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Nocardia in naturally acquired and experimental infections in animals

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INTRODUCTION

There are three commonly recognized species of *Nocardia* that cause disease in a large variety of animals including humans. In the United States, pulmonary or systemic nocardiosis in humans caused by *N. asteroides* is most frequently diagnosed. It should be noted that *N. brasiliensis* can cause nocardiosis also. In Central and South America mycetomas induced by *N. brasiliensis* appear to be more prevalent even though *N. asteroides* can be seen in this type of infection. Sporadic cases of both mycetoma and nocardiosis caused by *N. caviae* have been reported. These three species of *Nocardia* appear to be present in the soils of most countries; but *N. asteroides* is more frequently isolated in the temperate climates whereas *N. brasiliensis* predominates in the tropical and subtropical regions of the world. No specific geographic distribution has been noted with *N. caviae*. Infections involving these three species of bacteria are, therefore, worldwide in occurrence. Even though nocardial infections in both humans and animals were recognized as early as 1888, traditionally, they have been considered rare in frequency as compared to many other infectious diseases. This is a perception that probably is not accurate. During the past twenty years, greater diagnostic awareness combined with more intensive medical and veterinary surveillance have resulted in significantly increased recognition of disease caused by these aerobic actinomycetes.

NATURALLY ACQUIRED INFECTIONS IN ANIMALS

Nocardial infections in cattle

Bovine farcy

It has been established that the nocardiae are important, and probably relatively common, pathogens causing disease in domesticated cattle throughout the world (Anderson & Wilke, 1980; Bushnell *et al.* 1979; Eales *et al.* 1964; Mazzoni & Morgentis 1971; Moreyhra, Martinez & Villamar, 1980; Mugarula & Mchomba, 1980; Orchard, 1979; Pier, 1962; Pier, Gray & Fossgatti, 1958; Salmon, Bushnell & Pier, 1982). Indeed, as early as 1888, Nocard isolated a strictly aerobic, branching, filamentous organism from pus and organ fragments obtained from bovine farcy

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in Guadeloupe (Nocard, 1888). In 1889 the genus *Nocardia* was created by Trevisan and *Nocardia farcinica* became the type species (Gordon, 1981). Currently there is considerable confusion regarding the original isolates of Nocard combined with the more recent discovery that a *Mycobacterium* can be isolated from bovine farcy in Africa. Because of these, as yet unresolved, problems it is suggested that *N. farcinica* be considered a *nomen dubium* and that *N. asteroides* be made the type species of the genus (Gordon, 1981).

Bovine farcy is most frequently recognized in Africa and at least two forms of the disease are described. Usually it produces a chronic, subcutaneous inflammation involving the lymphatics; however, it may become a progressive, internalized disease with the formation of purulo-granulomatous lesions within the lungs, and other internal organs. Most often there is a development of slowly progressive abscesses along the shoulder joint, along the lymphatics of both the fore and rear legs, around the head, near the ears, in the prescapular, precrural and head lymph nodes, on the cheeks of the head, and along the mandible (Mostafa, 1967*a*, *b*). The lesions may contain colonies of acid-fast filaments arranged in a radiating form which is surrounded by phagocytes, dead cells and necrotic debris. Granulation tissue is actively being laid down and a fibrous capsule is formed on the outside in an attempt to wall off the expanding lesions (Mostafa, 1967*a*, *b*).

In 1888 Nocard isolated from cattle with farcy an organism that grew readily on solid media aerobically at 30–40 °C. The colonies were described as being yellow with a dusty or powdery surface. The isolates were pathogenic for guinea-pigs (Nocard, 1888). At a later date this isolate became American Type Culture Collection number 3318 and a duplicate isolate was deposited with the National Collection of Type Cultures as number 4524. During the 1970s an examination of these two 'original' cultures attributed to Nocard revealed that they were not identical (Lechevalier, 1977). Because of the confusion as to which isolate was Nocard's original, a series of studies were undertaken to re-isolate and re-examine the aetiology of bovine farcy. Thus cattle from Chad and Sudan were studied. The organisms isolated from these animals were subjected to extensive taxonomic analysis and it was found that the isolates were *Mycobacterium* and not *Nocardia* (Perpezat, Destombes & Mariat, 1967; Asselineau, Lanceelle & Chamoiseau, 1969; Chamoiseau, 1974; El Sanousi *et al.* 1979; Salih, El Sanousi & Tag El Din, 1978; Ridell & Goodfellow, 1983). Even after these extensive studies, the question of Nocard's isolates is not resolved. The *Mycobacterium* species isolated from bovine farcy are relatively slow growing and they do not produce colonies with a dusty surface (aerial filamentation); while in contrast, Nocard's original description most nearly resembles true nocardiae. In 1978, Salih *et al.* studied bovine farcy in lesions of Sudanese cattle and concluded that farcy is relatively common in Sudan with an incidence of 10·86% among the cattle in the Nuba mountains. Several isolates from these cattle were studied further and shown to be *Mycobacterium* and not *Nocardia*. Therefore, El Sanousi *et al.* (1979) concluded that the aetiology of bovine farcy in Sudan was due to *Mycobacterium*. More recently Shigidi, Mirgani & Musa (1980) isolated 21 strains of bacteria from cattle with bovine farcy in the Sudan and subjected them to taxonomic analysis. These investigators found that all 21 isolates were antigenically related to *N. asteroides* but not closely related to *Mycobacterium*. Furthermore, all of the isolates had nocardomycolic acids (LCN-A)

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and not mycolic acids characteristic of *Mycobacterium*. These authors concluded that the aetiology of bovine farcy in Sudan is *Nocardia* and not *Mycobacterium*.

Mycobacterium farcinogenes and *N. asteroides* can produce lesions that are indistinguishable; and both can appear as microcolonies of acid-fast radiating filaments within the purulogranulomatous lesions. Therefore it appears likely that both *Mycobacterium* and *Nocardia* may be involved in outbreaks of bovine farcy. Furthermore, it is tempting to speculate that Nocard, in 1888, may have isolated both organisms from pus and tissues from farcy. This could easily explain the discrepancy between isolates ATCC 3318 and NCTC 4524.

Bovine mastitis

Even though there may be some uncertainty about the role of *Nocardia* in bovine farcy, there is no question that *Nocardia* is an important aetiologic agent of mastitis in dairy cows (Argente *et al.* 1983; Barbesier, 1960; Barnum & Fuller, 1956; Bushnell *et al.* 1979; Ditchfield, Butas & Julian, 1959; Eales *et al.* 1964; Fuchs & Boretius, 1972; Gray, 1935; Hillermark, 1960; Johnston & Connole, 1962; Lindner, 1973; Mazzoni & Morganti, 1971; Moreyra, Martinez & Villamar, 1980; Munch-Petersen, 1954; Pier & Enright, 1962; Pier & Fichtner, 1981; Pier *et al.* 1958; Pier, Mejia & Willers, 1961; Pier, Thurston & Larsen, 1968; Pier, Willers & Mejia, 1961; Salmon *et al.* 1982; Shigidi & Mamoun, 1981; Verdura & Joa, 1977; Wendt, Pospisil & Fuchs, 1969).

Mastitis in cows caused by *Nocardia* often develops into clinically apparent disease 1–2 days after calving. There is usually an acute onset, and the mammary gland becomes enlarged and fibrotic. Sinus tracts may develop that drain purulent exudate to the exterior in severely progressive stages of the disease. Frequently the cows develop a fever in response to the infection. The infection may spread to the supramammary lymph nodes, and systemic nocardiosis may develop following dissemination by way of the blood stream. Those animals that are acutely infected have a relatively high mortality rate (probably greater than 10%). If nocardial mastitis occurs during mid-lactation, the course of the disease is usually less severe. However, chronic mastitis accompanied by significant fibrosis and the formation of encapsulated abscesses in the parenchyma result from infection at this stage of lactation (Bushnell *et al.* 1979).

N. asteroides is the most frequently recognized cause of nocardial mastitis; but *N. caviae* is also encountered. There have been a few reports of *N. brasiliensis* causing bovine mastitis; however, precise identification is lacking in these reports (Bushnell *et al.* 1979; Ditchfield *et al.* 1959; Fuchs & Boretius, 1972; Moreyra *et al.* 1980; Orchard, 1979; Pier & Fichtner, 1981; Pier *et al.* 1961; Salmon *et al.* 1982; Shigidi & Mamoun, 1980). Since the nocardiae are normal inhabitants of the soil and cattle are quite susceptible to infection, it is very likely that dairies sporadically have individual cows that develop nocardial-induced mastitis. In most instances these individual cases of mastitis would remain unrecognized or misdiagnosed because these organisms are not readily isolated or identified by the normal diagnostic procedures used in mastitis laboratories (Bushnell *et al.* 1979). It is the occurrence of significant numbers of cows simultaneously developing severely inflamed, fibrotic and therapeutically unresponsive mastitis in dairy herds with the concomitant inability to define a specific aetiology that calls the attention

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of the veterinarian to the problem and suggests a nocardial aetiology (Bushnell *et al.* 1979). *Nocardia* can be successfully recovered from udder secretions inoculated directly onto blood agar or brain–heart infusion agar and incubated at 37 °C for several days (> 3 days). It is important to emphasize that storage of the milk in ice, refrigerators or freezers for prolonged periods of time may result in the reduced ability to isolate *Nocardia* from the milk. For example, in one series of experiments, milk was obtained from a cow with mastitis and quantitatively plated onto bovine blood agar plates immediately. Some of the milk was then placed in ice, while other portions were not stored in this manner; these samples were then transported to the laboratory. At about 6 h after storage in ice or at ambient temperature, the milk was once again quantitatively sampled and plated for *Nocardia*. The plates prepared directly from the cow (no storage) demonstrated that there were approximately 10^6 c.f.u./ml of milk. In sharp contrast, the samples stored in the ice bath for 6 hours had fewer than 10 c.f.u. of *Nocardia* per ml of milk. The samples stored at ambient temperature for 6 h still had about 10^6 c.f.u. *Nocardia*/ml but contamination and overgrowth with bacteria presented some problems in sample determination (Beaman, unpublished data). In one cow *N. asteroides* could be readily isolated directly from udder secretions, but when the same secretions were transported in an ice chest to the laboratory, there was an inability to isolate *Nocardia* from this sample (Beaman, unpublished data). Not all strains of *Nocardia* in milk are equally sensitive to cold-shock. Isolates of *N. asteroides* from a different dairy appeared to be recovered equally well when taken directly from the udder or from milk after storage in an ice chest (Beaman, unpublished data). The results of these studies indicate that in order to maximize accurate recovery of *Nocardia* from mastitis the samples should always be plated immediately after they have been obtained (Beaman, unpublished data). Diagnostic, immunologic tests have been utilized for detection of bovine mastitis (Pier & Enright, 1962; Pier & Fichtner, 1971; Salmon, Bushnell & Pier, 1982). These tests appear to be an important adjunct to recognizing which cows within a heard have been infected with *Nocardia*, however, direct culture combined with udder palpitation and clinical history are essential (Bushnell *et al.* 1979). Within a herd with nocardial mastitis, approximately 50% of the cows that have clinically apparent disease fail to yield *Nocardia* when milk samples are taken. Nevertheless, biopsy and necropsy samples can be shown to yield positive cultures. Therefore a combination of serology, immunology, culture, clinical and physical findings combine to establish nocardial infection within a herd (Bushnell *et al.* 1979).

In the development of nocardial mastitis, the initial infection with *N. asteroides* probably occurs during the dry period where a focus of infection may remain clinically unrecognized until after parturition. As the cow begins to lactate and the udder fills with milk, the nocardial foci probably become disrupted and the organisms spread throughout the lactiferous tree resulting in massive infection and development of clinical signs. The infusion of materials contaminated with *Nocardia* during mid-lactation therapy can also result in chronic mastitis (Bushnell *et al.* 1979). Therefore, the development of nocardial mastitis can be acquired naturally or be induced by manipulation. There are many reports of individual cows developing nocardial mastitis without spread through the herd, however, once nocardiae become established within a herd, they tend to spread. It has been

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suggested that cows become infected by infusion and disinfection procedures within the dairy and therefore are related to improper dairy management. This certainly represents an important factor, but dairy management procedures do not necessarily account for all of the mastitis problems. Nevertheless, once a cow within a herd becomes infected with *Nocardia* (for whatever reason or from whichever source), the infection usually spreads to other cows by either multiple-use syringes and needles, lack of appropriate use of disinfectants, use of contaminated home-mixed udder infusions, or by inadequate dairy herd management during milking procedures (Argente *et al.* 1983; Barbesier, 1960; Barnum & Fuller, 1956; Bushnell *et al.* 1979; Ditchfield *et al.* 1959; Eales *et al.* 1964; Fuchs & Boretius, 1972; Hillermark, 1960; Johnston & Connole, 1962; Lindner, 1973; Mazzoni & Morganti, 1971; Moreyra *et al.* 1980; Munch-Petersen, 1954; Pier & Enright, 1962; Pier & Fichtner, 1981; Pier, Gray & Fossatti, 1958; Pier *et al.* 1961; Pier, Thurston *et al.* 1968; Pier *et al.* 1961; Salmon *et al.* 1982; Shigidi & Mamoun, 1981; Verdura & Joa, 1977; Wendt *et al.* 1969).

Bovine abortion

N. asteroides has been demonstrated to cause severe infections in cattle independent of its role in either farcy or mastitis. The specific routes of these infections are not clearly understood; however, it has been suggested that contamination of the genital system (especially during obstetrical manipulations) may lead to uterine infection. This in turn may result in necrotic lesions on the chorionic surface of the placenta leading to abortion of the fetus. In addition, it has been reported that the fetus can become heavily infected; and dissemination of the disease throughout the fetus results in abortion. The incidence of bovine abortion caused by *Nocardia* is not known; but, it is probable that many other agents have been incorrectly identified as the aetiology of nocardial-induced abortion. Therefore, misdiagnosis has almost certainly resulted in an underestimate of the importance of *Nocardia* in abortion in cattle (Kikopa & Bergmann, 1975; Monga, Kar & Dixit, 1978; Mugarula & Mchomba, 1980; Overgoor & Van Haaften, 1965; Van Fey, Holm & Teuscher, 1954; Walton & Libke, 1974, Wohlgemuth *et al.* 1972; Zanella, 1961).

Pulmonary and systemic bovine nocardiosis

Pulmonary nocardiosis has been described in cattle of varying ages, although most of the reported cases have been in calves less than 6 months of age. The disease is not commonly recognized. However, as with the pulmonary infections in humans, pulmonary disease in cattle may be more frequent, but often misdiagnosed or undiagnosed. In addition, nocardial lesions have been found in the liver of an apparently healthy bull; and in testes, in bronchial lymph nodes, mediastinal lymph nodes, thoracic lymph nodes, mesenteric lymph nodes, intestine, heart, brain and kidneys of cattle taken to slaughter (Beaman, unpublished data; Anderson & Wilcke, 1980; Mazzoni & Morganti, 1971; Norton, 1976; Orchard, 1979; Tjaberg, 1969; Van der Wall, 1964).

It is clear that healthy cattle are quite susceptible to a variety of infections caused by *Nocardia*, the most important of which appears to be mastitis. It is not known whether these infected animals represent a risk to humans since there have

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been no studies to indicate potential risks. However, it is certain that nocardial infections in dairy cattle result in substantial economic losses each year.

Nocardial infections in dogs

In 1888, Rabe described filamentous organisms that grew aerobically from lesions in a dog, and he named these isolates *Cladothrix canis*. In 1916, Chalmers and Christopherson renamed these dog isolates *Nocardia canis*, and they described them as growing both aerobically and anaerobically at 22 and 37 °C; as forming brown colonies on gelatin agar; and being isolated from dogs, cats and goats (it should be noted that these same authors describe *N. asteroides* as being able to grow both aerobically and anaerobically). They distinguished *N. canis* from *N. asteroides* by colonial pigmentation only. Based upon the incomplete information concerning these early isolates, it is not possible to state with certainty that they were indeed *Nocardia* since it is well established that strains of *Actinomyces viscosus* can also cause similar types of infections in dogs. However, the descriptions appear to be more compatible with *Nocardia* than with *Actinomyces* (Chalmers & Christopherson, 1916; Ginsberg & Little, 1948; George *et al.* 1972).

In 1902, MacCallum reported that dogs experimentally infected intravenously with *N. asteroides* developed metastatic lesions in various organs and died. Thus, they demonstrated that normal, healthy dogs were susceptible to infection with *Nocardia* (MacCallum, 1902).

In 1903, Trolldenier isolated an aerobic, branched, filamentous organism from a dog, and he considered this isolate to be a pathogenic *Streptothrix*. It was probably a *Nocardia*. Balozet and Pernot isolated '*Actinomyces*' *asteroides* from a case of canine meningitis in 1936, and they claimed to be the first to identify this species of organism from the dog. From their description it is clear that these individuals had indeed recovered *N. asteroides* from the brain and meninges of an 18-month-old dog (Balozet & Pernot, 1936). Since these early studies there have been numerous reports in the world literature describing the isolation of *Nocardia* from canine infections (Awad & Obeid, 1962; Blake, 1954; Bohl *et al.* 1953; Brodey, Cole & Sauer, 1955; Carol-Dimitriu & Elias, 1976; Correa *et al.* 1973; Cross, Nagao & Morrison, 1953; DeYoung & Imhoff, 1980; Elias, Shophet & Blaustein, 1980; Fawi, 1964; Fawi, Tag El Din & El Samousi, 1971; Frost, 1959; Ginsberg & Little, 1948; Grain, Ackerman & Castleman, 1978; Herin, 1969; Johnston, 1956; Jones *et al.* 1975; Kapes, 1973; Kinch, 1968; Kuttin *et al.* 1980; Langham, Schimer & Newman, 1959; Maddy, Stroud & Ajello, 1955; Manktelow & Russell, 1965; Mansi, 1952; McGaughey, 1952; Mitten, 1974; Moss, 1956; Mostafa, Cerny & Cerna 1968; Otcenasek, Veselsky & Dvorak, 1971; Rhoades *et al.* 1963; Studdert, 1971; Swerczek, Trautwein & Nielson, 1968; Thordal-Christensen & Clifford, 1953; Veselsky & Otcenasek, 1972).

As with bovine infections caused by *Nocardia*, most of the isolates recovered from infected dogs have been *N. asteroides*. However, both *N. brasiliensis* and *N. caviae* have been shown to cause canine infections (Buchanan *et al.* 1983; Herin, 1969; Kinch, 1968; Mostafa *et al.* 1968). Unfortunately, many reports in the literature ascribe canine infections to *Nocardia* solely on tinctorial and microscopic properties of the organisms within the infected tissues. Often cultures of these samples are negative for either *Actinomyces* or *Nocardia*. Furthermore, when cultures are

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obtained, they are not subjected to an adequate battery of taxonomic tests to permit speciation. Therefore, many investigators report *N. asteroides* as the aetiology of canine infections based upon inadequate criteria. Most of these cases probably are due to *N. asteroides*, but many may be due to other *Nocardia* species (or in some instances *Actinomyces*).

The clinical presentation of nocardial infections in the dog appears to be very similar to that seen in humans. In most instances, however, infection appears to be primary without recognized underlying predisposing conditions. In contrast, nocardiosis in humans has been recognized frequently associated with some underlying, predisposing condition. Nevertheless, it should be noted that approximately 50% of the cases of nocardiosis diagnosed in humans are in individuals that have no known predisposing factor (Beaman *et al.* 1976).

Nocardial infections in dogs probably result from either inhalation, ingestion or subcutaneous inoculation. Pulmonary nocardiosis is the most frequently recognized form of disease, and it often disseminates from the lungs to involve a variety of internal organs. Although there may be no specific clinical signs associated with pulmonary and systemic nocardiosis, the affected dog usually has fever, anorexia, emaciation and dyspnoea (DeYoung & Imhoff, 1980; Grain *et al.* 1978). In addition to pulmonary nocardiosis there is frequent recognition of skin lesions that are manifested as wounds with a chronic purulent discharge located mostly on the head and legs of the dog (Kuttin *et al.* 1980). Nocardial mycetoma has also been described in a dog (Brodey, 1955). Dogs infected with *Nocardia* have been shown to develop vertebral osteomyelitis (Mitten, 1974); brain and central nervous system infections including meningitis (Balozet and Pernot, 1936; Herin, 1969; Johnston, 1956; Kuttin *et al.* 1980; Rhoades *et al.* 1963; Swerczek *et al.* 1968); pulmonary infections including pleurisy, empyema, pneumonia, lung abscess, and thoracic lesions (Awad & Obeid, 1962; Blake, 1954; Campbell & Scott, 1975; DeYoung & Imhoff, 1980; Fawi *et al.* 1971; Frost, 1959; Johnston, 1956; Jones *et al.* 1975; Kinch, 1968; Kuttin *et al.* 1980; Manktelow & Russell, 1965; Moss, 1956; Thordal-Christensen & Clifford, 1953); and kidney, heart, lymph node, adrenal and liver infections (Bohl *et al.* 1953; Elias *et al.* 1980; Grain *et al.* 1978; Mostafa *et al.* 1968; Otcenasek *et al.* 1971).

The world literature on nocardial infections in dogs was reviewed and specific information was obtained concerning the sex, age, nature of disease, predisposing factors, final outcome and nocardial species involved. Only those cases in which *Nocardia* was proven were included in this study. Also included were cases from the University of California School of Veterinary Medicine at Davis. In this survey a total of 52 dogs was accepted for analysis. It was found that 63·5% of the dogs were males and 23% females while in 13·5% of the cases the sex of the dog was not reported. Thus, males were infected about three times more frequently than females. These data are very similar to those reported for nocardial infections in humans (Beaman *et al.* 1976). The age of the dog appears to have a profound effect on susceptibility to infection since 65·4% of the dogs were less than 1 year of age, and a total of 82·7% of the dogs were less than 2 years old. In contrast only 7·8% were greater than 6 years old with the oldest reported age in this series being 8 years. The age of only two dogs within this series was unknown. Thus, young male puppies are most likely to acquire nocardial infections. In contrast, it has

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been reported frequently that humans between the ages of 20 and 40 are most susceptible to *Nocardia*, and young children or infants with nocardial infections are only infrequently recognized (Beaman *et al.* 1976). Nocardial infections in dogs are serious since 50 % of the dogs died from the infection and 38·5 % were euthanized because of lack of response to therapy. Only 7·7 % of the cases were reported as cured. The outcome in 3·8 % of the cases was not indicated. No predisposing factor to infection was identifiable in 67·3 % of the dogs, while an underlying condition that may have predisposed the animal to nocardial infection was reported in 26·9 % of the cases. The most frequent predisposing factor reported was canine distemper. However, it was reported that nocardiosis in the dog could masquerade as canine distemper and only in four of the dogs reported was distemper proven to coexist with the nocardial infection. The species of *Nocardia* isolated was identified as *N. asteroides* in 71·1 % of the cases and *N. caviae* in 7·7 %. The cultures were identified only as *Nocardia* sp. in 21·2 %. One case caused by *N. brasiliensis* was reported by Herin (1969). Therefore, it appears that *N. asteroides* is the most frequent cause of nocardiosis, and it is a primary pathogen in young dogs.

Nocardia *in cats*

There have been several reports of nocardial infections in cats; however, the incidence appears to be substantially less than reported for either dogs or cattle (Ajello *et al.* 1961; Akun, 1952; Armstrong, 1980; Bakerspigel, 1973; Campbell & Scott, 1975; Frost, 1959; Langham *et al.* 1959; Orchard, 1979; Studdert, 1971). In approximately 80 % of all of the cats in which information could be obtained (this includes cases seen at the University of California) nocardial infections were observed in castrated males of middle age (between 3 and 6 years of age). Only one female cat and one female spayed cat were reported to have nocardial infection. Most of these cats were either euthanized or died as the result of their infection; but, there are reports of successful therapy (Campbell & Scott, 1975). All cats that were studied had either typical pulmonary nocardiosis with or without dissemination or mycetoma. Most cases were caused by *N. asteroides*; however, almost 30 % of the reported cases were caused by *N. brasiliensis* or *N. brasiliensis*-like nocardiae (Beaman, Buchanan, unpublished data; Ajello *et al.* 1961; Akun, 1952; Armstrong, 1980; Bakerspigel, 1973; Campbell & Scott, 1975; Frost, 1959; Langham *et al.* 1959; Orchard, 1979; Studdert, 1971). There are no reports of *N. caviae* causing infections in cats. These observations are in sharp contrast to those reported for either bovine or canine infections. No underlying predisposing factors except possibly castration were reported in most of the cases studied.

Nocardial infections in horses

Nocardia is not a frequent cause of disease in horses; however, when nocardial infection occurs it is usually fatal. Nocardiosis is most frequently seen in Arabian foals. Most of these animals that develop nocardial infection appear to have combined immunodeficiency disease (Confer *et al.* 1981; Beaman, unpublished observations). Thus, *Nocardia* appears to be an opportunistic pathogen in horses. *N. asteroides* is the usual aetiology, causing both pulmonary and systemic nocardiosis; however, abscess of the mandible and eye infections have been reported in older, mixed breed horses (McLaughlin *et al.* 1983; Pier & Fichtner,

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1981; Tritschler & Romack, 1965). There is one report of *N. brasiliensis* causing a primary pneumonia with pleuritis in a 15-month-old quarter horse (Deem & Harrington, 1980). There are no reports of *N. caviae* causing disease in horses.

Nocardial infections in goats, pigs and sheep

In addition to cattle and horses, nocardial infections have been reported in a variety of domesticated farm animals. Most prominent are reports of infection in goats in which mycetomas, pulmonary infections and mastitis have been described (Banerjee & Gupta, 1979; Dafalla & Gharib, 1958; Ellwood, 1973; Gumoa & Abu-Samra, 1981; Gumoa *et al.* 1978; Otcenasek & Vitovec, 1982; Sharma & Dwivedi, 1977). Unfortunately, most of these reports have relied upon microscopic examination of tissues rather than upon isolation and identification of the specific organisms involved. Even though the microscopic appearance of the lesions were more compatible with *Nocardia* than *Actinomyces*, proof of the aetiology is lacking in most of these reports. Dafalla & Gharib (1958) established that *N. asteroides* can cause mastitis in goats since they were able to isolate the nocardiae from the infected udder. The incidence of goat mastitis caused by *Nocardia* is not known, but it is believed to be much more common then generally recognized. Ellwood (1973) isolated *N. caviae* from the lungs of a goat that had developed a pneumonia. This investigation suggested that nocardial infections in the goats of Malawi might be relatively common but remain unrecognized because of a lack of surveillance (Ellwood, 1973). Although there are no reports in the literature of naturally acquired infections in goats caused by *N. brasiliensis*, Gumoa & Abu-Samra (1981) demonstrated that this organism could cause experimental mycetomas in goats.

Only *N. asteroides* has thus far been isolated from swine. Both abortion and pulmonary infections have been reported. These infections appeared in healthy animals and they represented sporadic, isolated cases. It has been suggested that swine abortion due to *N. asteroides* may be a more common but unrecognized problem (Cole & Holzinger, 1972; Gottschalk, 1971; Kirkbride & McAdaragh, 1978; Koehne, 1972; Koehne & Giles, 1981; Mazzoni & Morganti, 1971).

There are few reports of nocardial infections in sheep. Nocardiae have been implicated in ovine abortion and in pulmonary infections, but most reports are based entirely upon microscopic examination of infected tissues. Therefore, it has not been possible to identify the species of *Nocardia* that cause these ovine infections (Sharma & Dwivedi, 1977; Watson, 1977).

Recently a fatal infection of a llama caused by *N. asteroides* was seen at the University of California, Davis (Buchanan, personal communication).

Nocardial infections in fish

In 1963 Valdez & Conroy (1963) described a tuberculosis-like disease in neon tetras which are small aquarium fish. It was proved that this infection was caused by *N. asteroides* and not *Mycobacterium* as originally believed. Snieszko *et al.* (1964) reported an outbreak of nocardial infection in fingerling rainbow trout reared in a hatchery. Several fish were involved within different growing tanks, but the nocardial infections never spread to all of the fish within the tanks. The organisms isolated from these trout were identified as *N. asteroides*. The infected fish swam in a circular direction as though chasing their tails and they remained on their sides

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while swimming. This pattern of behaviour described by Snieszko *et al.* (1964) is very similar to the 'spinning' syndrome observed in mice experimentally infected with *N. asteroides*. The fish were shown to have compact lesions within the abdomen and the abdomen was distended. The nocardiae were also seen in the capsule of the brain. Thus the nature of infections in fish caused by *N. asteroides* appears to be similar to those described in other animals (Snieszko *et al.* 1964).

Since these initial reports of nocardial infections in fish, several additional cases of *Nocardia* infecting at least seven different species of fish have been described (Campbell & McKelvie, 1968; Heuschmann-Brunner, 1965, 1966; Kubota *et al.* 1968; Wolke & Meade, 1974). In most instances the causative organism was identified as *N. asteroides*; however, a new species of *Nocardia*, *N. kampachi* was suggested for isolates from the Japanese yellow tail (Kubota *et al.* 1968). The taxomonic validity of *N. kampachi* has not been accepted; and indeed, this organism is probably *N. asteroides* (Skerman, McGowan & Sneath, 1980). Therefore only *N. asteroides* has thus far been isolated from infections in fish.

Wolke & Meade (1974) describe nocardial lesions that produced protruding oral masses in two chinook salmon. Inflammatory tissue resembling granulomas surrounding bacterial colonies were observed in the gills, myocardium, pericardium, spleen, kidneys, pancreas, mesentery, pyloric caeca and anterior gut of these two salmon. There were no suppurative lesions within these fish which may reflect the fish's inability to produce 'pus' (Wolke & Meade, 1974). Ghittono (1972) reports that 'fish nocardiosis' is very similar to 'fish mycobacteriosis'. Both of these forms of disease are ubiquitous and occur in fish living in aquaria as well as growing wild in either fresh, marine, or brackish waters (Ghittino, 1972).

Nocardial infections in birds

Nocardiosis is not commonly recognized in birds; however, there are reports of *N. asteroides* from chickens, and nocardiosis has been diagnosed in a duck (*Anas boscas*), hill mynah (*Gracula religiosa*) and an African fish eagle (*Haliaetus vocifer*) (Cooper, 1973; Iyer & Rao, 1971; Iyer *et al.* 1972; Pier & Fichtner, 1981). In all cases the disease appeared to be pulmonary in origin with dissemination to other organs of the birds. All of the infected birds had died and diagnosis of nocardia appeared to be more by chance, which suggests that nocardiosis in birds may be much more prevalent. Cooper (1973) investigated the deaths of 43 birds of prey in East Africa. He found that only four of these birds died from an infectious disease and one of them (African fish eagle) had nocardiosis. The other 39 birds died from a variety of unrelated problems such as trauma. The observations support the concept that *Nocardia* may be an important, but unrecognized, pathogen in certain birds.

Nocardial infections in marine mammals

N. asteroides, *N. brasiliensis* and *N. caviae* have all been isolated from a variety of marine mammals. They have been diagnosed in animals found in Hawaii, Florida, New Zealand, Northeastern United States and Asia. Some of these animals were wild, but had recently been captured and kept in sea-life parks while the others appeared to have died at sea or to have beached themselves and died. *N. brasiliensis* was isolated from a Pacific bottlenose dolphin as was *N. caviae*. All

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of the other isolates appeared to be either *N. asteroides* or identified as *Nocardia* sp. These organisms were found in pilot whales, killer whales, spinner dolphin, Atlantic bottlenose dolphins, pygmy sperm whale, leopard seals and harbour porpoise. Dolphins were most frequently reported to have nocardiosis (Jasmin, Powell & Baucom, 1972; Orchard, 1979; Pier & Fichtner, 1981; Pier, Takayama & Miyhara, 1970; Sweeney *et al.* 1976). Most, if not all, of these animals had respiratory disease and evidence of dissemination to other organs. The source of the nocardiae that infected these marine animals is not known, and most of these cases appeared to represent primary infections. Based upon these fortuitous findings, it appears likely that nocardiae may represent an important pathogenic agent in most varieties of marine mammals throughout the world.

Nocardial infections in wild animals

A variety of wild animals have been reported to have acquired nocardial infections. Most frequent of these, except perhaps marine mammals, are non-human primates. Mycetomas in a squirrel monkey, pulmonary nocardiosis in an orangutan, localized *N. caviae* infection in a baboon and pulmonary nocardiosis in rhesus monkeys and vervet monkeys have been reported (Al-Doory *et al.* 1969; Boncyk *et al.* 1975; Jonas & Wyand 1966; Kessler & Brown, 1981; McClure *et al.* 1976). Further, it has been shown experimentally that normal rhesus monkeys are quite susceptible to pulmonary nocardiosis (Mahajan *et al.* 1977).

A rapidly progressive, disseminated nocardiosis caused by *N. brasiliensis* was reported in an armadillo (Gezuele, 1972). Furthermore, disseminated nocardiosis has been diagnosed in a North African antelope and in a deer in China (Ayers Garner & Griher, 1971; Dong *et al.* 1982). Pulmonary nocardiosis was discovered in both a fox (*Vulpes vulpes*) and a mongoose (*Herpestes javanica*) (Loupal, Schonbauer & Schonbauer-Langle, 1982).

EXPERIMENTAL INFECTIONS IN ANIMALS

The pathogenic nocardiae have been difficult organisms to work with in the laboratory. As a result, it has been only in the last 20 years that reliable and reproducible information has been forthcoming regarding various aspects of the mechanisms of pathogenesis and host immunity to nocardial infection. One of the major hurdles that had to be overcome was the development of defined experimental animal model systems that would permit careful and systematic investigation.

Early methods used for investigating the pathogenesis of nocardial infections were rather crude, which reflected the difficulties in handling the organism. Initial attempts to induce disease in laboratory animals such as mice and guinea-pigs resulted in conflicting or contradictory results. Thus, whether pathogenic strains of nocardiae could even infect mice or guinea-pigs was controversial (Drake & Henrici, 1943). For example, MacCallum in 1902 reported the rapid demise of both guinea-pigs and rabbits following either intraperitoneal, subcutaneous or intravenous injections of *N. asteroides*. Mice, however, had only local lesions following inoculation and no deaths occurred. In contrast, Nakayama in 1906 reported that intraperitoneal injection of *N. asteroides* into guinea-pigs produced only a mild peritonitis and no animals died. Later, Kulikowska (1930) reported

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that guinea-pigs were quite susceptible and that these animals died within 5 to 17 days following intraperitoneal injection with *N. asteroides*. Other investigators reported no deaths or illness in guinea-pigs, even after injection of up to 10 mg of live organisms into the peritoneal cavity. This state of confusion continued into the 1960s, with several groups of researchers administering *Nocardia* into mice, guinea-pigs and rabbits by every conceivable route and describing virtually every conceivable outcome.

Since reliable results could not be obtained in these early animal experiments, Strauss & Kligman (1951) used gastric mucin to increase the virulence of *N. asteroides* for mice. When this combination was given intraperitoneally, peritoneal abscesses were routinely produced. Kurup *et al.* (1970) compared the relative virulences of *N. asteroides*, *N. brasiliensis* and *N. caviae* by using hog gastric mucin as the vehicle for injecting dilutions of a specific packed-cell volume into the peritoneal cavity of mice and guinea pigs. By using these methods they found that in white mice, *N. caviae* was more virulent than *N. asteroides* and *N. brasiliensis*. The results reported by Kurup *et al.* are in sharp contrast to those presented by Uesaka and colleagues (1971) using the same procedures. The latter authors concluded that *N. asteroides* were consistently more virulent for mice than *N. brasiliensis* or *N. caviae* when injected intraperitoneally into mice (Uesaka *et al.* 1971). Gonzalez-Ochoa investigated the relative virulences of *N. asteroides*, *N. brasiliensis* and *N. caviae* when injected into the footpads of mice. He and his colleagues reported that by this method, *N. brasiliensis* was more virulent and consistently caused greater infection in the footpads of mice than *N. asteroides* and *N. caviae* (Gonzalez-Ochoa, 1973; Gonzalez-Ochoa & Sandoval-Cuellar, 1976).

In most of these previous studies, the inocula of the various species of *Nocardia* were prepared as crude cell pellets or suspensions obtained from a variety of media often one or more weeks of age. No attention was given to standardizing either the type of media used, the way the organisms were grown, or the specific culture age or stage of growth of each strain; often the inoculum was suspended in some adjuvant such as mineral oil (Bach, Gold & Finland, 1973; Destombes *et al.* 1961; Drake & Henrici, 1943; Folb, Jaffe & Altman, 1976; Gonalez-Ochoa, 1962, 1973; Gonzalez-Ochoa & Sandoval-Cuellar, 1976; Krick & Remmington, 1975; Kurup *et al.* 1970; Kurup & Sandhu, 1965; Macotella-Ruiz & Mariat, 1963; Mason & Hathaway, 1969; Mishra *et al.* 1973; Mohapatra & Pine, 1963; Runyon, 1951; Smith Hayward, 1971; Uesaka *et al.* 1971; Zlotnik & Buckley, 1980).

It has been clearly established that all strains of *Nocardia* that have been studied exhibit varying morphology, ultrastructure, and cell wall composition dependent upon the specific phase of the growth cycle, and the chemical composition and complexity of the growth media (Adams 1966; Beadles, Land & Knezeek, 1980; Beaman, 1975, 1976, 1981*a*; Beaman, Bourgeois & Moring, 1981; Beaman & Maslan, 1978; Beaman *et al.* 1983; Beaman, Serrano & Serrano, 1978; Beaman & Shankel, 1969; Dipersio & Deal, 1974; Farshtchi & McClung, 1967; Kinbara, 1968; Vistica & Beaman, 1983; Watanabe, Kumagaya & Murooka, 1963). Therefore each individual strain of *Nocardia* will have its own unique growth curve; some growing faster and others growing slower, under the same experimental conditions. This variability means that studies on each isolate must take into consideration the phase of growth of the organism as well as a meticulous account of the growth

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Table 1. *The relationship between virulence and phase of growth of* Nocardia *in brain–heart infusion broth*

Strain	Phase of growth*		Change in virulence
	Log	Stationary	
1. *N. asteroides* GUH-2	3×10^4	5×10^7	1667-fold
2. *N. asteroides*-C	$> 1 \times 10^5$	7×10^7	> 700-fold
3. *N. asteroides* 14759	3×10^5	2×10^7	67-fold
4. *N. asteroides* Mahvi	5×10^5	5×10^7	100-fold
5. *N. asteroides* AI	9×10^5	2×10^8	222-fold
6. *N. asteroides* R G	5×10^6	3×10^8	60-fold
7. *N. asteroides* 10905	3×10^7	5×10^8	17-fold
8. *N. asteroides* Ani Rev	6×10^7	1×10^9	17-fold
9. *N. brasiliensis* 17E	4×10^5	4×10^6	10-fold
10. *N. caviae* 112	2×10^6	5×10^7	25-fold

* LD_{50} based upon intravenous inoculation of single cell suspensions prepared in saline. All growth curves were standardized in BHI broth (Difco) and groups of either six or ten 4- to 6-week-old female Swiss Webster mice were used. The LD_{50} was calculated by the Reed–Muench method and the stated values denote colony forming units per mouse.

conditions (Beadles *et al.* 1980; Beaman *et al.* 1981; Beaman & Maslan, 1978; Beaman *et al.* 1983; Vistica & Beaman, 1983).

It was found that brain heart infusion broth (50 ml broth in a 250 ml flask) incubated at 34–37 °C at 150 rev./min rotational agitation resulted in the growth of most strains of *Nocardia* in a dispersed and uniform suspension. This permitted an accurate and reproducible method for determining growth phase characteristics, and the standardization of inocula used for animal experimentation (Beaman & Maslan, 1978). By using these methods it was shown that cells of *N. asteroides* GUH-2 in their logarithmic phase of growth were more than 1000 times more virulent for mice when injected intravenously than the stationary phase cells of the same culture (Beaman & Maslam, 1978). Further, it was observed that the way the growth studies were prepared had a significant effect on the final determination of virulence. Additionally, the type of media used to grow the organisms also affected virulence (Beaman & Maslan, 1978). Nevertheless, it was found that in all strains of *N. asteroides*, *N. brasiliensis* and *N. caviae* studied, log phase cells were more virulent than stationary phase cells of the same culture when injected intravenously into mice. Not all strains of *Nocardia* exhibited the same degrees of difference between the virulence of log and stationary phase. In some strains there were only 10-fold differences, while in others, 100-fold or more than 1000-fold differences were observed during these different stages of growth (Table 1).

The route of inoculation of *Nocardia* into mice has a profound effect on both virulence and host responsiveness (Beaman *et al.* 1980*b*). As an example of the alterations in virulence seen in these types of experiments, it was found that early stationary phase cells of *N. caviae* 112 were more than 30 times more virulent than early stationary phase cells of *N. asteroides* GUH-2 when administered intranasally into mice. In contrast, the same culture of *N. asteroides* was 10 times more virulent for mice than the same culture of *N. caviae* when injected intravenously into mice. However, the LD_{50}'s for these two organisms were the same when injected

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intraperitoneally (Beaman *et al.* 1980*a*). These observations explain the apparently contradictory results obtained in earlier experiments when inoculum preparation, strain characterization and growth curve studies were not included as a part of the study protocol. Therefore, when comparing the relative virulences of *N. asteroides*, *N. brasiliensis* and *N. caviae* these factors must always be taken into account.

Conde *et al.* (1982) studied the effect of the growth cycle of *N. brasiliensis* on its ability to induce mycetomas in mice using footpad inoculation. They found that under their controlled conditions the phase of growth of this strain of *Nocardia* had no effect on its ability to induce progressive disease. In contrast, Beaman (unpublished data) found that a different strain of *N. brasiliensis* had at least a fivefold difference in dose required to cause progressive mycetomas during its growth cycle. Similar methods were used in these studies. One of the major differences appeared to be the growth rate of the two strains of *Nocardia*. *N. brasiliensis* 17E (Beaman & Serrano, unpublished data) had a lag phase in BHI broth (37 °C) of approximately 12 h and a generation time of 3 h. The *N. brasiliensis* strain used by Conde *et al.* (1982) had a lag phase of 16 h, a log phase that lasted 45 h with a generation time of about 9 h. Thus, it grew much more slowly than *N. brasiliensis* 17E. Female BALB/c mice 6–8 weeks old were used in both sets of experiments. These data suggest that the relative size of individual cells of the *Nocardia* probably have no effect on the ability of *N. brasiliensis* to induce mycetomas since log phase cells (branching filaments) are at least 10 times larger than the fragmented coccoid in stationary phase. Therefore, it is likely that the rate of growth, but not the relative size of individual cells, the phase of growth, and the route of infection all have a significant effect on nocardial infectivity and virulence (Beaman & Maslan, 1978; Beaman *et al.* 1980*a*; Conde *et al.* 1982).

When selecting an animal model to study a disease process it is important that the disease within the model be representative of the naturally acquired condition. *N. asteroides* most frequently causes pulmonary disease in humans and a variety of other animals. As the cells of *Nocardia* are inhaled or aspirated into the lungs, they are probably phagocytosed by alveolar macrophages or they may be trapped on the mucus lining the respiratory tract and physically removed by the ciliary action of the epithelial cells. If the nocardial cells are not killed by the alveolar macrophages, then they grow within these phagocytic cells with the resultant production of an inflammatory response. Polymorphonuclear phagocytes, lymphocytes and additional macrophages accumulate. This response may lead to acute pneumonia, or abscess formation. Occasionally granulomatous infiltration occurs. Thus, pulmonary lesions may vary from an aggressive, fulminating disease to a mild or self-limited process that may remain unrecognized. Therefore pulmonary nocardiosis has an extremely variable clinical presentation, and it may be confused with a large variety of other pulmonary diseases. The nocardiae frequently disseminate from the lungs via the blood stream or lymphatics to other regions of the body, especially the brain and central nervous system (Schaal & Beaman, 1983). Strains of *N. asteroides* have been described that serve as ideal models for studying host–parasite interactions within the murine host since essentially all of the clinical aspects of disease caused in humans can be reproduced experimentally in a variety of well-defined strains of mice (Beaman, 1973; Beaman *et al.* 1982; Beaman, Gershwin & Maslan, 1978*a*; Beaman *et al.* 1980*a*; Beaman *et al.* 1978*b*; Beaman & Maslan, 1977; Deem, Beaman & Gershwin, 1982).

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During the last several years it has been emphasized that nocardial infections are more frequently recognized within the immunocompromised host (Beaman *et al.* 1976). These observations may be more apparent than real since it is the immunocompromised host that receives the greatest microbiological surveillance within the hospital setting. Nevertheless, nocardiosis is an important clinical problem in immunocompromised patients (Krick, Stinson & Remington, 1975; Simpson *et al.* 1981; Stevens *et al.* 1981). As a consequence, animal models of nocardiosis in the immunocompromised host have been established. Mishra *et al.* (1973) demonstrated that cortisone treatment of mice enhanced their susceptibility to *Nocardia*. Beaman & Maslan (1977) found that cyclophosphamide treatment was more effective in reducing host resistance to *N. asteroides* than either prednisolone or azathioprine. In contrast, Bullock found that in order to establish experimental infections in the eyes of rabbits, corticosteroids were much more effective than cyclophosphamide (J. Bullock, 1981, Abstracts of the Annual Meeting of the American Society for Microbiology, B126). Thus, when approximately 1000 c.f.u. of an early stationary phase of *N. asteroides* GUH-2 were injected into the carotid artery of rabbits, retinitis, eyelid and iris lesions were always produced. In the normal rabbit the lesions produced by this inoculum were self-limiting; however, methylprednisolone or glucocorticoid treatment resulted in progressive disease manifestations not only in the eye but also systemically with a lethal outcome. The rabbit model described by Bullock appears to be almost identical to the clinical aspects observed in immunosuppressed humans that develop intraocular nocardiosis (J. Bullock, 1983, AOS Thesis, Dayton, Ohio).

Nude mice have no thymus, therefore they serve as an excellent model for determining the roles of T-lymphocytes in host resistance to *Nocardia* because these animals are totally deficient in T-cell function (Beaman *et al.* 1978*a*; Pritchard & Micklem, 1974). *N. asteroides*, *N. brasiliensis* and *N. caviae* have been injected into nude mice by a variety of routes and the mice were then studied extensively (Beaman *et al.* 1978*a*; Beaman *et al.* 1978*b*; Beaman & Scates, 1981; Deem *et al.* 1982; Folb, Timme & Horowitz, 1977*b*). These studies clearly demonstrated that T-lymphocytes played an important role in host immunity to systemic and chronic infections caused by the pathogenic nocardiae. Nude mice appeared to be slightly more resistant to acute infections than mice with intact T-cell functions; however, after about 72 h, these T-cell-deficient animals tended to become more susceptible. At 2 weeks post-infection, nude mice were significantly more susceptible to *Nocardia* than their normal littermates. Further, it was demonstrated that nude mice were unable to produce typical mycetomatous lesions following infection with either *N. brasiliensis* 17E or *N. caviae* 112. Instead the athymic murine host developed purulent abscesses accompanied by systemic disease that resulted in death of the animals much earlier than their immunologically intact littermates (Beaman, Gershwin & Maslam, 1978*a*; Beaman *et al.* 1978*b*; Beaman & Scates, 1981; Deem *et al.* 1982).

B6.CBA asplenic mice have shown to express an age dependent deficiency in T-cell function concomitant with a development of decreased production of immunoglobulin (Fletcher, Ikeda & Gershwin, 1977; Lizzio & Wargon, 1974). Young, hereditarily asplenic mice which have an early decrease in T-cell activity are most susceptible to acute nocardial infections. Additionally, those mice that survive this acute infection have a depressed ability to eliminate nocardial cells

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from the body. Furthermore, these animals appear to be deficient in their ability to develop progressive mycetomas in response to infection with *N. brasiliensis* and *N. caviae*. Unlike the observations of host responsiveness to nocardial infections in athymic mice, the data obtained from asplenic mice would suggest that there may be an early role for T-cells in host resistance to *Nocardia*, and that immunoglobulins may be important in the development of the mycetomatous response at later time periods after infection (Beaman *et al.* 1978*a*; Beaman & Scates, 1981). These conclusions are supported further by the observations of Conde *et al.* (1983) who demonstrated an accumulation of both immunoglobulin and complement (C_3) within the infected tissues of developing mycetomas. It was suggested that immune complexes were formed within the lesions, and in the presence of C_3 these complexes might play a significant role in the pathology of disease (Conde *et al.* 1983).

CBA/N mice have a deficiency in certain B-cell functions, and as a result these animals respond poorly to certain antigens with the result that they produce abnormally low levels of IgM and IgG. If CBA/N female mice are mated with DBA/2 males, the male offspring (CBD2/F) are B-cell deficient while the female littermates appear to be normal (Boswell *et al.* 1980; Fidler, Morgan & Weigle, 1980). B-cell-deficient male mice appear not to be any more susceptible to nocardial infections that the females. Indeed, the females appear more susceptible to nocardiae than the males. Both deficient and normal CBD2/F mice appear to have identical abilities to develop cell mediated immunity to *Nocardia*. The observed enhanced susceptibility of the female mice may suggest a possible role for antibody in augmenting the development of disease. This would support further the suggestion that antibodies against *Nocardia* are detrimental to the host rather than beneficial (Beaman *et al.* 1982; Conde *et al.* 1983).

Host–parasite interactions have been studied in germ-free mice infected with *N. asteroides* (Beaman *et al.* 1980*b*). It was shown that germ-free mice were very different from conventionally maintained animals in their response to *N. asteroides* following either intravenous or intranasal infection. The germ-free mice were considerably more susceptible to fatal infection and they appeared to be unable to retard the rapid growth of nocardiae within the brain, adrenals, kidneys and lungs. Prior treatment of germ-free animals with LPS significantly enhanced their ability to retard the growth of *Nocardia* within these organs. LPS enhanced the ability of the mouse to eventually eliminate the bacteria at a rate equal to or greater than that observed in the conventionally grown mice. Therefore, host resistance to infection with *Nocardia* was dependent to some extent on a resident microflora within the host. This resident microflora probably played a critical role in mantaining a degree of non-specific activation within the host's defence systems, especially within macrophage populations (Beaman *et al.* 1980*a*).

CONCLUSIONS AND SUMMARY

The nocardiae are important pathogens in humans, cattle and dogs. Further, they cause significant infections in cats, horses, goats, sheep, pigs, fish, birds, cetaceans, and a large variety of wild and zoo animals. Many experimental animal models have been developed to study these infections in more detail.

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In summary, studies utilizing both naturally acquired and experimental animal infections combined with the *in vitro* use of purified host cells have resulted in the following information regarding host–parasite interactions and possible mechanisms of pathogenesis of the nocardiae:

(1) The stage of growth affects greatly the virulence of the nocardiae (Beaman & Maslan, 1978).

(2) The cells of the pathogenic strains of *Nocardia* are facultatively intracellular pathogens that grow within macrophages (Beaman, 1977, 1979; Beaman & Smathers, 1976; Black *et al.* 1983).

(3) Even though the filamentous form of the nocardiae are virulent and grow more rapidly within macrophages, they are also initially more fragile and more readily killed than the coccoid cells of the same culture (Beaman, 1979).

(4) There is a direct correlation between the nocardial strain's ability to inhibit phagosome–lysosomal fusion and the relative virulence of that particular strain for mice (Davis-Scibienski & Beaman, 1980*a*, *b*, *c*).

(5) *In vitro*, neutrophils and monocytes from normal adult humans are not able to kill virulent strains of *N. asteroides* even though they induce a significant oxidative metabolic burst (Filice, Beaman & Remington, 1980).

(6) Cell-mediated immunity, activated macrophages and T-lymphocytes are important in host resistance to *Nocardia* (Beaman, 1977, 1979; Beaman *et al.*, 1978*a*, *b*, 1980*a*; Davis-Scibienski & Beaman, 1980*c*; Deem *et al.* 1982; Deem, Doughty & Beaman, 1983; Filice *et al.* 1980; Krick & Remington, 1975; Melendro *et al.* 1978; Sundararaj & Agarwal, 1977; Uesaka *et al.* 1968; Ximenez *et al.* 1980).

(7) Immunologically specific T-lymphocytes can specifically bind to and directly kill cells of *N. asteroides* (Deem *et al.* 1983).

(8) Pulmonary defences cope less well with intranasally administered *N. asteroides* than with aerosolized organisms (Beaman *et al.* 1978*b*).

(9) Alveolar macrophages alone are not a sufficient barrier to nocardial infection and T-lymphocytes are important to both pulmonary clearance and prevention of dissemination of *Nocardia* from the lung (Beaman *et al.* 1978*b*).

(10) B-lymphocytes and humoral immunity play little role in protecting the host from *Nocardia*. Indeed, antibody produced by B-cells against certain nocardial antigens can be deterimental to the host and contribute to disease (Beaman *et al.* 1982; Conde *et al.* 1983; Rico *et al.* 1982).

(11) Both pathogenic and non-pathogenic strains of *Nocardia* produce within their cell walls a powerful mitogen that will activate B-cells independent of T-cells (Ortiz-Ortiz *et al.* 1979).

(12) The route of inoculation has a significant effect on host susceptibility to *Nocardia* (Beaman *et al.* 1980*b*).

(13) The virulent strains of *Nocardia* phagocytosed by *in vitro* maintained macrophages not only inhibit phagosome–lysosome fusion, but viable nocardial cells also reduce lysosomal acid-phosphatase levels while less virulent strains do not have this effect (Black *et al.* 1983).

(14) Certain strains of *N. asteroides* and *N. caviae* are readily induced into the cell wall-deficient (L-form) state of growth both *in vitro* and *in vivo* (Beaman, 1980, 1981*b*, 1982; Beaman & Bourgeois, 1981; Beaman & Scates, 1981; Bourgeois & Beaman, 1974, 1976).

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(15) L-forms of *N. caviae* and probably other nocardiae play a role in nocardial pathogenesis, bacterial persistence, and latency of disease (Beaman, 1980, 1981*b*; Beaman & Scates, 1981).

(16) L-forms of *N. caviae* are pathogenic for mice and induce mycetomatous lesions approximately 1 year after injection into mice (Beaman, 1982; Beaman & Scates, 1981).

(17) Both the ultrastructural appearance as well as the chemical composition of the cell walls of *Nocardia* undergo significant changes during the growth cycle. These changes appear to have corresponding affects on virulence and host–parasite interactions (Beaman, 1973, 1975; Beaman *et al.* 1981; Beaman & Maslan, 1978; Beaman & Shankel, 1969; Beadles *et al.* 1980; Vistica & Beaman, 1983).

(18) Virulent strains of *N. asteroides* produce a unique superoxide dismutase that becomes secreted into the growth medium and also becomes cell-surface associated. It may play a role in pathogenesis (Beaman *et al.* 1983).

(19) The nocardial cell envelope becomes modified during growth within the host. Less virulent strains appear to undergo greater cell wall modification than the more virulent organisms (Beaman, 1973, 1975, 1981*a*).

(20) Repeated injections of *Nocardia* into mice or chronic, progressive disease can lead to secondary amyloidosis (Folb, Horowitz & Greenwald, 1977*a*).

(21) The production and growth of nocardial L-forms either *in vitro* or within experimental animals can result in the induction and subsequent selection of either multiple or multifunctional mutations (Beaman, 1982; Beaman & Bourgeois, 1981; Beaman, Bourgeois & Moring, 1981).

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