “a flow of seed” the gonococcus also causes **arthritis**, and **ophthalmia neonatorum**.

The treatment of choice for neisserial infections is **penicillin**; if dealing with a penicillinase producing strain of gonococci, **spectinomycin** or **ceftriaxone** should be used.

**Primary atypical pneumonia** (as a disease entity) may be caused by various chlamydial and viral agents; however, it is most closely associated with *Mycoplasma pneumoniae*.

Penicillins and cephalosporins are not indicated in the **treatment of mycoplasmal infections** because these are inhibitors of cell wall synthesis and mycoplasma do not have a cell wall. Diseases caused by mycoplasma can be treated with **tetracyclines**.

The most common serologic tests for the identification of *Mycoplasma pneumoniae* (although they rely on heterophile antigens) are cold hemagglutinins and Strep MG agglutinins.

The two genera of **Gram positive rods** which form spores are *Clostridium* and *Bacillus*; the former will only grow anaerobically.

The two major virulence factors of the **anthrax bacillus** are the **polypeptide capsule** and **anthrax toxin**. The anthrax toxin is somewhat unique in biology in that its lethal effect on the host is due to the synergistic action of 3 proteins.

Although **gas gangrene** can be caused by several clostridia, the species most commonly associated with this disease entity is *perfringens*.

Three toxic enzymes which are of particular importance in **gas gangrene** are **lecithinase, collagenase and hyaluronidase**.

A common feature in the **treatment of clostridial infections** is the use of specific **antitoxin**.

Gas gangrene and tetanus are both contracted via soil contamination of wounds; their clinical pictures differ markedly in that **gangrene is an invasive process** whereas **tetanus is a very localized infection** the symptoms of which are due to **toxemia**.

**Botulism is an intoxication** caused by an organism which elaborates a potent heat labile **neurotoxin** in which acts on the autonomic nervous system and **interferes with transmission of nerve impulses at the myoneural junction**.

The etiologic agent of **Hansen's disease** has not been grown *in vitro*. Leprosy is thought to be transmitted to man via direct contact or respiratory droplet. Leprosy can be diagnosed by skin testing with an extract of lepromatous nodules referred to as **lepromin**.

**Diphtheria** is most effectively treated by the administration of specific **antitoxin**; antibiotics are insufficient alone because most of the symptomatology is due to the organism's excretion of toxin.

Three classical enteric diseases are **typhoid, dysentery, and cholera**, caused by *Salmonella, Shigella, and Vibrio*, respectively.

The chemical composition of **endotoxin** is **lipopolysacchride**; **lipid A** is the **toxic moiety**.

*Escherichia coli* is the most common cause of **urinary tract infections**.

**Capsular carbohydrate** is a major virulence factor of *Klebsiella pneumoniae*.

*Shigella dysenteriae* produces an **A-B exotoxin** that is an enterotoxin in man.; it inhibits protein synthesis.

The pathogenesis of *Vibrio cholerae* is dependent upon **cholera toxin**, an **A-B enterotoxin** which increases **adenyl cyclase activity**. **Rice-water stools**, fluid and electrolyte loss, and eventual **hypovolemic shock** are characteristics of cholera.

Of all the enteric bacilli *Salmonella typhi* is the most likely to be **isolated from blood**.

An **antiphagocytic polysaccharide capsule** similar to that of *S. pneumoniae* is a virulence factor of *Haemophilus influenzae*.

The etiologic agent of **whooping cough** is *Bordetella pertussis*. Heat-killed organisms are employed in the DPT vaccine; the **acellular vaccine** contains **pertussis toxoid**.

*Yersinia pestis* may be transmitted by **rat fleas** and human lice.

*Brucella abortus* demonstrates a **tissue tropism** in cattle since the organisms localize in the **placenta** which contains a high concentration of erythritol. The virulence of *Brucella* is attributed to their ability to resist intracellular killing.

There are three genera of spirochetes that cause human disease; *Leptospira*, *Treponema* and *Borrelia*. Two genera are **zoonotic** in nature (i.e., infect animals primarily with man as an incidental host); *Leptospira* and *Borrelia*. The primary organs affected in **leptospirosis** are the **liver** and **kidneys**. The agents causing the other spirochetel diseases are more diverse in their distribution throughout the body. **Leptospirosis** is contracted via **exposure to contaminated water**; **Lyme disease** occurs after tick (*Ixodes*) bites.

**Scarlet fever** is a local infection with toxemia (**erythrogenic toxin**).

*Chlamydia trachomatis* is the most common cause of sexually transmitted disease in the United States.

A rise in **antistreptolysin-O titer** or anti DNase B is an indication of recent infection with *Streptococcus pyogenes*.

Man is the only natural host for *Neisseria meningitidis*. Persons with meningococcal pharyngitis may fail to develop meningitis. Meningococcal petechial hemorrhages often contain *Neisseria meningitidis*.

In the routine **diagnosis of diphtheria**, positive identification of *Corynebacterium diphtheriae* is made by demonstration of its ability to **produce diphtheria toxin**.

**BCG**, which is used for active immunization against tuberculosis, consists of **attenuated bovine tubercle bacilli**.

The production of a water soluble, **blue-green pigment** in a culture indicates the presence of *Pseudomonas aeruginosa*.

The spirochetes associated with fusospirochetel infections, as well as the etiologic agents of relapsing fever, belong to the **genus Borrelia**; Lyme disease is caused by *B. burgdorferi*.

**Malarial relapses** are due primarily to emergence of persisting **exoerythrocytic merozoites**.

**Fatal malaria** most often results from infection with *Plasmodium falciparum*.

*Haemophilus influenzae* causes life-threatening **epiglottitis in neonates**.

One virulence factor of *Mycobacterium tuberculosis* is the **cord factor** (6, 6' trehalose dimycolate).

During oral antibiotic therapy (e.g., **clindamycin**), a patient may develop **pseudomembranous enterocolitis** caused by *Clostridium difficile*.

*Enterobius* is the most common helminth parasite infection of children in the United States. Enterobius female worms lay their eggs on the perianal skin and cause **pruritis**. Anal impression smears can be made to detect these eggs. **Pinworm** is treated with **mebendazole**.

The potential for **autoinfection** makes *Strongyloides* a dangerous infection, especially in the **immunologically compromised host**.

**Myalgia, ocular edema** and **eosinophilia** are symptoms associated with symptomatic **trichinosis**.

Adult **tapeworm infections** are acquired by ingesting animal tissue that harbors the larvae stage, e.g., *Taenia solium* in pork and *T. saginata* in beef. Cysticercosis may occur if man ingests *Taenia solium* eggs.

*Diphyllobothrium latum* competes with the host for Vitamin B<sub>12</sub>, this competition occasionally results in **pernicious anemia**.

*Entamoeba histolytica* may cause **abscesses** in the large bowel with secondary lesions in other organs, especially the **liver**.

**Giardiasis** is the most common protozoan diarrheal infection of man in the United States. Symptoms include **flatulence, foul smelling stools**, nausea and cramping; the disease is common in **day care centers**.

Numerous pathogens secrete an **IgA protease** which aids in infectivity; e.g., *H. influenzae*, *Neisseria gonorrhoeae*, *N. meningitidis*, *Streptococcus pneumoniae*, *mitis*, and *sanguis*, and *Bacteroides* spp.

*Candida albicans* is a part of the **normal flora**.

Fungi are **resistant** to most **antibacterial** chemotherapeutic **agents**.

Clinical malaria is best treated with **chloroquine**. **Primaquine** is necessary to eradicate persisting exoerythrocytic liver stages of *Plasmodium vivax*.

**Metronidazole** is an effective drug for treating *Trichomonas vaginalis*. Sexual partner(s) must also be treated to prevent reinfection.

**Bacteroides** are the predominant **flora of the gut**; they are anaerobic gram negative rods.

**Actinomycosis** is characterized by 1) an **endogenous origin** of the anaerobic infectious agent, and 2) **sulfur granules** in exudate of lesion which are really masses of Gram positive rods.

*Cryptococcus neoformans* is the **ONLY encapsulated yeast** that is pathogenic for man. It is identified by India ink preparations of spinal fluid.

Schistosomiasis is acquired by **larval penetration of the skin**; the larvae develop in snail hosts in fecally contaminated waters.

The etiologic agent of human **warts** (verrucae) is a **papovavirus**.

Commercially available **influenza vaccine** contains inactivated influenza viruses, **types A and B**.

**Coxsackie A and B** viruses cause **herpangina** and **myocarditis**, respectively. Coxsackie viruses of Group B are responsible for a considerable proportion of cases of aseptic meningitis.

The **hepatitis B surface antigen** (HBsAg), when found in banked blood, renders it undesirable for use in blood transfusions. The **incubation period** of serum hepatitis usually ranges from **50-180 days**.

The finding of **Negri bodies** (cytoplasmic inclusions in neurons) is specific for the pathologic diagnosis of **rabies**.

**Rhinoviruses** are acid labile and hence can not survive the acidity of the stomach; they do not colonize the GI tract as do the other Picornaviruses.

**Measles** is prevented by administration of an attenuated **monovalent vaccine**. It may be included with rubella and mumps vaccines to produce a polyvalent product.

Clinical signs and symptoms of **measles** include **photophobia**, cough, coryza, conjunctivitis and **Koplik spots**. Complications of measles include **encephalitis** and **pneumonia**. **Subacute sclerosing panencephalitis** is thought to be caused by measles.

**Mumps** is a disease of secretory cells which may involve the pancreas. Following the initial attack of mumps, long lasting protective immunity is produced. Mumps is spread from the infected patient by droplets (aerosol) or fresh fomites.

**Type A influenza** viruses are known to cause **pandemics** while types B and C influenza viruses are less likely to do so. Antibodies to the hemagglutinin spikes of influenza viruses are protective.

**Antigenic drift** is brought about by minor changes in type A influenza viruses while **antigenic shift** involves major changes in one or more of the glycoprotein spikes.

**Translocation of the c-myc gene** to one of the immunoglobulin gene loci is characteristic of **Burkitt's lymphoma**, but is not seen in infectious mononucleosis.

**Parainfluenza viruses** cause bronchitis, **bronchiolitis** and **croup** in children and a common cold-like disease in adults. **Respiratory syncytial virus** commonly produces severe disease (bronchitis, bronchiolitis and pneumonia) in infants.

The portal of entry of **enteroviruses** is the oral cavity and the viruses invade through the oropharyngeal and intestinal mucosa. They spread throughout the body via the lymphatics and blood. **Polio vaccines** must be polyvalent as there are **3 antigenically distinct viruses**. The **Sabin** polio vaccine contains **attenuated** virus which is taken **orally** while the **Salk** polio vaccine is formalin-inactivated and is administered by injection.

**Coxsackie B** viruses are responsible for many cases of **aseptic meningitis**.

**Rhabdoviruses** are single stranded, RNA-containing, bullet shaped viruses; **Rabies virus** is a rhabdovirus. Rabies virus is usually spread by the bite or lick of a rabid animal. The rabies vaccine of choice contains **inactive human diploid cell produced virus**.

**Type A hepatitis** is spread primarily by the **fecal-oral** route and **type B hepatitis** is spread primarily by **injection** but both viruses can be spread by either route. **Hepatitis C** is spread primarily by **injection**. **Hepatitis E** is spread by fecal-oral route

**Rotaviruses** are REO viruses which are the causal agents of **infantile diarrhea**, a particularly severe disease in the very young.

**Pharyngeal-conjunctival fever** is the most common syndrome associated with **adenoviruses**.

**Kuru** (a disease seen in New Guinea) and **Creutzfeldt-Jacob diseases** are transmissible **spongiform encephalopathies** of humans.

**Rubella virus** belongs to the **Togavirus** family. Lasting protective immunity is usually produced upon convalescence from rubella. Rubella virus is known to **cross the human placenta** and to infect the developing fetus. **Congenital rubella** is the result of fetal infection during the **first trimester** of pregnancy. Following birth, virus may be excreted and cause a rubella outbreak in a newborn nursery. An **attenuated viral vaccine** is effective in the prevention of rubella but should not be given to pregnant humans.

The **Epstein-Barr virus (EBV)** has been recovered from **Burkitt's lymphoma** tissue, from human patients with **nasopharyngeal carcinomas**, and from patients with **infectious mononucleosis**.

Reactivation of a latent infection in the form of **shingles (Herpes zoster)** occurs with the etiologic agent of varicella (chicken pox). **Zoster (shingles)** is a recurrent disease; the lesions appear unilaterally on the body, in a **dermatome** distribution.

**Herpes simplex virus** may cause **cold sores** and **aseptic meningitis**. Herpes simplex virus, type 2, is associated with genital herpes (lesions of genital tract) and neonatal herpes. **Acyclovir** has been used quite effectively in treating herpesvirus infections, including serious systemic infections.

**Aspirin therapy** in children with influenza or chickenpox is contraindicated due to the possible association of these conditions with **Reye syndrome**.

The predominant **cell in the spinal fluid in viral meningitis** is the **lymphocyte**. This is the same cell that would predominate in the **perivascular cuffing** also noted in these diseases.

**Rotavirus** is the most common cause of **pediatric infectious diarrhea** in the USA. *Campylobacter* spp. is the most common bacterial agent.

**Adenoviruses** are the most common cause of **viral pharyngitis**; among the bacteria, *Streptococcus pyogenes* is the most common, and is probably the most serious in light of the sequelae which can develop.

**Retroviral RNA** is transcribed into circular dsDNA and **inserted into the host genome** as an early event that precedes viral replication. Viral progeny and viral mRNA are made by transcription from this DNA.

**Parainfluenza** and **influenza viruses** are the most common cause of infections of the **larynx** and **bronchi**; viruses rarely affect the epiglottitis, however *Haemophilus influenzae* is a pathogen here.

## PATHOGENIC MICROBIOLOGY REVIEW EXAM

### SELECT THE SINGLE BEST COMPLETION FOR EACH QUESTION.

1. The virulence of *S. pneumoniae* is primarily associated with the presence of
  - A. cell wall teichoic acid.
  - B. pneumolysin.
  - C. polysaccharide capsule.
  - D. M protein.
  - E. peptidoglycan.
2. Viruses for which there are effective, live vaccines include
  - A. influenza A and coronavirus.
  - B. mumps, rubella, and parvovirus.
  - C. measles, mumps, and influenza A.
  - D. rubella and measles.
3. Which of the following streptococcal diseases is caused in part by erythrogenic toxin?
  - A. Impetigo
  - B. Puerperal sepsis
  - C. Rheumatic fever
  - D. Scarlet fever
  - E. Erysipelas
4. Which of the following would most likely be etiologically involved in meningitis in a 3 week old infant ?
  - A. *Neisseria meningitidis*
  - B. *Haemophilus influenzae*
  - C. *Streptococcus pneumoniae*
  - D. *Streptococcus agalactiae*
  - E. *Listeria monocytogenes*
5. Vaccine induced immunity to pneumococcal pneumonia is of what type?
  - A. Antitoxic
  - B. Bacteriocidal
  - C. Opsonic
  - D. Bacteriolytic
  - E. Neutralizing
6. Individuals vaccinated with the HB<sub>s</sub>Ag vaccine would be protected from infection by
  - A. hepatitis A virus only
  - B. hepatitis B virus only.
  - C. hepatitis C virus only.
  - D. delta hepatitis virus only.
  - E. Both hepatitis B and delta viruses.
7. What clinical condition may be produced by the germination of spores of *Clostridium botulinum* in the gastrointestinal tract of infants?
  - A. Pseudomembranous enterocolitis
  - B. Enteritis necroticans
  - C. Lockjaw
  - D. Floppy baby syndrome
  - E. Rice water stools
8. A key characteristic of the etiologic agent of bacillary dysentery is
  - A. strict localization of the pathogen in the small intestine.
  - B. the organism is found mainly in animals.
  - C. production of a potent cytotoxin responsible for invasiveness.
  - D. the organism is transmitted by droplet aerosol.
9. What is the most common source of salmonellosis in the United States?
  - A. Pet turtles
  - B. Rare roast beef
  - C. Potato salad
  - D. Poultry products
  - E. Partially cooked seafood

10. *Salmonella typhi* differs from other species of *Salmonella* in that it
- produces enteritis localized in the small intestine.
  - is found mainly in animals.
  - has a predilection for lymphoid tissues in the liver and spleen.
  - produces a heat-stable enterotoxin.
  - causes acute dysentery.
11. Which of the following are surface components of *Staphylococcus aureus* serves as an adherence molecule?
- Protein A
  - Carbohydrate capsule
  - Coagulase
  - Teichoic acid
  - Peptidoglycan
12. *Pseudomonas aeruginosa* strains isolated from cystic fibrosis patients are unique in that they
- are Gram positive.
  - are obligate anaerobes.
  - contain no endotoxin in the cell wall.
  - produce mucoid colonies due to excess extracellular polysaccharide.
  - produce an enterotoxin.
13. Which of the following vaccines could most safely be given to an immunosuppressed individual?
- Heptavax
  - Sabin
  - Yellow fever
  - Rubella
  - Mumps
14. The most common species of *Mycobacterium* isolated from AIDS patients is
- Mycobacterium kansasii*.
  - Mycobacterium avium-intracellulare* complex.
  - Mycobacterium leprae*.
  - Mycobacterium phlei*.
  - Mycobacterium scrofulaceum*.
15. A diagnostic test that is used for the confirmation of infection with HIV is
- radioimmune assay (RIA).
  - enzyme-linked immunosorbent assay (ELISA).
  - Ouchterlony.
  - Western blot assay.
  - latex agglutination assay.
16. Mycobacteria resist intracellular killing due to which cell wall constituent?
- Lipopolysaccharide
  - Lipoteichoic acid
  - Periplasm
  - Mycolic acids (wax D)
  - Peptidoglycan
17. Blood and leukocytes are seen frequently in the stool during
- cholera.
  - rotaviral diarrhea.
  - shigellosis.
  - salmonellosis.
  - traveler's diarrhea.
18. In cryptococcal meningitis, the level of this substance in spinal fluid can be diagnostic as well as prognostic.
- Anticryptococcal IgM antibody
  - Cryptococcal capsular carbohydrate
  - CEA
  - Anticryptococcal IgG antibody
19. Increasing levels of anti-Histoplasma complement-fixing antibody in the serum of a patient with histoplasmosis being treated with Amphotericin B is
- indicative of a poor prognosis.
  - indicative of a good prognosis.
  - of no prognostic value.
  - a signal to stop treatment.

20. The cellular oncogene that is translocated from chromosome 8 to chromosome 14 in the majority of the cases of Burkitt's lymphoma is the
- c-SRC gene.
  - c-MYC gene.
  - c-ERB gene.
  - c-RAS gene.
21. The antifungal activity of the polyene antibiotic Amphotericin B is related to its
- accumulation in keratinized tissue.
  - intercalation in mitochondrial DNA.
  - interaction with membrane sterols.
  - inhibiting cross linking in fungal cell walls.
  - inhibition of DNA dependent RNA polymerase.
22. Which of the following fungal agents is an endogenous cause of human disease?
- Cryptococcus neoformans*
  - Candida albicans*
  - Trichophyton rubrum*
  - Sporothrix schenckii*
  - Histoplasma capsulatum*
23. In AIDS patients autoinfection is a possible consequence of infection with
- Hookworm.
  - Ascaris*.
  - Strongyloides*.
  - Trichuris*.
24. The extra-intestinal site most frequently affected in amebiasis is
- lung.
  - liver.
  - genitalia.
  - brain.
  - skin.
25. Infectious hepatitis A
- is frequently asymptomatic.
  - can be caused by different serotypes of HAV.
  - can only be transmitted by fecal-oral route.
  - often leads to a chronic state.
26. Which of the following properties would allow the physician to distinguish between HBV and HAV infections?
- Jaundice
  - Fever
  - Alanine amino-transaminase (ALT) level
  - Incubation period
27. The most likely causative agent of amebic meningoencephalitis is
- Entamoeba histolytica*.
  - Acanthamoeba* sp.
  - Entamoeba gingivalis*.
  - Naegleria fowleri*.
  - Giardia lamblia*.
28. The three genes contained by the majority of retroviruses are
- gag, pol, tax
  - gag, onc, env
  - gag, pol, env
  - gag, env, env
29. The mode of transmission for *Schistosoma* is
- fecal contamination (ingestion of eggs or cyst stage).
  - ingestion of fish.
  - larva penetrates skin.
  - ingestion of pork.
  - ingestion of beef.

30. The chemotherapeutic agent most appropriate for *Trichomonas* infection is
- metronidazole.
  - ivermectin.
  - mebendazole.
  - praziquantel.
  - trimethoprim and sulfamethoxazole.
31. The major adherence factor of *Neisseria gonorrhoeae* is the
- lipopolysaccharide.
  - pilus.
  - capsule.
  - M protein.
  - teichoic acid.
32. Immunity to meningococcal infections is related to opsonizing and bactericidal antibodies to
- group specific polysaccharide (capsule).
  - type specific M protein.
  - pili variants.
  - endotoxin.
  - IgA protease.
33. Lyme disease is caused by *Borrelia burgdorferi*; the third stage of this disease is marked by the onset of
- arthritis.
  - carditis.
  - erythema chronicum migrans.
  - peripheral neuropathy.
  - atrioventricular heart block.
34. The most prevalent cause of sexually transmitted disease in the U.S. is
- Herpes virus.
  - Chlamydia trachomatis*.
  - Mycoplasma hominis*.
  - Neisseria gonorrhoeae*.
  - Treponema pallidum*.
35. What organism produces a frequently misdiagnosed food poisoning associated with fried rice?
- Bacillus cereus*
  - Clostridium bifermentans*
  - Bacillus stearothermophilus*
  - Bacillus subtilis*
  - Clostridium perfringens*
36. The most serious sequela following infection of the genital mucous membranes in women with *Neisseria gonorrhoeae* or *Chlamydia trachomatis* is
- conjunctivitis.
  - urethritis.
  - pelvic inflammatory disease.
  - salpingitis.
  - proctitis.
37. ST toxin of *E. coli* is so called because it
- is heat stable.
  - resembles shigella toxin.
  - causes severe temperature rises.
  - is also produced by *S. typhi*.
  - causes shaking tremors.
38. The most appropriate treatment for systemic candidiasis is
- flucytosine.
  - tolnaftate.
  - ketoconazole.
  - griseofulvin.
  - nystatin.
39. The most common cause of urinary tract infection is
- E. coli*.
  - S. aureus*.
  - K. pneumoniae*.
  - S. pyogenes*.
  - P. aeruginosa*.
40. Which of the following organisms has a cell wall with mycolic acids in it?
- P. aeruginosa*
  - M. tuberculosis*
  - L. monocytogenes*
  - S. marcescens*
  - A. fumigatus*
41. A violent windstorm occurred in the San Joaquin Valley in California; the incidence of coccidioidomycosis increased sharply. This was due to spread of highly resistant
- spherules.
  - arthroconidia.
  - budding yeast.
  - tuberculate chlamydo spores.

Directions (Items 42-59): Each of the numbered items or incomplete statements in this section is negatively phrased, as indicated by a capitalized word such as NOT, LEAST, or EXCEPT. Select the ONE lettered answer or completion that is BEST in each case.

42. A nineteen year old female was donating blood at her school blood drive. Routine screening revealed an elevated SGPT and the presence of Hepatitis B surface antigen. Which of the following is **FALSE**?
- A. Close contacts of this patient should receive Hepatitis B immune globulin.
  - B. This patient has acute Hepatitis B infection.
  - C. Prognosis cannot be determined at this time.
  - D. Immediate liver biopsy is indicated.
  - E. This patient is at risk of developing liver cancer.
43. Spore formation is important in the epidemiology of food poisoning caused by all of the following agents **EXCEPT**
- A. *Staphylococcus aureus*.
  - B. *Bacillus cereus*.
  - C. *Clostridium botulinum*.
  - D. *Clostridium perfringens*.
44. It has been proposed that oncogenic retroviruses can transform cells to an oncogenic state by all of the following mechanisms **EXCEPT**
- A. Insertional mutagenesis
  - B. Expression of oncogene present in virus
  - C. Expression of tax gene
  - D. Expression of vif gene
45. The enterotoxin of *Vibrio cholerae* does all of the following **EXCEPT**
- A. is composed of 1 A-subunit and 5 B-subunits.
  - B. ADP-ribosylates the catalytic subunit of adenylate cyclase.
  - C. localizes in the upper intestinal tract.
  - D. increases intracellular cyclic-AMP.
46. Which of the following is **LEAST** likely to cause vaginitis?
- A. *Trichomonas vaginalis*
  - B. *Candida albicans*
  - C. *Treponema pallidum*
  - D. *Gardnerella vaginalis*
47. All of the following are true about hepatitis C virus **EXCEPT**
- A. may cause chronic liver damage.
  - B. is the primary cause of transfusion associated hepatitis.
  - C. is an RNA virus.
  - D. contain an envelope.
  - E. it is defective
48. What characteristic listed below is **NOT** typical of *Clostridia*?
- A. Gram positive bacilli
  - B. Facultative anaerobes
  - C. Toxigenic
  - D. Opportunistic pathogens
  - E. Sporogenous
49. All of the following are associated with the cytomegalovirus **EXCEPT**
- A. congenital disease.
  - B. heterophile antibody.
  - C. latency.
  - D. inclusion bodies.
  - E. subclinical infections.
50. All of the following are characteristics of HIV **EXCEPT**
- A. contains its own oncogene.
  - B. infects and damages cells of the CNS.
  - C. contains several complex genes, including tat.
  - D. is a member of the *Retroviridae* family.

51. All of the following would be likely members of the normal bacterial flora of the oral cavity **EXCEPT**
- Staphylococcus aureus*.
  - Streptococcus pyogenes*.
  - Streptococcus salivarius*.
  - Neisseria pharyngis*.
  - Streptococcus mutans*.
52. Which of the following is **NOT** a pathway by which microbial toxins act?
- ADP ribosylation of host cell enzymes or control proteins.
  - Activation of adenyl cyclase.
  - Enhance neurotransmitter release from inhibitory neurons.
  - Activation of guanyl cyclase.
  - Activation of the complement cascade.
53. All of the following are characteristics of endotoxin **EXCEPT**
- toxicity due to lipid A.
  - heat stable.
  - part of outer membrane of cell wall of Gram-negative bacteria.
  - excellent immunogen.
  - pyrogenic.
54. Etiologic agents of food poisoning include all of the following **EXCEPT**
- Clostridium perfringens*
  - Bacillus cereus*
  - Salmonella typhimurium*
  - Salmonella typhi*
  - Escherichia coli*
55. Factors that appear to be important in the virulence of *Bordetella pertussis* include all of the following **EXCEPT**
- pertussis toxin
  - pili
  - capsule
  - endotoxin
  - IgA protease
56. Factors responsible for the pathogenicity of *Escherichia coli* include all of the following **EXCEPT**
- heat-labile enterotoxin.
  - capsular (K) antigens.
  - lipoteichoic acid adhesins.
  - heat stable enterotoxin.
  - endotoxin.
57. Epstein-Barr virus is associated with all of the following conditions **EXCEPT**
- Nasopharyngeal carcinoma
  - Infectious mononucleosis
  - Burkitt's lymphoma
  - Systemic lupus erythematosus
58. Which of the following is **LEAST** likely in a mother who has a primary infection of rubella virus during pregnancy? The fetus may
- fail to develop signs of infections.
  - be clinically normal but shed virus and have an IgM response.
  - have virus-host cell interactions manifested by thrombocytopenia, hepatitis, or pneumonia.
  - have virus-cell interactions manifested by heart malformation, cataracts, or mental retardation.
  - handle the virus well and develop IgG antibodies.
59. Poliovirus vaccine is correctly described by all of the following statements **EXCEPT**
- The Sabin vaccine is a live attenuated virus cell-culture preparation.
  - The Salk vaccine contains formalin-inactivated cell-culture prepared virus.
  - It is a polyvalent preparation.
  - Active virus is excreted in the feces of Sabin-vaccine-immunized individuals.
  - The Sabin vaccine does not cause disease in humans.

**DIRECTIONS (Items 60-77): Each set of matching questions in this section consists of a list of up to 26 lettered options, followed by several numbered items. For each numbered item, select the ONE lettered option this is most closely associated with it. EACH LETTERED OPTION MAY BE SELECTED ONCE, MORE THAN ONCE, OR NOT AT ALL.**

**MATCH THE INFECTIOUS AGENT WITH THE PATIENT DESCRIBED BELOW**

- |                                    |                                   |
|------------------------------------|-----------------------------------|
| A. <i>Streptococcus pneumoniae</i> | G. <i>Pseudomonas aeruginosa</i>  |
| B. <i>Klebsiella pneumoniae</i>    | H. <i>Viridans streptococci</i>   |
| C. <i>Mycoplasma pneumoniae</i>    | I. <i>Neisseria gonorrhoeae</i>   |
| D. <i>Streptococcus pyogenes</i>   | J. <i>Streptococcus mutans</i>    |
| E. <i>Legionella pneumophila</i>   | K. <i>Cryptococcus neoformans</i> |
| F. <i>Staphylococcus aureus</i>    | L. <i>Serratia marcescens</i>     |

60. This 16 year old white girl from Salt Lake City has a history of repeated streptococcal infections (pharyngitis) and cardiac abnormalities consistent with Rheumatic fever. Three weeks following extraction of an abscessed molar she develops fever and flu-like symptoms. Her condition worsens, a petechial rash appears, and she is hospitalized with a tentative diagnosis of subacute bacterial endocarditis caused by
61. Lower respiratory tract infection associated with 1) a non-productive cough and lobar pneumonia, 2) mucoid sputum containing a paucity of bacteria upon Gram stain, 3) high serum titers of cold agglutinins, and 4) growth of "fried egg" colonies from the sputum on special laboratory agar indicates presumptive infection by
62. A 4 year old child with a history of recurrent pulmonary infections has been brought to the Emergency room in obvious respiratory distress. Gram stain of the sputum reveals numerous polymorphonuclear neutrophils and gram positive cocci in grape-like clusters. The drug of choice to be employed until the antibiotic sensitivity report is received from the laboratory is methicillin. The agent most likely is
63. A 32 year old female astronaut developed otitis media during a voyage in outer space. Culture yielded a gram positive coccus in chains which grew on blood agar with alpha hemolysis. The organism was catalase negative; growth was inhibited by optochin. The isolated organism can be identified as
64. This 18 year old white male suffers from recurrent pulmonary problems associated with the cystic fibrosis disease which has plagued him all his life. He currently has pneumonia; the sputum stain reveals numerous Gram negative rods and PMNs. Cultures yield mixed flora with predominating mucoid colonies of a Gram negative bacillus. Antibiotic sensitivity tests are done on an isolate; the organism is found to be resistant to all antibiotics employed on the first plate. A green pigment is noted throughout the agar. The most likely organism is
65. A 62 year old Caucasian housewife was admitted to the hospital complaining of intermittent frontal headaches, malaise, and vertigo. This woman was a diabetic and had been on corticosteroid therapy for approximately 6 months. The nurses noted that the patient was disoriented at times. The patient's blood pressure was normal; temperature was 100°F. Skin tests with PPD, histoplasmin, and coccidioidin were negative. Chest X-ray showed nothing of significance. Cerebrospinal fluid was obtained and the cell count showed 220 cells per cubic millimeter; they were predominantly lymphocytes. Total protein was slightly elevated; sugar was slightly decreased. Encapsulated yeast cells were observed in the sediment after centrifugation of the spinal fluid.

**MATCH THE OPPORTUNISTIC PATHOGEN WITH THE DISEASE.**

| <b>Disease</b>                               | <b>Opportunist</b>                   |
|--|--------------------------------------|
| 66. Pneumonia in AIDS patient                | A. <i>Aspergillus fumigatus</i>      |
| 67. Post-neurosurgical meningitis            | B. <i>Pseudomonas aeruginosa</i>     |
| 68. Localized skin infection in burn patient | C. <i>Staphylococcus epidermidis</i> |
|  | D. <i>Streptococcus salivarius</i>   |
|  | E. <i>Pneumocystis carinii</i>       |
|  | F. <i>Candida albicans</i>           |
|  | G. <i>Streptococcus pneumoniae</i>   |
|  | H. <i>Neisseria meningitidis</i>     |

**MATCH THE VIRUS WITH THE NEOPLASM.**

| <b>Neoplasm</b>              | <b>Virus</b>                    |
|------------------------------|---------------------------------|
| 69. Kaposi's sarcoma         | A. Hepatitis A virus            |
| 70. Primary liver carcinoma  | B. Hepatitis B virus            |
| 71. Nasopharyngeal carcinoma | C. Hepatitis C virus            |
| 72. Burkitt's lymphoma       | D. Hepatitis D virus            |
| 73. Cervical carcinoma       | E. Herpes Simplex               |
|                              | F. Molluscum contagiosum        |
|                              | G. Papilloma virus              |
|                              | H. Parvovirus                   |
|                              | I. Epstein Barr virus           |
|                              | J. Human immunodeficiency virus |

**MATCH THE VIRUS WITH THE THERAPEUTIC AGENT.**

| <b>Virus</b>                     | <b>Therapeutic agent</b> |
|----------------------------------|--------------------------|
| 74. Human immunodeficiency virus | A. Amantadine            |
| 75. Influenza A                  | B. Acyclovir             |
| 76. Cytomegalovirus              | C. Cytosar               |
| 77. Respiratory syncytial virus  | D. Adenine arabinoside   |
| 78. Epstein Barr virus           | E. Pentamidine           |
| 79. Herpes zoster                | F. Azidothymidine        |
| 80. Hepatitis C                  | G. Ganciclovir           |
|                                  | H. Cyclosporin A         |
|                                  | I. Ribavirin             |
|                                  | J. Actinomycin D         |
|                                  | K. Alpha interferon      |
|                                  | L. Interleukin 2         |
|                                  | M. Methisazone           |
|                                  | N. Niclosamide           |

**KEY**

|       |       |       |         |
|-------|-------|-------|---------|
| 1. C  | 21. C | 41. B | 61. C   |
| 2. D  | 22. B | 42. D | 62. F   |
| 3. D  | 23. C | 43. A | 63. A   |
| 4. D  | 24. B | 44. D | 64. G   |
| 5. C  | 25. A | 45. B | 65. K   |
| 6. E  | 26. D | 46. C | 66. E   |
| 7. D  | 27. D | 47. E | 67. C   |
| 8. C  | 28. C | 48. B | 68. B   |
| 9. D  | 29. C | 49. B | 69. J   |
| 10. C | 30. A | 50. A | 70. B,C |
| 11. D | 31. B | 51. B | 71. I   |
| 12. D | 32. A | 52. E | 72. I   |
| 13. A | 33. A | 53. D | 73. G   |
| 14. B | 34. B | 54. D | 74. F   |
| 15. D | 35. A | 55. E | 75. A   |
| 16. D | 36. C | 56. C | 76. G   |
| 17. C | 37. A | 57. D | 77. I   |
| 18. B | 38. A | 58. E | 78. B   |
| 19. A | 39. A | 59. E | 79. B   |
| 20. B | 40. B | 60. H | 80. K   |