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JOHNE'S DISEASE IN CATTLE

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SUMMARY

Johne's (pronounced "yo-nees") *disease*, or paratuberculosis, is primarily an intestinal infection of ruminants. It is caused by *Mycobacterium paratuberculosis*, an organism in the same genus as the bacteria causing tuberculosis in humans, cattle, and other species. These two bacteria are closely related but cause very different diseases. About 22% of dairy and 8% of beef herds in the United States are estimated to be infected with Johne's disease.

Certain characteristics of Johne's disease compromise efforts to eradicate it from cattle herds. Infection occurs in the calf at an early age, but development and detection of the clinical disease occur later, usually after two years of age. The causative bacteria is excreted in the feces and milk of infected cows, which propagates the disease. Current treatment and vaccine modalities are not feasible control measures, and current diagnostic methods detect less than half of infected cattle (at one point in time).

Crohn's disease, a chronic, progressive, debilitating enteric disease of humans, has been associated with *M. paratuberculosis*. Whether the association is causal or incidental, however, has not been determined. Studies to determine how *M. paratuberculosis* could be transferred from animals to humans have focused on milk. A bulletin from the International Dairy Federation (2001) summarized state-of-the-art methods for detection and enumeration of *M. paratuberculosis* in milk; the bulletin also cited the most recent information on studies to evaluate the ability of pasteurization to kill the organism. Results of the relatively few published studies are conflicting. Most notably, results of a United States Department of Agriculture (USDA) study of pasteurization that showed the process to be 100% effective must be reconciled with studies that showed the recovery of *M. paratuberculosis* from retail pasteurized milk in the United Kingdom. Considerable work continues on this issue; resolution of the question of the ability of *M. paratuberculosis* to survive pasteurization is critical to implementation of effective Hazard Analysis Critical Control Point programs should this agent be found to cause infection of humans.

Stringent Johne's disease control programs in cattle herds will enhance dairy and dairy product food safety. To facilitate disease control recom-

mendations, the National Johne's Working Group (NJWG) was formed by a resolution of the Johne's Committee of the U.S. Animal Health Association (USAHA), and the NJWG cochairs were appointed by the USAHA president. The purpose of the NJWG is to educate veterinarians and producers about disease control and eventual eradication, to define research priorities, and to assist states with regulation development. Education efforts of the NJWG have done much to elevate the awareness level and increase the understanding of Johne's disease in the producer community. Work must continue towards providing effective systems for classifying herds at low risk of *M. paratuberculosis* infection as well as helping owners of infected herds control or even eliminate *M. paratuberculosis* in the most cost-effective manner.

INTRODUCTION

> *Johne's disease is not at all widespread. ...It does occur, however, and as the years go by it will become more and more common and will place a great tax on the cattle industry.*

In May 1922, Beach and Hastings recorded these comments in the *University of Wisconsin Agriculture Experiment Station Bulletin.* The prediction has become reality. Largely ignored by the industry in the past, Johne's disease has gained importance among livestock producers because of the economic losses they incur from herd infections and the potential human health hazards associated with the causative agent *Mycobacterium paratuberculosis.* Regulations and required reporting of disease occurrence have been in place in some states for decades, but enforcement has been lax, in part because of limited reporting of the disease and its complexity and difficult diagnosis. The strategy was (and perhaps still is) to hasten the sale of the suspect animal without diagnostic confirmation rather than to incur the stigma of a Johne's disease-infected herd. Elimination of the disease from some herds is not considered an economically viable process in light of current diagnostic tests.

Although most animals are infected at an early age, the onset of clinical signs usually is delayed for several years. Additionally, the prevalence of clinical disease in most herds is low; this low incidence is more true for beef than for dairy herds. The clinical signs of Johne's disease include chronic diarrhea and weight loss. Animal illness occurs in a "one-at-a-time" fashion in the herd, which often does not unduly alarm the producer. So it may come as no surprise that many cattle producers, even some with infected herds, have not heard of or have little awareness of Johne's disease. As predicted by Beach and Hastings, inattention to this disease has resulted in Johne's disease becoming one of the most prevalent and costly diseases of dairy cattle and some purebred beef herds in the United States (Collins 1994).

Studies to determine an association between Crohn's disease in humans and Johne's disease in ruminants have been conducted. To date, research evidence implicating *Mycobacterium paratuberculosis* as the cause of Crohn's disease has not been conclusive (Engstrand 1995, Van Kruiningen 1999). A potential route of exposure was suggested when U.K. researchers reported detecting viable *M. paratuberculosis* in retail pasteurized milk (Food Standards Agency 2000). Research by the USDA indicated that U.S. "high temperature, short time" (HTST) pasteurization methods are effective in killing the organism (Stabel, Steadham, and Bolin 1997). In an International Dairy Federation bulletin (2001) summarizing the state of knowledge on this controversial issue, the authors found such conflicting data among reported studies that they were unable to say with certainty that pasteurization is always fully effective.

Control of animal movement among farms is crucial for Johne's disease control because the primary means of introducing the infection into a herd is through the acquisition of infected cattle. Infected animals may test negative at the time of purchase but later shed the organism and transmit the disease. There is a risk of litigation for the producer selling infected, but apparently healthy, cattle, semen, and embryos or providing inaccurate or incomplete herd disease history information. Litigation can extend to the veterinarian who signs certificates of veterinary inspection (health certificates) for infected animals with no evidence of disease. The veterinarian's signed statement certifies that the animals identified on the certificate are not showing signs of infectious or contagious diseases. Some states add the words "or exposure thereto" to the certificate, which increases the burden of considering the animal's history.

The USDA, with the NJWG, is developing plans for the implementation of Johne's disease control. National regulatory coordination will bring uniformity to individual state regulations already in place or planned.

THE ISSUES

- **Diagnostic Inadequacies**. Currently used diagnostic tests detect less than 50% of infected animals at a single point in time. Hence, repeated testing is necessary. Improved diagnostic sensitivity would aid in Johne's disease control efforts.
- **Lack of Vaccine**. An efficacious vaccine is not available and would be an important tool in the control of Johne's disease in cattle.
- **Regulatory Deficiencies**. Uniform interstate disease definitions and regulations are needed to decrease confusion and litigation associated with animal movement.
- **Crohn's Disease Link**. A number of researchers have proposed that Crohn's disease in humans may be caused by the same organism that causes Johne's disease in cattle and other ruminants. Milk and milk products, raw or inadequately pasteurized, could provide a source of the organism.

THE DISEASE

Causative Agent

In 1895, Johne and Frothingham described the disease and demonstrated the presence of acid-fast staining bacilli in sections of the diseased bovine intestine. An atypical form of avian tuberculosis was suspected. At the turn of the century, the disease became recognized throughout northern Europe and the United States. In 1912, Twort isolated the causative organism and named it *Mycobacterium enteriditis chronicae pseudotuberculosae bovis* Johne, which was later referred to as *Mycobacterium paratuberculosis* (Chiodini 1993). This is the same genus as *M. bovis* or *M. tuberculosis* that causes tuberculosis in cattle, humans, and other species; however, the Johne's organism does not cause tuberculosis. *Mycobacterium paratuberculosis* is closely related to *M. avium*, and in some texts this organism is referred to as *M. avium* subspecies *paratuberculosis*. In this paper, *M. paratuberculosis* will designate the causative organism of Johne's disease.

Mycobacterium paratuberculosis survives outside the host animal for a significant period. The bacillus can remain viable for 163 days in river water, 270 days in pond water, and 11 months in bovine feces and black soil; but it survives only 7 days in urine. It can survive low temperatures, i.e., 14˚ C, for at least a year (Chiodini, Van Kruiningen, and Merkal 1984).

Transmission

An understanding of the transmission of Johne's disease is essential in controlling its spread. Most diseased cattle are infected before or soon after birth. The calf can be infected across the uterine and placental barriers before birth and after birth from ingestion of infected *colostrum* (first milk after delivery), milk, or feces. Feces-contaminated teats and udder provide a significant source of infection for the bovine neonate as well. The observation that resistance increases with age is substantiated by the difficulty of experimentally establishing an infection in adult animals (Sweeney 1996).

The primary mode of infection by post-weaned animals is by ingestion of feed or water contaminated with feces from infected animals shedding *M. paratuberculosis* (Sweeney 1996). As the animal's infection progresses, higher numbers of organisms are excreted in feces, which increases contamination of the premises and the opportunity for fecal/oral transmission of the disease to other young cattle in the herd.

Mycobacterium paratuberculosis organisms can be excreted in colostrum and in milk, including from cows with no clinical evidence of disease. The likelihood of organism detection in colostrum and feces increases with severity of disease. In a study of *M. paratuberculosis*–infected cows, the organism was found in 36% of colostrum samples from heavy shedders and 9% of samples from light shedders. Organisms were found nearly three times as often in colostrum as in milk (Streeter et al. 1995; Sweeney 1996).

In the later stages of infection, organisms are disseminated throughout body tissues and can penetrate the placenta tissues, thereby infecting a fetus. Multiple studies performed on fetuses obtained from cows showing clinical signs of Johne's disease revealed that 20 to 40% of fetuses were infected in the uterus before birth (Sweeney 1996).

Viable *M. paratuberculosis* has been found in semen. Bulls used for semen collection for artificial insemination usually are tested semi-annually for the disease; thus, this method of artificial breeding is an unlikely disease source (St. Jean 1996; Sockett 1996).

Embryo transfer is another possible means of transmission among animals. Organisms have been found in uterine washings from infected cows. Although theoretically possible, transmission by embryo transfer has not been documented. Embryo transfer from infected cows generally is regarded as safe for the offspring and the recipient, provided embryos are thoroughly washed. An infected embryo-recipient cow is more likely to cause fetal infection (Sweeney

1996).

Currently, wildlife is not considered a significant threat of infection to grazing cattle. Grazing adult cattle will more likely be exposed to wild ruminant feces than will the young nursing calves. The pelleted nature of deer feces disseminates the fecal material under forage and diminishes access for the nursing, vulnerable calf. Calves are more likely to graze the top of the grass rather than near the ground.

Transmission of the disease from one herd to another is replete with possibilities when between-herd traffic, fence-line contact, stream flows from pasture to pasture, and other means of transmission are considered. In most instances, introduction of Johne's disease into a susceptible herd has been by the addition of infected carrier animals (Sweeney 1996).

Clinical Signs, Lesions, and Herd Dynamics

The *incubation period* (time from infection to expression of the disease) of Johne's disease is long. Cattle rarely demonstrate signs of illness before two years of age. Animals exposed later in life, i.e., after weaning, are less likely to develop the disease (Whitlock and Buergelt 1996).

After oral ingestion, *M. paratuberculosis* organisms are taken up by mucosal cells of the small intestine and lymphoid tissue (Momotani et al. 1988). The primary site of bacterial replication is the terminal portion of the small intestine (*ileum*) and the large intestine. Bacterial replication proceeds at variable rates. Some animals can become resistant, never develop lesions or shed the organism, and have no signs of the disease. With high or repeated infective organism doses, rapid replication of organisms can occur, leading to earlier development of lesions and shedding of *M. paratuberculosis*. The course of the disease in most infected animals falls between these two extremes (Whitlock and Buergelt 1996).

Developing lesions in the intestinal wall gradually result in a malabsorption syndrome (nutrient absorption is retarded). Animals begin to demonstrate intermittent diarrhea and, occasionally later, edema in the submandibular jaw area. This edema may disappear and thirst increase as a result of fluid loss from diarrhea. Animals have no fever and continue to demonstrate a normal appetite. Feces are watery, homogeneous, without offensive odor, and absent of blood, epithelial debris, and mucus.

Lesions of Johne's disease are characterized by intestinal thickening with corrugation. Associated lymph nodes and lymphoid tissues are enlarged several times (Whitlock and Buergelt 1996). Caseous necrosis and tubercle formation are not features of Johne's disease in cattle but may be seen in sheep, goat, or deer (Barker, Van Dreumel, and Palmer 1993).

To aid in understanding herd dynamics, Whitlock and Buergelt (1996) described the "iceberg" effect of disease stages in the herd relative to numbers affected (Table 1). The clinical animal is the "tip of the iceberg."

When considering (1) the number of animals infected relative to that demonstrating clinical signs and (2) the slow development of the disease, one can envision why the disease proceeds for years unbeknownst to the owner. The occasional animal observed losing weight is often sold while still in economically viable condition without diagnosis of the condition.

Diagnosis

Johne's disease presents a diagnostic challenge because of unlikely detection until the animal has progressed to Stages III or IV of the disease. During the early stages (I or II) of this long incubation disease process, animals are clinically normal and current diagnostic methods are not apt to detect an immune response or the intermittent shedding of the organism.

Culturing the organism and determining antibody response to the organism are two major means of detecting Johne's disease in a herd. Culture (usually of feces) and microscopic examination of tissues

Table 1. "Iceberg" effect of Johne's Disease stages in herd relative to numbers affected, Whitlock and Buergelt (1996)

Stage	Disease state	Relative no. of animals
IV	Advanced clinical disease	1
III	Clinical disease (Early signs of disease; tests likely positive; shedding)	1–2
II	Subclinical disease, carrier adults (No evidence of disease; shedding intermittent; tests + or –)	4–8
I	Silent infection (No evidence of disease, test positives or shedding)	10–14
Total		15–25

(with an acid-fast stain) are two common methods of detecting the organism. Fecal cultures are advantageous for detecting cattle that are excreting the organism and, thus, disseminating the infection to others in the herd. The disadvantage is that *M. paratuberculosis* grows very slowly in laboratory cultures; conventional culture techniques generally require at least 12 to 16 weeks (Collins 1996). The sensitivity of the fecal culture method in subclinically infected cattle is approximately 40%; this method is likely to discover less than half of the infected animals in a herd. Currently, most state regulations define a *Johne's positive animal* as one from which *M. paratuberculosis* has been isolated, i.e., one with a positive fecal culture.

A genetic probe, referred to as a *deoxyribonucleic acid (DNA) probe*, employs a polymerase chain reaction (PCR) technique to determine the presence of the Johne's organism within three days. The DNA probe, however, is less sensitive and more expensive than the culture method and requires skilled technicians (Collins 1996). The specificity of the combined culture and DNA probe tests approaches 100%. Polymerase chain reaction testing potentially offers one of the most sensitive methods for detection of the *M. paratuberculosis* infection because the presence of only one organism should provide a positive signal.

Antibodies to *M. paratuberculosis* can be detected in the serum of infected animals by means of a variety of techniques: complement fixation, agar gel immunodiffusion, and an enzyme-linked immunosorbent assay (ELISA). The slow development of Johne's disease restricts detection by serum antibody tests until Stages III and IV of the disease. In a study comparing the ELISA for Johne's disease with the stage of infection (as measured by clinical signs and level of fecal shedding), the ELISA's sensitivity was only 15% in low-level fecal shedders. For animals with clinical signs of the disease with heavy fecal shedding of bacteria, the sensitivity of the ELISA was 87%; overall, the sensitivity of the ELISA was 45% (Sweeney et al. 1995). Generally, initial herd testing using ELISA or fecal culture methods will detect less than half the infected animals (Collins 1996; Whitlock and Buergelt 1996). Antibody detection methods may be limited by the inherent biological fact that detectable antibodies are not produced by the host until late in the disease process. Therefore, further enhancement of the sensitivity of this diagnostic method may be limited by tardy immune response.

Skin tests measuring cell-mediated immunity to the injected antigen have been used to determine exposure to tuberculosis in humans and cattle. However, skin testing for Johne's disease using extracts of *M. paratuberculosis* (the literature refers to this as the *johnin test*) has not been as successful as humoral immunologic techniques. Antigens shared with a number of other environmental mycobacteria are likely to cross-react, which results in test unreliability. Thus, the johnin skin test and the intravenous johnin test are not used for diagnosis, control, or prepurchase testing of animals for Johne's disease (Collins 1996).

Treatment and Vaccination

Treatment for Johne's disease is possible, but feasible only for valuable or companion animals. The expense is considerable, and the owner must be willing to forfeit income from the sale of milk or meat from the treated animal because of drug residues. Therapeutic agents do not cure the disease; rather, they may ameliorate the clinical condition, and the animal will likely have to receive medication for the rest of its life (St. Jean 1996). Treatment of the condition is not a viable option in herd control or eradication of Johne's disease.

Vaccines have been developed, and a few states approve their use in selected herds on a case-by-case basis. A heat-killed product is used in the United States and The Netherlands. In some European countries, a live vaccine is used. Both vaccine types are capable of inducing both cellular and humoral immune responses, but neither provides a satisfactory level of resistance (Chiodini 1996). The vaccine decreases the development of clinical disease, the amount of shedding, and the economic loss from animal removal. The vaccine, however, does not eliminate or prevent infection of the cow. An efficacious vaccine would offer a viable option for control of Johne's disease. Although much has been learned since the first vaccination products were developed 70 years ago, more research is needed on vaccine development.

Disease Control and Eradication

Without effective treatment or vaccination procedures, methods are directed toward management techniques to clear herds of the disease. Because (one time) diagnostic tests can detect less than half of infected animals, a long-term, dedicated effort is required. Failure to reduce the disease incidence and achieve eradication often can be traced to the owner's lack of compliance with herd management recommendations or to an insufficient time on the program (Sockett 1996).

The NJWG expanded efforts to include economic impact, regulatory aspects, research needs, and

educational priorities (Sockett 1996). The group formulated a voluntary herd disease status program approved as a model for state programs by the USAHA in 1998. This action may lead eventually to appropriate changes in the Code of Federal Regulations by USDA–APHIS and may stimulate revision of the USDA's Uniform Methods and Rules for a national disease control and/or indemnity program.

Strategies to control Johne's disease in an infected herd are (1) to eliminate transmission of the organism to susceptible animals and (2) to identify and to remove animals known to test positive for Johne's disease. Because test sensitivity is less than 50%, all carriers cannot be eliminated immediately. Thus, management changes must be instituted to limit fecal-oral transmission. In addition, calves should receive colostrum from test-negative cows and retaining calves from known positive cows as herd replacements is discouraged. These on-farm management practices, carefully and thoroughly instituted, may eventually rid a herd of the disease.

Animal transfer between herds of unknown disease status, however, is counterproductive to these efforts. As dairy herds have increased in size, purchase of replacement heifers (versus home-raising the animals) has become more commonplace. Replacements purchased from herds of unknown disease status represent a significant risk of introduction of the disease. Prepurchase ELISA testing of herd replacements (usually about two years old or less) provides only marginal safety. Further assurance (for dairy or beef cattle acquisitions) may be gained by requesting both the replacement source herd owner and the herd-veterinarian of record to sign statements that to the best of their knowledge, no evidence of Johne's disease has been detected in the herd for the past five years.

Impact on the Food Animal Industry

Impacts of Johne's disease on food animal production in the United States occur in the form of direct losses to producers (losses that are only partly visible to them) and indirect losses related to increased risks of decreased market access, liability, and future regulatory activity. In Pennsylvania, the prevalence of Johne's disease was 7.2% of 1,440 animals examined at slaughter (Whitlock et al. 1985). In New England, the prevalence was 18% (Chiodini and Van Kruiningen 1986), and in Wisconsin the prevalence was 10.5% in 1,000 animals examined at slaughter (Arnoldi, Hurley, and Lesa 1983).

To infected dairy and beef cattle enterprises, direct economic costs associated with the premature culling of a few individual cows with clinical Johne's disease have long been recognized, but only recently has awareness developed of other less visible losses. For dairy cattle, Hutchinson (1996) recently reviewed these costs, which include decreased milk production, body weight loss, and lowered fertility in subclinically infected cattle. Estimates of milk production losses have ranged from 2 to 19% greater in infected cows than in herdmates (Nordlund et al. 1996). In *heavily infected dairy operations* (defined as those with at least 10% of cull cows evidencing clinical signs of Johne's disease), the National Animal Health Monitoring System (NAHMS) has estimated an annual loss of $245 per cow in inventory (Ott, Wells, and Wagner 1999) compared with that of noninfected herds. These losses, estimated at the herd-level, were due to lower milk production (more than 1,600 pounds/cow yearly), higher cow-replacement costs, and lower cull-cow revenues. This study showed that economic losses associated with Johne's disease could be substantial. In lightly infected dairy operations there was marginal statistical difference in terms of economic performance between infected and uninfected herds. Nationally, the NAHMS (U.S. Department of Agriculture 1997) estimated the economic loss to the dairy industry from Johne's disease to be $200 million to $250 million annually. Such a loss, while significant, is considered smaller than that caused by other major production-related diseases (e.g., mastitis, reproductive inefficiency, or lameness).

According to the NAHMS Dairy 96 Study (U.S. Department of Agriculture 1997), about 22% of U.S. dairy operations have infected cows; the herd prevalence estimate for dairy herds with at least 300 milk cows is 40%. Major differences in prevalence by region of the country were not shown, indicating a relatively high herd-prevalence throughout the United States. Most studies performed to date have shown low prevalences of infected dairy cattle (2.9% of U.S. cull dairy cows [Merkal et al. 1987]; 5% of Wisconsin dairy cows [Collins et al. 1994]; and 3.4% of U.S. dairy cows [U.S. Department of Agriculture 1997]). Because of the low sensitivity of diagnostic tests, these figures may underestimate true infection prevalence. These prevalence estimates are similar to those from other major dairy producing countries of the world.

Economic loss estimates are unavailable for U.S. beef cattle, although NAHMS has estimated a national herd-level prevalence of 7.9% (by ELISA test) (U.S. Department of Agriculture 1997). Little is known about the cost or prevalence of Johne's dis-

ease infection in other ruminant livestock species in the United States, which include sheep, goats, cervids, South American camelids, and bison. From a recent review, Johne's disease seems widely distributed in U.S. sheep, goats, and cervids, with economic losses occurring as a result of decreased milk production and body weight (Stehman 1996).

In addition to direct costs to producers, Johne's disease has indirect impacts with economic importance that may, in the future, exceed direct costs. These indirect costs include increased risks of decreased market access as well as risks of civil liability and regulatory activities.

Sales of genetically valuable live animals, semen, and embryos to domestic and international markets are expanding in importance to U.S. ruminant production industries. Because breeding purebreds represents the genetic base of the industries, protecting and expanding these markets are critical to allowing sustainable ruminant production in the future. The recent global adoption of the General Agreement on Tariffs and Trade (GATT) to facilitate trade expansion allows for sanitary barriers based on scientifically valid animal (or public) health concerns. Certain countries, including parts of the European Community (Kalis, Barkema, and Hesseling 1999) and Australia (Kennedy and Neumann 1997) have begun implementing preventive and control strategies for Johne's disease and have stated the objective of preventing spread of infection to noninfected herds. Though major restrictions on international trade have not been created to date (Collins and Manning 1995), Johne's disease control programs under way in these countries may lead to market barriers.

Civil liability and regulatory aspects of control also must be considered (Sockett 1996). The most common method of introduction of Johne's disease into livestock operations is through purchase of infected animals. Producers who sell infected livestock, semen, or embryos, even with no evidence of disease, and who misrepresent their herd infection status may put themselves at risk of lawsuits from buyers who later detect infection in their herds that is traceable to purchase of certain cattle. Veterinary practitioners may be involved when signing certificates of veterinary inspection (health certificates) for animals destined for intrastate, interstate, or international movement. The veterinarian signs a statement certifying that the animals identified on the certificate are not showing signs of contagious or infectious diseases (some states add "or exposure thereto"). An animal originating from a herd known to be infected may be a carrier with no clinical or test evidence of disease and pose a risk to the herd of destination. According to USDA website information (http://www.usda.gov, Dec. 2000), 31 states have either developed or intend to develop plans for Johne's disease control without the benefit of a national standard or guideline. The USDA, working with the NJWG, is developing uniform methods and rules for Johne's disease control. With the adoption of a national standard, state agencies will have guidelines to develop uniform regulations.

Whether future control strategies for Johne's disease are implemented at the herd, state, or national level, decision makers must consider carefully the costs and benefits of the control program and who will bear the financial burden. Control costs include sampling and diagnostic testing, making management changes required on farms (Rossiter and Burhans 1996), and developing and maintaining the required regulatory infrastructure to support the program. To date, most control efforts have occurred at the herd level, with costs paid by interested producers. Some states, however, have Johne's disease programs that pay certain diagnostic testing fees and provide educational information.

As decision makers at each level of the food production industry (producers, food processors, retailers, and state and federal regulatory officials) evaluate the most important risks to the profitability and sustainability of their respective enterprises, Johne's disease should be considered seriously. For many commercial producers, excepting those dealing with a high prevalence of infection and disease, it may be difficult to measure the direct economic losses suffered. For the industries as a whole to lessen risks surrounding market access, liability, and regulatory activity, however, proactive control steps are warranted. If a causal relationship between Johne's disease and Crohn's disease in humans (discussed in the next section) is proven, the food animal industry impacts mentioned previously will be dwarfed by the potential threat to human health.

Impact on Human Health

An etiologic agent of mycobacterial origin has been suggested as the cause of human Crohn's disease, a severe inflammatory enteritis involving the lower intestinal tract (National Institutes of Health 2000). Clinical studies have demonstrated the presence of several species of mycobacteria including *M. paratuberculosis* in intestinal biopsy tissue from Crohn's patients (Chiodini 1989). It has not been proven, however, that any of the species isolated cause

Crohn's disease, and the presence of these various mycobacterial species may represent bowel mycobacteria invading already diseased tissue (Engstrand 1995). Experimental cross-species infection data derived from experiments using Crohn's disease tissue from humans are especially sparse, although in one reported case an isolate of *M. paratuberculosis* obtained from a clinical case of Crohn's disease was used to infect goats. The lesions produced were similar to Johne's disease (Van Kruiningen et al. 1986). Because the clinical symptoms of Crohn's disease are somewhat similar to those found in animals with Johne's disease and because noncaseating granulomatous inflammation is a feature of both entities, a number of laboratories have proposed that *M. paratuberculosis* is the causative agent of Crohn's disease. This disease generally afflicts people from 15 to 25 years and 50 to 80 years of age and, although gender nonspecific, appears in greater numbers of people of Jewish origin (Andres and Friedman 1999). Epidemiologic evidence from population and familial studies suggests that a genetic component may be involved in the susceptibility to Crohn's disease.

Though superficial, Crohn's disease and Johne's disease share similarities. Both are diseases of the small and large intestines and have a long incubation period and a prolonged course. Crohn's and Johne's (at least in cattle) include tuberculosis-like granulomas without caseation (or coagulative necrosis) (Clarke 1997). Although rare in Johne's disease, both can include lymphocytic or granulomatous lymphangitis and focal ulceration of Peyer's patches or intestinal mucosa.

Crohn's disease is a segmental disease of the intestine, whereas Johne's is a diffuse disease usually of the distal small intestine with extension in continuity into the cecum and colon. The disease extends through the intestinal wall in Crohn's but is confined to the internal layers in Johne's. (The muscularis propria and serosa are not affected in Johne's.) A number of other features of Crohn's are not found in Johne's disease; a few include fibrosis, fissures, fistulas, abscesses, bowel loop adhesions, blood in stools, and fibrous thickening of the mesentery (Mottet 1971; Van Kruiningen 1999). Lesion comparisons are tenuous. Across species, differences in morphologic change associated with a specific disease entity are common and offer inadequate evidence either to link or to differentiate the two disease syndromes.

The current concerns regarding a possible relationship between Crohn's and Johne's diseases have been stimulated by the detection of *M. paratuberculosis* DNA in pasteurized milk samples purchased from retail markets by United Kingdom researchers (Millar et al. 1996). This study implied that viable *M. paratuberculosis* organisms were present after pasteurization of milk and was the impetus for further research to evaluate optimal conditions of pasteurization to kill the organism in raw milk.

Studies using the test-tube model in which raw milk inoculated with *M. paratuberculosis* was treated at either 65˚C for 30 minutes (holder method) or 72˚C for 15 seconds (HTST) have demonstrated that a residual population of the bacteria will survive heat treatment. Grant et al. (1996) evaluated the effectiveness of both holder and HTST pasteurization methods for inactivation of *M. paratuberculosis* in raw milk and demonstrated that the survival rate of the organism was < 1% regardless of strain of bacteria or method of pasteurization. The thermal death curve was concave, with rapid initial killing of the bacteria followed by a significant "tailing" effect, resulting in low numbers of survivors after heat treatment. These experiments were designed to emulate heat exchange models used by industry; unlike with industry units, however, the milk remained static during heat treatment. Alternatively, studies conducted with a laboratory-scale pasteurizer unit, which was similar to that used in a commercial milk plant and allowed turbulent flow of milk during pasteurization, resulted in the killing of all viable *M. paratuberculosis* inoculated into raw milk samples. Further studies are required to determine definitively the effectiveness of current pasteurization methods in killing *M. paratuberculosis* in milk.

More recently, data have been reported suggesting that viable *M. paratuberculosis* can be cultured from retail-ready milk samples (Food Standards Agency 2000). The preliminary report stated that 2.1% of 476 cultured retail milk samples yielded *M. paratuberculosis*. Similar studies are reportedly underway in the United States.

Literature Cited

Andres, P. G. and L. S. Friedman. 1999. Epidemiology and the natural course of inflammatory bowel disease. *Gastroenterology Clinics of North America* 28:255–281.

Arnoldi, J. M., S. S. Hurley, and S. Lesa. 1983. Johne's disease in Wisconsin cattle. Pp. 493–496. *Proc World Assn Vet Lab Diagnosticians*, Ames, Iowa, June 13–15, 1983.

Barker, I. K., A. A. Van Dreumel, and N. Palmer. 1993. Mycobacterial enteritis: Paratuberculosis (Johne's Disease). Pp. 247–252. In K. V. F. Jubb, P. C. Kennedy, and N. Palmer (Eds.). *Pathology of Domestic Animals*. 4th ed., Vol. 2. Academic Press, San Diego.

Chiodini, R. J. 1989. Crohn's disease and the mycobacteriosies: A review and comparison of two disease entities. *Clin*

Microbiol Rev 2:90–117.

Chiodini, R. J. 1993. *The history of paratuberculosis (Johne's disease). A review of the literature 1895 to 1992.* Pp. 1–658. International Association for Paratuberculosis, Inc., Providence, Rhode Island.

Chiodini, R. J. 1996. Immunology: Resistance to paratuberculosis. Pp 313–343. In R. W. Sweeney (Ed.). Paratuberculosis (Johne's disease). *The Veterinary Clinics of North America: Food Animal Practice* 12 (2). Saunders, Philadelphia.

Chiodini, R. J. and H. J. Van Kruiningen. 1986. The prevalence of paratuberculosis in culled New England cattle. *Cornell Vet* 76:91–104.

Chiodini, R. J., H. J. Van Kruiningen, and R. S. Merkal. 1984. Ruminant paratuberculosis (Johne's disease): The current status and future prospects. *Cornell Vet* 74:217–262.

Clarke, C. J. 1997. The pathology and pathogenesis of paratuberculosis in ruminants and other species. *J Comp Pathol* 116:217–261.

Collins, M. T. 1994. Clinical approach to control of bovine paratuberculosis. *J Am Vet Med Assoc* 202:2.

Collins, M. T. 1996. Diagnosis of paratuberculosis. Pp 357–370. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Collins, M. T. and E. J. B. Manning. 1995. *Johne's disease – The international perspective.* Pp. 313–316. In Proceedings of the U.S. Animal Health Association Annual Meeting, Reno, Nevada.

Collins, M. T., D. C. Sockett, W. J. Goodger, T. A. Conrad, C. B. Thomas, and D. J. Carr. 1994. Herd prevalence and geographic distribution of, and risk factors for, bovine paratuberculosis in Wisconsin. *J Am Vet Med Assoc* 204(4):636–641.

Engstrand, L. 1995. Mycobacterium paratuberculosis and Crohn's disease. *Scand J Infect Dis Suppl* 98:27–29.

Food Standards Agency. Advisory Committee on the Microbiological Safety of Food. 2000. Preliminary results from the national study on the microbiological quality and heat processing of cows' milk: *Mycobacterium avium* subsp. *paratuberculosis*. ACM/485. Available: http://www.foodstandards.gov.uk/pdf_files/papers/acm485.pdf.

Grant, I. R., H. J. Ball, S. D. Neill, and M. T. Rowe. 1996. Inactivation of *Mycobacterium paratuberculosis* in cows' milk at pasteurization temperatures. *Appl Env Microbiol* 62:631–636.

Hutchinson, L. J. 1996. Economic impact of paratuberculosis. Pp. 373–381. In *Veterinary Clinics of North America: Food Animal Practice*. Saunders, Philadelphia.

International Dairy Federation. Task Force on *Mycobacterium paratuberculosis*. 2001. *Bulletin*. No. 362/2001. International Dairy Federation, Brussels.

Kalis, C. H. J., H. W. Barkema, and J. W. Hesseling. 1999. Herd certification for paratuberculosis in unsuspected dairy herds using cultures of strategically pooled faecal samples. P. 27. In *Proceedings of the Sixth International Colloquium on Paratuberculosis*, Melbourne, Victoria.

Kennedy, D. J. and G. B. Neumann. 1997. The Australian National Johne's Disease Market Assurance Program. Pp. 121–131. In *Proceedings of the Fifth International Colloquium on Paratuberculosis*, Madison, Wisconsin.

Merkal, R. S., D. L. Whipple, J. M. Sacks, and G. R. Snyder. 1987. Prevalence of Mycobacterium paratuberculosis in ileocecal lymph nodes of cattle culled in the United States. *J Am Vet Med Assoc* 190:676–680.

Millar, D., J. Ford, J. Sanderson, S. Withey, M. Tizard, T. Doran, and J. Hermon–Taylor. 1996. IS900 PCR to detect *Mycobacterium paratuberculosis* in retail supplies of whole pasteurized cows' milk in England and Wales. *Appl Env Microbiol* 62:3446–3452.

Momotani, E., D. L. Whipple, A. B. Thiermann, and N. F. Cheville. 1988. Role of M cells and macrophages in the entrance of M. paratuberculosis into domes of ileal Peyer's patches in calves. *Vet Path* 25:131–137.

Mottet, N. K. 1971. Histopathologic spectrum of regional enteritis and ulcerative colitis. Pp. 1–25, 63–107, 177–187. In J. L. Bennington (Ed.). *Major Problems in Pathology Series*. Vol. 2. W. B. Saunders, Philadelphia.

National Institutes of Health, National Institute of Allergy and Infectious Diseases. 2000. *Crohn's disease – Is there a microbial etiology? Recommendations for a research agenda*. Conference in Bethesda, Maryland on December 14, 1998. <http://niaid.nih.gov/dmid/crohns.htm> Accessed 2000 Sept 11.

Nordlund, K. V., W. J. Goodger, J. Pelletier, and M. T. Collins. 1996. Associations between subclinical paratuberculosis and milk production, milk components, and somatic cell counts in dairy herds. *J Am Vet Med Assoc* 208(11):1872–1876.

Ott, S. L., S. J. Wells, and B. A. Wagner. 1999. Herd–level economic losses associated with Johne's disease on U.S. dairy operations. *Prevent Vet Med* 40:179–192.

Rossiter, C. A. and W. S. Burhans. 1996. Farm–specific approach to paratuberculosis (Johne's disease) control. Pp 383–416. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Sockett, D. C. 1996. Johne's disease eradication and control: Regulatory implications. Pp 431–440. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12(2). Saunders, Philadelphia.

St. Jean, G. 1996. Treatment of clinical paratuberculosis in cattle. Pp 417–430. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Stabel, J. R., E. M. Steadham, and C. A. Bolin. 1997. Heat inactivation of *Mycobacterium paratuberculosis* in raw milk: Are current pasteurization conditions effective? *Appl Environ Microbiol* 63:4975–4577.

Stehman, S. M. 1996. Paratuberculosis in small ruminants, deer, and South American camelids. Pp. 441–445. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Streeter, R. N., G. F. Hoffsis, S. Bech–Nielsen, W. P. Shulaw, and M. Rings. 1995. Isolation of *Mycobacterium paratuberculosis* from colostrum and milk of subclinically infected cows. *Am J Vet Res* 56:1322–1324.

Sweeney, R. W. 1996. Transmission of paratuberculosis. Pp. 305–312. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease).* The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Sweeney, R. W., R. H. Whitlock, C. L. Buckley, and P. A. Spencer. 1995. Evaluation of a commercial enzyme linked

immunosorbent assay for the diagnosis of paratuberculosis in dairy cattle. *J Vet Diagn Invest* 7:488–493.

U.S. Animal Health Association. 2000. Committee on Johne's Disease, National Johne's Working Group (NJWG). <http://www.usaha.org/njwg/njwg.html> Accessed 2000 Sept 11.

U.S. Department of Agriculture. 1997. *Johne's disease on U.S. dairy operations*. N245.1097. U.S. Department of Agriculture Centers for Epidemiology and Animal Health, Animal and Plant Health Inspection Service, Veterinary Services. National Animal Health Monitoring System. Fort Collins, Colorado.

Van Kruiningen, H. J., R. J. Chiodini, W. R. Thayer, J. A. Contu, R. S. Merkal, and P. I. Runnels. 1986. Experimental disease in infant goats induced by a *Mycobacterium* isolated from a patient with Crohn's disease. A preliminary report. *Dig Dis Sciences* 31:1351–1360.

Van Kruiningen, H. J. 1999. Lack of support for a common etiology in Johne's disease of animals and Crohn's disease in humans. *Inflammatory Bowel Dis* 5(3):183–191.

Whipple, D. L. 1993. National Paratuberculosis Certification Program. Pp. 311–316. In *Proceedings of the Ninety–seventh Annual Meeting of the U.S. Animal Health Association*, Las Vegas, Nevada.

Whitlock, R. H. and C. Buergelt. 1996. Preclinical and clinical manifestations of paratuberculosis (including pathology). Pp. 345–356. In R. W. Sweeney (Ed.). *Paratuberculosis (Johne's disease)*. The Veterinary Clinics of North America: Food Animal Practice 12 (2). Saunders, Philadelphia.

Whitlock, R. H., L. T. Hutchinson, R. Merkel, L. T. Glickman, C. Rossiter, S. Harmon, P. Spencer, J. Fetrow, J. Bruce, C. E. Benson, and J. Dick. 1985. Prevalence and economic considerations of Johne's disease in the northeastern U.S. Pp. 484–490. *Proceedings of the 89th Annual Meeting of the U.S. Animal Health Association*, Milwaukee, Wisconsin.

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