

Genetic and management factors that influence the susceptibility of cattle to *Mycobacterium bovis* infection

Clive J. C. Phillips^{1*}, Charles R. W. Foster², Pat A. Morris³ and Rachel Teverson⁴

¹Department of Clinical Veterinary Medicine, University of Cambridge, Cambridge CB3 0ES,

²Mozie Law Veterinary Practice, Canonbie, Dumfriesshire DG14 0RE, ³Department of Zoology, Royal Holloway College, University of London and ⁴Ivycross Farm, Stonehouse, Gloucs GL10 3DH, UK

Received 17 April 2001; Accepted 12 October 2001

Abstract

Genetic variation in the susceptibility of cattle to *Mycobacterium bovis* infection exists in differences between families and species, but not breeds. Susceptibility to *M. bovis* infection increases with age of cattle. Natural exposure to *M. bovis* or environmental mycobacteria may assist in the development of specific immunity, but there is no direct evidence for such immunological priming of tuberculosis resistance in cattle. This has, however, been demonstrated in humans and other animals. Since non-specific mechanisms have a role in protective immunity, developing an effective vaccine will be difficult, even though some protection of other species has been achieved. Immunological suppression in the periparturient period can produce anergic reactors, which may act as a constant source of infection for cattle-to-cattle transmission. Circumstantial evidence suggests that an adequate intake of mineral, vitamin and protein reduces the susceptibility of cattle. Although weather patterns have been implicated in the susceptibility of herds to *M. bovis* infection, there is insufficient information to determine the risk factors precisely. It is concluded that some reduction in the susceptibility of cattle to *M. bovis* infection can be achieved by modifications to the management system to minimize risk factors, but that a considerable amount of further research is required.

Historical background

The bacillus *Mycobacterium bovis* was discovered in 1882 by Robert Koch (1843–1910), who first showed that different organisms cause tuberculosis in cattle and man. It has a wide range of both target organs (lungs, gastrointestinal tract, mammary gland, kidney and reproductive organs) and mammalian hosts. Bovine tuberculosis was recognized as a significant problem in cattle production in the early part of the last century (Smith, 1905) and probably existed long before that. In the 1920s, a control strategy was initiated in the UK, which included cattle testing and slaughter of reactor cattle combined with the

following management regulations (Fishwick, 1952): (i) 'Double fencing of attested farms to ensure adequate isolation from non-tested cattle'; (ii) 'Movement of attested cattle to shows or sales governed by movement permits issued by local Veterinary Officer of the Ministry of Agriculture'; (iii) 'Only attested cattle introduced directly into attested herds without being isolated (if from non-tested herds they had to be tested after isolation for not less than 60 days)'.

These strategies led to a reduction in prevalence of the disease to less than 0.05% of all herds in England and Wales in the late 1970s. Since that time, the incidence of *M. bovis* infection in England and Wales has increased steadily, so that by 1999 the rate of new infection was 2.4% of the number of unrestricted herds tested (Ministry of Agriculture, Fisheries and Food, 2000). In the current situation, increasing the frequency of testing cattle is not

*Corresponding author: Department of Clinical Veterinary Medicine, Madingley Road, University of Cambridge, Cambridge CB3 0ES, UK. E-mail: cjc2@cam.ac.uk

likely to influence the prevalence of tuberculosis where there is an extensive wildlife reservoir (Barlow *et al.*, 1997). However, in the USA, where there is no wildlife reservoir in regular contact with cattle, the disease has been reduced to a low level, at a cost of US\$450 million (Nelson, 1999). There has been an intensive programme of testing, removal and slaughter of infected cattle, begun in the first half of the 20th century (Yapp and Nevens, 1944). Many American cases of *M. bovis* infection are now in imported cattle from Mexico (Essey and Koller, 1994). However, in Michigan State, which has regions where cattle have been infected endemically with *M. bovis* (Towar, 1964), the infection has also been isolated in deer and even coyotes that consume the deer (Schmitt *et al.*, 1997; Bruning Fann *et al.*, 1998).

There have been several recent reviews of the epidemiology of *M. bovis* infections in animals and man (Morris *et al.*, 1994; O'Reilly and Daborn, 1995; Neill *et al.*, 2001). There are also reviews of the survival of *M. bovis* in dairy products (Keogh, 1971), its potential transmission to humans (Kovalyov, 1989; Collins, 2000) and transmission in cattle (Griffin and Dolan, 1995), badgers (Cheeseman *et al.*, 1989; Gallagher and Clifton-Hadley, 2000) and other wildlife (de Lisle *et al.*, 2001). Vaccine development has been reviewed recently by Buddle *et al.* (2000) and Skinner *et al.* (2001).

Genetic variation and selection pressure

Genetic variation in resistance to *M. bovis* infection is manifest at three levels: species, breed and family. In the middle of the twentieth century, when the prevalence of infection was high, the tuberculin testing and slaughter scheme produced significant selection pressure for disease resistance in British cattle. However, in the last three decades the prevalence of the disease has been very low; removal of infected animals has had much less impact on the genotype of the national herd and may have been compounded by the importation of semen from overseas.

Species

Bos indicus cattle are less susceptible than *B. taurus* to *M. bovis* infection (Carmichael, 1941; Ram and Sharma, 1955). If the genes for this effect could be identified within *B. indicus* cattle, they could potentially be transferred genetically to *B. taurus* cattle or used for marker-assisted selection within the *B. indicus* species.

Breed

There is little published information on breed susceptibility, a small study in Latvia having indicated no differences in susceptibility between the major *B. taurus*

cattle breeds in Latvia (Petukhov, 1981). Unpublished data from the UK also suggests no differences between British breeds (Benham, 1985). There is, however, some evidence of differences in susceptibility between pure-bred zebu (*B. indicus*) cattle and zebu crosses in Malawi (Ellwood and Waddington, 1972).

Familial genotypic variation

There is evidence that certain familial lines of cattle show particular susceptibility to *M. bovis* infection (Maddock, 1934; Petukhov, 1981). The latter author investigated two cattle farms with 2742 animals in Latvia, where 23% were infected, and noted that some families had 80% of their members infected, whereas others had none. However, it is not clear whether some cattle are completely resistant to the infection. A high rate of transmission from cattle that had been infected artificially with high doses to naive cattle was recorded by Cassidy *et al.* (1999), but in another study only 40% of steers that were initially negative reactors to the single intradermal (SID) comparative tuberculin test developed tuberculosis when housed with reactors for 1 year (Costello *et al.*, 1998). Cattle receiving lower doses, for example from contaminated pasture, show low rates of infection (Schellner, 1956), which is supported by the fact that the majority of herd outbreaks involve only a small number of animals.

In experimental animals, strains of tuberculosis-resistant and susceptible mice and rabbits have long been recognized and utilized for research purposes (Wright and Lewis, 1921; Lurie, 1941; Anderson *et al.*, 1991). Furthermore, in mice there is a specific single dominant autosomal gene (*Bcg*), the presence of which results in increased macrophage action and interleukin 2 secretion (Schurr *et al.*, 1991; Skamene, 1991). In humans, there is both racial and ethnic variation in susceptibility to tuberculosis (Bellamy *et al.*, 2000; Lim, 2000), and it has been shown that genetic differences in macrophage protein expression partially determine the resistance shown by humans to *M. tuberculosis* infection (Agranoff *et al.*, 1999). In deer, *M. bovis*-resistant stock have been bred by selecting resistant sire lines. The heritability of resistance to tuberculosis has been estimated as 0.48, and both innate and acquired mechanisms of immunity are believed to be involved (Mackintosh *et al.*, 2000).

It can be concluded that familial variation in resistance is likely to exist, but at present there is little information on which to base selective breeding. The low and unpredictable level of exposure to infection in the field and the possibility of detecting only those cattle that have mounted a cellular immune response both mitigate against the identification of cattle that are able to eliminate the organism. Experimental identification of resistant cattle would require a significant resource provision, given the need for disease containment facilities for the infected cattle.

Mechanisms of immunity and possible genetic influence

Established infection with *M. bovis* is still a relatively rare event in the UK. The rate of new infection in 1999 was 2.4% of the number of unrestricted herds tested (Ministry of Agriculture, Fisheries and Food, 2000), and most herd breakdowns involved only very few reactor animals (Wilesmith *et al.*, 1986; Wilesmith and Williams 1986). Natural infection is thought to be frequently derived from the multiplication of a single bacillus (Neill *et al.*, 1991). The exposure rate of cattle in high-risk herds remains unknown. Low-dose exposure may be common, the animals' non-specific immune mechanisms eliminating the mycobacteria before infection becomes established. It has been estimated that an antigenic load of approximately 1000 mycobacterial organisms is required before cell-mediated immunity is activated (Smith and Wiegshauss, 1989; Dannenburg, 1991). Therefore, animals with a negative skin test may have been exposed to a low-dose challenge of *M. bovis* bacilli and successfully eliminated the organisms by non-specific immune mechanisms before they multiplied. Neill *et al.* (1992) reported a case of transient nasal excretion of *M. bovis* from an in-contact calf which showed no skin test response and no lesions at slaughter. If low-dose exposure to *M. bovis* is widespread in herds with repeated evidence of infection, the efficiency of non-specific immune responses may be critical in determining whether an animal develops infection.

Many mechanisms of non-specific immunity could be effective in eliminating a low-dose *M. bovis* challenge. Those under genetic influence might include the chemical nature of the bronchial mucus, the efficiency of the mucociliary escalator, the number of active non-specific macrophages in the lungs and the destructive efficiency of these macrophages' lysosomal enzymes. Other genetically controlled factors influencing susceptibility to bovine tuberculosis may be behavioural. The animals' grazing habits with respect to the avoidance of excretory products, the amount of social behaviour that might facilitate cattle-to-cattle transmission, and investigation by cattle of badgers or their excreta, may all be genetically influenced.

Specific mechanisms of immunity will almost certainly be genetically influenced. The type of immune response effected in human tuberculosis depends largely on the way mycobacterial antigen is presented by the genetically controlled major histocompatibility complex class II molecule (Orme, 1991). The mycobacterial epitopes presented will determine the classes and proportions of lymphocytes recruited. The predominant classes of lymphocytes recruited will greatly influence whether the disease progresses to the fulminating stage or is effectively limited.

Active immune responses to *M. bovis* infection

Specific active immunity to *M. bovis* through the generation of appropriate classes of sensitized lymphocytes

and memory cells may theoretically be generated by three mechanisms: natural exposure to *M. bovis*, exposure to other mycobacteria, and vaccination. The use of a supplementary humoral test may detect the presence of some anergic cows (Plackett *et al.*, 1989; Wood *et al.*, 1990; Hanna *et al.*, 1992; Whipple *et al.*, 1995), in which the cellular immune mechanism is suppressed in both the peripheral blood and at the site of the disease (Lepper *et al.*, 1977; Rhodes *et al.*, 2000). Plackett *et al.* (1989) identified a group of cattle that had high levels of antibody response against *M. bovis* but were negative to the tuberculin test. The interferon- γ released by lymphocytes can prime macrophages to greater microbicidal activity prior to mycobacterial infection, and a blood culture interferon- γ enzyme immunoassay system is a useful adjunct to skin testing for the detection of bovine tuberculosis infection.

Natural exposure to *M. bovis*

Francis (1947) took the pessimistic view, that unlike in man, in cattle the primary lesions are rarely if ever arrested. However, in natural infection in the field, the prevalence rate rarely exceeds 50% within a group (Waddington and Ellwood, 1972). This suggests that in the field, when disease prevalence is greatest (and cattle-to-cattle exposure to *M. bovis* is almost inevitable) a substantial proportion of animals are able to mount an effective protective response to *M. bovis* exposure. As most of these animals remain negative in the tuberculin test, any effective but non-specific immune response (e.g. through powerful microbicidal macrophages) will remain undetected. If specific cellular immunity is generated by natural exposure to *M. bovis*, such animals will be positive to the tuberculin test (yet reveal no visible lesions or positive culture) at slaughter. Interestingly, Wilesmith and Williams (1987) showed that, for the period 1979–1983, 70% of non-visible lesioned tuberculin test reactors in south-west England were probably caused by exposure to *M. bovis*. Undoubtedly, a proportion of these animals had lesions present at slaughter that remained undetected (Corner *et al.*, 1990). It remains unclear whether some of these animals mounted a successful specific immune response to *M. bovis*.

In New Zealand, an experimental model has been developed in red deer in which an *M. bovis* infection indistinguishable from natural infection is produced by very low-dose tonsillar crypt challenge with *M. bovis* (Mackintosh *et al.*, 1995). Experimentally challenged animals produced a spectrum of immune responses and clinical disease ranging from no disease to severely disseminated tuberculosis (Mackintosh *et al.*, 2000). Plackett *et al.* (1989) identified a group of cattle with high levels of antibody against *M. bovis* but negative to the SID tuberculin test. Harboe *et al.* (1990) and Ritacco

et al. (1991) were able to demonstrate an inverse relationship between titers of specific *M. bovis* antibody and cellular responses in experimental cattle. Other workers also accept this concept of a spectrum of immunological response to mycobacteria (Lepper and Corner, 1983; Buchan and Griffin, 1990; Buchan *et al.*, 1991; Neill *et al.*, 1994).

Exposure to other mycobacteria

Pre-exposure to environmental mycobacteria may, by mechanisms of immunological cross-reactivity, alter the course by which the disease progresses when an individual is challenged with a mycobacterial pathogen (Stanford *et al.*, 1976; Shield, 1983; Pallen, 1984; Grange, 1986, 1987; Grange and Collins, 1987). Other, naturally occurring mycobacteria grow well in soil (Iivanainen *et al.*, 1999) and saprophytic vegetation, particularly bryophytes (Cooney *et al.*, 1997). Members of the *Mycobacterium avium-intracellulare-scrofulaceum* complex predominate in water, dust and human sputum samples and *M. fortuitum* links with organisms in the soil (Kamala *et al.*, 1994). Environmental mycobacteria are also ubiquitous in natural water supplies (Dailloux *et al.*, 1999), where they inhabit the surface biofilm (Hall-Stoodley and LappinScott, 1998).

Most environmental mycobacteria are capable of inducing non-specific reactions to bovine and avian tuberculin (Cooney *et al.*, 1997; Corner and Pearson, 1979), which may influence the susceptibility of cattle to *M. bovis* infection. Guinea-pigs that have been immunized with *M. fortuitum* show a modulated protective response with the BCG vaccine (Kamala *et al.*, 1996). There is no direct evidence for this in cattle, but the immunological priming of humans and other animals by exposure to environmental mycobacteria is well established (Donoghue *et al.*, 1997). A study in south-west England found that a change in the distribution of predominating mycobacteria coincided with the introduction of organic farming practices, which, it is suggested, could increase the potential immunity afforded by exposure to non-pathogenic types (Donoghue *et al.*, 1997). However, although there is circumstantial evidence, there is no definitive research that suggests that alterations in susceptibility are possible as a result of prior or concurrent exposure to mycobacteria of different species or to other, less closely related organisms (Morris *et al.*, 1994).

The possibility that the consumption of environmental mycobacteria enhances the immune response to *M. bovis* cannot be dismissed, but it is unclear why such immunological priming was not effective in the early part of the last century, when *M. bovis* infection was even more common than it is today. It is possible that any effect was not sufficient to overcome major challenges from other highly infectious cattle at that time.

Many cattle in those days were poorly nourished in winter and were kept in under-ventilated and densely stocked buildings.

Vaccination

Other pathogenic mycobacteria affecting cattle, such as *M. avium* ssp. *paratuberculosis*, cannot be entirely controlled by vaccination, even after 100 years of research (Johnson-Ifeorlundu and Kaneene, 1997). In New Zealand, some protection of possums from *M. bovis* infection has been possible by injecting them with the BCG vaccine (Aldwell *et al.*, 1995). However, assuming that an extensive wildlife reservoir exists in the UK, any cattle vaccine would have to have an efficacy of more than 97% (Kao *et al.*, 1997).

The development of a cattle vaccine against *M. bovis* infection is at present a priority research objective in the control of bovine tuberculosis. An effective vaccine would prove a most practical and useful husbandry tool in the control of *M. bovis* infection in cattle. However, any live tuberculosis vaccine is unlikely to confer complete protection within a population and should be seen as a tool for disease control, not eradication. Since non-specific mechanisms have an important role in protective immunity, vaccination is likely to have less effect compared with improving nutrition or selecting for disease resistance.

Recent studies using a BCG and red deer model in New Zealand have been more encouraging, low-dose vaccination being able to protect a proportion of vaccinees against infection and lessen the severity of disease in others (Mackintosh *et al.*, 2000). However, Mackintosh *et al.* suggest that genetically susceptible deer may be incapable of developing a protective immune response to the *M. bovis* BCG vaccine.

Type of cattle enterprise

Cattle farming systems have increased the intensity of production in recent decades, as evidenced by increases in the milk yield and growth rate of cattle. However, in non-refereed Irish reports of the risk of herd breakdown by enterprise type (dairy, suckler and drystock units), no differences in breakdown rate were observed (Fallon, 1994; Mairtin, 1994). A smaller study in Italy showed that mixed dairy and beef enterprises were at greater risk of breakdown than either dairy or beef herds, which may have been due to increased likelihood of cattle movement, a major risk factor (Marangon *et al.*, 1998). Herd size does not influence the chance of a breakdown in the herd (Marangon *et al.*, 1998); thus the risk per animal is greater in small herds. This may be because the field boundaries are less contiguous in large herds.

In conclusion, there appears to be little evidence yet that changes in the type of cattle enterprise following a breakdown would be beneficial, but large herds have a reduced risk per animal.

Age

An increase in disease prevalence with the age of cows has been recorded both in Latvia, where the mean age of onset was 6 years (Petukhov, 1981), and in the UK, where the relative risk to cows over 8 years of age was 12 times the risk to cows aged 1–2 years (Benham, 1985). In Mexico, where there is a significant proportion of infected cattle, most reactors are adult females in fair to good body condition (Milian-Suazo *et al.*, 2000). Francis (1947) writes ‘the evidence suggests that even when young cattle are pastured with heavily infected old stock, the incidence in the former remains low until they enter the cow shed.’

Physiological state

Pregnancy has been implicated in anergy to the tuberculin test. There is a suppression of skin reactivity for about 15 days around parturition (5 days before to 10 days after calving) (Kerr, 1949). A similar reduction in skin reactivity after calving was observed by Buddle *et al.* (1994), together with a temporary reduction of the response in the interferon- γ immunoassay. This could be associated with the periparturient immunosuppression in dairy cows, which derives partly from nutrient deficiencies (Kehrli, 1998). There is no effect of pregnancy on disease susceptibility (Buddle *et al.*, 1994).

Exogenous corticosteroids

Corticosteroids are well known for their immunosuppressive effects, and corticosteroid production by the calf at parturition may be associated with the periparturient immunosuppression referred to above. Kerr *et al.* (1949) report suppressive effects of corticosteroids on the tuberculin test. Corticosteroids are used in medicine to prevent the rejection of foreign tissue grafts and in the treatment of allergic disease, and they may be used therapeutically (e.g. for the induction of parturition or the treatment of ketosis). Their use may increase an animal's susceptibility to infection. With the recent availability of licensed non-steroidal anti-inflammatory drugs for cattle, corticosteroids are now used much less commonly in general practice. Corticosteroids could theoretically be used by unscrupulous cattle owners to conceal tuberculous animals, but this might not be effective and would be counterproductive.

Concurrent diseases

Immunosuppressive disease

The effect of concurrent immunosuppressive disease on *M. bovis* infection in cattle does not appear to have been investigated. However, the major influence of HIV infection in humans on the risk of subsequent infection with *M. tuberculosis* or other mycobacteria is well documented (e.g. Glynn *et al.*, 2000; Mukadi *et al.*, 2001). A severe outbreak of *M. bovis* infection in housed calves with concurrent bovine viral diarrhoea (BVD) infection has been reported (Monies and Head, 1999). BVD is capable of producing immunosuppression (Potgieter *et al.*, 1984). Concurrent infection with feline immunodeficiency virus (FIV) and *M. bovis* in farm cats has been reported (Monies *et al.*, 2000). It is to be expected that immunosuppressive diseases will increase susceptibility to infection: examples are BVD, enzootic bovine leukaemia and bovine immunodeficiency-like virus, even though the latter may not produce an immunodeficiency syndrome like HIV or FIV, and hemolytic diseases such as babesiosis and tick-borne fever.

Diseases that are not intrinsically immunosuppressive may also affect susceptibility to *M. bovis* infection, such as those affecting vascular permeability or serum protein levels, which may indirectly affect cell-mediated immune responses (e.g. protein-losing enteropathies/nephropathies, fascioliasis, haemonchosis and ostertagiasis).

Respiratory disease

Dictyocaulus viviparus (Husk), *Pasteurella* spp., *Mycoplasma* spp., *Haemophilus* spp., infectious bovine rhinotracheitis virus, BVD, parainfluenza type 3 virus and Rous sarcoma virus are all pathogens responsible for causing respiratory disease in cattle. Their influence on susceptibility to infection with *M. bovis* remains unclear. Clinical effects associated with these diseases include pneumonia, bronchitis, tracheitis and altered bronchial mucus and secretions. Not only is it likely that they make the respiratory membrane more susceptible to infection with *M. bovis*, but those agents which induce coughing may also facilitate increased dissemination of *M. bovis* in aerosol form.

Nutrition

Low food intake did not increase the risk of transmitting *M. bovis* infection between steers in a study by Costello *et al.* (1998), but replication of the experimental unit was low. In a study in Mexico, cattle that were infected with *M. bovis* were reported to be mostly in fair to good

body condition (Milian-Suazo *et al.*, 2000). However, since protein deficiency has been shown to reduce immunocompetence in guinea-pigs (McMurray *et al.*, 1989), it is possible that there are nutritional effects in cattle that have not been elucidated. Experience from collective farms in Czechoslovakia suggests that deficiencies in vitamins A and C, calcium and protein, as well as carbohydrate excess, are likely to increase the risk of cattle acquiring *M. bovis* infection (Kabrt, 1962).

Mineral supplements

There is epidemiological evidence of an association between the provision of mineral licks and *M. bovis* infection. An Irish study found that the provision of mineral licks reduced the risk of a herd acquiring *M. bovis* infection in a study of breakdown herds, with an odds ratio of 2.7 (Griffin *et al.*, 1992, 1993). As in early 20th-century experience (Garner, 1946), the risk was also greater on farms with rough grazing, which may have been due to protection from sunlight or inadequate nutrition of the cattle. In the study by Griffin *et al.* (1992, 1993), the risk of breakdown was much greater on farms where there was a combination of no mineral lick being available and rough grazing. The effect of rough grazing was attributed to inadequate mineral supply from low-quality pasture. This led to the conclusion that mineral deficiencies predispose cattle to the disease. However, later (non-refereed) reports from Ireland found no relationship between three of the minerals likely to be deficient in cattle (copper, selenium and iodine) and the prevalence of *M. bovis* infection (Fallon and Rogers, 1993). However, it is possible that the provision of other minerals commonly provided in mineral licks (sodium, magnesium, zinc and cobalt) was responsible for the observed benefits in the work of Griffin *et al.* (1992). Published requirements for sodium for dairy cows are now believed to be too low, and there is evidence that increased sodium intake can reduce other diseases in dairy cows (Phillips *et al.*, 2000). This may be due to enhanced magnesium absorption, as the inhibition of magnesium absorption in the rumen by potassium is negated by the presence of sodium (Chiy and Phillips, 1993). In laboratory animals at least, magnesium status is an important factor in the immune response, magnesium deficiency leading to reduced antibody concentrations and activity (McCoy and Kenny, 1992). Magnesium is commonly deficient in grazing cattle, and in another pathogenic mycobacterial disease, leprosy, the magnesium status of the host is reduced (Jain *et al.*, 1995).

There is evidence that specific mineral deficiencies play an important role in predisposing animals to other mycobacterial infections. The low iron status of rodents increases their susceptibility to paratuberculosis; however, in cattle high susceptibility to copper deficiency may also mean that a high iron intake could predispose

cattle to the disease, since iron competes with copper for absorption sites (Lepper *et al.*, 1989). Copper and zinc superoxide dismutases protect against exogenous superoxide radicals and thereby may determine the virulence of pathogenic mycobacteria (Wu *et al.*, 1998). Alternatively, cadmium is a well-known antagonist of zinc and there is some evidence that badgers, a major intermediate host in Eire, are susceptible to the increased levels of cadmium in pasture in recent years, which reduces their reproductive rate and could impair kidney function (Vandenbrink and Ma, 1998). The possibility that in the Irish research the mineral licks at pasture improved the health of badgers rather than cattle cannot be ruled out. The licks usually contain zinc, which could offset high cadmium intakes.

The sporadic distribution of mycobacteria in the environment is partly due to their high susceptibility to the supply of minerals, particularly iron. Most mycobacteria are tolerant of acid soil conditions but are inhibited by the reduced iron availability in alkaline soils (Mitscherlich and Marth, 1984). Mycobacteria are not good at chelating iron and they secrete siderophores to sequester the element externally (Johnson-Ifeorlundu and Kaneene, 1997). In a review of the effects of soil type on the prevalence of paratuberculosis in cattle, Johnson-Ifeorlundu and Kaneene (1997) noted many studies reporting that the disease is more prevalent in areas with acidic soils, in which there is increased availability of minerals. The prevalence of other diseases, most notably anthrax, which is caused by *Bacillus anthracis*, and fusarium wilt, which is caused by *Fusarium oxysporum*, has been demonstrated to vary directly with soil pH (Johnson-Ifeorlundu and Kaneene, 1997). This is due, at least in the case of fusarium wilt, to the restriction of iron availability at high pH. An association between the prevalence of paratuberculosis in cattle and soil pH, while not proven empirically, is supported by evidence from the geographical distribution of the disease and the significant requirements of *M. paratuberculosis* for iron (Johnson-Ifeorlundu and Kaneene, 1997). No such association has yet been demonstrated for *M. bovis* infection of cattle, but outbreaks occur regularly in regions with calcareous soils.

Another pathogenic mycobacterium, *M. leprae*, reduces the systemic status of zinc and iron in its hosts (Jain *et al.*, 1995). In *M. bovis* infection, siderotic macrophages containing mycobacteria are seen in early granulomas, but in later stages epithelioid and giant cell differentiation reduces the intracellular concentration of iron and the number of mycobacteria (Lepper and Wilks, 1988). Whilst it might be suspected that this is due to localized effects in the affected region, and in particular the high zinc content of the bacteria, the same changes in mineral status have been observed in humans with pulmonary tuberculosis (Narang *et al.*, 1995). Changes in the levels of biometals in the sera of leprosy patients may be due to a systemic effect, in par-

ticular the release of interleukin 1. This product of inflammatory cells causes hypercupremic, hypozincemic and hypoferremic responses in the hosts (Jain *et al.*, 1995), which may reduce mycobacterial proliferation. Again, no such relationship has been demonstrated for *M. bovis* infection, and preliminary (non-refereed) evidence is that the copper status of cattle is not involved in herd breakdowns (Fallon and Rogers, 1993). However, further investigations of the micronutrient status of breakdown herds would appear worthwhile.

In summary, there is evidence that other pathogenic mycobacterial diseases alter the mineral status of animals, but it is unlikely that the micronutrients most commonly believed to be deficient in cattle are associated with the risk of *M. bovis* infection. It seems unlikely that the elements which protect the host from oxidative damage, such as copper and selenium, can explain differences in susceptibility. Some other minerals commonly believed to be in deficit could explain why the presence of mineral licks reduces the risk of *M. bovis* infection.

Weather

It is likely that the transmission of *M. bovis* is affected by weather conditions, since it can be destroyed by ultraviolet light in sunlight (Soparker, 1917). King *et al.* (1999) found that the annual prevalence of *M. bovis* increased in direct proportion to rainfall in the previous year, but this association is based on only a single study area. They also examined seasonal weather effects, but the large number of possible associations tested meant that those demonstrated could be spurious. Climate may help to explain the geographical localization of *M. bovis* infection in the south-west region of the UK. According to King *et al.* (1999), the link with climate also suggests that infection is more likely to be field-based than to act through infection indoors. If cattle were infected in early summer, disease could spread to others during confinement the following winter, leading to high numbers of infected animals being detected early in the following year. However, testing in the region studied by King *et al.* is more intensive in spring, obscuring seasonal patterns, and annual testing is insufficiently frequent to determine patterns of infection within years. As well as affecting cattle management and *M. bovis* survival, climatic factors may also affect the behaviour of cattle (Phillips, 1993) and badgers, which could influence the likelihood of transmission.

Housing

Despite the assertion by King *et al.* (1999) that transmission of infection is more likely at pasture, the authors of books on cattle in the first half of the last century, when

bovine tuberculosis was endemic, did not doubt that transmission between cattle was much more likely indoors than at pasture (Smith, 1905; Garner, 1946; Francis, 1947). However, at that time the disease would normally have progressed to a more infectious state than today, when there is regular tuberculin testing. It is also recognized that housing type and quality are significant risk factors for human tuberculosis and for paratuberculosis in cattle (Collins *et al.*, 1994; LoBue *et al.*, 1999).

Conclusions

There is evidence for genetic variation between cattle in resistance to *M. bovis*, but it is not clear either how complete the resistance is in the face of a major challenge or whether the variation is greatest between different species, breeds or families. Research to determine whether there are genetic differences in the specific and non-specific responses to infection could ultimately enable resistant cattle to be bred. Immunological priming may also influence the scale of the responses, but there is no direct evidence of this yet in the responses to *M. bovis* infection in cattle. Vaccination may eventually provide a means of control, not eradication, and has proved to be effective in deer. The major risk factors associated with management that have been linked to *M. bovis* transmission include small herds, mixed beef and dairy herds, older cows, probably undernutrition, particularly of minerals, and inadequate ventilation of cattle buildings. There is probably also an increased risk to cows around parturition. A considerable amount of further research is required on most of these factors before farmers can substantially reduce the risk of *M. bovis* transmission by modifications of their husbandry techniques. (For a summary of husbandry practices that could influence the disease prevalence, see Appendix.)

Acknowledgment

The authors acknowledge funding from the Ministry of Agriculture, Fisheries and Food (UK) to support this study.

References

- Agranoff D, Monahan IM, Mangan JA, Butcher PD and Krishna S (1999). *Mycobacterium tuberculosis* expresses a novel pH-dependent divalent cation transporter belonging to the Nramp family. *Journal of Experimental Medicine* **190**: 717–724.
- Aldwell FE, Keen DL, Stent VC, Thomson A, Yates GF, de Lisle GW and Buddle BM (1995). Route of BCG administration in possums affects protection against bovine tuberculosis. *New Zealand Veterinary Journal* **43**: 356–359.
- Anderson P, Ljungqvist L, Haslov K, Bentzon MW and Heron I (1991). Mpb 64 possesses tuberculosis-complex-specific B-cell and T-cell epitopes. *International Journal of Leprosy and Other Mycobacterial Diseases* **59**: 58–67.

- Barlow ND, Kean JM, Hickling G, Livingstone PG and Robson AB (1997). A simulation model for the spread of bovine tuberculosis within New Zealand cattle herds. *Preventive Veterinary Medicine* **32**: 57–75.
- Bellamy R, Beyers N, McAdam KP, Ruwende C, Gie R, Samaai P, Bester D, Meyer M, Corrah T, Collin M, Camidge DR, Wilkinson D, Hoal Van Helden E, Whittle HC, Amos W, van Helden P and Hill AV (2000). Genetic susceptibility to tuberculosis in Africans: a genome wide scan. *Proceedings of the National Academy of Sciences of the United States of America* **97**: 8005–8009.
- Benham PFJ (1985). A study of cattle and badger behaviour and farm husbandry practices relevant to the transmission of bovine tuberculosis (*Mycobacterium bovis*). Reading, UK: Ministry of Agriculture, Fisheries and Food. Report to the Ministry of Agriculture, Fisheries and Food.
- Bruning Fann CS, Schmitt SM, Fitzgerald SD, Payeur JB, Whipple DL, Cooley TM, Carlson T and Friedrich P (1998). *Mycobacterium bovis* in coyotes from Michigan. *Journal of Wildlife Diseases* **34**: 632–636.
- Buchan GS and Griffin JFT (1990). Tuberculosis in domesticated deer (*Cervus elaphus*): a large animal model for human tuberculosis. *Journal of Comparative Pathology* **103**: 11–22.
- Buchan GS, Grimmet DJ and Griffin JFT (1991). Cervine T-lymphocyte growth factors and their measurement in tuberculosis. *Veterinary Immunology and Immunopathology* **29**: 115–126.
- Buddle BM, Aldwell FE, Pfeffer A, Delisle GW and Corner LA (1994). Experimental *Mycobacterium bovis* infection of cattle—effect of dose of *M. bovis* and pregnancy on immune-responses and distribution of lesions. *New Zealand Veterinary Journal* **42**: 167–172.
- Buddle BM, Skinner MA and Chambers MA (2000). Immunological approaches to the control of tuberculosis in wildlife reservoirs. *Veterinary Immunology and Immunopathology* **74**: 1–16.
- Carmichael J (1941). Bovine tuberculosis in the tropics with special reference to Uganda. Part 1. *Veterinary Journal* **97**: 329–339.
- Cassidy JP, Bryson DG, Pollock JM, Evans RT, Forster F and Neill SD (1999). Lesions in cattle exposed to *Mycobacterium bovis*-inoculated calves. *Journal of Comparative Pathology* **121**: 321–337.
- Cheeseman CL, Wilesmith JW and Stuart FA (1989). Tuberculosis—the disease and its epidemiology in the badger: a review. *Epidemiology and Infection* **103**: 113–125.
- Chiy PC and Phillips CJC (1993). Sodium fertilizer application to pasture. 4. Effects on mineral uptake and the sodium and potassium status of steers. *Grass and Forage Science* **48**: 260–270.
- Collins CH (2000). The bovine tubercle bacillus. *British Journal of Biomedical Science* **57**: 234–240.
- Collins MT, Sockett DC, Goodger WJ, Conrad TA, Thomas CB and Carr DJ (1994). Herd prevalence and geographic distribution of, and risk-factors for, bovine paratuberculosis in Wisconsin. *Journal of the American Veterinary Medical Association* **204**: 636–641.
- Cooney R, Kazda J, Quinn J, Cook B, Muller K and Monaghan M (1997). Environmental mycobacteria in Ireland as a source of non-specific sensitisation to tuberculin. *Irish Veterinary Journal* **50**: 370–373.
- Corner LA and Pearson CW (1979). Response of cattle to inoculation with atypical mycobacteria isolated from soil. *Australian Veterinary Journal* **55**: 6–9.
- Corner L, Melville L, McCubbin K, Small KJ, McCormick S, Wood PR and Rothel JS (1990). Efficiency of the inspection procedures for the detection of the tuberculous lesions in cattle. *Australian Veterinary Journal* **67**: 389–392.
- Costello E, Doherty ML, Monaghan ML, Quigley FC and O'Reilly PF (1998). A study of cattle-to-cattle transmission of *Mycobacterium bovis* infection. *Veterinary Journal* **155**: 245–250.
- Cresswell WJH (1988). The effects of weather conditions on the movements and activity of badgers (*Meles meles*) in a suburban environment. *Journal of Zoology (London)* **216**: 187–194.
- Dailloux M, Laurain C, Weber R and Hartemann P (1999). Water and nontuberculous mycobacteria. *Water Research* **33**: 2219–2228.
- Dannenburg AM (1991). Delayed-type hypersensitivity and cell-mediated immunity in the pathogenesis of tuberculosis. *Immunology Today* **12**: 228–233.
- de Lisle GW, Mackintosh CG and Bengis RG (2001). *Mycobacterium bovis* in free-living and captive wildlife, including farmed deer. *Revue Scientifique et Technique de l'Office International des Epizooties* **20**: 86–111.
- Donoghue HD, Overend E and Stanford JL (1997). A longitudinal study of environmental mycobacteria on a farm in south-west England. *Journal of Applied Microbiology* **82**: 57–67.
- Ellwood DC and Waddington FG (1972). A second experiment to challenge resistance to tuberculosis in BCG vaccinated cattle in Malawi. *British Veterinary Journal* **128**: 619–626.
- Essey MA and Koller MA (1994). Status of bovine tuberculosis in North America. *Veterinary Microbiology* **40**: 15–22.
- Fallon RJ (1994). Effect of cattle enterprise type on the rate of disclosure of tuberculin reactors. Dublin, Ireland: Tuberculosis Investigation Unit, University College, Dublin.
- Fallon RJ and Rogers PAM (1993). Relationship of herd trace mineral status to the occurrence of tuberculosis. Selected papers 1993. Dublin, Ireland: Tuberculosis Investigation Unit, University College, Dublin.
- Fishwick VC (1952). *Dairy Farming Theory and Practice*, 7th edn. London: Crosby, Lockwood and Sons.
- Francis J (1947). *Bovine Tuberculosis, Including a Contrast with Human Tuberculosis*. London: Staples Press.
- Gallagher J and Clifton-Hadley RS (2000) Tuberculosis in badgers: a review of the disease and its significance for other animals. *Research in Veterinary Science* **69**: 203–217.
- Garner FH (1946). *British Dairying*. London: Longmans, Green.
- Glynn JR, Warndorff DK, Malema SS, Mwinuka V, Ponnighaus JM, Crampin AC and Fine PE (2000). Tuberculosis: associations with HIV and socioeconomic status in rural Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **94**: 500–503.
- Grange JM (1986). Environmental mycobacteria and BCG vaccination. *Tubercle* **67**: 1–4.
- Grange JM (1987). Infection and disease due to the environmental mycobacteria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**: 179–182.
- Grange JM and Collins CH (1987). Bovine tubercle bacilli and disease in animals and man. *Epidemiology and Infection* **99**: 221–234.
- Griffin JM and Dolan LA (1995). The role of cattle-to-cattle transmission of *Mycobacterium bovis* in the epidemiology of tuberculosis in cattle in the Republic of Ireland—a review. *Irish Veterinary Journal* **48**: 228–234.
- Griffin JM, Haehesey T and Lynch K (1992). The role of farm management practices and environmental factors in chronic tuberculosis. *Irish Veterinary Journal* **45**: 120–122.
- Griffin JM, Haehesey T, Lynch K, Salman MD, McCarthy J and Hurley T (1993). The association of cattle husbandry practices, environmental factors and farmer characteristics with the occurrence of chronic bovine tuberculosis in dairy

- herds in the Republic of Ireland. *Preventive Veterinary Medicine* **17**: 145–160.
- Hanna J, Neill SD and O'Brien JJ (1992). ELISA tests for antibodies in experimental bovine tuberculosis. *Veterinary Microbiology* **31**: 243–249.
- Hall-Stoodley L and LappinScott H (1998). Biofilm formation by the rapidly growing mycobacterial species *Mycobacterium fortuitum*. *FEMS Microbiology Letters* **168**: 77–84.
- Harboe M, Wiker HG, Duncan JR, Garcia MM, Dukes TW, Brooks BW, Turcotte C and Nagai S (1990). Protein G-based enzyme-linked immunosorbent assay for anti-MPB70 antibodies in bovine tuberculosis. *Journal of Clinical Microbiology* **28**: 913–921.
- Iivanainen E, Sallantausta T, Katila ML and Martikainen PJ (1999). Comparison of some decontamination methods and growth media for isolation of mycobacteria from northern brook waters. *Journal of Environmental Quality* **28**: 1226–1234.
- Jain A, Mukherjee A, Chattopadhyaya D and Saha K (1995). Biometals in skin and sera of leprosy patients and their correlation to trace-element contents of *Mycobacterium leprae* and histological types of the disease—a comparative study with cutaneous tuberculosis. *International Journal of Leprosy* **63**: 249–258.
- Johnson-Ifeorundu YJ and Kaneene JB (1997). Relationship between soil type and *Mycobacterium paratuberculosis*. *Journal of the American Veterinary Medical Association* **210**: 1735–1740.
- Kabrt J (1962). Report—tuberculosis and the winter feeding of dairy cows. *Veterinarstvi* pp. 50–52.
- Kamala T, Paramasivan CN, Herbert D, Venkatesan P and Prabhakar R (1994). Isolation and identification of environmental mycobacteria in the *Mycobacterium bovis* Bcc trial area of South India. *Applied and Environmental Microbiology* **60**: 2180–2183.
- Kamala T, Paramasivan CN, Herbert D, Venkatesan P and Prabhakar R (1996). Immune response and modulation of immune response induced in the guinea-pigs by *Mycobacterium avium* complex (MAC) and *M. fortuitum* complex isolates from different sources in the south Indian BCG trial area. *Indian Journal of Medical Research* **103**: 201–211.
- Kao RR, Roberts MG and Ryan TJ (1997). A model of bovine tuberculosis control in domesticated cattle herds. *Proceedings of the Royal Society of London Series B Biological Sciences* **264**: 1069–1076.
- Kehrli ME, Kimura K, Goff JP, Stabel JR and Nonnecke BJ (1998). Periparturient immunosuppression in dairy cows: nutrition and lactation effects. In: Wensing T (editor). *Production Diseases in Farm Animals*. Utrecht: Wageningen Pers, pp. 41–53.
- Keogh BP (1971). Reviews of the progress of dairy science. Section B. The survival of pathogens in cheese and milk powder. *Journal of Dairy Research* **38**: 91–111.
- Kerr WR, Lamont HG and McGirr JL (1949). Further studies on tuberculin sensitivity in the bovine. *Veterinary Record* **61**: 466–475.
- King EL, Lovely DJ and Harris S (1999). Effect of climate on the survival of *Mycobacterium bovis* and its transmission to cattle herds in south west Britain. In: Cowan DP and Feare CJ (editors). *Advances in Vertebrate Pest Management*. Furth: Filander Verlag.
- Kovalyov, GK (1989). On human tuberculosis due to *M. bovis*. A review. *Journal of Hygiene, Epidemiology, Microbiology and Immunology* **33**: 199–206.
- Lepper AW and Corner LA (1983). Naturally-occurring mycobacterioses of animals. In: Ratledge C and Stanford J (editors). *The Biology of the Mycobacteria, Volume 2. Immunological and Environmental Aspects*. London: Academic Press, pp. 418–521.
- Lepper AW and Wilks CR (1988). Intracellular iron storage and the pathogenesis of paratuberculosis. Comparative studies with other mycobacterial, parasitic or infectious conditions of veterinary importance. *Journal of Comparative Pathology* **98**: 31–53.
- Lepper AW, Pearson CW and Corner LA (1977). Anergy to tuberculin in beef cattle. *Australian Veterinary Journal* **53**: 214–216.
- Lepper AWD, Embury DH, Anderson DA and Lewis VM (1989). Effects of altered dietary iron intake in *Mycobacterium paratuberculosis*-infected dairy cattle: sequential observations on growth, iron and copper metabolism and development of paratuberculosis. *Research in Veterinary Science* **46**: 289–296.
- Lim TK (2000). Human genetic susceptibility to tuberculosis. *Annals of the Medical Academy of Singapore* **29**: 298–304.
- LoBue PA, Cass R, Lobo D, Moser K and Catanzaro A (1999). Development of housing programs to aid in the treatment of tuberculosis in homeless individuals: a pilot study. *Chest* **115**: 218–223.
- Lurie MR (1941). Heredity, constitution and tuberculosis, an experimental study. *American Review of Tuberculosis* **44** (Supplement 1): 1–125.
- Mackintosh C, Waldrup K, Labes R, Buchan G and Griffin F (1995). Intra-tonsil inoculation: an experimental model for tuberculosis in deer. In: Griffin F and de Lisle G (editors). *Tuberculosis in Wildlife and Domesticated Animals*. Otago Conference Series, No. 3. Dunedin: University of Otago Press, pp. 121–122.
- Mackintosh CG, Qureshi T, Waldrup K, Labes RE, Dodds KG and Griffin JFT (2000). Genetic resistance to experimental infection with *Mycobacterium bovis* in red deer (*Cervus elaphus*). *Infection and Immunity* **68**: 1620–1625.
- Maddock ECG (1934). Further studies on the survival time of the bovine tubercle bacillus in soil, soil and dung, in dung and on grass, with experiments on feeding guinea-pigs and calves on grass artificially infected with bovine tubercle bacilli. *Journal of Hygiene* **34**: 372–379.
- Mairtin DO (1994). The effect of enterprise type on the prevalence of tuberculin reactors in the East Offaly badger research project. Selected papers. Dublin, Ireland: Tuberculosis Investigation Unit, University College, Dublin, pp. 18–19.
- Marangon S, Martini M, Dalla Pozza M and Neto JF (1998). A case-control study on bovine tuberculosis in the Veneto region (Italy). *Preventive Veterinary Medicine* **34**: 87–95.
- McCoy H and Kenny MA (1992). Magnesium and immune function: recent findings. *Magnesium Research* **5**: 281–293.
- McMurray DN, Mintzer CL, Bartow RA and Parr RL (1989). Dietary protein deficiency and *Mycobacterium bovis* BCG affect interleukin-2 activity in experimental pulmonary tuberculosis. *Infection and Immunity* **57**: 2606–2611.
- Milian-Suazo F, Salman MD, Ramirez C, Payeur JB, Rhyan JC and Santillan M (2000). Identification of tuberculosis in cattle slaughtered in Mexico. *American Journal of Veterinary Research* **61**: 86–89.
- Ministry of Agriculture, Fisheries and Food (2000). www.maff.gov.uk/animalh/tb.
- Mitscherlich E and Marth EH (1984). *Microbial Survival in the Environment*. Berlin, Springer-Verlag.
- Monies RJ and Head JCS (1999). Bovine tuberculosis in housed calves. *Veterinary Record* **145**: 743.
- Monies RJ, Cranwell MP, Palmer N, Inwald J, Hewinson RG and Rule B (2000). Bovine tuberculosis in domestic cats. *Veterinary Record* **146**: 407–408.
- Morris RS, Pfeiffer DU and Jackson R (1994). The epidemiology of *Mycobacterium bovis* infections. *Veterinary Microbiology* **40**: 153–177.

- Mukadi YD, Maher D and Harries A (2001). Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* **15**: 143–152.
- Narang APS, Whig J, Mahajan R, Gill DS, Punia AK, Goyal SC and Chawla LS (1995). Serum copper and zinc levels in patients with pulmonary tuberculosis. *Trace Elements and Electrolytes* **12**: 74–75.
- Neill SD, O'Brien JJ and Hanna J (1991). A mathematical model for *Mycobacterium bovis* excretion from tuberculous cattle. *Veterinary Microbiology* **28**: 103–109.
- Neill SD, Hanna J, Mackie DP and Bryson TG (1992). Isolation of *Mycobacterium bovis* from the respiratory tracts of skin test-negative cattle. *Veterinary Record* **131**: 45–47.
- Neill SD, Pollock JM, Bryson DB and Hanna J (1994). Pathogenesis of *Mycobacterium bovis* infection in cattle. *Veterinary Microbiology* **40**: 41–52.
- Neill SD, Bryson DG and Pollock JM (2001). Pathogenesis of tuberculosis in cattle. *Tuberculosis* **81**: 79–86.
- Nelson AM (1999). The cost of disease eradication—smallpox and bovine tuberculosis. *Annals of the New York Academy of Sciences* **894**: 83–91.
- Newell DG and Hewinson RG (1995). Control of bovine tuberculosis by vaccination. *Veterinary Record* **136**: 459–463.
- Orme IM (1991). Processing and presentation of mycobacterial antigens: implications for the development of a new improved vaccine for tuberculosis control. *Tubercle* **72**: 250–252.
- O'Reilly LM and Daborn CJ (1995). The epidemiology of *Mycobacterium bovis* infections in animals and man: a review. *Tubercle and Lung Disease* **76** (Supplement 1): 1–16.
- Pallen MJ (1984). The immunological and epidemiological significance of environmental mycobacteria on leprosy and tuberculosis control. *Tubercle and Lung Disease* **76**: 1–46.
- Petukhov VL (1981). [Genetics of cattle resistance to tuberculosis. I. The age of having the disease, milk productivity and the maternal influence on the incidence of the infection in progeny]. [in Russian]. *Genetika* **17**: 729–733.
- Phillips CJC (1993). *Cattle Behaviour*. Ipswich, Farming Press.
- Phillips CJC, Chiy PC, Arney DR and Kart O (2000). Effects of sodium fertilizers and supplements on milk production and mammary gland health. *Journal of Dairy Research* **67**: 1–12.
- Plackett P, Ripper J, Corner LA, Small K, de Witte K, Melville L, Hides S and Wood PR (1989). An ELISA for the detection of anergic tuberculous cattle. *Australian Veterinary Journal* **66**: 15–19.
- Potgieter LND, McCracken MD, Hopkins FM, Walker RD and Guy JS (1984). Experimental production of bovine respiratory tract disease with bovine diarrhoea virus. *American Journal of Veterinary Research* **45**: 1582–1585.
- Ram T and Sharma RM (1955). Tuberculosis infection in Haryana Hissar cattle. *Indian Journal of Veterinary Science and Animal Husbandry* **25**: 99–104.
- Rhodes SG, Buddle BM, Hewinson RG and Vordermeier HM (2000). Bovine tuberculosis: immune responses in the peripheral blood and at the site of active disease. *Immunology* **99**: 195–202.
- Ritacco V, Lopez B, De Kantor IN, Barrera L, Errico F and Nader A (1991). Reciprocal cellular and humoral immune responses. *Research in Veterinary Science* **50**: 365–367.
- Schellner H (1956). Risk of infection in cattle grazing pastures contaminated with tubercle bacilli. *Rindertuberkulose* **5**: 179–188.
- Schmitt SM, Fitzgerald SD, Cooley TM, Bruning Fann CS, Sullivan L, Berry D, Carlson T, Minnis RB, Payeur JB and Sikarskie J (1997). Bovine tuberculosis in free-ranging white-tailed deer from Michigan. *Journal of Wildlife Diseases* **33**: 749–758.
- Schurr E, Malo D, Radzioch D, Buschman E, Morgan K, Gros P and Skamene E (1991). Genetic control of innate resistance to mycobacterial infections. *Immunology Today* **12**: A42–A45.
- Shield MJ (1983). The importance of immunologically effective contact with environment mycobacteria. In: Ratledge C and Stanford J (editors). *The Biology of the Mycobacteria, Volume 2*. London: Academic Press, pp. 343–415.
- Skamene E (1991). Population and molecular genetics of susceptibility to tuberculosis. *Clinical Investigations in Medicine* **14**: 160–166.
- Skinner MA, Wedlock DN and Buddle BM (2001). Vaccination of animals against *Mycobacterium bovis*. *Revue Scientifique et Technique de l'Office International des Epizooties* **20**: 112–132.
- Smith F (1905). *A Manual of Veterinary Hygiene*. London: Baillière, Tindall and Cox.
- Smith DW and Wiegand E H (1989). What animal models can teach us about the pathogenesis of tuberculosis in humans. *Reviews of Infectious Diseases* **11** (Supplement 2S): S385–S393.
- Soparker MB (1917). The vitality of the tubercle bacillus outside the body. *Indian Journal of Medical Research* **4**: 627–650.
- Stanford JL, Paul RC, Penketh A, Thurlow S, Carswell JW, Barker DJP and Barot S (1976). A preliminary study of the effect of contact with environmental bacteria on the pattern of sensitivity to a range of new tuberculin amongst Ugandan adults. *Journal of Hygiene (Cambridge)* **76**: 205–214.
- Towar DR (1964). An epidemiologic study of endemic bovine tuberculosis in Marion Township, Michigan. *Proceedings of the Annual Meeting of the United States Animal Health Association* **68**: 320–326.
- Vandenbrink NW and Ma WC (1998). Spatial and temporal trends in levels of trace metals and PCBs in the European badger *Meles meles* (L., 1758) in The Netherlands: implications for reproduction. *Science of the Total Environment* **222**: 107–118.
- Waddington FG and Ellwood DC (1972). An experiment to challenge the resistance to tuberculosis in B.C.G. vaccinated cattle in Malawi. *British Veterinary Journal* **128**: 541–552.
- Whipple DL, Bolin CA, Davis AJ, Jarnagin JL, Johnson DC, Nabors RS, Payeur JB, Saari DA, Wilson AJ and Wolf MM (1995). Comparison of the sensitivity of the caudal fold skin test and a commercial gamma-interferon assay for diagnosis of bovine tuberculosis. *American Journal of Veterinary Research* **56**: 415–9.
- Wilesmith JW, Bode R, Pritchard DG, Stuart FA and Sayers PE (1986). Tuberculosis in East Sussex. I. Outbreaks of tuberculosis in cattle herds (1964–1984). *Journal of Hygiene (Cambridge)* **97**: 1–10.
- Wilesmith JW and Williams DR (1986). Tuberculosis lesions in reactor cows [letter]. *Veterinary Record* **119**: 51.
- Wilesmith JW and Williams DR (1987). Observations on the incidence of herds with non-visible lesioned tuberculin test reactors in south-west England. *Epidemiology and Infection* **99**: 173–178.
- Wood PR, Corner LA, Plackett P (1990). Development of a simple, rapid in vitro cellular assay for bovine tuberculosis based on the production of gamma interferon. *Research in Veterinary Science* **49**: 46–49.
- Wright S and Lewis PA (1921). Factors in the resistance of guinea pigs to tuberculosis with especial regard to inbreeding and heredity. *American Naturalist* **55**: 20.
- Wu CHH, Tsai Wu JJ, Huang YT, Lin CY, Lioua GG and Lee FJS (1998). Identification and subcellular localization of a novel Cu,Zn superoxide dismutase of *Mycobacterium tuberculosis*. *FEBS Letters* **439**: 192–196.
- Yapp WW and Nevens WB (1944). Dairy cattle, selection, feeding and management. 3rd edn. New York: John Wiley.

Appendix

Potential husbandry practices to reduce *M. bovis* infection

This review suggests that a range of factors may predispose cattle to *M. bovis* infection. Although there is no clear evidence of the relative importances of these factors, the following husbandry advice may be recommended on the strength of current knowledge.

- The pursuit of a breeding programme to identify resistant sires may be beneficial, but changes in cattle breed are unlikely to offer any improved resistance. Changes in the type of cattle enterprise are unlikely to reduce the risk of *M. bovis* infection, but larger herds will have a reduced risk per animal.

- Farmers should be aware that old cows are particularly susceptible to infection by *M. bovis* and in some cases may be able to adopt strategies to reduce risk in these cows. For example, they could be kept away from high-risk areas of the farm.

- The provision of mineral licks is associated with a reduced risk of cattle acquiring *M. bovis* infection, but supplementary copper, selenium or iodine is unlikely to affect the risk. The potential exists for badgers visiting mineral licks to transmit the disease via their sputum, but this could be avoided by raising mineral blocks out of the reach of badgers and other relevant wildlife.

- Concurrent disease, particularly of the respiratory tract, and possibly BVD, may increase the susceptibility of cattle. Effective treatment or vaccination is likely to reduce susceptibility to *M. bovis* infection.

**NEW BOOK
INFORMATION**
From
CABI PUBLISHING

Animal Domestication and Behavior

*E O Price, Department of Animal Science, University of California,
Davis, USA*

ISBN 0 85199 597 7
October 2002 320 pages
Hardback £49.95 (US\$85.00)

Readership

Animal and veterinary science, zoology and conservation biology

Description

This book synthesizes existing knowledge of the process of domestication and how it has affected the behaviour of captive wild and domesticated animals. Three broad themes are addressed:

- Genetic contributions to the process of domestication
- Experimental contributions to the process of domestication
- The process of feralization (i.e. the adaptation of domesticated animals when returned to their natural habitat)

To view full contents or to order online please visit
www.cabi-publishing.org/bookshop

Postage & Packing: For pre-paid orders in the UK, please add £2.75 for the 1st book and 60p for each additional book ordered (up to max. of 10). For pre-paid orders elsewhere, please add £4.00 for the 1st book and £1.00 for each additional book. For orders not pre-paid, postage and packing will be charged according to the weight of the book.

**CABI Publishing,
CAB International**
Wallingford,
Oxon OX10 8DE, UK
Tel: +44 (0)1491 832111
Fax: +44 (0)1491 829292
Email: orders@cabi.org

**CABI Publishing,
CAB International**
10 East 40th Street, Suite 3203,
New York, NY 10016, USA
Tel: +1 212 481 7018
Fax: +1 212 686 7993
Email: cabi-nao@cabi.org

 **CABI Publishing**
A division of CAB International