Zoonotic Disease

- **A disease primarily of animals which can be transmitted to humans as a result of direct or indirect contact with infected animal populations.**
- **Vector – An arthropod which carries the infection from one host to another.**
- **Reservoirs –disease cycle is normally from one one animal to another with humans as accidental hosts (Rabies and Anthrax).**

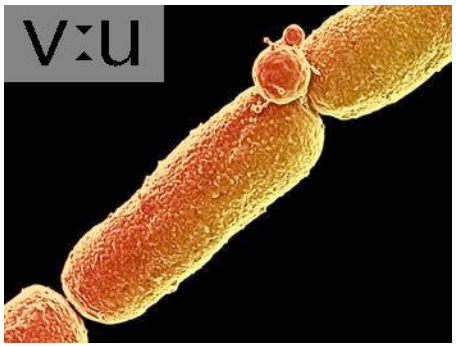
Anthrax

‘*Infectious Disease is one of the few genuine adventures left in the world.’*

Hans Zinsser (1878-1940)

Rats, Lice and History

Bacillus anthracis



Definitions and History

- **More the 3000 years after the fifth plague resulted in the destruction of livestock in Egypt (as noted in the biblical book of Exodus), and 130 years after Robert Koch performed his landmark experiments with the anthrax bacillus, there remain numerous unanswered questions about anthrax.**

(1843-1910)

Koch's Postulates

- **The bacteria must be present in every case of the disease.**
- **The bacteria must be isolated from the host with the disease and grown in pure culture.**
- **The specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host.**
- **The bacteria must be recoverable from the experimentally infected host.**

Definitions and History

- **Zoonotic disease**
- **Primarily a disease of herbivores.**
  - **can infect humans and other mammals**
    - **humans infected by contact with infected animals or animal products**
  - **carnivores and carrion eaters resist infection**
- **Tremendous variability to susceptibility.**
- **In Europe during from the 17th-19th centuries, anthrax caused many human deaths, as well as enormous losses of domestic livestock.**
- **Occurs most frequently in agricultural workers exposed to infected animals or in workers handling spore-contaminated hides or wool fibers.**

Definitions and History

- **Also known as**
  - **Woolsorter's disease**
  - **Charbon**
  - **Milzbrand**
  - **Black bain**
  - **Rag picker's disease**
  - **Tanner's disease**
  - **Siberian or splenic fever**

Definitions and History

- **With improved wool- and hide-handling procedures that reduce and inactivate spores, and vaccination of livestock and workers, human anthrax in the Western world has become rare.**
- **One of the largest epidemics on record was in Zimbabwe in the early 1980s.**
  - **6000 people infected**
- **Sverdlovsk (now Yekaterinberg), Russia in 1979...**

Definitions and History--

Sverdlovsk, Russia

- **64/96 people died from inhalation anthrax.**
- **The actual number has never been established because official information was suppressed by the former USSR.**
- **The outbreak, as originally reported in 1980, resulted from cutaneous exposure and ingestion of contaminated meat.**
  - **autopsy consistent with aerosol exposure.**
- **Actually caused by the accidental release of infectious anthrax spores from a military facility in the district where most patients lived.**
- **This incident is the best existing source of data on low-dose human exposure to inhalation anthrax from which to model a bioterrorism scenarios.**

Bioterrorism Policy Issues

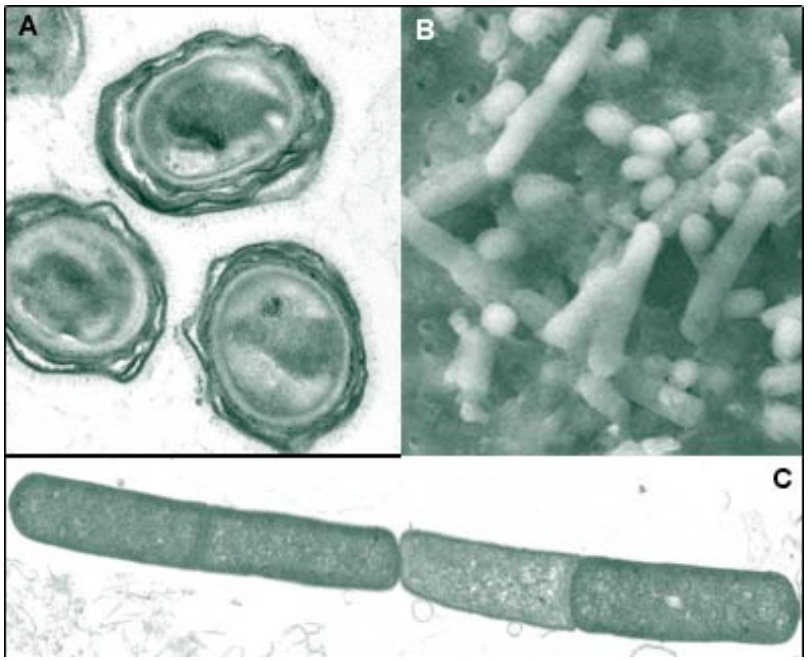
- **Number of people infected by an atmospheric release depends on the dose-response function, particularly at low doses.**
- **The time at which the first victims become symptomatic.**
  - **incubation period**
  - **alertness of physicians**
- **Efficacy of appropriate medical intervention depends largely on its speed relative to the rate at which victims become symptomatic.**
  - **related to host population susceptibility (age, gender, health status)**

Geographic Distribution

- **Worldwide.**
  - **highest incidence in tropical and subtropical climates.**
  - **Parts of Africa, Asia, southern Europe, Australia, and North and South America**
- **Alkaline soil with high levels organic matter and poor drainage combined with alternating rain and drought promote sporulation and subsequent multiplication of *B. anthracis* in the soil.**

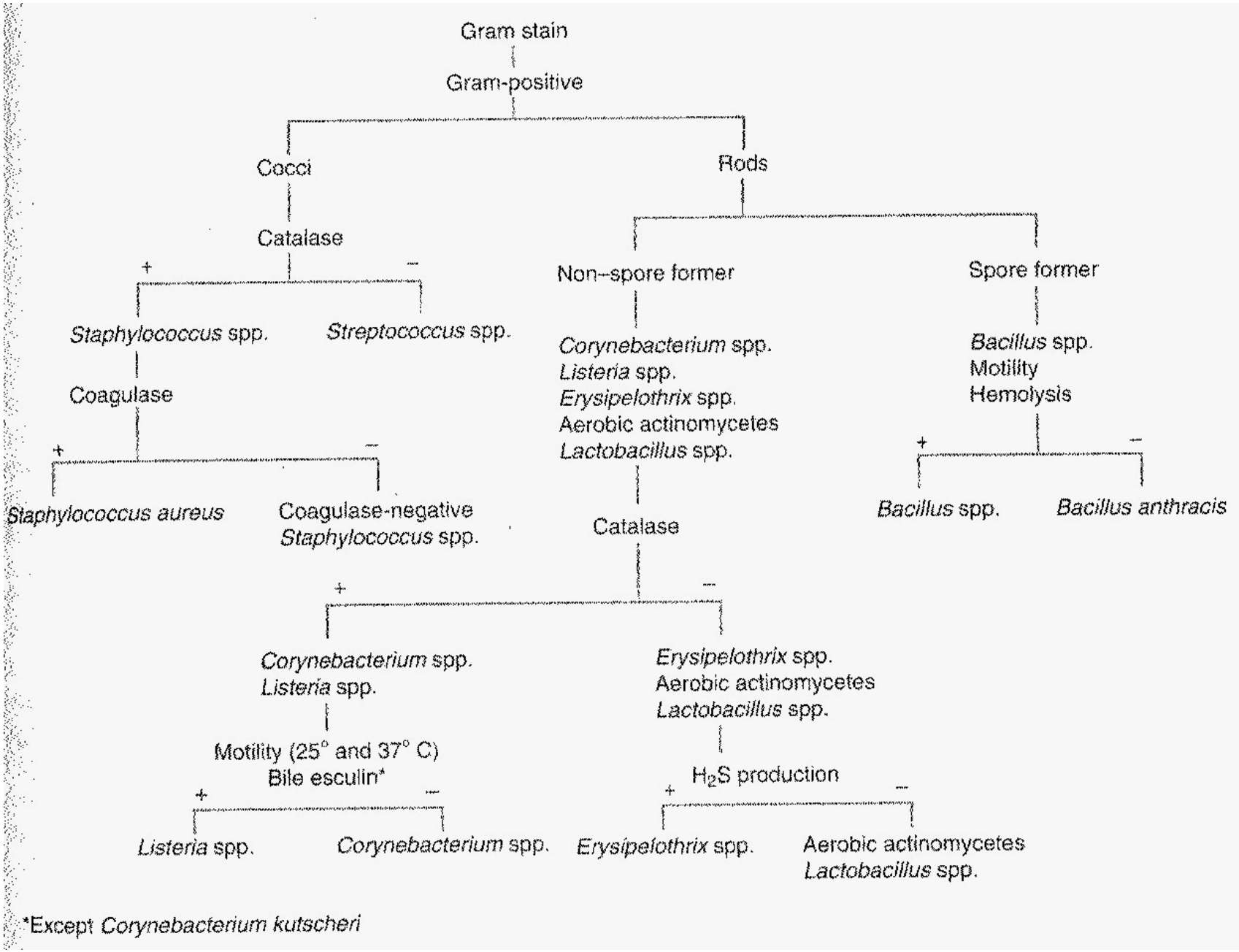
Morphology and Characteristics

- **Large, Gram-positive or Gram-variable**
  - **spores may look like 'empty spaces'**
- **Morphologically indistinguishable from *B. cerus* or *B. thuringiensis*.**



Morphology and Characteristics

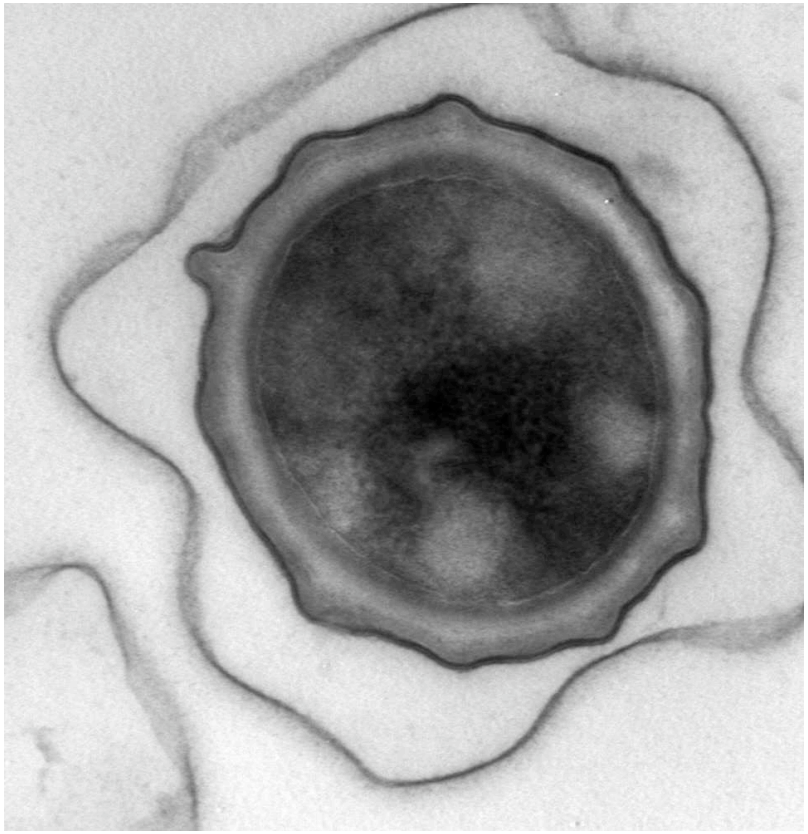
- **Catalase positive and aerobic or facultative.**
- **Spore formation takes place aerobically; this feature, along with a positive catalase test, differentiate *Bacillus sp*. from clostridia.**
- ***B. anthracis* is non-motile, distinguishing it from other members of the genus *Bacillus*.**



*Except *Corynebacterium kutscheri*

Morphology and Characteristics

- **Capsule is composed of a high-molecular weight polypeptide, poly-D-glutamic acid.**
- **Acts as virulence factor by virtue of its negative charge.**
  - **inhibits phagocytosis**



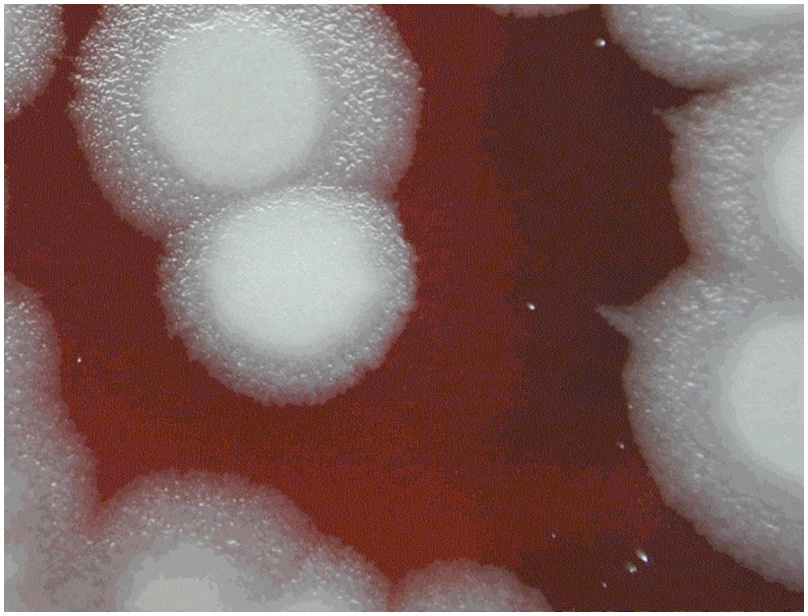
Morphology and Characteristics

- **In mammalian hosts, bacilli are in pairs or short chains, but in smears from agar colonies they they are 'boxcar' or 'bamboo' in appearance.**
- **The vegatative form is not as hardy as the spore form, and is quickly destroyed by autolytic enzymes and putrefactive organisms in the degenerating animal carcass.**

Sporulation induced when the bacillus is exposed to the environment.

Morphology and Characteristics

- **On solid culture media, *B. anthracis* forms large, raised, granular colonies with irregular borders referred to as "medusa head."**



Clinical Features of Anthrax

- **Classifications**
  - **Cutaneous**
  - **Gastrointestinal**
  - **Inhalational**

    - **Septicemic anthrax with bacteremia, toxemia, and associated secondary manifestations may follow any mode of infections (but more rare with cutaneous disease).**

Clinical Features of Anthrax--

Cutaneous

- **95% of all cases**
- **Occurs in humans, swine, rabbits, and horses.**
- **Lesions occur where spores come in contact with abraded skin.**
- **Can be transmitted by biting flies**
- **Black eschar**
- **Infections usually self-limiting and relatively painless but treatment recommended.**

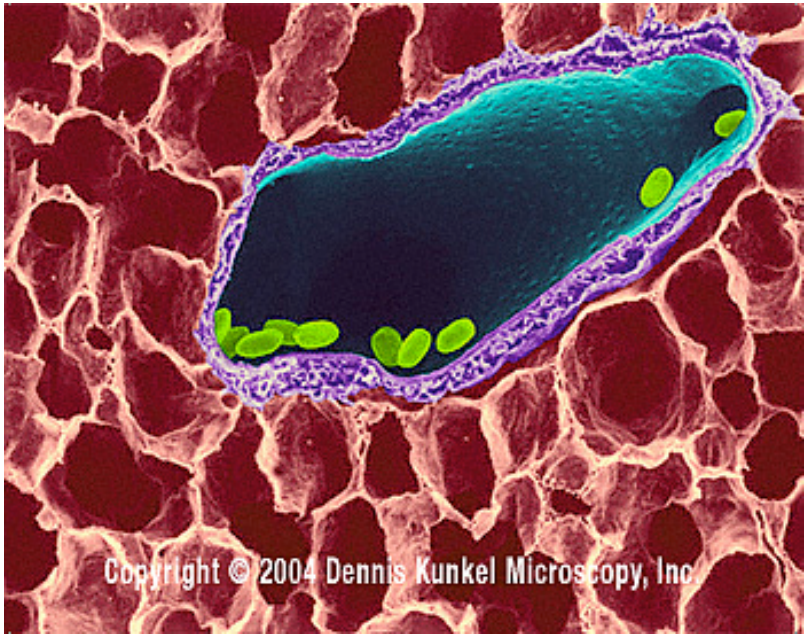
***Anthrax* means...?**

Clinical Features of Anthrax--
Gastrointestinal

- **Extremely rare**
  - **no cases ever reported in the U.S.**
- **Majority of outbreaks have been in Africa and southeastern Asia.**
- **Presents as a single oropharyngeal lesion or as a severe systemic disease with a primary lesion in the terminal ileum or cecum.**
- **Spores on food.**
- **Patients present with nausea, vomiting, anorexia, and fever accompanied by abdominal pain.**
  - **in the septicemic phase, hematemesis and bloody diarrhea may also develop with shock and death.**

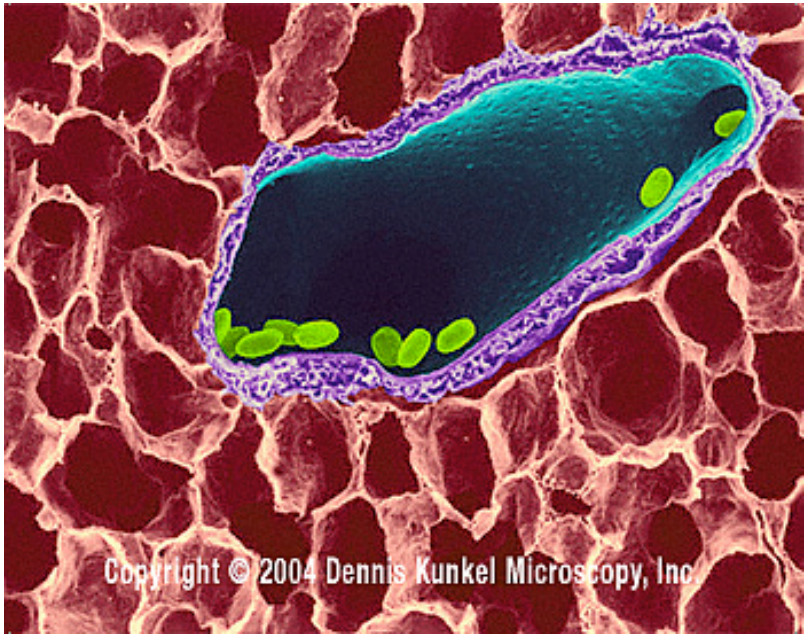
Clinical Features of Anthrax--
Inhalational

- **Only 18 cases reported in the U.S from 1900-1980.**
  - **9/11**
    - **5/22 fatal cases**
- **Onset 1-5 days after spore inhalation.**
- **Fever, myalgia, nonproductive cough (similar to influenza or bronchitis.**
- **Depression of blood O_2 levels.**



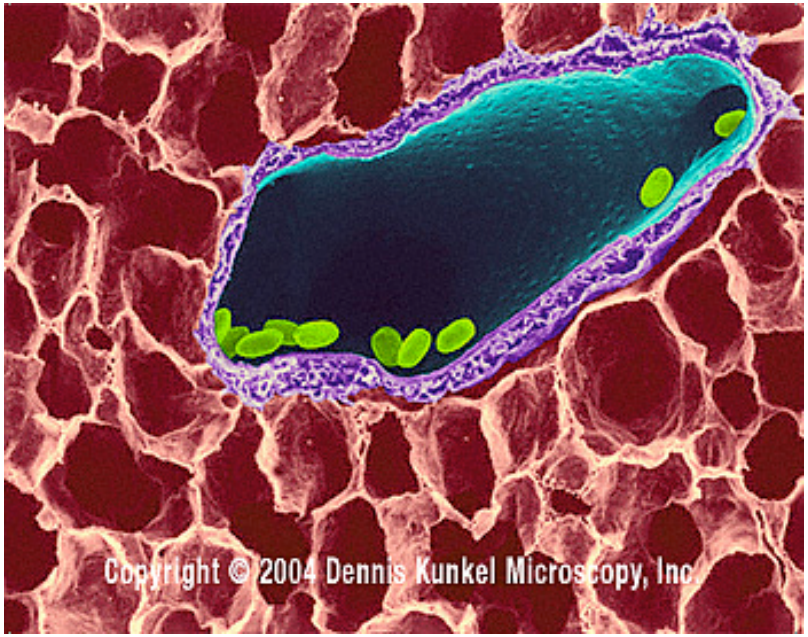
Clinical Features of Anthrax--
Inhalational

- **The World Health Organization estimated that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations.**



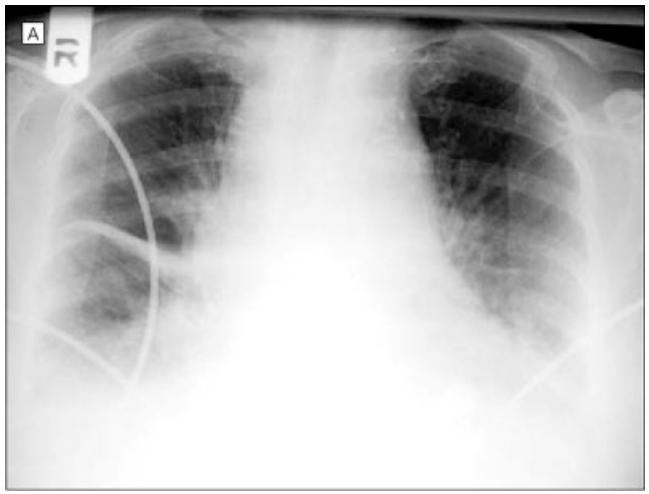
Clinical Features of Anthrax--
Inhalational

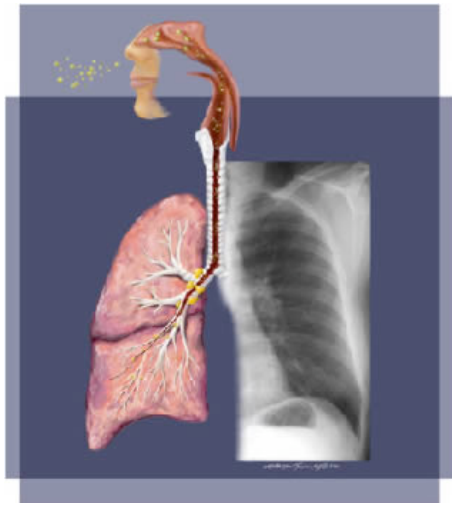
- **The estimated infectious dose by the respiratory route required to cause inhalation anthrax in humans is 8,000-50,000 spores.**



Clinical Features of Anthrax--
Inhalational

- **Severe respiratory distress develops suddenly, with stridor, dyspnea, and cyanosis.**
- **Radiographically, there is often a characteristic expansion of the mediastinal space by edema.**
- **Shock frequently develops, and death usually occurs within 24-48 hours of onset.**





Anthrax--Pathogenesis

- **Capsule...**
  - **Encoded by the pX02 plasmid**
    - **pX02-deficient strain is the attenuated Sterne strain**
- **Exotoxins composed of 3 different proteins**
  - **Protective antigen (PA)**
  - **Edema factor (EF)**
  - **Lethal factor (LF)**

  - **Encoded by the pX01 plasmid.**

Anthrax--Pathogenesis

- **Lethal toxin-composed of heptameric PA bound to LF (metalloproteinase).**
- **Edema toxin-composed of heptameric PA bound to EF (adenylate cyclase with homology to a similar enzyme in *Bordetella pertussis*).**
  - **Classic AB toxins**
    - **PA binds the edema factor and the lethal factor**

Anthrax--Pathogenesis-LT

- LT cytotoxic for macrophages (?)
- Genetic variability
- LT modulates both innate and adaptive host immune responses.
  - Innate
    - disrupting intracellular signaling pathways and inducing apoptosis in macrophages.
    - impairs neutrophil chemotaxis
  - Acquired
    - impairing APC function of dendritic cells
    - inhibit T and B cell activation

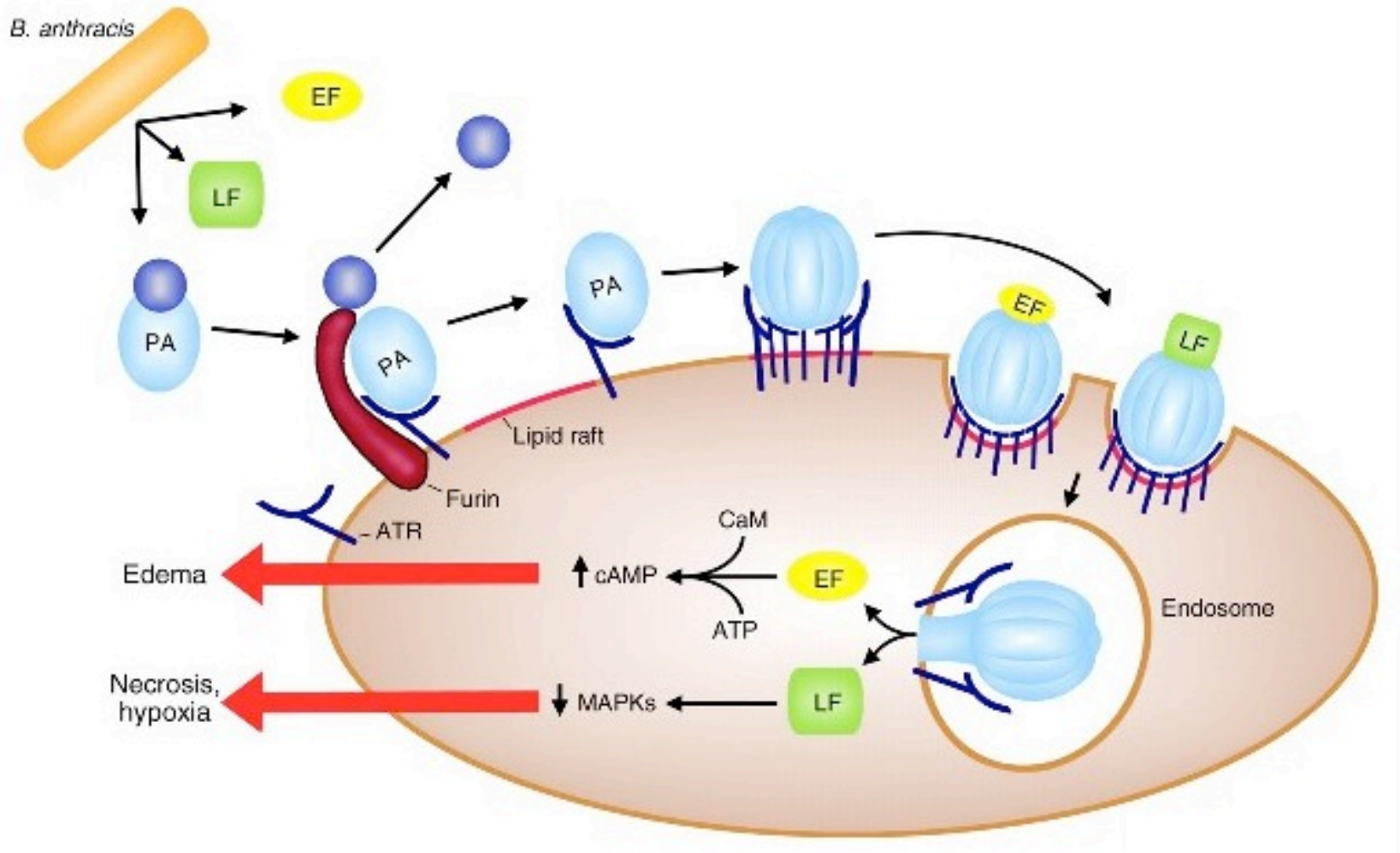
Anthrax--Pathogenesis-ET

- **ET historically has received less attention than LT (LT found first).**
- **However, ET can alone or in concert with LT play a larger role in disease than was suspected earlier.**
- **Unlike the rapid cytotoxicity observed with LT, ET induces dramatic increases cAMP levels in mammalian cells, resulting in tissue edema**
  - **Disrupts cytokine networks**
    - **results in immune evasion**

Anthrax--Pathogenesis

- **The pathophysiology of inhalational anthrax in humans has been assumed to be similar to shock associated with LPS--outpouring of inflammatory cytokines *e.g.*, IL-1 and TNF-α.**
- **However, data published in 2003 demonstrated that macrophages were not involved in protection against infection and that toxin-mediated tissue hypoxia may present like toxic shock but isn't.**

Anthrax--Pathogenesis



Anthrax--Pathology

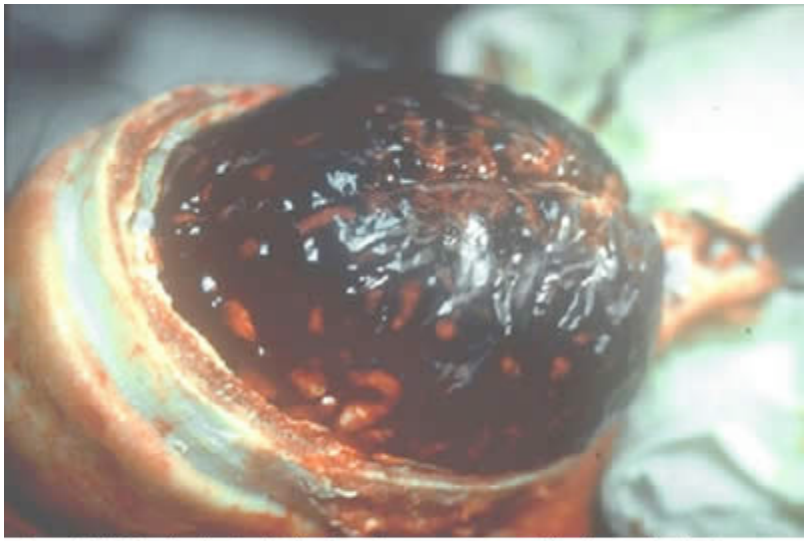
- **Hallmark lesions of anthrax-**
  - **hemorrhage**
  - **edema**
- **A localized primary necrotizing and hemorrhagic lesion at the portal of entry is considered specific enough to establish the mode of infection in humans.**

Anthrax--Pathology

- **Inhalational anthrax is characterized by hemorrhagic thoracic lymphadenitis and hemorrhagic mediastinitis (42/42 inhalation anthrax patients studied in Sverdlovsk).**
- **Manifestations of hematogenous spread of *B. anthracis* included hemorrhagic leptomeningitis (21), hematogenous spread to the submucosa of the GI tract (39), and mesenteric lymphadenitis (9).**
- **Blood films and tissues reveal a myriad of typically shaped ('boxcar'), encapsulated gram-positive bacilli.**

Anthrax--Pathology

- **The hemorrhagic meningitis is striking and is often referred to as a "cardinal's cap."**



So-called "Cardinal's Cap", the classic appearance of the human brain in some fatal anthrax cases. Source: http://www.usafe.af.mil/direct/sg/anthrax/Pictures/anthrx22.jpg; accessed January 22, 2006.

Anthrax--Differential Diagnosis

- **Obtain history.**
  - **anthrax without exposure to infected animals or animal products is rare.**
- **Patients with cutaneous lesions only--acute staphylococcal cellulitis may be mistaken for an anthrax pustule (check gram stain: morphology).**
- **In patients with systemic disease & a cutaneous lesion, other infections must be considered: tularemia, plague, cat scratch disease, and rat bite fever.**
  - **inhalation anthrax:widening mediastinum.**

Anthrax--Diagnosis

- History
- Clinical signs
- Gram-positive bacilli on smears
- Test for pathogenicity in laboratory animals
- ELISA

Anthrax--Treatment

- **Successful treatment requires and understanding of the pathogenesis.**
  - **think of treatment in two phases**
    - **one to protect against bacteria multiplication**
    - **one to protect against effects of toxins if there is septicemia**
- **Prompt therapy if suspected.**
  - **once a critical level of bacterimia is reached, eradicating *B. anthracis* will not prevent fatal toxemia.**
- **Penicillin, ciprofloxacin, doxycycline**
  - **spores can be detected up to 42 days post exposure!!!**

Anthrax--Prophylaxis

- **Sterne strain vaccination of livestock populations at risk.**
- **Human vaccine prepared from culture supernatants of an avirulent strain of *B. anthracis*, and is composed primarily of PA.**
  - **AVA (anthrax vaccine absorbed)**
  - **BioPort Corp., Lansing, MI**
  - **3 subcutaneous injections @ 0, 2, and 4 weeks and additional boosters at 6, 12, and 18 months, followed by annual boosts.**
  - **90% effective.**

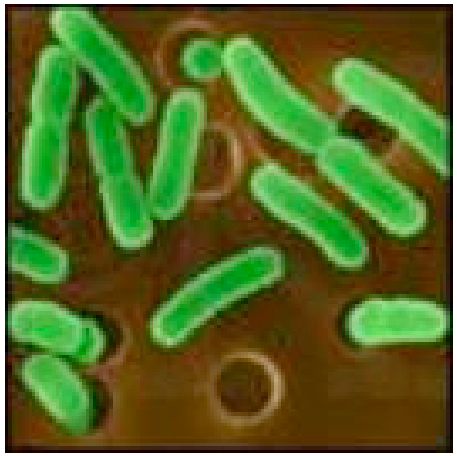
Tularemia

‘*Medicine is a science of uncertainty and an art of probability.’*

Sir William Osler (1849-1919)

Tularemia--Definition

- **Zoonotic bacterial infection caused by the small Gram-negative pleomorphic coccobacillus *Francisella tularensis* (formerly *Pasteurella tularensis*).**
- **Characterized by a mucocutaneous ulcer at the site of entry, high fever, enlargement of regional lymph nodes.**



Tularemia-History

- **Discovered in 1910 by George McCoy during his investigation of a plague-like episode in ground squirrels in Tulare County, CA.**
  - **isolated the pathogen and showed it could cause disease in humans**
- **In 1919, Dr. Edward Francis demonstrated that deerfly fever, described 8 years earlier, was tularemia.**
  - **also referred to as 'rabbit fever.'**

Tularemia-Etiologic Agent

- ***Francisella tularensis*** **is a weakly Gram negative, non-motile coccobacillus.**
- **Bipolar staining pattern with Giemsa stain.**
- **Thick capsule (associated with virulence).**
- **Obligate aerobe**
- **Exposure to 56°C for 10 minutes can kill the organism but freezing will not.**

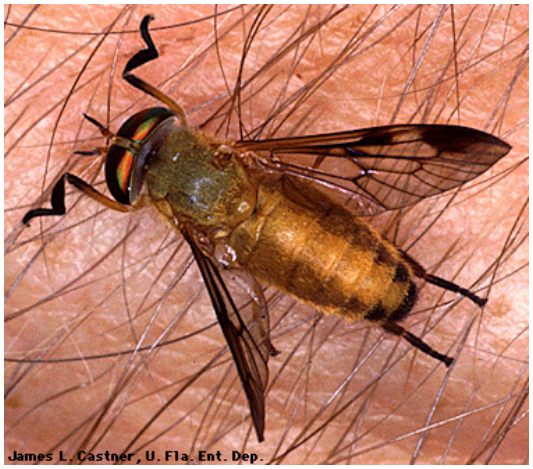
Tularemia-Epidemiology

- Occurs throughout the Northern Hemisphere.
- In the U.S., most infections are in the south central regions.
- Peak in the summer from tick transmissions and in the winter from infected animal carcasses.
- More than 100 species can be infected.
  - most are rabbits, but also rodents, raccoons, squirrels, and cats
  - also domestic animals can be infected

Tularemia: Epidemiology

- **Worldwide distribution- Northern Hemisphere**
- **~200 US cases/yr.**
- **Most cases found in Missouri, Oklahoma and Arkansas**
- **Infects humans, and animals (rodents)**
- **Vectors: ticks, deer flies**
- **Very low infectious dose (1-10 organisms)**

U.S. cases 1990-1998



Transmission & Pathogenesis

- **Resembles *Y. pestis* in pathogenicity, organ pathology, affinity for rodents, and transmission by an insect vector.**
- **Multiple modes of transmission**
  - **deer flies and tick bites**
  - **respiratory droplets**
  - **contact with an infected animal**
  - **consumption of infected meat**
- **Intracellular pathogens of fixed macrophages of RES and within mononuclear phagocytes.**

Tularemia: Clinical Manifestations

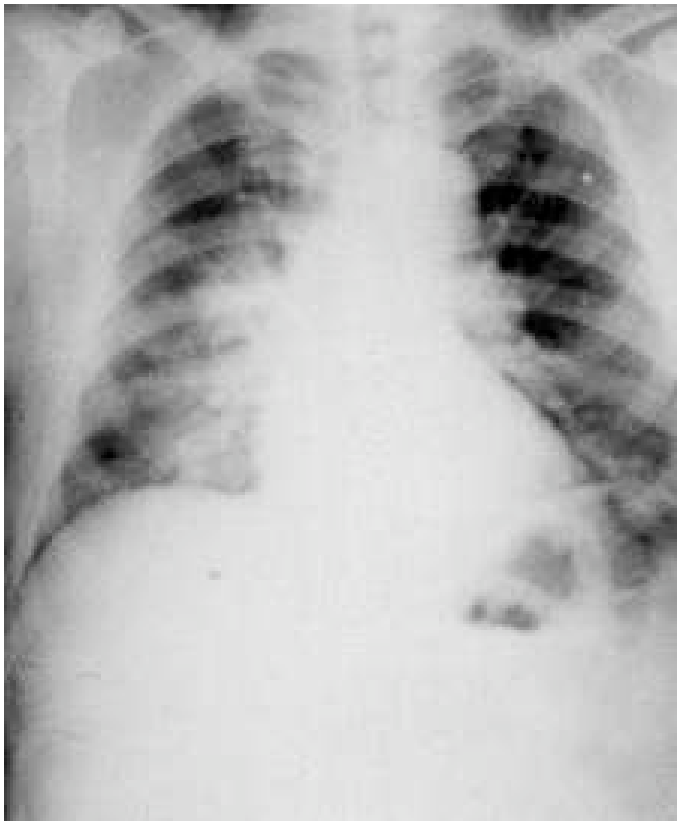
- **Incubation period 1-21 days**
- **Major syndromes depend on the mode of transmission:**
  1. **Ulceroglandular/glandular – most common manifestation (70-80%). Skin infection. Results form an insect bite.**
  2. **Enteric or typhoidal– features of sepsis; diagnosis is established by blood culture. 50% have pulmonary infiltrates--can be confused with legionellosis.**
  3. **Oropharyngeal – variant of ulceroglandular; occurs when the pharynx is entry portal.**
     1. **pseudomembrane can form**
  4. **Oculoglandular – involves direct contamination of the eye**
  5. **Pulmonary--inhaled aerosolized droplets**
     1. **rare**

Ulceroglandular tularemia

- Painful papule at bite site
- Ulcer with regional adenopathy
- Necrotic center and raised border
- Low mortality

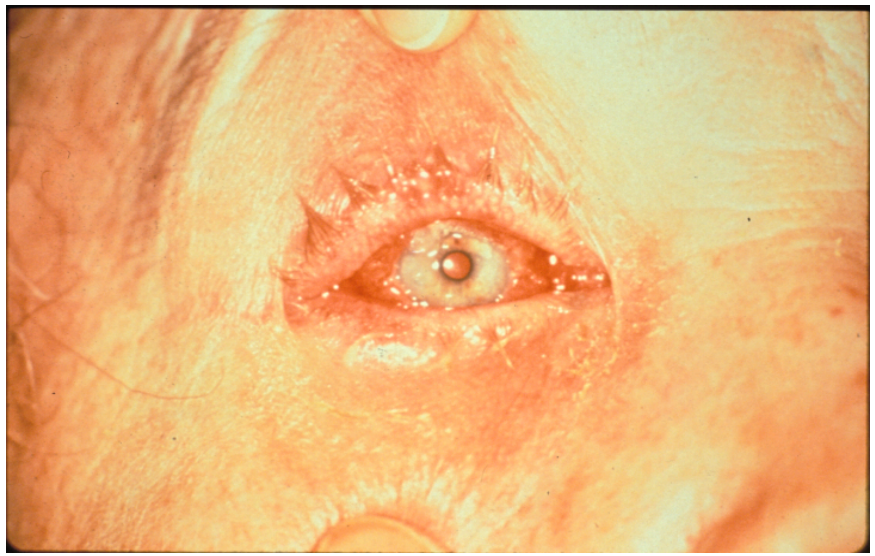
Pulmonary Tularemia

- **Incubation 3-5 days**
- **Abrupt onset of fever, headaches, anorexia, chills, sweats, prostration and non-productive cough**
- **Segmental/lobar infiltrates, effusions**
- **Mortality 30% untreated; less than 10% if treated**
- **Microorganism rapidly isolated from blood (not in sputum)**



Other Forms

- **Oculoglandular**
  - painful conjunctivitis
  - regional lymphadenopathy
- **Typhoidal**
  - <5% of the cases
  - high mortality due to septicemia
  - multi-organ involvement



Tularemia: Diagnosis and Treatment

- **Serology**
- **Treated with Streptomycin or Gentamycin**
- **Prophylaxis for exposures:**
  - **Watch for fever for 7 days**
  - **Doxycycline or tetracycline for 14 days**

Prevention

- **Avoid contact with reservoirs and vectors**
- **Wear gloves when skinning and eviscerating animals**
- **Promptly remove of ticks**
- **Wear protective clothing**
- **Use insect repellents**
- **Vaccines (live attenuated, inactivated)**

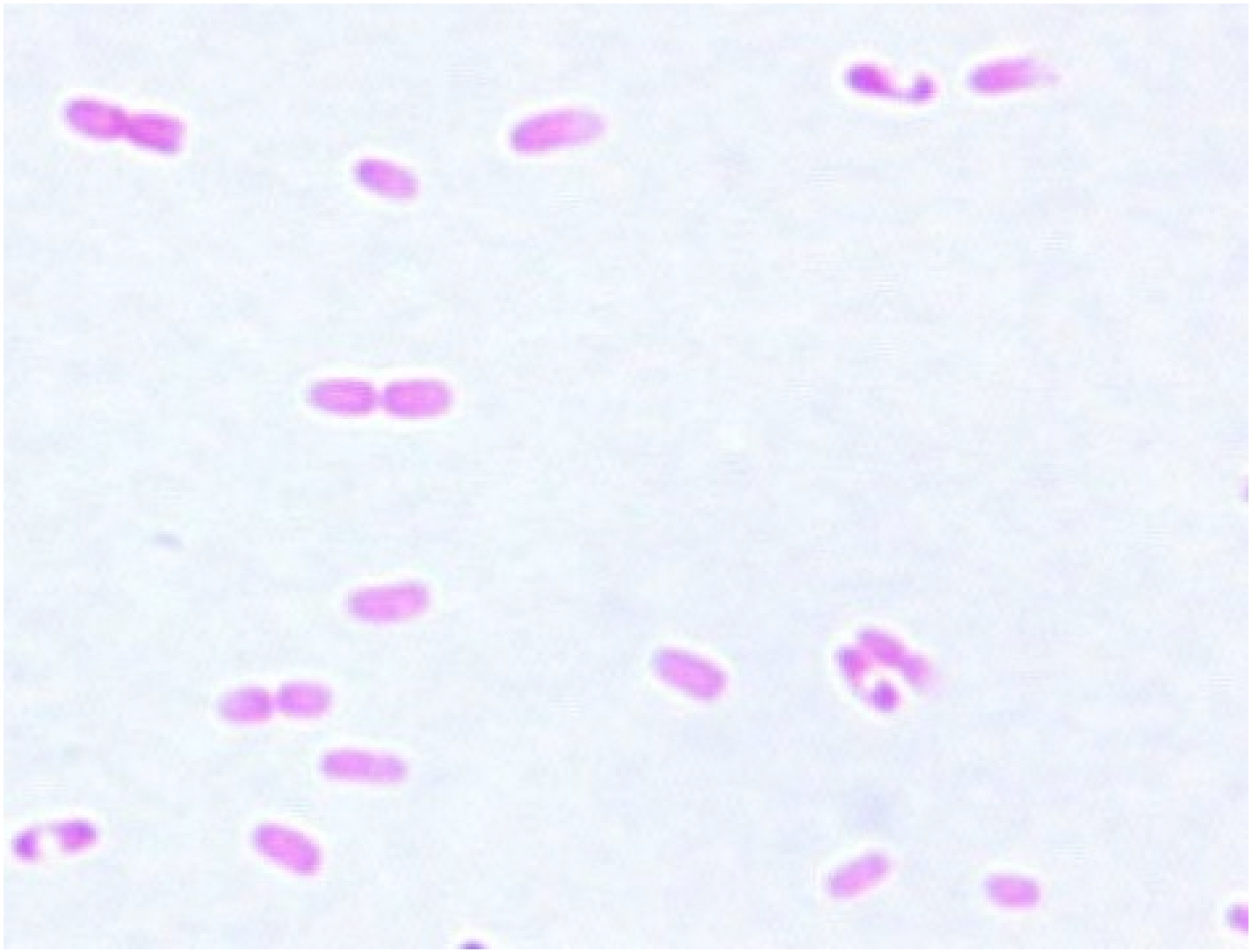
Plague

'Lord! how sad it is to see the streets empty of people, and very few upon the 'Change. Jealous of every door that one sees shut up, lest it should be the plague; and about us two shops in three, if not more, generally shut up.

Samuel Pepys Diary, August 16, 1665

Plague--Definition

- **Acute, febrile, contagious disease caused by *Yersinia pestis* (formerly *Pasteurella pestis*).**
- **Bipolar gram-negative bacillus of the family Enterobacteriaceae.**
- **Aerobic, facultatively anaerobic.**



Plague--Synonyms

- Black plague
- Black death
- the pest
- pestis
- Bubonic plague
- septicemic plague
- pneumonic plague

Plague--Synonyms

- **Some contend that the black splotches on the skin resulting from hemorrhages is why it was called the 'Black Plague.'**
- **Others speculate that '*black*' is a mistranslation of '*pestis atra*,' meaning , not black, but a '*terrible*' or '*deadly*' disease.**

The Plague--History

- During the last 2000 years, three great bubonic plague pandemics have resulted in social and economic upheavals that are unmatched by those caused by any armed conflict or any other infectious disease (to date).

***The Plague*, by Felix Jenewein (1900), shows a mother carrying a coffin with her child.**

The Plague-Three Pandemics

- **542-543-Constantinople, Roman capital in the East. Plague contributed to Justinian's failure to restore imperial unity.**
- **1346-1352-By the time it dissipated, the population of Europe and the Middle East had been reduced from 100 million to 80 million.**
  - **put an end to the rise in human population that had begun in 5000 B.C.**
  - **150 years to recover**
- **1860s-Yunnan region of China**
  - **killed more than 200 million people**

The Plague-Three Pandemics

- In the early part of the nineteenth century, India bore the heaviest plague burden, but this was exhausted by 1950.
- In the 1960s, Vietnam had 10,000 deaths/yr.
- In recent times, plague has existed principally as sylvatic foci in the southwestern U.S., Africa, South America, and the Far East.
  - sporadic accidental human infections occur with these sylvatic foci

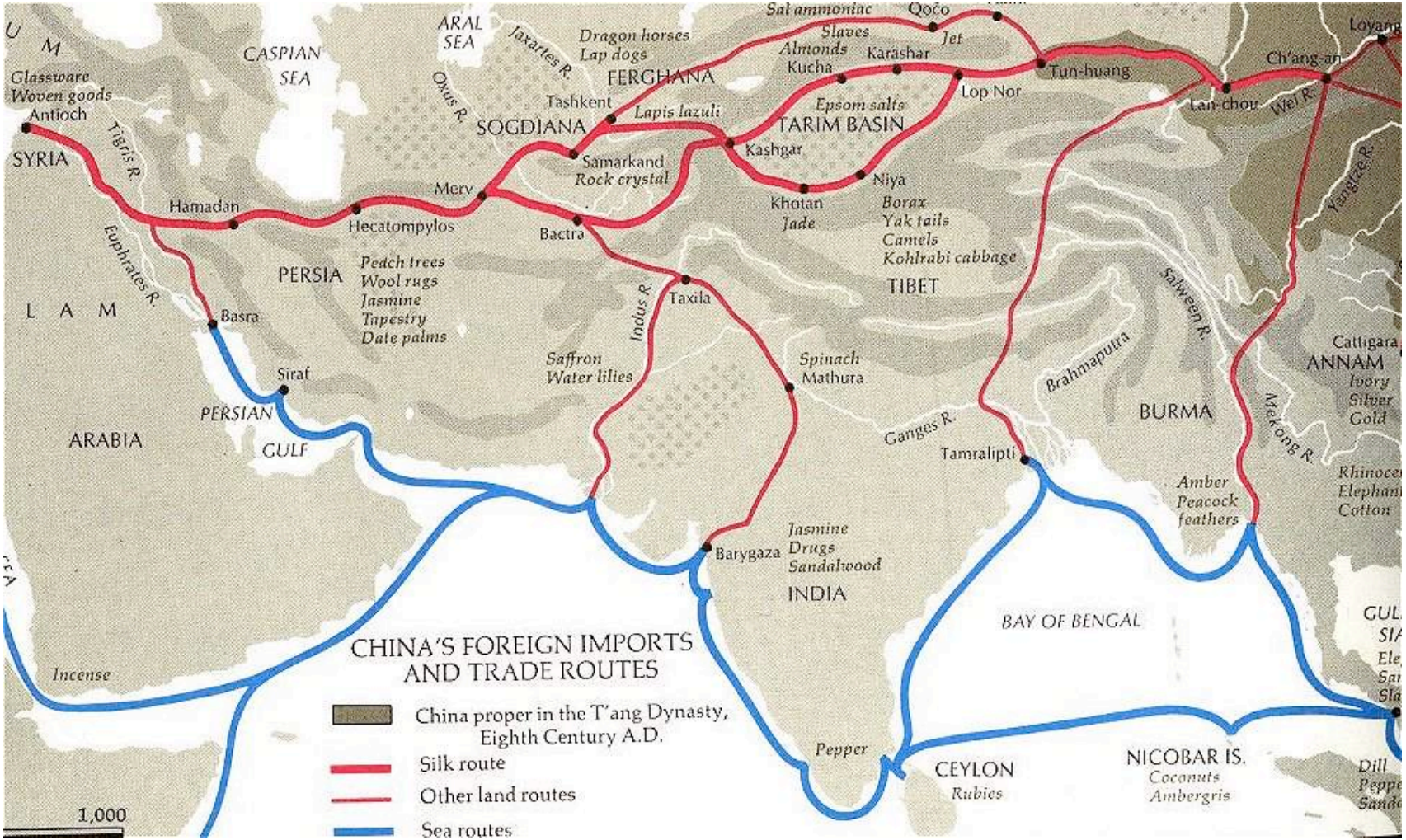
The Plague--History

- **Although those living in the medieval period recognized that plague was a contagious disease spread from person-to-person, its cause was not identified.**
- **We now know that the source of the second pandemic was microbes left over from the first pandemic (Justinian plague).**
- **Disease had moved eastward and remained endemic for 7 centuries in voles, marmots, and the highly susceptible black rats (*Rattus rattus*).**

The Plague--History

- **Plague-infected rats moved along the the caravan routes between Asia and the Mediterranean known collectively as the Silk Road.**
- **Asia--around the Caspian Sea--Crimea.**
- **There the rats boarded ships and moved from port to port and country to country, spreading plague to the human populations living in filthy, rat-infested cities.**

The Silk Road



The Plague--History

- **The story of the Pied Piper of Hamelin (or Hameln) may have had its roots in the plague-ridden cities of Germany.**
- **Legend has it that on June 26, 1284, the city became infested with rats.**
- **A pied piper was hired to lure the rats to their death by drowning them in a river.**
- **Grimm Brothers (1812).**

The Plague--History

- **The contagious nature of the plague led to the belief that only way security could be achieved was total isolation of the sick.**
- **In 1374, the Venetian Republic required that all ships, their crew, passengers and cargo had to remain on board for 40 days while tied up a the dock; this gave rise to the term "quarantine" (from the Italian word *quaranta* meaning 40).**
- **However....**

The Plague--History

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- **However....**

The Plague--History

- Cordon sanitaires or people shut up in their homes.
- Burning of clothes from the sick or dead.
- Led to societal and religious changes:
  - feudal structure began to break down
  - laboring classes became more mobile
  - merchants and craftsmen became more powerful
  - decline in papal authority

  - From 1347-1722, plague epidemics occurred in Europe at infrequent intervals
  - In England, every 2-5 years (1361-1480)
  - Half the population of Milan died in 1630
  - 60% of the population in Genoa died in 1656-1657

The Plague--History-Religion

- 500 people died/day in cities of 50,000.
  - Priests who gave last rites had a very high mortality
  - loss of faith in the clergy.
- The Roman Catholic Church passed the responsibility for the plague on to God.
  - however, even God's servants were not spared.
  - all of the friars of a monastery near Avignon, and another near Marseilles, succumbed to the plague
- Healer saints and pilgrim movements (the Brethren of the Flagellants) further threatened the Church.

‘A Procession of Flagellants,’ Goya

St. Roch

The Plague--History-Medicine

- **Medieval society had four kinds of medical practitioners:**
  - **academic physicians-followed the teachings of Galen (remember the Gonorrhea genius?)**
    - **believed disease was an imbalance in the humors**
    - **usually older men**
    - **people lost confidence**
  - **surgeons**
  - **barbers**
  - **folk medicine**

“Baa baa black sheep, have you any wool? Yes have I, three bags full: One for my master, one for my dame and one for the little boy that lives in the lane.”

The Plague--History-Medicine

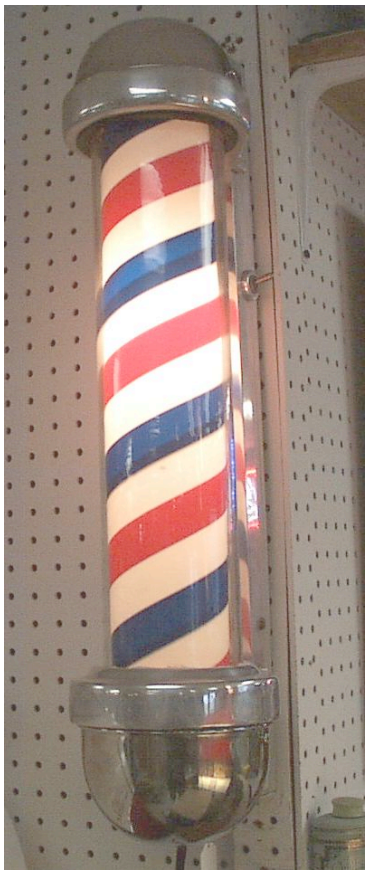
- **Surgeons**
  - **died at higher rates than did other medical practitioners.**
  - **Role in curing disease was little valued.**
  - **Beak contained perfumes or spices.**

The Plague--History-Medicine

- **The stench of death was so great during the plague years that to 'purify' the air, the perfume eau de cologne was invented in Germany and named after the city of Cologne.**
- **Today the perfume is know as '4711,' the street address of the household where it was first made.**

The Plague--History-Medicine

- New prestige fell to barbers, bloodletting and surgery.
- A new emphasis on studies of human anatomy in health and disease.
- Galenic system (which had no clear theory of contagion, declined in importance.



Plague--Finding the Killer

- **Even in medieval Europe, it was obvious the disease was contagious.**
- **However, even if Francastoro's idea of "seeds of contagion" was accepted, there were no means of identifying the agent of disease.**
- **Two schools of thought (one in France-*Pasteur* and the other in Germany-*Koch*) were responsible for firmly grounding the germ theory.**
  - **Throughout their lives, these microbe hunters remained fierce competitors.**

Plague--Finding the Killer

- **As the plague ravaged China during the 3rd pandemic, Pasteur dispatched Alexandre Yersin (1863-1943).**
- **On June 24, 1894, he wrote to Pasteur that the fluid taken from the bubo contained Gram negative bacilli.**
- **Now referred to as *Y. pestis* NOT *P. pestis.***
- He did not, however, find the means by which it was transmited.
  - **Paul-Louis Simond identified the flea vector in 1898.**

Plague--the Vector

- **The rat flea (*Xenopsylla cheopis*) is the most important vector species.**
- **On ingesting blood from an infected mammal, *Y. pestis* replicates unchecked.**
- **Bacteria produce a coagulase active at 20-28°C (but inactive at 35-37°C).**
  - **this prevents the flea from digesting the blood meal**
  - **no plague when it is too hot**

Plague--Clinical Features

- Three clinical forms:
  - bubonic
  - primary septicemic
  - primary pneumonic

Plague--Clinical Features

- **Bubonic**
  - **most common; contracted by flea bite**
  - **minute lesion at bite sight in 25% of patients**
    - **phenotype of lesion variable**
  - **following a 2-4 day incubation there is an onset of chills, high fever, tachycardia, tachypnea, anxiety accompanied by the appearance of the bubo with its sharp stabbing pain and swollen, nonfluctuant lymphadenitis**

Plague--Clinical Features

- **Bubonic**
  - **neutrophilic leuckocytocis with the WBC count reaching 40,000/μl.**
  - **in children it can reach 100,000/μl**
  - **blood cultures are positive in 50% of patients**
  - **buboes very painful.**
    - **mainly inguinal but in children can by axillary or cervical**

Plague--Clinical Features

- **Bubonic**
  - **Lymph node involvement progresses proximally.**
  - **Septecemia and secondary pneumonic plague follow.**
  - **Terminal petechiae and hemorrhagic cutaneous infarcts caused by DIC result in 'black' lesions.**
  - **Untreated mortality is 60-90%.**
  - **Death is rapid, sometimes within 1 day (usually 5).**
    - **If treatment is delayed, the endotoxemia may kill the patient even though all bacilli are dead.**

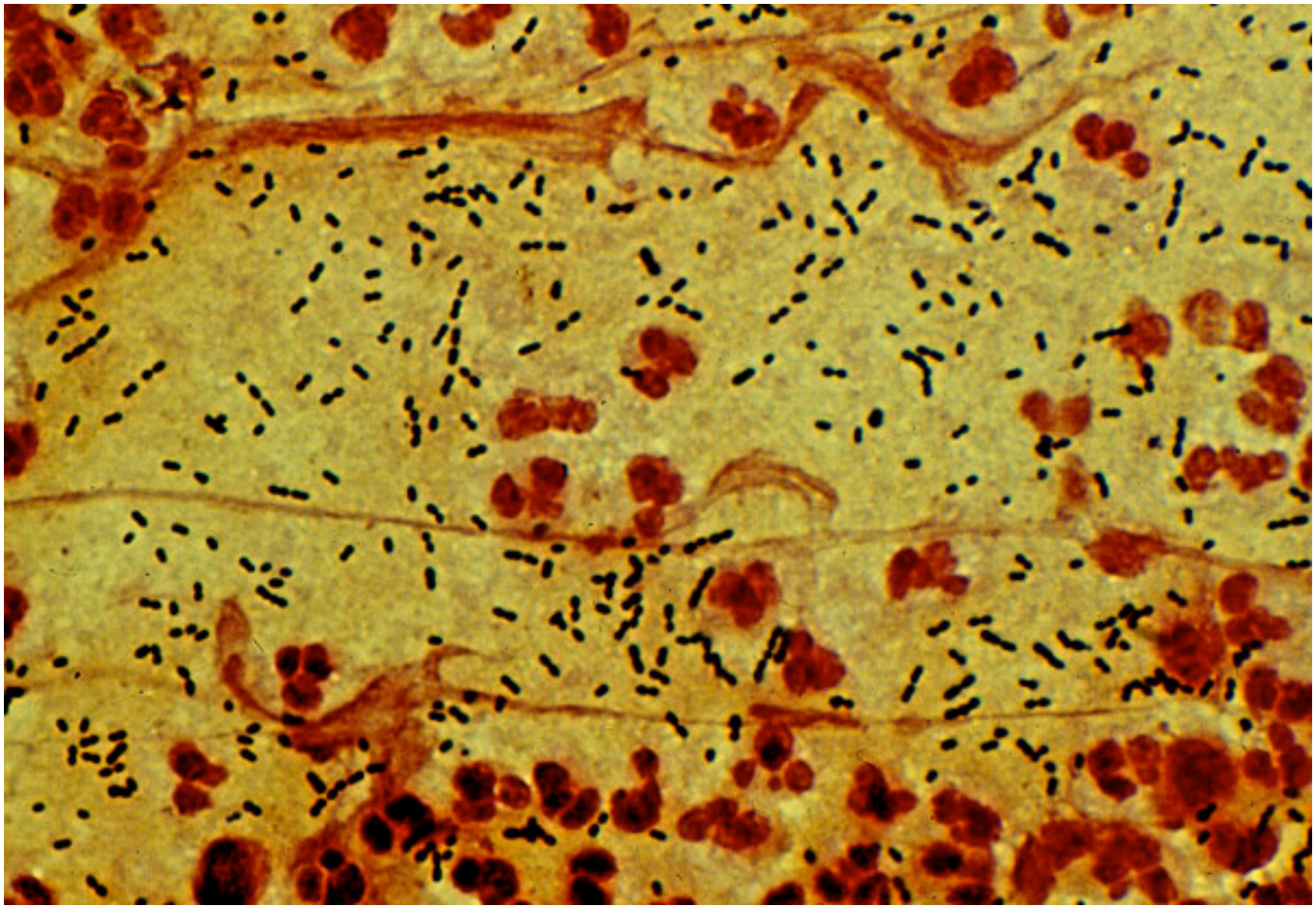
Plague--Clinical Features

- **Primary septicemic**
  - **1% of infections**
  - **sudden clinical onset with chills, fever, anxiety and prostration**
  - **meningitis is common**
  - **course of disease is rapid--90% fatal with 1-2 days**
  - **Pneumonia and hemorrhage are common**
  - **Pathogenesis is not clear but it has been postulated that the flea may introduce bacilli directly into the blood stream.**

Plague--Clinical Features

- **Primary pneumonic**
  - **develops when airborne bacilli are inhaled, usually from cadavers or animal carcasses or more commonly from the cough of a patient with pneumonic plague.**
  - **24-60 hour incubation results in sudden chills, high fever, severe cough, and dyspnea.**
  - **sputum is watery and frothy, occasionally bloody, and teeming with bacteria**
  - **mortality is 90% in 8-24 hours if untreated**
  - **death results from respiratory insufficiency or endotoxic shock**

Primary Pneumonic Plague--
Sputum



Plague--Differential Diagnosis

- **Buboes can can be present in the following diseases: tularemia, chancroid, lymphogranuloma venerum, sporotrichosis, and cat scratch disease.**
  - **but these diseases rarely present with a sudden onset**
- **Definitive diagnosis accomplished by making smears and cultures of bubo aspirates.**