Changing patterns of infectious diseases and human behavior

- Bioterrorism
- More air conditioners in big buildings - Legionella pneumonia
- Superabsorbent tampons (in the '70's, now off the market) - Toxic shock
- More deer, more ticks close to humans - Lyme disease
- IV drug use, unprotected sexual behavior, encroaching in other primates' habitats - HIV
- Microbial resistance arising fromo large scale use of antibiotics
New: HIV, Hanta, Ebola, mad cow disease, Legionnaire’s

Recurring: Anthrax

Old but lethal in developing countries: malaria, TB, measles

Eradicated - smallpox.
  Candidates: polio, syphilis, diphtheria, others. How does this work?

Infections are most common cause of death in immunocompromised
  (cancer chemo, radiation, AIDS)
How to Control ID’s

• **Sanitation** - fecal-oral route - typhoid, dysentery

• **Vaccination** - smallpox, diphtheria

• **Antibiotics** - effective vs. most bacteria, fair vs. fungi, only a few vs. viruses

• **Drug resistance**
Generalization # 1.
Steps in Pathogenesis common to ALL infections

Encounter
Entry
Spread and Multiplication
Damage
Outcome

Generalization # 2.
The establishment of infections requires the breaching of defenses at EACH step
Most buggy places in the body

<table>
<thead>
<tr>
<th>Location</th>
<th>#bacteria/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingival crevice</td>
<td>(\sim 10^{11})</td>
</tr>
<tr>
<td>Feces</td>
<td>(\sim 10^{11})</td>
</tr>
<tr>
<td>Skin, vagina</td>
<td>(10^6 - 10^8)</td>
</tr>
</tbody>
</table>
Modes of Entry

- **inhalation** (influenza, Hanta virus)
- **ingestion** - usually fecal-oral route
  - (*Salmonella*, cholera, *E. coli*)
- **insect bites** (malaria, Lyme disease)
- **sexual contact** (STD’s, HIV)
- **wound infection** (natural or surgical)
- **organ transplants** - cornea, blood transfusion
A microbe’s view of the human body

- Respiratory system
- Digestive system
- Genitourinary system
Kinds of damage caused by microbial agents

**Cell death**
Lysis - toxins (staph, strep), rapid multiplication (chlamydia), cell-mediated immunity (viruses, TB)
Apoptosis

**Pharmacological**
Toxins that don't kill cells, e.g., neurotoxins (tetanus, botulism), inducers of cAMP (cholera)

**Mechanical**
Clog up vessels, e.g., venules (strep), lymph (elephantiasis), but (worms)
Staphylococcus aureus \( \alpha \)-hemolysin

- Transmembrane segment is a \( \alpha \) hairpin (two \( \alpha \)-strands) from each monomer, creating a 14-stranded \( \beta \)-barrel that spans the membrane
Pharmacological Alterations

Exotoxins

- Elevate cyclic AMP (ex. cholera, H. influenzae)
- Block protein synthesis (ex. diphthe pseudomonas,)
- Block nerve function (ex. tetanus, botulism)

(Other exotoxins cause cell death, etc.)
Endotoxin = Lipopolysaccharide (LPS)

• made by Gram negatives only

Effects:
• fever
• edema
• inflammation

• in high amounts --> shock. Seen in bacterial sepsis
Damage due to Host responses

Inflammation

Immunopathology
Host defenses

Innate, non-specific - skin, mucous membranes, complement, phagocytes

Adaptive, specific - antibodies, cell-mediated immunity
Complement

- dormant system
- something like the clotting mechanism (proteolytic cascade).
- activated rapidly (alternative pathway) by bacterial products, e.g., LPS, peptidoglycan
- or slowly (classical pathway) by antibodies
Substances involved in inflammation made by complement activation:

- **chemotaxins** (recruit phagocytes)
- **opsonins** (make bacteria easier to phagocytize)
- **membrane attack complex**
  (make holes in bacteria and foreign cells)
Polymorphonuclears (neutrophils)

• short lived cells (a few weeks)

• loaded with huge lysosomal granules with hydrolytic enzymes that can destroy some bacteria, and oxidative capable of making toxic compounds, especially hypochlorite (bleach).

• recruited to site of bacteria by several chemotaxins, some derived from complement, others are products of bacterial metabolism
Monocytes/macrophages

• long lived and arrive more slowly

• garbage collectors, clear up microbial debris and remaining bacteria

• become activated by cytokines, proteins made in response to microbial invasion

• make cytokines that attract and activate neutrophils, thus contribute to inflammation.
Macrophage with bacteria

- Macrophage nucleus
- Bacteria
Macrophage moving towards bacterial peptides

Macrophage engulfing fungal cells
How do bacteria withstand phagocytosis?

• playing hard to get - By avoiding being taken up - capsules, destroy chemotaxins

• murder - By killing phagocytes, e.g., by punching holes in lysosomes, thus inducing the cells to commit suicide

• indifference - Surviving inside phagocytes by resisting the lysosomal onslaught or by slipping out of the phago-lysosomal vacuoles and into the cytoplasm
A few examples of infectious diseases

1. Tetanus - a relatively simple disease
A 22-year-old farm worker came to the doctor's office complaining of pain in his jaw for the previous three days and inability to open his mouth fully. Ten days before, he had pushed inadvertently against a rusty nail sticking out from a plank in a horse corral. The nail had penetrated deep through the skin, and although the wound hurt and bled, he had not sought medical attention. He had received his tetanus shots as a child and had gotten his last booster more than 10 years ago.
A complicated bacterial infectious disease caused by *E. coli* O157:H7, the “undercooked hamburger” infection
In 1999, a food borne outbreak took place among people attending the Washington County Fair in New York State. The causative organism was found to be a strain of *Escherichia coli* called 0157:H7. The source of the organisms may have been from a well on the fairgrounds that was probably contaminated with cow manure. In other outbreaks, the source of this organism has been traced to undercooked hamburger meat. In this outbreak, a 3-year old girl and a 79-year-old man died from complications of the infection. Hundreds of others became ill with a bloody diarrhea, a condition known as **hemorrhagic colitis**. Seventy-one people had to be hospitalized. Of these, 14 developed a severe complication of *E. coli* O157:H7 infection (the hemolytic uremic syndrome) that can lead to kidney failure.
Virulent → Conjugation, Transfection, Transformation → Benign → Conversion to Virulence → Virulent

1. Conjugation, Transfection, Transformation
   - Plasmids
   - Chromosomal DNA
   - Transposons
   - Naked DNA

2. Conversion to Virulence

3. Transcription/translation of acquired genes
   - Production of virulence factors
   - Pathogenesis in host
Pathogenicity or Genomic Islands

• Carry many genes
• Plasmid- or chromosome-borne

Hints that they are acquired by horizontal transmission
• Missing in some strains
• Sometimes differ from host in G+C ratio
• Integrated within dispensable genes such as tRNA or prophages
• Flanked by direct repeats and often encode for integrases or transposases
Tuberculosis - chronic infectious disease
**Intracellular life** - Another important strategy to resist defenses

Avoid antibodies, phagocytes, many antibiotics.

Typically, macrophages, e.g., TB

Penetration. No problem with professional phagocytes, but must “teach” other cells how to take them up.