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Yersinia enterocolitica: The Charisma Continues

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INTRODUCTION

In the fraction of a moment that represents the passing of 20 years since I undertook a review of *Yersinia enterocolitica* (30), the microorganism has been the subject of innumerable publications which have simultaneously expanded the knowledge of its basic biology, epidemiology, and clinical correlates while elucidating concepts of virulence through molecular biology technology. The earlier review concluded that "*Yersinia enterocolitica* remains poised on the threshold of the microbiologic horizon simultaneously inviting and yet defying total elucidation." Time has neither diminished the allure of this "charismatic" microbial species nor tended its innermost secrets. At best, this review will endeavor to cull the efforts of superb global investigators to place before us evolving correlates of a truly versatile microbial species.

HISTORY

The first recognized reference to *Y. enterocolitica*, a gram-negative coccobacillus, was made in the United States in 1934 by McIver and Pike (152). These authors described, under the name *Flavobacterium pseudomallei* Withmore, a small gram-negative coccobacillus that they isolated from two facial abscesses of a 53-year-old farm dweller who also had involvement of the cervical lymph nodes. As the infection was characterized by sinus tract formation, the authors suspected actinomycosis, glanders, or tuberculosis. Ultimately, the infection responded to X-ray therapy. Biochemically, because the isolate did not conform to the glanders agent (*Pseudomonas mallei*) or even *P. pseudomallei*, the authors concluded that "the possibility that we are dealing with a new species is perhaps less likely than that the organism here described is an atypical form or variant of some well-known species."

In 1939, Schleifstein and Coleman (199), working at the New York State Department of Health, called attention to the isolate described by McIver and Pike (which they had received in 1934) and to four others they described as resembling *Actinobacillus lignieri* and especially *Y.* (*Pasteurella*) *pseudotuberculosis*. Because, however, the microbiologic properties of the five isolates were sufficiently different from those of the last two species and because three of the four isolates were from enteric contents, Schleifstein and Coleman proposed the name *Bacterium enterocoliticum* for this "unidentified microorganism" (199). Little did these early New York State investigators realize the foundation they had established as a backdrop for the 1976 outbreak of *Y. enterocolitica* gastrointestinal infection that struck the hamlet of Holland Patent, N.Y. In my estimation, this singular occurrence propelled unheralded interest in *Y. enterocolitica* in the United States which, up to this outbreak, was being spearheaded by European investigators (see reference 30 for an extensive review).

TAXONOMY

The differentiation of present *Y. enterocolitica* from "*Y. enterocolitica*-like" isolates, which have been described since VanLoghem first established the genus *Yersinia* in 1944 (in honor of A. J. Yersin, who first described the plague bacillus), has been excruciatingly, if not devotedly, achieved through classic and molecular biology techniques. Setting the taxonomic stage was Frederiksen in 1964 (83), who enjoined the Schleifstein and Coleman "enterocoliticum" with *Yersinia* and introduced *Y. enterocolitica* within the family *Enterobacteriaceae*. Leading the taxonomic assault through a morass of species ascription were Brenner et al. (41), who in 1976 applied classic biochemical and DNA-DNA relatedness studies to elucidate four DNA relatedness groups among true *Y. enteroco-*

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litica and the "*Y. enterocolitica*-like" isolates of major concern to the Subcommittee on the Taxonomy of *Yersinia*, *Pasteurella*, and *Francisella* (131). As a consequence of these studies, Brenner colleagues (17, 42, 238) in 1980 established four *Yersinia* species (*Y. enterocolitica*, *Y. intermedia*, *Y. frederiksenii*, and *Y. kristensinii*) distinguishable on the basis of fermentation of sucrose, L-rhamnose, raffinose, and melibiose (Table 1). Critical to the studies of Brenner et al. (41) and of Moore and Brubaker (160) was the recognition that both indole-negative and indole-positive strains of *Y. enterocolitica* were sufficiently closely related (DNA hybridization relatedness of 79 to 100%) to be considered *Y. enterocolitica* rather than the different species *Y. enteritidis* (indole negative) and *Y. enterocolitica* (indole positive).

Within *Y. enterocolitica* sensu strictu, there exists sufficient biochemical heterogeneity to have initially warranted the establishment of five biogroups (249), which were subsequently expanded to eight (Table 2). Wauters et al. in 1988 (252), however, ascribed the species designations *Y. mollaretii* and *Y. bercovieri* to isolates comprising biogroups 3A and 3B, respectively, which differed biochemically and antigenically from well-characterized *Y. enterocolitica* biogroups. Completing the species designations for *Y. enterocolitica*-like isolates are *Y. aldovae*, proposed by Bercovier et al. (18), who recovered isolates from water sources, and *Y. rohdei*, isolated from human and canine feces and surface waters by Aleksic et al. (6). "*Y.*" *ruckeri* is of uncertain status. Although not the subjects of this review, two premier species, *Y. pestis*, the plague bacillus, and the closely related *Y. pseudotuberculosis*, complete the named species within the genus *Yersinia* of the family *Enterobacteriaceae*.

ECOLOGY AND HOST RANGE

Y. enterocolitica is widely distributed in nature in aquatic and animal reservoirs, with swine serving as a major reservoir for human pathogenic strains. Interestingly, the majority of nonporcine *Y. enterocolitica* isolates are of the nonpathogenic biogroup 1A and lack the virulence determinants of invasive isolates. Furthermore, as shown in Table 3, there is a close association of pathogenic species with a particular animal reservoir.

PATHOGENESIS

Human clinical infections with *Y. enterocolitica* ensue after ingestion of the microorganisms in contaminated food (23) or water (128) or by direct inoculation through blood transfusion (217). In the gastrointestinal tract, *Y. enterocolitica* can cause acute enteritis (especially in children), enterocolitis, mesenteric lymphadenitis, and terminal ileitis. For virulent *Y. enterocolitica* to manifest its presence through a clinical syndrome, however, it must assemble an array of attributes that enable it to successfully transcend its environmental nidus to infect a human host.

Initially, it is to be appreciated that as the usual route of acquisition of *Y. enterocolitica* is through contaminated foods, this microorganism must first adapt its surface antigens to accommodate an increase (to 37°C) in temperature. This is achieved in part through the presence of a 64- to 75-kb plasmid that is absent in avirulent strains (91, 178, 179). In the presence of this plasmid, several outer membrane proteins (polypeptides) are expressed at 37°C but not at 25°C.

The presence of the 64- to 75-kb plasmid, designated pYV by Portnoy and Falkow (179), codes for an array of proteins which, in a virtual stepwise fashion, guides the invading yersinial patho-

TABLE 1. Characteristics differentiating *Y. enterocolitica* from closely related species

Test	Result[a] for:										
	Y. enterocolitica[b]	*Y. pseudotuberculosis*	*Y. pestis*	*Y. fredericksenii*	*Y. intermedia*	*Y. kristensenii*	*Y. mollaretii*	*Y. bercovieri*	*Y. aldovae*	*Y. rhodei*	*Y. ruckeri*
Fermentation											
Glucose	+	+	+	+	+	+	+	+	+	+	+
Sucrose	+	0	0	+	+	0	+	+	0	+	0
Rhamnose	0	+	0	+	+	0	0	0	+	0	0
Raffinose	0	0	0	0	+	0	0	0	0	+	v
Melibiose	0	+	v	0	+	0	0	0	0	v	0
Cellobiose	+	0	0	+	+	+	+	+	0	+	0
Sorbose	v	0	0	+	+	+	+	0	0	ND	ND
Ornithine decarboxylase	+	0	0	+	+	+	+	+	+	+	+
Voges-Proskauer (25°C)	+	0	0	+	+	0	0	0	+	0	0
Indole	v	0	0	+	+	v	0	0	0	0	0
Urease production	+	+	0	+	+	+	+	+	+	+	+
Motility (25°C)	+	+	0	+	+	+	+	+	+	+	+

[a] +, positive; 0, negative; v, variable; ND, not determined.
[b] Biotype 5 strains may vary in some reactions. See Table 2.

TABLE 2. Biochemical tests used to biogroup *Y. enterocolitica* strains[a]

Test	Biogroup reaction[b]					
	1A	1B[c]	2	3	4	5
Lipase activity	+	+	0	0	0	0
Salicin (acid production in 24 h)	+	0	0	0	0	0
Esculin hydrolysis (24 h)	+/0	0	0	0	0	0
Xylose (acid production)	+	+	+	+	0	v
Trehalose (acid production)	+	+	+	+	+	0
Indole production	+	+	v	0	0	0
Ornithine decarboxylase	+	+	+	+	+	+ (+)
Voges-Proskauer test	+	+	+	+	+	+ (+)
Pyrazinamidase activity	+	0	0	0	0	0
Sorbose (acid production)	+	+	+	+	+	0
Inositol (acid production)	+	+	+	+	+	+
Nitrate reduction	+	+	+	+	+	0

[a] Modified from reference 251.
[b] +, positive; 0, negative; (+), delayed positive; v, variable.
[c] Biogroup 1B is comprised mainly of strains isolated in the United States.

gen past numerous host defense mechanism to establish itself within its ecologic niche extracellularly or within macrophages. Thus, in conjunction with chromosomally encoded invasion genes (*inv*, *ail*), ingested virulent *Y. enterocolitica* cells possess or synthesize (perhaps in response to host factors, including temperature) traits enabling their invasion of and establishment within the susceptible host. Sequentially, these will be presented as the bacterium orchestrates its formidable armamentarium in response to its immediate environment.

Colonization of the intestinal tract is the primary event of the successful enteric pathogen. To achieve this state, the microbe must traverse the intestinal lumen, attach to and penetrate the mucus layer overlying mucosal epithelial cells, and ultimately adhere to intestinal cell brush border membranes.

Studies conducted by Mantle and coworkers (146, 147) have shown that virulent (plasmid-containing) *Y. enterocolitica* can adhere to purified rabbit and human intestinal mucin to a greater degree than its isogenic, plasmid-cured derivative can. Although surface hydrophobicity is also a plasmid-encoded property in *Y. enterocolitica* (135), Mantle and Husar (147) have shown that the binding of *Y. enterocolitica* to mucin does not involve hydrophobic interactions because suspending *Y. enterocolitica* in tetramethyl urea, a known inhibitor of hydrophobic interactions, did not reduce mucin binding. Although it appears that a carbohydrate moiety accounts for mucin binding by *Y. enterocolitica*, the exact mechanism through which mucin adherence occurs is still unknown.

Having traversed the mucus barrier overlying intestinal brush border membranes, virulent yersiniae localize to the distal small intestine (terminal ileum) and proximal colon, where the majority of their pathologic effects and hence clinical manifestation (pseudoappendicitis) occurs. To achieve such localization, virulent plasmid-containing *Y. enterocolitica* cells synthesize a large outer membrane protein (YadA), which is fibrillar, covers the bacterial surface, and mediates binding to HEp-2 cells (109) and intestinal brush border membranes (146, 166), especially in the ileocecal region of the gut. YadA, which also accounts for surface hydrophobicity (135) and autoagglutination (210), is produced at 37°C but not at 25°C, thus aiding the transition from the environment to the host. Furthermore, the dynamics of bacterium-mucus interaction is also facilitated by the YadA surface component, which promotes bacterial adherence to mucus. Paerregaard et al. (166) have nicely shown that mucus-entrapped yersiniae multiply at a high rate in this matrix by metabolizing either mucin itself or some other constituent of mucus. Additionally, mucus coating of yersinial cells alters its surface from hydrophobic to hydrophilic, which may enhance its binding to brush border membranes. On the other hand, while it may be argued that "sticking" to mucin is a host defense mechanism against mucus penetration and colonization, for yersiniae mucus entrapment could allow the synthesis of other plasmid-encoded, temperature-related virulence traits necessary for invasion (e.g., bacteremia) as a function of host status (e.g., immunosuppression, iron overload) at the time of bacterial entry.

Ingested virulent *Y. enterocolitica* cells, perhaps aided by plasmid-encoded YadA, journey to their preferential site of attachment, M cells overlying Peyer's patches. To continue to escape host defenses operative in the bowel, *Y. enterocolitica* cells, like other enteroinvasive bacterial species such as *Salmonella* and *Shigella* spp., penetrate M cells (specialized cells in the follicle-associated epithelium of Peyer's patches involved in antigen uptake) to gain access to and multiply in subjacent tissue. Invasion is multifactorial requiring chromosomally encoded gene products coupled to the natural phagocytic activity of M cells.

Prior to the molecular elucidation of cellular penetration by *Y. enterocolitica*, it was recognized that pathogenic serogroups (strains) of *Y. enterocolitica* invaded HeLa cells (141, 195). Subsequent elegantly conceived and executed molecular analyses conducted by Isberg and Falkow (119) of cellular penetration by *Y. pseudotuberculosis* led to the cloning of a chromosomal locus termed *inv*. The *inv* locus was found to be necessary for invasion of HEp-2 cells by this bacterium, and its transfer to a noninvasive *Escherichia coli* K-12 strain confers cell culture invasiveness on this innocuous strain (119). The *inv* gene encodes a 987-amino-acid (103-kDa) outer membrane protein, which directly initiates cell penetration by attaching to

TABLE 3. Virulence of *Y. enterocolitica* correlated with biogroup, serogroup, and ecologic and geographic distribution

Associated with human infections	Biogroup	Serogroup(s)	Ecologic distribution
Yes	1B	O:8, O:4, O:13a,13b, O:18, O:20, O:21	Environment, pigs (O:8), mainly in the United States
	2	O:9, O:5,27	Pigs, Europe (O:9), United States (O:5,27), Japan (O:5,27)
	3	O:1,2,3, O:5,27	Chinchilla, pigs (O:5,27)
	4	O:3	Pigs, Europe, United States
	5	O:2,3	Hare
No[a]	1A	O:5, O:6,30, O:7,8, O:18, O:46, nontypeable	Environment, pigs, food, water animal and human feces, United States

[a] *Y. enterocolitica* isolates comprising biogroup 1A may be opportunistic pathogens in patients with underlying disorders.

receptors determined to be a subset of B1 integrins (120). Continued investigations by Miller and Falkow (155) showed that *inv* was also present in *Y. enterocolitica* and that another chromosomal gene locus, named *ail* (for attachment invasion locus), encodes a factor that also promotes the invasion of epithelial cells (155). Thus, in addition to the plasmid-encoded YadA attachment factor, *Y. enterocolitica* adherence to cultured mammalian cells is a function of two chromosomally encoded gene products ("entry proteins") that confer tissue specificity with regard to cultured mammalian cells (119). Furthermore, environmentally derived *Y. enterocolitica* strains lacking chromosomal sequences homologous to the *ail* gene are avirulent and are not associated with human disease (156).

To this juncture, we have seen that virulent strains (serogroups) of *Y. enterocolitica* possess both plasmid-mediated and chromosomally encoded outer membrane proteins necessary for adherence to and invasion of cell cultures. On the other hand, avirulent isolates of *Y. enterocolitica* from human or environmental sources do not contain functional *inv* homologous sequences and lack the *ail* locus (173). Before the discovery of pYV, however, Lee et al. (141) showed that isolates of *Y. enterocolitica* from human infections invaded HeLa cells whereas nonpathogenic strains of biogroup 1A (esculin positive) lacked this property. Subsequently, Scheimann and Devenish (195) showed that tissue invasiveness was not dependent on the presence of pYV, an observation confirmed in due time by Lian et al. (144). These latter authors did, however, postulate a significant role for the virulence plasmid in the proliferation of *Y. enterocolitica* within mucosal tissues (not epithelial cells [74, 212]) to establish infection in the lamina propria and Peyer's patches.

Using an intradermal rabbit model, Lian et al. (144) further showed that plasmid-encoded cell surface components of *Y. enterocolitica* act as antiphagocytic factors and that resistance to phagocytosis was eliminated by pronase treatment of whole cells, which removed the plasmid-encoded outer membrane proteins. Additionally, a plasmid-negative strain was readily phagocytized by polymorphonuclear leukocytes and mononuclear cells. While both plasmid-negative and positive strains are capable of invasion of colonic mucosa, only the plasmid-bearing strains synthesize outer membrane components at 37°C, are resistant to phagocytosis, and are able to multiply in the lamina propria. Preliminary studies by Lian et al. (143) have shown that once adapted to a 37°C environment, plasmid-encoded surface structures are fully expressed in the small intestines of rabbits as early as 6 h after oral administration of virulent *Y. enterocolitica*.

As noted above, human pathogenic *Yersinia* species (*Y. enterocolitica*, *Y. pestis*, and *Y. pseudotuberculosis*) synthesize and secrete several outer membrane proteins (Yops) which play a major role in yersinial virulence (68, 221). Genes encoding yersinial Yops are located on a 70- to 75-kb plasmid and are temperature and calcium regulated, being expressed maximally at 37°C in response to the presence or absence of millimolar concentrations of calcium (220, 222). In the absence of Ca^{2+} at 37°C, a set of plasmid-borne operons is induced (low calcium response) which is down regulated at 37°C when Ca^{2+} is present (222). A number of these Yops enable pathogenic yersiniae to resist phagocytosis (81) (Table 4).

Among the critical plasmid-encoded virulence determinants is a secreted protein tyrosine phosphatase (YopH), which acts to dephosphorylate eucaryotic proteins, especially in phagocytic cells (24, 89). Dephosphorylation interferes with the signal transduction pathways of the target cell(s), especially macrophage-like cells and other immune cells (24), and thereby hinders phagocytosis. Specifically, Bliska et al. (24) showed that two tyrosine-phosphorylated proteins of 120 and 55 kDa are the primary J774A.1 macrophage targets of the YopH. Thus, by dephosphorylating proteins in the signal transduction pathway, the signal to a cellular response is aborted. This activity, which is referable to a phagocytic cell, could impede phagocytic activity directly or indirectly by inhibiting signals (chemoattractants) that would call forth phagocytic cells to an invaded focus.

TABLE 4. Temperature-regulated chromosomal and plasmid-encoded determinants of *Y. enterocolitica* virulence

Genetic origin	Determinant	Expressed at:	
		37°C	25°C
Chromosome	Chemistry of lipopolysaccharide	Rough[a]	Smooth[a]
	Cellular morphology	Pleomorphic	Coccoid
	Adherence to phagocytic cells	Weak	Strong
	Presence of flagella	No	Yes
	Invasin	Poorly	Highly
	Attachment invasion locus	Highly	Poorly
	Enterotoxin production	No	Yes
	Yersiniabactin	Yes[b]	No
Plasmid	Outer membrane proteins	Yes	No
	Surface hydrophobicity	Yes	No
	Serum bactericidal resistance[c]	Yes	No
	Calcium dependence for growth	Yes	No
	Autoagglutination	Yes	No
	Tyrosine phosphatase	Yes	No
	Resistance to phagocytosis	Yes	No
	Resistance to intracellular killing by macrophages	Good	Poor

[a] Rough, deficient in O side chains. Smooth, full complement of O side chains.
[b] Serogroups O:4, O:4,32, O:8, and O:21 (108).
[c] May vary with serogroup (59, 170).

The ability of *Y. enterocolitica* to evade an ensuing immune defense after ingestion is centered about an outer membrane protein, YopB, which suppresses the production of a macrophage-derived cytokine, tumor necrosis factor alpha (TNF-α), known to play a central role in the regulation of cellular immunity and inflammatory responses to infection (20). Using *Y. enterocolitica* serogroup O:8, Beuscher et al. (20) showed that release of plasmid-encoded YopB caused a dramatic decrease in the steady state level of TNF-α mRNA. These authors speculated that since YopB has sequence similarity to contact hemolysins, such as IpaB of *Shigella* species, pore formation on the macrophage membrane could alter a signal transduction for TNF-α gene expression or affect TNF-α mRNA translation. The exact molecular target on the macrophage membrane for YopB is presently unknown.

Prior to dissecting the actual histology of gastrointestinal infection by *Y. enterocolitica*, one must recapitulate the definitive role of temperature as it bears on the expression of plasmid-encoded and chromosomally transcribed determinants of virulence (Table 4). Among the latter affected by growth at elevated (35 to 37°C) temperatures are changes in the sugar and fatty acid composition of *Y. enterocolitica* lipopolysaccharide (150). Cells grown at 25°C have a "smooth" lipopolysaccharide and express complete O-antigen side chains, whereas cells grown at 37°C are rough and lack bacteriophage X1 surface receptors (127).

Concordant with thermally regulated chromosomal features are the virulence determinants encoded by the 40- to 50-MDa plasmid. Among those expressed at 37°C are Ca^{2+} dependence for growth (91), serum resistance of some isolates (59, 170),

and morphologic changes correlated with the presence or absence of four major outer membrane proteins (181), e.g., a bacillary morphology at 37°C and coccobacillary morphology at 25°C (30).

After the initiation of infection, the pYV virulence plasmid plays a major role in *Yersinia*-host cell interactions, among which resistance to serum bactericidal activity is paramount for extracellular growth and systemic spread. Resistance to complement-mediated killing by *Y. enterocolitica* is manifested at 37°C and has been correlated with the presence of two outer membrane proteins, YadA (11, 148) and Ail (148, 174, 244). YadA (protein 1) enhances serum resistance independent of its role as an adhesin. Balligand et al. (11) constructed a mutant of *Y. enterocolitica* serogroup O:9 which lacked the largest outer membrane protein, YadA, and concomitantly lost serum resistance. However, these authors, as well as Pai and DeStephano (170), noted that strains lacking the virulence plasmid may retain some degree of serum resistance, suggesting that perhaps a secondary component, either chromosomally or plasmid encoded, contributed to serum resistance at 37°C.

Almost simultaneously, Bliska and Falkow (26), and Pierson and Falkow (174) showed that the chromosomally located *ail* gene plays a role in *Y. enterocolitica* resistance to serum bactericidal activity. When expressed, the *ail* gene product, a 17-kDa outer membrane protein (Ail), mediates *Y. enterocolitica* attachment to and invasion of cultured epithelial cells. When transferred to a serum-sensitive *E. coli* strain, the *ail* gene confers serum resistance, in addition to bacterial attachment properties, to this strain. Further studies conducted by Bliska and Falkow with a *Y. enterocolitica* strain lacking invasin and YadA but containing *ail* confirmed the role of the Ail protein in serum resistance at 37°C (26). Bliska and Falkow (26) speculate that Ail may act by binding a serum factor or complement component which could prevent the formation of an active membrane attack complex.

Wachtel and Miller (244) further confirmed the role of *ail* in serum resistance and showed that serum resistance in *Y. enterocolitica* was Ail dependent and was affected by the growth phase of the bacterium and the copy number of the *ail* gene. Serum resistance levels were higher for stationary-phase *Y. enterocolitica* cells than for cells obtained from the mid-logarithmic phase. Wachtel and Miller suggest that another *Y. enterocolitica* surface component interacts with Ail to confer serum resistance. Expression of the second component may vary with the growth phase, being partially expressed or absent during early growth (serum sensitivity) and maximally expressed during stationary-phase growth (serum resistance). Alternatively, another surface component present during early growth could mask Ail, thereby reducing serum resistance. Loss of this component during stationary-phase growth would expose Ail residues and confer serum resistance.

It is stressed that there may well exist a thermal gradient over which the virulence plasmid expresses its determinants. While 37 to 35°C is needed for full expression of outer membrane proteins affecting virulence, cells grown at 25°C may have low copy numbers of these proteins or, as postulated by Portnoy and Martinez (180), the virulence plasmid-encoded outer membrane proteins may be present in the cytoplasmic compartment of *Y. enterocolitica* grown at 25°C but not transported to the external membrane until an environmental shift to 37°C is perceived. These data reaffirm that *Y. enterocolitica* undergoes a "hot-cold" cycle of transmission (30) in which the organisms may exit a warm host containing its armamentarium of temperature-inducible characteristics, contaminate an environmental source such as food or water, down regulate (not abolish) the synthesis of these attributes, and increase protein copy numbers upon reexposure to 37°C.

Support for this concept may be inferred by noting that *Y. enterocolitica* organisms grown at 25°C are more efficient at adhering to and invading cultured mammalian cells than are those grown at 37°C (141). This phenomenon coincides with the thermoregulation of invasin synthesis, which is expressed maximally after growth at 28°C. With adaptation to a 37°C host temperature, the second adherence and invasion factor *ail* is produced and highly expressed on the surface of *Y. enterocolitica*. Concomitant with adaptation to 37°C, plasmid-encoded virulence factors, such as resistance to phagocytosis by polymorphonuclear leukocytes (143), intracellular killing by macrophages (236), and resistance to the bactericidal effect of human serum (59, 170), all favor in vivo establishment.

It appears as if there is an exquisitely tuned, temperature-regulated, inverse relationship among virulence traits of *Y. enterocolitica*. Initially, after oral ingestion, usually from a cold food source, e.g., chocolate milk (23) or water (128), virulent *Y. enterocolitica* organisms use chromosomally mediated determinants expressed at low temperatures to establish colonization, and, as acclimation to mammalian host temperatures ensues, plasmid-encoded determinants are gradually expressed to offset early host defense mechanisms, e.g., phagocytosis and intracellular killing. It may therefore be envisioned that in this thermally responsive adaptation process, many *Y. enterocolitica* cells in the initial inoculum are removed by host defenses and what governs the clinical outcome (enteritis, systemic spread) is determined not only by the serogroup of the ingested strain but also by the rapidity with which surviving yersinial cells may express host-refractory determinants. Such a balance between the thermoregulation of virulence determinants by individual ingested cells may also affect the incubation period between the ingestion of virulent yersiniae and clinical manifestation(s), if any.

Y. enterocolitica invokes a wide array of gastrointestinal syndromes such as enteritis, enterocolitis, acute mesenteric lymphadenitis, and terminal ileitis, which are determined in part by the age of the host, serogroup of the invading *Y. enterocolitica* strain, and underlying host condition. However, despite the recognition of these syndromes in human hosts and of the numerous observations of *Y. enterocolitica* showing adherence and invasiveness in cultured mammalian cells in vitro, it remains unanswered whether this species is transported across epithelial borders into the lamina propria by M cells, as has been demonstrated for other enteroinvasive (*Shigella*, *Salmonella*, and *Campylobacter*) genera (100, 133, 245, 247).

Y. enterocolitica and *Y. pseudotuberculosis* penetration of M cells is mediated by three invasion genes (*inv*, *ail*, and *yadA*); two of these, *inv* and *ail*, are chromosomally located, and the third, *yadA* is found on the virulence plasmid (25, 119, 155, 258). The *inv* gene encodes an outer membrane protein, invasin, which initiates cellular entry by binding to integrin receptors on epithelial cells (120, 155, 172), while *yadA* confers low-level *Y. enterocolitica* invasion by encoding an outer membrane protein (YadA) which promotes adhesion to cultured epithelial cells (109, 244). The role of *yadA* in invasion was determined by the use of *Y. enterocolitica* (244) and *Y. pseudotuberculosis* (258) *inv* mutants, which showed residual internalization in the presence of the *Yersinia* virulence plasmid containing only *yadA* sequences (258). Furthermore, mutations in the *yadA* gene alone, or together with *inv*, eliminated uptake (258).

Early histologic studies by Carter (56), Une (236), and Robins-Browne et al. (190), using a variety of animal models, established that the initial site of infection after oral challenge

with *Y. enterocolitica* serogroup O:8 (56) or O:3 (190) occurs in Peyer's patches of the distal cecum, resulting in microabscesses which enlarge to obliterate the Peyer's patches, ulceration of the overlying epithelium, and an inflammatory reaction. Infection subsequently spreads to the mesenteric lymph nodes and may cause large abscesses in the medullary region (56).

While these early studies made use of examination of histologic sections by light microscopy, Hanski et al. (105), using immunohistochemistry and electron microscopy, confirmed that oral ingestion of *Y. enterocolitica* serogroup O:8 does involve Peyer's patches as the main route of infection. In fact, these investigators showed that Peyer's patches were about 1,000 times more heavily colonized than was the surrounding epithelium of a comparable surface area, a characteristic attributed to a putative facilitated passage through the dome (M-cell) epithelium. As noted above, colonies of *Y. enterocolitica* could be observed beneath but not within the intact epithelium of Peyer's patches. At 3 days postinfection, the whole Peyer's patch was colonized and its normal architecture was destroyed. Interestingly, the initial basement membrane of M cells overlying Peyer's patches exhibited gaps (>10 mm) through which the bacteria could freely pass into the lamina propria.

Continuing the elegant studies of Hanski et al. (105), Grützkau et al. (101), in the same laboratory, confirmed their earlier studies that plasmid-bearing and non-plasmid-bearing *Y. enterocolitica* serogroup O:8 strains are transported from the host lumen into the lamina propria by M cells. Through the use of scanning electron microscopy, these investigators assembled a constellation of montages that showed the transport of *Y. enterocolitica* through M cells and the resistance of plasmid-bearing strains to phagocytosis by professional phagocytes (neutrophils and macrophages). Continued proliferation of bacteria in the lamina propria enabled bacterial survival and spread to other organs, e.g., liver, spleen, and mesenteric lymph nodes, which is consistent with the histologic manifestations of infection. Nonpathogenic yersiniae also cross the intestinal tract via M cells but are eliminated without disturbing the histologic structure of Peyer's patches.

CLINICAL DISEASE

Gastroenteritis

Historically, *Y. enterocolitica* is primarily a gastrointestinal tract pathogen with, under defined host conditions, a strong propensity for extraintestinal spread. When it infects the gastrointestinal tract, acute enteritis with fever and inflammatory, occasionally bloody, watery diarrhea is the most frequent occurrence, particularly in children. In young adults, acute terminal ileitis and mesenteric lymphadenitis mimicking appendicitis appear to be a more common clinical syndrome (23, 58) (Table 5). In more protracted cases of yersinia gastrointestinal tract involvement, fatal necrotizing enterocolitis may occur, as well as a "pseudo-tumorgenic" form of suppurative mesenteric adenitis, even in infants (12, 40). The yersinial nuance in the extent of gastrointestinal tract pathologic findings centers largely about the serogroup of the invading strain, with serogroup O:8 producing the more catastrophic events, including extensive ulceration of the gastrointestinal tract and death (39, 103), whereas serogroups O:3 (140, 241) and O:9 are less destructive in the gastrointestinal tract.

The clinical course of gastroenteritis in infants and children is accompanied by fever, vomiting, and diarrhea with blood-streaked stools (140). Illness in infants may last for 3 to 28 days (140), whereas adults generally present with a 1- to 2-week history of fever, diarrhea, and abdominal pain usually localized to the right lower quadrant (102, 241). While the incidence is unknown, infants with *Y. enterocolitica* enteritis may show a concomitant bacteremia (36, 206).

TABLE 5. Clinical spectrum of *Y. enterocolitica* infections

Gastrointestinal
Enterocolitis, especially in young children; concomitant bacteremia may also be present
Pseudoappendicitis syndrome (children older than 5 years; adults)
Acute mesenteric lymphadenitis
Terminal Ileitis
Septicemia
Especially in immunosuppressed individuals and those in iron overload or being treated with desferrioxamine
Transfusion related
Metastatic infections following septicemia
Focal abscesses in the liver, kidneys, spleen, and lungs
Cutaneous manifestations, including cellulitis, pyomyositis, pustules, and bullous lesions
Pneumonia, cavitary pneumonia
Meningitis
Panophthalmitis
Endocarditis, infected mycotic aneurysm
Osteomyelitis
Postinfection sequelae (associated with HLA-B27 antigen)
Arthritis
Myocarditis
Glomerulonephritis
Erythema nodosum
Pharyngitis

Although *Y. enterocolitica* is known to produce a heat-stable chromosomally encoded enterotoxin, known as Yst (168), its role in diarrheal disease remains controversial largely because it is maximally produced below 30°C in late-log-phase broth cultures (38). Additionally, although virulent *Y. enterocolitica* strains are enterotoxigenic (73), the presence of *Y. enterocolitica* in a diarrheal stool in experimental animal models is not accompanied by detectable levels of enterotoxin (192) and nontoxigenic serogroup O:3 *Y. enterocolitica* is capable of producing diarrhea in mice (197).

Despite contradictory reports, DeLor and Cornelis (72) postulate a role for Yst in the pathogenesis of *Y. enterocolitica* diarrhea. Using a young-rabbit model, these investigators showed that orogastric inoculation of 1.6×10^{10} CFU of a serogroup O:9 Yst^+ *Y. enterocolitica* resulted in diarrhea and death in 10 of 14 rabbits inoculated. In this group, the inoculated strain was secreted for the duration (7 days) of the diarrheal syndrome and could be recovered in large numbers (10^2 to 10^3 CFU) from the spleens of six animals that died 8 days postinoculation. By way of contrast, of 19 rabbits inoculated with an isogenic Yst^- O:9 strain, 4 developed diarrhea; 2 of the 4 died, but neither the diarrheic stools nor the spleens of these animals contained *Y. enterocolitica*. Based upon their data, DeLor and Cornelis (72) concluded that in the young-rabbit model at least, Yst played a major role in the *Y. enterocolitica*-induced diarrhea and promoted in vivo persistence of *Y. enterocolitica* as evidenced by protracted shedding in feces and spread to the spleens of infected animals. Because the young-rabbit model has many similarities to the human infant, these authors further inferred that Yst could also be involved in acute enterocolitis in the young child.

Continuing investigations of enterotoxin production by virulent *Y. enterocolitica*, Robins-Browne et al. (192) isolated a noninvasive biotype 1A, serogroup O:6 *Y. enterocolitica* strain from a child with diarrhea. This strain produced a novel heat-stable enterotoxin (Yst II) but did not hybridize with a synthetic oligonucleotide DNA probe derived from the chromosomal Yst gene of virulent *Y. enterocolitica*. Nevertheless, Yst II is antigenically related to Yst and was recognized by monoclonal and polyclonal antibodies raised against Yst. As Yst II was the only potential virulence factor associated with this biotype 1A strain, the authors thought that it could have accounted for the diarrheal illness in the child from whom it was recovered.

Septicemia

Septicemia caused by *Y. enterocolitica* traverses the spectrum of host health status and may occur in normal (37, 80, 128) and immunocompromised (142, 159, 177) hosts, as well as in those with an underlying disorder (37, 48, 80, 159). The clinical course of *Y. enterocolitica* septicemia may include abscess formation in the liver and spleen (184), pneumonia (21, 177, 213), septic arthritis (111, 216, 228), meningitis and panophthalmitis (214), cellulitis (3), empyema (63), and osteomyelitis (203) and may evolve into endocarditis (7, 237) or localize in the endovasculature of major blood vessels, leading to a mycotic aneurysm (176). Acquisition of the infecting strain may be via the oral route or associated with blood transfusion (217).

In the course of bacteremia or enteritis, pharyngitis with or without cervical adenopathy has also been reported (194, 225). Rose et al. (194) documented a patient who developed an extensive exudative pharyngitis with massive cervical lymphadenopathy mimicking streptococcal infection. *Y. enterocolitica* was isolated from the patient's throat, blood, and stools.

Perhaps one of the most intriguing correlates underscoring septicemia with *Y. enterocolitica* is the almost exclusive association with patients in iron overload or those being treated with the iron-chelating agent desferrioxamine (52, 61, 87, 118, 186, 188, 189, 248). While it is well recognized that iron is an indispensable growth factor for all life forms, including bacteria (79), this nutritional need as an antecedent to *Y. enterocolitica* (and *Y. pseudotuberculosis*) sepsis in the patient with iron overload is exquisitely honed.

To establish an infection, pathogenic bacteria must obtain iron from mammalian tissues. In this setting, however, host iron is tightly complexed to carrier proteins such as serum transferrin or lactoferrin in tissue secretions. Under conditions of low iron availability, most bacteria produce and secrete siderophores which are high-affinity iron chelators. These compounds bind exogenous iron and transport it to the interior of the bacterial cell through specific outer membrane protein surface receptors (79).

Siderophore production by *Y. enterocolitica* may be regarded as a virulence factor and has been detected in mouse-lethal strains of serogroups O:8, O:13, O:20, and O:40 but not in mouse-avirulent serogroups O:3, O:5,27, and O:9 (57, 108). Concomitant with chromosomally encoded siderophore production, the virulence of *Y. enterocolitica* of both groups is also associated with an iron-repressible outer membrane polypeptide termed FoxA (14, 15), which functions as a receptor for transporting chelated iron to the interior of the bacterial cell (53, 110). Yersinial siderophore production is iron regulated and stimulates yersinial growth under conditions of low iron (57). In part, the innate virulence of serogroup O:8 *Y. enterocolitica* over other, more commonly occurring serogroups, e.g., O:3 and O:9, resides in its ability to produce and secrete its own catechol-type siderophore termed yersiniabactin (110) (482 Da) or yersiniophore (57) rather than rely on an exogenous source of an iron chelator such as desferrioxamine. Furthermore, although the generally nonpathogenic species *Y. intermedia*, *Y. kristensenii*, and *Y. frederiksenii* do produce a hydroxamate siderophore, aerobactin (223), they are avirulent for mice, indicating that this particular siderophore does not contribute to virulence even when these species are transfected with the virulence plasmid of *Y. enterocolitica* (108).

Under conditions of iron starvation, *Y. enterocolitica* is induced to synthesize several polypeptides, two of which are high-molecular-weight polypeptides (HMWP) of 240,000 (HMWP1) and 190,000 (HMWP2) (54, 55). These proteins are not thermoregulated, being synthesized at both 25 and 37°C only by highly mouse virulent serogroup O:8 strains. The chromosomal gene encoding HMWP2 has been designated *irp2* (iron-regulated protein 2) and is absent from the weakly pathogenic serogroups O:3, O:5,27, and O:9 and from avirulent environmental isolates (71). Although the weakly pathogenic serogroups harbor the virulence plasmid, infection with these serogroups of *Y. enterocolitica* in the absence of the *irp2* gene is restricted mainly to the gastrointestinal tract. However, in the presence of an excess of iron, as may be encountered in iron-overloaded patients, systemic infection may ensue.

The exact role of the HMWPs has not been determined, although HMWP2 is thought to play a role in the nonribosomal synthesis of small biologically active molecules (102). Functions, however, have been ascribed to several smaller iron-regulated outer membrane proteins of *Y. enterocolitica*. FoxA (75.7 kDa) and FcuA (81.7 kDa) are receptors for ferrioxamine and ferrichrome (15, 132), respectively, hydroxamate siderophores utilized but not manufactured by *Y. enterocolitica* (14, 132). While a 78-kDa protein was determined to be a hemin receptor (HemR) (219), hemin uptake from heme-containing compounds by *Y. enterocolitica* requires the hemin-specific outer membrane receptor which operates similarly to other siderophore iron-scavenging transport systems in gram-negative species. Iron internalization is a TonB energy-dependent translocation process of the siderophore-loaded complex in the outer membrane and the TonB-ExbBD protein in the cytoplasmic membrane (132a).

Siderophores of *Y. enterocolitica* function analogously to those produced by many other gram-negative species. They bind to a specific outer membrane receptor and are transported to the interior part of the cell in an energy-dependent TonB transport system (219). Therefore, yersinae are able to use siderophores produced by other organisms such as *E. coli* to obtain iron (13).

In the setting of iron overload or of an exogenous siderophore, intrinsically low-virulence *Y. enterocolitica* serogroups O:3 and O:9, the most common causes of yersinial infections worldwide, may achieve virulence equal to that of serogroup O:8. In fact, Robins-Browne and Prpic (189) have shown that intraperitoneal administration of desferrioxamine B, a trihydroxamate siderophore obtained from *Streptomyces pilosus*, into individual mice concomitant with representative *Y. enterocolitica* of serogroups O:3, O:9, and O:8 reduced the 50% lethal dose 100,000-fold for serogroups O:3 and O:9 and 10- to 100-fold for serogroup O:8, the normally more virulent strain. According to these authors (189), the enhanced virulence of serogroup O:8 yersiniae may be related to their low iron requirement. The subsequent finding of intrinsic siderophore (yersiniabactin) production and its outer membrane receptor, a 65-kDa iron-regulated protein, in serogroup O:8 strains (53, 54, 108, 110) lends credence to this early observation.

Desferrioxamine may increase host susceptibility to yersinial

TABLE 6. Reported cases of transfusion-associated *Y. enterocolitica* bacteremia[a]

Yr	No. of cases	Country	Serotype(s)	Blood product transfused	Outcome	Reference(s)
1975	1	Netherlands	O:9	Whole blood	Shock	44
1982	1	France	O:9	Whole blood	Shock	201
1982	2	South Africa	O:3	Packed erythrocytes	Shock, death	217
1984	1	Norway	O:3	Packed erythrocytes	Death	22
1985	1	United States	O:3(?)	Packed erythrocytes	Death	43, 64, 257
1986	1	Australia	O:3	Packed erythrocytes	Death	88
1988	1	France	O:5,27		Death	246
1989	1	Belgium	O:3	Packed erythrocytes	Fever	121
1989	1	United States	O:3	Packed erythrocytes	Shock, DIC[b]	46
1989	1	France	O:3	Packed erythrocytes	Shock	122
1990	7	United States	O:3 (4)[c] O:1,2,3, O:5,27, O:20	Packed erythrocytes	Shock (2), death (5)[c]	230
1991	1	United States	O:5,27	Packed erythrocytes	Death	224
1992	1	United States	O:3	Autologous	Shock	187
1993	1	France	O:3	Autologous, packed erythrocytes	Shock	209
1994	1	Austria	O:9	autologous, packed erythrocytes and frozen plasma	Shock	104
1994	1	England	O:9	Whole blood	Death	106
1994	2	Scotland	O:9	Packed erythrocytes	Death	123

[a] Two additional cases (no. 8 and 16) due to *Y. enterocolitica* serotypes O:5,27 and O:3 occurred in Australia in 1986 and 1988 (cited in reference 2).
[b] DIC, disseminated intravascular coagulation.
[c] Numbers indicate the number of patients with each outcome.

infection by enhancing organism growth through the provision of iron and by immunomodulation of human lymphocyte function (9). Regardless of the exact mode of action, the correlation between iron overload and the use of desferrioxamine as a chelating therapeutic in patients suffering from iron overload and *Y. enterocolitica* sepsis is well established (27, 57, 153, 157, 159). Among the risk factors contributing to iron overload are underlying hematologic dyscrasias such as thalassemia (111, 193, 204), aplastic anemia (111), sickle cell disease (218), and defects in iron metabolism. Furthermore, Cantinieaux et al. (51) have shown an impairment of neutrophil phagocytic and killing activity against *Y. enterocolitica* in patients with iron overload. Paradoxically, iron overload and its therapeutic control through desferrioxamine treatment may actually be additive in the provision of growth-promoting iron for siderophore-bearing serogroup O:8 strains and desferroxiamine for non-siderophore-containing serogroup O:3 and O:9, strains and may concomitantly induce aberrations in neutrophil phagocytic killing activity and in immune system function.

Bacterial contamination of blood for transfusion is uncommon, but when such an event occurs, morbidity and mortality per individual may be significant (162). Among the bacterial species, *Y. enterocolitica* has emerged as a significant cause of transfusion-associated bacteremia and mortality (64%), with 27 cases reported since this condition was first documented in 1975 (44). A review of these cases (Table 6) reveals several common themes reflective of the proclivity of the bacterium to survive low temperatures, its ability to utilize liberated iron from aging erythrocytes, and the suggestion that a transient, even occult bacteremia, may occur in a subpopulation of individuals with *Y. enterocolitica* gastrointestinal infection. Furthermore, *Y. enterocolitica* may persist in human tissues and cells from which they may enter donated blood long after a primary intestinal involvement (116).

The use of cold enhancement at 4°C for the growth and recovery of *Y. enterocolitica* from human clinical specimens is well documented (78, 97, 169, 254), and Highsmith et al. (113) have shown that environmental (biotype 1A) strains isolated from well water are capable of growth in sterile distilled water at 37°C in which their doubling time was 8.4 h. Stenhouse and Milner (217) further demonstrated that when *Y. enterocolitica* (80 CFU/ml) was inoculated into a fresh unit of whole blood, it achieved counts of 5×10^6 after 21 days of incubation at 4°C. These authors showed that after an initial 4-day lag phase accompanied by a slight drop to 35 CFU/ml, growth proceeded briskly throughout the duration of incubation. These results suggest, and are borne out by a review of transfusion-associated cases, that as erythrocytes begin to age, they lyse and liberate iron stores, which enhance *Y. enterocolitica* growth. Amazingly, in 27 reported cases to date, only non-siderophore-producing serogroups (O:3, O:9, O:5,27, O:123, and O:20) have been recovered from transfused and recipient blood (Table 6).

In the course of their studies, Stenhouse and Milner (217) pondered the rationale underscoring the persistence of *Y. enterocolitica* in fresh blood containing "complement, opsonic activity, and polymorphonuclear leukocytes." To elucidate these factors, Gibb et al. (92) extended the experiment of Stenhouse and Milner and also showed the lag phase (10 days) followed by logarithmic growth. Using fresh and 14-day-old blood, these authors showed that the initial drop in CFU and the prolonged lag phase could not be attributed to phagocytosis of bacteria by polymorphonuclear leukocytes, which are nonviable after 14 days at 4°C. Additionally, when blood units are inoculated with virulence plasmid-containing *Y. enterocolitica* grown at 37°C to express complement resistance, the early drop in CFU is delayed, suggesting that the early loss of *Y. enterocolitica* cells, as indicated by a drop in CFU, is complement mediated.

However, the recovery and growth of *Y. enterocolitica* in human blood after the lag phase has not been fully explained (8, 82, 92, 217). Among the explanations advanced are the entry of *Y. enterocolitica* into polymorphonuclear or other cells (e.g., platelets), aided by chromosomally encoded invasin (and, to a lesser extent, Ail), a surface protein expressed at lowered growth temperature. Thus, while complement-mediated resistance is lost at 4°C in plasmid-bearing strains, penetration into nucleated cells is maintained. Furthermore, in two independent studies (45, 175) of blood units artificially contaminated with *Y. enterocolitica* O:3, incubation of donated blood at 25°C

for 7 h (45) to 20 h (175) before leukocyte removal by filtration resulted in a substantial diminution in *Y. enterocolitica* CFU. A correlation existed between the number of CFU of *Y. enterocolitica* introduced into whole-blood units and their subsequent recovery after room temperature incubation and leukocyte removal. Units artificially contaminated with inocula ranging from 43 to $\geq 10^2$ CFU/ml showed recovery of *Y. enterocolitica* in the packed-erythrocyte fraction as early as 24 h to 3 weeks after storage at 4°C (41). Inocula of ≤43 CFU/ml were completely removed from artificially contaminated units after a holding period of 7 to 20 h at 25°C followed by leukocyte removal (45, 175).

Several facets of the above studies are worthy of note. Both Buchholz and colleagues (45) and Pietersz et al. (175) showed that after room temperature incubation, the passage of artificially contaminated units of erythrocytes through a leukocyte reduction filter resulted in the removal of small inocula of *Y. enterocolitica*. These data strongly suggest a role for both complement- and phagocyte-mediated removal of *Y. enterocolitica*. Support for actual killing of *Y. enterocolitica* through combined activities may be derived from noting that in both studies cultures of the leukocyte-filtered components were generally negative in blood units challenged with ≤100 CFU of *Y. enterocolitica*/ml. Unexplained, however, is the persistence of even single *Y. enterocolitica* clones in the leukocyte-depleted fraction derived from blood units challenged with higher inocula.

Serogroup O:3 *Y. enterocolitica* accounts for 15 (55%) of the 27 episodes of transfusion-acquired *Y. enterocolitica* followed by serogroups O:9 (6 cases), O:5,27 (4 cases), and O:123 and O:20 (1 case each). Of note, serogroup O:8 has not been encountered to date in transfusion-related *Y. enterocolitica* infection. Review of the data presented by Buchholz et al. (45), who tested both serogroup O:3 and O:8 *Y. enterocolitica*, reveals that serogroup O:8, in contrast to O:3, was rapidly (7 days) removed from filtered whole blood stored at 4°C, regardless of inoculum densities. This result corroborates the finding that serogroup O:8 *Y. enterocolitica* more readily loses serum resistance at lower incubation temperatures than does serogroup O:3 (59). Hence, organisms not removed by leukocyte filtration are ultimately killed during storage at 25°C and at refrigeration temperatures. Serogroup O:3 isolates, which have been shown by Chiesa and Bottone (59) to be serum resistant at 25°C, are not removed by leukocyte filtration, survive 25°C holding temperatures, and ultimately multiply during storage at 4°C.

It would appear that donated blood containing small numbers of *Y. enterocolitica* cells should be cleared of most non-O:3 isolates merely by incubation at 25°C for 7 to 20 h through the combined effects of serum bactericidal activity, phagocytosis, and leukocyte filtration. The susceptibility of serogroups O:9 and O:5,27 to serum bactericidal activity has also been demonstrated (59) but to a lesser degree than that of serogroup O:8 (59). This observation could account for their survival and recovery from stored human blood; a similar phenomenon may pertain to serogroups O:1,2,3 and O:20.

Another hypothesis accounting for the survival of *Y. enterocolitica* in donated blood is their sequestration in leukocytes (114). Hogman et al. (114) tested this hypothesis by inoculating *Y. enterocolitica* serogroup O:3 (100 CFU/ml) into whole blood and buffy coat preparations and then removing leukocytes from some whole-blood units by filtration. They showed the typical lag phase shortly after inoculation, followed, after 4 of weeks incubation at 4°C, by massive growth of *Y. enterocolitica* in the (leukocyte-containing) whole-blood units but not in the leukocyte-reduced units. These investigators concluded that phagocytosis of yersinial cells in whole blood had ensued but internalized cells were released upon leukocyte disintegration, with resultant bacterial multiplication. They therefore recommended leukocyte reduction of whole blood as a means of curtailing transfusion-related yersiniosis. It is to be stressed, however, that total removal of leukocytes from a blood unit may not be achievable (70).

Several other strategies have been proposed to eliminate transfusion-associated yersiniosis. These include screening donors for a history of gastrointestinal illness within 4 weeks of donation (2, 44, 99, 106). A study conducted by Grossman et al. (99) showed that 6% of 11,323 donors gave a positive response to a question about a history of gastroenteritis. The authors deemed this percentage to be too high to exclude donors on the basis of a general question which could not differentiate the etiology of the diarrheal illness. Furthermore, not all blood donors with asymptomatic *Y. enterocolitica* infection give a history of diarrhea prior to donation (158).

Reducing allowable storage times for packed erythrocytes has also been proposed as a measure to reduce both the microbial burden and endotoxin levels in *Y. enterocolitica*-contaminated blood. It has clearly been shown that *Y. enterocolitica* inoculated into a fresh unit of whole blood could achieve counts of 10^6 CFU/ml 21 days postinoculation at 4°C (217), and mean endotoxin levels of 240 to 600 ng/ml were detected between 21 days and 6 weeks of storage (8). Studies conducted by Hastings et al. (106), however, have shown that even if the storage times were reduced to 14 days, blood contaminated with *Y. enterocolitica* would contain sufficient endotoxin levels (>75 ng/ml) to cause severe shock and even death. Perhaps, as suggested by Pietersz et al. (175), an alternative to reducing storage times is to hold whole blood at 22°C for 6 to 24 h, which would allow complement- and leukocyte-mediated removal of yersinial contamination prior to leukocyte removal and refrigeration. This approach is also supported by the data of Kim et al. (130), who advocate the removal of leukocytes with leukocyte reduction filters as a means of reducing the growth potential of *Y. enterocolitica* by 80% in contaminated blood units. A cautionary note regarding the filtration of all blood after a holding period was enunciated by Nusbacher (165), who stated that such a policy should be considered after all risks, costs, and benefits have been carefully weighed. More somberly, Hastings et al. (106) speculated on the future use of molecular biology techniques such as PCR to detect a single bacterial cell in contaminated blood but concluded that "in the meantime, this very rare complication of blood transfusions would appear to be unavoidable."

Sequelae

Secondary immunologically mediated sequelae of acute *Y. enterocolitica* infection such as arthritis and erythema nodosum, which are the most common, and Reiter's syndrome, glomerulonephritis, and myocarditis have been reported predominantly among Scandinavians and in the setting of *Y. enterocolitica* serogroup O:3, biotype 4, phage type 8 infections (138) (Table 7). Most patients manifesting postyersinial reactive arthritis are HLA-B27 positive. The reasons underscoring this predisposition are unknown.

Several putative yersinial arthritogenic factors have been suggested to account for the postinfective arthritis associated with *Y. enterocolitica* infection. Yersinial antigens within immune complexes have been found in the synovial fluid of patients with postyersinial arthritis (136), while yersinia *O*-polysaccharide antigen has been detected in synovial biopsy specimens (231) and in synovial fluid cells of patients with

TABLE 7. Correlation among geographic distribution, serogroup, biogroup, and phage type of *Y. enterocolitica* and secondary sequelae of infection

Geographic distribution	Serogroup	Biogroup	Phage type	Secondary sequelae[a]
United States	O:8	1B	10[a]	No
	O:3	4	9B	No
	O:3	4	8	Unknown
Canada	O:3	4	9B	No
Europe	O:3	4	8	Yes
	O:9	2		Yes
Japan	O:3	4	8	Rare
South Africa	O:3	4	9A	No

[a] Secondary sequelae include arthritis and erythema nodosum.

reactive arthritis (96). Mertz et al. (154) described a 19-kDa antigen derived from *Y. enterocolitica* O:3, which, upon intra-articular injection into preimmunized rats, resulted in joint inflammation followed by fibrosis and thickening of the joint capsule. Sera from *Y. enterocolitica* O:3-infected patients reacted with the 19-kDa antigen. Subsequently, Skurnik et al. (211) cloned, sequenced, and identified the 19-kDa arthritogenic antigen as a small b-subunit of the *Y. enterocolitica* urease. These authors speculated that upon release from its supposed cytoplasmic location by living or disrupted yersinial cells, the 19-kDa antigen could function as an arthritogenic or immunogenic peptide and bind to the HLA-B27 molecule to be presented to cytotoxic T lymphocytes. However, since post-yersinial secondary sequelae are associated only with infections caused by *Y. enterocolitica* serogroup O:3 phage type 8 and since urease activity is common to *Y. enterocolitica* of all serogroups, the role of the urease b-subunit in the induction of yersinial postinfection arthritis awaits further elucidation.

Based on serologic studies, a connection has been noted between yersinia and thyroid disorders (16, 208). Antibody titers to serogroup O:3 *Y. enterocolitica* were detected in up to 52% of patients with thyroid disorders in New York (208). There are, however, two lines of evidence to suggest that *Yersinia*-specific antibodies are cross-reactive with thyroid tissue rather than having a causal role in thyroid disorders. Initially, in the United States, when the report of Shenkman and Bottone appeared in 1976 (208), serogroup O:3 *Y. enterocolitica* had not yet emerged as the predominant serogroup causing human infection. Second, Lidman et al. (145) have shown by immunofluorescence studies that antibodies to *Y. enterocolitica*, arising as a consequence of infection, do cross-react with thyroid epithelial cells. Furthermore, the outer membrane of *Y. enterocolitica* contains binding sites for thyrotropin which are recognized by immunoglobulins from individuals with Graves' disease (112). As noted by Toivanen and Toivanen (233), yersinia-specific immunoglobulin A (IgA) class antibodies are induced irrespective of the pathogenic potential of the *Yersinia* strain and in the absence of overt infection. These data are further evidence of the cross-reactivity of surface components of *Y. enterocolitica* and thyroid tissue, thereby lessening arguments for a direct causative role of *Y. enterocolitica* in thyroid disorders which may arise in genetically predisposed individuals for diverse reasons.

Y. enterocolitica is widespread in nature, occurring in reservoirs ranging from the intestinal tracts of numerous mammals, avian species, and cold-blooded species (134). *Y. enterocolitica* has also been recovered from terrestrial and aquatic niches (19). While most environmental isolates are avirulent (19), isolates recovered from porcine sources comprise human pathogenic serogroups (e.g., O:3, O:9, and O:5,27) and the highly virulent O:8 serovar (19, 75, 76, 86, 229). Furthermore, a close correlation has been established between ecologic distribution, serobiovar, and human pathogenic potential (Table 3).

Because of such a wide and diverse reservoir in nature, food products such as dairy products, meats (e.g., pork and poultry), and vegetables would seem to be at greatest risk for contamination with *Y. enterocolitica*. However, although individual cases are centered about regions in which pig reservoirs predominate, e.g., in Europe (229), only sporadic outbreaks of food-borne illness have occurred. The close association with ingesting raw or undercooked pork products and *Y. enterocolitica* infection has been epidemiologically strengthened by the study of Tauxe et al. (229) conducted in Belgium and by two reports in the United States of yersiniosis developing after the handling of raw pig intestines (chitterlings) (129, 218). Sporadic or outbreak cases of yersiniosis have also occurred in the setting wherein household dogs have also been symptomatic, suggesting that domestic animals may also serve as reservoirs (103) but not necessarily as direct vectors of *Y. enterocolitica*. Because *Y. enterocolitica* infections occur most frequently in young children, it is conceivable that an association with domestic animals may serve as a link in transmission. Against this concept is the fact that children with diarrhea are more readily brought to medical facilities, where a stool specimen is cultured for "enteric pathogens." Thus, the vehicle of transmission may be identical for children and adults alike and unrelated to domestic animals.

Food-Borne Outbreaks

Outside the setting of outbreaks of *Y. enterocolitica* infection involving several individuals or family members, most sporadic infections cannot be traced to a particular vehicle or event. In contrast, in five of six major outbreaks that have occurred in the United States since 1976, a source could be identified (Table 8).

Two of these outbreaks (23, 207) were milk-borne, and in a third (226), pasteurized milk was statistically associated with the outbreak. Serogroup O:8 *Y. enterocolitica* accounted for four of the six episodes, while serogroups O:13a,13b and O:3 and O:1,2,3 accounted for one each (Table 8). One of the outbreak strains of serogroup O:8 associated with tofu consumption was unusual in being indole negative, a finding substantiated by Toma et al. (234) in their examination and description of the O:13a,13b strain isolated from the putative milk-borne outbreak that occurred in the southern United States (226). This particular outbreak strain, which agglutinated most strongly with antisera to *Y. enterocolitica* serogroups O:13 and O:18, as well as eight nonhuman isolates were characterized as forming a new serogroup, O:13a,13b (234).

The most recent (1989) outbreak of *Y. enterocolitica* serogroup O:3 infection associated with the household preparation of chitterlings (140) may actually reflect the overall shift in *Y. enterocolitica* infection from serogroup O:8 to serogroup O:3. More disturbing from a clinical point of view is the occurrence of phage type 8 among 5 of the 14 *Y. enterocolitica* serogroup O:3 patient isolates. The nine remaining isolates and five of eight chitterling isolates tested were phage type 9b, the predominant O:3 phage type in North America (36). Phage type 8 is common among European O:3 isolates and is associated

TABLE 8. Common-source food-borne outbreaks of *Y. enterocolitica* in the United States

Yr (reference)	Location and state	No. of cases	Vehicle	Serogroup(s)
1976 (23)	High school in New York	228	Chocolate milk	O:8
1981 (207)	Summer Camp in New York	159	Powdered milk	O:8
1981–1982 (227)	Washington	50	Tofu and untreated spring water used to wash tofu at plant	O:8
1982 (1)	Brownie troop in Pennsylvania	16	Bean sprouts immersed in contaminated well water	O:8
1982 (226)	Tennessee, Arkansas, Mississippi	172	Pasteurized milk (statistically associated)	O:13a,13b[a]
1989 (140)	Household in Georgia	15	Handling of raw pork intestines (chitterlings)	O:3 (14), O:1,2,3 (1)

[a] According to Toma et al. (234).

with secondary autoimmune phenomena (Table 7). Furthermore, the findings suggest the emergence of phage type 8 in the United States and reveal that two different O:3 strains of *Y. enterocolitica* were responsible for the outbreak, in addition to one serogroup O:1,2,3. Multiple serogroups (strains) of *Y. enterocolitica* were also recovered in two other food-borne outbreaks (207, 227).

Nosocomial Infections

Nosocomially acquired *Y. enterocolitica* outbreaks of diarrheal disease have also been documented (151, 185, 233). The first recorded outbreak occurred in Finland (233) and involved six members of a hospital staff on two different wards who had taken care of a schoolgirl treated consecutively on the wards. *Y. enterocolitica* serogroup O:9 was isolated from the stools of the index patient and hospital personnel. Abdominal pain and diarrhea developed in the patients with secondary cases about 10 days after the index patient was admitted. The route of transmission was suspected to be person-to-person. However, since the tested inocula necessary to produce yersinial gastroenteritis is 10^9 CFU/ml (77), it seems questionable that person-to-person spread had actually occurred. More probable, a common-source contamination had occurred linking the hospitalized patient and the infected hospital personnel.

Ratnam et al. (185) described a nosocomial outbreak of *Y. enterocolitica* serogroup O:5, biogroup 1 (1A) diarrheal illness which involved nine hospitalized patients. The index patient was asymptomatic upon admission but had a rectal drainage culture performed after a temporary colostomy. *Y. enterocolitica* serogroup O:5, biogroup 1 (1A) was isolated only after enrichment in selenite broth and culture to MacConkey agar. Taking into account the index patient, six of the nine individuals involved had *Y. enterocolitica* isolated only after enrichment of their stool specimens for 24 h at 37°C while the remaining three patients yielded *Y. enterocolitica* serogroup O:5, biogroup 1 (1A) both on direct plating and after enrichment of their stool specimens. Cold enrichment of stool specimens for the recovery of *Y. enterocolitica* has been advocated by several investigators (78, 97, 169, 254). Van Noyen et al. (239, 240), however, have clearly shown that cold enrichment is of no value in the diagnosis of acute gastroenteritis caused by serogroups O:3 and O:9, as numerous yersiniae are being shed and hence are recoverable upon direct stool culture. Furthermore, these authors (239, 240), as well as Weissfeld and Sonnenwirth (254), have shown that *Y. enterocolitica* strains, including serogroup O:5, isolated after cold enrichment for up to 21 days are nonpathogenic members of biogroup 1 (1A).

The report of Ratnam et al. (185) raises many questions in search of a clearer resolution of this problem. First, their serogroup O:5 isolates lacked virulence plasmid-associated markers such as autoagglutination (137). Second, the isolates were recovered from an asymptomatic index patient and from six of the nine patients only after broth enrichment. Third, many of the patients, including a neonate (patient 9), did not have contact with each other. Yet six patients developed diarrhea subsequent to hospital admission of the index patient and one patient (patient 6) was admitted to the hospital with severe gastroenteritis and *Y. enterocolitica* serogroup O:5, biogroup 1 (1A) was isolated from the stool only after broth enrichment. Taken together, the evidence indicates that a common-source community or hospital outbreak may have taken place rather than person-to-person spread as the authors speculate. This scenario could account for the diarrheal illness that occurred in the 9 patients, all of whom had an underlying disorder or were compromised by age (elderly, neonate), and the absence of illness among 152 asymptomatic healthy hospital staff members surveyed and 42 randomly selected hospitalized patients. Regardless of the mode of transmission, the report of Ratnam et al. (185) does confirm earlier publications that so-called atypical *Y. enterocolitica*, now known as *Y. intermedia* and *Y. kristensenii*, is capable of causing infections in rare instances (31, 32, 191).

The third instance of hospital-acquired *Y. enterocolitica* gastroenteritis was reported by McIntyre and Nnochiri (151). The index patient was an 81-year-old diabetic woman who was admitted to a six-bed unit with a 3-day history of diarrhea, intermittent abdominal pain, nausea, and low-grade fever. At 72 h later, a 68-year-old female patient in the opposite bed, admitted 5 weeks previously with hypothermia, developed gastroenteritis. *Y. enterocolitica* serogroup O:6,30, biogroup 1 (1A) was recovered from the stools of both patients. Stool specimens from four other patients in the same unit as well as 41 staff members were negative for *Y. enterocolitica*. Although both isolations were achieved on yersinia selective media (CIN agar) (195), it is unclear if recovery was by direct plating or after selenite broth enrichment. This instance may again reflect the capability of an "innocous" serobiogroup of *Y. enterocolitica* to produce disease in compromised hosts.

DIAGNOSIS

Culture

The microbiologic diagnosis of *Y. enterocolitica* infections is best achieved by isolation of the bacterium from a clinical specimen representative of the infectious process. However, isolation and biochemical identification are functions of the nuances imposed by incubation temperature and colony characteristics of *Y. enterocolitica* on a variety of commonly used routine and "enteric" media (28).

Y. enterocolitica grows well on most enteric media with the

exception of Salmonella-Shigella agar, on which it grows poorly. Since *Y. enterocolitica* ferments lactose slowly, colonies are colorless on media such as MacConkey agar, which incorporates lactose as a fermentable indicator substrate. *Y. enterocolitica* ferments sucrose and xylose, and therefore colonies developing on Hektoen-Enteric (salmon-colored) and xylose-lysine-deoxycholate (yellow) agars resemble those of the normal enteric flora. Furthermore, after a 24-h incubation at 37°C, colonies of *Y. enterocolitica* are pinpoint and barely perceptible against a background of more rapidly growing colonies of other enteric bacterial species present in fecal samples. Because of the slower growth of *Y. enterocolitica* at 37°C, stool specimens should be plated to a duplicate set of media for incubation at 25°C; alternatively, after the 37°C incubation, inoculated media can be reincubated at 25°C for an additional 24 h and examined for pinpoint colonies suspicious for *Y. enterocolitica*.

While several technical approaches, e.g., scanning agar surfaces under stereoscopic microscopy (249), have been advanced for the recognition of *Y. enterocolitica* colonies, the use of a selective medium appears to be easiest. Several media have been developed (reviewed in reference 30); of these, two formulations, CIN agar developed by Schiemann in 1979 (196) and virulent *Yersinia enterocolitica* agar (VYE) formulated by Fukushima in 1987 (85), seem the most useful. Head et al. (107) conducted comparative studies of several selective media including MacConkey agar for the recovery of *Y. enterocolitica*. They found that CIN agar was the most effective, yielding 100% recovery of *Y. enterocolitica* in a test suspension containing 10 CFU/ml. CIN agar dramatically inhibits normal flora organisms while *Y. enterocolitica* gives rise to distinctive colonies with deep-red centers (196) and a sharp border surrounded by a translucent zone. The red pigmentation is a result of mannitol fermentation. The decision to routinely use a selective medium such as CIN agar should be tempered by the incidence of *Y. enterocolitica* infections in a given geographical area (124).

Fukushima and Gomyoda (84) showed that many *Y. enterocolitica* serogroup O:3, biotype 3B bacteriophage type 2 strains (now *Y. bercovieri*) and *Y. pseudotuberculosis* are inhibited on CIN agar. Fukishima (85) later found that *Y. enterocolitica* serogroups O:5,27, O:9, and O:8 produce colonies on CIN agar that resemble those of *Y. intermedia*. Therefore, Fukishima (85) developed a modified CIN agar that incorporated esculin. On this medium, virulent, esculin-nonhydrolyzing *Y. enterocolitica* strains form red colonies (mannitol fermentation) that are easily differentiated from avirulent environmental isolates of *Y. enterocolitica* and other *Yersinia* species, which form dark colonies with a dark peripheral zone as a result of esculin hydrolysis.

Continuing with the theme of using an agar medium to differentiate between virulent and avirulent *Y. enterocolitica* isolates, Prpic et al. (182) utilized Congo red agar to achieve this goal. Virulent *Y. enterocolitica* strains take up Congo red (CR^+), which is correlated with the presence of the 60- to 75-kb plasmid. Colonies that do not take up Congo red (CR^-) are plasmidless and negative in assays for virulence.

Biochemically, an isolate may be suspected to be *Y. enterocolitica* (or even *Y. pseudotuberculosis*) if it displays anaerogenic fermentation of glucose and other carbohydrates, produces urease, is motile at 25 but not 37°C, and lacks oxidase, phenylalanine deaminase, lysine decarboxylase, and arginine dihydrolase activities (Table 1). Furthermore, because *Y. enterocolitica* ferments sucrose, Kliger's iron agar should be used to screen stool samples to obviate "coliform"-type acid slant/acid butt reactions obtained on triple sugar iron agar slants. When inoculated onto Kliger's iron agar, *Y. enterocolitica* produces an alkaline slant/acid butt reaction which mimics that rendered mainly by *Shigella* species, which prompts further characterization of the isolate.

Y. enterocolitica isolates may be biogrouped according to the updated scheme of Wauters et al. (251) (Table 2). As a close correlation exists between serogroup O:3 and serogroup O:2,3 isolates and their biogroup profile (Table 3), except during a *Y. enterocolitica* outbreak, serogrouping of an isolate conforming to biogroup 4 and biogroup 5, respectively, is optional. Similarly, serogrouping of an isolate conforming to biogroup 1A, which contains mainly avirulent members, is also optional. Because biogroups 1B ("American strains") and biogroups 2 and 3 may contain multiple serogroups, e.g., O:5,27, O:9 (biogroup 2), O:1,2,3, and O:5,27 (biogroup 3), serogrouping should be undertaken. Whereas *Y. enterocolitica* isolates may be separated into approximately 60 serogroups (250, 253), numerous nontypeable strains have been recovered, especially from environmental sources (250, 253). Furthermore, there is some overlap between strains belonging to pathogenic serogroups, "avirulent" biogroup 1A *Y. enterocolitica* strains (60), and non-*Y. enterocolitica* species. For instance, serogroup O:8 antigen has been detected among *Y. bercovieri* isolates and serogroup O:3 antigen has been detected among *Y. frederiksenii* and *Y. mollaretii* isolates.

Serologic Diagnosis

The serologic diagnosis of *Y. enterocolitica* infection through assessment of serum agglutinins has limited applicability for individual patients in the United States (34). In contrast, serologic testing has been used extensively outside of the United States, especially for the diagnosis of serogroup O:3, phage type 8 and serogroup O:9 infections, which account for over 90% of *Y. enterocolitica* infections in Europe and Japan. Serum antibody responses ranging in titer from 80 to 20, 480 have been recorded within 2 to 7 days of acute infection. A trend toward higher titers during late reactive sequelae has also been noted (5, 255, 256). Furthermore, elevated titers may persist for years.

In the United States, brisk antibody titers detected by bacterial agglutination are elicited in response to serogroup O:8 infections (23, 34, 103, 128), but when documented, spurious responses have been obtained in individual cases of infection due to other serogroups (34). In an outbreak setting, however, such as the multistate outbreak attributed to *Y. enterocolitica* serogroup O:13a,13b (226), the median antibody titer was 2,048 among 15 adult patients and 64 among healthy controls. In 15 patients aged 16 years or less, the median antibody titer was 1,024; for 23 controls of similar age, the titer was 8. Under outbreak circumstances, antibody detection may prove valuable, especially among symptomatic patients from whom *Y. enterocolitica* has not been isolated.

The utility of serologic testing as a diagnostic adjunct for *Y. enterocolitica* infections is also tempered by the geographic locale and the potential for cross-reactions with other members of the *Enterobacteriaceae*, e.g., *Morganella morganii* and *Salmonella* spp. (65) and cross-reactions between serogroup O:9 *Y. enterocolitica* and *Brucella abortus* (65) and between serogroup O:3 and *Rickettsia* spp. (200). Additionally, as noted previously (208), patients with thyroid diseases may show persistent antibody titers ($\leq$256) to serogroup O:3 *Y. enterocolitica* in the absence of exposure to *Y. enterocolitica*.

To circumvent some of the spurious results obtained with agglutination studies, Granfors (93), by using formalinized or heat-treated cells of serogroups O:3 and O:9, respectively, developed an enzyme-linked immunosorbent assay (ELISA) for

the detection of IgM, IgG, and IgA antibodies against *Y. enterocolitica*. The ELISA compared favorably with the agglutination test but, additionally, allowed for the detection of class-specific antibodies (IgA and IgG) not identified through agglutination studies. Furthermore, a single sample assayed by ELISA for IgM antibodies could prove diagnostic for a recently acquired infection. Of particular value was the persistence (9 to 12 months) of IgA class *Yersinia* antibodies in patients whose yersiniosis was complicated by arthritis. This was in contrast to an absence of IgA antibodies within 3 months in the sera of patients with uncomplicated cases of yersiniosis. High levels of IgA and IgG antibodies to *Yersinia* persist longer in the circulation of HLA-B27-positive patients with arthritis than in the circulation of HLA-B27-negative patients with gastrointestinal symptoms only (94).

Since its introduction, the ELISA has been modified by using *Y. enterocolitica* serogroup O:3 lipopolysaccharide rather than whole cells as the binding antigen (98). In comparing whole-bacterium ELISA with lipopolysaccharide, Granfors et al. (95) showed good correlation for each immunoglobulin class. Cross-reactions between *Y. enterocolitica* serogroup O:9 and *B. abortus* were still apparent in both assays but could be differentiated by an inhibition ELISA with whole bacteria or lipopolysaccharide for the inhibition.

The serologic diagnosis of *Y. enterocolitica* infections is still troublesome. While the ELISA technique affords increased sensitivity in assessing antibodies (IgG and IgA) not detected by bacterial agglutination, cross-reactive and false-positive results also occur with the ELISA technique (242). Vesikari et al. (242) studied the use of ELISA in the diagnosis of *Y. enterocolitica* diarrhea in children. Six sera showed elevated IgM titers, which were considered to be falsely positive because of an absence of a concomitant rise in the level of IgG or IgA antibodies. These authors concluded that a positive diagnosis of acute *Y. enterocolitica* gastroenteritis should be accompanied by a rise in the level of IgM, IgG, and IgA anti-yersinia antibodies. In contrast to this conclusion, Paerregaard et al. (167), using whole pYV^+ O:3 cells as a capture antigen, found that testing for IgA and IgM antibodies did not add any diagnostic utility to tests for IgG antibodies alone for the detection of recent infection.

The above-cited studies regarding the use of the ELISA technique have been conducted largely in Finland, where the background level of anti-*Yersinia* antibodies is relatively high: 4% in the general population, 9% in patients with inflammatory joint disease, and 19.4% in patients with ankylosing spondylitis, Reiter's disease, or other reactive arthritis (95). Furthermore, few patients with culture-proven *Y. enterocolitica* infection were studied. Therefore, in the absence of culturally confirmed cases of *Y. enterocolitica* infection, it is difficult to assess the significance of a single positive antibody test. Additionally, as pointed out by Lange and Larsson (139), to fully establish the utility of serologic testing in the diagnosis of *Y. enterocolitica* infection, only cases of culture-verified infection should be included and the sera should be reacted against serogroup-specific antigens to correlate with the isolated *Y. enterocolitica* strain. In this regard, these authors concluded that too few such studies have been conducted to permit definitive conclusions on the reliability of serum antibody determination as a diagnostic tool in *Yersinia* infection.

The diagnosis of *Y. enterocolitica* infection has also been sought by indirect immunofluorescence (IF) examinations of mesenteric or cervical lymph node, ileocecal biopsy, pus, and colonic resection specimens (115). Using serogroup-specific *Y. enterocolitica* antisera, Hoogkamp-Korstanje et al. (115) could identify *Yersinia* organisms in 17 histologic preparations obtained from eight patients. In five of these patients, an earlier diagnosis was achieved by culture or serologic testing and confirmed by IF. The three remaining patients with extensive *Y. enterocolitica* serogroup O:8 infection, from whom there was no material for culture, were all diagnosed by IF of deparaffinized tissue specimens. Although cross-reactions between the various *Yersinia* serogroups were observed in IF studies, the use of IF in either an immediate or retrospective analysis of tissue samples for *Y. enterocolitica* merits strong consideration because, as noted by the authors, the use of a limited number of antisera (O:3, O:8, and O:9) may actually detect the majority of *Y. enterocolitica* infections.

Assessment for Virulence Traits

With certain bacterial species recovered from enteric contents, the significance of the isolate is inherent in the species designation. Thus, the laboratory report of a *Salmonella*, *Shigella*, *Campylobacter*, or *Vibrio* species may connote significance in the setting of a diarrheal illness. With *Y. enterocolitica*, however, in contrast to *Y. pseudotuberculosis*, the significance resides mainly in whether the isolate belongs to a pathogenic serogroup or biogroup (Table 3). In the absence of antisera to serogroup *Y. enterocolitica* isolates in routine microbiology laboratories, significance remains a function of assessing an isolate for plasmid-encoded virulence factors. These include autoagglutination, production of V (immunogenic protein) and W (nonprotective lipoprotein) antigens (55), serum resistance, calcium dependency for growth at 37°C, Congo red binding, and even plasmid profile (35). Other virulence assays include lethality for mice, production of conjunctivitis in guinea pig eyes (Sereny test) (205), and absence of pyrazinamidase activity (125). Many of these plasmid-related tests are beyond the capability of routine microbiology laboratories. Following the biogroup scheme of Wauters et al. (251) (Table 2), however, nonpathogenic isolates of *Y. enterocolitica* can be quickly recognized because they rapidly ferment salicin (35°C), hydrolyze esculin (25°C), and are pyrazinamidase positive. As slow (>4 days) utilization of salicin and esculin may occur on prolonged incubation of pathogenic strains, the results of these tests should be read in 24 to 48 h.

I believe that it is prudent to temper the significance of isolation of an "avirulent" yersinial isolate from diarrheagenic patients. For instance, Bottone and Robin (31) reported the isolation of two *Yersinia* species from a patient with acute enteritis. One isolate presently conforms to *Y. intermedia* and the other conforms to *Y. kristensenii*. An antibody titer of 64 against *Y. kristensenii* only was obtained in a single serum sample from the patient which was drawn 3 days into her illness. Because of this finding, clinical significance was ascribed to the *Y. kristensenii* isolate and it was concluded that *Y. kristensenii* may be intermediate in virulence between *Y. enterocolitica* and rhamnose-fermenting (*Y. intermedia*, *Y. frederiksenii*) *Yersinia* species (32). Subsequently, Robins-Browne et al. (191) clearly showed that 24 (51%) of 47 *Y. kristensenii* isolates were lethal to mice pretreated with iron dextran. As iron-overloaded mice succumbed within 24 h of intraperitoneal inoculation, the authors suggested that mouse pathogenicity of *Y. kristensenii*, especially O serogroups O:11, O:12,25, and O:16, may be attributed to a mechanism not previously recognized in yersiniae. Perhaps the same is true for *Y. intermedia*-like isolates and *Y. frederiksenii* (4, 10, 29, 183) recovered from diarrheagenic stools.

What, then, is the significance of performing virulence-related assays for a yersinial isolate from feces? It may be inferred from the preceding that although good correlation exists

among virulence assays and pathogenic serobiogroups of *Y. enterocolitica* isolates (62), discordant results have also been noted (161, 243). To define the utility of virulence assays as an indication of clinical significance, Noble et al. (164) correlated virulence assays with the presence of symptoms in patients with stool culture-positive yersiniosis. Using a combination of CIN agar and cold enrichment during a 42-month period, these investigators isolated 80 *Y. enterocolitica* and 52 *Y. enterocolitica*-like strains (42 *Y. frederiksenii*, 8 *Y. intermedia*, and 2 *Y. kristensenii*) from 215 fecal specimens from 171 patients. By using individual tests or groups of tests, these authors found no consistent correlation between in vitro assays and the presence of symptoms in the patients studied. For instance, many of their non-O:3 isolates that were esculin, salicin, and pyrazinamidase positive, contained the virulence plasmid; some were calcium dependent, and others autoagglutinated. Some of the classic serogroups (O:3, O:4,32, and O:5,27) whose virulent phenotypes were salicin, esculin, and pyrazinamidase negative did not bind Congo red, did not autoagglutinate, and lacked a plasmid. Furthermore, four of seven *Y. intermedia* isolates were found to harbor a plasmid and bind Congo red. As noted by Wachsmuth et al. (243) and Chiesa et al. (60), yersiniae may carry plasmids that are similar in size (64 to 73 kb) to the *Y. enterocolitica* virulence plasmid but may not be the virulence plasmid.

The dilemma posed by attempting to ascribe clinical significance to a *Y. enterocolitica* or non-*enterocolitica* species applies mainly to stool isolates. Perhaps the decision of clinical significance may not be a microbiologic parameter but, rather, one of exclusion. The recovery of a *Y. enterocolitica* strain or other *Yersinia* species from the stool of a symptomatic patient by direct cultivation or after minimal (24 to 48 h) cold enrichment and the absence of another potential etiologic agent may imply significance regardless of the virulence attributes. If need be, tests for esculin hydrolysis, salicin fermentation, and pyrazinamidase activity may be performed, recognizing that most (but not all) isolates conforming to recognized virulent *Y. enterocolitica* serobiogroups will render a negative reaction. For non-*Y. enterocolitica* isolates, significance may reside in the number of colonies present on direct isolation media, the number of times they were isolated, and epidemiologic parameters such as isolation from other family members or the potential source of the infecting strain; e.g., food or water. Continued studies may show that so-called "avirulent *Y. enterocolitica*" or non-*enterocolitica* species may induce gastrointestinal disturbances analogous to those due to enteropathogenic *Escherichia coli*, e.g., through enteroadherence or some other mechanism(s).

Presence in Foods

Y. enterocolitica, like *Listeria monocytogenes*, is thought to be a food-borne pathogen, having been recovered from a food source in five of six outbreaks (Table 8). While it is recognized that *Y. enterocolitica* is able to multiply in foods kept at refrigeration temperatures, several factors may preclude the more widespread overgrowth of *Y. enterocolitica* in foods. In pasteurized foods devoid of a resident bacterial flora, *Y. enterocolitica* may proliferate unimpeded once introduced after pasteurization (23), perhaps as a function of its tolerance to alkaline conditions (198). However, in foods with an indigenous bacterial flora, *Y. enterocolitica* may be inhibited as a consequence of lower pH and the production of antagonistic metabolites (bacteriocins) active against *Y. enterocolitica* (33, 49, 50). For instance, in the pasteurized-milk-associated outbreak of *Y. enterocolitica* (serogroups O:3 and O:6,30) infection involving 11 individuals in New South Wales, Australia, Butt et al. (47) isolated 11 *Yersinia* strains from 39 pasteurized milk samples during a 2-month period. Nine were *Y. enterocolitica*, and one each were *Y. fredericksenii* and *Y. intermedia*. Six of the eight *Y. enterocolitica* milk isolates studied were of serogroup O:6,30, and one each were serogroups O:5 and O:41,43. All eight strains were of biogroup 1. No serogroup O:3 isolates were recovered from the milk samples.

Close analysis of the data presented by Butt et al. (47) is worthwhile. First, all 39 pasteurized milk samples were obtained from one vendor during a 2-month period. *Y. enterocolitica* O:6,30, *Y. intermedia*, and *Y. kristensenii* were the sole isolates in 11 of these samples. It is reported (33, 50), however, that *Y. intermedia*, *Y. frederiksenii*, and *Y. kristensenii* produce a bacteriocin at 25°C that is active against *Y. enterocolitica* and that milk (235) and clinical (49) isolates of *Y. enterocolitica* produce a bacteriocin that is active against other *Y. enterocolitica* strains including virulent serogroups (158). Because all milk samples tested by Butt et al. (47) were derived from a single source, the sole recovery of *Y. intermedia* and *Y. kristensenii* from two milk samples could in fact represent selective isolation of these species over *Y. enterocolitica* O:6,30 as a consequence of bacteriocin production during incubation in milk. Alternatively, one must then assume the chance contamination of two milk samples with two different *Yersinia* species.

Could these species have also been present in the nine milk samples yielding *Y. enterocolitica* O:6,30? Yes, simply because bacteriocin production and action are time dependent and are functions of the original inoculum densities of the producer and susceptible strains at the time of milk contamination. Thus, inoculation of a milk sample to agar media with 37°C incubation would result in the indistinguishable colony growth of both species because bacteriocin activity by *Y. intermedia* and *Y. kristensenii* is absent at 37°C (33, 235). In most routine bacteriology laboratories, one or two colonies only are selected for advanced biochemical characterization. Therefore, chance could have favored the extensive workup of one clone (*Y. enterocolitica*) at the expense of another (*Y. intermedia*, *Y. kristensenii*) if it was present. Furthermore, the fact that *Y. enterocolitica* O:6,30 was recovered from milk in the absence of serogroup O:3 raises the question whether the O:3 strain was overlooked by chance for the same technical reasons. Finally, left unanswered is the question whether serogroup O:3 *Y. enterocolitica* was inhibited by serogroup O:6,30 *Y. enterocolitica* because of bacteriocin production. Obviously, many questions still need clarification during a search for *Y. enterocolitica* in food incriminated during an outbreak. Data on whether other bacterial species were present in addition to *Y. enterocolitica* are usually missing. Furthermore, data on how many colonies are selected for definitive biogroup and serogroup designation should be provided.

Unlike bacteriocin production by *Y. intermedia*, *Y. kristensenii*, and *Y. frederiksenii*, bacteriocin production by "avirulent" *Y. enterocolitica* strains occurs at both 25 and 37°C (49, 235). This antagonistic substance inhibits isolates of serogroups O:3, O:8, and O:9 whether or not they contain the plasmid (49). This finding raises the intriguing possibility of feeding such a natural antagonist to known reservoirs of virulent *Y. enterocolitica* such as pigs. As "avirulent" *Y. enterocolitica* strains have been recovered from pigs (126, 163, 198), colonization of the pig intestine by a bacteriocin-producing strain could either prevent or abort colonization by virulent *Y. enterocolitica*.

Antibiotic Susceptibility

Antibiotic susceptibility patterns of *Y. enterocolitica* are serogroup specific and are governed in part by the production of two chromosomally mediated β-lactamases designated β-lactamases A and B (66, 67). Produced predominantly among serogroup O:3 and O:9 isolates, these β-lactamases account for resistance to ampicillin, cephalothin, carbenicillin, and penicillin (66). Type A β-lactamase hydrolyzes a variety of penicillins and cephalosporins, whereas type B β-lactamase exhibits strong cephalosporinase activity. Protection against other β-lactam antibiotics is exerted synergistically by both enzymes (67). Thus, a two-enzyme system is operable in *Y. enterocolitica* serogroups O:3 and O:9 whereas only a type B β-lactamase is produced in serogroup O:5,27 (149). Serogroup O:8, however, unlike the more commonly occurring serogroups, is susceptible to ampicillin but is variably resistant to carbenicillin and cephalothin. β-Lactamase activity among serogroup O:8 isolates is distinct from that of serogroups O:3 and O:9. Hence, strains of different serogroups produce different β-lactamases, and, with rare exceptions, all strains produce more than one β-lactamase. The similar isoelectric focusing patterns of the type A and B β-lactamases from *Y. enterocolitica* serogroups O:1, O:2, O:3, and O:9 and β-lactamase type B from serogroup O:5,27 suggests a close taxonomic relationship among these strains. Furthermore, isoelectric focusing of *Y. enterocolitica* β-lactamases tends to group pathogenic strains irrespective of their geographic origin (149).

Since the early recognition of β-lactamase activity among *Y. enterocolitica* strains, newer β-lactam antibiotics such as ceftriaxone, ceftazidime, cefoxitin, moxalactam, and cefamandole, with marked activity against this microorganism, have become available (202, 215). It is to be cautioned, however, that studies conducted in the early 1980s either reflect data for serogroup O:3 *Y. enterocolitica* (202) or do not give serogroup designation(s) (215). More recently, Hornstein et al. (117a), studying 126 geographically diverse *Y. enterocolitica* isolates, showed that the earlier data regarding the newer broad-spectrum cephalosporins also applied to 11 serogroup O:8 isolates tested as well as to members of 19 other serogroups, although one strain each was tested from these serogroups. As expected, the pattern of susceptibility of the four major serogroups (O:3, O:5,27, O:8, and O:9) to ampicillin, carbenicillin, cephalothin, cephaloridine, cephalexin, and cefoxitin was distinct for the serogroup. For all serogroups tested, a marked antibacterial activity of imipenem and aztreonam was shown. Clinically, the use of broad-spectrum cephalosporins, often in combination with an aminoglycoside, has resulted in a successful outcome in patients with extraintestinal *Y. enterocolitica* infection (e.g., septicemia) (90). Fluoroquinolones alone or in combination have also proven efficacious (90, 117). Trimethoprim-sulfamethoxazole shows in vitro efficacy (117, 215) but has little effect on the clinical course (duration) of *Y. enterocolitica* gastroenteritis (171). Cover and Aber (69) recommend treating enterocolitis in compromised hosts. They advise withholding desferoxamine (when indicated) and treating with doxycycline or trimethoprim-sulfamethoxazole for complicated *Y. enterocolitica* gastrointestinal infection and focal extraintestinal infections.

CONCLUDING COMMENTS

Y. enterocolitica remains a most versatile bacterial pathogen. Endowed with an array of temperature-controlled chromosomal and plasmid-mediated virulence factors, this microorganism has emerged as the prototypical species capable of navigating through various host defense mechanisms to establish itself in the human body. Through arduous and impassioned research, numerous investigators have sought out and elucidated the molecular and biologic nuances underscoring its passage from an environmental reservoir to its adaptation in human hosts. Along the way, correlates of public health concerns have emerged, e.g., acquisition through donor blood and food, which require further study for containment and prevention.

No chapter in the exposition of a bacterial pathogen as evasive as *Y. enterocolitica* is ever fully written. It will therefore be in retrospect that we may marvel at the ingenuity of dedicated yersiniologists in their research efforts to gain full appreciation of this consummate bacterial pathogen.

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