Bacteria of Medical Importance

Introduction

Historically, bacteria have been the cause of some of the most deadly diseases and widespread epidemics of human civilization. Although smallpox and malaria, diseases caused by other microbes, may have killed more humans than bacterial diseases, bacterial diseases such as tuberculosis, typhus, plague, diphtheria, typhoid fever, cholera, dysentery, and pneumonia have taken a mighty toll on humanity. Water purification, immunization (vaccination) and modern antibiotic treatment continueto reduce the morbidity and the mortality of bacterial disease in the Twenty-first Century, at least in the developed world where these are acceptable cultural practices. However, many new bacterial pathogens have been recognized in the past 25 years (see Table 1) and many "old" bacterial pathogens, such as *Staphylococcus aureus* and *Mycobacterium tuberculosis,* have emerged with new forms of virulence and new patterns of resistance to antimicrobial agents.

Table 1. Bacterial pathogens and diseases recognized or reemerged since 1977

Bacterium	**Disease**
Legionella pneumophila	Legionnaires' pneumonia
Listeria monocytogenes	listeriosis
Campylobacter jejuni	gastroenteritis distributed world-wide
Staphylococcus aureus	toxic shock syndrome
E. coli O157:H7	hemorrhagic colitis; hemolytic uremic syndrome
Borrelia burgdorferi	Lyme Disease and complications
Helicobacter pylori	gastric and duodenal ulcers
Ehrlichia chaffeensis	human ehrlichiosis
Clostridium difficile	antibiotic induced diarrhea; pseudomembranous colitis
Vibrio cholerae O139	epidemic cholera
Salmonella enterica Serotype Typhimurium DT 104	salmonellosis
Bartonella henselae	cat scratch fever
Streptococcus pyogenes	necrotizing fasciitis (GAS); streptococcal toxic shock syndrome
Chlamydia pneumoniae	atherosclerosis
Clostridium botulinum	sudden infant death syndrome (SIDS)
Vibrio vulnificus	woumd infection, septicemia, gastrointestinal disease
Parachlamydia	Pneumonia

Corynebacterium amycolatum	Hospital-acquired endocarditis

Most of the bacterial pathogens of humans are classified as **Gram-positive** or **Gram-negative**, some notable exceptions being the mycoplasmas, chlamydiae, spirochetes and the mycobacteria. In this article the major pathogens of humans are organized into natural groups based on bacteriological criteria, rather than on the basis of affected organ, mode of transmission, or type of disease. This goes with being written by a bacteriologist.

Spirochetes

The spirochetes are a phylogenetically distinct group of bacteria which have a unique cell morphology and mode of motility. Spirochetes are very thin, flexible, spiral-shaped procaryotes that move by means of structures called axial filaments or endoflagella. The flagellar filaments are contained within a sheath between the cell wall peptidoglycan and an outer membrane. The filaments flex or rotate within their sheath which causes the cells to bend, flex and rotate during movement. Most spirochetes are free living (in muds and sediments), or live in associations with animals (e.g. in the oral cavity or GI tract). A few are pathogens of animals *Treponema pallidum* is the agent of syphilis, a sexually transmitted disease, and *Borrelia burgdorferi* causes Lyme Disease. which is transmitted by the bite of the deer tick.

Figure 1. Spirochetes: A. Cross section of a spirochete showing the location of endoflagella between the inner membrane and outer sheath; B. *Borrelia burgdorferi,* the agent of Lyme disease; C. *Treponema pallidum,* the spirochete that causes syphilis. (CDC)

Spirilla and other curved bacteria

Spirilla are Gram-negative bacteria with a helical or spiral shape. Their metabolism is respiratory and never fermentative. Unlike spirochetes, they have a rigid cell wall and are motile by means of ordinary polar flagella. Two important pathogens of humans are found among the spiral forms. *Campylobacter jejuni* is the cause of bacterial diarrhea, especially in children. The bacterium is transmitted via contaminated food, usually undercooked poultry or shellfish, or untreated drinking water. *Helicobacter pylori* is able to colonize the gastric mucosal cells of humans, i.e., the lining of the stomach, and it has been well established as the cause of peptic ulcers and there is strong evidence for its involvement in adenocarcinoma.

Figure 2. *Helicobacter pylori*

Vibrios

The term vibrio refers to a Gram-negative bacterium which has the cell shape of a curved rod or a comma. Members of the genus *Vibrio* are common bacteria in aquatic environments, especially marine environments. They have structural and metabolic properties that overlap with both the enterics and the pseudomonads. Vibrios are facultative (grow in the presence or absence of O_2), like enterics, but they have polar flagella, are oxidase-positive, and degrade sugars in the same manner as the pseudomonads. In aquatic habitats they overlap with the pseudomonads in their ecology, although pseudomonads favor fresh water and vibrios prefer salt water. Some marine vibrios are bioluminescent (they emit light) and some are symbionts of fish, squid and other marine life. *Vibrio cholerae*causes epidemic or Asiatic cholera which, untreated, is one of the most rapidly fatal infectious diseases known. The pathology is related to diarrheal diseases caused by the enteric bacteria, except it is relentless, and a patient can die rapidly from dehydration. The cholera toxin, which is the classic model of a bacterial enterotoxin, is also produced by some strains of *E. coli.*

Figure 3. *Vibrio cholerae,* the agent of Asiatic or epidemic cholera.

The Gram-negative aerobic rods and cocci

The name refers to Gram-negative bacteria phenotypically related to members of the genus *Pseudomonas.* Their metabolism is respiratory and never fermentative. Important

human pathogens include *Pseudomonas aeruginosa,Neisseria gonorrhoeae,Neisseria meningitidis, Bordetella pertussis, Haemophilus influenzae, Legionella, Brucella* and *Francisella,* and a few others. Many bacteria in this physiological group are free-living in soil and water, and they play an important role in decomposition, biodegradation, and the C and N cycles. Also, many bacteria which are pathogens of plants are found in this group, including *Pseudomonas, Xanthomonas* and *Agrobacterium.*

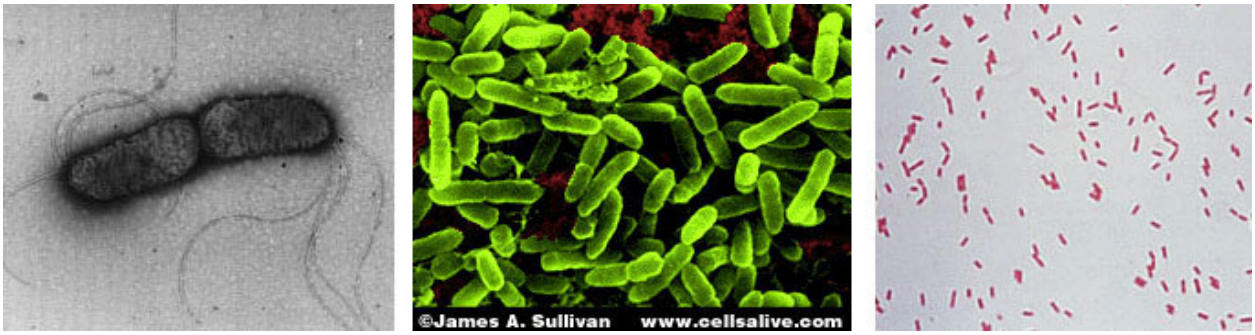

Figure 4. Three looks at *Pseudomonas,*the head of the Gram-negative aerobic rods. A. Electron micrograph, negative stain. B. Scanning electron micrograph. C. Gram stain.

Pseudomonas aeruginosa is the quintessential opportunistic pathogen of humans. It is a leading cause of hospital-acquired infections (nosocomial infections), and it is difficult to erradicate due to its resistance to most antimicrobial agents. There is probably no tissue that cannot become infected by *Pseudomonas* if the host defenses are weakened, and it is difficult to erradicate due to it's resistance to antimicrobial agents. It is usually involved in soft tissue infections, urinary tract infections and pneumonia

Whooping cough (or **pertussis**) is caused by *Bordetella pertussis.* The disease is particularly serious in infants and young children and has a high mortality rate. Whooping cough is controlled by vaccination with the acellular pertussis vaccine, which is usually given in association with diphtheria, tetanus and sometimes *H. influenzae* type b (Hib), as part of the childhood immunization program in the U.S.

Legionaires' pneumonia is caused by ***Legionella pneumophila.*** This pneumonia, and the bacterium, were not discovered until 1976, when there was an outbreak of disease at a Legionaire's meeting in Philadelphia. It took several months to find, culture and grow the bacterium. The incident was a wake-up call to public health officials that there were probably a lot of disease-producing bacteria outthere that they know nothing about.

Neisseria gonorrhoeae causes the sexually-transmitted disease gonorrhea, and *Neisseria meningitidis*is the agent of meningicoccal meningitis. The Neisseriae are discussed below with the Pyogenic Cocci.

Haemophilus influenzae is also a cause of **meningitis**, but the icidence of the disease has declined rapidly with the use of the Hib vaccine which began in 1994. *Haemophilus* is sometimes involved in infections of the upper respiratory tract, particularly the sinuses.

Brucellosis is a chronic debilitating infection in humans associated with reproductive failure in domestic animals. Person-to-person transmission of brucellae is extremely rare. *Brucella abortus* is the species usually involved in human disease. The primary reservoir of the organism is in cattle, although bison are sometimes wrongfully accused.

Enterics

Enteric bacteria are Gram-negative rods with facultative anaerobic metabolism that live in the intestinal tracts of animals in health and disease. This group consists of *Escherichia coli* and its relatives, the members of the family *Enterobacteriaceae.* Enteric bacteria are related phenotypically to several other genera of bacteria such as *Pseudomonas* and Vibrios. Generally, a distinction can be made on the ability to ferment glucose; enteric bacteria all ferment glucose to acid end products while similar Gram-negative bacteria (e.g. pseudomonads) cannot ferment glucose. Because they are consistent members of the normal flora humans, and because of their medical importance, an extremely large number of enteric bacteria have been isolated and characterized.

Escherichia coli is, of course, the type species of the enterics. *E. coli* is such a regular inhabitant of the intestine of humans that it is used by public health authorities as an indicator of fecal pollution of drinking water supplies, swimming beaches, foods, etc. *E. coli* is the most studied of all organisms in biology because of its occurrence, and the ease and speed of growing the bacteriium in the laboratory. It has been used in hundreds of thousands of experiments in cell biology, physiology, and genetics, and was among the first cells for which the entire chromosomal DNA base sequence (genome) was determined. In spite of the knowledge gained about the molecular biology and physiology of *E. coli,* surprisingly little is known about its ecology, for example, why it consistently associates with humans, how it helps its host, how it harms its host, etc. A few strains of *E. coli* are pathogenic (one is now notorious, strain 0157:H7, that keeps turning up in raw hamburger headed for a fast-food restaurants). *Escherichia coli* causes intestinal tract infections (usually acute and uncomplicated, except in the very young) or uncomplicated urinary tract infections and neonatal meningitis.

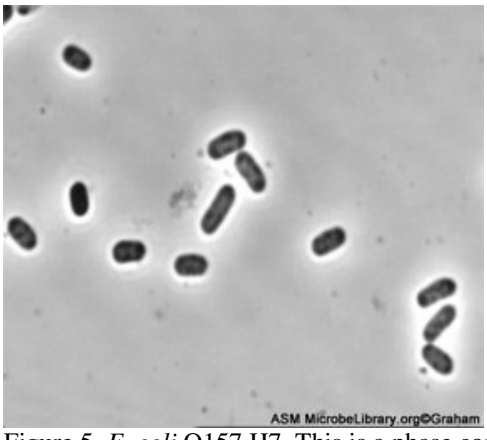

Figure 5. *E. coli* O157.H7. This is a phase contrast image of cells immobilized on an agar-coated slide.

The enteric group also includes some other intestinal pathogens of humans such as *Shigella dysenteriae,* cause of bacillary dysentery, and *Salmonella enteritidis,* cause of

food poisoning and gastroenteritis. *Salmonella typhi,* which infects via the intestinal route, causes typhoid fever. Some bacteria that don't have an intestinal habitat resemble *E. coli* in enough ways to warrant inclusion in the enteric group. This includes *Proteus,* a common saprophyte of decaying organic matter and *Yersinia pestis,* which causes bubonic plague. Also classified as an enteric is *Erwinia,* a pathogen of plants that causes fireblight in pear and apple trees and soft rot of carrots and potatoes.

Pyogenic Cocci

The pyogenic cocci are spherical bacteria that cause various suppurative (pus-producing) infections in animals. Included are the Gram-positive cocci *Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus pneumoniae,*and the Gram-negative cocci, *Neisseria gonorrhoeae* and *N. meningitidis.* In terms of their phylogeny, physiology and genetics, these genera of bacteria are unrelated to one another. They share a common ecology, however, as parasites of humans.

The Gram-positive cocci are the leading pathogens of humans. It is estimated that they produce at least a third of all the bacterial infections of humans, including strep throat, pneumonia, food poisoning, various skin diseases and severe types of septic shock. The Gram-negative cocci, notably the neisseriae, cause gonorrhea and meningicoccal meningitis.

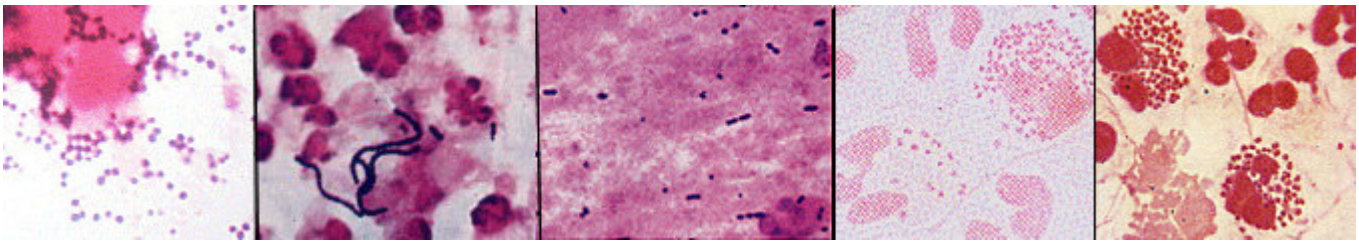

Figure 6. Gallery of pyogenic cocci, Gram stains of clinical specimens (pus), L to R: *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis.*The large cells with lobed nuclei are neutrophils. Pus is the outcome of the battle between phagocytes (neutrophils) and the invading cocci. As the bacteria are ingested and killed by the neutrophils, the neutrophils eventually lyse (rupture) and release their own components, plus the digested products of bacterial cells, which are the make-up of pus. As a defense against phagocytes the staphylococci and streptococci produce toxins that kill the neutrophils before they are able to ingest the bacteria. This contributes to the pus, and therefore these bacteria are "pyogenic" during their pathogenic invasions.

Two species of *Staphylococcus* live in association with humans: *Staphylococcus epidermidis* which lives normally on the skin and mucous membranes, and *Staphylococcus aureus* which may occur normally at various locales, but in particular on the nasal membranes (nares). *S. epidermidis* is rarely a pathogen and probably benefits its host by producing acids on the skin that retard the growth of dermatophytic fungi.

S. aureus always has the potential to cause disease and so is considered a pathogen. Different strains of *S. aureus* differ in the range of diseases they can cause, including boils and pimples, wound infections, pneumonia, osteomyelitis, septicemia, food intoxication, and toxic shock syndrome. *S. aureus* is the leading cause of nosocomial

(hospital-acquired) infections by Gram-positive bacteria. Also, it is notoriously resistant to penicillin and many other antibiotics. Recently, a strain of *S. aureus* has been reported that is resistant to all known antibiotics in clinical usage, which is a grim reminder that the clock is ticking on the lifetime of the usefulness of current antibiotics in treatment of infectious disease.

Staphylococcus aureus is a successful bacterial pathogen because it has a very wide range of virulence determinants (structural, biochemical or genetic features that allow the bacterium to cause disease), and it occurs as normal flora of humans (on skin, nasal membranes and the GI tract), which ensures that it is readily transmitted from one individual to another.

Streptococcus pyogenes, more specifically the beta-hemolytic group A streptococci, like *S. aureus*, causes an array of suppurative diseases and toxinoses (diseases due to the production of a bacterial toxin), in addition to some autoimmune or allergic diseases. *S. pyogenes* is occasionally found as normal flora in the upper respiratory tract(<15% of individuals), but it is the main streptococcal pathogen for man, most often causing tonsillitis or strep throat. Streptococci also invade the skin to cause localized infections and lesions, and produce toxins that cause scarlet fever and toxic shock. Sometimes, as a result of an acute streptococcal infection, anomalous immune responses are started that lead to diseases like rheumatic fever and glomerulonephritis, which are called post-streptococcal sequelae. Unlike the staphylococci, the streptococci have not developed widespread resistance to penicillin and the other beta lactam antibiotics, so that the beta lactams remain drugs of choice for the treatment of acute streptococcal infections.

Streptococcus pneumoniae is the most frequent cause of bacterial pneumonia in humans. It is also a frequent cause of otitis media (infection of the middle ear) and meningitis. The bacterium colonizes the nasopharynx and from there gains access to the lung or to the eustachian tube. If the bacteria descend into the lung they can impede engulfment by alveolar macrophages if they possess a capsule which somehow prevents the engulfment process. Thus, encapsulated strains are able to invade the lung and are virulent (cause disease) and noncapsulated strains, which are readily removed by phagocytes, are nonvirulent.

The *Neisseriae* cause gonorrhea and meningitis. *Neisseriaceae* is a family of Gram-negative bacteria with characteristics of enterics and pseudomonads. The neisseriae are small, Gram-negative cocci usually seen in pairs with flattened adjacent sides. Most neisseriae are normal flora or harmless commensals of mammals living on mucous membranes. In humans they are common residents of the throat and upper respiratory tract. Two species are primary pathogens of man, *Neisseria gonorrhoeae*and *Neisseria meningitidis.*

Neisseria gonorrhoeae is the second leading cause of sexually-transmitted disease in the U.S., causing over 300,000 cases of gonorrhea annually. Sometimes, in females, the disease may be unrecognized or asymptomatic such that an infected mother can give birth and unknowingly transmit the bacterium to the infant during its passage through the birth canal. The bacterium is able to colonize and infect the newborn eye resulting neonatal

ophthalmia, which may produce blindness. For this reason (as well as to control Chlamydia which may also be present), an antimicrobial agent is usually added to the newborn eye at the time of birth.

Neisseria meningitidis is an important cause of bacterial meningitis, an inflammation of the meninges of the brain and spinal cord. Other bacteria that cause meningitis include *Haemophilus influenzae,Staphylococcus aureus* and *Escherichia coli*. Meningococcal meningitis differs from other causes in that it is often responsible for epidemics of meningitis. It occurs most often in children aged 6 to 11 months, but it also occurs in older children and in adults. Meningococcal meningitis can be a rapidly fatal disease, and untreated meningitis has a mortality rate near 50 percent. However, early intervention with antibiotics is highly effective, and with treatment most individuals recover without permanent damage to the nervous system.

Endospore-forming bacteria

Endospore-forming bacteria produce a unique resting cell called an endospore. They are Gram-positive and usually rod-shaped, but there are exceptions. The two medically important genera are *Bacillus,* the members of which are aerobic spore formers in the soils, and *Clostridium,* whose species are anaerobic spore formers of soils, sediments and the intestinal tracts of animals.

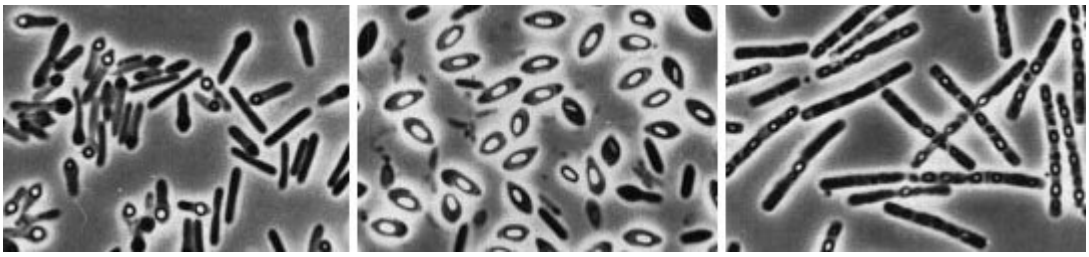

Figure 7. Endospore-forming bacilli (phase contrast illumination). Endospores are dehydrated, refractile cells appearing as points of bright light under phase microcsopy. Endospore-forming bacteria are characterized by the location (position) of the endospore in the mother cell (sporangium) before its release. The spore may be central, terminal or subterminal, and the sporangium may or may not be swollen to accomodate the spore.

Some sporeformers are pathogens of animals, usually due to the production of powerful toxins. *Bacillus anthracis* causes anthrax, a disease of domestic animals (cattle, sheep, etc.), which may be transmitted to humans. *Bacillus cereus* causes food poisoning. *Clostridium botulimum* causes botulism, a form of food poisoning, and *Clostridium tetani* is the agent of tetanus. *Clostridium perfringens* causes food poisoning, anaerobic wound infections and gas gangrene, and *Clostridium difficile* causes asevere form of colitis called pseudomembranous colitis. Whenever the spore-formers act as pathogens, it is not uncommon or surprising that their spores are somehow involved in transmission or survival of the organism between hosts.

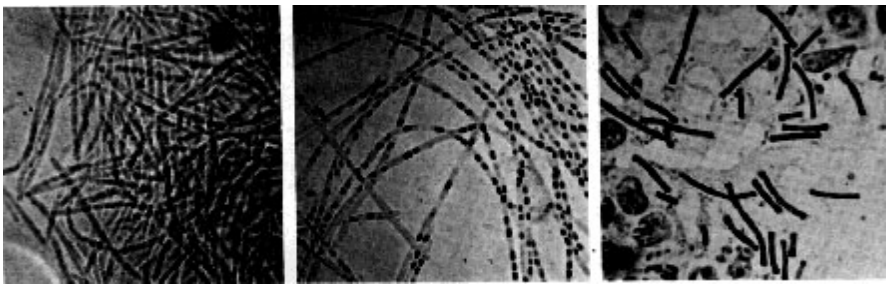

Figure 8. Robert Koch's original photomicrographs of *Bacillus anthracis*. In 1876, Koch established by careful microscopy that the bacterium was always present in the blood of animals that died of anthrax. He took a small amount of blood from such an animal and injected it into a healthy mouse, which subsequently became diseased and died. He took blood from that mouse and injected it into a another healthy mouse. After repeating this several times he was able to recover the original anthrax organism from the dead mouse, demonstrating for the first time that a specific bacterium is the cause of a specific disease. In so doing, he established Koch's Postulates, which still today supply the microbiological standard to demonstrate that a specific microbe is the cause of a specific disease.

Listeria monocytogenes is a Gram-positive rod-shaped bacterium related to bacillus and Clostridium but it does not form endospores. *Listeria monocytogenes* is the agentof listeriosis, a serious infection caused by eating food contaminated with the bacteria. Listeriosis has recently been recognized as an important public health problem in the United States. The disease affects primarily pregnant women, newborns, and adults with weakened immune systems.

Figure 9. *Listeria monocytogenes.* Transmission EM.

Actinomycetes and related bacteria

The actinomycetes are not thought of as pathogenic bacteria, but two of their relatives are among the most important pathogens of humans, these being the agents of tuberculosis and diphtheria. Actinomycetes are a large group of Gram-positive bacteria that usually grow by filament formation, or at least show a tendency towards branching and filament formation. Many of the organisms can form resting structures called spores, but they are not the same as endospores. Branched forms superficially resemble molds and are a striking example of convergent evolution of a procaryote and a eukaryote together in the soil habitat. Actinomycetes such as *Streptomyces* have a world-wide distribution in soils. They are important in aerobic decomposition of organic compounds and have an important role in biodegradation and the carbon cycle. Actinomycetes are the main producers of antibiotics in industrial settings, being the source of most tetracyclines, macrolides (e.g. erythromycin), and aminoglycosides (e.g. streptomycin, gentamicin, etc.).

Two genera of bacteria that are related to the actinomycetes, *Corynebacterium* and *Mycobacterium,* contain portant pathogens of humans: Otherwise, many nonpathogenic mycobacteria and corynebacteria live in normal associations with animals.

Mycobacterium tuberculosis is the etiologic agent of tuberculosis (TB) in humans. Tuberculosis is the leading cause of death in the world from a single infectious disease. *Mycobacterium tuberculosis* infects 1.7 billion people/year which is equal to 33% of the entire world population. The bacterium is responsible for over 3 million deaths/year. After a century of decline in the United States, tuberculosis is increasing, and multiple drug-resistant strains have emerged. This increase in cases is attributable to changes in the social structure in cities, the HIV epidemic, and patient failure to comply with treatment programs. A related organism, *Mycobacterium leprae,* causes leprosy.

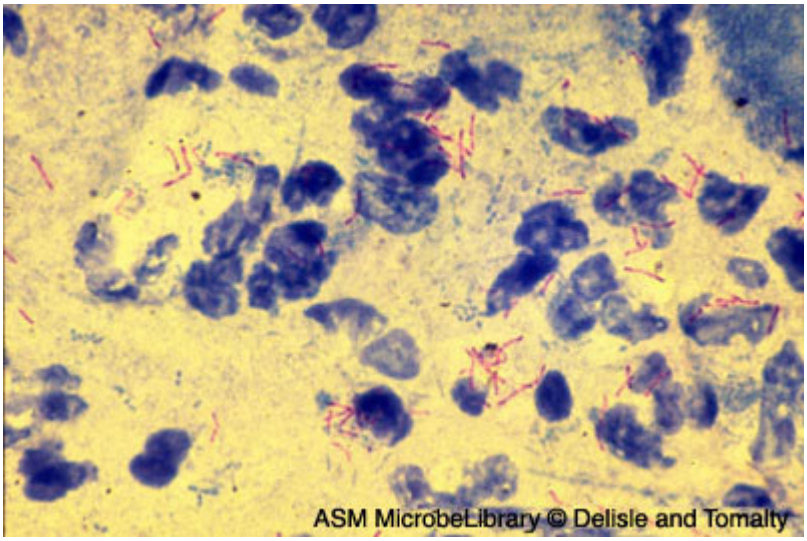

Figure 10. *Mycobacterium tuberculosis* Acid-fast stain. 1000X magnification

The genus *Corynebacterium* consists of a diverse group of bacteria including animal and plant pathogens, as well as saprophytes. Some *corynebacteria* are part of the normal flora of humans, finding a suitable niche in virtually every anatomic site. The best known and most widely studied species is *Corynbacterium diphtheriae,* the causal agent of diphtheria. The study of *Corynebacterium diphtheriae* traces closely the development of medical microbiology, immunology and molecular biology. Many contributions to these fields, as well as to our understanding of host-bacterial interactions, have been made studying diphtheria and the diphtheria toxin.

Rickettsias and chlamydiae are two unrelated groups of bacteria that are obligate intracellular parasites of eukaryotic cells. Rickettsias cannot grow outside of a host cell because they have leaky membranes and are unable to obtain nutrients in an extracellular habitat. Chlamydiae are unable to produce ATP in amounts required to sustain metabolism outside of a host cell and are, in a sense, energy-parasites.

Rickettsias occur in nature in the gut lining of arthropods (ticks, fleas, lice, etc.). They are transmitted to vertebrates by an arthropod bite and produce diseases such as typhus fever, Rocky Mountain Spotted Fever, Q fever and ehrlichiosis.

Chlamydiae are tiny bacteria that infect birds and mammals. They may colonize and infect tissues of the eye and urogenital tract in humans. *Chlamydia trachomatis* causes several important diseases in humans: chlamydia, the most prevalent sexually transmitted disease in the U.S., trachoma, a leading cause of blindness worldwide, and lymphogranuloma venereum.

Chlamydia pneumoniae is a cause of pneumonia and has been recently linked to atherosclerosis.

Figure 11. *Ehrlichia chaffeensis Ehrlichiae* obligate intracellular parasites related to the rickettsiae that are tick-borne pathogens of dogs and humans. In humans, they cause human granulocytic ehrlichiosis (HGE) and human monocytic ehrlichiosis (HME). In this electron micrograph, dense-core cells of *E. chaffeensis* are seen exiting the host cell following rupture of the cytoplasmic membrane. The Ehrlichiae will now go on to infect additional host cells or they may be ingested by a feeding tick, and spread to another animal.

Mycoplasmas are a group of bacteria that lack a cell wall. The cells are bounded by a single triple-layered membrane. They may be free-living in soil and sewage, parasitic inhabitants of the mouth and urinary tract of humans, or pathogens in animals and plants. In humans, *Mycoplasma pneumoniae* causes primary atypical pneumonia, also called walking pneumonia.