Brucellosis is one of the most frequently encountered zoonotic diseases, with approximately 500,000 cases identified annually worldwide. *Brucella* are small, gram-negative, nonmotile, non–spore-forming, aerobic coccobacilli that can reproduce intracellularly only. Historically, human disease was thought to be caused by several different species, including *Brucella melitensis*, *Brucella abortus*, *Brucella suis*, and *Brucella canis*. However, these are now thought to be closely related organisms in a single species. The bacteria can survive for many days to weeks in dairy products but are killed by boiling, pasteurization, and souring or lactic acid fermentation of milk.

Brucellosis was first described in 1859 by British Royal Army Medical Corps (BRAMC) physician J.A. Marston among troops in Malta during the Crimean war. In 1886, David Bruce, another BRAMC physician, isolated the bacteria, later named for him, from the spleen of an affected patient in Malta. Approximately 10 years later, a Danish veterinarian, Bernhard Bang, isolated *Brucella* species (*B. abortus*) from cattle with contagious abortions.

Disease is most commonly acquired from contaminated, unpasteurized sheep, cow, goat, and camel milk, and less frequently from direct contact with infected animals among farmers, veterinarians, and abattoir workers. Brucellosis is found worldwide but especially in developing countries, with the highest incidence in the Mediterranean basin, Arabian Peninsula, Indian subcontinent, Mexico, and South and Central America. The illness has also reemerged in Eastern Europe since the collapse of the Soviet Union. Historically, human brucellosis was found in the United States, but rates have declined with the eradication of bovine brucellosis by cattle immunization programs and test-and-slaughter techniques. Currently, in the United States there are fewer than 0.5 cases per 100,000 people, with the highest concentration of cases found along the US-Mexico border.

*Brucella* can be transmitted via inhalation, and this route has been the cause of laboratory-associated outbreaks, making it essential to inform the clinical microbiology laboratory whenever brucellosis is suspected. For safety reasons, serologic diagnosis is preferred at the local laboratory level, and if bacterial culture is to be performed, appropriate biosafety level 3 precautions need to be followed. Human-to-human transmission is rare, but congenital, sexual, and human milk transmissions have all been reported. Although once considered uncommon in younger age groups, disease is now more frequently recognized in children; they are at particular risk given their diet rich in milk (especially when unpasteurized) and in settings where animals share human living spaces.

Organisms enter the host via ingestion or inhalation or through mucous membranes or nonintact skin. The organisms are then taken up by polymorphonuclear cells or macrophages, where they can survive and replicate, evading the immune system. They are then transported to local lymph nodes, where bacterial replication continues, before spreading to reticuloendothelial organs, including the liver, spleen, and bone marrow.
Incubation of disease is typically 2 to 4 weeks but can be several months. Infection can remain subclinical or can result in an acute febrile illness, an insidious illness, or a chronic illness. The clinical picture is often marked by nonspecific symptoms, including fever, arthralgia, and fatigue. Fever often waxes and wanes, which is why the disease is also known as undulant fever. Young children can present with low energy, refusal to bear weight, or failure to thrive. In endemic areas, brucellosis can be the cause of fever of unknown origin.

Focal or localized infection complicates more than half of all cases, and almost any organ system can be involved:
- Osteoarticular infection occurs in 50% of cases of brucellosis. Children typically have large peripheral joint involvement, which can present similarly to other types of septic arthritis, and adults can present with sacroiliitis or spondylodiskitis. Osteomyelitis can also occur.
- Neurologic involvement occurs in 10% of patients. Direct central nervous system invasion is rare; more common are headache, inattention, and depression.
- Gastrointestinal involvement is frequent in children, with two-thirds of pediatric cases accompanied by nausea, vomiting, anorexia, weight loss, and abdominal pain.
- The liver is likely always involved in brucellosis, although liver transaminase levels can be normal or only mildly elevated. Granulomas and liver abscesses can also occur.
- Cardiovascular disease is rare but can present with a range of disease, including endocarditis, myocarditis, pericarditis, endarteritis, thrombophlebitis, or mycotic aneurysms. Endocarditis causes much of the morbidity associated with brucellosis.
- Orchitis or epididymitis complicates 2% to 20% of cases of brucellosis.
- Respiratory complications are relatively rare, found in only approximately 1% of cases, but can present as a range of disease from bronchitis and pneumonia to pulmonary granulomas, nodules, and abscesses. Nodular disease can be confused with pulmonary tuberculosis. Laboratory workers exposed to Brucella via the airborne route can develop pneumonia.
- Bone marrow suppression is commonly encountered. The spleen is also often involved, given its role in the reticuloendothelial system, and hypersplenism can exacerbate hematologic abnormalities.

- A range of cutaneous or mucosal lesions has been reported and may represent hypersensitivity response, immune complex deposition, or direct bacterial invasion.
- Ocular involvement is also encountered, most commonly as anterior uveitis or chorioretinitis.
- Of women affected with brucellosis during pregnancy, one-half to one-third develop complications, which include intrauterine infection, fetal death, spontaneous abortion, premature delivery, and low birthweight. Neonates born to mothers with brucellosis may have congenital infection and malformations. Maternal treatment can help improve outcomes.

As with other intracellular pathogens, cell-mediated immunity is important for controlling established infection. Antibodies play a limited role in fighting infection but are helpful for diagnosis. Immunoglobulin (Ig) M levels increase in the first week of infection, followed by increased IgG levels in the second week. High or rising antibody titers can help establish the diagnosis. After treatment, IgG and IgM levels decline, but IgG decreases more quickly and IgM can persist at low titers for months to years. Persistently elevated IgG and IgA levels beyond 6 months indicate chronic infection or relapse. However, serology should be interpreted with caution because negative test results cannot exclude a recent infection, and antibodies (particularly IgM) can persist after recovery. The IgG avidity test can be useful because high avidity suggests immune memory (indicating old infection) and low avidity suggests more recent infection. B canis is not detected on standard serologic testing because of differences in the antigens it presents.

The diagnosis of brucellosis can also be made by isolating the bacteria from blood, bone marrow, or tissue cultures provided that biosafety level 3 precautions are followed to protect laboratory personnel from infection. In vitro, Brucella have slow growth, so cultures should be monitored for up to 28 days. Newer continuously monitored blood culture systems can detect growth within 7 to 10 days. Polymerase chain reaction–based testing can provide a more rapid diagnosis and can detect bacteria within 10 days of inoculation.

Treatment of brucellosis demands a multidrug regimen because there is a high rate of relapse with monotherapy. In vitro, many drugs show activity against Brucella but clinically are less effective. The cornerstone of treatment for uncomplicated disease in adults and children older than 8 years is doxycycline, with the addition of an aminoglycoside (strep-tomycin or gentamicin) or rifampin. In younger children...
and pregnant women, for whom tetracyclines are contraindicated, trimethoprim-sulfamethoxazole can be used as an alternative, with the addition of rifampin. Treatment of uncomplicated disease is usually for 6 weeks. Neurobrucellosis and endocarditis typically require longer treatment courses of 4 to 6 months with doxycycline or trimethoprim-sulfamethoxazole plus rifampin. Unfortunately, relapses are common (5%–15% cases) and frequently result from poor compliance with a prolonged course of therapy, inappropriate antibiotic drugs, or inadequately treated focal infection. Primary drug resistance to tetracyclines and aminoglycosides has not occurred, so these medications can be used to treat relapsed disease.

**COMMENT:** I must admit I’d never heard, as far as I can remember, of David Bruce before reading this In Brief by Drs Harrison and Posada. His story, it turns out, is interesting on several counts. Born in Australia to Scottish parents, Bruce and his family returned to their homeland when he was a young child, and he eventually earned his medical degree at the University of Edinburgh. Early in his career he joined the BRAMC and was posted to Malta, where he led the investigatory commission that eventually identified the cause of a serious outbreak of fever among British soldiers stationed on the island: So-called Malta fever turned out to be an infection caused by a bacterium initially named *Micrococcus melitensis*, later renamed in honor of Bruce. Shortly afterward, Bruce was sent to South Africa, where he studied an outbreak of cattle disease that he determined to result from a trypanosome transmitted by the tsetse fly. African trypanosomiasis, of course, causes not only the animal disease known as nagana but also sleeping sickness in humans, and the protozoan agent is named *Trypanosoma brucei*.

To his credit, on another front, Bruce insisted that his wife, Mary, who assisted him in all his work as a microbiologist, share credit for his accomplishments, and her name appears as coauthor on many of his published papers. His name is 1 of 23 that decorate the façade of the London School of Hygiene & Tropical Medicine as a leading founder in public health.

— Henry M. Adam, MD
Associate Editor, In Brief

**Correction**
An error appeared in the print version of the January 2018 In Brief “Contiguous Gene Syndromes” (Pereira E, Marion R. Pediatrics in Review. 2018;39(1):46-49, DOI: 10.1542/pir.2016-0073). In the Table, the description of 22q11.2 deletion syndrome should include “hypocalcemia” instead of “hypercalcemia.” The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

**ANSWER KEY FOR APRIL 2018 PEDIATRICS IN REVIEW**
Vitamin Excess and Deficiency: 1. A; 2. C; 3. B; 4. D; 5. D.
Atopic Dermatitis: 1. D; 2. D; 3. E; 4. C; 5. A.
Clinical Presentation, Evaluation, and Management of Neuroblastoma: 1. C; 2. E; 3. D; 4. C; 5. D.