Chapter 6

Stress, Disease and Tuberculosis in Elephants

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Tuberculosis (TB) is one of the most serious diseases affecting captive elephants today. It also has potentially grave consequences for wild populations. Although animals are the source of many human diseases, it appears that humans are most often the source of TB for elephants. The interrelationship between stress and disease is now widely acknowledged in human and veterinary medicine. Can this information benefit elephants? What do we know about TB in elephants? Is further research needed? Can information about stress and TB in humans be of value for infected elephants? Can we prevent the introduction of this devastating disease to the wild before it affects this endangered species as it has affected our own species?

An understanding of TB in humans will lay the groundwork for a clearer understanding of TB in elephants. I will discuss TB and stress in humans and then present a brief history of TB in elephants and the challenges to diagnosis and treatment in our largest land mammal. I will explore the implications of stress in the pathogenesis of TB in elephants. I will explore the potential introduction of TB into wild elephant populations and conclude with a discussion of current and future research.

Tuberculosis: a global crisis

In an age when the human immunodeficiency virus (HIV), Ebola virus, cancer and heart disease command the health news headlines, TB is an often-forgotten disease. Yet, worldwide, it is the leading cause of death from an infectious agent. Thirty million people died from TB in the decade between 1995 and 2005. A startling two billion people—one-third of the earth’s population—are currently infected. TB is endemic in Southeast Asia and 33 percent of all cases occur in this region. The highest mortality, however, occurs in Africa due to co-infection with HIV and a lack of resources for surveillance and drugs for treatment. Tuberculosis has been reported in every state in the United States and between 10 and 15 million Americans are infected.

One observer describes TB as “Ebola with wings” to depict the ease with which it has spread across the globe. The World Health Organization (WHO) has designated TB a “global crisis,” and a major initiative, The Global Plan to Stop TB 2006-2015, aims to cut human TB deaths in half by 2015 compared to 1990 levels (See the “Stop TB Partnership” [http://www.stoptb.org/globalplan/] for more information).
What causes TB?

Tuberculosis is caused by a bacterium discovered by Robert Koch in 1882. Unlike most bacterial diseases that run their course quickly, TB is an insidious and chronic disease that may linger for decades or remain hidden only to explode into an acute crisis.

The causative agent in humans is *Mycobacterium tuberculosis*, a member of the *Mycobacterium tuberculosis* complex. Other members and their target species include *M. bovis* (cattle), *M. africanum* (the human form in Africa), *M. microti* (voles) and *M. bovis BCG* (the strain used to make vaccines). There are over 100 other species of mycobacteria, including an avian form (*M. avium*) and numerous non-tuberculous forms that are found commonly in the environment. These are also known as MOTT (mycobacteria other than tuberculous).

Mycobacteria can infect humans, non-human primates, domestic and wild ungulates and carnivores, marine mammals, psittacine birds, reptiles and fish. Susceptibility to specific mycobacteria varies with the species (Montali, Mikota & Cheng 2001). The human form of TB occasionally infects dogs and parrots and has even been diagnosed in cattle and bongo antelope. Humans are susceptible to the bovine form of TB and immuno-compromised individuals may become infected with avian TB. The discovery that bovine TB was transmitted to humans via cow’s milk precipitated legislation requiring the pasteurization of milk and cheese.

Tuberculosis in elephants in the United States is caused primarily by the human strain, although one case due to *M. bovis* has been reported and an unusual non-tuberculous mycobacteria has affected two elephants (Lacasse, Terio, Kinsel, Farina et al. 2007). Tuberculosis due to *M. bovis* may be more common in Asian range countries where captive elephants share grazing land with domestic cattle.

How is TB transmitted?

TB is transmitted by aerosolization. Infective droplets may be released into the air when an infected person speaks, coughs or sneezes. Tuberculosis can only be transmitted from individuals with active infections. A number of factors influence the probability that an individual will become infected after an exposure. The virulence of the organism, the infectiousness of the carrier, the environment in which the exposure occurred and the duration of the exposure all come into play. A casual exposure is less likely to result in infection than a chronic exposure. Health care workers are therefore at greater risk. Many TB cases are clustered in households because there are multiple opportunities for infection to be transmitted among family members. A single concentrated exposure may also result in infection (Dalovisio, Montenegro-James, Kemmerly, Genre et al. 1996).

How is TB diagnosed in humans?

The intradermal tuberculin test (also known as the Mantoux test) is used in humans as a screening test for TB. A small amount of tuberculin is injected intradermally (within the skin). Tuberculin is a diagnostic agent derived from particular strains of bovine TB (bovine strains are used because bovine and human TB are very closely related and will cross-react). The test is read at 48 hours by observing the injection site for evidence of induration (swelling). The measurement of the induration, together with the individual's risk category, determine whether the test is positive. A 15-mm swelling is considered positive in almost all cases. A 10-mm reaction is positive in drug users and in recent arrivals from certain high-TB-risk countries. A five-mm reaction is positive in individuals who are immuno-compromised (from chemotherapy or HIV, for example) or if there has been a recent contact with a known active TB case.
After exposure to TB, there are five possible scenarios: 1) no infection occurs; 2) infection is established and there is acute disease; 3) infection is established but later eradicated; 4) infection is established and contained—this is latent disease; or 5) infection is established, contained and then reactivated. In all but the first scenario, a human will have a positive tuberculin test. Following a positive skin test, further diagnostics such as sputum cultures and chest radiographs are employed to determine whether active disease is present. According to the WHO, latently infected humans with normal immune systems have a four to 10 percent chance of developing active TB at some point in their lives. Immunodeficiency disorders such as HIV present a significant risk factor for the development of active TB. Further information about TB in humans is available from the Centers for Disease Control [http://www.cdc.gov/nchstp/tb/default.htm].

**Stress and TB in humans**

While the association between stress and disease has been noted as far back in time as Aristotle (fourth century BCE), it is only recently, through the development of the field of psychoneuroimmunology, that a scientific basis for this association has been elucidated.

Stress and the underlying neuro-endocrine mechanisms that define the stress response were discussed in detail by Bradshaw (Chapter 4). Numerous factors affect how an individual animal will respond to stress. These include species differences, individual differences, sex, age, reproductive stage, social position and prenatal, neonatal or early experiences. Animal studies have shown that susceptibility to disease may increase, decrease or remain unchanged depending on the species-stressor-pathogen combination.

Chronic stress (distress) suppresses the immune system, diminishes wound healing and decreases the inflammatory response. Glucocorticoids decrease circulating lymphocytes (B cells, T cells and Natural Killer cells) that modulate the response to invading pathogens. The central nervous system, which has a direct effect on the organs where lymphocytes are produced and stored (the bone marrow, thymus, spleen and lymph nodes), is also involved. These pathways are complex and a detailed discussion is beyond the scope of this chapter. Simply stated, the status of the immune system determines how a human (or an elephant) will respond after a TB exposure and stress can profoundly influence the immune system.

Social deprivation has been shown to affect immunity and long-term survival in monkeys (Lewis, Gluck, Petitto, Hensley et al. 2000) and it is reasonable to expect that this may also be true for elephants. Many elephants in captivity were wild-caught as youngsters and separated from their mothers and families. African elephants in particular likely witnessed the slaughter of related adults during the capture process (Bradshaw, Chapter 4; Lee & Moss, Chapter 2; Poole & Granli, Chapter 1; Sheldrick, Chapter 16). These young elephants were weaned prematurely and transported to live in conditions drastically different from those to which they are ecologically and evolutionarily adapted. Movement of elephants between facilities was (and to an extent still is) a common practice, thus further preventing or disrupting social bonds critical to elephant well-being. While the effects of these early stressors on the elephant immune system and survivability have not been studied, it would be interesting to do so, and to compare the life histories of elephants that become infected following exposure to TB, with those that do not.

The association between stress and TB was presented to the scientific community in a landmark study “The Influence of Psychic Acts on the Progress of Pulmonary Tuberculosis,” published in 1919. The author, Thoru Ishigami, reported that he and numerous other colleagues had observed that the mental state of their patients significantly influenced the course of TB progression. Nervous patients or those experiencing financial or personal loss were more likely to succumb to TB.
than optimistic patients with few worries (Ishigami 1919).

Ishigami also demonstrated that adrenaline (i.e. stress) inhibited the phagocytosis (engulfing) of *M. tuberculosis* by macrophages *in vitro*. Ishigami suggested that the high rate of TB among Japanese students was due to the inherent stress of the educational system in place at the time. His appeal for educational reform went unheeded.

The body’s defense systems determine the outcome of events following exposure to TB. One person may avoid infection altogether and another develop overwhelming disease. It all depends on the individual’s immune response. In 1956, Hans Selye, the father of the “General Adaptation Syndrome” (the stress response) suggested that these varying responses to TB might be mediated via adreno-cortical-tropic hormone (ACTH) and cortisol. Selye did not think that stress directly caused disease. Rather he believed that the body’s capacity to resist disease and overcome the stress component often meant the difference between succumbing and not succumbing to a disease (Selye 1956).

Rats are naturally resistant to TB and will not become infected even when injected with the organism. Rats injected with TB and ACTH, however, not only become infected; they die. Under the influence of ACTH (mimicking stress), their innate genetic resistance to TB is overcome. Of this experiment, conducted in 1952, Selye commented:

“This experiment gives food for thought and raises the question: What is disease due to? It shakes our certainty in the pathogenesis of disease being due to any one particular agent. It makes us think rather that many diseases are due to pathogenic situations, to a constellation of disease-producing circumstances, all of which must be present at the time in order to cause the disease.”

(Selye 1956, p. 60-61)

While it appears that stress can overcome the inherent resistance of a species, genetics is another determinant of individual resistance or susceptibility to TB. Genetic epidemiology is an active area of TB research in humans (Kim, Lee, Lee, Sin et al. 2003; Liu, Cao, Zhang, Tian et al. 2004; Malik, Abel, Tooker, Poon et al. 2005; Barreiro, Neyrolles, Babb, Tailleux et al. 2006; Li, Zhang, Zhou, Huang et al. 2006). Genetic differences may explain why dexamethasone (a steroid drug that induces the same changes in the body as a stress response) administration will increase the growth of TB in blood monocyte cells from some donors but will have no effect on TB growth in monocytes from other donors (Boomershine & Zwilling 2000).

While we owe a debt of gratitude to Louis Pasteur and Robert Koch for advancing our knowledge of pathogens and disease, the germ theory has left a legacy that suggests that microorganisms are the sole perpetrators of disease, when indeed they are but one factor in the complex constellation that Selye described. Even Pasteur on his deathbed said, “Le germe n’est rien, c’est le terrain qui est tout” (“The microbe is nothing, the soil is everything,” as quoted in Selye 1956, p. 59).

T. H. Holmes studied patients at a TB sanatorium and demonstrated a positive correlation between TB and stressful events that occurred years prior to the disease. His later studies also showed higher rates of recidivism, compared to controls, among patients who experienced emotional problems while hospitalized (Holmes 1956).

Prior to the discovery of antibiotics, TB was treated with rest, fresh air, sunshine and good nutrition and many patients improved. The “home sanatorium” method of Joseph Hersey Pratt utilized these basic therapies but added class meetings (a forerunner of group therapy) and a “friendly visitor” (today’s social worker or public health nurse). That Pratt achieved better results than two
traditional sanatoriums is likely due to the stress-reducing effects of the social support that is now accepted as a component in the treatment of many diseases (Sabin 1990).

The body's immune response to TB is complex and has not yet been thoroughly explained. Recent research is helping to explain why some of the treatments employed prior to the availability of antibiotics were effective. We know that the TB organism is killed by sunlight. A team of researchers at the University of California, Los Angeles (UCLA) and the Harvard School of Public Health has recently demonstrated that vitamin D plays a crucial role in the production of cathelicidin, which kills TB bacteria. Vitamin D is produced by the body when sunlight reaches the skin; however, the skin pigment melanin, more abundant in darker skin, shields the body from the sun's rays and reduces vitamin D production. This finding explains why people of African descent are more susceptible to TB than Caucasians and have more severe disease. It also explains why sanatoriums in sunny mountain locations were an effective traditional treatment (Liu, Stenger, Li, Wenzel et al. 2006).

A brief history of TB in elephants

TB has plagued both man and animal since ancient times. Tuberculous scarring has been observed on the bones of mastodon skeletons recovered in North America and dating to the last ice age (Rothschild & Laub 2006), and DNA from the human form of TB has been isolated from a 17,000-year-old bison bone (Hecht 2001).

The first evidence that elephants might contract tuberculosis derives from Sanskrit documents over 2,000 years old (Iyer 1937). While the causative organism was obviously unknown at this time, the disease was described clearly. In more recent times, a case at the London zoo in 1875 (Garrod 1875) was followed by sporadic reports in the early and mid-1900’s (Damman 1909; Thieringer 1911; Narayanan 1925; Bopayya 1928; Baldrey 1930; Gorovitz 1962; Seneviratna, Wettimuny & Seneviratna 1966; Gorovitz 1969; Pinto, Jainudeen & Panabokke 1973; Greenberg, Jung & Gutter 1981; Gutter 1981; Jones & Good 1982; Saunders 1983). African elephants are susceptible to TB (Gorovitz 1962, 1969), but most cases have occurred in Asian elephants. Whether or not this reflects a greater susceptibility to TB among Asian elephants is unknown. Asian elephants have been maintained in captivity for over 2,000 years, a history that is not shared by African elephants. The seemingly greater susceptibility of Asian elephants to TB may simply reflect their closer relationship and exposure to TB-infected humans.

The year 1996 is often regarded as the year that elephant TB “emerged” in the United States. The highly publicized deaths of two circus elephants from advanced TB within a three-day period prompted concern from both the public and the United States Department of Agriculture (USDA). Other cases were soon to follow in the United States (Binkley 1997; Mikota, Larsen & Montali 2000; Mikota, Peddie, Peddie, Isaza et al. 2001) and Europe (Gavier-Widen, Hard Af Segerstad, Roken, Moller et al. 2002; Lewerin, Olsson, Eld, Roken et al. 2005; Moller, Roken, Petersson, Vitaud et al. 2005).

The circus elephant deaths led to the formation of an Elephant TB Advisory Panel and subsequently to the National Tuberculosis Working Group for Zoo and Wildlife Species. These groups were charged with the task of developing strategies to diagnose and control the disease in elephants and non-domestic ungulates. What resulted in 1998 was a document entitled “Guidelines for the Control of Tuberculosis in Elephants” that specifies methods for diagnosis, surveillance and treatment. It is administered by the USDA as Policy 21 under the Animal Welfare Act. The Guidelines were revised in 2000, 2003 and 2007 (in progress) as research led to a better understanding of TB
in elephants (USDA 2003).

**How is TB diagnosed in elephants?**

Determining whether an elephant has active TB can present a diagnostic challenge. Many elephants do not show clinical signs until the disease is quite advanced. Radiography is not feasible in elephants as x-rays cannot penetrate their large mass. The intradermal tuberculin test is not accurate in elephants (Mikota et al. 2001; Lewerin et al. 2005). What has evolved as the “gold standard” test is the “trunk wash”—the elephant equivalent of a sputum culture. The sample is collected by training elephants to accept the instillation of sterile saline into their trunks. The saline “washes” the lining of the trunk and serves as a vehicle to collect any pathogenic organisms that may be present. Elephants are taught to exhale into a zip-lock bag that serves as a collection device, and then the sample is transferred to a secure tube, and submitted to a laboratory for culture. From this point on, the lab procedures are the same for elephants as for humans.

While culture is the current “gold standard,” it has inherent limitations. Similar to humans, elephants can shed TB intermittently so a triple sample method is used (three samples collected on separate days over the course of a week) to increase the chances of detection. Although a positive culture is diagnostic for TB, a negative culture does not necessarily rule out disease, because an infected animal may not have been shedding at the time of sample collection.

Experimental serological tests have shown great promise to diagnose TB in elephants (Larsen, Salman, Mikota, Isaza et al. 2000; Lyashchenko, Singh, Colangeli & Gennaro 2000; Anon 2005; Lyashchenko, Miller & Waters 2005; Lyashchenko, Greenwald, Esfandiari, Olsen et al. 2006). In some cases, these tests have been positive years in advance of culture. Serological tests are indirect—that is, they detect antibodies to TB rather than detecting the actual TB organism.

**Is TB in elephants a health risk for humans?**

Tuberculosis is a zoonotic disease and can potentially be transmitted from animals to humans. In the only published report of an elephant and human infected with the same TB strain, it could not be proven whether the transmission was from elephant to human or human to elephant (Michalak, Austin, Diesel, Bacon et al. 1998). While many variables determine the course of events following exposure to TB, the duration of exposure is one of the most significant, thus placing elephant handlers and veterinarians at greatest risk (Davis 2001; Oh, Granich, Scott, Sun et al. 2002). While contracting TB from an elephant during a casual exposure is possible, it is not likely in healthy humans with functional immune systems.

**How is TB in elephants treated?**

Ironically, while animals are typically the model for human diseases, in the case of TB, humans are the model for elephants. This has occurred for two reasons. First, there is no acceptable animal model upon which to base our approach to TB in elephants. Tuberculosis in cattle is controlled by a test and slaughter program that cannot be applied to animals like elephants. There is very little information available on TB treatment in cattle or any other animal species. Secondly, as elephants are affected primarily by the human form of TB, it is logical to apply to elephants what is known about the disease in humans.

The treatment protocols that are a part of the Guidelines for the Control of Tuberculosis in Elephants are therefore based on protocols used for humans. The same drugs are used, although elephants are generally treated for a longer period. This is to provide for a greater margin of safety while we continue to study the pathogenesis of TB in elephants. Studies that we have conducted
in elephants to measure blood levels of anti-tuberculosis drugs have supported this approach and we can achieve drug levels in elephants known to be effective (i.e. curative) in humans (Maslow, Mikota, Zhu, Isaza et al. 2005; Maslow, Mikota, Zhu, Riddle et al. 2005; Zhu, Maslow, Mikota, Isaza et al. 2005; Peloquin, Maslow, Mikota, Forrest et al. 2006). Depending on the drug, it may be administered orally or rectally. Elephants have an exquisite sense of taste and will often reject oral medications, even if hidden in the tastiest of treats. Conversely, they can be readily conditioned to accept rectal administration and this route is preferred for the anti-tuberculosis drugs isoniazid and pyrazinamide. Rifampin, one of the main drugs, can only be given orally however, as adequate blood levels cannot be achieved with rectal administration. Like humans, elephants may experience drug side effects such as appetite loss and elevation of liver enzymes from some of the anti-tuberculosis drugs. Careful monitoring is required during treatment.

**Stress and TB in elephants**

There is much that we do not yet know about TB in elephants. As of this writing, about 12 percent of Asian elephants in the United States were diagnosed with TB between 1994 and 2006. It is likely that this is an underestimation of the true number of infected elephants, as TB can remain latent for years. The serological tests discussed above have predicted the onset of disease years in advance of positive cultures and it is likely that more infected elephants will be identified once these tests become more widely available.

Are elephants as a species more susceptible to TB? Other species kept in captivity in close association with people (tigers in circuses, for example) have not become infected.

Genetics is a primary determinant of disease susceptibility of resistance in humans. Do elephants carry genes that confer susceptibility of resistance to TB? A pilot study to investigate this is about to begin (see http://www.elephantcare.org).

What about Vitamin D? Perhaps the dark skin of the elephant also affects Vitamin D production and cathelicidin as described in the human study above. It would be interesting to investigate this possibility.

It is widely accepted that stress influences both susceptibility to TB and its severity once infection is established (Boomershine 2000). Given the clear association between stress and TB in humans it is logical to assume a similar association between stress and TB in elephants (and perhaps other diseases as well). The numerous stressors experienced by captive elephants have been described adequately above and in other chapters of this book. Recall that TB is a human disease and that elephants in captivity are exposed to a disease they would not normally encounter living in their natural habitat in the wild.

Although prompt identification of infected individuals, initiation and completion of appropriate therapy and ongoing surveillance of the population are critical to the control of TB in elephants, the role of stress should not be overlooked. Differences (or variations) in husbandry, nutrition and social well-being may influence which elephants succumb to disease following exposure, and which elephants—once infected—respond to treatment.

The occurrence of TB in elephants may be a symptom of a greater problem—namely our inability to meet the social and biological needs of this amazing and intelligent animal.

**Implications for wild elephant populations**

Tuberculosis has not yet been reported in wild elephants. There is undoubtedly the potential for this occurrence and the absence of reports may only reflect a lack of surveillance. Tuberculosis has been reported in the literature and anecdotally in captive elephants in several of the 13 Asian
range countries (where elephants are still found in the wild). These are the same countries where TB is highly endemic within the human population.

The elephant is revered in many parts of Asia and is both a cultural and religious icon. Elephants are common at temples, festivals and tourist attractions in India, Nepal and Thailand. These events present ample opportunity for elephant-human intermingling and the spread of disease between species. Although TB in elephants probably originated from humans, infected elephants may be a potential reservoir to pass the disease back to humans. This epidemiological possibility is yet to be explored.

In some countries it is common for wild and captive elephants to intermingle. Captive elephants may be released into the forest to browse at night or wild bulls may enter camps to breed receptive elephant cows. Such management practices pose a great risk for disease transfer to wild elephants. The transfer of a primary human pathogen into free-ranging wildlife has already occurred with the introduction of *M. tb* to free-ranging banded mongooses (*Mungos mungo*) in Botswana and suricates (*Suricata suricatta*) in South Africa (Alexander, Pleydell, Williams, Lane et al. 2002), suggesting that free-ranging African elephants, as well as Asian, may be at risk. The potential for the introduction of TB into wild elephant populations is of great concern. Prevention is crucial—if it is not already too late.

**Research needs**

Elephant tuberculosis research is ongoing and is a major focus of Elephant Care International (http://www.elephantcare.org/projects.htm#Initiative). Additional studies are needed to identify alternative therapeutic agents that minimize some of the side effects that have been observed. More cost-effective treatments must be identified if captive elephants in Asia are to be treated. The cost of treating a single elephant in the United States exceeds $50,000.

The new serological tests promise improved means of diagnosis, but still lacking is a rapid diagnostic test to identify elephants that are shedding the bacteria. Currently under investigation in both humans and elephants is a biosensor—a breathalyzer that detects the *Mycobacterium tuberculosis* organism instantly. Improved diagnostics like the above, and others as yet undeveloped, will be critical to the management of elephants in Asia where segregation may be an alternative to costly treatment to prevent the spread of disease to other elephants or humans.

If the genetic study described above reveals that elephants have a gene that confers susceptibility (or resistance) to TB, this too could be used as a management tool to limit exposure of elephants at risk and prevent TB introduction to already threatened wild populations.

**References**


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