Enteric Microorganisms in Rheumatoid Diseases: Causative Agents and Possible Mechanisms

DOUGLAS L. ARCHER

Division of Microbiology, Food and Drug Administration, Washington, DC 20204

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ABSTRACT

The role of foodborne enteric pathogens in the development of three seronegative spondarthropathies (ankylosing spondylitis, Reiter's disease and reactive arthritis) is discussed. Although the prevalence of the HLA-B27 antigen in blood-related individuals suggests a genetic predisposition to these diseases, exogenous environmental factors are also indicated. A clinical profile is given to clarify certain relationships of the seronegative arthropathies. Evidence of the involvement of enteric pathogens in the onset of these conditions following gastrointestinal illness is considered along with the interactions of general and molecular mechanisms of the disease processes and the immune response.

Although the interrelatedness of the seronegative spondarthritides (47) or seronegative spondarthritis diseases (78) is still a topic of debate, the most recent rheumatology review (78) lists the following nine conditions as belonging to this group: ankylosing spondylitis, Reiter's disease, reactive arthritis, acute anterior uveitis, ulcerative colitis, psoriatic arthritis, juvenile chronic arthritis, Crohn's disease and Whipple's disease. The diseases are considered related because they appear to be linked to ankylosing spondylitis (AS), a rheumatoid inflammation of the vertebrae.

The major criteria which differentiate the seronegative arthropathies (arthropathy = any joint disease) from seropositive conditions such as rheumatoid arthritis are

(a) absence of rheumatoid factors and antinuclear antibody (thus seronegative);
(b) absence of subcutaneous (or rheumatoid) nodules;
(c) inflammatory peripheral arthritis usually asymmetrical;
(d) radiological evidence of sacroiliitis, with or without AS;
(e) overlap of symptoms between members of the spondarthritis group; and
(f) familial aggregation or increased prevalence of disease in blood relatives; and
(g) a prevalence of the HLA-B27 antigen in persons with the diseases. While familial aggregation is generally evidence for involvement of genetic or environmental factors, the fact that monozygous twins may be discordant for AS strongly suggests that exogenous environmental factors play a role.

HUMAN LEUKOCYTE ANTIGEN (HLA)

The HLA system [recently reviewed by Carpenter (11)] was identified as an antigen group separate from the erythrocyte blood group antigens when it was discovered that multiple-transfused individuals, transplant recipients and multiparous females developed antileukocyte antibodies, which react with certain white blood cells in agglutination and cytotoxicity assays. Grouping a large collection of such antisera according to reaction patterns suggested that alleles (alternative genes) were being detected. The HLA antigens are coded for on at least four or five loci (A, B, C, D and DR) on the short arm of chromosome 6 and within the major histocompatibility complex genes. An offspring inherits one A allele from one parent and most likely a different one from the other
parent. The same holds true for the B, C and D (and DR) loci. The alleles of the HLA system code for antigens which are present on most body tissues, including B- and T-lymphocytes and platelets, but not red blood cells, in varying amounts. The major antigens are subdivided into two classes. In both class I and class II, the antigenic material is glycoprotein. Class I antigens are coded by the HLA–A, –B and –C loci; presently there are more than 60 defined A and B antigens and 8 C antigens. Class II antigens are coded by the more recently recognized HLA–D locus and are defined by use of one-way mixed lymphocyte responses. Serologically, in contrast to HLA–A, –B or –C antigens, the defined antigenic specificities of HLA–D are not found on platelets or unstimulated T-lymphocytes and are coded by closely linked genes called HLA–DR (D-related). The HLA–DR system is becoming extremely important with regard to disease associations.

**CLINICAL PROFILE**

A clinical profile of the seronegative arthropathies is considered here with regard to those environmental triggers, the enteric pathogens; a general background discussion, therefore, is required to clarify certain disease relationships.

Either reactive arthritis or Reiter’s disease may occur in a certain (variable) portion of the affected population. A percentage of those individuals who develop reactive arthritis or Reiter’s disease as a sequela to gastroenteritis ultimately show signs of AS or permanent damage in joints other than the spine. Sometimes this is expressed as classical (seropositive) rheumatoid arthritis.

Reiter’s disease may be more properly termed Reiter’s syndrome, as it is a triad of symptoms, one of which is an aseptic arthritis. In a recent complete review and discussion, Keat (34) proposed that reactive arthritis is incomplete Reiter’s syndrome, i.e., it is identical to the aseptic arthritis which is one part of the Reiter’s triad. The concept of “incomplete” or “atypical” Reiter’s syndrome was also discussed by Ford (22).

Reiter’s syndrome of the classical sort is characterized by post-diarrheal onset of urethritis, conjunctivitis and migratory polyarthritis. Keratotic skin lesions may occur, although they are not always part of the classical triad. Initiating infections that elicit the onset of the triad are either genital (Chlamydia trachomatis, Ureaplasma urealyticum, Neisseria gonorrhoea) or enteric (Shigella dysenteriae or Shigella flexneri, Salmonella spp., Yersinia enterocolitica, Campylobacter jejuni and possibly others). Predisposition to arthritic symptoms following genital or enteric infection is associated with the HLA–B27 antigen. About 8% of the Caucasian population in the United States is HLA–B27-positive (21), whereas 60-80% of patients with Reiter’s syndrome or reactive arthritis express the HLA–B27 antigen (34). Thus, although HLA–B27 individuals are in the highest risk group, those lacking this antigen may also acquire arthritis following enteric infection. Reactive arthritis is an aseptic arthritis, i.e., no organisms are isolated from the synovial fluid.

Early after onset of disease, the pathology of reactive arthritis differs from that of rheumatoid arthritis, showing little evidence of synovial lining cell hyperplasia. Later in the disease process the two forms of arthritis are nearly indistinguishable pathologically (34). Our picture of the immunology of the joints, however, is incomplete and at times contradictory. Jennette et al. (32) reported on three patients with seronegative spondarthropathy, two with AS and one with incomplete Reiter’s disease. All three patients were found to have IgA nephropathy, a likely indication that CICs were being deposited. The authors speculate that HLA–B27-positive individuals may hyper-react to mucosal stimulation by environmental antigens and that this results in IgA-containing CIC. Antibody to Salmonella typhimurium H antigen was recovered from the sterile joint fluid of one of two brothers suffering from post-Salmonella reactive arthritis (57). Granfors (29) used ELISA to detect Y. enterocolitica-specific IgM, IgG and IgA in studies on 356 patients whose sera gave positive tube agglutination titers to Y. enterocolitica O:3 and O:9 or Yersinia pseudotuberculosis IA. IgM antibody persisted for 1 to 3 months: IgA and IgG antibody persistence was variable. In three patients who subsequently developed reactive arthritis, yersinia-specific IgA persisted from 9 to 14 months in contrast to nonarthritic patients whose IgA disappeared within 3 months of disease onset (29). Trull et al. (71) and Panayi (52) examined the sera of AS patients with either active or inactive disease (as judged by standard rheumatologic criteria) and found that IgA specifically reactive to Klebsiella pneumoniae was detected only in patients with active disease. Manicourt and Orloff (45) followed the clinical course of a patient with S. typhimurium gastroenteritis who subsequently developed reactive arthritis. Immune complex levels were always higher in joint fluid than in blood serum, and levels of CIC paralleled the progression of the arthritis. CICs were shown to activate both the classical and alternative complement pathways (45). Theofilopoulos et al. (69) demonstrated the presence of C3 and IgG Fc receptors on synovial cells. Furthermore, gram-negative bacteria that fixed complement also bound linearly to synovial tissues (69). Erythrocyte-antibody-complement complexes failed to bind to synovial cells, suggesting some specificity for gram-negative bacteria. It seems possible then that antigens from gram-negative bacteria, like whole organisms, may similarly fix complement and bind to synovial tissue, thus forming the focus for inflammation in joint tissues.

The duration of symptoms also differentiates reactive arthritis from rheumatoid arthritis. Although the first episode of reactive arthritis after enteric infection usually resolves completely within 6 months of onset (34), symptoms may recur. Depending on the triggering organism, 5-18% patients may have symptoms that last more than 1 year, and 15-48% may experience multiple episodes of arthritis (34). In one epidemic of Reiter’s disease following a shipboard outbreak of shigellosis, 9 of the 602 patients with dysentery developed the Reiter’s triad and one patient was permanently disabled. Leirisalo
et al. (41) analyzed 160 patients with Reiter’s disease and noted that those with the HLA-B27 antigen had more severely acute symptoms and developed chronic conditions more frequently. A similar observation was made by Eastmond (17). Catteral (12) states that the relapse rate of Reiter’s syndrome is 60% and that permanent joint erosion is not uncommon. In a follow-up study of 52 yersiniosis patients, conducted 4-6 years after an outbreak, Kalliomaki and Leino (33) found two patients with sacroilitis and one with confirmed rheumatoid arthritis. A follow-up study of 38 (31 later confirmed) cases of suspected yersinia arthritis, conducted 4-5 years after initial diagnosis, revealed three patients with AS and one with seropositive rheumatoid arthritis. Only 6 of the 31 confirmed cases were free of joint symptoms (66).

Although most reactive arthritis episodes may be of short duration, some cases may evolve into long-term debilitating disease. As Marsal et al. (46) noted: “Although the acute symptoms of yersinia arthritis disappear within 12 months, the long-term prognosis may be less favorable than previously thought.” This observation is extendable to reactive arthritis triggered by other organisms as well.

**ENTERIC ORGANISM INVOLVEMENT IN PATHOGENESIS**

The clinical reports concerning gastroenteritis leading to Reiter’s disease or reactive arthritis can be separated into two categories: (a) prospective epidemiologic follow-up studies on confirmed outbreaks of gastroenteritis, and (b) retrospective studies whereby arthritis is present and evidence of prior enteric infection is either lacking (i.e., the pathogen is not isolated from feces because of resolution of infection) or is obtained by serologic or other immunologic means. Obviously the former method carries more weight than the latter. No evidence should be discounted, however, as there is substantial evidence that diarrhea may not always be present in enteric infections.

The enteric organisms reported to be, or suspected of being, the causative agents of reactive arthritis, Reiter’s syndrome and/or AS are listed in Table 1. The publication cited there, particularly the foreign journals, are by no means a complete reference list.

Historically, most reports of reactive arthritis or Reiter’s disease following gastroenteritis involved outbreaks of shigellosis (34). Table 1 indicates that most of the more recent reports involved arthritis (or Reiter’s triad) after infection with *Y. enterocolitica* or, to a lesser extent, *Y. pseudotuberculosis*. The greatest problem appears to be monoarthritis or polyarthritis after yersinia infection, and the geographic region most often affected is Europe, particularly Scandinavia and Finland. The predominant serotypes of *Y. enterocolitica* are O:3 and O:9 (15,37,39,40); however, other serotypes, such as O:4, O:7 and O:21, have also been implicated (77). Although the O:3 and O:9 serotypes of *Y. enterocolitica* are more frequently encountered in Europe than in the United States or Canada, isolations in both these North American countries have been reported. In northern California, an outbreak of yersiniosis resulted in several cases of reactive arthritis or incomplete Reiter’s disease (77). The authors suggest that *Yersinia* may be a common cause of these illnesses in the United States (77); the same conclusion has been reached by Canadian investigators concerning the cause of arthritic conditions in their country (23).

Curiously, *Yersinia* infection may occur without diarrhea (15,34) and enter a carrier state, ultimately resulting in chronic connective tissue damage (1,37). Although arthritis is a frequent sequella to yersiniosis, the Reiter’s triad does not occur as frequently as after infection with other enteric pathogens such as *Shigella* (1). Investigators in the United Kingdom have suggested that even non-pathogenic *Y. enterocolitica* may play a role in seronegative arthropathies, particularly AS (53).

As previously mentioned, reactive arthritis or Reiter’s triad following dysentery has historically been the mainstay of the association of enteric pathogens with seronegative arthropathies. Gastroenteritis caused by *Salmonella* is also followed frequently by arthritis. Fewer reports are available on arthritis caused by *C. jejuni* and *Escherichia coli* (Table 1). Notably few, if any, reports associate *K. pneumoniae* with reactive arthritis or Reiter’s disease. *K. pneumoniae* is nearly always associated with AS, which is thought by some to be the end point illness of the seronegative arthropathies.

**GENETIC PREDISPOSITION**

The high association of persons with HLA-B27 and AS has been known since 1973 (54). Ethnic grouping is also a consideration: 90-95% of Caucasians with AS have the HLA-B27 antigen, whereas only 50% of blacks with the disease have this antigen (54). The association of HLA-B27 with reactive arthritis is somewhat weaker: from 72 to 84% of patients possess the antigen. Thus the association is not absolute and human genotypes other than B27 are susceptible to the seronegative arthropathies. From 6 to 8% of the U.S. population possess the HLA-B27 allele; the rate in Finland is 14%. It is not surprising on
this basis alone that Finland has a higher case incidence of seronegative arthropathies following enteric infections. One group of Finnish investigators reported that in addition to B27, a second gene (possibly C1 or C2) may predispose for Reiter's disease and reactive arthritis (41). The A2 gene also has a strong association with AS, but not with Reiter's disease (31). For seropositive arthropathies such as rheumatoid arthritis, still other genes (DR4 and possibly DR3) have been implicated. In two studies of yersinia arthritis, one in Finland (41) and one in Belgium (14), opposite conclusions were reached with regard to the role of B27. The Finland study suggested that B27 may increase the severity of arthritis and be somehow involved in late sequelae such as AS, but the Belgian study noted no differences in severity of symptoms between B27 positives and negatives.

The genetics and, even more so, the genetic predispositions involved in the seronegative arthropathies are not completely characterized or fully understood. It is clear, however, that compared with a B27-negative individual, one who is B27-positive has an 18-times greater relative risk of acquiring reactive arthritis (11) after enteric infection, a 37-fold higher relative risk of acquiring Reiter's disease (11,54) and an 87- (11) to 126- (54) fold higher relative risk of acquiring AS. Whether this trend indicates a progression to AS remains to be determined. It should be pointed out again, however, that HLA-B27-negative individuals can and do acquire seronegative spondarthropathies after enteric infections.

**MECHANISM INVOLVED**

The underlying mechanisms contributing to acquisition of seronegative spondarthropathies after enteric pathogen-mediated gastroenteritis remain speculative. Yet, some clear trends have surfaced. For convenience, the general mechanisms involved in reactive arthritis and Reiter's disease (and possibly AS) will be treated separately from the molecular mechanisms which have been proposed for AS alone. It is curious that far more basic molecular genetic work has been conducted on AS.

**General mechanisms**

It has long been known that some strains of *Klebsiella*, usually *K. pneumoniae*, cross-react with the HLA-B27 antigen. There are many other such known cross-reactions between various bacteria or parasites and human tissue. The underlying hypothesis for such evolutionary events is simple: It is advantageous for the invading organism to mimic the host's tissue as closely as possible so that an effective immune response cannot be mounted (54). When autoimmune disease occurs, the antigenic mimicry is not perfect, but only partial. The "cross-tolerance" hypothesis of Ebringer (19) clearly expresses this theory wherein the patient's own antibacterial antibody attacks the tissues containing self-antigens. However, this explanation raises questions because the HLA-B27 antigen is found in varying amounts on almost all tissues except erythrocytes (4). Why then does joint tissue, particularly that of the spine, become damaged by *Klebsiella*-induced autoantibody while other HLA-B27-carrying tissue seemingly remains undamaged? This question aside, there is ample evidence that antibody to the invading organism is developed and that some correlation with the clinical status exists. A recent report by Tenner et al. (68) expands on the observation of Theofilopoulos et al. (69) regarding the binding of gram-negative organisms which fix complement to synovial cells and the possibility that surface antigens shed from gram-negative organisms may do the same. Several strains of *E. coli*, including clinical isolates, bound and activated C1, the first component of the classical complement pathway (68). The activation of C1 was regulated by physiological concentrations of natural C1 inhibitor (68). Whether certain body sites are deficient in C1 inhibitor is not certain.

The relationship of the occurrence of *Klebsiella* in the fecal contents with AS is somewhat controversial. Although Ebringer et al. (21) correlated the fecal incidence of *Klebsiella* with the relative disease activity of AS, this was not supported by Warren and Brewerton (74). Ebringer (19) did show, however, that the relationship between the fecal incidence of *Klebsiella* extended to acute anterior uveitis (one of the Reiter's triad of symptoms) as well as AS. Radiobinding assays showed that antisera to *Klebsiella* binds to vitreous humor and uveal antigens, but whether uveal antigens cross-react with (or contain) HLA-B27 was not determined (19).

Crude extracts from *K. pneumoniae* induce arthritis in rats, a property shared by many microorganisms, both gram-positive and gram-negative (18). The rat adjuvant arthritis model demonstrates many of the clinical features of Reiter's disease and AS, such as arthritis, urethritis, uveitis/conjunctivitis, keratotic skin lesions and ultimately, spondylitis (18), and thus may be a valid model for studying the human condition.

Panayi (52) and Trull et al. (70) reported the elevation of serum IgA for *Klebsiella* in AS patients with active disease or with demonstrable *Klebsiella* in their feces. No elevation of serum IgA specific for *E. coli* or Candida albicans was shown. Trull et al. (71) extended these studies and showed a significantly higher mean serum IgA level in active AS patients than in a matched, healthy HLA-B27 control group. Again, only specific elevation of IgA antibody to *Klebsiella* was demonstrated, with no significant differences among patients and controls regarding IgA against *S. typhimurium*, *Y. enterocolitica* or *Pseudomonas aeruginosa*. Measuring in vitro antibody production, Vuento et al. (72) showed that pokeweed mitogen-stimulated IgA secretion by lymphocytes was identical from AS patients, persons who once had yersinia arthritis, recovered yersiniosis patients who failed to develop arthritis and healthy controls. Lymphocytes from AS patients and former yersiniosis patients without arthritis showed a higher number of IgG plaque-forming cells in response to *Yersinia* antigen. This suggests altered immunoregulation in patients with yersinia arthritis (72). As previously mentioned, CICs are
often associated with enteric infections of such organisms as Yersinia (35) or in patients with seronegative spondarthropathies (32). In the latter, IgA-containing CIC resulted in IgA nephropathy. A unifying hypothesis states that a genetically controlled hypermucosal response occurs in some HLA-B27 individuals (32). It has also been suggested that the so-called enterobacterial-common antigen may play a role in eliciting reactive arthritis caused by various enteric pathogens (2,40). Other investigators indicate that an exaggerated inflammatory response occurs in HLA-B27 individuals, as suggested by the presence of several factors or cell types normally associated with inflammation of the joints (8,27,30,58,59).

Molecular mechanisms

Probably owing to the reported link between the fecal incidence of Klebsiella (20,21,52,70) and AS, although discounted by some (73,74), Australian workers in particular turned their attention to possible interactions of Klebsiella and HLA-B27. The original experiments conducted by Seager et al. (64) showed two potential links: (a) lymphocytes from B27-positive AS patients responded poorly in vitro to Klebsiella antigens compared with those of disease-free B27 positives or B27-negative controls, whereas lymphocytes from the three groups responded equally to the nonspecific T-lymphocyte mitogen phytohaemagglutinin; (b) antibody raised in rabbits against one particular strain of Klebsiella lysed B27-positive lymphocytes of AS patients, but not those of B27-positive or B27-negative healthy individuals or B27-negative individuals with AS. Likewise, sera raised against other enteric pathogens were unable to lyse the lymphocytes of B27-positive AS patients. The cytotoxic antibodies could be absorbed only by lymphocytes of B27-positive AS patients (64). Independently and nearly concurrently, Welsh et al. (76) showed that rabbits immunized with B27-positive lymphocytes produced antisera which cross-reacted with Klebsiella antigens and extracts from some Y. enterocolitica and Shigella sonnei (demonstrated by four immunoassays), and that antisera to Klebsiella lysed B27-positive, AS-positive lymphocytes. The same group further showed that human tissue typing sera for HLA-B27 had greater binding activity for Klebsiella extracts (three assay systems used) than non-B27 typing sera (6). The Australian workers, Geczy et al. (24), then showed that culture supernatant fluids of particular strains of Klebsiella modified B27-positive lymphocytes from healthy individuals, rendering them susceptible to lysis by antisera to Klebsiella, which previously (64) lysed only lymphocytes of B27-positive AS patients but not those of B27-positive healthy donors. Sera against other enteric bacteria failed to lyse the lymphocytes modified by filtrates of Klebsiella. Geczy and Yap (26) surveyed clinical isolates of K. pneumoniae and found that about 8% cross-reacted with the HLA-B27-associated cell surface marker on the lymphocytes of AS patients. Alexander et al. (4) studied distribution of the anti-Klebsiella-sensitive B27-linked component on various cells of AS patients. The component was not detected on sperm, although these cells contained the B27 antigen, but was detected on platelets and fibroblasts and on Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines derived from AS patients. The “modified” B27 was still detectable after 20 generations on EBV-transformed cell lines and after 10 generations on the fibroblasts (4). These findings suggest that the modification of the B27 antigen may be genetically determined and does not require the continued presence of the Klebsiella factor. Sullivan et al. (67) characterized the Klebsiella-derived modifying factor and found that it was located in the outer membrane of some Klebsiella cells and was being excreted into the culture fluid; this cell component and excretory product was probably a glycoprotein with an acidic isoelectric point and a molecular weight of 26,000-30,000.

Prendergast et al. (55) surveyed 185 clinical isolates of Salmonella, Shigella, E. coli, and Campylobacter for their ability to absorb antibody activity to the modified B27 surface component on lymphocytes of AS patients. Three Salmonella, two Shigella, one E. coli and one Campylobacter species were able to do so, and thus cross-reacted with B27-positive lymphocytes of AS patients. The cross-reactive organisms elaborated a factor with properties identical to the Klebsiella-derived modifying factor, suggesting possible plasmid involvement in the interspecies transfer of the ability to elaborate this factor (55). Cameron et al. (10) were subsequently able to isolate a plasmid capable of coding for the “modifying factor.” Curing Klebsiella of the plasmid resulted in loss of its ability to elaborate modifying factors; conversely, the plasmid could be transferred to a plasmid-free laboratory strain of E. coli, which then acquired the ability to elaborate a modifying factor (10). The plasmid’s size was determined to be approximately $1.86 \times 10^7$ D (10).

The problem now faced by the Australian investigators was to reconcile in vitro results with the in vivo situation. An observation of Orban et al. (51) aided in forming a working hypothesis. EBV-transformed cell lines from B27-positive AS patients produced a modifying factor nearly identical, both chemically and serologically, to that produced by some Klebsiella species and other specific-plasmid-bearing enteric organisms (51). EBV-transformed lymphocytes of B27-positive healthy donors failed to produce the modifying factor. The trait of modifying factor production was stable for more than 20 generations, thus suggesting a stable genetic alteration. Although bacterially derived modifying factor could modify B27-positive lymphocytes to a form similar to B27 lymphocytes from AS patients, the factor had to remain present; when it was removed, modified lymphocytes again became resistant to lysis by antisera previously capable of lysing them (25) in the presence of the factor. If one assumes it to be possible that the bacterial plasmid has become stably incorporated into the B27-positive mammalian host cell, with subsequent constant production of modifying factor in vivo, the conceptual gap narrows (25,66). Although the incredible similarity between bacterially derived modifying factor and that produced by AS
patient-derived lymphoid cell lines is established (51), this is only circumstantial evidence that the transfer of prokaryotic DNA to an eukaryotic cell has occurred. With the plasmid in hand, the Australian workers undoubtedly are proceeding to gather direct proof of the presence of a gene that codes for the modifying factor and is identical to the plasmid gene in HLA-B27-positive lymphocytes from AS patients.

Significantly, these workers have also shown that antisera to Klebsiella, capable of lysing 80% of the lymphocytes of B27-positive AS patients, are cytotoxic to the lymphocytes from 60% of patients with B27-positive Reiter’s syndrome and asymmetrical arthritis, and for 20% of lymphocytes from patients with B27-positive uveitis in the absence of clinical arthritis or spondylitis (35). Thus these diseases may be linked mechanistically.

The possibility of a bacterial plasmid being incorporated stably into human DNA and mediating chronic disease is certainly a novel pathogenic mechanism. If proven to be correct, there will emerge an entire new field of investigation into the causes of all diseases of unknown etiology and of known association with the HLA system.

**SUMMARY AND FUTURE PROGNOSIS**

The ability of enteric pathogens to cause debilitating disease in the form of the seronegative spondarthropathies is well-supported by the clinical literature. The extent to which arthritic conditions in the United States are sequelae to enteric infections and gastroenteritis is not known, just as the true extent of foodborne pathogen-mediated diarrheal disease is unknown. Several questions do emerge, however, one of which relates to the frequency of reactive arthritis, Reiter’s syndrome and AS in the United States versus the rest of the world. Although cases of these illnesses attributed to enteric infections are reported in the United States, most are in Europe, particularly Scandinavia. This may in part be accounted for by genetic predisposition, such as the higher percentage of individuals? Mol. Immunol. 20:563-566.


REFERENCES


