

Tuberculous and tuberculoid lesions in free living small terrestrial mammals and the risk of infection to humans and animals: a review

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ABSTRACT: The present study describes pathogenesis and morphology of tuberculous and tuberculoid lesions in small terrestrial mammals, above all, in rodents. The most serious infectious agents that cause tuberculous and tuberculoid lesions in these animals are also cited. Besides others, the diseases caused by pathogenic mycobacteria that are members of *Mycobacterium tuberculosis* and *M. avium* complexes, *M. lepraemurium*, tularaemia, brucellosis and salmonellosis are included in the present study.

Keywords: bovine tuberculosis; paratuberculosis; avian tuberculosis; mycobacteriosis; terrestrial mammals; zoonoses

List of used abbreviations

AFR = acid-fast rods, **BCG** = Bacillus Calmette-Guerin, **CPM** = conditionally pathogenic mycobacteria, **HIV/AIDS** = human immunodeficiency virus/acquired immunodeficiency syndrome, **IFN- γ** = interferon gamma, **M.** = *Mycobacterium*, **MAC** = *Mycobacterium avium* complex, **MHC** = major histocompatibility complex, **MTC** = *Mycobacterium tuberculosis* complex, **NK** cells = natural killer cells, **PPD** = purified protein derivative, **RFLP** = restriction fragment length polymorphism, **ZN** = Ziehl-Neelsen

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1. Introduction

Tuberculosis of animals has been put under control in many European countries (Thoen et al., 2006). According to the OIE data concerning the incidence of bovine tuberculosis in cattle and according to the geographic situation, European countries may be classified as insular or continental (Western, Central and Eastern Europe). However, the outbreak situation is different in respective countries in association with a number of factors, such as the presence of reservoir animals in nature, the absence of national health control programmes brought into practice, unfavourable economic situation, non-stable political system, etc. However, despite these facts, both the numbers of new outbreaks in cattle and the numbers of infected cattle have been successfully reduced in the majority of European countries (Anonymous, 2004).

In domestic animals, the causative agents of bovine tuberculosis (*Mycobacterium bovis* and *M. caprae*) have been eradicated, above all, in the Central European countries (Pavlik, 2006). Decreased incidence of all members of the *M. tuberculosis* complex (*MTC*) that cause tuberculous lesions in the infected host tissues have also been recorded in the other domestic and wild animals (Pavlik et al., 2003a,b, 2005a,b). However, this favourable epidemiological situation needs not be stable, primarily because of chronic characteristics of the disease and because all the risk factors that some European countries must face have not been clarified yet. Above all, the emergence of reservoirs of bovine tuberculosis among free living animals, particularly badgers (*Meles meles*) in Great Britain and in Ireland are viewed as a risk factor (Delahay et al., 2000).

In continental Europe, a comparable risk is nowadays represented mostly by wild boar (*Sus scrofa*; Machackova et al., 2003, Trcka et al., 2006), European bison (*Bison bonasus*; Pavlik et al., 2005b; Pavlik, 2006) and occasionally other free living animal species (Trcka et al., 2006). Incidence of tuberculous and tuberculoid lesions in small terrestrial mammals is rather high in both Great Britain (Cavanagh et al., 2002) and Central Europe (unpublished data). However, published data concerning the incidence of etiological agents causing tuberculous and tuberculoid lesions in small terrestrial mammals in Europe is scarce.

Accordingly, the purpose of the present study is to analyse and review the available literature data concerning the incidence of causative agents of tuberculous and tuberculoid lesions found in small terrestrial mammals in Europe, as well as the risks associated with a zoonotic potential of some etiological agents. As detected by gross examination, characteristic lesions, tuberculous nodules, are designated as tuberculous lesions if caused by mycobacterial infection. Most frequently they are caused by *MTC* and *M. avium* complex (*MAC*) members. In contrast, tuberculoid lesions are caused by other infectious agents.

2. Tuberculous lesions

2.1. Pathogenesis of tuberculosis

In a vast majority of cases, a characteristic lesion appears at the site of tuberculous agent penetration into the organism; it is the response of a tissue to the presence of mycobacteria, which is designated as a primary lesion. Localisation of a primary le-

sion is associated with the site of pathogen penetration. The inhalation route of infection is the most common way of spreading mycobacteria. Local inflammation is the response of an organism to a foreign particle, usually the protein and glycolipid constituents of mycobacteria.

Transient exudate and immigration of leukocytes occur at the initial stage of infection. This initial stage is not specific by its cell composition. Macrophages appear at the site of the tissue response in the first days. They mature into cells of irregular polygonal shape with a large vesicular nucleus, i.e. epithelioid cells. Immigrated leukocytes gradually die in the centre of a lesion and central necrosis develops in association with a minute amount of fibrin. That is surrounded with epithelioid cells and macrophages. Macrophages present in the site of infection are recruited either from blood monocytes or from phagocytising tissue cells – histiocytes. Cell composition of a granuloma is associated with the characteristic mononuclear phagocyte system response that is genetically coded (Hogan et al., 2001; Nadeev et al., 2005).

During an inflammatory process, multinucleate giant Langhans' cells develop from epithelioid cells. They are characterised by the location of the nuclei at the periphery of the cell in an accurate configuration or by a ring of nuclei surrounding a central eosinophilic zone. One cell may contain up to several tens of nuclei. As the infection proceeds, adjacent lymph nodes are concurrently affected; that is a characteristic feature of the disease. The status of concurrent gross lesions in an organ and in an adjacent lymph node is designated as a primary complex. The stage of primary infection is followed by generalisation of the process at different points of time. Progression of the process of tuberculosis in the host organism occurs by the spread of the pathogen via lymphatic vessels.

2.2. Characterisation of the genus *Mycobacterium* members

Obligatory pathogenic species, conditionally pathogenic species and saprophytic species are classified in this genus. Mycobacteria were named on the basis of their fungus-like growth characteristics on liquid agars. However, microscopic examination revealed that the growth line was composed of bacteria. Those are pleomorphic, rod shaped and have low stain ability according to

Gram (however, they are usually Gram-positive). Mycobacteria are straight or slightly bent thin rods 1.5 to 5 µm in length and 0.3 to 0.5 µm in width. They are immotile aerobic organisms that do not sporulate. Pleomorphism of saprophytic strains of mycobacteria is higher in comparison with other pathogenic agents. Those may also occur as fibre- or mycelium-like forms; some of them undergo fragmentation into rods or coccoid forms (Wayne and Kubica, 1986).

Mycobacteria are usually aggregated in preparations made from material with detected gross changes. The rods grown on agars are usually slightly longer than rods from biological material. Mycobacteria are characterised by certain specific features that may serve for their discrimination from other bacteria. They retain the stains added at warm temperatures and cannot be removed either by alcohol or acids. Therefore, staining according to Ziehl-Neelsen (ZN) is used; that takes advantage of the bacterial wall ability to take up the carbolfuchsin dye and retain it during rinsing with the bleaching solution of ethanol containing acid. After staining by this method, all mycobacteria appear red and all the other particles including the other bacterial species are stained according to the type of counter stain used; when bromthymol blue is used, the background is blue (Ris et al., 1988).

2.3. Occurrence of tuberculosis in small terrestrial mammals

2.3.1. *M. tuberculosis* complex members

Nowadays, eight strains of mycobacteria are classified as members of *MTC*: *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. bovis* BCG (attenuated vaccine Strain), *M. microti*, *M. canettii*, *M. caprae* and *M. pinnipedii* (van Soolingen et al., 1997; Aranaz et al., 2003; Cousins et al., 2003). Presence of the specific insertion sequence *IS6110* is typical for all these members (van Soolingen et al., 1997; Aranaz et al., 2003; Cousins et al., 2003). A few of them have only been detected in small terrestrial mammals to date; *M. microti* is viewed as the most consequential.

Tuberculosis caused by *M. microti* in natural populations of small terrestrial mammals was described for the first time in Great Britain (Wells and Oxon, 1937). The detected agent was designated as *M. tuberculosis* subsp. *muris*. It was renamed

as *M. microti* in 1957 and classified as a member of *MTC* (Reed, 1957). *M. microti* has long been considered as a non-significant human infection agent (Wayne and Kubica, 1986). It differs from the other *MTC* members by morphology: the rods are of S- (sigmoidal) shape, slow growing *in vitro* and showing a significant pathogenicity for laboratory animals (van Soolingen et al., 1998). Based on the biochemical methods of identification, it is very difficult to discriminate between *M. microti*, *M. tuberculosis*, *M. bovis* and *M. africanum* (Imaeda, 1985; Brosch et al., 2002). Nowadays, the diagnosis is possible by RFLP (restriction fragment length polymorphism) typing and spoligotyping may also be performed (Foudraïne et al., 1998, van Soolingen et al., 1998; Dvorska et al., 2001). Incubation of at least 8-week is necessary for the *M. microti* culture (van Soolingen et al., 1998; Cavanagh et al., 2002).

M. microti may be found in foodstuffs, human dwellings and rodent faeces (Horvathová et al., 1997). Insectivores and small rodents come into contact with mycobacteria and ingest them together with food of plant and animal origin (Chitty, 1954). Mycobacteria are highly acid-resistant and therefore tolerate the action of digestive juices in vertebrates (Pavlik et al., 1994). They are ingested by small mammals, pass through their digestive tract intact and then they are shed through faeces. Pathogenic and conditionally pathogenic mycobacteria may survive in tissues and organs of small mammals and may be spread to great distances where they become sources of infection for predators feeding on small mammals (Fischer et al., 2001).

Some species, such as the golden hamster (*Mesocricetus auratus*) and striped dwarf hamster (*Cricetulus barabensis*), have been found to be susceptible to the infection in experimental studies. Voles are also highly susceptible, whereas guinea pigs (*Cavia porcellus*), rabbits (*Oryctolagus cuniculus*), mice (*Mus musculus*) and rats (*Rattus norvegicus*) were quite resistant to rather high infection doses (Wells, 1938; Griffith, 1939a,b, 1941a,b, 1942). Among other mammals, Huitema and van Vloten (1960) described the infection with *M. microti* in a cat and Huitema and Jaartsveld (1967) in pigs. An increasing number of case reports are indicating that *M. microti* has a pathogenic potential for a wider range of mammalian populations and may induce a systemic disease (Deforges et al., 2004).

Several cases have been reported where *M. microti* was isolated from llamas with diagnosed general-

ised tuberculosis characterised by a number of caseous nodes in various organs (Pattyn et al., 1970; Oevermann et al., 2004). Isolation of *M. microti* was described for the first time in a dog (Deforges et al., 2004) and in a bull (Jahans et al., 2004). Frequent miliary nodules were observed in the lungs of the bull after slaughter. Cases of infection with pulmonary tuberculosis caused by *M. microti* have been described, above all, in *HIV/AIDS* positive patients (Niemann et al., 2000; Horstkotte et al., 2001). However, cases of infection among immunocompetent individuals have also been documented (Frota et al., 2004; Geiss et al., 2005). Transmission of this and other pathogens may be associated with domestic cats and ferrets that prey on rodents (Baxby et al., 1994). With respect to people, *M. microti* has been diagnosed in areas, where a peak of population density of small terrestrial mammals was documented (Kremer et al., 1998; Cavanagh et al., 2002).

M. microti causes tuberculoid lesions in voles, hamsters, rats, mice, rabbits and guinea pigs (Wells, 1946). Non-caseous nodes develop from epithelioid cells at the beginning of the process. They become caseous with the progression of the process concurrently to epithelioid cell fusion and the development of occasionally huge polykaryons in livers, spleen and lymph nodes. Generalized caseous lesions have been observed in guinea pigs. Cavanagh et al. (2002) isolated *M. microti* from rodents with skin lesions and lymphadenitis as described by Wells. Since 1998, 101 (2%) of 4 852 trapped rodents showed signs of clinical tuberculosis. The infection was confirmed in 24 of them by spoligotyping and RFLP. Granulomas in various organs and mycobacteria in macrophages were found by ZN staining for histopathology. The authors also detected exudative tuberculosis and a high number of intracellular mycobacteria in skin lesions of field voles. Granulomatous interstitial and bronchoalveolar lesions were also detected in the lungs. Besides intestines and bone marrow, all the organs showed gross abnormalities such as microgranulomas and calcifications containing variable amounts of mycobacteria.

M. microti was recently successfully used for the vaccination of people against tuberculosis (Dannenberg et al., 2000; Manabe et al., 2002; Brodin et al., 2002). An attenuated strain of *M. microti* (VO166) was used as a vaccine in the former Czechoslovakia (1951–1969) and in the UK (1950–1952). The results obtained in both coun-

tries were similar conferring about 72% of protection, though 3 to 17% of vaccinated individuals showed cutaneous reactions (Paul, 1961; Sula and Radkovsky, 1976; Hart and Sutherland, 1977). Moreover, the *M. microti* vaccine showed a lower allergic potency that makes it less likely than the BCG to compromise the tuberculin test in the vaccinated population and induced fewer than 30% positive skin test conversions in response to *M. tuberculosis* PPD (Brooke, 1941; Wells, 1949; Wells and Wylie, 1954; Sula and Radkovsky, 1976; Bloom and Fine, 1994).

Recent comparison tests employed between the Pasteur sub-strain of BCG and the *M. microti* showed that both could provide protection against tuberculosis in rabbits (Dannenberg et al., 2000) and mice (Manabe et al., 2002). Moreover, Manabe et al. (2002) indicated that naturally attenuated aerosol and oral (high dose orogastric) vaccinations showed a significant improvement and efficacy in protection against tuberculosis compared to the subcutaneous *M. bovis* BCG vaccine. Although *M. microti* is known to provide protection against tuberculosis, like the BCG vaccine, its application can bring health hazards for immunocompromised individuals (van Soolingen et al., 1998). Intracorneal administration of the *M. bovis* BCG and *M. microti* vaccination strains to rabbits resulted in the development of tuberculous nodules in the cornea (Struplova and Obrucnik, 1974, 1975).

Of the other *MTC* members, *M. bovis* was isolated from the following small terrestrial mammals: bank vole (*Clethrionomys glareolus*), common shrew (*Sorex araneus*), yellow necked mouse (*Apodemus flavicollis*), wood mouse (*Apodemus sylvaticus*), field vole (*Microtus agrestis*), mole (*Talpa europaea*) and ermine (*Mustela erminea*; Delahay et al., 2001). Pulmonary granulomas developed in the lungs of laboratory mice after intraperitoneal infection with *M. tuberculosis* (Brett et al., 1992) and infections in free living small terrestrial mammals were also described (Montali et al., 2001). Laboratory mice (particularly their various genetic lines) have been long used in laboratory experiments, above all, in those focused on the causative agents of human tuberculosis (*M. tuberculosis*), vaccination strains (*M. bovis* BCG) and the causative agent of bovine tuberculosis (*M. bovis*). Yamamoto et al. (1988) described the development of liver and spleen granulomas in nu/nu mice after *intra ve-*

nam administration of *M. bovis* BCG; Vordermeier et al. (1996) likewise described development of granulomas and the activity of B-lymphocytes during tuberculosis in mice infected with *M. tuberculosis* and *M. bovis* BCG.

2.3.2. *M. avium* complex members

Tuberculous lesions may also be caused by members of the *M. avium* complex (MAC) in susceptible hosts. The MAC comprises 28 serotypes (Wolinsky and Schaefer, 1973). According to the currently accepted taxonomy, it has been divided into three groups by affiliation with serotypes and/or the contents of specific insertion sequences and/or virulence for birds (Runyon et al., 1986; Wayne and Kubica, 1986; Thorel et al., 1990; Kunze et al., 1992; Guerrero et al., 1995; Pavlik et al., 2000; Mijs et al., 2002; Bartos et al., 2006) as follows: *M. avium* subsp. *avium* (serotypes 1–3), *M. a. hominissuis* (serotypes 4–6, 8–11 and 21) and *M. intracellulare* (serotypes 7, 12–20, 22–28). *M. chimaera* is a new member of the MAC which had been described recently, however, the serotypes are unknown (Tortoli et al., 2004).

The alimentary route of infection is the most common. Initial lesions develop in Peyer's patches of the ileum. No tubercles have been observed by gross examination after the experimental infection of rabbits and mice. MAC is not pathogenic for guinea pigs and rats (Wayne and Kubica, 1986). Pedrosa et al. (1994) described the investigation focused on the virulence of various MAC isolates in naturally susceptible BALB/c mice. Gross lesions that develop after the infection with MAC members differ from lesions caused by the *MTC* members in the majority of animal species. They are characterised by diffuse granulomatous inflammation lesions containing high numbers of epithelioid macrophages. The lesions are free from necrosis, calcification and fibrosis. Huge multinuclear cells are not always present. Lymphocyte response is usually lower compared with *MTC* infections. The lesions are usually multifocal, confluent or diffuse. They spread into regional lymph nodes and may be disseminated through blood vessels.

M. a. avium was diagnosed in insectivores, such as the common shrew (*Sorex araneus*) and small rodents such as the yellow-necked mouse (*Apodemus flavicollis*) that were free of gross lesions (Fischer et al., 2000). Comparable findings were described for *M. a. hominissuis* (Fischer et al., 2004).

2.3.3. *M. lepraemurium*

Leprosy occurs spontaneously in free living animals and the lesions are usually of lepromatous character (Krakower and Gonzales, 1937; Shepard, 1960; Johnstone, 1987; Rojas-Espinoza and Lovik, 2001). A lot of studies of gross lesions in *M. lepraemurium* infections were performed on mice and rats (Ishaque, 1981; Adu et al., 1983; Nakamura, 1985; Ha et al., 1988). Lepromatous lesions include a wide complex of gross tuberculoid and lepromatous lesions associated with the host cell immunity state.

Typical features of tuberculoid lesions are as follows: occasional skin nodules of granulomatous inflammation at the site of infection and in locations on the body surface with lower temperatures. Granulomas comprise various amounts of epithelioid macrophages and giant multinuclear cells surrounded with lymphocytes. Acid-fast rods (AFR) are rarely observed in granulomas, which is a result of a marked cell immunity response and most probably of a low production of antibodies. The nerves present in the site of inflammation are often affected; that results in neuropathic deformities of tissues and their spontaneous amputation as a consequence of infected Schwann cells (Yager et al., 1993).

Lepromatous lesions develop in a cutaneous-nodular form. These are characterised by a number of irregular, confluent lesions caused by a granulomatous infiltrate from epithelioid macrophages and a lot of mycobacteria that are either phagocytised or present outside the cells. The occurrence of giant cells and lymphocytes are occasional. Mycobacteria cause extensive necrotic skin and bone lesions, whole regions of the body may be damaged. These lesions indicate a low level of host cell immunity. The titre of antibodies is high. The lesions overlap each other and transitional forms may also be found (Yager et al., 1993).

2.3.4. Other mycobacterial species

Diseases in small terrestrial mammals may also be caused by other mycobacterial species that are classified either as conditionally pathogenic mycobacteria (CPM) or saprophytic mycobacteria according to their capability to induce a pathologic process in a host (particularly in humans). The HIV/AIDS infection in humans largely contributes

to the process. *M. fortuitum*, *M. phlei*, *M. chelonae*, *M. marinum*, *M. smegmatis*, *M. ulcerans* and others are the atypical mycobacteria most commonly isolated from such lesions (Karbe, 1987; Walsh et al., 1999; Bercovier and Vincent, 2001; Portaels et al., 2001; Dega et al., 2002). Accordingly, a comparable complex of mycobacterial species is likely to be found in small terrestrial mammals in the case of their immunosuppression, e.g. if their living environment is polluted with xenobiotic substances.

Infections in small terrestrial mammals are usually manifested by skin lesions or subcutaneous granulomas. Karbe (1987) observed granulomatous inflammations in spleen, livers and lungs of a golden hamster infected with *M. chelonae*. Fischer et al. (2001) detected conditionally pathogenic mycobacteria (*M. fortuitum*, *M. chelonae*, and *M. vaccae*) in the following insectivores and small rodents: The lesser white-toothed shrew (*Crocidura suaveolens*), common vole (*Microtus arvalis*) and common shrew (*Sorex araneus*). However, no gross lesions were detected in any of these animals.

Conditionally pathogenic mycobacteria may survive in an external environment for a long time and may also propagate under temperatures from 18 to 20°C as a constituent of a series of ecosystems. Significant reservoirs of these mycobacterial species are predominantly soil, water, wooden products, peat etc. (Kazda, 2000). Gross lesions may initially appear after skin damage and treatment of skin or hypodermis. That may be followed by dissemination of the process in immunocompromised patients.

3. Tuberculoid lesions

Tuberculoid or tuberculous-like lesions are usually nodular formations; their gross and microscopic structure resembles granulomatous tuberculous nodules. They often develop as a response to endogenous and exogenous foreign bodies or as an inflammatory response to intracellular parasites. Developmental stages of a focal purulent inflammation with a marked infiltration of macrophages and lymphocytes, also necrosis with central caseation-pyogranuloma, may resemble tuberculoid lesions.

A special type of a chronic inflammation is tuberculoid lesions where activated epithelioid-like macrophages and lymphocytes, with occasional plasmatic cells, prevail in the exudate. Giant multi-

nuclear cells of various sizes are formed by mutual fusion of epithelioid cells. Nodular or diffuse cell accumulations are found. Fibrous encapsulations develop in long matured processes.

Pathogenesis of granulomatous inflammation is closely related to immune responses. Serum antibody titres are not elevated and the immune response is T-lymphocyte mediated. The primary precondition is a persisting antigen, which is not easy to undergo degradation by phagocytising macrophages. The host immune system is consistently sensitised by an antigen permanently presented by macrophages. Macrophages residing in the site of antigenic irritation are steadily attracted, activated and immobilised by the release of lymphokines by sensitised T-lymphocytes. These migrate into regional lymph nodes and reside in paracortical regions where they give rise to a future generation of lymphocytes. Those that get into the blood circulation, return to the site of antigenic irritation and thus cause enlargement of a granuloma. Cytotoxic cells and their factors also participate in the development of central necrosis. They represent a special type of chronic, granulomatous inflammation, during which the defence of an organism and tissues is provided by immune mechanisms of the cells.

The ways and extent by which respective cells contribute to the formation of a granuloma are highly variable. A granuloma formation is a positive response of the host and gives evidence of their immunocompetence. Based on the pathogenesis, two types of granulomatous inflammation (granuloma) exist: non-infectious, caused by a foreign body and infectious, caused by various bacterial, mycotic or parasitic agents. Non-infectious granulomas are characterised by the presence of foreign bodies. These granulomas (according to the type of foreign body) are surrounded with macrophages, comprise giant multinuclear cells, occasional lymphocytes and, relative to the degree of progression, also peripheral fibrous encapsulations. Infectious granulomas are caused by obligatory and usually facultative intracellular micro-organisms. Causative agents of specific granulomatous inflammations are the members of genus *Mycobacterium*.

Granulomatous inflammations may also be caused by the species of the following genera of bacteria: *Actinomyces*, *Nocardia*, *Pseudomonas*, *Yersinia*, *Brucella*, *Francisella*, *Salmonella* etc. This type of response may also be induced by the following mycomyceta: *Cryptococcus neoformans*,

Coccidioides immitis, *Emmonsia parva* and species of genera *Mucor*, *Absidia*, *Rhizopus*, *Hyphomyces*, *Sporotrichum* etc. Infectious granulomas may be caused by some species of protozoan parasites such as *Encephalitozoon* sp., *Toxoplasma gondii*, *Capillaria hepatica*, *Echinococcus multilocularis*, *Schistosoma* sp. ova, strobilocerci of tapeworms etc. (Shadduck and Pakes, 1978).

Bacteria present outside (extracellularly) cells of a host during infection usually exert their activity via their exogenous products, e.g. toxins. These micro-organisms induce damage to tissues by an acute inflammatory reaction, usually of a purulent character. The majorities of extracellular bacteria are mortally sensitive to phagocytosis and complement system. An effective immune response consists in elimination of bacteria and neutralisation of their toxins.

Intracellular parasitism is a strategy by which bacteria strive to escape defence mechanisms of the host or to weaken phagocytic activity. Bacteria have mechanisms active at all stages of phagocytosis ensuring survival or even propagation of bacteria inside macrophages. These mechanisms are: inhibition at the point of attachment, inhibition of lysosome fusion with phagosome, the leak from phagolysosome into cytoplasm and resistance to lysosomal enzymes (Martino et al., 2006). The pathogenesis of the infection caused by intracellular bacteria is varied according to the extent of their parasitism and genetic coding. Mechanisms of the immune response and persistent infections are usually of the type IV hypersensitivity reaction concurrent to inflammatory granulomatous response.

The characteristic feature of intracellular bacteria in most cases is tropism to lymphoid tissues and a high degree of capability to resist non-specific immune responses. The pathogenesis of respective bacterial infections is variable according to whether they are obligatory or facultative parasites. Protective immunity against intracellular bacteria is ensured by cell-mediated immunity. Antigenic oligopeptides presenting macrophages, linked with MHC II molecules, activate Th lymphocytes and direct their differentiation process towards Th 1 cells. Interferon- γ (IFN- γ) produced by them activates Natural killer (NK) cells and macrophages (Co et al., 2004).

IFN- γ activated macrophages can markedly reduce bacterial counts. However, inhibitory mechanisms of intracellular pathogens often result in the

survival of at least a certain proportion of bacteria. Consequently, the infection is chronic and persistent. Surviving micro-organisms cause chronic antigenic stimulation; this leads to aggregation of macrophages and formation of a granuloma (Ehlers, 2003). The granulomatous inflammatory response is an example of damage to tissues by their own immune mechanisms.

The most common intracellular bacterial parasites include both Gram-negative and Gram positive bacteria. Of the Gram-negative microorganisms, some species of the genus *Brucella*, *Salmonella*, *Shigella* and *Yersinia* are classified as facultatively intracellular bacteria. Among the Gram-positive bacteria, the most common intracellular pathogens are certain *Listeria*, *Rhodococcus* and *Mycobacterium*. A host cell is essential for the life of obligatory intracellular bacteria. These are mostly Gram-negative bacteria such as *Chlamydia* spp., *Rickettsia* spp., *Coxiella burnetii*, *Ehrlichia* spp., *Legionella* spp. and *Lawsonia intracellularis* (Paradise et al., 1999).

Certain antigens common to the genera *Mycobacterium*, *Nocardia*, *Corynebacterium* and *Rhodococcus* are significant from the antigenic structure perspective. The virulence factor described first is the cord factor. This toxic glycolipid administered in repeated doses is lethal for mice. Mycosides and sulphatides associated with the protection of mycobacteria from degradation by intracellular enzymes are present in the upper layers of the cell walls. Pathogenic mycobacteria cause a lot of humoral and tissue alterations in an infected organism; these manifest by increased sensitivity – an allergy that may be detected by the tuberculin test (Thoen and Himes, 1981).

4. Infections with tuberculoid lesions

4.1. Pseudotuberculosis

Pseudotuberculosis in rodents is an infectious disease with an acute or chronic course manifested by inflammatory-necrotic lesions in internal organs, where formation of abscesses later occurs. It affects, above all, rodents and hares, occasionally domestic mammals. Prevalence is related to the density of susceptible animals and various factors of the external environment. The causative agent is *Yersinia pseudotuberculosis*, which is Gram-negative, pleomorphic bacterium in the size of 1 to 2 µm. It is immotile at 37°C; in case it grows at tempera-

tures lower than 30°C, it moves by means of the flagella. It grows under anaerobic conditions on conventional agars in a form of smooth, humid and transparent colonies of 2 to 3 mm in size. It neither forms envelopes nor sporulates (Bercovier and Mollaret, 1984).

The oral route of infection, after the intake of contaminated feed, is most common, and infection after an injury is occasional. The causative agent is transferred from the digestive tract into the blood circulation system and causes septicaemia that is usually lethal. In animals that survived septicaemia, caseous, tuberculoid lesions develop in organs affected by the causative agent; those lesions later become dry and friable (Obwolo, 1977; Percy and Barthold, 2001). The incubation time is 5 to 8 days. Among mammals, free living rodents are most susceptible and they significantly participate in the transmission of the disease, together with birds. They also contaminate feeds, water, stable environment etc. with their faeces (Slee and Skilbeck, 1991).

By gross examination, an acute course is characterised by splenomegaly, swollen lymph nodes and enteritis. A subacute or chronic course is characterised by necrotic nodules present in organs and lymph nodes containing caseous matter of greyish to off-white colour arranged in concentric layers (Carlton and Hunt, 1978). Microscopy reveals that the layers are surrounded with a zone of lymphocytes and macrophages; giant cells are not usually present. Above all liver, spleen, less commonly lungs, kidneys and mesenteric lymph nodes are affected (Wetzler, 1981).

Another two pathogenic species of *Yersinia* genus are *Y. pestis* (causative agent of plague in humans) and *Y. enterocolitica*. *Y. pestis* is a small, Gram-negative coccobacillus, which frequently shows strong bipolar staining. Pleomorphic and club-shaped forms are not unusual. Freshly isolated cultures often exhibit substantial slime production, due to a so-called capsular or envelope antigen, which is heat labile and is readily lost when the organism is growing *in vitro* or in the insect vector.

Fully virulent strains possess V and W (virulence) antigens, which are highly toxic for the mouse and, to a lesser extent, for guinea pigs. Plague primarily affects rodents but is also an important disease transmissible to humans. It is characterised by an acute, necrotising lymphadenitis in the regional lymph nodes that drain the intradermal flea bite site. Septicaemia rapidly follows with spread to spleen, liver and other organs. Sporadic outbreaks

of sylvatic plague still occur in wild rats, squirrels and prairie dogs in the Western United States. Sebbane et al. (2005) developed a model of bubonic plague using the inbred Brown Norway strain of *Rattus norvegicus* to characterise the progression and kinetics of the infection and the host immune response after intradermal inoculation with *Y. pestis*.

Y. enterocolitica causes enteritis and lymphadenopathy that are later complicated by septicaemia (Odaert et al., 1996). Most *Y. enterocolitica* isolates are avirulent for laboratory rodents. Recently, several mouse virulent strains have been isolated from human pathologic material. Orally infected mice develop progressive involvement of the ileal Payer's patches, with pyogranuloma formation in the mesenteric lymph nodes, liver and spleen. Eventually, most of the animals die when these intestinal abscesses undergo perforation and peritonitis. The lesions typically contain large numbers of polymorphonuclear cells but there is also a strong mononuclear cell response (Pepe et al., 1995).

4.2. *Corynebacteriosis*

Pseudotuberculosis-like lesions are caused by *Corynebacterium kutscheri* in small terrestrial mammals. *C. kutscheri* was isolated from mice (Amao et al., 1995b), rats (Amao et al., 1995a) and Syrian hamsters (Tansey et al., 1995) among others.

4.3. *Tularaemia*

Tularaemia is an infectious disease with either an acute or chronic course that above all affects rodents and hares and may be transmitted to the other species of free living and domestic mammals and birds. The acute form is manifested by haemorrhagic septicaemia and the chronic form is manifested by body wasting and the development of pyogranulomas. Tularaemia has been described in all the countries of the northern hemisphere where the density of rodents is quite high and the conditions for life and propagation of arthropods are favourable.

The causative agent is *Francisella tularensis*, Gram-negative, immotile rod or coccobacillus sized 0.5 to 1 µm. It does not sporulate and grows under anaerobic conditions on special agars. Egg-

yolk agar, according to Mc Coy and Chapin, or agar, according to Francis, may be used for culturing. Its isolation on a chicken embryo is also possible. The infection is usually spread by ingestion of infected dead animals and by blood sucking insects. The incubation time is a few hours up to two weeks. The role of small rodents is important from an epizootiological aspect.

Gross lesions may be commonly found in swollen lymph nodes manifested by haemorrhages and later by pyogranulomas. Disseminated miliary necrotic lesions, sized 1 mm in average are found in the liver. Splenomegaly, concurrent to miliary necrotic lesions, surrounded by neutrophils and macrophages is also found (Carlton and Hunt, 1978). The nodules in liver and spleen resemble tuberculous nodules and they may be enucleated of the capsule (Bell and Reilly, 1981).

4.4. *Brucellosis*

Some species of the *Brucella* genus also cause the formation of tuberculoid lesions. Gross examination reveals numerous small nodules in lymph nodes, spleen and liver that are grey or yellow in colour. Under the microscope, the lesions appear to be granulomatous or pyogranulomatous and noticeably resemble tuberculosis (Stableforth, 1959). Rodents probably play one of the most significant parts in terms of zoonoses risks (Moutou and Artois, 2001).

4.5. *Salmonellosis*

Some species of the genus *Salmonella* may also cause a granulomatous inflammation at a certain stage in the process of infection. *Salmonella* is an obligatory intracellular parasite that primarily affects the liver, spleen and mesenteric lymph nodes. Focal necrosis that is off-white in colour and variable in size is usually found in these organs (Carlton and Hunt, 1978).

4.6. *Other infections with granulomatous lesions*

Besides bacterial infections, granulomas may be caused by some fungi of the following genera: *Blastomyces*, *Histoplasma*, *Cryptococcus*,

Mucor, *Absidia*, *Aspergillus*, *Rhizopus*, *Emmonsia* etc. (Migaki et al., 1978; Jellison, 1981). Among protozoan causative agents, species of the genera *Encephalitozoon* and *Toxoplasma gondii* may be isolated from granulomatous inflammations. Among helminths, ova of liver flukes of the genera *Schistosoma* and *Capillaria hepatica*, cysts of *Echinococcus granulosus* and strobilocerci of *Taenia taeniaeformis* etc. may cause granulomatous inflammations (Chitwood and Lichtenfels, 1973).

5. The potential risk of zoonoses to humans

Rodents and domestic animals (particularly ruminants and carnivores) are a group of vertebrates that are the most significant sources of zoonotic diseases, i.e. diseases of animals transmissible to humans. In several consequential zoonotic diseases, which are characterised by outbreaks in nature, voles are among the most significant reservoir animals, with the common vole (*Microtus arvalis*) being most abundant in the central European region. Voles are known to exhibit population cycles, i.e. more or less regular multiannual population fluctuations in numbers at intervals of 2 to 5 years (Krebs and Myers, 1974). This demographic feature makes them the most significant source of infection for humans. Due to the fact that they are food sources for other animals, they allow propagation of the disease vectors (ectoparasites) and intensive circulation of the causative agents. Other species that cause zoonotic diseases include those that come into closer contact with humans, such as synanthropic species, but also species that occasionally invade human dwellings (e.g., in winter or in the case of a massive surge in population numbers).

5.1. The important species of small terrestrial mammals in Europe

Among synanthropic species, the house mouse (*Mus musculus*) and Norway rat (*Rattus norvegicus*) are the most important small terrestrial mammals, with respect to disease transmission. Of exoanthropic species, the common vole (*Microtus arvalis*), field vole (*Microtus agrestis*), bank vole (*Clethrionomys glareolus*) and water vole (*Arvicola terrestris*) are of great importance. Occasionally, the introduced muskrat (*Ondatra zibethicus*) and three species of the genus *Apodemus*, i.e. wood mouse (*Apodemus*

sylvaticus), striped field mouse (*Apodemus agrarius*) and yellow-necked mouse (*Apodemus flavicollis*) may be classified as important among small terrestrial mammals. Epidemiological significance has not yet been sufficiently studied in the pygmy field mouse (*Apodemus microps*), European pine vole (*Microtus subterraneus*) with a mosaic distribution, or the common hamster (*Cricetus cricetus*). The population numbers of the latter has been decreasing for several decades, especially in Western Europe. In the Czech Republic, its demographic status is largely unknown and the species is now protected (Zejda et al., 2002).

Small terrestrial mammals differ in their habitat requirements. The common vole, pygmy field mouse and common hamster are primarily associated with the open agricultural land, whereas the field vole is associated with wet grasslands with high vegetation and sometimes situated at rather high altitudes. The yellow-necked mouse and bank vole are typical forest species, also occupying grassy habitats interspersed with shrubberies from lowlands to mountains. The occurrence of the water vole, muskrat and striped field mouse is associated with the banks of water biotopes. A very wide range of biotopes are populated by the wood mouse; that can also be found in open agricultural land and field ecotones, in shrubberies and in the vegetation of forest areas (Zejda et al., 2002).

5.2. Seasonal migration in small terrestrial mammals

The degree of attachment of terrestrial mammals to a particular habitat varies depending on seasonal changes in food availability. Highly mobile members of the genus *Apodemus* can migrate to sites with optimum food resources (seeds and fruit of plants). Accordingly, wood mice, striped field mice and yellow-necked mice are found in fields at the time when cereal is ripe or in the shrubby ecotones where they may come into contact with the field voles and pygmy field mice. Seasonal migration from the sides of water reservoirs was observed in water voles that migrate from the sides of big rivers to localities not affected by autumn floods, i.e. into biotopes inhabited by common voles or field voles (Pikula et al., 2002).

Mass migrations of species that regularly experience massive surges in population numbers (e. g. common voles, field voles, bank voles and striped

field mice) from areas with the highest densities to suboptimum biotopes are usually observed. Some populations of synanthropic species migrate from human habitats to the fields when cereals grow and return after the harvest of cereals and maize. Here, they come into contact with the other rodent species living in agroecosystem. The small terrestrial mammals attract lots of weasels and foxes (*Vulpes vulpes*) to the vicinity of straw stacks (Gaisler et al., 1967; Pelikan and Nesvadbova, 1979; Sebastianova et al., 2001). Straw stacks where small terrestrial mammals aggregate and come into contact with each other are therefore very important with respect to disease transmission. However, other areas in a cultivated agricultural area, such as fallow land, field margins, grassy balks and shrubberies that act as refugium for small mammals are also believed to play a significant role in the long-term persistence of the disease (Pikula et al., 2002).

In Central Europe, massive outbreaks of the common vole, experienced every 2 to 4 years are viewed as a significant epidemiological risk (Rosicky, 1959). When these cycles culminate, the density of animals is often about 2 000/ha (Zejsda et al., 2002). The high density may cause stress in these animals, concurrent to decreased immunity against infections and frequent cannibalism (feeding on dead animals is common). Stressed animals that are carriers of causative agents of the diseases shed them more intensively than the non-stressed carriers. Those causative agents are Hantaviruses, *Leptospira* sp. and *Francisella tularensis* (Danes et al., 1991; Trembl and Nesnalova, 1993; Hubalek et

al., 1996; Hoflechner-Potl et al., 2000). An epidemiological risk may also result from the mass migration of voles into straw stacks or to the vicinity of barns in autumn (Pejcoch et al., 2003).

5.3. Infectious agents causing granulomatous or pyogranulomatous inflammations

A number of bacteria, fungi and parasites are infectious agents causing granulomatous or pyogranulomatous inflammatory lesions that are similar in appearance. Table 1 presents an overview of the most significant and most common pathogens detected in free living small terrestrial mammals.

5.4. Small terrestrial mammals as a source of mycobacterial infections for carnivores and omnivores

Small terrestrial mammals are an integral part of the diet of some carnivores, above all the red fox (*Vulpes vulpes*), domestic cat (*Felis catus*) and mustelids (Mustelidae), particularly the weasel (*Mustela nivalis*) and ermine (*Mustela erminea*). Some omnivores, above all wild boars (*Sus scrofa*), also feed on them. Small terrestrial mammals may constitute up to 60% of domestic cat feed (Gillies, 2001), 65 to 96% of weasel feed and up to 73% of ermine feed (Grulich, 1959). With reference to the isolation of

Table 1. Causal infectious agents causing granulomatous or pyogranulomatous inflammation*

Bacteria		Fungi	Parasites
Gram negative	Gram positive		
<i>Brucella</i> sp.	<i>Corynebacterium</i> sp.	<i>Aspergillus</i> sp.	Eggs (<i>Capillaria</i> sp., <i>Schistosoma</i> sp.)
<i>Francisella</i> sp.	<i>Mycobacterium</i> sp.	<i>Blastomyces</i> sp.	<i>Echinococcus</i> sp.
<i>Pseudomonas</i> sp.	<i>Nocardia</i> sp.	<i>Coccidioides</i> sp.	<i>Encephalitozoon</i> sp.
<i>Salmonella</i> sp.	<i>Rhodococcus</i> sp.	<i>Cryptococcus</i> sp.	<i>Neospora</i> sp.
<i>Yersinia</i> sp.		<i>Emmonsia</i> sp.	<i>Toxoplasma</i> sp.
		<i>Histoplasma</i> sp.	<i>Strobilocercus</i> (<i>Taenia taeniaeformis</i>)
		<i>Mucor</i> sp.	
		<i>Rhizopus</i> sp.	

*Summarised according to Chitwood and Lichtenfels (1973), Jellison (1981) and Paradise et al. (1999)

pathogenic mycobacteria from the small terrestrial mammals, these infected animals may become potential sources of mycobacterial infections for carnivores and omnivores. That was indicated by *M. microti* isolation from a cat (Huitema and van Vloten, 1960; Huitema and Jaartsveld, 1967; Gunn-Moore et al., 1996), ferret (*Mustela putorius furo*; van Soolingen et al., 1998) and dog (Deforges et al., 2004). Isolation of *M. microti* from wild boar was also described (Huitema and Jaartsveld, 1967).

6. Conclusions

Despite the fact that a wide range of pathogens with zoonotic potential may be isolated from free living terrestrial mammals, tuberculosis is still one of the most serious diseases transmissible to humans. Though the causative agent of tuberculosis has been recognised and both a protective vaccination and efficient treatment is available, tuberculosis is still viewed as a serious disease nowadays, which is sometimes difficult to cure. Previously, tuberculosis used to be one of the most widespread diseases all over the world and a primary cause of mortality in children and young people. It was a cause of one-fourth of mortality cases in the 1950s. Incidences of tuberculosis in developed countries have markedly dropped; however, they are not negligible nowadays. From an aspect of transmission of mycobacterial infections and *M. tuberculosis* complex members by small rodents to humans, the infection with *M. microti* is the most serious.

Although this disease occurs in other animals, available recent information concerning the infection of small terrestrial mammals with *M. microti* is scarce. In general, infections due to *M. microti* have been underestimated and little attention has been paid to this effect. Nevertheless, the recent human case incidences are alarming and consideration of the disease is of paramount importance.

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