HEALTH EFFECTS OF
PROJECT SHAD
BIOLOGICAL AGENT:

PASTEURELLA
[FRANCISELLA]
TULARENSIS

[TULAREMIA]

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by
The Center for Research Information, Inc.
9300 Brookville Rd
Silver Spring, MD 20910
http://www.medresearchnow.com
(301) 346-6501
cri@ix.netcom.com

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Principal Investigator: Victor Miller

Text Draft & Editing: Victor Miller & Matthew Hogan
Project Manager: Matthew Hogan
Administration: Linda Roberts
SPECIAL NOTE ON PSYCHOGENIC SEQUELAE OF PERCEIVED EXPOSURE TO BIOCHEMICAL WARFARE AGENTS

This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates by reference and attachment a supplement "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may apply as well to simulants and tracers. Therefore a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
SPECIAL NOTE ON CITATIONS AND AUTHORITIES

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I. EXECUTIVE SUMMARY

*Pasteurella tularensis* is currently known as *Francisella tularensis*, which is the term employed throughout this report. Its newer name derives from the one developed by U.S. Public Health Service physician and scientist Edward Francis who pioneered the study of the microbe and its associated affliction, tularemia. Francis's work on infectious pathology would result in his nomination for a Nobel Prize, as well as his failure to follow through on that nomination process due to his hospitalization from the effects of another infectious agent he acquired from his dogged field and laboratory research. Ultimately considered a possible pathogen for Cold War-era biowarfare, *Pasteurella tularensis* was eventually renamed *Francisella tularensis* to give Francis his due, an effort initiated and pursued by admiring scientists from America's Cold War enemy, the Soviet Union.

*Francisella tularensis* is a Gram-negative small pleomorphic facultative intracellular coccobacillus. It is a zoonosis, most associated with tick bites or being in contact with infected animal carcasses or meats. Transmission of the pathogen to humans in an aerosol or dust form is also possible and is the likely method for bioterrorism or biowarfare use. Culturing a sample of *F. tularensis* can be dangerous (biosafety level 3 is the usual laboratory requirement), and so determination of the pathogen's presence is typically performed by serology. An agglutin titer greater than 1:160 is the standard determinant. Generally, however, those levels are not reached until close to the second week of infection. A skin test developed by the US Army (Active E-rosette test) has a high degree of specificity but also can yield a positive result over 3 decades after infection and illness by *Francisella tularensis*.

The incubation period of tularemia normally falls within a 3-6 day range but shorter and longer periods have been observed. When not asymptomatic, the infection usually presents as an acute febrile illness, along with some or all of the following generalized symptoms: chills, headaches, weight loss, emesis, diarrhea, muscle aches, joint pains, dry cough, hepatitis, and jaundice in serious cases. The fever is often biphasic, peaking twice in the first month of debilitation. In general, the full course of the illness is one month of fever, one month of complete weakness, and one and a half months of gradual but complete recovery.

More extended infections have been reported to have durations lasting for several months to a few years. Only one case exists in the literature, however, in which a person continued to manifest recurrences (fever and ulcerations) over a clearly observed period (by the National Institutes of Health) lasting over a decade, and with no complete recovery ever recorded. Another older report also exists of an acute and atypical case which involved a peripheral neuropathy in which the elderly patient could no longer dorsflex his foot, and this ability was not known to have subsequently returned.

No case has been found of a person who first manifested symptoms many months to years after initial infection. This is so despite the likelihood of a long-term persistence of some *Francisella tularensis* pathogens in previously diseased individuals. In light of this,
it is not surprising that tularemia is normally considered a strictly acute disease granting extraordinary immunity, if one survives it. In pre-antibiotic times, death rates of about 20% were reported, associated particularly with pre-existent health debilitations, delays in seeking treatment, and septicemia. In more recent times, this rate has been reduced to less than 4% through therapeutic intervention.

Locally and systemically, tularemia manifests acutely in several syndromes, often related to the manner of contact and inoculation. These syndromes are the ulceroglandular, the glandular, the oculoglandular, the pneumonic, the oropharyngeal, and the typhoidal. The rare typhoidal form is more deadly than the others, and also the most likely to result from aerosol contact. Respiratory involvement and lymphadenitis is very common in all varieties, however, though patients may not always present overt respiratory troubles. In the most common syndrome, the ulceroglandular (as well as the oculoglandular and glandular syndromes) local lymphadenopathies, skin eruptions and ulcerations, are the common manifestations of tularemia in addition to the generalized symptoms. The manifestations in those syndromes typically occur at the place of initial inoculation (e.g. the eye in the case of oculoglandular tularemia).

*F. tularensis* has an affinity for the skin, the lymph system, the lungs and, to a lesser extent, the liver. Differential diagnoses include "ulcer node" syndrome, rat-bite fever, cat-scratch disease, mycobacterial infection, chancroid, chancre, nocardiosis, sporotrichosis, cutaneous anthrax, inhalational anthrax, *Erysipelothrix*, pneumatic plague, influenza, mycoplasma pneumonia, staphylococcal streptococcal lymphadenitis, Legionnaire's disease, Q-fever, bacterial pneumonia, brucellosis, *Listeria*, syphilis, lymphogranuloma venereum, scrub typhus, and plague.

Reflecting tularemia’s protean manifestations, cases have been known to also present atypical signs and effects affecting involving systems beyond the more common ones described above. Some neuropathies (peripheral and central) are reported, and meningeal and meningoencephalitic involvements have occurred (especially among children). Pericarditis, typically among those with pre-existing cardiac-impairments, is an unusual but nevertheless well-known complication of tularemia. Cardiac complications tend to resolve with recovery from tularemia from infection. Recovery tends to be complete after the acute period of about 3.5 months but cases of greater duration are known.

Abdominal involvement is rare but liver and spleen enlargement, sometimes with systemic jaundice, does occur. Tularemic disorders of the gastrointestinal tract are relatively rare; enteritis and appendicitis are mentioned in the literature but not as significant effects. Psychogenic effects specific to *F. tularensis* exposure have not been reported. The general question of possible psychogenic effects arising from the awareness of exposure to chemical and biological warfare agents is contained in the supplement "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

Treatment for tularemia is usually the early administration of aminoglycoside antibiotics. Streptomycin and gentamicin are the common therapeutic agents. A vaccine (LVS – “live vaccine strain”) was developed at Ft. Detrick in the 1960s but it has proved only of
limited effectiveness, primarily against the typhoidal form of tularemia and a weaker strain of *F. tularensis*.

The secondary literature, including that of the Department of Defense, does not offer significant contradictions to each other or to the information in the literature on tularemia. They acknowledge that it is an acute disease with no significant demonstrated long-term or late developing effects, but nevertheless they note that it can be serious and life-threatening, especially if untreated.
II. GENERAL BACKGROUND

The discovery of the pathogen Pasteurella tularensis and its association with the conditions which would come to be known collectively as tularemia happened in the early part of the twentieth century in the United States. Nevertheless, the first systematic examination of the disease appears to have taken place in Japan when Homma Soken in 1837 noticed a form of “poisoning” that afflicted those who had eaten hare meat. (Evans) In 1925 in the same country, Dr. Hachiro Ohara identified the bacterium known there as Haga's coccus as the causative agent of tularemia after examining 3 patients who had died from the same presenting affliction. (Evans)

Several years earlier in the United States, in 1911, two researchers, McCoy and Chapin, had found the same organism in infected ground squirrels. They named it Bacterium tularense because of its prevalence in Tulare County, California. (Evans) In 1914 Wherry and Lamb identified the pathogen's presence in humans after studying meat cutters who had acquired it and who had manifested their infections as conjunctivitis and lymphadenopathy. (Evans) In 1919, Edward Francis, a US Public Health Service physician, identified the first fatal cases of human infection, after being summoned by the State Health Commissioner of Utah to investigate an outbreak of a mysterious condition which afflicted farmers during the harvest season, and was associated with deer fly bites. (Jellison)

In 1921, Francis named the disease tularaemia [sic], noting that bacteremia was associated with "deer fly fever" transmission and that the pathogen was originally cultured from blood. (Evans) In 1925, Japanese visitors to Francis' laboratory at the U.S. Public Health Service recognized in Francis' description the disease studied by Ohara. Subsequent contact and exchange of tissue and cultures between Francis and Ohara would in 1928 confirm Ohara's separate discovery. In 1924, Park and Spencer identified the role of ticks as a reservoir in nature for the bacterium. (Evans)

In 1928, Edward Francis' work resulted in the award of a gold medal from the American Medical Association and a nomination from the same body for a Nobel Prize in Medicine. It was felt later that Francis might have won the prestigious award had he not delayed responding to the Nobel Prize committee in Sweden. His delay was caused by his hospitalization with brucellosis, another infectious disease he was studying. (Jellison)

In World War II, the tularemia pathogen was aerosolized and considered for use as a biological weapon. In 1969, President Nixon ordered the termination of biological weapons development. In the early 1970s, the United States also signed the Biological Weapons Convention banning the development and use of biological weapons. (Dennis in Cohen)

By the mid-20th Century, the common taxonomic name for the tularemia pathogen had changed to Pasteurella tularensis. Nevertheless, a new and successful effort to change the name to Francisella tularensis was launched in 1959, as another way to honor the
Nobel-nominated Francis. Ironically, perhaps, the renaming was undertaken by three Soviet scientists whose work would be used in the study of *Francisella tularensis* as an enemy biological weapon in the Cold War. (Evans)

*Francisella tularensis* is now the standard name for the pathogen that causes tularemia. *Francisella tularensis* will therefore be generally used throughout this paper for *Pasteurella tularensis*, the more common name at the time of its use in Project SHAD testing.
III. MICROBE

General

Size: Small
Stain: Gram-negative
Shape: Pleomorphic coccobacillus
Variants: Jellison Type A (*Francisella tularensis var tularensis*); Jellison Type B (*Francisella tularensis var palaeartica*)
Infectious Route: Zoonosis

Abbreviations: *F. tularensis*, ZZ, TT (used in Project SHAD literature)

Alternate Names: *Pasteurella tularensis*, *Haga's coccus*, *Ohara-Haga's coccus*, *Bacterium tularense*

Sources for above: Dennis in Cohen, Evans, Rohrbach, Pitt, Bartlett, Jellison.

*Francisella tularensis* is a facultatively intracellular pathogen. Mononuclear cells can take it up without opsonizing antibody. (Pitt) It possesses a lipidated envelope. *Francisella tularensis* can be destroyed by 10 minutes of exposure to temperatures above 55-60 degrees C. Exposure to 10 to 50 aerosolized organisms can result in full infection. (Rohrbach)

*Francisella tularensis* is considered a Category A bioterrorism agent by the Centers for Disease Control and Prevention (CDC). This is the highest category, and includes *bacillus anthracis* (Anthrax), Variola virus (Smallpox), the Filoviruses (Ebola), and *Clostridium botulinum* (Botulism). The World Health Organization has theorized that an aerosol release of 50 kg *Francisella tularensis* over an urban area of 5 Millerion people would result in 250,000 cases of seriously debilitating illness, and 19,000 fatalities. (Artenstein, Bartlett)

Microbial Diagnosis

Microbial diagnosis is best done by culturing, but because there is a very high risk of infection among laboratory workers, serology is the preferred method of diagnosis. (Miller) If culturing is performed, it is usually done on cysteine heart agar or glucose cysteine agar with thiamine. Indications of *Francisella tularensis* may include Gram-negative coccobacilli stains on respiratory secretions. (Bartlett)

Note: Laboratories dealing with *Francisella tularensis* are expected to operate at biosafety level 3 for culturing and animal work, and at biosafety level 2 for routine activities. (Dennis in Cohen)
Serology

Standard methods can be used. An agglutin titer ≥ 1:160 is the presumptive diagnostic titer, although levels of 1:20 have been accepted. (Evans, Rodgers) The rise in titer to 1:160 levels tend not to occur before the 11th day of the infection (but usually before the 16th.) (Miller) Testing is directed at agglutination reaction for combined IgM and IgG immunoglobulins. (Dennis in Cohen)

Cross - Reactivity

Cross-reactivity exists with brucellosis. Brucellosis may show a rise in tularemia titers. Tularemia infection or vaccine exposure can also stimulate brucellosis pathogen antibodies. (Evans, Rodgers)
IV. TULAREMIA EPIDEMIOLOGY

The name tularemia has been applied to all manifestations of infection by the *Francisella tularensis* bacterium. Therefore the term tularemia is used herein to describe any infectious health effect of *Francisella tularensis*.

**Alternate Names**

Alternate names for tularemia have included: Tularaemia [sic], Phavant Valley Plague, Deer Fly Fever, Hare Meat Poisoning, Rabbit Fever, Ohara's Disease (Japan). (Evans, Jellison)

**Disease Distribution**

The spread of the pathogen may be underreported and understudied as many infections of humans with *Francisella tularensis* appear to be asymptomatic. In one study, 41% of rabbit handlers were found to have been exposed to *Francisella tularensis* without significant symptoms. As high as 32% of the population in rural areas of Sweden have been found to have antibodies for tularemia without symptoms. (Evans)

Outbreaks and residual appearances of tularemia have been reported over the past century in Scandinavia, the countries of the former Soviet Union, Spain, Mexico, and Kosovo, among others. Generally, however, the disease is confined to the Northern Hemisphere, with practically no reporting of tularemia in South America, Australia, and sub-Saharan Africa. (Dennis in Cohen, Evans)

Since 1940, the rates of infection have been declining in the Northern Hemisphere. The general use of antibiotics is almost certainly the cause of their decline. Nonetheless, in the United States, tularemia has been reported in every state except Hawaii. (Evans, Rodgers)
V. PATHOGENESIS/INCUBATION

Transmission to Humans

Human-to-human transmission is not demonstrated in the literature. (Bartlett)

In general, humans have been exposed to Francisella tularensis from tick or other arthropod (e.g. deer fly) bites, handling rabbit, rodent, and other infected animal carcasses, contact with contaminated water, mud, birds, vole feces, and inhalation. Ticks are a major reservoir of Francisella tularensis in nature. (Bartlett, Ev, J)

Francisella tularensis in dust has been found to have caused a tularemia outbreak; aerosolized F. tularensis is the likely means of a biowarfare or bioterrorist delivery. (CDC)

Skin abrasions/lacerations are believed to be responsible for transmission of Francisella tularensis into the body where exposure to the pathogen is dermal but nevertheless not from a percutaneous invasion (e.g. arthropod bite). There is some evidence, however, suggesting that surface contact may be sufficient. (There have been penile lesions from contact with infected fingers, as well as "kissing lesions" where two fingers touch.) Contact with the mucous membranes of the eye, respiratory tract, or oropharynx are believed to permit the pathogen into the body. (Evans, Miller)

At-risk groups for infection have typically included the immunosuppressed, laboratory workers (accidental exposure during culturing), hunters, farmers, and meat cutters. (Bartlett, Evans, Dennis in Cohen)

Incubation

Incubation typically occurs in 3-5 days after Francisella tularensis exposure. (CDC, Bartlett) Shorter periods manifesting as an unusual sudden septic shock-like presentation are known, as well as longer periods of up to 10 days. (Evans, Pitt) Rare cases of less than one day's appearance of symptoms in less than one day after first exposure have been shown. (Foshay 1940)
VI. GENERAL COURSE & EFFECTS

When symptomatic, the typical manifestation of tularemia is a rapid onset of a fever which can run as high as 104 degrees Fahrenheit. (CDC, Bartlett) Francis discovered in the 1920s that the fever was commonly phasic. The fever would rise for 1-3 days, followed by a remission. Then body temperature would begin a second rise over 1-3 days, peak, and then last for 2-3 weeks until its return to normal. (Jellison)

Common general symptoms in addition to fever are chills, headaches, weight loss, emesis, diarrhea, muscle aches, joint pains, dry cough, hepatitis, and, in more serious cases, jaundice. (Dienst, CDC, Bartlett, Evans) Hepatomegaly and splenomegaly are occasional manifestations of a general infection. (Dienst) Erythema nodosum also occurs occasionally. (Evans, Penn, Dienst)

In non-fatal cases, the course of the disease is usually about 3.5 months. In the first month, the person manifests general symptoms along with various acute syndromes (see next section). After the first month, the victim would be continuously debilitated to the point of inability to work for another month. In the third month and after, the victim would normally function at half-strength, an employed individual might work half a normal work shift for that entire month. Recovery would follow, though some sequelae have known to linger for varying additional periods. (Dennis in Gorbach)

Francisella tularensis exhibits a general tendency upon infection to attack the lung, lymph nodes, liver, and skin. (Raphael, Dennis in Cohen) Its place of entry will affect the particular sets of manifestations. Bacteremic spread, secondary sepsis, and tularemic pneumonia also represent a common course. (Penn) The protean syndromic manifestations of Francisella tularensis are treated in the next section.

Biologic Effects

Hemoglobin and platelet levels tend to remain normal during tularemic infection. Fibrinogen levels tend to rise. Microcytic hypochronic anemia and an altered sedimentation rate are commonly observed. (Dienst)

Microscopic pyuria was seen in about 22% of those afflicted, in one study. At least one serum enzyme becomes elevated – typically LDH, ALT, AST, and/or bilirubin. (Evans, Penn) Cerebrospinal fluid (CSF) tends to remain normal. One study, however, found a modest increase in CSF protein in about 20% of the afflicted, along with a few cases of low CSF glucose, with a general increase in the number of CSF cells. (Evans)

Granulocytes cannot kill Francisella tularensis without opsonizing antibody because of the capsule of the organism. Therefore polymorphonuclear leukocytes play only a small role in body defense. Macrophages and lymphocytes play the more important role in host protection in the case of tularemia. Therefore, it usually takes about two weeks for T-lymphocytes to become activated and develop a sensitivity specific to Francisella.
*Francisella tularensis*. (Evans) (Hence the difficulty of early diagnosis through serology.) The ratio of *Francisella tularensis*-sensitive macrophages to infectious organisms decides the outcome of the challenge to the host.

**General Diagnosis**

Culture, typically from blood, or serology are the definitive means of confirming a diagnosis of tularemia. Section III, above, details the parameters of the culture and serologic methodology.

Evans notes the existence of a non-commercially available tularemia skin test (Active E-rosette test) with a specificity of over 98%. The disadvantage in a clinical setting is that it can continue to yield a positive result decades after the original infection and disease resolution. (While that is a disadvantage in terms of clinical diagnostic evidence, it may be advantageous for a retrospective investigation on exposures.) (Evans)

**Differential Diagnoses**

The diverse involvements, signs, symptoms, and complications of tularemia yield a broad set of differential diagnoses. These include "ulcer node" syndrome, rat-bite fever, cat-scratch disease, mycobacterial infection, chancroid, chancre, nocardiesis, sporotrichosis, cutaneous anthrax, inhalational anthrax, *Erysipelothris*, pneumatic plague, influenza, mycplasma pneumonia, staphylococcal/streptococcal lymphadenitis, Legionnaire's disease, Q-fever, bacterial pneumonia, brucellosis, *Listeria*, syphilis, lymphogranuloma venereum, scrub typhus, mumps, viral pharyngitis, and plague. (Artenstein, Dennis in Cohen, Miller)

**Mortality**

Over the past few decades, the mortality rate from tularemia has been reduced greatly, due to the development and availability of antibiotics. Figures for post-antibiotic era tularemia mortality tend to lie between 1 to 4% of those afflicted. In earlier days, mortality ran as high as 18.8%. (Dienst) Mortality has tended to happen in the third week of infection. (Foshay 1936)

Mortality from tularemia has been associated particularly with septicemia or the preexistence of underlying debilitating medical conditions, especially cardiac lesions. Delay or failure in seeking treatment has been another factor. (Dienst, Foshay 1936)

Peripheral vascular collapse, hyperglycemia, hypoglycemia, acidosis, oliguria, and uremia (lower nephron lesion) are common complications found to be associated with mortality in tularemia. Jaundiced sclera, a non-protein nitrogen level averaging 152.2 and creatinine levels averaging 7.2 are other complications associated with mortality. (Dienst)
Additional mortality-associated findings in necropsy are minute military seeding of the lung and gross areas of consolidation or abscess formation. Focal necrotic lesions (but not in brain or meninges), areas of necrosis in liver, spleen, and upper abdominal lymph node involvement have been found in the tissue of patients who have had fatal infection. (Dienst)

Cases of tularemia with pneumonia as a manifestation are associated with greater chances of mortality, especially if the pneumonia manifests with large areas of consolidation and neurobehavioral challenges like delirium and confusion. The growth of antibiotic therapy has unquestionably helped reduce the mortality and severity of the disease. (Dienst)

**General Prognoses/Outcome**

In the absence of death, tularemia is generally said to resolve after about 3 months, leaving behind a powerful immunity. Respiratory collapse and shock are noted possible severe debilitations. (Dennis 2001)

The important questions of the existence and nature of lingering effects or chronic sequelae remains ill-studied, and ill-defined. Because of the relevance of long-term health effects for this health effects series, this issue will be addressed in greater detail in section VIII below, on chronic effects.
VII. MAJOR ACUTE SYNDROMES

Tularemia comes in several forms of clinical presentation. In the past, only two forms were typically described: ulceroglandular and typhoidal. Today, it is more common to describe several syndromes: typhoidal (septic), pneumonic (inhalation), oropharyngeal, ulceroglandular, glandular, and oculoglandular.

Although the most common syndrome is ulceroglandular tularemia this discussion begins with the forms most likely to result from contact with aerosolized *Francisella tularensis*. The following subsections describe the symptoms that occur in addition to the generalized symptoms of tularemia. A discussion of atypical manifestations is included.

**Typhoidal (Septic) Tularemia**

This form of tularemia presents overtly with only generalized symptoms. This form nevertheless produces a disproportionate share of tularemia-induced mortality. Because of the rarity of overt local effects, typhoidal tularemia is also difficult to diagnose quickly. (Dennis in Cohen)

Persons who manifest this syndrome are three times more likely than other tularemia patients to manifest pneumonia (pneumonic tularemia) as a secondary complication. Pharyngitis can occur as a secondary complication as well. In the general population, typhoidal tularemia usually represents less than 5% of cases of tularemia, but it is more likely to be associated with aerosol delivery. (Dennis in Cohen) Nonetheless, Evans found an incidence of 25% in his 1985 study of 88 cases from Nashville, Tennessee. (Evans)

Associated effects include prominent abdominal pain, vomiting, and diarrhea in the early stages of illness. The systemic inflammatory response syndrome can occur. Sepsis is possible too. (Evans, Dennis in Gorbach, Dienst) Other possible complications are disseminated intravascular coagulation and bleeding, acute respiratory distress syndrome, shock, and organ failure. Kidney and meningeal infection may also occur. (Dennis in Gorbach, Dienst)

**Pneumonic (Inhalation) Tularemia**

Direct inhalation of an infected aerosol or dust can also give rise to pneumonic tularemia. Primary pneumonic form appears to occur in less than 5% of cases. Pneumonic tularemia mostly arises as a secondary complication of other forms of tularemia, as the pathogen spreads hematogenously. (Dennis in Cohen)

Whether primary or secondary, pneumonia in tularemia is common, and there has been some evidence that lung involvement occurs even in cases where no overt clinical pulmonary signs (i.e. patient complaints) are present. In one study, 30% of tularemia
victims with abnormal X-rays presented with no other respiratory signs or symptoms. (Evans)
Cough (with minimal production), chest discomfort with occasional pleuritic pain, dyspnea, tachypnea, mild hemoptysis are commonly observed. (Evans) Moist rales, vocal fremitus, dullness, and bronchial breathing have been noted with tularemic pneumonia. (Dienst) Shortness of breath, productive sputum, and hemoptysis have been noted in a minority of cases of pneumonic tularemia.

All areas of the lung can be affected in pneumonic tularemia, although infiltrates in most cases tend to concentrate in one lobe. Pleural effusion has been found to be associated with contiguous pneumonia in about one third of cases with tularemic pneumonia. (Evans)

Ovoid pulmonary infiltrate and hilar adenopathy are usually found on X-ray examination. (Evans)

**Oropharyngeal Tularemia**

In the general population, this form accounts for less than 5% of tularemia cases, but among pediatric patients it occurs in about 23% of cases of tularemia. (Dennis in Gorbach) Aerosol exposure is a possible route for this syndrome although ingesting contaminated food (e.g. ill-cooked meat) or fluids.

Sore throat, painful swollen anterior and posterior neck lymph nodes, exudative tonsillitis or pharyngitis, occasionally ulcerated stomatitis are noted effects. (Dennis, Evans) Drainage of the nodes may also occur, along with fistula formation and suppuration. (Evans)

**Ulceroglandular Tularemia**

This is the most common form of tularemia. Typically it comes from dermal penetration through a tick bite or the handling of contaminated matter. The femoral-inguinal, axillary, and cervical areas tend to be the most common sites of inoculation. (Dennis in Cohen)

The illness starts with a papule at the inoculation site soon after the inoculation event. The lesion becomes pustular usually about the time generalized symptoms begin. Then, it becomes a crustal erythematous one, and finally a dirty shallow ulcer with a gray necrotic base which can spread to up to 2 cm in diameter. (Dienst)

A secondary regional painful lymphadenopathy in the adjacent nodes of the afferent pathway follows as the ulceration develops. These nodes can suppurate, which then may form a sinus tract which will discharge purulent material. (Dennis in Cohen)

Of those afflicted with this form, 31% in one study also manifested pneumonia. (Evans)
Glandular Tularemia

Glandular tularemia is essentially the same as the ulceroglandular form just described but without external ulceration. There also tends to be a somewhat lower frequency of fever. The lower fever frequency and the lack of external ulceration may delay a patient from seeking timely treatment.

Oculoglandular Tularemia (Parinaud's Syndrome)

This is sometimes referred to as ulceroglandular tulermia with eye involvement. (Evans, Dennis in Cohen) The conjunctival sac becomes infected resulting in a painful conjunctivitis with edematous inflamed eyelids. Ulceration may follow on the palpebral conjunctivae, accompanied by small yellowish nodules. The lymph nodes most likely to become affected are the preauricular, submandibular, and cervical chain nodes.

Less than 5% of tularemia cases tend to be of this type. (Dennis in Cohen)

Atypical & Suspected Effects

This section provides examples of far less common signs, symptoms, and complications of tularemia infection reported or suspected.

Meningitis/Meningoencephalitis

Meningitis is said to be present in less than 4% of all reported cases. (Rodgers) Stiff neck, severe headache, elevated white blood cell and protein levels in the cerebrospinal fluid are commonly observed. (Rodgers)

A four-year-old girl manifested malaise, irritability, lethargy, and later projectile emesis. Her physical symptoms were a painful postauricular swelling, an erythematous scalp papule, a painful postauricular lymph node, mental status changes, and finally pneumonia. Her cerebrospinal fluid white blood cell count was 1135/mm³ and protein went to 369 mg/dl. The effects went away after antibiotic treatment with no reported sequelae. (Rodgers)

In one case with encephalitic involvement, the patient manifested hallucinations, hyperkinesias, positive Babinski reflex, and dilated pupils. (Dienst) Encephalitis has been reported rarely. (Raphael)

Other CNS/Neurological Effects

In an unusual case a tularemic shunt infection in a child resulted in irritability and lethargy with enlargement of the lateral ventricles. There was transient bacteremia but this case was unique in that only the central nervous system was involved. (Pitt)
A peripheral neuritis was seen in an older man. He manifested paresis in his right lower extremities with both sensory and motor impairment. He was unable to dorsflex his right foot. His right hand had paresthesia; he could not feel a pin prick. (The inability to flex his right foot never recovered, a rare reported permanent debilitation.) (Raphael)

Following septicemia, a neuropathy was reported in one person that involved delirium, stupor, and restlessness. It was speculated that the symptoms may have been of lymphocytic meningitis. (Raphael)

Acute Cardiac Complications

Pericarditis is the most common cardiac tularemic syndrome reported, though still very rare (less than 5% of all tularemia cases in one study). (Evans) Pericardial friction rub has been reported manifested typically by characteristic electrocardiographic abnormalities (ST-, T-wave changes), and enlarged cardiac shadow in chest radiograph. Patients typically recovered fully after antibiotic therapy. (Evans) (A reported chronic case, however, is discussed in the next section.)

There is little evidence of endocarditis or significant myocarditis but Dennis reports them as occasional unusual manifestations (but without direct references to sources). (Dennis in Cohen, Dennis in Gorbach)

Abdominal/Gastrointestinal

Abdominal involvement aside from occasional spleen or liver enlargement is rare. Enteritis, peritonitis with ascites, and appendicitis were not found by Evans though they were reported by Foshay. (Evans) Dennis reports enteritis, appendicitis, mesenteric adenitis, and ascites as rare manifestations resulting from uncooked game consumption. (Dennis in Gorbach)
VIII. CHRONIC EFFECTS

Most literature today tends to treat tularemia as strictly an acute condition. (\(^\)\) The issue of long-term effects, other than mortality, tends to be passingly addressed in the literature. This may reflect the fact that it appears that only one case of carefully documented permanent chronic tularemia debilitation can be found in the literature.

Nevertheless, signs of persistence in the body of *Francisella tularensis*, including cases of extended duration or relapse of tularemia, and problems with subsequent immunity, do exist though they are very rare in the literature. Older literature speaks only passingly and without clarity of the possibility of "chronic tularemia" or a "chronic progressive form" (Foshay 1936), or of "chronic disability" (Dienst).

**Persistence/Relapse/Recrudescence**

Serology tests for *Francisella tularensis* can continue to show elevation for several years, with a mean of 5 years. One case showed >1:20 elevation 40 years after the acute infection. (Evans) No recurrent illness was reported, however. This suggests chronic *Francisella tularensis* persistence, as also may the Active E-rosette test reported by Evans which yields a positive result decades after initial infection. (Evans) "Prolonged survival [of F. tularensis] in human tissues" was concluded by Foshay, noting "permanent residual living bacteria held in certain tissues. . . ." (Foshay 1940)

Cases of symptoms lasting "several months" to "one year" were observed in the pre-antibiotic era. A severe fever manifesting again 21 months after the onset of the original acute disease is reported; a patient who experienced recurrent bouts of fever and nodal enlargements in the arms, forearms, and axillary regions is recorded. (Foshay 1940)

Foshay also reported a case studied intently by the National Institutes of Health in which a female patient who had had 6 weeks of acute illness in 1927 saw at least 4 abscesses on her legs and finger return in an unspecified later period. After that, over a period of 5 ½ years, symptoms of fever, malaise, sweats, adenopathies, weakness, and mental depression would recur. For the remaining 8 years in which she was studied, recurrent episodes of this type were noted. (Foshay 1940)

In the above section VIII under “Atypical & Suspected Manifestations,” there is a reference to the man who experienced peripheral polyneuritis in which his ability to dorsflex his right foot ceased. This condition was reported to have never healed.

One other case which is described as "chronic constrictive pericarditis" resulting from tularemia is reported. This single case study, from 1943, only follows the patient over a period of about 5 months and reports no follow-up. (Jager)

Searches found no cases or studies specifically finding a delayed onset of symptoms, i.e. symptoms first manifesting months or years after initial infection.
Cases of Limited Immunity/Reinfection

A study at Ft. Detrick, Maryland in the 1960s demonstrated reinfection among humans who had suffered from tularemia in the past or had been inoculated with a “live vaccine strain” vaccine. (Green) Typically, however, these cases were of laboratory workers who were exposed to extremely high concentrations of the pathogen. Nevertheless, Francis had also noted that reinfection (i.e new infection from new exposure) was seen in some cases ranging from 2.5 to 15.5 years after first infection. (Green)

Nevertheless it appears that the immunity to tularemia among those exposed is very high and nearly universal. Foshay declared the immunity conferred by *Francisella tularensis* to be an "extraordinary" level for an infectious pathogen. (Foshay 1940)
IX. PSYCHOGENIC EFFECTS

No psychogenic effects specific to *Francisella tularensis* as an infectious agent are reported. The health effects of perceived exposure to biological warfare agents appear in the supplement "Health Effects of Perceived Exposure to Biochemical Warfare Agents" which has been submitted as part of this contract and is incorporated by reference.
X. TREATMENT/PREVENTION

Aminoglycosides are the standard treatment for tularemia. Streptomycin was the original preferred treatment, with gentamycin as an alternative. (Bartlett) Other aminoglycosides are untested.

Treatment is usually successful in alleviating symptoms within 3 days, and within 1 week in cases involving pneumonia. (Evans)

Bacteriostatic agents, e.g. chloamphenicol, tetracycline, are considered of little use because relapse is likely on withdrawal, but chloramphenicol and ciprofloxacin have been recommended as supplemental therapy. (Evans, Dennis 2001)

Standard administration is streptomycin 15-20 mg/kg/day in divided doses over 7-10 days. (Bartlett) In the relatively rare instances of relapse after therapy, a 14 day repeat of the course should suffice. (Miller) One study recommends floroquinolones as a first line defense. 10 strains of Francisella tularensis were significantly affected by ciprofloxacin, norflaxcin, and ofloxacin.

Nevertheless, therapeutic failure has been known. It is usually associated with severe infection, an associated chronic illness, and a delay in initiation of antibiotic therapy. (Bartlett)

Prophylactic use of doxycycline or ciprofloxacin may be useful in the early postexposure period. (Dennis 2001)

For prevention, a live vaccine strain (LVS) vaccination was produced in Ft. Detrick for civilian employees in 1961. It proved effective against the typhoidal form but was not especially effective in preventing ulceroglandular infection. The LVS vaccine has been shown to be more effective against the less virulent type B form of Francisella tularensis. (Chen)
XI. SECONDARY SOURCE INFORMATION

Secondary sources do not seem to vary in their treatment of *F. tularensis* health effects.

The brief summary in the "Disclosure of Information on Project 112" by the Department of Defense, available online as of March 25, 2004, appears to agree with the general thrust of the literature on *Francisella tularensis*.

. . . . [This] bacterial species can cause acute infection of the lung, bloodstream, and other body sites (tularemia), and is considered a potential biological warfare agent. While complications of the acute infection may be serious, even life threatening, long-term or late-developing health effects would be very unlikely.


Interestingly, the 1996 edition of *Ocular Infection & Immunity* by Pepose et al. (Mosby: St. Louis) does not mention tularemia or its pathogen despite the existence of oculoglandular tularemia.
XII. BIBLIOGRAPHY WITH ABSTRACTS


Brucellosis is a world-wide re-emerging zoonosis and the most frequent laboratory-acquired bacterial infection, causing severe disease in humans with unspecific clinical signs affecting numerous organs. Contact with infected animals, ingestion of contaminated animal products and handling of Brucella isolates in laboratories are risk factors. Various other febrile illnesses, e.g. malaria, tuberculosis, typhoid fever and tularemia may present with the same symptoms. Therefore, clinical diagnosis is difficult to establish but effective therapy requires an early diagnosis. Vaccines for humans are still not commercially available. Blood culturing of Brucella is time-consuming and not reliable. Thus diagnosis is usually based on indirect serological tests, i.e. serum agglutination test, complement fixation or the Coombs test. However, these 'conventional' serological tests lack sensitivity and specificity. Hence, a combination of various tests is mandatory for a definite diagnosis. Enzyme-linked immunosorbent assays can be used for screening and confirmation of brucellosis in one step. Molecular techniques like the polymerase chain reaction and restriction fragment length polymorphism are needed to differentiate species and strains within the genus Brucella. This review will summarize advantages and disadvantages of the techniques used in clinical laboratories for direct detection and identification of Brucella spp.


In this monograph are analysed the principal infections transmitted by ticks and particularly those interesting Europe and North America. Besides the main species of these arthropods are described in consideration of their characteristics and geographic diffusion. In particular the infections caused by Borrelia genus and tick born encephalitis virus are treated more exhaustively in consideration of their potential severity and because the diagnosis of these infections is sometimes difficult. However also the main rickettsial infections transmitted by ticks are reported together the hemorrhagic fevers transmitted by such arthropods. In particular it is exhaustively analysed the
Mediterranean tick fever in consideration of its presence in some regions of Italy and of the wrong opinion of considering this pathology not very severe. Lastly has been included a treatment about some emergent infections transmitted by ticks, like as the ehrlichiosis and babesiasis, but also the mention of tularaemia that can be considered a re-emergent infection, also in consideration of the epidemic focus now present in Kossovo. The above-mentioned pathologies are analysed also as regards the laboratory diagnosis (direct and serologic methods), the therapeutic treatment and the prophilaxis, both directed against the arthropods vectors and that of individual type, employing also some vaccines, when disposable.

Tularemia as a potential biological weapon is of great concern because F. tularensis is a hardy organism that can be spread with a small inoculum. In addition, tularemia can be contracted through nature, predominately in rural areas. This disease can be spread by a wide variety of animals and can range from skin lesions to multi-organ involvement. The severity varies with amount of inocula, the virulence of the bacterium, and the port of entry. Exposure to aerosolized forms of F. tularensis, the major concern with bioterrorism, can rapidly lead to respiratory failure and death. Untreated, other forms of tularemia can spread through the blood stream to other organs, leading to sepsis and death. Early recognition and treatment is tantamount to treatment and prevention of morbidity and mortality. Occupational health nurses are on the front line and must be assertive in identifying risk factors associated with exposure. Furthermore, education of the general population about exposure through nature can potentially decrease the incidence of tularemia. Occupational health nurses, as one of the largest health specialties in the workplace, may be the first contact for the exposed individual. Tularemia is treatable with knowledge of prevention, astute assessment, prompt identification, and treatment. Combined, they are powerful nursing tools in achieving optimal outcomes.

Ready your nursing staff for potential bioterrorism with this review of the symptoms and treatment of anthrax, smallpox, plague, tularemia, and botulism.


In this report, we describe a 57-year-old woman with oropharyngeal tularemia who presented with tonsillopharyngitis and cervical lymphadenitis. Clinical and radiological manifestations and histopathological characteristics of this disease are discussed with a review of the world literature. The oropharyngeal form of tularemia should be considered in the differential diagnosis of cases involving tonsillopharyngitis and cervical lymphadenitis, particularly in those not responding to penicillin treatment.

**Artenstein. 2004.** Bioterrorism and Biodefense. in Cohen ed. *Infectious Diseases.*


The fears and predictions of attacks with biological weapons, which were increasing at the close of the twentieth century, were transformed into reality not long after September 11, 2001, when several anthrax-laden letters were sent through the U.S. postal system. The attack challenged our medical preparedness and scientific understanding of the epidemiology of biothreat agents. It is fortunate that this was not a massive aerosol release that could have exposed hundreds of thousands. Rapid diagnoses and medical treatments limited casualties and increased survival rates, but tragically some individuals died of inhalational anthrax. Even as physicians tested new treatment regimes and scientists employed new ways of detecting anthrax and decontaminating the mail, new predictions were made for potentially even more devastating attacks with anthrax, smallpox, plague, tularemia, botulism, or hemorrhagic fever viruses. Fear gripped the nation. Law enforcement sought to find the villain(s) who sent the anthrax letters and to deter future bioterrorist attacks. The biomedical community began to seek new ways of protecting against such future threats of bioterrorism.


The protection of patients from diseases carried in blood transfusions remains an ongoing
effort. The viruses that cause long-term human infection and death have received much attention in the United States and testing has significantly diminished the risk of infection from a transfusion. As the risk of these diseases has decreased, other transfusion-transmitted organisms with a lower incidence in the community or newer diseases with rapidly expanding endemic areas are receiving additional attention. One group of these infections includes infections in which the normal route of human infection is a vector.


This review describes the scope, complexity, and magnitude of host nutritional responses throughout the course of an infectious process. These responses include prominent changes in nitrogen and protein metabolism, altered rates of carbohydrate and lipid production and utilization, and changes in mineral, electrolyte, trace element, and vitamin metabolism. It is postulated that these responses develop in a relatively predictable sequence that is influenced by the adequacy of host antimicrobial defense mechanisms, the severity and duration of illness, and specific localization of an infectious process within the body. In addition to hormonal regulatory effects, the host’s metabolic and nutritional responses are also influenced by biologically active substances released when host cells participate in phagocytic activity and local inflammatory responses.


Inasmuch as terrestrial fauna are an integral part of our natural environment and are directly exposed to disease and pollutants, it follows that certain wild populations could serve to detect subtle alterations within ecosystems. A collection of studies on raccoons is presented to stimulate other researchers to develop the potential of our wildlife resources as monitors of environmental health. Raccoons have been used as serologic sentinels for St. Louis encephalitis and Venezuelan equine encephalomyelitis. Studies suggest that the raccoon may be used as an indicator of leptospirosis, tularemia, and some enteric bacteria and viruses. Baseline surveys have defined (1) residue levels of organochlorine and
organophosphate compounds and (2) body burdens of mercury, cesium-137, and strontium-90. Physiologic responses, parasite burdens, and reproductive processes are also considered as measures that may reflect pertinent information about environmental health.

The recent anthrax attacks in the United States have demonstrated the reality of bioterrorist threats, as well as the need for preparedness and planning to mount a successful response to such events. Medical practitioners have a key role in responding to bioterrorist activity, because they can contribute to the timely recognition of an event and to the mitigation of morbidity resulting from a bioterrorist attack. The medical community needs to become familiar with how to recognize and manage diseases produced by the biologic agents that might be used by terrorists. This review summarizes the microbiological and clinical aspects of the agents of anthrax, smallpox, plague, and tularemia, which are all considered likely bioterrorist weapons.

With the development and licensure of a recombinant vaccine for the tick-borne infection Lyme disease, more attention has been paid to other vaccines that have been used or are being developed for the prevention of other tick-borne infections. This review highlights vaccine information for Lyme borreliosis, tick-borne encephalitis (TBE), Rocky Mountain spotted fever, tularemia, Query (Q) fever, Kyasanur Forest disease (KFD) and tick paralysis. Additionally, discussion on the use of immunization against the tick itself is included that not only can decrease veterinary tick burdens, but may also decrease the transmission of arthropod-transmitted diseases.

The potential use of biological agents such as viruses, bacteria or bacterial toxins as weapons of mass destruction (WMD) has fuelled significant national and international research and development in novel prophylactic or therapeutic countermeasures. Such measures need to be fast-acting and broadly specific, a hallmark of target-specific polyclonal antibodies (pAbs). As reviewed here, pathogen-specific antibodies in the form of human or animal serum have long been recognized as effective therapies in a number of infectious diseases. This review focuses in particular on the potential biowarfare agents prioritized by the National Institute of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention (CDC), referred to as the category A
organisms. Furthermore, it is propose that the last decade of development in recombinant antibody technologies offers the possibility for developing highly specific human monoclonal or polyclonal pathogen-specific antibodies. In particular, pathogen-specific polyclonal human antibodies offer certain advantages over existing hyperimmune serum products, monoclonal antibodies, small molecule drugs and vaccines. Here, the rationale for designing pAb-based therapeutics against the CDC category A microbial agents causing anthrax, botulism, plague, smallpox, tularaemia and viral haemorrhagic fevers, as well as the overall design of such therapeutics, are discussed.


The use of microorganisms as agents of biological warfare is considered inevitable for several reasons, including ease of production and dispersion, delayed onset, ability to cause high rates of morbidity and mortality, and difficulty in diagnosis. Biological agents that have been identified as posing the greatest threat are variola major (smallpox), Bacillus anthracis (anthrax), Yersinia pestis (plague), Clostridium botulinum toxin (botulism), *Francisella tularensis* (tularaemia), filoviruses (Ebola hemorrhagic fever and Marburg hemorrhagic fever), and arenaviruses Lassa (Lassa fever) and Junin (Argentine hemorrhagic fever). The pathogenesis, clinical manifestations, diagnosis, and treatment of these agents are all discussed. Rapid identification and diagnosis using molecular diagnostic techniques such as PCR is an essential element in the establishment of coordinated laboratory response systems and is the focus of current research and development. Molecular techniques for detection and identification of these organisms are reviewed.


Pulmonary signs and symptoms may provide important differential clues to the diagnosis of tick-borne illness incurred in the southern United States.

The diagnosis of pneumonia is often difficult, when only staining and culture of clinical specimens are used. Testing for antigens or antibodies in serum provides an alternative method. Many different tests have been described or are currently being used for detecting bacterial pathogens that cause pneumonia, and many more are being developed. It is often difficult to decide which tests to use or how to interpret their results. Frequently, the sensitivity and specificity of each test is not well characterized. A practical approach to serodiagnosis of bacterial pneumonias other than pneumococcal pneumonia is presented. In addition to the sensitivity, specificity, and interpretation of standard serologic tests, the proper role of newer serologic techniques is discussed for each bacterial agent.


We report the case of a 63-year-old man who developed ulceroglandular tularemia complicated by pneumonia following a cat bite. A review of the literature revealed 51 cases of cat-related tularemia reported since 1928. Details of 15 cases (including the present case) were available and analyzed. If, following feline contact, patients develop pneumonia or if patients with skin and soft-tissue infection fail to respond to therapy with penicillin, physicians should be alerted to the possibility of tularemia. A greater awareness of this complication following a cat bite or cat scratch is important for recognizing this uncommon infection.


The potential threat of biological warfare with a specific agent is proportional to the susceptibility of the population to that agent. Preventing disease after exposure to a biological agent is partially a function of the immunity of the exposed individual. The only available countermeasure that can provide immediate immunity against a biological agent is passive antibody. Unlike vaccines, which require time to induce protective immunity and depend on the host's ability to mount an immune response, passive antibodies can theoretically confer protection regardless of the host's immune status. Passive antibody therapy has substantial advantages over antimicrobial agents and other measures for postexposure prophylaxis, including low toxicity and high specific activity. Specific antibodies are active against the major agents of bioterrorism, including anthrax, smallpox, botulinum toxin, tularemia, and plague. This article proposes a biological defense initiative based on developing, producing, and stockpiling specific antibody reagents that can be used to protect the population against biological warfare threats.
Tularemia was first described 90 years ago by McCoy as an animal disease. At the beginning of 1920s, it was recognized by E. Francis as a disease transmittable by animals to man. Tularemia is caused by a gram-negative microbe, *Francisella tularensis*. Epidemiological and clinical manifestations of the disease are highly diverse. The characteristic sign is the primary complex consisting of an initial ulceration and a regional lymphadenitis. In the Czech Republic, tularemia was first identified in 1936, in the south of Moravia. For the next years it occurred sporadically or in epidemic form also in western Moravia, in the northwest region and east of Bohemia. It affected persons manipulating diseased animals, namely hares along with workers in animal farms and those working in the cold sections of sugar Millers. After a longer pause, during the last six years, the incidence of tularemia has increased again. That’s why we decided to work at renewing understanding of the disease.


BACKGROUND: The first epidemic of ulceroglandular forms of tularemia acquired in coincidence with the manipulation with tularaemic hares took place in 1936, in the surroundings of Breclav and Valtice. The largest epidemic occurred in the 1960s, when hundreds of agricultural workers in the initial phases of the production of sugar within sugar refineries were afflicted by pulmonary forms of the disease. In the subsequent period, at the beginning of 1990s, a time that was interrupted only by smaller local epidemics, the number of new cases was gradually decreasing to the minimum. However, since 1994, the number of cases has began to increase again, namely concerning those afflicted by ulceroglandular and oroglandular forms of the disease. SUBJECTIVES: In consequence of the long absence of this disease in clinical practice, the diagnostic awareness has decreased, and, therefore, the author has decided to indicate and review the current basic data on epidemiology and clinical manifestations of tularemia. GROUP OF PATIENTS AND METHODS: The author has analyzed the documentation of 577 of adults afflicted by tularemia and medically treated at the clinic of the Faculty Hospital in Brno, in the period from 1959 to 1999. The study reviews the onset of the disease and the pathway of transmission of infection and its clinical manifestation. MAIN RESULTS:
Following the long-termed sporadic occurrence of tularaemia after major epidemics of pulmonary forms of this disease in 1960s, and interrupted only by smaller local epidemics, the incidence began to increase again in 1994. The number of pulmonary forms has decreased, whereas the occurrence of ulcerulceroglandular and oroglandular forms has increased. Hares have emerged as the source of infection again.

CONCLUSIONS: The fact that tularaemia has repeatedly become a threat in Southern Moravia should be taken into account, in the assessment of diagnosis in cases with unclear lymphadenitis and febrile states that defy penicillin treatment, especially in winter. (Tab. 3, Fig. 3, Ref. 23.)


The real risk posed by biological weapons was demonstrated with the distribution of anthrax spores by the US postal service, in 2001. This review outlines the central roles of physicians in optimizing biopreparedness in Australia, including maintaining awareness of the risk, promptly recognizing an event, notifying appropriate authorities upon suspicion of an event, and instituting appropriate management. Management aspects covered include appropriate diagnostic tests, infection control procedures, and empirical therapy of agents considered possible biological weapons. The critical role of physicians as public health advocates working to prevent the use of biological weapons is also outlined.


Until the 1990s, Amblyomma americanum was regarded primarily as a nuisance species, but a tick of minor importance, as a vector of zoonotic pathogens affecting humans. With the recent discoveries of *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *[1]* the public health relevance of lone star ticks is no longer in question. During the next 25 years, the number of cases of human disease caused by *A. americanum*-associated pathogens will probably increase. Based on current trajectories and historic precedents, the increase will be primarily driven by biological and environmental factors that alter the geographic distribution and intensity of the transmission of zoonotic pathogens. Sociologic and
demographic changes that influence the likelihood of highly susceptible humans contacting infected lone star ticks, in addition to advances in diagnostic capabilities and national surveillance efforts, will also contribute to the anticipated increase in the number of recognized cases of disease.

**Choi. 2002.** Tularemia and Q fever. *Med.Clin.North Am.* 86(2): 393-416. The zoonotic infections caused by *Francisella tularensis* and *Coxiella burnetii*, tularemia and Q fever, respectively, are two of the less commonly encountered clinical illnesses becoming increasingly recognized as epidemiologically important human diseases. The prevalence of tularemia and Q fever can be impacted positively by increased awareness of the clinical entities that arise from infection by these arthropod-borne organisms. Improved recognition of these clinical syndromes will lead to greater diagnostic accuracy in recognizing these diseases in patients. Ultimately, more stringent measures to prevent infection may be required through raising public awareness, since current therapeutic regimens for these two diseases are limited, and knowledge of the pathogenesis of these two organisms is still in the developing stages.


**Cleri, et al. 1997.** Plague pneumonia disease caused by Yersinia pestis. *Semin.Respir.Infect.* 12(1): 12-23. Plague is a zoonotic infection caused by Yersina pestis, a pleomorphic, gram-negative non-spore-forming cocacobacillus that is more accurately classified as a subspecies of *Y* pseudotuberculosis. Animal reservoirs include rodents, rabbits, and occasionally larger animals. Cats become ill and spread pneumonic disease to man. Dogs may be a significant sentinel animal as well as a reservoir, although they do not usually become ill. Flea bites commonly spread disease to man. Person to person spread has not been a recognized feature, until the purported outbreak of plague and plague pneumonia in India, in 1994. Other factors that increase risk of infection in endemic areas are occupation-veterinarians and assistants, pet ownership, direct animal-reservoir contact especially during the hunting season, living in households with an index case, and, mild winters, cool moist springs, and early summers. Clinical presentations include subclinical plague (positive serology without disease); plague pharyngitis; pestis minor (abortive bubonic plague); bubonic plague; septicemic plague; pneumonic plague; and plague meningitis.
Most prominent of plague's differential diagnosis are Reye's syndrome, other causes of lymphadenitis, bacterial pneumonias, tularemia, and acute surgical abdomen. Treatment has reduced mortality from 40-90% to 5-18%. The drug of choice (except for plague meningitis) is streptomycin, with tetracyclines being alternatives. Parenteral chlamphenicol is the treatment of choice for plague meningitis. A tetracycline should be administered as chemoprophylaxis to all contacts over the age of 8. Plague vaccine is available, but is only partially protective.


**Craven, et al. 1991.** Plague and tularemia. *Infect.Dis.Clin.North Am.* 5(1): 165-175. Human plague is a local or systemic, flea-transmitted infection caused by *Yersinia pestis*. It is maintained in well established enzootic foci among wild rodents. This article discusses the clinical findings in plague, diagnosis, treatment, and prevention of plague, and the management of contacts of human plague cases and of exposures to epizootic plague. Tularemia shares many features with plague, but is widespread in animal and arthropod vector populations and essentially throughout the United States.

**Cunha. 2002.** Anthrax, tularemia, plague, ebola or smallpox as agents of bioterrorism: recognition in the emergency room. *Clin.Microbiol.Infect.* 8(8): 489-503. Bioterrorism has become a potential diagnostic consideration in infectious diseases. This article reviews the clinical presentation and differential diagnosis of potential bioterrorist agents, when first presenting to the hospital in the emergency room setting. The characteristic clinical features of inhalation anthrax, tularemia pneumonia, plague pneumonia, including laboratory and radiographic finding, are discussed. Ebola virus and smallpox are also discussed as potential bioterrorist-transmitted infections from the clinical and epidemiologic points of view. In addition to the clinical features of the infectious diseases mentioned, the article discusses infectious disease control and the epidemiologic implications of these agents when employed as bioterrorist agents. The review concludes with suggestions for postexposure prophylaxis and therapy.


With recent events, the threat of bioterrorism has become a reality. In late 2001, multiple cases of cutaneous and inhalation anthrax were spread through the US mail. On the front line were dermatologists who diagnosed the first cases of cutaneous anthrax in New York City. Since then, physicians who are unsure if they are facing a new form of bioterrorism frequently have consulted dermatologists to evaluate rashes. Because most biological
weapons (anthrax, tularemia, plague, smallpox) can have cutaneous manifestations, dermatologists will continue to play an important role in evaluating these potential threats.

A 25-year-old healthy man died suddenly while playing social soccer. An autopsy revealed an infiltrative lesion involving the left ventricle with overlying pericarditis. No other significant pathologic changes were observed. Histologic examination showed necrotizing granulomatous inflammation. No acid-fast bacilli were demonstrated in the pericardial fluid or on histologic examination. The presence of *Mycobacterium tuberculosis* DNA complex was confirmed by use of the ligase chain reaction technique. The differential diagnosis of myocardial tuberculosis includes sarcoidosis, rheumatic fever, rheumatoid arthritis, giant-cell-containing tumors, idiopathic (giant-cell) myocarditis, and bacterial infections such as tularemia and brucellosis. This case illustrates the protean manifestations of tuberculosis and highlights the use of molecular biologic techniques in making a definitive diagnosis in cases of suspected tuberculosis.

Although once considered unlikely, bioterrorism is now a reality in the United States, since the anthrax cases began appearing in fall 2001. Intelligence sources indicate that there are many countries and terrorist organizations that either possess biological weapons or are attempting to procure them. In the future, it is likely that we will experience additional acts of bioterrorism. The CDC category A agents represents our greatest challenge because they have the potential to cause grave harm to the medical and public health systems of a given population. Thus, it is imperative that plans be developed now to deal with the consequences of an intentional release of one or more of these pathogens.


**Dennis. 2004.** “Tularemia”. In Cohen, ed. *Infectious Diseases.* (Mosby: London)

**Dennis. 2004.** “Tularemia”. In Gorbach, ed. *Infectious Diseases* (Lippincott: Philadelphia).

**OBJECTIVE:** The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals, if tularemia is used as a biological weapon against a civilian population.

**PARTICIPANTS:** The working group included 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions and agencies. **EVIDENCE:** MEDLINE databases were searched from January 1966 to October 2000, using the Medical Subject Headings *Francisella tularensis, Pasteurella tularensis,* biological weapon, biological terrorism, bioterrorism, biological warfare, and biowarfare. Review of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other references and sources. **CONSENSUS PROCESS:** Three formal drafts of the statement that synthesized information obtained in the formal evidence-gathering process were reviewed by members of the working group. Consensus was achieved on the final draft. **CONCLUSIONS:** A weapon using airborne tularemia would likely result 3 to 5 days later in an outbreak of acute, undifferentiated febrile illness with incipient pneumonia, pleuritis, and hilar lymphadenopathy. Specific epidemiological, clinical, and microbiological findings should lead to early suspicion of intentional tularemia in an alert health system; laboratory confirmation of agent could be delayed. Without treatment, the clinical course could progress to respiratory failure, shock, and death. Prompt treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin is recommended. Prophylactic use of doxycycline or ciprofloxacin may be useful in the early postexposure period.


Ticks may transmit a variety of human pathogens and are second in importance *only* to the mosquito as a vector of human disease. The majority of tick-borne diseases are nonspecific in their initial clinical and laboratory presentation and may be confused with a variety of more common illnesses. A history of tick exposure is frequently unavailable. Although specific serologic tests exist for confirming the diagnosis of many of these diseases, the time required for confirming the results makes them of little use in the acute situation. Recognition of the epidemiology of tick-borne pathogens and clinical suspicion are of key importance in making the appropriate diagnosis. Early and specific therapy is a principal factor in reducing the morbidity and mortality associated with these diseases.

Since 1990, Mongolia's health system has been in transition. Impressive gains have been accomplished through a national immunization program, instituted in 1991. Nevertheless, the country continues to confront four major chronic infections: hepatitis B and C, brucellosis, tuberculosis, and sexually transmitted diseases (STDs). As of 2001, only two cases of HIV infection had been detected in Mongolia, but concern grows that the rate will increase along with the rising rates of STDs and increase in tourism. Other infectious diseases of importance in Mongolia include echinococciosis, plague, tularemia, anthrax, foot-and-mouth, and rabies.


Despite the introduction of newer, less toxic antimicrobial agents, the aminoglycosides continue to serve a useful role in the treatment of serious enterococcal, mycobacterial, and gram-negative bacillary infections. Gentamicin, because of its low cost, remains the aminoglycoside of choice in hospitals with low levels of resistance among Enterobacteriaceae and *Pseudomonas aeruginosa*. Typically, it is administered in combination with beta-lactam antibiotics, but it may also be used as monotherapy for urinary tract infections or tularemia. Amikacin is useful against gentamicin-resistant gram-negative bacilli and also in the treatment of infections caused by susceptible *Nocardia* and nontuberculous mycobacteria. Streptomycin serves an important role in the treatment of multidrug-resistant tuberculosis and may be useful in the treatment of some gentamicin-resistant enterococcal infections. Despite an alarming increase in aminoglycoside-resistant enterococci, most institutions have noted little change in patterns of resistance among gram-negative bacilli. Although the development of newer, less toxic aminoglycosides is unlikely in the near future, single daily dosing regimens have been proposed as a convenient, cost-effective strategy. In selected patients, this novel approach seems to be as safe and effective as traditional, multidose regimens.


The immune response to intracellular bacterium, *Francisella tularensis*, which causes tularemia and is proposed to be a potential bioterrorism pathogen, has been studied in mice, using the attenuated live vaccine strain (LVS). Here we review this infection.
model, which provides a convenient means of studying protective immune mechanisms not only for *Francisella*, but also for the large and important class of intracellular pathogens.


*Francisella tularensis* is the etiological agent of tularemia, a serious and occasionally fatal disease of humans and animals. In humans, ulceroglandular tularemia is the most common form of the disease and usually develops as a consequence of a bite from an arthropod vector that has previously fed on an infected animal. The pneumonic form of the disease occurs rarely but is the likely form of the disease, should this bacterium be used as a bioterrorism agent. The diagnosis of disease is not straightforward. *F. tularensis* is difficult to culture, and the handling of this bacterium poses a significant risk of infection to laboratory personnel. Enzyme-linked immunosorbent assay- and PCR-based methods have been used to detect bacteria in clinical samples, but these methods have not been adequately evaluated for the diagnosis of pneumonic tularemia. Little is known about the virulence mechanisms of *F. tularensis*, though there is a large body of evidence indicating that it is an intracellular pathogen, surviving mainly in macrophages. An unlicensed, live, attenuated vaccine is available, which does appear to offer protection against ulceroglandular and pneumonic tularemia. Although an improved vaccine against tularemia is highly desirable, attempts to devise such an agent have been limited by the inability to construct defined allelic replacement mutants and by the lack of information on the mechanisms of virulence of *F. tularensis*. In the absence of a licensed vaccine, aminoglycoside antibiotics play a key role in the prevention and treatment of tularemia.


Because of the recent lack of availability of streptomycin--currently considered the drug of choice for the treatment of tularemia--we reviewed the literature on alternative drugs that have been used for this purpose. In addition, we reviewed data on the *in vitro* susceptibility of *Francisella tularensis* to a wide variety of agents. The rate of cure for streptomycin was 97%, with no relapses. For gentamicin and tetracycline, the rates of cure were 86% and 88%, respectively; the rates of relapse were 6% and 12%, and the rates of failure were 8% and 0. The duration of therapy with gentamicin and a delay in its initiation may have affected the outcomes in severe cases. For chloramphenicol and tobramycin, cure rates were 77% and 50%, respectively; relapse rates were 21% and 0; and failure rates were 2% and 33%, respectively. Treatment with imipenem/cilastatin was successful in a single case, and that with ciprofloxacin or norfloxacin was successful in
six cases; in contrast, therapy with ceftriaxone was ineffective in eight cases. On the basis of this review, we conclude that gentamicin is an acceptable alternative to streptomycin for the treatment of tularemia.


Drawing upon our experience with 88 cases and a survey of the English literature, we reviewed the clinical, pathophysiological, and epidemiological aspects of tularemia. Tularemia can be thought of as two syndromes—ulceroglandular and typhoidal. This dichotomy simplifies earlier nomenclature and emphasizes the obscure typhoidal presentation. Clinical manifestations suggest that the two syndromes reflect differences in host response. In ulceroglandular tularemia the pathogen appears to be well contained by a vigorous inflammatory reaction. Pneumonia is less common and the patient's prognosis is good. In typhoidal disease there are few localizing signs; pneumonia is more common; and the mortality without therapy is much higher, suggesting that the host response is somehow deficient. *Francisella tularensis* is an extremely virulent pathogen capable of initiating infection with as few as 10 organisms inoculated subcutaneously. During an incubation period of 3 to 6 days the host responds first with polymorphonuclear leukocytes and then macrophages. Granulocytes are unable to kill the pathogen without opsonizing antibody leaving cellular immunity to play the major role in host defense. One to 2 weeks after infection, a vigorous T-lymphocyte response can be detected in vitro with lymphocyte blast transformation assays and in vivo with an intradermal skin test, which, unfortunately, is not commercially available. Humoral immunity, often used as a diagnostic modality, appears 2 to 3 weeks into the illness. Cellular immunity is long-lasting, accounting for the common reoccurrence of localized disease upon repeated exposures to the pathogen. There are no symptoms that distinguish the ulceroglandular from the typhoidal syndrome. A pulse-temperature dissociation is seen in less than half of the patients. The location of ulcers and enlarged lymph nodes give a clue to the likely vector since lesions located on the upper extremities are more commonly associated with mammalian, and those of the head and neck and lower extremities with arthropod, vectors. Pharyngitis, pericarditis, and pneumonia can complicate both syndromes, although the latter is much more common in typhoidal disease. Hepatitis, usually of a mild degree, is common and occasionally erythema nodosum is seen. No specific laboratory tests characterize tularemia, and cultures of the pathogen are often difficult to obtain because of the special growth requirements of Francisella tularensis and the inability of many clinical laboratories to handle the dangerous pathogen.(ABSTRACT TRUNCATED AT 400 WORDS)
Tularemia is a rare but potentially fatal disease that develops in numerous wild and domestic animals, including lagomorphs, rodents, cats, and humans. The disease occurs throughout much of the United States and should be considered in the differential diagnosis of acute febrile illness, particularly when risk factors such as contact with wild mammals or tick exposure is present. Veterinarians may be at increased risk of acquiring tularemia from contact with infected animals, but standard precautions should greatly reduce this risk. Outbreaks of tularemia warrant investigation, especially given the possibility of the use of *F. tularensis* as an agent of bioterrorism.


Fernandez Jorge, et al. 2001. [Lung involvement in tularemia]. *An.Med.Interna.* 18(1): 32-34. We present three cases of pneumonia by *Francisella tularensis* recently diagnosed. We also review this disease with the literature. All the studied patients were adults; two of them had epidemiological antecedents because of being in contact with hares. They present clinical-radiological symptoms compatible with the pneumonic case described in the literature. The diagnosis was realized through serology in two cases and hemoculture in the other one. All patients had a positive answer to the antibiotic treatment, two cases with gentamicine and the other one with macrolide. There are not references about the subject in the bibliographical research we have realized in Medline. We did not find information in the Spanish base (IME), perhaps because these were the first cases found in the Spanish literature.


The use of micro-organisms as agents of biological warfare is considered inevitable for several reasons, including ease of production and dispersion, delayed onset of symptoms, ability to cause high rates of morbidity and mortality and difficulty in diagnosis. Therefore, the clinical presentation and pathogenesis of the organisms posing the highest threat (variola major, *Bacillus anthracis*, *Yersinia pestis*, *Clostridium botulinum* toxin, *Francisella tularensis*, filoviruses, arenaviruses and Brucella species), as well as the available diagnostic techniques and treatments for such infections, will be reviewed in this article. Due to the necessity for rapid identification and diagnosis, molecular techniques have been the ongoing focus of current research. Consequently, the molecular
diagnostic techniques that have recently been developed for the diseases associated with these agents will be emphasized.


**Foshay et al., 1936.** Viability of Bacterium Tularense in Human Tissues. *Jour. AMA* 106(25), 2142.

Over 2,000 species of fleas parasitize mammals and birds. A simplified study of their morphology indicates for the main identification criteria. After listing the main families of fleas, the author outlines the identification of species most often encountered by veterinarians. Knowledge of the different types of flea parasitism and their life cycles is essential for effective control measures. Control is justified by the direct and indirect pathogenic roles of fleas (transmission of plague, tularemia, myxomatosis, Dipylidium caninum). Effective agents are organochlorine compounds, organophosphorus compounds, pyrethroids and insect growth regulators, available in various formulations to destroy parasitic fleas on animals or in the environment. A novel method is to administer a systemic growth regulator to dogs and cats, which persists in the bloodstream and inhibits the reproduction of fleas which feed on a treated animal. Advantages and disadvantages of each formulation are presented.


Concern regarding the use of biological agents--bacteria, viruses, or toxins--as tools of warfare or terrorism has led to measures to deter their use or, failing that, to deal with the consequences. Unlike chemical agents, which typically lead to violent disease syndromes within minutes at the site of exposure, diseases resulting from biological agents have incubation periods of days. Therefore, rather than a paramedic, it will likely be a physician who is first faced with evidence of the results of a biological attack. We provide here a primer on 10 classic biological warfare agents to increase the likelihood of their being considered in a differential diagnosis. Although the resultant diseases are
rarely seen in many countries today, accepted diagnostic and epidemiologic principles apply; if the cause is identified quickly, appropriate therapy can be initiated and the impact of a terrorist attack greatly reduced.


*Francisella tularensis*, the causative agent of tularemia, is a highly infectious gram-negative coccobacillus. Due to its high infectivity, it is of major concern to public health officials as a possible biological weapon. Although accidental exposure can occur through arthropod bites, handling infected animals, or breathing in aerosols, cases are usually isolated and contained. In the event of an intentional exposure such as in a bioterrorist attack, inhalation of aerosols can result in devastating consequences with much causality. Although a vaccine is available, sufficient quantities may not be readily accessible in an actual attack. Therefore, it is very important for both medical professionals and public health officials to be prepared to contain and control the situation should it actually occur.


Tick-borne diseases are the most common vector-borne illnesses in the United States. Lyme disease is the most common, but several others also occur. The ehrlichioses have only been identified as agents of human disease in the United States in the past few decades, and knowledge about them is still evolving. Rocky Mountain spotted fever is relatively common and can be severe, especially in children, if the diagnosis is not made quickly. Tularemia has long been known to cause disease in humans, but there is renewed interest because of its potential as a biologic warfare agent. These diseases can be severe or even fatal. Most of them are easily treatable when identified early. These diseases result from a variety of infectious agents including bacteria, rickettsia, viruses and protozoa, or they may be caused by substances produced by the tick. Most of these diseases present initially with nonspecific symptoms and are often difficult to recognize. Few definitive diagnostic tests are available. Therefore, knowledge of the epidemiology and common presentations, as well as the diagnostic options and treatments available, are important issues for family physicians.
Tularemia pneumonia may complicate the various clinical presentations of tularemia, or present as an uncommon zoonosis. Approximately 200 cases of tularemia are reported in the United States every year, and 10% to 20% present with pneumonia, either as a primary event or as a complication of ulceroglandular or typhoidal tularemia. Tularemia pneumonia also occurs with the other tularemic forms, glandular, oculoglandular, and oropharyngeal tularemia as a result of secondary bacteremic spread to the lungs. Pneumonia usually occurs within 2 days to months after infection. The mortality rate of primary tularemic pneumonia and pneumonia complicating typhoidal tularemia is high. The clinical and roentgenographic presentations of tularemia pneumonia are highly variable and is one of the zoonotic atypical pneumonias. Tularemic pneumonia may mimic fungal and bacterial pneumonias, tuberculosis, or malignancy. The diagnosis of tularemic pneumonia should be considered in any patient presenting with an atypical pneumonia with the finding of an ulcer and/or lymphadenopathy and a history of outdoor activity. Serum agglutination tests and ELISA are the basis of serological diagnosis. Francisella tularensis can be cultured from the sputum, skin ulcer, pleural fluid, and the lymph nodes, but cultures should not be obtained because of the danger to laboratory personnel. The drug preferred for treatment of tularemic pneumonia is streptomycin for 1 to 2 weeks.

Animal-transmitted diseases are remarkable not because they occur frequently, but because they are almost always unsuspected and unrecognized. The physician who attends an ill veterinarian or zookeeper will immediately suspect an exotic disease. The pediatrician who attends the child who recently received a puppy for his birthday, will not. Our public attitude toward animals as disease carriers is utterly thoughtless. If a human were to urinate and defecate in the street or park, he would be incarcerated without delay. Yet we tolerate and even encourage the same activity in dogs, known to carry scores of diseases to humans. Animals as pets are here to stay. Children are their frequent companions. It would serve all those who deal with the medical problems of children to know as much as possible about the diseases carried by animals, for their consequences are quite significant.

To discover how nitric oxide (NO) synthesis is controlled in different tissues as cells...
within these tissues combat intracellular pathogens, we examined three distinctively different experimental murine models designed for studying parasite-host interactions: macrophage killing of Leishmania major; nonspecific protection against tularemia (*Francisella tularensis*) by Mycobacterium bovis (BCG); and specific vaccine-induced protection against hepatic malaria with Plasmodium berghei. Each model parasite and host system provides information on the source and role of NO during infection and the factors that induce or inhibit its production. The *in vitro* assay for macrophage antimicrobial activity against *L. major* identified cytokines involved in regulating NO-mediated killing of this intracellular protozoan. *L. major* induced the production of two competing cytokines in infected macrophages: (1) the parasite activated the gene for tumor necrosis factor (TNF), and production of TNF protein were both enhanced by the presence of interferon-gamma (IFN-gamma). TNF then acted as an autocrine signal to amplify IFN-gamma-induced production of NO; and (2) the parasite upregulated production of transforming growth factor-beta (TGF-beta), which blocked IFN-gamma-induced production of NO. Whether parasite-induced TNF (parasite destruction) or TGF-beta (parasite survival) prevailed, depended upon the presence and quantity of IFN-gamma, at the time of infection. The relationship between NO production in vivo and host resistance to infection was demonstrated with M. bovis (BCG). (ABSTRACT TRUNCATED AT 250 WORDS)


There is general consensus that the bacterial agents or products most likely to be used as WMD are *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis* and the neurotoxin of *Clostridium botulinum*. Modern supportive and antimicrobial therapy for inhalational anthrax is associated with a 45% mortality rate, reinforcing the need for better adjunctive therapy and prevention strategies. Pneumonic plague is highly contagious, difficult to recognize and frequently fatal. Therefore, the development of vaccines against this agent is crucial. Although tularemia is associated with low mortality, the highly infectious nature of aerosolized F. tularensis poses a substantive threat that is best met by vaccine development. Safer antitoxins and a vaccine are required to meet the threat of the use of botulinum toxin as a weapon of mass destruction. In this article, the current status of research in these areas is reviewed.


Bacterial pathogens have been identified as agents that have been, or could be, used as weapons of biological warfare and/or biological terrorism. These agents are relatively easily obtained, prepared, and dispersed, either as WMD or for more limited terrorist
attacks. Although phylogenetically diverse, these agents all have the potential for aerosol dissemination. Physicians in the United States and most of the developed world have never encountered most of these agents and the diseases they produce. Public health programs must be prepared, and individual primary care providers must be able to recognize, diagnose, treat, and prevent infection with these agents.


The events of 11 September and the subsequent anthrax outbreaks in the United States have opened the world's eyes to the threat posed by terrorist groups, criminal organizations and lone operators who will stop at nothing to achieve their goals. The open or covert use of pathogens and toxins as biological warfare agents can no longer be ruled out. Against this background, the appearance of an unusual disease must be studied to clarify whether it is a natural or artificially caused occurrence. This issue was recently raised in discussions with local representatives and relief organizations, during a tularemia epidemic in Kosovo from October 1999 to May 2000. This paper will present a procedure which attempts to use certain criteria to identify or rule out the use of biological warfare agents in the event of an unusual outbreak of disease. Data and findings gathered by routine epidemiologic and microbiological studies often provide only an indirect answer to this problem. For this reason, various criteria were formulated and points allocated to represent their importance, allowing us to deduce in a semiquantitative manner the degree of possibility of an artificial genesis of outbreaks. The significance and characterization of each criterion are discussed. An analysis of the tularemia epidemic in Kosovo, based on the procedure described here, indicates that a deliberate release of the causative agent of tularemia, *Francisella tularensis*, as a biological warfare agent, is doubtful. In this paper, an approach is described to discriminate between the intentional use of biological warfare agents and natural outbreaks of infectious disease. The developed model is flexible and considers the political, military and social analysis of the crisis-afflicted region, the specific features of the pathogen, and the epidemiologic and clinical characteristics of the epidemic.

**Guerrant, et al. 1976.** Tickborne oculoglandular tularemia: case report and review of seasonal and vectorial associations in 106 cases. *Arch.Intern.Med.* 136(7): 811-813. A patient acquired tickborn oculoglandular tularemia in early summer, in rural Virginia. Tick exposure may afford a clue to the diagnosis of tularemia, in the eastern as well as the western United States, especially in the summer months. A review of the experience with tularemia in Virginia for the last 13 years shows a bimodal seasonal incidence of tularemia, with an associated vector exposure in 77.4% of 106 cases. The majority of cases occurring during the winter months has been associated with rabbit exposure, while those in summer months are often associated with tick exposure.

BACKGROUND: Dentists' responses to catastrophe have been redefined by bioterrorism. Informed response requires accurate information about agents and diseases with the potential to be used as weapons. METHODS: The authors reviewed information about the most probable bioterrorist weapons (those from the CDC’s Prevention’s Category A) from the World Wide Web (WWW) print journals and distilled it into a resource list that is current, relevant to dentistry and noncommercial. The Web sites cited include those sponsored by federal agencies, academic institutions and professional organizations. The articles cited include those published in English within the last six years in refereed journals available in most higher education institutions. RESULTS: The authors present the information in a table that provides a quick-reference guide to resources describing agents and diseases with the greatest potential for use as weapons: anthrax, botulism, plague, smallpox, tularemia and viral hemorrhagic fevers. This article presents Web site and journal citations for background and patient-oriented information (fact sheets), signs and symptoms, and prophylactic measures and treatment for each of the agents and diseases. The table facilitates quick access to this information, especially in an emergency. This article also points out guidelines for response, should a suspected attack occur. CONCLUSIONS: Armed with information about biological weapons, dentists can provide faster diagnosis, inform their patients about risks, prophylaxis or treatment and rethink their own role in terrorism response. CLINICAL IMPLICATIONS: Fast, accurate diagnosis limits the spread of exceptionally contagious diseases. Providing accurate information to patients minimizes misinformation and the associated public fear and panic that, unchecked, could overwhelm health care systems.

Health Effects of *Pasteurella (Francisella) Tularensis*

diagnosed as pleuropulmonary tularemia. He was successfully treated with erythromycin. We review the case and briefly discuss the literature on this point.


**BACKGROUND:** Bacterial pathogens and their products are potential agents of biological terrorism and biological warfare. These agents can be deployed through simple aerosol delivery systems and thereby cause widespread disease and death. **METHODS:** This report is a review of bacterial species that have been employed for development of biological terrorism, relying on a system for classification of their threat developed by the Centers for Disease Control. **RESULTS:** Physicians must understand how to recognize early signs and symptoms caused by bacterial agents. Clinical findings often seen on presentation are emphasized along with a summary of therapeutic approaches. **CONCLUSIONS:** Initiation of immediate therapy and supportive care provides the best chance for survival from these potentially lethal and devastating infections. A high index of suspicion must be maintained, especially in the setting of a sudden influx of cases with what are often relatively nonspecific symptoms.


**Jager. 1943.** *Constrictive Pericarditis Due to Bacterium Tularense.* Place: Press, ??166.


The microbiological, pharmacokinetic, toxicological and clinical aspects of aminoglycosides are reviewed. Aminoglycosides still have an important place in serious infections in neutropenic patients, endocarditis and Pseudomonas aeruginosa infections, all in combination with *beta-lactams*. Monotherapy (with streptomycin) is indicated in less common diseases like tularemia and bubonic plague. Several experimental studies support a once-daily dosing regimen for aminoglycosides (comparable or better efficacy with less ototoxicity and nephrotoxicity). Only a very limited number of prospective comparative studies have been performed, and much more data on efficacy, development of resistance and toxicity are needed before once-daily administration can be recommended. The choice of an aminoglycoside should be based primarily on the local
sensitivity patterns and cost. Differences in ototoxicity and nephrotoxicity are usually minor. If the acquisition costs of amikacin decline, it is to be expected that amikacin will be the aminoglycoside of choice.


A bioterrorist attack of any kind has the potential to overwhelm a community and, indeed, in the case of smallpox, an entire nation. During such an attack the number of patients requiring hospitalization and specifically critical care is likely to be enormous. Intensivists will be at the forefront of this war and will play an important role in dealing with mass casualties, in an attempt to heal the community. A high degree of suspicion and prompt recognition of an event will be required to contain it. Specific knowledge of the possible agents that can be used will be key in managing patients and in estimating the needs of a health care facility and community to deal with the future course of events. Intensivists play various roles aside from the delivery of critical care to the patient in the ICU. These roles include making triage decisions regarding the appropriate use of critical care beds (that automatically dictates how other non-ICU beds are used and managed) and serving as a team member of ethics committees (on such issues as dying, futility, and withdrawal of care). Indeed, intensivists are no strangers to disaster management and have served on the forefront of many. A biologic weapons attack, however, is likely to push the multidimensional nature of the intensivist to the maximum, because such an attack is likely to result in a more homogeneous, critically ill population where the number of critical care staff and supplies to treat the victims may be limited. One hopes that such an event will never occur. Sadly, however the events of September 11, 2001, have only heightened the awareness of such a possibility.


Tularemia is a zoonosis, caused by the Gram-negative bacterium, *Francisella tularensis.* The organism penetrates the human body through interrupted skin or mucous membranes, via animal contact or bites from ticks, deer-flies and mosquitoes. Contaminated aerosol
and water represent alternative modes of transmitting the germ through the respiratory and alimentary tracks. In light of its high infectivity in aerosol and its offensive occupation in the past, tularemia may appear in a biological warfare context. After an incubation period of 3-5 days, the disease begins with systemic symptoms, which abate, leaving a clinical picture, dominated by one of the listed patterns: ulceroglandular, typhoidal, glandular, occuloglandular, pharyngeal or pneumonic. Diagnosis and identification of the bacterium is difficult, even hazardous. Most diagnoses are established by serology that is positive in 50-70% of the patients after 2 weeks of illness, and in most of them, by 4-8 weeks. The treatment of choice is streptomycin intramuscular, or gentamicin intra-venous for 10-14 days. Prophylaxis may be achieved by tetracycline treatment, beginning up to 24 hours from exposure, for 2 weeks, or by a live attenuated, investigational vaccine. Nevertheless, post-exposure, or even better so, pre-exposure intervention is the most effective way of preventing the devastating results of the attack.


Understanding and quantifying the impact of a bioterrorist attack are essential in developing public health preparedness for such an attack. We constructed a model that compares the impact of three classic agents of biologic warfare (*Bacillus anthracis*, *Brucella melitensis*, and *Francisella tularensis*) when released as aerosols in the suburb of a major city. The model shows that the economic impact of a bioterrorist attack can range from an estimated $477.7 Millerion per 100,000 persons exposed (brucellosis scenario) to $26.2 billion per 100,000 persons exposed (anthrax scenario). Rapid implementation of a postattack prophylaxis program is the single most important means of reducing these losses. By using an insurance analogy, our model provides economic justification for preparedness measures.


A report is given on the epidemiology and clinical signs of some selected zoonoses that may be of significance for ocular infections in man: brucellosis, leptospirosis, Lyme borreliosis, lymphocytic choriomeningitis, Newcastle Disease, ornithosis (chlamydiosis), rabies, Streptococcus suis infection, larva migrans ocularis by Toxocara canis or Baylisascaris procyonis, toxoplasmosis and tularemia.

Clinical and histologic characteristics of tularemia are reviewed in this report of a 65-year-old man who presented with fever, cutaneous ulceration, and regional lymphadenopathy. Examination of a biopsy specimen failed to demonstrate the granulomatous inflammation one would expect according to the current dermatologic literature. We review the diagnostic implications of this finding.

31 subjects with tularemia recently or up to 11 years earlier were studied for cell-mediated immunity against Francisella tularensis using formalin-killed bacteria as antigen in the lymphocyte blast transformation test. Lymphocytes from all the subjects responded to F. tularensis antigen both in separated mononuclear cell and whole blood cultures, whereas lymphocytes from 12 controls responded not at all or only weakly to high antigen concentrations and only in separated mononuclear cell cultures. The strength of the response remained on the same level as in the cases of recent infection up to 11 years. There was no correlation between the lymphocyte responses and the serum antibodies of agglutinating F.l tularensis antigen. Purified protein derivative of tuberculin equally stimulated the cells from the tularemia and control subjects. The lymphocyte stimulation methods can be used to diagnose infections caused by F. tularensis and to measure cell-mediated immunity and resistance against such infections.

PURPOSE: To describe nodular lymphangitis by reviewing the clinical and epidemiologic features of this disease with an emphasis on distinguishing specific etiologic agents. DATA SOURCES: English-language articles were identified through a MEDLINE search (1966 to September 1992) using sporotrichosis, lymphangitis, and sporotrichoid as key words; additional references were selected from the bibliographies of identified articles. In addition, three new patients with nodular lymphangitis are described. STUDY SELECTION: One hundred fifty articles were reviewed to determine details of the etiologic agents and clinical signs and symptoms of patients with nodular lymphangitis. DATA SYNTHESIS: Nodular lymphangitis develops most commonly
after cutaneous inoculation with Sporothrix schenckii, Nocardia brasiliensis, Mycobacterium marinum, Leishmania braziliensis, and Francisella tularensis. The setting in which infection is acquired is useful in differentiating among the various organisms causing infection. Sporotrichosis and leishmaniasis can have longer incubation periods than do the other common causes of nodular lymphangitis. A painful ulcer at the site of the initial lesion suggests tularemia; frankly purulent drainage often accompanies infections with Francisella and Nocardia species. Ulcerated or suppurating lymphangitic nodules occur commonly with Nocardia infections. Patients with nodular lymphangitis who fail to respond to empiric treatment for sporotrichosis should be evaluated for other organisms with appropriate biopsies and cultures. CONCLUSIONS: Nodular lymphangitis has distinctive clinical signs and symptoms, most commonly due to infection with a limited number of organisms. A detailed history, accompanied by information obtained from skin biopsy specimens using appropriate stains and cultures, should allow specific, effective therapy for most of these infections.


Many of the feline zoonoses occur more frequently in veterinary personnel owing to their direct contact with cats and the potential for exposure to infected body tissue or fluids. Infection of humans with Afipia felis, Yersinia pestis, Francisella tularensis, and other aerobic/anaerobic bacteria may cause great discomfort and in some situations terminal illness. Although many systemic fungal agents infect humans and cats, only Sporothrix schenckii has been shown to infect humans following direct exposure to infected cats. Various parasites, enteric protozoans and bacteria, and Toxoplasma gondii infections also may cause significant human illness. Therefore, routine handling of cats may expose
human personnel in a veterinary facility to an array of important or emerging feline-associated human illnesses that occur in the United States.


Bioterrorism is an emerging public health and infection control threat. Potential biological agents include smallpox, anthrax, plague, tularemia, botulinum toxin, brucellosis, Q fever, viral encephalitis, hemorrhagic fever, and staphylococcal enterotoxin B. An understanding of the epidemiology, clinical manifestations, and management of the more likely candidate agents is critical to limiting morbidity and mortality from a biological event. Effective response requires an increased index of suspicion for unusual diseases or syndromes, with prompt reporting to health authorities to facilitate recognition of an outbreak and subsequent intervention. Hospital epidemiology programs will play a crucial role in this effort.


Tick-borne zoonotic pathogens are well known in many areas worldwide. Among the tick-borne transmitted diseases in Switzerland, Lyme disease caused by Borrelia burgdorferi, and ehrlichiosis caused by various species of Ehrlichia and tick-borne encephalitis caused by the tick-borne encephalitis virus (TBEV) are the most important zoonotic diseases. Early diagnosis and treatment are necessary to prevent fatal infections and chronic damage to various tissues. Due to the variety of uncharacteristic clinical signs, tick-borne diseases are not easily recognized. Diagnosis is based on clinical findings, a record of tick exposure, and direct or indirect detection of the pathogen. Here we discuss briefly the most important tick-borne infections and their diagnoses with emphasis on a new molecular diagnostic tool--the real-time TaqMan PCR--and its importance for the diagnosis of tick-borne pathogens.


Streptomycin, gentamicin, and tetracycline are currently considered the antimicrobials of choice for the treatment of tularemia. Preliminary data suggest that quinolones may be
effective alternative agents; however, clinical experience is limited, and their role in treating severe disease is uncertain. We recently treated two acutely ill immunocompromised patients who had presumed "atypical" pneumonia with levofloxacin. Both patients had an excellent clinical response and were diagnosed with tularemia only when blood cultures subsequently yielded Francisella tularensis. Neither patient relapsed during 12 months of follow-up. Including our 2 cases, a total of 10 cases of tularemia treated with quinolones have been reported. In all 10 cases, a favorable clinical response was documented, and no relapses occurred. We conclude that the quinolones appear promising for the treatment of even severe tularemia, and they should be considered efficacious alternative agents for patients who do not require parenteral therapy or are intolerant of more standard treatment regimens.

In the period 1960 to 1979, 177 cases of tularemia occurred in residents of Georgia. A tick bite was the implicated source of exposure in 8 cases (4.5%), whereas 91 cases (51.4%) were associated with direct contact with infected rabbits. In Georgia and other southeastern states, the epidemiology of human tularemia infection primarily involves rabbits. However, a diagnosis of tularemia should still be considered in this region in a febrile patient with or without a primary lesion or reported exposure to rabbits. A history of having been bitten by a tick may be the major clue in determining the diagnosis. A primary ulcerative lesion on the legs or in concealed body areas such as the axillary or intergluteal regions, is frequently the presenting sign in the patient with tick-borne tularemia.

Vaccination programs are very successful as a preventive strategy against many infectious diseases that have had a major impact on human morbidity and mortality. One of these diseases, smallpox, has been eliminated as a natural infection. The recent concern over biological attacks has turned attention to the use of an immunization program to prevent infection with what are considered the most significant potentially harmful biowarfare pathogens. This review puts into perspective the available information on current immunization and newer vaccine options for anthrax, smallpox, tularemia, plague and botulism.

As a continuation of Libich's monograph (Tularemie. Prague, Avicenum 1981) the author
presents findings assembled in experiments pertaining to postinfectious immunity on a model of intracellular infection with the microorganism *Francisella tularensis*.


**Maranan. 1997.** Pneumonic Tularemia in a Patient with Chronic Granulomatous Disease. *Clinical Infectious Diseases* 25, 630-633.

Bacteria were the first organisms recognized for their potential as agents of bioaggression and the possibility of their use by a terrorist or rogue nation is considered a significant threat. Five of the more likely agents (anthrax, plague, tularemia, Q fever, and brucellosis) are reviewed with emphasis on their epidemiology, clinical presentation, diagnosis, and pathology. Particular emphasis is given to the presentation of the diseases as they may appear after use in a biowarfare scenario.

The atypical pneumonia syndrome usually implies a benign illness where systemic complaints predominate over respiratory symptoms. Cough is prominent; chest radiographic findings are varied. Many organisms are associated with this syndrome. *Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydia pneumoniae, Coxiella burnetii,* and *Francisella tularensis* are reviewed in this article.


Ticks are ectoparasites that cause dermatologic disease directly by their bite and indirectly as vectors of bacterial, rickettsial, protozoal, and viral diseases. In North America, where ticks represent the leading cause of vector-borne infection, dermatologists should recognize several tick species. Basic tick biology and identification will be reviewed. Tick bites cause a variety of acute and chronic skin lesions. The tick-borne diseases include Lyme disease, tick-borne relapsing fever, tularemia, babesiosis, Rocky Mountain spotted fever, other spotted fevers, ehrlichiosis, Colorado tick fever, and

The specter of biological warfare (BW) looms large in the minds of many Americans. The US government has required that emergency response teams in more than 100 American cities be trained by 2001 to recognize and contain a BW attack. The US military is requiring active duty soldiers to be immunized against anthrax. Dermatologists need not feel helpless in the face of a potential BW attack. Many potential agents have cutaneous manifestations that only a dermatologist’s trained eye can recognize. Through early recognition of a BW attack, dermatologists can aid public health authorities in diagnosing the cause, so that preventive and containment measures can be instituted to mitigate morbidity and mortality. This article reviews bacterial, viral, and toxin threat agents and emphasizes those that may have cutaneous manifestations following an aerosol attack. We conclude with clues that can help one recognize a biological attack.


The purpose of this article is to discuss briefly the following cutaneous manifestations of selected systemic diseases: poxvirus; feline leukemia virus (FeLV); feline immunodeficiency virus (FIV); herpesvirus; calcivirus; pseudorabies; plague; tularemia; toxoplasmosis; leishmania; hypothyroidism; hyperthyroidism; hyperadrenocorticism; diabetes mellitus; acromegaly; thallium poisoning; pancreatic disease; hypereosinophilic syndrome; mucopolysaccharidosis; and pansteatitis. Recognition of these cutaneous signs may help alert the clinician to the possibility of an internal disorder so that the appropriate diagnostic tests can be considered.


This paper addresses the issue of using airborne tularemia as a potential biological weapon of terrorists. Because of its extreme infectivity, easy dissemination and substantial pathogenic ability, it may become a dangerous biological agent. An outbreak of acute febrile illness with pneumonia, pleuritis and hilar lymphadenitis in urban healthy populations, regardless of age and gender, should suggest an action of terrorism. The

Health Effects of Pasteurella [Francisella] Tularensis
presumptive diagnosis should be based on epidemiological and clinical findings as the final microbiological confirmation may take several weeks. The treatment with aminoglicosides or alternatively doxycycline and ciprofloxacin administered parenterally is recommended. In a mass casualty situation, oral doxycycline and ciprofloxacin are the preferred drugs. Vaccination is recommended only in the laboratory personnel working routinely with *Francisella tularensis*. Isolation and special precautions are not necessary because the illness is not transmitted from one person to another.


Bioterrorism preparedness is clearly a goal for the health care community, working in concert with city, county, state, and federal public health and emergency authorities and in collaboration with law enforcement at the local and federal levels. Opening the channels of communication between all groups involved, obtaining the necessary resources, and maintaining an understanding of the potential agents and the diseases they cause will foster a smooth transition to a rational program directed at patient, personnel, and community safety.


OBJECTIVE: To report the clinico-epidemiological characteristics of 16 patients with the diagnosis of tularemia. METHOD: Retrospective review of clinical records of patients admitted to the hospital or examined at health centers in Vizcaya, with clinical course and epidemiology consistent with tularemia, from January to March 1998. CASE DEFINITION: Patient with suggestive clinical course and epidemiology (exposure to hares coming from the epizootic area) and positive serology (antibodies to *Francisella tularensis* &gt; 1/160 in convalescent phase serum). RESULTS: Sixteen patients (8 males, 8 females) with a mean age of 53 years. The incubation period ranged from 1 to 8 days (mean: 5). Nine patients came do with the ulceroganglionar form, two with the pharyngeal form, one with the oculoganglionar form and one with the typhoidal form. In three patients, only a cutaneous lesion or lesions were observed. The antibiotic treatment administered included streptomycin for five patients, tobramycin for two patients, and ciprofloxacin, azithromycin and amoxicillin (plus doxycycline) for the other
patients. Three patients initially received antitermic drugs (with poor response) and later two of them received doxycycline. The antibiotic administered to the remaining three patients was unknown. The clinical course was satisfactory in all of them and so far no relapses have been detected. CONCLUSIONS: The ulceroglandular form, as it appears in literature, was the most common form in this series of patients with tularemia. Neither severe diseases nor complications were observed. Although streptomycin is considered the drug of choice, other antibiotics are likely equally effective, at least for the non complicated forms of the disease.


Tick-borne diseases are common in Oklahoma, especially the eastern part of the state where tick prevalence is highest. Three species of hard ticks are present in Oklahoma that are known vectors of human disease--the American dog tick (Rocky Mountain spotted fever; RMSF), the lone star tick (ehrlichiosis) and the black-legged tick (Lyme disease). Oklahoma consistently ranks among the top states in numbers of reported RMSF cases, and Ehrlichiosis may be as prevalent as RMSF. Although Lyme disease is frequently reported in Oklahoma, over-diagnosing of this disease due to false-positive test results is common; positive or equivocal screening tests should be confirmed by Western immunoblot. At present, it is unclear whether the disease seen here is Lyme disease or another Lyme-like disease. If true Lyme disease is present in the state, it is probably rare. Physicians should be aware of the most recent recommendations for diagnosis, therapy and prevention of tick-borne diseases.


Tularaemia, a zoonotic disease caused by the bacterium Francisella tularensis McCoy, 1912, is reported from North America, Europe and northern parts of Asia, but not from the Southern Hemisphere. Two subspecies of F. tularensis are recognized: the highly virulent type A and the milder type B, with additional subdivisions reported. Tularaemia has been reported in more than 250 animal species including man, other mammals, birds, fish, amphibians, arthropods and protozoa. Type A is reported to have a terrestrial cycle with the main reservoirs being cottontail rabbits (Sylvilagus spp) and ticks. Type B is reported to have a mainly water-borne cycle with aquatic rodents as reservoirs, e.g. muskrats (Ondatra zibethicus) and beaver (Castor canadensis) in North America, and ground voles (Arvicola terrestris) in the former Soviet Union. In Europe, tularaemia is most frequently seen in hares (Lepus spp) although hares probably do not constitute a reservoir for the disease. Tularaemia is transmitted by direct contact with infected animals, through contaminated water or food, or by vectors such as mosquitoes or ticks. The disease normally occurs as an epidemic, both in man and in animals,
depending on the types of reservoir involved and the means of transmission at different times of the year.

Although unusual, human tularemia continues to be reported from areas of the United States that are not heavily endemic for the disease. Two patients with ulceroglandular tularemia diagnosed in Ohio are described here. The causative microorganism, *Francisella tularensis*, is a small, pleomorphic gram negative coccobacillus, which requires special a microbiological medium for laboratory isolation. In nature, the organism is usually transmitted to man by the handling of infected animal tissues and body fluids or by an arthropod vector. There are several clinical forms of tularemia of which the ulceroglandular type is most common. Laboratory diagnosis is usually made by demonstrating a four-fold increase in the serologic agglutinating antibody titer to *Francisella tularensis*. Streptomycin is the drug of choice in the treatment of tularemia.

The arthropod-borne rickettsial, borreliial, and bacterial diseases of North America form a diverse group of disorders that produce a wide variety of cutaneous abnormalities. These dermatologic abnormalities are often valuable clinical clues that may reveal or suggest the correct diagnosis to the astute clinician. We review the usual and unusual dermatologic manifestations of Rocky Mountain spotted fever, murine and sylvatic typhus, rickettsialpox, ehrlichiosis, Lyme disease, tick-borne relapsing fever, Colorado tick fever, and tularemia. In some of these diseases, skin manifestations may be diagnostic; in others, dermatologic findings may be the initial and only clues leading to the initiation of life-saving therapy. In other arthropod-borne infections, the appearance or evolution of the skin rash may be characteristic enough to suggest the proper diagnosis.


Infectious or inflammatory stress in rats causes very typical functional and metabolic alterations. Among the most typical are elevation in body temperature, insulin, and glucagon and depression in the concentrations of plasma ketones and free fatty acids. These changes occur only with infectious or inflammatory stress and not with
noninflammatory stresses, such as femoral fracture, screen restraint, or exercise. It appears that the depression in plasma ketone bodies during infection or inflammation is closely related to the rise in plasma insulin. During infection imposed on experimentally-induced diabetes, inhibition of plasma ketones does not show up. In a similar fashion, infection in hypophysectomized rats causes no elevation in plasma insulin and no depression in plasma ketones. The report includes some discussion of the implications of these rat and primate observations.

Recent events have demonstrated that bioterrorists have the ability to disseminate biologic agents in the United States and cause widespread social panic. Family physicians would play a key role in the initial recognition of a potential bioterrorism attack. Familiarity with the infectious agents of highest priority can expedite diagnosis and initial management, and lead to a successful public health response to such an attack. High-priority infectious agents include anthrax, smallpox, plague, tularemia, botulism, and viral hemorrhagic fever. Anthrax and smallpox must be distinguished from such common infections as influenza and varicella. Anthrax treatment is stratified into postexposure prophylaxis and treatment of confirmed cutaneous, intestinal, or inhalation anthrax. Disease prevention by vaccination and isolation of affected persons is key to preventing widespread smallpox infection. Many resources are available to physicians, when a bioterrorism attack is suspected, including local public health agencies and the CDC.

Although the use of microorganisms as weapons is as old a practice as war itself, the sense of our collective vulnerability to these agents has seldom been as great. The events of late 2001 demonstrated that the United States is vulnerable to terrorist attack carried out by highly motivated, organized, well-funded, and trained individuals. It is our collective good fortune that the perpetrator of the anthrax mailings was not bent on destruction of the scale witnessed on September 11, 2001. Because acute care and critical care nurses are on the forefront of community disease surveillance, they must be aware of the signs and symptoms of illness that may indicate that a biological attack has taken place. Many symptoms of infection or intoxication by biological warfare agents (bacterial, viral, and toxic) are nonspecific and flulike in nature, at least early in the disease process. The essential details of the presentation, diagnosis, treatment, and prophylaxis of the biological warfare agents that merit greatest concern are provided, and five biological warfare agents of particular interest are described in detail: anthrax, ricin
(castor bean) toxin, smallpox, plague, and tularemia. Recommendations are given for additional Web-based resources to allow further study.


A total of 1372 cases of tularemia observed in Japan since 1924 were analyzed. More than 90% of the cases were reported in the northeastern part of the main island of Japan. After World War II, more than 40 cases were reported yearly for 20 years. Since 1966, however, there have been less than 10 cases per year. Ninety-three % of the cases were caused by contact with infected wild rabbits. The pattern of monthly distribution showed a peak in December and also a lower peak in May. The number of patients older than 40 years of age and the proportion of cases in females have gradually increased. In the earlier survey periods almost 70% of the cases were engaged in agriculture but at present this rate is less than 50%. The changes in the occurrence of tularemia in Japan is thought to be related to the change of life style caused by the rapid growth of the Japanese economy after World War II.


Literary data and antiplague institutions' reports demonstrate that Norway rats carry over 24 nosological forms and groups of infectious diseases: plague, tularemia, pseudotuberculosis, intestinal yersiniosis, salmonellosis, erysipeloid, listeriosis, leptospirosis, pasteurellosis, brucellosis, dysentery, paratuberculosis, hemorrhagic nephroso-nephritis, Omsk hemorrhagic fever and Q fever, tick-borne and Japanese encephalitis, lymphocytic choriomeningitis, tick-borne rickettsiosis and rickettsial pox, murine typhus, tsutsugamushi disease and toxoplasmosis.


Infectious diseases have been used as warfare agents, since ancient times. Since the 1920s, military organizations have studied the bacteria of anthrax, plague, tularemia, botulism, brucellosis, glander, Q-fever, and smallpox virus, Filo-, Arena-, Bunyaviruses...
causing hemorrhagic fever or Alphaviruses eliciting encephalitis. These can be dispersed by aerosol. Salmonellae, Shigellae, Vibrio cholerae, distinguished Escherichia coli strains are capable of contaminating food, water, pharmaceutical products. Fanatical groups or terrorist individuals deploy microbial weapons. In the future, genetically engineered recombinant microbes could be used with genomes containing elements with a multiple resistance to antimicrobial compounds and to additional virulence factors. Eventually, these become resistant to all known treatment regimens, vaccination and the host immune response. Microbial terrorist attacks result in an outbreak on a restricted area with a large number of casualties. The disease course is severe and unusually followed by high mortality. Identification of microbes is complicated and delayed. Most countries have neither laboratories at high biosafety level nor specially trained personnel. Physicians might misdiagnose these diseases. Health care systems with minimal elasticity face difficulties in maintaining mass quarantine. A considerable part of health care workers leave hospitals. No plan is available to stockpile medicines. Robust surveillance and laboratory systems coordinated at the international level must be established. All health care personnel should be trained periodically to gain important practical skills. Additional standards governing working conditions with selected microbes will be enforced by law. Related scientific data might be published with restricted access only.


Ticks are currently considered to be second only to mosquitoes as vectors of human infectious diseases in the world. Each tick species has preferred environmental conditions and biotopes that determine the geographic distribution of the ticks and, consequently, the risk areas for tickborne diseases. This is especially the case when ticks are vectors and reservoirs of a pathogen. Since the identification of Borrelia burgdorferi as the agent of Lyme disease in 1982, 15 ixodid-borne bacterial pathogens have been described throughout the world, including eight rickettsiae, three ehrlichiae, and four species of the Borrelia burgdorferi complex. This article reviews and illustrate various aspects of the biology of ticks and the tickborne bacterial diseases (rickettsioses, ehrlichioses, Lyme disease, relapsing fever borrelioses, tularemia, Q fever), particularly those regarded as emerging diseases. Methods are described for the detection and isolation of bacteria from ticks and advice is given on how tick bites may be prevented and how clinicians should deal with patients who have been bitten by ticks.
Since October 3, 2001, the CDC and other organizations have been investigating potential bioterrorist-related anthrax cases. The pediatrician may be faced with complex issues related to diagnosis and treatment of illnesses caused by intentionally released biological agents. The agents that pose a major potential bioterrorist threat are reviewed according to the clinical syndromes they produce: acute respiratory distress with fever, influenza-like illnesses, acute rash with fever, neurologic syndromes, and blistering syndromes. Specific and detailed diagnostic, treatment, and prophylaxis information is provided for anthrax, plague, tularemia, smallpox, botulism, viral hemorrhagic fevers, and other diseases. In cases of suspected bioterrorism, the pediatrician must be able to obtain diagnostic and treatment information efficiently and expeditiously. The system controlling the interaction between public and nonpublic health laboratories in suspected cases of bioterrorism is described. Finally, information regarding emergency contacts and links to educational resources is provided.

The immunological and genetic properties of *Francisella tularensis* vaccine strain are discussed with regard to its use in producing recombinant vaccines. This bacterium-based vector is supposed to be an excellent object for investigating the role of protective antigens in the development of immunity against intracellular bacteria.

Intracellular parasites are those that spend most of their lives within host cells. The fluoroquinolones demonstrate favorable intracellular pharmacokinetics for the treatment of intracellular infections; these agents diffuse and accumulate in the phagocytes, mainly in the cytosol, and do not associate with cellular organelles. The fluoroquinolones are generally active against Salmonella spp. *in vitro*, and have been used successfully in treating typhoid fever, Salmonella bacteraemia in patients with AIDS, and chronic enteric carriage. Fluoroquinolone monotherapy has also been satisfactory in the treatment of tularemia and Mediterranean spotted fever. Quinolones, alone or in combination with other agents, have also shown promise in animal models of legionellosis and in limited clinical studies. Quinolones, particularly ciprofloxacin and ofloxacin, have notable antimycobacterial activity. Both agents have been used in combination with other antimycobacterial drugs in treating infections caused by *Mycobacterium tuberculosis*, M. avium-intracellulare complex, rapidly growing mycobacteria and *M. leprae*, and deserve consideration as part of a multidrug regimen in treating otherwise resistant mycobacterial infections. Clinical data regarding fluoroquinolone monotherapy in brucellosis indicate
 unacceptable failure rates that preclude the use of these agents in this indication (WHAT DOES THIS MEAN?). The quinolones have shown some efficacy in treating genital chlamydial infections, but may be limited in this situation also. In conclusion, as a result of the in vitro activity of the quinolones and their favorable pharmacokinetics, these agents now form an important part of the armamentarium against intracellular infections.

**Penn. 1987.** Factors Associated with a Poor Outcome in Tularemia. *Arch. of Internal Medicine* 147, 265.

**Pepose et al. 1996.** *Ocular Infection & Immunity.* (Mosby: St. Louis).


September 11, 2001, made us aware of the possibility of biologic acts of terrorism against the United States. As the American people brace themselves for this new and ongoing threat to the national well-being, clinicians must understand how to prevent, recognize, and treat the biologic agents that could be used in terrorist attacks. This article discusses the most likely biologic agents, including diagnostic laboratory procedures, treatment options, psychological effects, special populations, and reporting requirements.


We report the first case of a child with a shunt infection caused by Francisella tularensis, the causative agent of tularemia. This patient is also unique in that the disease was limited to the central nervous system.


Affine magnetic sorbents that have no analogs in the practice of our country have been for the first time developed for the rapid diagnosis of various life-threatening diseases (plague, cholera, anthrax, glanders, melioidosis, tularemia, leptospirosis, dysentery, viral hepatitis A) and for the identification of their causative agents. The
The efficacy of new magnet-controlling test systems has been repeatedly confirmed by their applications in epidemiological events and emergencies: in the epidemiological surveillance of viral hepatitis A in Stavropol and in the Caucasian Mineralnye Vody towns, Stavropol Territory (1994), in the identification of cholera patients, in the detection of transmission factors, when monitoring during large epidemic out-bursts of cholera in Stavropol (1990), Daghestan (1994), as well as in the microbiological monitoring during military conflicts in the Chechen Republic (1995). The application of the sorbents has shown that their sensitivity is 4-5 times as much as that of conventional serological assays. In addition, biotechnologies for the production of polyacrylamide and composite aluminosilicate affine immunosorbents with magnetic properties have been developed. They have been used as the basis for designing immobilized granulated antigen reagents for the immunodiagnosis, differential diagnosis, evaluation of the time course and severity of a disease, the efficiency of therapy in patients with systemic scleroderma, proliferative arthritis, systemic lupus erythematosus, juvenile rheumatoid arthritis, osteochondrosis.

The isolation of *Francisella tularensis* from blood culture is extremely rare; a review of the literature produced only five documented cases. However, over a recent 17-month period we saw four cases of tularemia in which the organism was isolated in blood culture. The clinical presentations of our patients and those reported previously were very similar. Most of the patients had a significant underlying disease and presented with the typhoidal form of tularemia. Furthermore, all our patients had sepsis, pleuropulmonary disease, and rhabdomyolysis. Tularemia agglutinins were not performed on admission serum specimens or were nondiagnostic. All the *F. tularensis* isolates from blood culture in our series and most of the recent documented cases were obtained in radiometric blood culture systems, which may be more sensitive than conventional systems for detecting this fastidious microorganism.


We describe a patient with ulceroglandular tularemia who initially responded to therapy
with gentamicin, but then clinically relapsed. Ciprofloxacin was subsequently given for 28 days, and the patient was clinically cured. Aminoglycosides have been considered the drugs of choice in the treatment of tularemia; however, potential alternative treatments do exist. We review the English-language literature on this topic.


CONTEXT: Bioterrorism has existed since before the 14th century; however, the specter of such an attack is much greater today than ever before. Technical expertise in microbiology and molecular testing, combined with the rapidity of worldwide air travel, has ensured that no geographic area would be untouched in a widespread attack. Clinical microbiology laboratories will play a pivotal role in the detection of attacks involving weapons of mass destruction. OBJECTIVE: To identify and discuss the microorganisms most likely to be used as agents of bioterrorism. DATA SOURCES: Data were obtained from literature searches from 1997 through June 2001, using the subject headings of bioterrorism, biological weapons, biological warfare, anthrax, brucellosis, tularemia, smallpox, plague, and botulism. In addition, information was obtained from publications of the Center for Civilian Studies, Johns Hopkins University, the CDC, American Society for Microbiology, and the United States Army Medical Research Institute of Infectious Diseases. DATA EXTRACTION AND SYNTHESIS: Findings obtained from these studies and publications were analyzed for the most likely microorganisms that would be involved in a bioterrorist attack and the most efficient means by which they could be identified. In all instances, the guidelines from the CDC for Level A laboratories were observed. CONCLUSIONS: The most likely microorganisms to be used as biological weapons include *Bacillus anthracis* (anthrax), *Brucella* species (brucellosis), *Clostridium botulinum* (botulism), *Francisella tularensis* (tularemia), *Yersinia pestis* (plague), and *variola major* (smallpox). While knowledge of the potential of these microorganisms is critical, clinical microbiologists and medical technologists possess the basic tools to rule out the suspected pathogens or to refer these isolates to public health laboratories for identification and susceptibility testing.


Cervical lymphadenopathy is the most common presentation of granulomatous inflammation of the neck in children and is usually caused by NTM infection. Although certain granulomatous infections have characteristic imaging features, there is considerable overlap in the imaging appearance of the various disorders. The diagnosis is usually based on a combination of clinical features, histopathologic examination, serologic tests, and culture results.


The objective of this article is to provide a concise overview of the most likely biological and chemical agents that could be used as biochemical weapons. The diagnosis, pathology, prevention, decontamination, treatment, and disposition of these biological and chemical agents are presented in a tabular format for quick reference purposes. The information provided outlines the bare essentials needed to deal with any emergency or catastrophic event involving these agents.


Patients with atypical pneumonias, whether caused by bacterial, fungi, or viruses are associated with pleural effusions. The effusions generally are small and ipsilateral to the parenchymal infiltrate. Usually, the pleural fluid is a serous exudate with a predominance of mononuclear cells. The pleural fluid glucose and, presumably, the pleural fluid pH are not low. The etiologic organism has been isolated from pleural fluid, but usually is not necessary to establish the diagnosis. Pleural biopsy is not helpful in diagnosis with the exception of acute coccidioidal pneumonia and effusion. Pleural effusions in the atypical pneumonias are more common than generally appreciated, rarely provide a definitive diagnosis, and resolve spontaneously with treatment of the pneumonia without pleural space manipulation. Furthermore, evidence of pleural effusion is a marker of the atypical pneumonias and directs the clinician along the appropriate diagnostic pathway based on the clinical presentation.

1. As a result of recent terrorist events, there is an immediate need for occupational nurses to review their disaster plans and to develop strategies to cope with bioterrorism in their workplaces. 2. The CDC has identified three major categories of biological weapons. Category A, the highest priority category (and the focus of this article), includes smallpox, anthrax, botulism, plague, tularemia, filoviruses, and adenoviruses. Dealing with bioterrorism requires occupational health nurses to be familiar with these
organisms, including their pathophysiology and methods of prevention, detection, and treatment. 3. Five principles are useful can be useful in guiding responses to a biological attack. Incorporation of these principles into disaster planning will increase the effectiveness of responses to bioterrorism, if and when it occurs. Developing a plan of action before an event occurs, will greatly enhance the likelihood that the repercussions of such an event are minimized.


Sandstrom. 1994. The tularaemia vaccine. J.Chem.Technol.Biotechnol. 59(4): 315-320. Tularaemia is a disease caused by the facultative intracellular bacterium Francisella tularensis. Vaccination resulting in protective immunity is induced by live vaccine only. Such vaccination can be performed by scarification utilizing the live vaccine strain of F. tularensis (F. tularensis LVS), which results in good but incomplete protection. Humoral as well as cell-mediated immunity are induced by vaccination and it has been shown that cell-mediated immunity is a prerequisite for protection. Since the live vaccine strain is attenuated and the genetic background of attenuation is unknown it is important to consider process parameters so that the immunogenicity of the vaccine is preserved.

Sanford. 1983. Landmark perspective: Tularemia. JAMA. 250(23): 3225-3226. The landmark studies on tularemia by Dr Francis have been recognized by designating the causative organism Francisella tularensis rather than Bacterium tularense. A review of his original 1925 article clearly demonstrates the lasting value of critical clinical, epidemiologic, and laboratory studies. Except for expansion of knowledge concerning some aspects of the epidemiology and clinical spectrum and advances in treatment and prevention, the 1925 article is as contemporary as the current literature and textbooks.

Sarria, et al. 2003. Fatal infection caused by Francisella tularensis in a neutropenic bone marrow transplant recipient. Ann.Hematol. 82(1): 41-43. Francisella tularensis is one of the most infectious pathogenic bacteria known. Even though immunity against this organism is thought to be primarily T cell mediated, some evidence suggests that neutrophils may also play an important protective role. We report a case of tularemia in a neutropenic bone marrow transplant recipient that sheds light on the importance of neutrophils in protection against this infection and review clinical aspects of this fascinating infection emphasizing areas of interest for immunocompromised hosts.

Altogether 105 cases of tularemia were reported to the nationwide notification system for infectious diseases (MSIS) in Norway during the period 1975-90. The zoonosis appears annually in Northern Norway. The first epidemic outbreak was reported from Central Norway in 1984-85. During the nineteen eighties the disease has reappeared in Southern Norway. We review the clinical features and epidemiological patterns of tularemia in Norway. Preliminary investigations indicate that the future drug of choice for treatment of tularemia is one of the gyrase-inhibitors.


Ticks, obligate, blood-sucking members of the order Acarina and class Arachnida, are the most common agents of vector-borne diseases in the United States. Ticks play an important role in transmitting viruses, bacteria, spirochetes, parasites, and rickettsia. This article reviews the epidemiology, microbiology, diagnosis, and treatment of the major tick-borne diseases in the United States.


Very little is known about virulence mechanisms of the highly virulent bacterium *Francisella tularensis*. Specific genetic features of F. tularensis have been obstacles for the development of effective tools for genetic manipulation. However, recent genomic sequencing and large-scale proteomic work have resulted in a substantial increase in the knowledge of F. tularensis. There is also a paucity of information on potential vaccine candidates. Recent work assessing the protective efficacy of the F. tularensis lipopolysaccharide has resulted in important contributions to the understanding of host-protective mechanisms. T-cell-mediated immunity appears to be crucial to protect against virulent F. tularensis strains. Few other vaccine candidates have been identified.

The lymphocutaneous syndrome can be caused by a number of diverse microorganisms requiring very different antimicrobial therapy for resolution. The epidemiology and geographic occurrence of the infection often can provide important first clues to the microbiologic etiology. Accurate diagnosis can be accomplished usually by punch or wedge biopsy of a primary lesion or proximal subcutaneous nodule submitted for histopathologic examination and culture. The microbiology laboratory staff should be alerted to the diagnostic possibilities so that appropriate cultural and incubation techniques, procedures, and precautions can be initiated. Provision of a correct microbiologic diagnosis and institution of appropriate antimicrobial therapy will result in a complete cure in almost all instances. Adjunctive surgical debridement may be required for certain organisms such as Nocardia or Mycobacterium chelonae.


The epidemic situation in the context of many infectious diseases caused by bacteria is presently assessed as being poor in Russia and other countries. The spectrum of pathogens that can reduce national well-being is very wide. The epidemic situation in terms of many infectious diseases, including those caused by such causative agents as Bacillus anthracis, Vibrio cholerae, Yersinia pestis, *Francisella tularensis* and others may deteriorate due to the emergence of their modified forms owing to their specific variability. The above generates the necessity of improving controlling measures or developing the techniques for monitoring the pathogens of infectious diseases, including those in the framework of international cooperation.


The paper summarizes the results of development of the aerosol method, one of the mass ways of human vaccination. Analysis of materials suggests that Russia has designed highly effective live plague, tularemia, and anthrax vaccines that can be used to immunize in different ways: by epicutaneous and subcutaneous, and inhalation routes. The advantages and disadvantages of aerosol vaccination are shown. The correct use of this method provides a substantial effect when the epidemic situation is complicated and when there is a need for vaccination of large cohorts at the earliest possible time.

Recent bioterror attacks and other world events have focused the medical community's attention on agents that might be used in biological warfare. One of these potential biological weapons is *Francisella tularensis*, a gramnegative coccobacillus that is one of the most infectious bacteria known. *F. tularensis* can cause severe, even fatal, systemic tularemia. Under normal circumstances, *F. tularensis* is transmitted by infected ticks, insects, and other animals. As a weapon of terrorism, the bacterium would likely be disseminated as an aerosol and contracted by inhalation. Because many cases of tularemia are characterized by head and neck symptoms, otolaryngologists should be familiar with the diagnosis and management of this disease. In this article, we describe a case of zoonotic tularemia that manifested as a neck mass, and we review the pathophysiology, diagnosis, and treatment of tularemia. We also summarize what is known about its potential as a biological weapon.


**Tarnvik. 1991.** [The Ockelbo disease, nephropathia epidemica and tularemia. A great deal is known about the infectious diseases in the north--but quite a few question-marks are left]. *Lakartidningen.* 88(30-31): 2515-2518.

Tularemia is caused by the facultative intracellular bacterium *Francisella tularensis*. Attenuated live vaccines, such as *F. tularensis* LVS (live vaccine strain), afford good--although not complete--protection; how to judge the degree of this protection has long been a problem. Both natural infection and vaccination result in immunospecific and long-lasting humoral and cell-mediated immunity. The latter is the crucial protective mechanism, whereas the humoral response protects only against strains of reduced...
virulence, like those used in the vaccines. Immune serum has been used to screen for structures of *F. tularensis* with the ability to induce a protective immune response. This immune serum is, however, primarily directed toward antigens different from those involved in cell-mediated immunity. Serum antibodies from primed individuals recognize carbohydrate capsule antigens of *F. tularensis*, whereas T lymphocytes recognize membrane polypeptides of the organism. The preparation of membrane polypeptides from *F. tularensis* is now facilitated by the availability of a capsule-deficient mutant of *F. tularensis* LVS. In vitro, several membrane polypeptides of the mutant stimulate T lymphocytes from vaccinees and from naturally infected individuals. Further studies of the mechanisms of induction of protective immunity should focus on these membrane polypeptides.


Tularaemia is a zoonotic bacterial disease of the Northern hemisphere. The causative agent, *Francisella tularensis*, is spread to humans by direct contact with infected rodents or lagomorphs, aerogenic exposure, ingestion of contaminated food or water, or by arthropod bites. The prevalence of tularaemia shows a wide geographic variation. In some endemic regions, outbreaks occur frequently, whereas nearby rural parts of a country may be completely free. *F. tularensis* is a facultative intracellular pathogen and its primary mammalian target cell is the mononuclear phagocyte. When tularaemia is acquired through the skin, a primary ulcer is often detected and in general, regional lymph nodes become prominently enlarged. When contracted by inhalation, the disease may present with pneumonia. Nearly as frequent, however, is the development of fever and general illness with no respiratory symptoms and no pulmonary radiological changes. When present, the changes vary widely and may sometimes include hilar enlargement indistinguishable from that of lymphoma. Within an outbreak, the first case of tularaemia is not always readily diagnosed. A decade may have lapsed since the disease was encountered and its existence may be more or less forgotten. The difficulty refers especially to the respiratory form, in which symptoms are less specific. In cases of atypical pneumonia or acute febrile disease with no local symptoms, a history of exposure to hares or rodents or merely living in an endemic region should be sufficient to include tularaemia among differential diagnoses. The microbiological diagnosis of tularaemia relies mainly on serology, and the treatment by broad-spectrum antibiotics. For decades, a live vaccine has been used successfully in risk groups but is presently not available due to difficulties in standardization.


Since 1931, when tularaemia was first recognized in Sweden, the annual incidence has varied widely. Except for a few cases, ulceroglandular and respiratory tularaemia have been the only forms of the disease observed. Here, cases from Sweden of oropharyngeal tularaemia and of tularaemia septicaemia and meningitis, are reviewed. Since the cases occurred outside manifest outbreaks, diagnostic difficulties were encountered and the diagnosis was reached more by chance than due to clinical suspicion. Possibly, cryptic cases of tularaemia may be more frequent than what appears from clinical reports.


Atypical organisms such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila are implicated in up to 40 percent of cases of community-acquired pneumonia. Antibiotic treatment is empiric and includes coverage for both typical and atypical organisms. Doxycycline, a fluoroquinolone with enhanced activity against Streptococcus pneumoniae, or a macrolide is appropriate for outpatient treatment of immunocompetent adult patients. Hospitalized adults should be treated with cefotaxime or ceftriaxone plus a macrolide, or with a fluoroquinolone alone. The same agents can be used in adult patients in intensive care units, although fluoroquinolone monotherapy is not recommended; ampicillin-sulbactam or piperacillin-tazobactam can be used instead of cefotaxime or ceftriaxone. Outpatient treatment of children two months to five years of age consists of high-dose amoxicillin given for seven to 10 days. A single dose of ceftriaxone can be used in infants when the first dose of antibiotic is likely to be delayed or not absorbed. Older children can be treated with a macrolide. Hospitalized children should be treated with a macrolide plus a beta-lactam inhibitor. In a bioterrorist attack, pulmonary illness may result from the organisms that cause anthrax, plague, or tularemia. Sudden acute respiratory syndrome begins with a flu-like illness, followed two to seven days later by cough, dyspnea and, in some instances, acute respiratory distress.


*Francisella tularensis* is one of the most infectious bacterial pathogens known and is the causative agent of the zoonotic disease tularemia. In spite of the importance of this pathogen little is known about its virulence mechanisms. However, it is clear that the
bacterium is an intracellular pathogen, replicating mainly in macrophages, with replication in amoebae also having been reported. The genome sequence of a high virulence strain of *F. tularensis* is close to completion and when available, will stimulate further research into virulence mechanisms.


Recognition of an increasing incidence of uncommon pneumonias with a high mortality rate, clusters of cases, or a high incidence of pet illnesses or death should alert medical personnel to the possibility of terrorism with bacteriologic agents. Prompt reporting of such unusual occurrences to the local health department is of paramount importance for early identification of cases, treatment initiation, and institution of preventive measures.


Cyclophosphamide (CY) given before immunization causes greatly increased delayed hypersensitivity skin reactions. Increased cell-mediated immunity is associated with depletion of B-lymphocytes from lymphoid tissue and a depression of those lymphocytes whose precursors turn over more rapidly. In the guinea pig, replacement studies showed that the depleted cells were not T-lymphocytes and had immunoglobulin adherent to their surface, a characteristic of B-lymphocytes. Delayed hypersensitivity reactions increased by CY include chemical contact sensitivity, the tuberculin reaction, delayed hypersensitivity to tularemia vaccine and the Jones-Mote reaction to soluble protein antigens. Pretreatment with CY can also increase the antibody response to some antigens, but depress the response to others. In addition, CY has been found to reverse immunological tolerance where this form of unresponsiveness is due to suppressor cells. CY can also enhance the immune response following depression by antigenic competition or desensitization. Other drugs with a similar, but lesser, effect include melphalan, azathioprine and methotrexate.


Existing data on tularemia infections in children caused by the biovar *Francisella tularensis* palaeartica (type B) are limited. The case histories of all patients younger than the age of 16 years in northern Finland who had tularemia, based on the antibody response, during the years 1967 to 1986 are reviewed. A total of 67 children, 28 girls and 39 boys, were identified as having had tularemia. The occurrence of the disease varied greatly among years. Most of the cases occurred in July, August and September. The epidemiology differed significantly from that reported for *F. tularensis biovar tularensis*.
(type A). This is most probably attributable to the different vector, which was the mosquito in our series, but the tick in areas where type A is common. There were also clear differences in the clinical picture. The ulceroglandular clinical type was the most common. The clinical symptoms and signs were usually quite benign, but the symptoms lasted for a median duration of 26 days. The patients were treated with different antibiotics and there were no differences in the outcome related to the treatment given. Prospective comparative investigations of antibiotic therapy given for tularemia are needed. It is also important to try to identify which strain is causing the disease in each case.


The events surrounding September 11, 2001, and its aftermath have compelled the public health and medical community to face the hitherto unfamiliar reality of bioterrorism. Physicians and public health personnel are frontline soldiers in this new form of warfare. This article provides a general overview of the pathophysiology, clinical presentation, diagnosis, and management of patients infected with the 6 highest priority agents that could potentially be used in bioterrorism. The diseases discussed include anthrax, smallpox, tularemia, plague, botulism, and viral hemorrhagic fevers. Despite the unpredictable nature of bioterrorism, disaster preparedness and knowledge of essential diagnostic and epidemiological principles can contribute substantially toward combating this new threat.


The physician's approach to the differential diagnosis of obscure, atypical pneumonias has changed. The physician needs to expand the diagnostic search when confronted with a perplexing, progressive atypical pneumonia. Diseases examined in this article include anthrax, psittacosis, Q fever, tularemia, pasteurellosis, melioidosis, Rocky Mountain spotted fever, and the plague.

Weapons of mass destruction can be used to harm and terrorize populations. Such weapons include those with chemical, nuclear or biological properties. Obviously computer viruses can add additional barriers to a quick response. The most effective, least costly and greatest threats are biologicals. Biological terror is not new, and biological weapons have been used for centuries. However, as a result of modern technology, the risks are greater now and the outcomes more terrible. Today they include live pathogens, various toxins, and theoretically “bioregulators”--biochemicals affecting cell signaling. Altered cell signaling could be used to induce apoptosis-cell death, or a heightened outpouring of cytokines mimicking overwhelming sepsis, or even an intracellular, biochemical “strike”; causing cellular paralysis. Biological weaponeers now have the frightening ability to alter the genetic makeup of pathogens, rendering them resistant not only to available antibiotic therapy but also to currently effective vaccines. In dark corners of some fringe groups, bioweaponeers are searching for the capability of designing pathogens that target specific races, by virtue of discriminating ligands (1). The resulting morbidity and mortality from use of any biological weapons will be accompanied by chaos, governmental and social instability, panic, an extraordinary utilization of available resources, and an ongoing epidemic of sleepless nights (2,3). Herein I will review some of the issues and some of the currently available biological weapons. The major goal is to highlight the clinical presentations of patients with infections that could be used as biological weapons.


Signs and symptoms related to the gastrointestinal tract and liver may provide important clues for the diagnosis of various tick-borne diseases prevalent in different geographic areas of the United States. We review clinical and laboratory features that may be helpful in detecting a tick-borne infection. Physicians evaluating patients who live in or travel to areas where tick-borne diseases are endemic and who present with an acute febrile illness...
and gastrointestinal manifestations should maintain a high index of suspicion for one of these disease entities, particularly if the patient has received a tick bite. If detected early, many of these potentially serious illnesses can be treated easily and effectively, thereby avoiding serious morbidity and even death.