CHAPTER

13

Animals and Human Health: Where Do They Meet?*

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INTRODUCTION

Humans share the planet with a bewildering variety of other animals and plants, forming an intricate web of interactions. Disturbances that negatively impact the environment or the health of biological organisms will affect the harmonious functioning of their interactions; thus, human health depends on the health of the organisms with which we interact and the environment in which we all live.

The interrelationships between society and nature and the importance of environmental health to human health have become widely acknowledged (Alves and Rosa, 2007; WHO, 2005), drawing attention to the fact that biodiversity losses will have direct or secondary effects on human well-being. Thus, human health must not be considered in isolation, for it depends on the quality of the environment in which we live—for people to be healthy, the environment must be healthy (Alves and Rosa, 2007). The recognition that human, animal, and environmental health are linked generated the "One Health" concept, which is defined by the One Health Commission (2010) as "the collaborative effort of multiple disciplines to obtain optimal health for people, animals, and our environment." Mi et al. (2016) emphasized that one health seeks to understand the interactions between humans, animals, and environmental factors, and their impacts on health.

Extremely close connections have existed between humans and animals throughout history (Alves, 2012), and we likewise share hundreds of illnesses. Cross-species transmissions and the emergence and eventual evolution of a plethora of infectious pathogens have been observed ever since the establishment of human–animal interfaces (Reperant et al., 2012), with links between human and animal health having profound effects on almost every aspect of our lives.

*This chapter is a revised and updated version of the section "The role of fauna in human health," extracted from an article by Alves, R.R.N., 2012. "Relationships Between Fauna and People and the Role of Ethnozoology in Animal Conservation. Ethnobiology and Conservation 1," 1–69.

Ethnozoology
http://dx.doi.org/10.1016/B978-0-12-809913-1.00013-2

The links between animals and human health have been substantiated throughout the history of mankind, from causes to cure of human diseases. Seven main aspects should be highlighted when considering this connection: (1) animals as the cause/disseminator of diseases for humans and vice versa; (2) animals as sentinels of human health; (3) the use of animals in traditional medicine systems; (4) animal-assisted therapy; (5) biotherapy; (6) animals as a source of drugs; and (7) use of animals in medical research. These aspects will be briefly discussed in this chapter.

Animals as Cause/Disseminator of Disease in Humans and Vice Versa

Since ancient times, human beings have related the appearance of certain diseases and epidemics to the presence or influence of animals that are considered to presage bad omens, diseases, and death (Ávila-Pires, 1989). This is not surprising, considering that the natural world has a strong influence on the transmission of disease to humans from animals and vice versa, and the perception of more primitive societies therefore certainly reflects daily experiences. As pointed by Wolfe et al. (2007), human hunter/gatherer populations currently suffer, and presumably have suffered for millions of years, from infectious diseases similar or identical to diseases of other wild primate populations.

When an infectious agent responsible for a human disease is also capable of infecting other species, these species may act as reservoirs or vectors for the disease (European Commission, 2011). Arthropods, for example, transmit hundreds of different known infectious and parasitic agents to humans and animals around the world. These vectors include almost all forms of blood-sucking arthropods: mosquitoes, ticks, mites, biting midges, sand flies, kissing bugs, bed bugs, black flies, lice, fleas, and deer and horse flies (Seymour, 1984).

Diseases and infections that are naturally transmitted between animals and humans are known as zoonoses (Bell et al., 1988; Krauss, 2003) and have been known to affect human health throughout history (Kruse et al., 2004). Such diseases have an important impact on public health and economy, and on the conservation of wildlife (Cleaveland et al., 2001). Exposure of humans to zoonoses occurs in different ways, from well-known or well-understood direct transmission routes, such as bites and rabies, to less obvious pathways, the risk factors or potential exposure routes of which are difficult to recognize and are interlinked in a relationship network between human beings, animals, and the environment (Friend, 2006). The most frequent sources of zoonose transmission comprise food and contaminated water, vector insect bites and scratches, or bites from infected animals (Chomel, 2002).

Zoonotic diseases account for approximately 75% of emerging infectious diseases (Chomel et al., 2007; Taylor et al., 2001). A literature search showed that more than 800 human pathogens are zoonotic (Taylor et al., 2001; Woolhouse and Gowtage-Sequeria, 2005). According to Weiss (2001), some of these pathogens may cause serious diseases in wild animals but, in some cases, the animals act as reservoirs, without showing any clinical symptoms (Williams et al., 2002). As mentioned above, zoonoses can be transmitted by direct contact with infected animals, dead or alive, which are used by humans in several ways, including consumption as food or as pets. The consumption of animal products as food or in traditional medicine, for example, facilitates the transmission of serious and widespread zoonoses, such as tuberculosis or rabies (De Smet, 1991; Schnurrenberger and Hubbert, 1981; Still, 2003). Another example deserving mention is avian influenza (Influenza A) viruses; these are responsible for highly contagious acute illness in humans, pigs, horses, marine mammals, and birds, occasionally resulting in devastating epidemics and pandemics (Bengis et al., 2004).

Wild animals constitute an important but poorly known reservoir of emerging infectious diseases, most of which are of zoonotic concern (Pérez, 2009). The trade in wildlife for food consumption, medicines, and as pets, among other uses, involves the capture and sale of billions of animals of incredibly wide varieties of species (Alves et al., 2010a; Alves et al., 2013a; Pérez, 2009; Roldán-Clarà et al., 2014). Wildlife commercialization, both legal and illegal, is considered a significant driver of zoonotic diseases—leading to the introduction of zoonoses and/or foreign diseases that may impact domestic animals and/or native wildlife species (Karesh et al., 2005; Rostal et al., 2012). Hunting and the consumption of bushmeat are important routes for the introduction and transmission of zoonotic diseases (Van Vliet et al., 2017). Any wildlife species harvested for bushmeat could be a potential source of zoonotic diseases that could be transferred during hunting, butchering, or preparation (Karesh and Noble, 2009; Wolfe et al., 2000). Armadillos, for example, are widely hunted as food resources and for medicinal uses, but are natural reservoirs of etiological agents of several zoonotic diseases that affect humans—such as leprosy, trichinosis, coccidioidomycosis (valley fever), Chagas disease, and typhus (Silva et al., 2005). More than 100 occurrences of pulmonary mycosis, for example, were recorded in 40 municipalities in Piauí state in northeastern Brazil (Alves et al., 2016). The exotic pet trade deals with an increasing range of wild animal species, from invertebrates to mammals (Pérez, 2009), and it is believed that epidemics such as SARS (severe acute respiratory syndrome), monkey pox, and avian influenza H5N1 emerged from wildlife markets (Brown, 2004; Burgos and Burgos, 2007; Check, 2004; Karesh et al., 2007; Sleeman, 2006; Warwick et al., 2011).

There is a rising threat from emerging infectious diseases spreading to people and other animals, fueled by human activities ranging from the handling of bushmeat and the trade in exotic animals to the destruction of wild habitat (Lilley et al., 1997; Patz et al., 2000; Walsh et al., 1993). Despite warnings of the potential significance for human disease of changing patterns in their relationship with animals and the natural world, scientists have continued to treat human and animal health as largely independent disciplines, while historians have also neglected this important aspect of human disease (Hardy, 2003). In this sense, it is crucial that the interdependence between animal and humans be considered in the development of new public health practices.

Animal as Sentinels of Human Health

As discussed previously, animals suffer a similar spectrum of disease as humans (Bell et al., 1988; Krauss, 2003) and, therefore, may be sensitive indicators of environmental hazards and provide an early warning system for public health intervention (Reif, 2011). The concept that disease occurrence in nonhuman animal populations (wild and domestic) can serve as a sentinel warning of an environmental threat to human health has a long history (Rabinowitz et al., 2005).

Animals have served in numerous cases as “sentinels” of environmental threats near the living or working environments (Van der Schalie et al., 1999), and humans can, in return, sometimes serve as sentinels for animal health. The potential for animals to serve as sentinels for humans (or vice versa) depends on the type of linkages and contacts between specific animal populations and neighboring humans (Rabinowitz and Conti, 2013). Terrestrial wildlife, companion animals, food production animals, and aquatic animal populations can be monitored as sentinels for environmental impacts caused by pathogens, contaminants, and/or land-use changes (Rabinowitz and Conti, 2013).

Several historical examples illustrate animals’ usefulness as predictors of human illness (Rabinowitz and Conti, 2013; Reif, 2011). In the 1870s, fattened cattle experienced high mortality at a stock show in London’s Smithfield Market associated with a dense industrial fog—a precursor to the air pollution episodes typified by the infamous London Fog of 1952, during which thousands of residents died (Glickman et al., 1991). In the 1950s, recognition of neurobehavioral disturbances in the cat population of Minamata, Japan, preceded a severe episode of neurological disease among local residents caused by consumption of seafood contaminated with methylmercury (Tsuchiya, 1992). Sediments, shellfish, and fish in Minamata Bay became contaminated with mercuric chloride as the result of effluent discharges from a chemical plant. The ataxic "dancing cats of Minamata" were a warning sign. Unfortunately, it was not recognized in time to prevent the human epidemic (Reif, 2011). In 1962, it was cases of lead poisoning in cattle and horses living in the vicinity of a smelter that alerted the Minnesota State Health Department to conduct surveillance for lead exposure in local human populations (Hammond and Aronson, 1964). Another classic example of this is the historic use of canaries by miners to detect the presence of toxic gases in coal mines (Burrell and Seibert, 1916). Dying crows and other birds signaled the appearance and spread of the West Nile virus infection in the Western hemisphere. As the disease spread, monitoring of dead crows was used as a sentinel system for early warning of human disease risk (Julian et al., 2002).

Animal sentinels may potentially be used to address a range of surveillance questions including: (1) detection of a known pathogen in a new area; (2) detection of changes in the prevalence or incidence of a pathogen or disease over time; (3) determining the rates and direction of pathogen spread; (4) testing specific hypotheses about the ecology of a pathogen; and (5) evaluating the efficacy of potential disease control interventions (McCluskey, 2003). Appropriate use of animal sentinels can facilitate the early detection and identification of outbreaks, which is of critical importance both for the success of control and prevention efforts (Chomel, 2003; Kahn, 2006) and for reducing the magnitude of subsequent outbreaks (Ferguson et al., 2005). However, the potential of animal sentinel surveillance can only be fully realized if information sourced from animal populations is acted upon. For example, an Ebola outbreak in central Africa was the result after insufficient preventive health measures were taken despite warnings of an imminent human outbreak being provided from monitoring of Ebola deaths in primate sentinels (Rouquet et al., 2005).

Studies of the effects of environmental exposure on domestic and wild animals can corroborate or inform epidemiologic studies in humans (Reif, 2011). Currently, however, physicians assessing environmental health risks to patients do not routinely include animal sentinel data in their clinical assessments. Public health practitioners are unlikely to respond to mortality events in animals that are not clearly due to West Nile virus or other known zoonoses, such as rabies (Rabinowitz et al., 2005). Reasons for the underuse of animal sentinel data by human health professionals may include limited understanding of the relationships existing between animal, human, and ecosystem health; insufficient knowledge of veterinary medicine; and few institutional protocols to incorporate animal data into public health surveillance (Stephen and Ribble, 2001). Both human and animal health professionals have gained an increasing awareness that disease events in animal populations may have direct relevance to human health (Scotch et al., 2009).

Traditional Medicine

It is known that at the dawn of recorded history humans often ate, or wore on their person, some portion of an animal that was thought to have a healing or protective influence (MacKinney, 1946); this highlights the intertwining of the origin of the medicinal use of faunal elements with their use as food. In the same context, Chemas (2010) remarked that the treatment of illnesses using animal-based remedies is an extremely old practice, the most remote antecedent of which is a carnivore diet, closely followed by the ritual ingestion of deceased persons (e.g., close relatives, warriors) as a means of absorbing their virtues (e.g., courage, virility), and subsequently by a true medicinal use inseparable from magical-religious elements. These observations are in line with the view of nature as providing many things for humankind, including tools for the first attempts at therapeutic intervention (Nakanishi, 1999).

Although plants and plant-derived materials make up the majority of the ingredients used in most traditional medical systems worldwide, whole animals, animal parts, and animal-derived products also constitute important elements of the materia medica (Alakbarli, 2006; Alves et al., 2013b; Alves and Rosa, 2005; Moquin-Tandon, 1861; Scarpa, 1981; Stephenson, 1832; Unnikrishnan, 2004). Products derived from medicinal animals are directly used in the confection of popular remedies and magical items such as charms, amulets, and talismans that are widely sought after in traditional medicinal practices (Alves and Rosa, 2013a; Anyinam, 1995).

The antiquity in the use of medicinal animals and its persistency through times are a testimony to the importance of those therapeutic resources to mankind (Alves et al., 2013b). In modern societies, zootherapy constitutes an important alternative to the many other known therapies practiced worldwide (Alves and Rosa, 2013a). Wild and domestic animals and their byproducts (e.g., hooves, skins, bones, feathers, tusks) form important ingredients in the preparation of curative, protective, and preventive medicine (Adeola, 1992; Alves and Alves, 2011; Alves et al., 2012; Ashwell and Walston, 2008; Martinez, 2013; Whiting et al., 2011; Williams et al., 2013).

Many cultures still employ traditional medicine incorporating animal-derived remedies. Probably the most famous of these are the Chinese, who use animals to treat a variety of ailments. Although less known and less frequently studied, Latin America and Africa both have a long tradition of using their equally varied and rich fauna, including many endangered species, to treat all kinds of ailments (Alves and Rosa, 2013b). Zootherapeutic practices are also found in Europe (Ceríaco, 2013; Quave et al., 2010; Voultsiadou, 2010).

Mammals, fish, reptiles, birds, mollusks, and insects, including many threatened species, are prominently used in traditional medicine (Figs. 13.1 and 13.2) (Alves et al., 2010b; Alves et al., 2008; Alves et al., 2013g; Ferreira et al., 2012, 2013; Williams et al., 2013), substantiating the importance of taking into account their harvesting in the context of animal conservation. Many marine (Alves and Dias, 2010; Alves et al., 2013c) and terrestrial invertebrates (Costa-Neto, 2005; Figueirêdo et al., 2015; Kritsky, 1987; Pemberton, 1999) make up part of the therapeutic arsenal of popular medicine (Figs. 13.3–13.5).

Articles and review texts have revealed the high numbers of animal species used in traditional medicinal practices throughout the world (Table 13.1). Researchers have reported more than 1500 animal species that have some medicinal use in traditional Chinese medicine (Yinfeng et al., 1997). In Latin America, at least

FIGURE 13.1 Medicinal animal-derived products (crocodile skulls, antelope horns, and a diversity of carnivore and nonhuman primate skulls) for sale in Benin, West Africa. *Photo credits: Anthony B. Cunningham.*

FIGURE 13.2 The tegu lizard (*Salvator merianae*) and boa snake (*Boa constrictor*), reptiles species often used in Brazilian traditional medicine. *Photo credits: John Philip Medcraft.*

FIGURE 13.3 Dried starfish for sale in the traditional Chinese medicine market in Chengdu, Sichuan. *Photo credits: Anthony B. Cunningham.*

584 animal species have been reported as being used in traditional medicinal practices (Alves and Alves, 2011). Worldwide, at least 284 reptiles and 47 amphibians (Alves et al., 2013g), 110

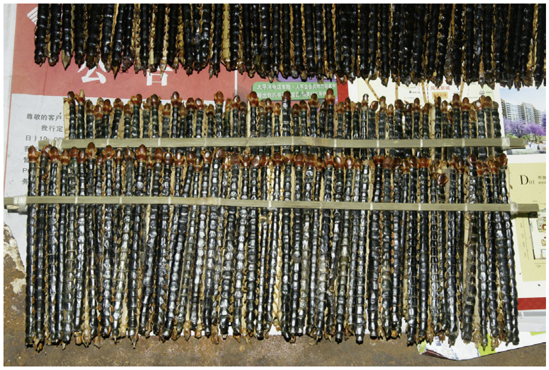

FIGURE 13.4 The centipedes (*Scolopendra subspinipes*), known as wugong in Chinese, widely sold in traditional Chinese medicine markets. *Photo credits: Anthony B. Cunningham.*

primates (Alves et al., 2013e), 108 mammalian carnivores (Alves et al., 2013d), and 266 marine invertebrates (Alves et al., 2013c) are used in popular medicines. Research in 25 African countries has shown that at least 354 bird species are used there in traditional curing practices (Williams et al., 2013) (Table 13.1). Some groups, such as seahorses (*Hippocampus* spp.) are widely employed for medicinal purposes (Fig. 13.6). Rosa et al. (2013) reported that of 48 species recognized as valid by Project Seahorse (2016), 20 species were cited in the literature as having medicinal uses. It is important to point out that the number of animal species used in popular medicinal practices must certainly be larger than what has so far been recorded, as in spite of studies focusing on this theme, many regions have not been closely examined—indicating that further studies will be indispensable to increasing our understanding of the links between the traditional uses of animals and conservation biology, the sustainable management of natural resources, public health policies, and biological prospection (Alves and Rosa, 2006).

The world's animals and plants—including a number of species used in traditional medicine—face threats ranging from habitat loss to the global wildlife trade (Alves and Rosa,

FIGURE 13.5 Examples of raw materials derived from medicinal animals sold in Brazilian cities. *Photo credits: Rômulo R.N. Alves.*

2013a). There has been an increasing demand for traditional medicines (Alves and Rosa, 2007; Robinson and Zhang, 2011), and the link between traditional medicine and the loss of certain species has become apparent (Alves et al., 2007; Call, 2006). This trend bears important implications for the conservation of the many species of flora and fauna, on which traditional remedies are based (Alves and Rosa, 2013a; Lee, 1999). Unfortunately, whereas the use of traditional remedies used to be a localized practice, the globalization of commerce in combination with the increased popularity of natural approaches to health worldwide has created a level of demand that threatens the survival of many vulnerable species of wildlife (IFAW, 2011). The case of vertebrates threatened by trade for traditional medicine, including rhinos, tigers, bears, pangolins, turtles, seahorses, monkeys, tigers, rhinoceros, and bears is well-known (Fig. 13.7).

Medicinal use of fauna represents an additional pressure for many species, and has been indicated as an important cause of population decline. Thus, not only should the use of these animals in popular medicine be considered, but also their exploitation by the pharmaceutical industry (Marques, 1997). As Shaw (2009) points out, any pharmaceutical scientist who is involved in contemporary natural product research has to get involved in, or at the very least become familiar with, global issues of species conservation and/or biodiversity.

TABLE 13.1 Richness of Animal Species Used in Traditional Folk Medicine According to Literature

Animal Group	Number of Medicinal Species	Geographic Coverage	References
Herpetofauna	331	Worldwide	Alves et al. (2013g)
Primates	110	Worldwide	Alves et al. (2013e)
Carnivorous mammals	108	Worldwide	Alves et al. (2013d)
Aquatic mammals	24	Worldwide	Alves et al. (2013f)
Seahorses	20	Worldwide	Rosa et al. (2013)
Marine invertebrates	266	Worldwide	Alves et al. (2013c)
Birds	354	Africa (25 countries)	Williams et al. (2013)
All taxons combined	584	Latin America	Alves and Alves (2011)
All taxons combined	54	Portugal	Ceríaco (2013)
All taxons combined	109	India	Mahawar and Jaroli (2008)
All taxons combined	137	Nigeria	Soewu (2013)
All vertebrate groups	147	South Africa	Whiting et al. (2013)
Mammals	87	Benin (West Africa)	Djagoun et al. (2013)

BIOTHERAPY

The use of live organisms for treating human and animal illnesses is known as biotherapy (Grassberger et al., 2013). As pointed out by those authors, this is an ancient practice, although it has now attracted the interest of many clinicians, biologists, biochemists, and patient advocates and has emerged as a rapidly advancing multidisciplinary field of medicine. Some of the principal animals used in biotherapy are maggots, leeches, bees, parasitic worms, and fish (Table 13.2), giving rise to the fields of maggot therapy, hirudotherapy, apitherapy, helminth therapy, and ichthyotherapy, which will all be briefly discussed below.

Hirudotherapy

The use of medicinal leeches for curative purposes is one of the oldest known practices in medicine (Gileva and Mumcuoglu, 2013) and is called hirudotherapy or leech therapy. Although more than 650 species of leeches have been described, only a few are used for medicinal (therapeutic) purposes. The European medicinal leech, *Hirudo medicinalis*, is one of the most extensively studied annelids and the most frequently used in modern medical practices (Gileva and Mumcuoglu, 2013). Similar results have also been obtained in some cases with *Hirudo verbana* and *Hirudo michaelseni* (Van Wingerden and Oosthuizen, 1997; Whitaker et al., 2012). Medicinal leeches apparently reduce blood coagulation and relieve venous pressure resulting from blood pooling (especially after plastic surgery) and stimulate blood circulation (Godfrey, 1997). Leeches are now applied to treat a wide array of diseases or conditions, including reconstructive plastic surgery; venous, cardiovascular, neurological, gynecological, osteomuscular, and ophthalmologic disorders; periodontal and oral mucosal diseases; and cancer (Gileva and Mumcuoglu, 2013; Gilyova, 2005; Scott, 2002). Specific applications of hirudotherapy can vary in different countries or regions. Hirudotherapy is officially

FIGURE 13.6 The longsnout seahorse, *Hippocampus reidi* (A), species commonly used for medicinal purposes in Brazil, traded in the dried form. Dried seahorse specimens for sale (B–D) in Brazilian cities. *Photo credits: (A) Thelma L.P. Dias, (B and D) Rômulo R.N. Alves, (C) Ierecê L. Rosa.*

recognized as an alternative therapy for numerous internal diseases including osteoarthritis, phlebitis, hypertension, and glaucoma in some Eastern Europe, Russian, and Asian countries, while American and European practitioners emphasize the value of leeches in microvascular and reconstructive surgery for both pediatric and adult populations (Gilyova, 2005).

Maggot Therapy

One of the most interesting applications of insects as therapeutic agents is maggot therapy, which involves the treatment of superficial or deep wounds with the help of blowfly larvae (Costa-Neto, 2005). This method was accidentally discovered during the World War I and was widely used during the 1930s and 1940s, being indicated for infected wounds that are difficult to heal, such as osteomyelitis, abscesses, burns, wounds on diabetic patients, pressure ulcers, traumatic lesions, tumors, and untreatable gangrene (Martini and Sherman, 2003). The advantages of maggot therapy, also called larval therapy, maggot debridement therapy, and biosurgery, include its profound efficacy in debriding necrotic tissue and its relative safety and simplicity; it is frequently

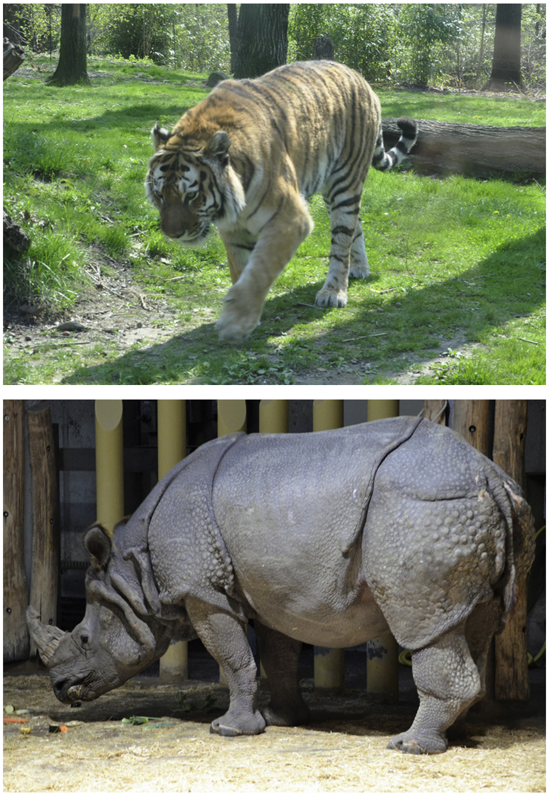

FIGURE 13.7 Tigers and rhinos, examples of endangered animals impacted due to use and traffic of their parts for traditional medicines. *Photo credits: Rômulo R.N. Alves.*

utilized when conventional medical treatments and surgeries are not capable of deterring progressive tissue destruction (Sherman et al., 2013). The therapy treatment consists of applying live, sterile, laboratory raised, blowfly larvae (Diptera: *Calliphoridae*) to lesions or chronic and/or infected wounds to remove necrotic/infected tissues and promote healing (Martini and Sherman, 2003). The larvae can be applied to a wound in a direct (free-range) or indirect (contained) manner (Gunjegaonkar et al., 2016). Blowfly larvae, *Lucilia sericata*, are frequently used, although other species have also been employed, such as *Lucilia cuprina*, *Phormia regina*, and *Calliphora vicina* (Sherman et al., 2000). Maggots like those of *L. sericata* feed on dead tissue where gangrene-causing bacteria thrive. As they eat, they also secrete allantoin, a chemical that inhibits bacterial growth (Costa-Neto, 2005). Medicinal maggots have three actions: they clean wounds by dissolving the dead (necrotic) infected tissue, disinfect the wound by killing bacteria, and stimulate wound healing (Sherman et al., 2000). The larva debride the necrotic tissue using their oral suction apparatus, which liberates digestive enzymes and dissolves the infected tissue; the wound is disinfected through the secretion of antibacterial substances liberated by the larva that activate macrophages, induce wound healing, and stimulate healthy tissue growth (Dallavecchia et al., 2011).

Use of maggot therapy declined with the introduction of modern antibiotics and improvements in surgical debridement, although the use of maggot therapy has been returning due to growing antibiotic resistance and potential adverse effects associated with antibiotic use (Gunjegaonkar et al., 2016). Initially, maggot therapy was used for treating chronic wounds in humans, but was later used with animals as a likewise safe and effective method of curing serious wounds (Munir et al., 2016). Numerous researchers have shown that larval therapy is much more effective at debriding wounds than conventional treatments (Dallavecchia et al., 2011; Sherman et al., 1986). Maggot therapy is commonly used in the United States, Israel, and Europe to treat various types of infected wounds, such as those on the feet of diabetics, postoperative infections, ulcer scabs, and leg ulcers (Ratcliffe et al., 2011; Sherman et al., 2000).

Apitherapy—Bee Venom Therapy

Bee venom therapy is a biotherapeutic medical treatment that uses bee venom to treat numerous illnesses (Kim, 2013). Bee venom has a long history of use as a folk remedy for treating diseases such as arthritis, angiocardiopathy, back pain, musculoskeletal pain, cancerous

TABLE 13.2 Animals Species Used in Biotherapy

Species	References
HIRUDOTHERAPY	
Hirudo medicinalis (Linnaeus, 1758)	Gileva and Mumcuoglu (2013)
Hirudo verbana (Carena, 1820)	Van Wingerden and Oosthuizen (1997) and Whitaker et al. (2012)
Hirudo michaelseni (Augener, 1936)	Van Wingerden and Oosthuizen (1997) and Whitaker et al. (2012)
Poecilobdella granulosa (Savigny, 1822)	Lone et al. (2011)
MAGGOT THERAPY	
Calliphora vicina (Robineau-Desvoidy, 1830)	Teich and Myers (1986)
Chrysomya rufifacies (Macquart, 1842)	Teich and Myers (1986)
Lucilia caesar (Linnaeus, 1758)	Baer (1931) and McLellan (1932)
Lucilia cuprina (Wiedemann, 1830)	Fine and Alexander (1934)
Lucilia illustris (Meigen, 1826)	Lerclercq (1990)
Lucilia sericata (Meigen, 1826)	Baer (1931)
Phormia regina (Meigen, 1826)	Baer (1931), Horn et al. (1976), Reames et al. (1988), and Robinson (1933)
Protophormia terraenovae (Robineau-Desvoidy, 1830)	Lerclercq (1990)
Wohlfahrtia nuba (Wiedemann, 1830)	Grantham-Hill (1933)
Musca domestica (Linnaeus, 1758)	Grantham-Hill (1933)
APITHERAPY	
Apis melifera (Linnaeus, 1758)	Kim (2013)
ICHTHYOTHERAPY	
Garra rufa (Heckel, 1843)	Grassberguer and Sherman (2013)
HELMINTH THERAPY	
Ascaris lumbricoides (Linnaeus, 1758)	Correale and Farez (2007, 2011)
Enterobius vermicularis (Linnaeus, 1758)	Correale and Farez (2007, 2011)
Hymenolepis diminuta (Rudolphi, 1819)	Correale and Farez (2007, 2011)
Hymenolepis nana (Siebold, 1852)	Correale and Farez (2007, 2011)
Strongyloides stercoralis (Bavay, 1876)	Correale and Farez (2007, 2011)
Trichuris suis (Schrank, 1788)	Fleming et al. (2011)
Necator americanus (Stiles, 1902)	Wolff and Broadhurst (2012)
Trichuris trichiura (Linnaeus, 1771)	Wolff and Broadhurst (2012)

tumors, multiple sclerosis, and skin diseases, and it is known to promote wound healing (Alqutub et al., 2011; Beck, 1935; Cherniack, 2010; Roy et al., 2015). The use of bee venom is quite ancient, but has attracted growing interest now due to its positive therapeutic results (Moreira, 2012). Bee venom is a colloidal substance that can be dialyzed through membranes and absorbed through the skin (Shimpi et al., 2016); it is composed of approximately 18 active compounds including enzymes, bioamines, and peptides with important biological effects (Yasui, 2012). Bee venom has been reported to have both a central analgesic mechanism and peripheral analgesic action due to its anti-inflammatory action (Shin et al., 2012).

Bee venom can be applied by direct stings from bees (apipuncture or bee sting therapy) or through injections of a venom extract (bee venom therapy)—both requiring the experience of a qualified health professional (Lucache et al., 2015). Bee venom therapy involves the use of the venom produced by *Apis melifera*, marketed under the names of Apitoxina and Apitox. The venom is applied intradermally, never intravenously, and used for treating various autoimmune diseases, neurological disturbances, and chronic and inflammatory illnesses (Kim, 2013). Apipuncture is a method used by health professionals or licensed practitioners of acupuncture, with the venom being injected by holding a live bee (with forceps) on the affected area of the patient and allowing it to sting that person. Before initiating this type of treatment, however, the patient must be examined for allergic reactions to the venom (Kim, 2013; Yasui, 2012). Bee venom therapy stimulates the immunological system through the hypothalamus, pituitary gland, and suprarenal glands, inducing the body to produce its own curative substances. The efficiency of bee venom therapy has been evaluated in both laboratory and clinical experiments with humans (Yasui, 2012); however, this curative mechanism is not yet well understood, but a series of chemical compounds acting together in the body have been identified (Lucache et al., 2015).

Ichthyotherapy

The term "ichthyotherapy" was proposed in 2006 (Grassberguer and Sherman, 2013) and readily adopted, being defined as an alternative therapy for treating skin diseases with the so-called "doctor fish of Kangal," *Garra rufa* (Fig. 13.8) (Heckel, 1843) (Grassberguer and Sherman, 2013), a small, freshwater cyprinid fish native to the Middle East (Froese and Pauly, 2016). The use of this species is directed toward treating skin problems such as psoriasis, eczema, dermatitis, acne, calluses, and hardness (Ozcelik and Akyol, 2011). Several underlying mechanisms have been suggested for the observed efficacy of ichthyotherapy. One obvious mechanism is physical contact with the fish, which feeds on desquamating skin, leading to a rapid reduction of superficial skin scales (Grassberguer and Sherman, 2013). *G. rufa* are toothless fish that consume the dead skin cells of people that they come into direct contact with in the water, without affecting healthy skin (Cabral and Carneiro, 2014). The

FIGURE 13.8 "Doctor fish of Kangal," *Garra rufa*, fish species used in ichthyotherapy. *Photo credits: Tacyana P.R. Oliveira.*

underlying mechanisms of ichthyotherapy are not yet totally understood, but the most visible effect of exposure to this fish is the removal of excess skin layers, although the dramatic observed reductions in the inflammatory component, especially among patients with psoriasis, suggest additional mechanisms (possibly molecular). More complete biochemical studies will need to be undertaken to identify and characterize the properties of *G. rufa* in that context (Grassberguer and Sherman, 2013).

Helminth Therapy

The therapeutic uses of helminths (parasitic worms) have been tested in laboratory trials as new approaches to treating a variety of allergic and autoimmune illnesses (Khan and Fallon, 2013). This type of therapy is called helminth therapy and consists of the inoculation of the patient with specific parasitic intestinal nematodes (helminths). Diseases such as ulcerative colitis, multiple sclerosis, rheumatoid arthritis, Crohn disease, celiac disease, and autism are among the health problems potentially treatable with helminths. A number of such organisms are currently being investigated for their use in therapeutic treatments (see Table 13.2), including *Trichuris suis* (Fleming et al., 2011), *Necator americanus* (Elliot et al., 2013), *Trichuris trichiura* (Correale and Farez, 2011); *Hymenolepis diminuta*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Enterobius vermicularis*, and *Hymenolepis nana* (Correale and Farez, 2011; Leonardi-Bee et al., 2006).

It is appropriate to note that helminth therapies will probably be increasingly used in developed societies where epidemics of inflammatory disorders are most prevalent, and thus in people never previously exposed to helminths, while the desirable protective effects of helminth infections of humans in field studies have been reported for people in endemic areas (Scrivener et al., 2001). The theory that helminth infection protects against autoimmune diseases can be tested by comparing the prevalence of those diseases in highly helminth-exposed and less- or nonexposed human populations. There is strong evidence that helminth exposure results in changes to the immune system that decrease the risk of developing immune disorders, thereby preventing the onset of immune-mediated diseases that have become common in developed countries (Elliot et al., 2013).

Animal-Assisted Therapy

Another way in which animals can be used to ameliorate human health conditions is through human involvement with living creatures as a form of therapy (Alves et al., 2009). For centuries people have noted that animals can have positive influences on human health and functioning (Nimer and Lundahl, 2007). Florence Nightingale suggested in the 19th century that a bird might be a primary source of pleasure for people confined to their rooms due to medical problems (McConnell, 2002). The use of animals as therapy has intensified now and has received many names, such as animal-assisted therapy, pet therapy, animal-assisted activities, pet-facilitated therapy, pet-assisted therapy, animal-facilitated therapy, animal-assisted interventions, and animal visitation (Connor and Miller, 2000; Fine, 2010; Hooker et al., 2002; Kruger et al., 2006). All of these practices have the common focus of utilizing animals as facilitators for patient recovery and for establishing positive therapies, especially for patients with special needs, children with cognitive or emotional disturbances, and older people (Oliva, 2010).

Both domestic and domesticated animals have found medicinal uses as co-therapists (Silveira, 1998). Among the animals most commonly used for therapeutic purposes are dogs, cats, horses, dolphins, small tame animals such as rabbits and gerbils, and aquarium fish. Typically, reptiles are frowned upon in therapeutic settings because of their high risk of carrying disease or causing injuries to clients, and because of the difficulty of providing those animals with proper care and safe environments. Farm animals are often useful therapy animals, with the most common being llamas and pot-bellied pigs (Chandler, 2012).

Animal-assisted activities can occur in a variety of settings in which people interact with (talk to, pet, groom) companion animals while the animal's handler is present. Intense attachments can rapidly develop between people and pets during these encounters (Reperant et al., 2012), and researchers have shown that animal-assisted therapies provide numerous positive effects to patient health and can stimulate the development of diverse abilities such as learning, language acquisition, motricity, among others (Oliva, 2010). Contact with animals has proven to be an efficient method for stimulating and helping individuals with mobility problems, mental disabilities, or behavioral problems (Alves and Rosa, 2013b). Animal-assisted therapy can be used, for example, as part of a patient's physical therapy treatment plan, to decrease anxiety in psychiatric patients and agitation in older adults with dementia (Barker and Dawson, 1998; Batson, 1998). Examples include gradually increasing the number of brush strokes on a dog in order to exercise an impaired hand, and eliciting a relaxation response through horseback riding activities with children with spastic cerebral palsy (McGibbon et al., 1998). Children with autism spectrum disorders were more likely to respond appropriately in therapy sessions involving live dogs than with a stuffed toy dog or a ball (Martin and Farnum, 2002). Some nursing home residents were found to show lower cortisol levels during dog visits than human visits. During and after animal visits, hospitalized patients used fewer analgesics, reporting less pain and less depression, and heart failure patients showed decreased anxiety and epinephrine levels (Beck, 2000; Cole et al., 2007).

Fauna as Source of Drugs

Throughout human history, people have used various natural materials to cure their illnesses and improve their health (Alves and Rosa, 2007). Wildlife not only contributes to traditional medicine but also modern medicine, with natural extracts being used by pharmaceutical companies as raw material for the manufacture of drugs (Rose et al., 2012; Sifuna, 2012). The drugs we use to maintain human health are still predominantly derived from plant and animal species (Fitter, 1986). Historically, while the use of plants as medicines has been extensively recognized, studied, and reviewed, studies on the use of fauna as a source of drugs have only been produced now, and have demonstrated the enormous potential of fauna as a source of natural products and drugs (Alves and Albuquerque, 2013).

Several studies have shown that natural animal resources are highly promising in the search for new products of medicinal or pharmaceutical interest (Alves and Albuquerque, 2013; Chivian, 2002; Dossey, 2010; Fusetani, 2000). This potential is perhaps even greater for animals than for plants, considering that the number of animal species is several times greater (Alves and Albuquerque, 2012). For example, Trowell (2003) points out that there are at least 16 times as many insect species as there are plant species, yet plant chemistry has been studied 7000 times more than insect chemistry, based on a comparison of the amount of research undertaken per species.

Marine animals also represent an exceptional source of bioactive natural products, many of which exhibit structural features not found in terrestrial natural products (Faulkner, 1998; Ireland et al., 1993; Seedhouse, 2010). Drugs have been derived from sharks, sting rays, corals, sea anemones, mollusks, annelids, sponges, sea squirts, sea cucumbers, and horseshoe crabs (Alves and Albuquerque, 2013; Fitter, 1986). Shark liver contains lipids that enhance human resistance to cancer, and the horseshoe crab *Limulus* not only has a serum that isolates tumor cells and white blood cells from the whole blood of cancer patients, but is also the source of substances used to detect bacterial toxins in human body fluids (Fitter, 1986). Invertebrates are proving to yield increasing numbers of antibiotic agents, blood coagulants and anticoagulants, and neuromuscular, as well as anticancer compounds (Alves and Albuquerque, 2013; Fitter, 1986; Myers, 1979; Seedhouse, 2010). Approximately 2500 new metabolites were reported from a variety of marine organisms during the decade of 1977–87 (Ireland et al., 1993). Already, more than 15,000 natural products have been discovered, and this number continues to grow. While bioprospecting and deep-ocean exploration are in their infancy, the novel biology of the organisms discovered to date and their potential for revolutionizing the medical realm means that scientific interest will be increasingly focused on realizing the potential that exists in the deep ocean. And, inevitably, as a growing body of science reaffirms that deep-sea biodiversity holds major promise for the treatment of human diseases, exploration will surely venture ever deeper in search of untapped resources (Fusetani, 2000; Seedhouse, 2010).

Various terrestrial vertebrates, particularly amphibians and reptiles, have been of great interest in pharmacological studies (Alves and Albuquerque, 2013). One excellent example of successful drug development from a component of snake venom (*Bothrops jararaca*, Wied, 1824) is that of the inhibitors of angiotensin-converting enzyme. This enzyme is responsible for converting an inactive precursor into the locally active hormone angiotensin, which causes blood vessels to constrict and hence raises blood pressure (Bisset, 1991). Another good example is the work initially conducted by Daly during the 1960s on the skin secretions of dendrobatid frogs from Ecuador, and of other "poison dart" frog species in Central and South America. This work has led to the identification of a number of alkaloid toxins that bind to multiple receptors in the membranes of nerve and muscle cells (Chivian, 2002). The anticarcinogenic activities of Indian monocellate cobra and Russell's viper venom were studied in carcinoma, sarcoma, and leukemia models. Under in vivo experiments, it was found that the sublethal doses of the Indian *Elapidae* (monocellate cobra) and *Viperidae* (Russell's viper) venom caused cytotoxicity in Ehrlich ascites carcinoma (EAC) cells; it increased the life span of EAC-bearing mice and reinforced its antioxidant system (Debnath et al., 2007). Similarly, antitumor activity of *Hydrophidae* (*Lapemis curtus*) venom was also established against EAC in Swiss albino mice in vivo and HeLa and Hep2 tumor cell cultures in vitro (Karthikeyan et al., 2008). Ferreira et al. (2010) evaluated the anti-inflammatory activity of topically administered *Tupinambis merianae* fat in animal models (male and female Swiss mice—*Mus musculus*). In this first experimental test of the antiinflammatory activity of *T. merianae* fat in in vivo models, the authors found that it had significant topical anti-inflammatory activity and reduced inflammation edema in mouse ears caused by croton oil (single and multiple applications), phenol, and arachidonic acid. Similarly, numerous animals produce substances with antimicrobial activities that are effective as defense mechanisms against infections by microorganisms and have synergetic effects when associated with antibiotics (Coutinho et al., 2004)—and researchers have demonstrated positive results in relation to these activities in diverse species (Table 13.3).

There has been increasing attention paid to animals, both vertebrates and invertebrates, as a source for new medicines (Chivian, 2002). Animals have been methodically tested by pharmaceutical companies as sources of drugs for modern medical science (Kunin and Lawton, 1996), and the current percentage of animal sources for producing essential medicines is

TABLE 13.3 Examples of Animal Species With Pharmacological Activities

Species	Activity	References
Macoma birmanica (Philipi, 1949)	Antibacterial	Adhya et al. (2009)
Trionyx sinensis (Wiegmann, 1935)	Antibacterial	Thammasirirak et al. (2006)
Amyda cartilaginea (Boddaert, 1770)	Antibacterial	Thammasirirak et al. (2006)
Chelonia mydas (Linnaeus, 1758)	Antibacterial	Thammasirirak et al. (2006)
Nasutitermes corniger (Motschulsky, 1855)	Modulation of the antibiotic activity	Coutinho et al. (2009, 2010) and Chaves et al. (2014)
Atta sexdens rubropilosa (Forel, 1908)	Antifungal	Masaro et al. (2001)
Squalus acanthias (Linnaeus, 1758)	Antibacterial	Donia and Hamann (2003)
Leptodactylus macrosternum (Miranda-Ribeiro, 1926)	Antibacterial	Cabral et al. (2013)
Leptodactylus vastus (Adolf Lutz, 1930)	Antibacterial	Cabral et al. (2013)
Pseudocanthotermes spiniger	Antibacterial and antifungal	Lamberty et al. (2001)
Gallus gallus domesticus (Linnaeus, 1758)	Modulation of the antibiotic activity	Coutinho et al. (2014)
Rhinella jimi (Stevaux, 2002)	Modulation of the antibiotic activity	Sales et al. (2015)
Rhynocoris marginatus (Fabricius, 1794)	Antibacterial	Sahayaraj et al. (2006)
Catamirus brevipennis (Servile)	Antibacterial	Sahayaraj et al. (2006)
Tropidurus hispidus (Spix, 1825)	Modulation of the antibiotic activity; antiinflammatory	Santos et al. (2012, 2015)
Tropidurus semitaeniatus (Spix, 1825)	Modulation of the antibiotic activity	Santos et al. (2012)
Spilotes pullatus (Linnaeus, 1758)	Modulation of the antibiotic activity	Oliveira et al. (2014)
Dinoponera australis (Roger, 1861)	Antibacterial	Cologna et al. (2005)
Dinoponera quadriceps (Santschi, 1921)	Antibacterial	Cardoso et al. (2010)
Boa constrictor (Linnaeus, 1758)	Modulatory of the antibiotic activity; antiinflammatory	Ferreira et al. (2011, 2014)
Crotalus durissus (Lineu, 1758)	Antiinflammatory	Ferreira et al. (2014)
Iguana iguana (Linnaeus, 1758)	Antiinflammatory	Ferreira et al. (2014)
Euphractus sexcinctus (Linnaeus, 1758)	Antiinflammatory	Ferreira et al. (2014)
Tupinambis merianae (Linnaeus, 1758)	Antiinflammatory	Ferreira et al. (2010)
Naja atra (Cantor, 1842)	Antiinflammatory	Zhu et al. (2016)

fairly significant. Of the 252 chemicals selected as essential by the World Health Organization, 11.1% are derived from plants and 8.7% from animals (Marques, 1997). Of the 150 prescription drugs currently in use in the United States of America, 27 have animal origin (World Resources Institute, 2000). Although the potential of faunal biodiversity is well known, a careful strategy is required if species are to be exploited sustainably. One of the main conservation concerns about the exploitation of fauna in the search for bioactive compounds is the possible overharvesting of target organisms (Alves and Albuquerque, 2013). Some taxa with known pharmacological potential are especially susceptible to overexploitation; for example, marine species such as cone shells and mollusks have been overharvested as sources of clinical neuropharmaceuticals (Sukarmi and Sabdono, 2011). Harvesting of reef organisms for the discovery and development of pharmaceuticals is causing increased concern, since it has been perceived by many as unsustainable and a threat to conservation (Hunt and Vincent, 2006; Sukarmi and Sabdono, 2011).

Bioprospecting continues to generate considerable debate (Alves and Albuquerque, 2013), as critics dispute the idea that the commodification of nature will contribute to conservation (Simpson, 1997), or that natural products have a future in the discovery of new drugs (Firn, 2003). Regardless of the perspective adopted, as highlighted by Barrett and Lybbert (2000), the need to conserve precious biodiversity is clear, especially as we begin to appreciate the magnitude of the spiritual, social, and economic services it provides.

Animals in Biomedical Research

In addition to their use in traditional medicine, in biotherapies, and as sources of medicinal drugs, animals are essential to research projects—with both direct and indirect implications for human health. Animal experimentation in the context of scientific research has contributed greatly to the development of medical science and technology, including the development of prophylactic measures and treatments for diseases that affect humans (Chorilli et al., 2009).

Although research using animals intensified during the last century, this technique is known to have been employed since ancient times (Alves, 2012), and animal research has formed the basis for much of the progress in understanding and treating human (and animal) diseases (Schacter, 2006). There are records of experimentation with animals reaching back to ancient Rome, but not until the Renaissance did scholars begin to seriously study how the body works. Leonardo da Vinci (1452–1519) and other artists and anatomists made early anatomical investigations of muscle and bone structure, and William Harvey (1578–1657) discovered the circulation of blood through his experiments with live deer. Much of the live animal experimentation during this period, both in England and France, was based on the view of the French philosopher René Descartes (1596–1650) that animals were incapable of feeling pain. The 19th century French physiologist, Claude Bernard (1813–78) and his teacher, François Magendie (1783–1855), conducted wide-ranging animal experiments, including surgery, the use of drugs, and the removal of body parts from many species (Bishop and Nolen, 2001).

From ancient to modern times, the use of animals in research has become one of the most important ways to better understand aspects of the anatomy, biochemistry, genetics, nutrition and physiology of humans. Additionally, knowledge of the transmission mechanisms and treatment of human diseases are associated with such research. According to Bishop and Nolen (2001), many, if not most, of the spectacular innovations in medical understanding and treatment of today's human maladies have been based on research using animals.

Animals are used, for example, to develop new surgical techniques; test the efficacy and possible side effects of new drugs; determine the preventative and curative virtues of new medicines against diseases; test the safety of new chemicals used in the food industry; and check the quality of new batches of drugs and medicines (Bowman, 1977; Fitter, 1986). The discovery of antibiotics, analgesics, anesthetics, and antidepressants; the success of organ transplant development; catheterization; cardiac pacemaker and several other surgical techniques; practically all research protocols about safety, toxicity, effectiveness, and quality control of new drugs—all these pass through the use of laboratory animals. Other examples of scientific contributions arising from studies of animals are the discovery of insulin, the development of vaccines against several diseases, and serum production (Fagundes and Taha, 2004). Many drugs used by humans are directly produced from animals, for example, hormones used to overcome problems of fertility in humans are derived from cattle; insulin used to keep diabetics alive comes mainly from the pancreases of cattle and pigs. In addition, many vaccines are produced on animal tissue and on chicken eggs. Measles vaccine, for example, is produced on canine kidney tissue, as well as on eggs (Bowman, 1977).

Approximately 35 million animals are used worldwide in research each year, including dogs, monkeys, and cats, although 90% are laboratory rats, mice, and birds (Bishop and Nolen, 2001). Nonhuman primate species, because of their similarity to humans, are among the principal groups of animals used in biomedical research (Carlsson et al., 2004; Fitter, 1986), which are associated with significant contribution to advances in human health and disease control (Fitter, 1986). A wide variety of nonhuman primate species are used in these studies, involving at least 56 different extant species or subspecies (Carlsson et al., 2004), notably the Asian rhesus monkey *Macaca mulatta* and the African green or vervet monkey *Cercopithecus aethiops* (Carlsson et al., 2004; Fitter, 1986). These mammals are important and often essential for research in HIV/AIDS, malaria, cardiovascular diseases, cancers, and hepatitis, and also for the production and testing of drugs and vaccines. Similarly, armadillos have been used in medical research since the mid-1800s (Sharma et al., 2013). Studies involving these mammals have contributed to our knowledge of various infectious diseases, including syphilis and Chagas disease (Sharma et al., 2013; Wicher et al., 1983). However, the nine-banded armadillo *Dasypus novemcinctus* Linnaeus, 1758 has been most exploited as a model for leprosy (Peña et al., 2008; Scollard, 2008; Sharma et al., 2013) The armadillo is the only animal model in which protection against dissemination of leprosy bacilli or progress of nerve damage can be evaluated. Bacterins of heat-killed *Mycobacterium leprae* or viable BCG have been shown to protect armadillos against *M. leprae* challenge or enhance their immunity to the organism (Kirchheimer et al., 1978). Armadillos can also be used for testing new diagnostic candidates because they are the only host in which the true status of infection can be determined, and the long incubation period of leprosy in humans can cause confounding results (Sharma et al., 2013). Another animal group used in medical research experiments are marsupials (Jurgelski, 1984). The opossum, *Didelphis virginiana*, for example, is used in endocrinological, embryological, anatomical, psychiatric, and neurological research (Wiedorn, 1954).

A dynamic tension exists between support for scientific enquiry, mostly to alleviate human disease and public concern about animal suffering (Bishop and Nolen, 2001). This discussion is not new, however, and as early as the 16th century philosophers were debating the morality of animal experimentation, with their arguments centering on whether animals felt pain and the moral status of animals as living, sentient creatures (Schacter, 2006). Although the discovery of anesthetics and their use in animal experiments might have been expected to somewhat quiet this issue, revulsion at the use and potential misuse of animals for human betterment sustains a significant activism opposed to any use of animals in research (Schacter, 2006).

CONCLUSIONS

Humans are animals that live in association with thousands of other animal species and share the same environment and a wide diversity of diseases that can be mutually transmitted. If, on one hand, animals are vectors of human diseases, they are also indispensable for their treatments and cures. Products derived from animals are fundamental ingredients of both traditional remedies and modern drugs; live animals can alert us to approaching epidemics and are protagonists and agents in many therapies, and are fundamental to research efforts that seek to understand human illnesses and test modern medicines. It is therefore clear that human health depends on the health of both animals and our environment, and that health strategies must always take this intricate interdependence into consideration.

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