From Farm to Table to Brain: Foodborne Pathogen Infection and the Potential Role of the Neuro-immune-endocrine System in Neurotoxic Sequelae

Larry H. Garthoff & Thomas J. Sobotka

To cite this article: Larry H. Garthoff & Thomas J. Sobotka (2001) From Farm to Table to Brain: Foodborne Pathogen Infection and the Potential Role of the Neuro-immune-endocrine System in Neurotoxic Sequelae, Nutritional Neuroscience, 4:5, 333-374, DOI: 10.1080/1028415X.2001.11747373

To link to this article: http://dx.doi.org/10.1080/1028415X.2001.11747373

Published online: 13 Jul 2016.

Article views: 2

View related articles
Review

From Farm to Table to Brain: Foodborne Pathogen Infection and the Potential Role of the Neuro-immune-endocrine System in Neurotoxic Sequelae

LARRY H. GARTHOFF* and THOMAS J. SOBOTKA

United States Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Applied Research and Safety Assessment, Division of Toxicology and Nutrition Product Studies, Neurotoxicology Branch, FDA, 8301 Muirkirk Road, MOD-1 Research Facility, Laurel, MD 20708, USA

(Received 15 December 1999; Revised 24 April 2000; In final form 17 April 2001)

The American diet is among the safest in the world; however, diseases transmitted by foodborne pathogens (FBPs) still pose a public health hazard. FBPs are the second most frequent cause of all infectious illnesses in the United States. Numerous anecdotal and clinical reports have demonstrated that central nervous system inflammation, infection, and adverse neurological effects occur as complications of foodborne gastroenteritis. Only a few well-controlled clinical or experimental studies, however, have investigated the neuropathogenesis. The full nature and extent of neurological involvement in foodborne illness is therefore unclear. To our knowledge, this review and commentary is the first effort to comprehensively discuss the issue of FBP induced neurotoxicity. We suggest that much of this information supports the role of a theoretical model, the neuro-immune–endocrine system, in organizing and helping to explain the complex pathogenesis of FBP neurotoxicity.

Keywords: Foodborne pathogen; Hazard identification; Neuro-immune–endocrine system; Neurotoxic sequelae

INTRODUCTION

The American diet is among the safest in the world partly in response to efforts that control livestock diseases and reduce toxic industrial chemical contamination, see review by Ahl and Buntain (1997). Foodborne pathogen infection (FBPI), however, still represents a significant public health burden (Shalala, 1999); it is reported to cause the second highest incidence of infectious disease in the United States (Archer and Young, 1988). Mead et al. (1999) estimated that illness from foodborne agents occurs at a rate of 75 million cases per year. Hospital admission was required for 325,000 cases of serious illness, and 5000 cases ended in death. Health care costs may total 5 billion dollars annually (Altekruse et al., 1997). Bacteria such as Salmonella enteritidis,

Corresponding author. Tel.: +1-301-827-8443. Fax: +301-594-0517. E-mail: lgarthof@cfsan.fda.gov
### TABLE I  FBPs producing bacteremia and neurotoxicity in humans and animals

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clinical effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Listeria</em>†</td>
<td>Sepsis</td>
<td>(Farber and Losos, 1988; Art and Andre 1991)</td>
</tr>
<tr>
<td></td>
<td>Meningitis with severe acute, subacute, and chronic neurological effects; decreased consciousness, sudden unconsciousness, headache, fever</td>
<td>(Yersin <em>et al.</em>, 1981; Hernandez <em>et al.</em>, 1990; Bula <em>et al.</em>, 1995)</td>
</tr>
<tr>
<td></td>
<td>Circling, hemiparesis, depression, gliosis, malacia, abscesses, paresia, ataxia, and rolling in animals (e.g. cattle, sheep, goats, gerbil, and dog)</td>
<td>(Seimiya <em>et al.</em>, 1992; Schroeder and van Rensburg, 1993)</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td>Neurological dysfunction: meningitis, meningoencephalitis (pig)</td>
<td>(Challa and Marx, 1980; Saebo <em>et al.</em>, 1993; Najdenski <em>et al.</em>, 1998)</td>
</tr>
<tr>
<td><em>Campylobacter fetus</em></td>
<td>Sepsis, meningitis, meningoencephalitis</td>
<td>(Clavelou <em>et al.</em>, 1988; Rennie <em>et al.</em>, 1994)</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Gullian-Barre syndrome; acute postinfectious encephalopathy, sepsis</td>
<td>(Clavelou <em>et al.</em>, 1988; Nasrallah <em>et al.</em>, 1993; Smally <em>et al.</em>, 1996)</td>
</tr>
<tr>
<td><em>E. coli</em> (entero-hemorrhagic)</td>
<td>Sepsis; meningitis with high mortality</td>
<td>(Hurlie and deLouvois, 1981; Cimolai and Carter, 1998)</td>
</tr>
<tr>
<td></td>
<td>Neurological dysfunction with seizures, CNS edema, flaccid paresis, hemorrhage, neuronal necrosis, and encephalomalacia in rabbits, pigs, and mice</td>
<td>(Kim <em>et al.</em>, 1992; Moxon <em>et al.</em>, 1977)</td>
</tr>
<tr>
<td></td>
<td>Acute septic encephalopathy, stupor, menismus, seizures, myoclonus, hemiparesis</td>
<td>(Richardson <em>et al.</em>, 1992; Baker <em>et al.</em>, 1997; Isogai <em>et al.</em>, 1998)</td>
</tr>
<tr>
<td><em>Salmonella</em> (non-thyphoid)</td>
<td>Sepsis; meningitis, seizures, leptomenigitis</td>
<td>(Ruiz <em>et al.</em>, 1995; Frado-Munoz <em>et al.</em>, 1997)</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>(Ferrera <em>et al.</em>, 1996)</td>
</tr>
<tr>
<td></td>
<td>Neurological dysfunction confusion, delirium, memory loss, abnormal motor activity, rigidity, tremors, myoclonus, seizures</td>
<td>(Belnico and Grassi, 1995)</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Transplacental septicemia, meningitis, permanent eye damage, meningoencephalitis, cranial calcification, medullary necrosis</td>
<td>(Marshman and Lyons, 1998)</td>
</tr>
<tr>
<td><em>Plesiomonas shigelloides</em></td>
<td>Transplacental septicemia, meningitis, permanent eye damage</td>
<td>(Funada <em>et al.</em>, 1998)</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>Sepsis, meningoencephalitis</td>
<td>(Funada <em>et al.</em>, 1998)</td>
</tr>
<tr>
<td><em>Brucella</em></td>
<td>Sepsis meningitis, optic nerve neuropathy, spinal nerve neuropathy, cerebellar syndrome</td>
<td>(McLean <em>et al.</em>, 1992)</td>
</tr>
</tbody>
</table>

---

†Severe CNS manifestations may occur acutely, subchronically, or chronically. Acute neurotoxic manifestations are more likely to be completely reversible than chronic manifestations but serious neurological sequelae are possible in all cases (Pachner, 1996). Unless noted all effects were observed in human patients.

‡CNS disease reported in the human, sheep, cattle, and dog. The CNS infection is the most frequent presentation in healthy adults (Hernandez *et al.*, 1990; McLauchlin 1990; Goulet and Marchetti, 1996). Numerous pre-existing conditions are often a predisposing factor for bacteremia. E.g. transplantation, diabetes, dialysis, immunosuppression, alcoholism, liver failure, cancer, pregnancy, gastric ulcer, and aplastic anemia (Nakajima *et al.*, 1990).

§Sepsis may be occult leading to diagnostic difficulties since meningitis can still develop subacutely (Wiswell *et al.*, 1995).

¶E. coli penetrate BBB after binding to glycoproteins on brain endothelial cells (Stins *et al.*, 1994).

*Purified verotoxin produced neuronal necrosis in brain and spinal cord associated with specific binding of toxin to vascular endothelium. Verotoxin receptors in rabbit brain are associated with CNS lesions (Zoja *et al.*, 1992).*
Escherichia coli (E. coli) O157:H7, Campylobacter jejuni, Listeria monocytogenes, Shigella spp., Group A Streptococci, and Staphylococcus aureus are found on or in fresh fruits and vegetables, soft cheese, meat, raw milk, untreated water, eggs, and poultry (Altekruse et al., 1997). For these reasons, the National Food Safety Initiative was developed (Binder et al., 1998) to coordinate strategies that might reduce the incidence of disease from such microbes.

Comprehensive food safety clearly requires identification and control of the most common and generally self-limiting gastrointestinal (GI) manifestations of foodborne disease. It also should address the potentially more serious effects, such as autoimmune and neurological disorders. These complications may occur in 2–3% of human foodborne illness (Bunning et al., 1997; Lindsay, 1997; McDowell and McElvaine, 1997) although the actual number is difficult to determine. The prevalence of foodborne disease is thought to be significantly under-reported (Jacobson et al., 1997; Mead et al., 1999), and chronic sequelae such as neurological dysfunction are often difficult to link with bacterial illness (Cassell, 1998). The clinical literature contains many reports of severe neurological symptoms in patients with foodborne pathogen (FBP) disease (see Table 1) and microbiologists often observe neurological effects in experimentally inoculated animals (Darcy Hanes, personal communication). The significance of these animal and human observations is not clear since there are few well-controlled or systematic studies.

A primary goal of this paper is to present a summary of reported neurotoxic sequelae from FBPIs. A second goal is to marshall support for the hypothesis that many of these effects might be organized and explained by a conceptually integrated neuro-immune–endocrine system (NIES) model. This model is derived from the emerging disciplines of neuroimmunomodulation, psychoneuroimmunology, neuroendocrinimmunology (for review see Reichlin, 1993) and neuroimmunotoxicology (El-Fawal et al., 1999; Lawrence and Kim, 2000). We hope that this effort will raise awareness of potential neurotoxic sequelae from FBPIs and support the goals of the National Food Safety Initiative (Koplan, 1999).

The first part of this paper illustrates several mechanisms by which FBPIs may cause neurotoxicity. The second part provides background for the NIES model and its utility for explaining, in part, the neurotoxicity of FBPI. This is followed by a summary of clinical reports describing neurotoxic effects seen in common FBPIs. Recommendations for needed research, and speculation concerning potentially important non-enteric adverse effects of FBPIs are also made.

Occasionally neurological complications caused by non-foodborne pathogen (NFBP) infections are introduced to help illustrate essential factors that may also be involved in the neurotoxic effects of FBPIs. This strategy appears to be valid since acute (Bolton et al., 1993; Nasralla et al., 1993), subacute (Yersin et al., 1981), and chronic clinical neurological manifestations were reported to be similar in several foodborne and non-foodborne bacterial diseases (Larsson et al., 1978). Furthermore the distinction between FBPIs and NFBPIs is often unclear (Mead et al., 1999), and numerous pathogens cause disease both by foodborne and non-foodborne routes of transmission.

Many of the known FBPIs also transmit disease by other routes (Mead et al., 1999). For example, C. jejuni, enterotoxigenic E. coli (ETEC), Shigella spp., Cryptosporidium, Group G and Group A Streptococci appear to be transmitted by water or direct person–person contact as well as by food (Black et al., 1989; Mead et al., 1999). The route of exposure may help determine the virulence and pathogenesis of microbes (Mainous et al., 1991). Pasteurella multocida produced greater mortality by the iv route than the oral, intranasal, intraocular, or sc routes (Pehlivanoglu et al., 1999). Yersinia enterocolitica with, but not without,
a virulence plasmid, produced enteric infection by ip, iv, and oral routes (Ruiz-Bravo et al., 1999). *Listeria* spp. are widely recognized as important FBPs (Marco et al., 1997); however, *L. monocytogenes* may be more virulent as a respiratory pathogen (Bracegirdle et al., 1994) and via ip exposure (Pine et al., 1990; Barbour et al., 1996). Experimentally, *Salmonella typhimurium*, was more effective as a respiratory pathogen in chickens and produced greater infection of eggs and muscle by this route (Leach et al., 1999). This suggests that aerosols (Chart et al., 1992) may infect farm eggs. Effects observed by the oral route of exposure may be related to the distinctive enteric nervous system (ENS) (Gershon, 1999) and its interaction with the efficient antigen specific humoral, T helper cell, and cytotoxic responses (Medina et al., 1999). All of the issues mentioned here help to blur clear distinctions between many FBPs and non-FBPs.

Recent history indicates that in the future other pathogens, not currently thought to be transmissible in food, may also be found to cause disease by this route (Mead et al., 1999). Bacteria with new characteristics, such as entero-hemorrhagic (EHEC) and enterotoxigenic (ETEC) *E. coli* are appearing as etiological agents in foodborne disease (Hedberg et al., 1997; Nauschuetz, 1998) and will likely continue to appear (Todd, 1997). Despite our best efforts to safely manage food, the food supply may always contain human pathogens (Plaut, 2000).

POTENTIAL MECHANISMS OF PATHOGEN ASSOCIATED NEUROTOXICITY

The brain is susceptible to damage from a variety of human pathogens and, despite the use of antimicrobial drugs, morbidity and mortality with frequent neurological deficits often characterize bacterial infection in the central nervous system (CNS) (Pfister et al., 1994; Spranger et al., 1996; Bale and Murph, 1997). Pathogenic bacteria have produced meningitis, encephalitis, encephalopathy, or meningoencephalitis with chronic neurological sequelae in survivors (Unhanand et al., 1993). These manifestations occur with pathogens that are transmitted by different routes including those that are foodborne.

Evidence suggests that FBPs may produce neurological damage by at least five different mechanisms: (1) direct inflammatory invasion of the CNS, (2) toxin-induced encephalopathy, (3) direct non-inflammatory (silent) invasion of the CNS, (4) molecular mimicry, and (5) NIES dysfunction. Various streptococcal species (some of which are foodborne) can mount a direct pathogenic attack into the CNS (Tunkel et al., 1990; Weisgerber and Troy, 1990; Beaman et al., 1994) resulting in meningitis or encephalitis. Encephalopathy was produced by toxins released from foodborne micro-organisms such as *Clostridium botulinum* (Lubran, 1988; Schiavo et al., 1993; Montecucco et al., 1996), *Clostridium perfringens* (Miyamoto et al., 1998); *Shigella* spp. (Avital et al., 1982; Wiley et al., 1985), *S. aureus* (Harshman and Sugg, 1994; Granum et al., 1995), and *E. coli* O157 (Dykstra et al., 1993; Granum et al., 1995; Ephros et al., 1996). Invasion of the CNS has also occurred either with a brief or absent inflammatory response and continued without general inflammation in the early stages of infection. This may lead to subclinical (silent), slowly developing, but progressive neurodegeneration. Such subclinical or silent invasions of the brain have been suggested as a mechanism of foodborne infections by intracellular pathogens like *L. monocytogenes*, even though they typically produce an acute inflammatory response mediated by neutrophils and macrophages (Beaman et al., 1994). If antibodies are generated against the invading bacteria and these antibodies cross-react with host proteins, molecular mimicry may contribute to an autoimmune disorder. The highly conserved heat shock proteins from foodborne *Salmonella* and *Yersinia* (Lo et al., 2000; Mertz et al., 2000) as well as from unknown sources (Shingai et al.,...
1995; Xu et al., 1999) are implicated in the pathogenesis of several chronic systemic and degenerative human diseases (McFarland, 1996; Kim et al., 1999). Another possible mechanistic basis for some autoimmune disorders is suggested by clinical trials of therapeutic pro-inflammatory cytokines (PICI’s). These trials were associated with elevated incidence of diabetes and thyroiditis (Vial et al., 2000). Finally, this paper discusses evidence that supports the role of FBPis in the pathophysiological dysfunction of the NIES, an essential regulator of homeostasis.

DESCRIPTION OF THE NIES MODEL

The basis of the NIES model, as it relates to neurological effects of FBP, is the presence of intercommunicating neural, immune, and endocrine functions in both the GI tract and the brain. The NIES, in toto, appears able to respond to both psychological and non-psychological (chemical, physical, and biological) signals received by the host. Infectious stimuli as well as genetic, toxic, traumatic, ischemic, pharmacological, or psychosocial signals may become stressors for the host. It is the role of the NIES to defend the host against these threats to homeostasis (Deschaux, 1988; Panerai, 1992; Reichlin, 1993; Blalock, 1994; Berczi et al., 1996; Torpy and Chrousos, 1996; Johnson et al., 1997; Maier and Watkins, 1998; Turrin and Plata-Salaman, 2000).

The tripartite functions of neural, immune, and endocrine activity integrate GI function. The lining of the GI system, like that of other mucosal membranes, is continuously exposed to the external environment. The intestinal lining represents the largest exposed surface of the body, and it may serve as a sensory organ that continuously samples the luminal environment (Ferencik and Stvrtinova, 1997; Furness et al., 1999). Through this sensory function, the intestinal mucosa serves as the first line of host defense against food antigens and FBPs that enter the gut. The GI system has the most extensive immune capabilities in the body (Theodorou et al., 1996) with up to 70–80% of the body’s immune cells (Furness et al., 1999). The endocrine cells of the gut and pancreas contain more than 20 known hormone-like molecules. These compounds represent the second largest, next to the brain, source of regulatory peptides in the mammalian body (Sundler et al., 1989; Furness et al., 1999). The ENS contains upwards of 100 million neurons. The neural, immune, and endocrine cell types in the intestine are closely and densely juxtaposed (Shanahan, 1999). This facilitates transmission of signals from activated immune cells and endocrine cells to the enteric neural cells, and on to the brain (Theodorou et al., 1996), possibly by way of the vagus nerve (reviewed by Goehler et al. (2000)).

The brain also appears to serve these tripartite functions of neural, immune, and endocrine activity. The brain alone has a larger and more complex nervous system than the gut with up to 200 billion neurons and 1 trillion glia (Abou-Denia, 1992). Brain glia include astrocytes, oligodendrocytes, and microglia. About 5–10% of all brain cells, or 100 billion, are microglia (Arenander and de Vellis, 1994; Rezaie and Male, 1999). The microglia are derived from bone marrow during fetal development, and they serve as the resident macrophages of the brain. Astrocytes have long been known to support neural functions, but now it is clear that they, along with the microglia, also serve immune-like and endocrine-like functions. Astrocytes appear to serve the primary steroidogenic function of the brain in alliance with oligodendrocytes and neurons (Zwain and Yen, 1999a). Brain cells express steroidogenic enzymes and synthesize numerous steroids including pregnenolone, progesterone, dihydroepiandrosterone (DHEA), testosterone, estradiol, and estrone. These steroids appear to be involved in immune regulation, e.g. DHEA almost totally inhibits TNFα and IL-6 production in vitro and in vivo; they also
<table>
<thead>
<tr>
<th>Disease</th>
<th>Elevated cytokines</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood Level (pg/ml)</td>
<td>CSF Level (pg/ml)</td>
</tr>
<tr>
<td>Controls</td>
<td>TNFα</td>
<td>ND†</td>
</tr>
<tr>
<td></td>
<td>IL-1β</td>
<td>ND, 20–40</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IFNγ</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IL-1Ra</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Ramilo et al., 1990; Frei et al., 1993; Tsai et al., 1994; Akalin et al., 1994; Ishiguro et al., 1996; Ishiguro et al., 1997; Ichiyama et al., 1998)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>IL-6</td>
<td>(Frei et al., 1991; Matusevicius et al., 1996; Carrieri et al., 1998; Liu et al., 1998)</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IL-1β</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Sivieri et al., 1997)</td>
</tr>
<tr>
<td>Guillain-Barre</td>
<td>IL-1β</td>
<td>M-CSF</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-2</td>
</tr>
<tr>
<td></td>
<td>M-CSF</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>IFNγ</td>
<td>ND</td>
</tr>
<tr>
<td>AIDS encephalitis</td>
<td>TNFα</td>
<td>IL-6 (a),(b)</td>
</tr>
<tr>
<td></td>
<td>IL-6 (a),(b)</td>
<td>(Wiley et al., 1992; Persidsky et al., 1997)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>IL-1β</td>
<td>(Blum-Degen et al., 1995; Mogi et al., 1996)</td>
</tr>
<tr>
<td></td>
<td>IL-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>TGFα</td>
</tr>
<tr>
<td>Alzheimer’s disease‡</td>
<td>IL-6</td>
<td>IL-1</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>(Dickson et al., 1993; Blum-Degen et al., 1995; Singh and Guthikonda, 1997)</td>
</tr>
<tr>
<td>Obsessive compulsive disease¶</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia§</td>
<td>IFNγ</td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>TNFα and β</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed Th1 &amp; Th2</td>
<td>(Mittleman et al., 1997)</td>
</tr>
<tr>
<td>Disease</td>
<td>Elevated cytokines</td>
<td>Blood Level (pg/ml)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td></td>
<td>IL-6 14,000</td>
</tr>
<tr>
<td>Tuberculosis meningitis</td>
<td>IFN-γ</td>
<td>780</td>
</tr>
<tr>
<td>Coccidial meningitis</td>
<td>IL-1β/IL-10Ra</td>
<td>5</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>IL-1β</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Mollaret meningitis</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>Lethal acute experimental sepsis (c)</td>
<td></td>
<td>TNF-α 20,000</td>
</tr>
<tr>
<td>CNS inflammation without infection</td>
<td>IL-6</td>
<td>34</td>
</tr>
<tr>
<td>Systemic lupus erythromatosis</td>
<td>IL-6, IL-2, TNF-α</td>
<td>71</td>
</tr>
</tbody>
</table>
### Table II - continued

<table>
<thead>
<tr>
<th>Disease</th>
<th>Elevated cytokines</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood Level (pg/ml)</td>
<td>CSF Level (pg/ml)</td>
</tr>
<tr>
<td>Neuroborreliosis</td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>TNFα</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>ND</td>
<td>IL-1β</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td>Shigellosis†</td>
<td>IL-6</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>5</td>
</tr>
<tr>
<td>Shigellosis‡‡</td>
<td>IL-6</td>
<td>IFNγ (a)</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>IL-6</td>
</tr>
<tr>
<td>Yersiniosis†††</td>
<td>il-1</td>
<td>IFNγ (a)</td>
</tr>
<tr>
<td></td>
<td>IFN-2</td>
<td>IL-12</td>
</tr>
<tr>
<td>Verotoxic E. coli (HUS)</td>
<td>IL-1β*</td>
<td>IL-8</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>TNFα*</td>
<td>IL-10</td>
</tr>
<tr>
<td></td>
<td>IL-1Ra</td>
<td>G-CSF</td>
</tr>
<tr>
<td>Entericaggregative E. coli</td>
<td>IL-8 (fecal)</td>
<td>IL-1β (fecal)</td>
</tr>
<tr>
<td>E. coli infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli sepsis (c)</td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>IL-8</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td>IL-10</td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td>MCP-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200,000</td>
</tr>
<tr>
<td></td>
<td>IL-12</td>
<td>LIF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4400 (sublethal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIF</td>
</tr>
<tr>
<td>E. coli sepsis(a)</td>
<td>TNFα</td>
<td>IL-1</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-6</td>
</tr>
<tr>
<td>E. coli sepsis (rat)</td>
<td>TNFα</td>
<td></td>
</tr>
<tr>
<td>Listeriosis (a)</td>
<td>Corticosterone</td>
<td></td>
</tr>
</tbody>
</table>
### Table II - continued

<table>
<thead>
<tr>
<th>Disease</th>
<th>Elevated cytokines</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood Level (pg/ml)</td>
<td>CSF Level (pg/ml)</td>
</tr>
<tr>
<td></td>
<td>IL-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TNFα^††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-10^††</td>
<td>MIP-1α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MIP-1β</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCP-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-8, IFNγ</td>
</tr>
<tr>
<td></td>
<td>IL-1α and β</td>
<td></td>
</tr>
<tr>
<td>Scrapie</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TNFα</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
inhibit gliosis (Akwa et al., 1993; DiSanto et al., 1996; Garcia-Estrada et al., 1999; Kipper-Galperin et al., 1999; Zwain and Yen, 1999a,b; Brown et al., 2000). Simply stated, in both the GI tract and the brain, immune and endocrine cell-derived biochemicals regulate nerve cells, and nerve cell-derived biochemicals regulate immune and endocrine cells through exceedingly complex receptor–ligand interactions. Although NIES mediators and their physiological receptors are present throughout the body, we will concentrate on the gut and the brain (Cassileth and Drossman, 1993; Reichlin, 1993; Berczi et al., 1996; 1998; Shanahan, 1999; Lawrence and Kim, 2000).

The ENS also regulates several classically typical GI functions that facilitate the elimination of potentially neurotoxic agents. These functions include increased secretion of gastric acid, pancreatic proteolytic enzymes, gut water, electrolytes, and mucopolysaccharides, and stimulation of peristalsis (Theodorou et al., 1996).

THE ROLE OF THE NIES MODEL IN FBPI AND NEUROTOXICITY

As described above, the NIES model receives primary input from three major classical physiological systems of the mammalian organism, i.e. the immune, endocrine, and nervous systems. If the NIES model is to help explain FBP induced neurotoxicity, then basic markers of these primary systems, e.g. cytokines, hormones, and behaviour, respectively, should reflect or play key roles in that process.

An early event in the pathogenesis of FBPIs is thought to involve penetration of intestinal epithelial cells and activation of the mucosal immune system. The selectivity of the GI lining is exquisite. Although continuously bathed by a broth (10^{11} organisms/g colon contents) of over 400 different commensal microbes (Rowland, 1988), the enteric system remains unperturbed until pathogenic bacteria invade the epithelium and activate the potent and rapidly responsive innate immune function (Hecht and Savkovic, 1997). Neutrophils and activated immune cells of the macrophage/monocyte lineage are stimulated to infiltrate the intestinal mucosa and phagocytose the invaders (Jung et al., 1995). Yersinia enterocolitica, for example, invade the intestinal epithelium via the M cells of Peyer’s patches and then replicate inside the lymphoid follicles (Siebers and Finlay, 1996). Shigella, Listeria and Salmonella spp. are also taken up by M cells and macrophages in the gut wall (Jones et al., 1994; Marco et al., 1997). During the digestion of the pathogens, cell wall components may be released. Shigella, for example, are phagocytosed by macrophages that release PICKs such as IL-1 (Zychlinsky and Sansonetti, 1997), but Salmonella must be further attacked by another type of peripheral immunocyte, the interdigitating dendritic cell (Yrlid and Wick, 2000).

The cell walls of Gram-negative or Gram-positive pathogens contain either lipopolysaccharide (LPS) (Rietschel and Brade, 1992; Chikanza and Grossman, 1996) or a variety of other bacterial proteins, carbohydrates, and lipids, respectively (Elmquist et al., 1993). LPS is a molecule composed of negatively charged, complex glycolipids (Takayama et al., 1995; Brade et al., 1987). LPS (4–2000 ng/ml) is found in the cerebrospinal fluid (CSF) of patients acutely ill with Gram-negative bacterial meningitis but not in non-meningitis controls. The LPS level falls rapidly with effective treatment (Berman et al., 1976). The level of LPS also correlates well with both IL-1β levels and long-term neurological sequelae in non-foodborne H. influenzae meningitis, indicating that LPS may be an important factor in the pathogenesis of this illness (Metsola et al., 1991). Studies have shown that cytokines are also elevated in FBPIs (Table II).

LPS and other bacterial products are potent mammalian inflammogens. They contain molecules with pathogen-associated molecular patterns (PAMPs) that are highly conserved
structures. These structures are readily and quickly recognized by the effector cells of the innate immune system of mammals (Medzhitov and Janeway, 2000) and they induce a vigorous inflammatory response that is "initiated, amplified, perpetuated and resolved by cytokines" (McAlindon and Mahida, 1997). Cytokine induction appears to be specific for pathogenic and invasive microbes since isogeneic non-invasive variants do not stimulate cytokine synthesis (Henderson and Wilson, 1996). Several proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNFα) are produced by these host immune cells. Both peripheral and central proinflammatory and anti-inflammatory cytokines appear to play a major role in the pathophysiological responses to FBPs just as they do in nonfoodborne disease (Hecht and Savkovic, 1997; Proulx et al., 1998; Delves and Roitt, 2000). These host responses may lead to both autoimmune and neurological diseases (Zhao and Schwartz, 1998) (see Table II). Quantitative and qualitative changes in host cytokines may therefore be useful biomarkers for assessing the neurotoxic potential of FBPs just as they are for NFBPs.

Circulating levels of several PICKs are elevated during the host defensive response to FBPI and are required to clear enteric pathogens such as EHEC (Cross et al., 1995; Hecht and Savkovic, 1997), Yersinia enterocolitica (Beuscher et al., 1997; Bohn et al., 1998), Salmonella spp. (Eckmann et al., 1996; Pie et al., 1997), L. monocytogenes (Langermans and van Furth, 1994), and Shigella (Nicholls et al., 1993; Sansonetti et al., 1995). In mice, high septic levels of LPS or IL-6 increased the permeability of the cerebral spinal fluid (CSF) brain barrier. Cerebral arterioles were dilated, and there was increased uptake of lead and glutamate. This led to synergistic toxicity of LPS with these neurotoxins (Dyatlov et al., 1998a,b). Subseptic doses of peripheral LPS caused no disruption of the blood brain barrier (BBB), but they still acutely induced PICKs at the choroid plexus, meninges, and the circumventricular organs (Quan et al., 1999). The magnitude and spatial-temporal characteristics of cytokine levels, therefore, may be indicative of disease nature and severity (Pitossi et al., 1997; Stahel and Barnum, 1997; Hesse, 1988). These results suggest the need to investigate the potential interactions of FBP disease with clinically relevant doses of environmental and endogenous neurotoxins (Teitelbaum et al., 1990; Landrigan et al., 1993; Cendes et al., 1995; Schantz et al., 1996; Codd et al., 1997).

Increased production of cytokines and direct pathogen attack on microglia and astrocytes are often observed in animal models of NFBP meningitis (Kim et al., 1995a; Kim et al., 1995b). Symptoms are significantly reduced by inhibitors of cytokine production and by glutamate receptor antagonists (Kim and Tauber, 1996; Bogdan et al., 1997). Glutamate excitotoxicity and increased cytokine activity may therefore be involved in the neurotoxic effects found in both this neonatal rat model of NFBP meningitis (Olney, 1994; Leib et al., 1996) and in humans, since CSF glutamate and cytokine levels are positively correlated with clinical outcome (Spranger et al., 1996). Elevated plasma and CSF levels of LPS and PICK (van Deuren et al., 1995) that occur early in the disease (Glimaker et al., 1993; Ohga et al., 1994; Matsuzono et al., 1995; Tsai et al., 1996) are associated with the central effects of meningitis; effective treatment leads to disappearance of these cytokines in the CSF (Kondrusik and Hermanowska-Szpakowicz, 1997). Qualitative cytokine profiles in biological fluids, especially CSF, are useful diagnostic biomarkers of these NFBP infections. These profiles identify differential inflammatory responses to specific pathogens and their antigens, and can discriminate between different forms of CNS disease, the severity of the disease, and the clinical course (Ramilo et al., 1990; Glimaker et al., 1993; Ohga et al., 1994; Matsuzono et al., 1995; Tsai et al., 1996; Diab et al., 1997a,b; McAlindon and Mahida, 1997; Ichiyama et al., 1998; Mastroianni et al., 1998).
Meningitis and elevated cytokines are also often observed in human patients with FBPI (Tables I and II) (Phillips and Simor, 1998). It seems reasonable to expect that the effects of FBPIs may be similar to those caused by NFBPIs. The response to FBPIs that do not cause direct CNS infection remains to be determined.

Increased production of cytokines is a key step in the activation of the gut mucosal immune function and leads to several other key defensive steps in the host response to FBPIs. Cytokines activate the classical neuroendocrine release of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) with subsequent alterations in endocrine, immune, and neural parameters (Anisman et al., 1996a). This is a cascade of defensive responses that can all be initiated by bacterial PAMPs such as LPS, or by PICKs produced endogenously from monocytes and macrophages, or from exogenous administration of PICKs (Anisman et al., 1996b). Activation of the HPA axis serves to counter-regulate the catabolic destructive effects of excessive immune stimulation (Lynch et al., 1997). The defensive response also activates a centrally mediated sympathetic innervation of the mucosal immune system and induction of the complex immune activities of brain cells (Felten et al., 1987a,b; 1991; Livnat et al., 1987; Uehara and Namiki, 1992; Felten et al., 1998). If the HPA counter-regulatory response to immune challenge is defective, the host may have increased susceptibility to damage. For example, the Lewis rat has susceptibility to peripheral inflammatory disease (Misiewicz et al., 1997), and adrenalectomized animals have increased mortality and dramatically increased sensitivity to LPS (Kapcalca et al., 1995; Anisman et al., 1996b). Stimulation of the HPA axis, therefore, may help prevent excessive immune damage to the host.

Although the mechanism by which the cytokine signal enters the brain is unclear, there is strong evidence that these cytokines are responsible for the acute phase response (APR) that includes the commonly observed behavioral symptoms of sickness. The sickness syndrome includes lethargy, fever, anorexia, adipsia, decreased libido, and decreased behavioral activity (Witek-Janusek, 1988; Anisman et al., 1996a,b). The APR also includes intrinsic and defensive host activities that result directly from activation of an organism’s own immune, endocrine, and neural mediators, i.e. the NIES system. In addition to the sickness syndrome, about 30 acute phase plasma proteins either increase or decrease within 90 min after infection begins (Zeisberger, 1999). It is currently thought that the APR is an intrinsic host response. It does not result from the infectious or inflammatory agent per se, nor is it the result of the adverse effects of a pathogen on the host. Fever, for example, appears to be a sign of an otherwise healthy host, and it may help the host to defend itself against a stressor, e.g. invader or trauma (Zeisberger, 1999). The normal immune response may also disrupt normal neurophysiology and contribute to cognitive and behavioral dysfunction (Danzter et al., 1992). Studies using both exogenous and endogenous delivery of cytokines clearly demonstrate that unregulated levels are highly toxic to both animals and humans (Johnson, 1997).

Cytokine neurotoxicity has been observed in both animals and humans. The best evidence for cytokine neurotoxicity in humans comes from clinical trials of purified and peripherally injected cytokines, primarily interferon-α (reviewed by Vial et al. (2000)). Therapeutic doses induced sickness syndrome-like effects at low levels, and they induced serious neural and endocrine toxicity at high levels. The effects included flu-like symptoms, with fever, anorexia, fatigue, headache, dementia, delirium, encephalopathy, severe depression, manic episodes, and other psychoses. The best evidence for direct cytokine neurotoxicity in animal models come from studies of transgenic mice (Campbell et al., 1994; 1997; Campbell and Chiang, 1995; Campbell, 1998). These mice expressed low
constitutive levels of IFNa, TNFa, IL-3, or IL-6 in the CNS. Dysregulated brain cytokine levels were associated with dramatic and devastating cytokine-specific CNS pathology and unique functional deficits (Campbell and Chiang, 1995; Campbell, 1998). The disorders included progressive neuropathological changes and learning impairment (Heyser et al., 1997). These results suggest that dysregulated cytokine production by astrocytes and microglia may also play a role in the pathogenesis of major human CNS disorders (Gahtan and Overmier, 1999). Dysfunctional glia have been reported in Alzheimer’s disease (AD), and some neurological manifestations of AD and multiple sclerosis (MS) are similar to effects produced by over-expression of IL-6 in transgenic animals (Geiger and Sarvetnick, 1996). These are dramatic examples of cytokines as primary neuropathic molecules when present at inappropriate times or levels. This suggests that other inflammatory stimuli, such as FBPI, should be evaluated for similar and hopefully less profound effects in the CNS.

As we have seen, the brain is intimately involved in the host response to stressors. The brain coordinates and regulates the host defense by integrating central and peripheral nervous, immune, and endocrine functions. This may be viewed as an extension of the original “fight or flight” stress paradigm described by Walter Cannon in the 1920s (Cannon, 1929) and the general adaptation syndrome described by Hans Selye in the 1930 and 1940s (Selye 1936a,b; 1946). The current model is a complex bi-directionally regulated NIES network, of neural, immune, and endocrine subsystems that is both anatomically and functionally integrated. The integration is coordinated by nerve tracts linking the subsystems and by a panoply of neural, endocrine, and immune/inflammatory mediators (Maier and Watkins, 1998; Maier et al., 1998). These mediators are produced by immune cells but also by neurons and glial cells in both the CNS and ENS. Due to the tightly integrated network, inflammatory processes in one component rarely occur alone. Exemplified by inflammatory processes in AD, activation of any one subsystem, therefore, leads over time to changes in the others (Akiyama et al., 2000). Inappropriate host response to stressors can lead to either hyperactive or hypoactive host responses; both may cause damage to self that results in sickness (Sternberg et al., 1992; Feuerstein et al., 1994). A number of adverse effects, including neurotoxicity have been associated with NIES dysfunction; others include autoimmunity, abnormal immunosuppression (Wilder, 1995), altered HPA responsiveness to stress (Reul et al., 1994; Shanks et al., 1994), abnormal social development in rats (Granger et al., 1996), behavioral disorders such as depression and anxiety (Sternberg et al., 1992; Anderson, 1996; Heim and Nemeroff, 1999), rheumatic diseases, chronic inflammatory disease, chronic fatigue syndrome, fibromyalgia, allergy, asthma, and GI inflammatory disease in humans (Anisman et al., 1996a).

The NIES model predicts that endocrine factors will also interact with the immune response. Gender dimorphic sexual responses to immune activation have been observed in the rat. Sexually specific behavior is suppressed for several hours in response to either peripheral or central administration of endotoxin. The suppression occurs only in females (Avitsur and Yirmiya, 1999). A number of other endocrine-immune interactions have been reported in both experimental animals and humans; these interactions suggest important manifestations for both men and women (Angele et al., 2000).

Endocrine factors may contribute to the observation that the female of several species, e.g. rats, mice and humans, has a greater NIES response than the male to bacterial LPS at all stages of life (Ansar et al., 1985; Wilder, 1995). Females have higher immunoglobulin levels, higher antibodies levels, and a higher rate of corticosteroidogenesis than males (Wilder, 1995; Gaillard and Spindei, 1998). Females also generate a Th1 helper T cell response to infection more often than males except during pregnancy.
when a Th2 response prevails (Whitacre et al., 1999). Increased cortisol from activation of the HPA axis also favors an anti-inflammatory Th2 cytokine profile. The Th1/Th2 cytokine ratio appears to help determine whether an autoimmune response, at the molecular level, leads to clinical disease (Charlton and Lafferty, 1995). A Th1 bias favors pro-inflammatory, cell mediated organ specific autoimmunity, and a Th2 bias favors a humorally mediated systemic autoimmunity (Agarwal and Marshall, 1998; Hassig et al., 1998). Lest it appear that only females express negative manifestations of neuroimmune-endocrine interactions, the male gender is an important risk factor for immunosuppression and major infection after surgery, trauma, shock, or sepsis (Offner et al., 1999; Angele et al., 2000). Under similar conditions females were immunoprotected (Angele et al., 2000). This differential response of females and males to NIES activation may contribute to the much higher incidence of autoimmune diseases in women than men (Homo-Delarche et al., 1991; Steinman, 1993; Wilder, 1995; 1996; Bebo et al., 1998a,b). Exacerbations of autoimmune diseases by recent infections and psychosocial stress as well as increased estrogen levels (Steinman, 1993; Kim et al., 1999) suggest immune and neural interaction also. The possible contribution of FBPs to these autoimmune diseases should be investigated.

Intermediates in the synthetic pathway of sex hormones may also contribute to these immunoregulatory effects. Treatment with DHEA and androstenedione both protected mice from the lethal effects of Gram-negative and Gram-positive bacteria and endotoxin (Ben-Nathan et al., 1999). These effects may be mediated by alterations in T cells, cytokines, and glucocorticoids (Catania et al., 1999; Ba et al., 2000). The neural arm of the NIES may be affected by activation of the APR. Again the response is sexually dimorphic, and it occurs in learning ability. Male rats showed an enhanced rate of associative learning under moderate stress; however, female rats had enhanced procedural memory formation only if they were not stressed prior to testing. The impaired learning of female rats after stress was reversed by ovariectomy or tamoxifen treatment (Wood and Shors, 1998); therefore, these effects are consistent with a gender dimorphic stress response of the NIES (MacNiven et al., 1992; Suescun et al., 1994). It remains to be determined whether similar dimorphic NIES responses occur in humans and whether they may explain any of the differential incidences of autoimmune disease. The current model of the NIES defense (Wilder, 1995; McEwen et al., 1997; McEwen, 1998) suggests that the sensitivity of females to the stress of FBPs should be examined for susceptibility to autoimmune and neurotoxic sequelae (Wilder, 1995). The effects of immune activation on critical brain functions like learning and behavior also suggest the need for precise behavioral methods that can assess these conditions (Gahtan and Overmier, 1999).

All of this evidence from immune, endocrine, and neural function suggests mechanisms by which an inflammatory NIES response may disrupt CNS function without direct bacterial invasion. These mechanisms may be mediated by cytokines, other inflammatory molecules, immunologically active astrocytes, and activated microglia. Such a response is exemplified by the generalized inflammatory autoimmune response of the retina, brain, spinal cord, and peripheral nerves of the Lewis rat induced by a non-infectious synthetic antigen (Schleusener, 1996). Such an inflammatory host response to a bacterial antigen with a potential imbalance of Th1 and Th2 helper T cell cytokines (Th1/Th2 cytokine ratio) has shown that certain FBPs may be risk factors for neurological manifestations and autoimmune sequelae even in the absence of direct pathogen invasion of the CNS (Jander et al., 1993; Townsend and Scheld, 1993; Aschner, 1998). It seems reasonable to speculate that similar effects may also occur from FBPs. The extent of neurological risk for FBPs would
be expected to depend on the severity of illness, the level of cytokines, and the duration of any CNS inflammatory response. The characteristics of brain inflammation caused by FBPIs have not been rigorously determined, but we suggest that this should be examined.

Many general characteristics of the NIES model that have been discussed above can be seen to appear frequently throughout the clinical and experimental observations of common FBPIs presented below.

**NEUROTOXIC EFFECTS OF FOODBORNE PATHOGENS**

Currently there are more than 200 known foodborne diseases. Some are transmitted by viruses, bacteria, parasites, toxins, metals, and prions, but the majority are caused by unidentified agents (Stolle and Sperner, 1997; Mead et al., 1999). The primary clinical presentation of microbial foodborne disease is usually acute and self-limiting gastroenteritis. Symptoms may include nausea, vomiting, abdominal pain, diarrhea, headache, fever, and chills along with the other manifestations of the sickness syndrome. Adverse sequelae most clearly associated with foodborne disease include septic and reactive arthritis, inflammatory bowel disease, hemolytic uremic syndrome (HUS) (Lindsay, 1996; Bunning et al., 1997), diabetes, and possibly endometriosis (Taketani et al., 1992; Khorram et al., 1993; Grimes et al., 1995; Akoum et al., 1995; Braun et al., 1996; Taylor et al., 1997). Although it may not be as widely appreciated nor as well studied by neuroscientists, enteric infection by common foodborne bacteria may also have cytopathic effects on brain cells that result in acute neurotoxicity and chronic neurodegeneration (Hamano et al., 1992; 1993; Beaman et al., 1994). Clinical neurotoxicity has been reported following acute gastroenteritis caused by FBP species belonging to Salmonella, Shigella, Listeria, Yersina, Campylobacter, Escherichia, Streptococci, and Staphylococci bacterial genera (Hamano et al., 1992; 1993; Ephros et al., 1996) (see Table 1).

**COMMON FOODBORNE PATHOGENS ASSOCIATED WITH NEUROTOXICITY**

**Enterohemorrhagic E. coli**

Prior to 1982, E. coli was not known as an enteropathogen; however, it now causes about 20,000 cases of hemorrhagic colitis per year in the United States (Nauschuetz, 1998). Neurological manifestations from invasive E. coli have been reported in both animals and humans (Ostroff et al., 1989; Boyce et al., 1995). In kindergarten children, acute effects produced by EHEC included stupor, deep coma, convulsions, and death. Subacute effects in survivors included action tremors, nystagmus, incontinence, and phrenic nerve palsy (Hamano et al., 1992; 1993) possibly due to verotoxin (Joh, 1997). Plasma cytokine levels are positively correlated with the presence of EHEC induced HUS (Inward et al., 1997; Murata et al., 1998; Proulx et al., 1998). E. coli O144:NM also produced CNS effects in children with diarrhea; encephalopathy presented with profound stupor and symptoms of meningeal irritation without actual infection of the meninges (Ephros et al., 1996). In piglets, oral infection with wild type EHEC, or injection with verotoxin produced incoordination, ataxia, and convulsions. Vascular damage, ischemic necrosis, and infarcts were observed in both the intestine and brain even with the non-colonizing strains that did not produce diarrhea (Tzipori et al., 1995). These lesions resembled those seen in calves and in humans with E. coli associated hemorrhagic colitis (Dykstra et al., 1993). Similar neurological effects were seen in the child that served as the source of the E. coli (Tzipori et al., 1988). Infection of mice with an E. coli O157 strain produced a primary acute and fatal encephalopathy, with weakness, flaccid paraly-
sis, and HUS. Epithelial cells and neurons were damaged in the cortex, spinal cord, gut, and kidney (Fujii et al., 1994; Karpman et al., 1997). The TFNα level was increased in the CSF of neonatal piglets (Park et al., 1998) and in the brain of germ free mice infected with EHEC. These mice exhibited neurological symptoms, and the neurotoxic and nephrotoxic pathologies were exacerbated by administration of exogenous TFNα (Isogi et al., 1998).

Verotoxin 2 from E. coli O157:H (E32511/HSC) produced death of experimental animals with lesions of the hypothalamus and damage to the BBB (Fujii and Yoshida, 1997). Rabbits challenged with verotoxin exhibited limb paralysis with pericellular and perivascular edema, focal hemorrhage, vascular lesions, and severe alterations of Purkinje cells possibly mediated by verotoxin receptors found in the CNS of these rabbits (Zoja et al., 1992).

Shigella

Neurotoxic symptoms such as convulsions and encephalopathy with hallucinations, confusion, lethargy, and severe headache are the most common non-enteric complications of Shigella infection (Ashkenazi et al., 1989; Yuhas et al., 1995) especially in children. Although the pathogenesis is not clear (Avital et al., 1982; Ashkenazi et al., 1994), it may involve Shiga-toxin (Ashkenazi et al., 1990), TNFα, and nitric oxide (NO). TNFα and NO levels were higher in serum of children with neurological sequelae than in others (Mor et al., 1996). Elevated NO levels were also observed in viral CNS disease (Hooper et al., 1995).

Shigellosis causes morbidity in endemic areas and, in rare cases, the toxic encephalopathy may be rapidly fatal (Goren et al., 1992). Generalized necrotic areas, pontine hemorrhage, and demyelination have been seen in the CNS of these patients (Sandyk and Brennan, 1983). Yuhas et al. (1995) found that the combination of shiga toxin and LPS from Shigella or E. coli increased the sensitivity of mice to seizures caused by a subepileptic dose of pentylenetetrazol.

Listeria

L. monocytogenes was first isolated and described in 1926 (Low and Donachie, 1997). An intracellular pathogen, it is now known to cause serious foodborne disease in both humans and agricultural animals, especially sheep (Urbanovich, 1975; Low and Renton, 1985). It often produces sepsis and may have a predilection for the CNS. Common clinical manifestations are shown in Table I. Listeria can invade cells of the brain and grow in the cytoplasm and axons causing extensive localized neuronal damage and neurodegeneration (Beaman et al., 1994). Bacteria are also found in the axons of CNS white matter tracts and in the peripheral nerve axons of infected sheep (Otter and Blakemore, 1989). In one adult human outbreak, 30% of the survivors developed neurological sequelae (Bula et al., 1995). Rhomboencephalitis, a complication of human listerial meningitis, is associated with mortality and severe neurological sequelae (Blanot et al., 1997) in as many as 60% of survivors (Shaffer et al., 1998). Lymphocyte recruitment across the BBB by CSF chemokines appears to be necessary to kill Listeria in the CNS of the mouse; however, this inflammatory response itself may exacerbate CNS damage (Seebach et al., 1995).

The fetal-maternal unit has increased susceptibility to foodborne listeriosis (Manganiello and Yarke, 1991; Abram and Doric, 1997) possibly due to the Th2 bias of the pregnant female’s immune defenses. A pregnant woman may exhibit flu-like symptoms only, but for the fetus (MacGowan et al., 1991) stillbirth (Pitkin, 1987), abortion, premature delivery, malformations (Romana et al., 1989), inflammatory CNS lesions (Liner, 1990; Cherubin et al., 1991;
Lallemand et al., 1992), and neurodevelopmental handicap (Evans et al., 1984) are possible outcomes. The complete effects on fetal development, however, are not fully understood (Abram and Doric, 1997) and further study seems warranted.

A gerbil model produced by aural injection of L. monocytogenes exhibited severe neurotoxic sequelae including circling, paresis, ataxia, and rolling behavior. The clinical course correlated with magnetic resonance imaging (MRI) and histological changes that mimicked the human disease (Blanot et al., 1997). In Swiss CD1 mice, s.c. administration of L. monocytogenes produced leptomeningitis and inflammatory infiltration of the ventricles. The pathogen appeared to enter the CNS through the choroid plexus (Prats et al., 1992).

Intercerebral administration of Listeria to animals produced severe or fatal leptomenigitis, ventriculitis, and encephalitis (Schluter et al., 1996). Results from perhaps the most relevant model for human disease found that the exposure schedule was an important variable in initiation of disease. Repeated oral administration of sublethal doses produced a high incidence of severe CNS lesions that mimicked human listeriosis, while single oral administration produced only subclinical disease (Marco et al., 1992; Altimira et al., 1999).

**Staphylococci**

Enterotoxins produced by Staphylococcal spp. are causative agents in food poisoning (Ayulo et al., 1994; Khabat et al., 1994; Levine et al., 1996; Tsen et al., 1997) and toxic shock syndrome (Rosene et al., 1982); both conditions have neurological sequelae. From 1977 through 1981, staphylococcal foodborne infections produced the second highest incidence of all reported foodborne illnesses in the United States (Holmberg and Blake, 1984). In 1999, there were over 185,000 estimated cases (Mead et al., 1999). Enterotoxin A (SE-A) produced by S. aureus is pathogenic at a dose of 100 ng and produces in vitro T cell proliferation at a level of 1 pg/ml (Rasooly et al., 1997). Staphylococcal enterotoxins may also stimulate the expression of autoimmune diseases such as multiple sclerosis, diabetes, and AIDS by activating anergic T cells (Micasan and Thibodeau, 1993; Racke et al., 1994). These activated T cells promote inflammation via production of large amounts of cytokines (Steinman, 1993; Johnson et al., 1996) that favor development of autoimmune neurological diseases (Dalakas, 1995). In humans, persistent neurological sequelae have been found 2–12 months after recovery from toxic shock syndrome. The symptoms included difficulty concentrating, headache, recent memory lapses, inability to compute, loss of other higher integrative functions, and electroencephalographic abnormalities (Rosene et al., 1982). Both lethality and cytokine induction by staphylococcal enterotoxins in experimental animals were potentiated by LPS. Serum TNFα, IL-6, and interferon-gamma (IFNγ) levels were increased 5-, 10-, and 15-fold, respectively, by simultaneous SE-A toxin and LPS administration compared to each alone (Stiles et al., 1993).

**Campylobacter**

One of the better documented relations between FBPs and neurological illness occurs in the demyelinating Guillain-Barre syndrome (GBS) that may develop following an infection with C. jejuni (Peterson, 1994; Jacobs et al., 1996). C. jejuni is the leading cause of acute bacterial gastroenteritis in many developing countries and accounts for 3–6% of diarrheal illness (or more than 2 million cases) in the US (Mead et al., 1999). It is a widespread, microaerophilic, Gram-negative rod associated with contaminated water, poultry, and raw milk. In addition to the most common presenting syndrome of abdominal pain and fever, it also has been associated with bacteremia, septic arthritis, septic abortion,
reactive arthritis, Reiter's syndrome, and pancreatitis (Peterson, 1994). One-third of patients with GBS had serological evidence of a recent C. jejuni infection (Jacobs et al., 1996) even though enteric symptoms often were not present (Ropper and Victor, 1998). LPS from C. fetus ss. fetus and C. jejuni adversely affected fetal development in mice (O'Sullivan et al., 1988). C. jejuni has therefore emerged as a risk factor for GBS (Guarino et al., 1998) that is associated with slow recovery and residual disability (Rees et al., 1995). However, even with these data, it is difficult to prove a cause and effect relation since GBS is heterogenous with regard to antecedent infection, immunological profile, clinical symptoms, and response to treatment (Jacobs et al., 1996).

Salmonella

Salmonella infection was recently the most commonly reported foodborne disease in the United States (Hanes et al., 1995) and is now in second place following Campylobacter spp. (Mead et al., 1999). It is most often a self-limited enteric illness (Allen and Wei, 1992); however more severe enteric symptoms are associated with a worse chronic prognosis (Thomson et al., 1995). Reactive arthritis, urethritis, eye inflammation, low back pain, sacroilitis, spondyloarthropathy, and neurotoxicity are possible sequelae (Leirisalo-Repo et al., 1997).

S. typhi causes typhoid fever and it was a common FBP in the United States until 1945. Typhoid fever commonly produced ataxia, tremors (Trevett et al., 1994), and delirium associated with colitis (Nakamura et al., 1990). Non-typhoid salmonellosis is also associated with neurological symptoms in humans (Pagliano-Sassi, 1977) including visual loss (Kwok et al., 1994), focal CNS infection (Fiteni et al., 1995) seizures, coma, cerebral infarct, and death (Arentoft et al., 1993).

In experimental studies, salmonellosis produced blindness in chickens (Dwivedi et al., 1973). Treatment of pregnant ewes with LPS from S. enteritidis caused septic shock in the fetuses and NIES effects characterized by dramatic stimulation of the maternal and fetal HPA axes. Hypoxia and either death or premature birth occurred (Schlafer et al., 1994). Salmonella LPS also produced a sexually dimorphic HPA response in both rats and mice. Treated females had a greater increase in circulating ACTH and corticosterone than males. Gonadectomy enhanced the response of both sexes, while testosterone reversed the effect (Spinedi et al., 1992; Frederic et al., 1993; Shanks et al., 1994; Spinedi et al., 1997; Leon et al., 1998).

Meningitis from Salmonella infection in young children has produced convulsive disorders, neurological coma, and spastic paralytic changes (Olivares-Lopez et al., 1981). Salmonella virchow food poisoning has presented with a primary meningeal inflammation without evidence of actual CNS infection (Norris, 1986). Antibiotic drug use within 30 days of infection increased the risk of salmonellosis by a factor of 4.3 (Pavia et al., 1990), and antibiotic drug resistance for this and other bacteria is continuing to develop in the United States (Lee et al., 1994).

Group A β Hemolytic Streptococci

Group A and group G Streptococci are the well known bacteria that produce "strep-throat" pharyngitis by person–person contact, but foodborne group A streptococci also produces an estimated 50,000 cases of FBPI per year (Stryker et al., 1982; Mead et al., 1999) with a high secondary attack rate in at-risk populations (Bar-Dayan et al., 1996). Both routes produced an upper respiratory tract infection with some differences in clinical manifestations; more severe symptoms are produced by the foodborne route (Bar-Dayan et al., 1997). The incidence of
TABLE III  Chronic diseases and adverse sequelae associated with human pathogens•

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease/sequelae</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Stomach ulcers, cancer, coronary artery disease, autoimmune disorders</td>
<td>(Wisniewski and Peura, 1997; Hunt, 1997; Kuipers, 1997; Peura, 1997; Gasbarrini et al., 1999)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Reactive arthritis</td>
<td>(Rich et al., 1996)</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Juvenile chronic arthritis, neurotoxicity, persistent verbal and memory deficits</td>
<td>(Farrell and Marth, 1991; Burmester, 1993; Benke et al., 1995; Cimmino et al., 1996; Steere, 1997)</td>
</tr>
<tr>
<td><em>Oral bacteria</em></td>
<td>Atherogenesis, stroke</td>
<td>(Loesche, 1994; Beck et al., 1996; Beck and Slade, 1996; Herzberg and Meyer, 1996; Loesche, 1997)</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em>‡</td>
<td>Low birth weight, Cardiovascular disease, early death from any cause</td>
<td>(Loesche, 1997)</td>
</tr>
<tr>
<td></td>
<td>Asthma, chronic obstructive</td>
<td>(Johnston, 1997)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>(Cosentini and Blasi, 1996)</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em>†</td>
<td>Atherosclerosis, stroke, transient ischemic events</td>
<td>(Wimmer et al., 1996; Mehta et al., 1998; Molestina et al., 1998)</td>
</tr>
<tr>
<td></td>
<td>Acute, febrile, aseptic, neurological disorder</td>
<td>(Lind et al., 1979)</td>
</tr>
<tr>
<td></td>
<td>Acute aseptic, meningoencephalitis and cerebellitis with white, matter lesions in cerebellum</td>
<td>(Kosatsu et al., 1998)</td>
</tr>
</tbody>
</table>
| *Borna virus, Leptospira, Cysticercus*, *Influenza virus, Streptococcus* sp. Other childhood CNS pathogens* | Neuropsychiatric disorders of childhood                                           | (Wright et al., 1993; Evans et al., 1997; Rantakallio et al., 1997; Mittleman et al., 1997; Kurlan 1998; Swedo et al., 1998;)

* Cysticercus, Group A Streptococci (Mead et al., 1999) and possibly H. pylori (Vaira et al., 1992; Hopkins et al., 1993; Velazquez and Feirtag, 1999) are known to be transmitted in food.
‡ Acute CNS infections often resolve with few sequelae; the complexity of the NIES may have delayed the growing understanding that chronic CNS infection can be a cause of severe neurological sequelae (Pachner, 1996).
‡‡ Although indirect evidence suggests an association of atherosclerotic disease with pathogens, the nature of this chronic and slowly progressive disease will likely prevent direct confirmation by Koch's postulate (Viniker and Chattopadhyay, 2000).
† A maximum of 10% of patients with M. pneumoniae (a classical respiratory tract pathogen) had neurological syndromes with no evidence of bacterial invasion into the CNS.
enteric symptoms was low despite its transmission in food (Briko et al., 1993).

A number of non-enteric sequelae are associated with post-streptococcal illness. Sydenham's chorea is currently the best recognized example of an immunologically mediated neurodegenerative process deriving from a prior bacterial infection (Beaman et al., 1994). This bacterium is associated with autoimmune attack of the heart (rheumatic fever) and brain. Recent studies also suggest that a spectrum of childhood neurobehavioral disorders including Tourette's syndrome and pediatric autoimmune neuropsychiatric disorders (PANDAS) may be part of the post-streptococcal sequelae (Kurlan, 1998). This syndrome includes obsessive-compulsive disorder, tic disorders, emotional liability, cognitive deficits, and motor hyperactivity (Swedo et al., 1998). It may be due to cross-reactions of autoimmune effectors with structures in the basal ganglia (Giedd et al., 1996).

Prions

Several studies suggest that the gut-brain axis may serve as a route for pathogens such as enteric virus particles (Morrison et al., 1991) and prions (Kimberlin and Walker, 1989; Beeckes and McBride, 2000; Andreolletti et al., 2000) to infect the brain. In the hamster, mouse, and sheep, the active agent in scrapie (abnormal pion protein) appeared to be taken up initially by the Peyer's patches of the gut mucosa following oral exposure. After replication in the gut associated lymphoid tissue, migration through autonomic nerve fibers, known to innervate the GI system, is one possible manner in which prions reach the brain. If prions are transmitted by linked immune and neural pathways, it will be of interest to determine whether inducers of the NIES, such as foodborne endotoxin, influence susceptibility to oral prion infection just as they appear to affect chemical toxicity (Roth et al., 1997).

FACTORS AFFECTING DIAGNOSIS OF FOODBORNE PATHOGEN ASSOCIATED NEUROTOXICITY

Bacteremia

Bacteremia in patients with FBPI, just as in those with NFBPI, leads to a more severe illness and a greater risk of neurotoxic sequelae. Septicemia occurs in about 10% of acute nontyphoid Salmonella gastroenteritis (Novak and Feldman, 1979) and is especially important in young infants (Yang and Chi, 1994). In malnourished children, Listeria annually causes several thousand cases of sepsis and meningitis worldwide (Ho et al., 1986; Khong et al., 1986; Belouni and Rahal, 1992; Bula et al., 1995; Suda et al., 1997). In the mouse, i.v. Listeria invaded the CNS in the early phase of the infection leading to meningoencephalitis that appeared to be highly dependent on the level and duration of sepsis (Berche, 1995). Klebsiella pneumoniae, E. Coli (Sabata et al., 1998), C. perfringens (Lantelme et al., 1995), C. jejuni (Peterson, 1994), and Vibrio vulnificus (Klontz et al., 1988) infections may also be complicated by bacteremia (Moxon et al., 1977; Berkowitz, 1984).

It is generally accepted that bacteremia leads to global production of PICKs in the brain. Subseptie doses of peripheral LPS induce PICKs at the choroid plexus, meninges, and the circumventricular organs (Quan et al., 1999). This recent study begins to address the dose-response issue and may help to quantify the extent of neurological risk that is dependent on the severity of illness and the level of measurable cytokines in the CNS.

Diagnostic Difficulties

Identification of potential neurotoxic sequelae in human FBPI disease may be underestimated for several reasons. A major factor is underreporting of FBPI illness itself (Mead et al., 1999). It is estimated that less than 2% of acute
FBP-mediated gastroenteritis cases are diagnosed and treated (Nelson, 1985; Doyle, 1991; CDC, 1998). This is compounded by the low rate of FBP identification; the CDC estimated that unidentified agents cause 82% of total illnesses, 82% of serious illnesses, and 64% of deaths from foodborne disease (Mead et al., 1999). Special concerns for diagnosis and treatment arise when pathogens produce neurotoxicity either prior to, or in the absence of gastroenteritis. This has been reported for Shigella spp. (Avital et al., 1982; Sandyk and Brennan, 1983; Yuhas et al., 1995), Salmonella enteritidis (Biro et al., 1995), C. jejuni (Ropper and Victor, 1998), and verotoxin producing E. coli O157 strains (Tzipori et al., 1988; Fujii et al., 1994; Tzipori et al., 1995). Diagnosis is also limited by changes in the nature of community foodborne disease outbreaks. When traditional outbreaks were generally acute and highly localized, patients could be more easily identified and evaluated. The new kind of outbreak, even with hundreds of thousands of illnesses, is likely to be low-level and widely distributed; therefore, it is difficult to identify cases and follow them medically (Hennessey et al., 1996; Traux and Hughes, 1996; Trauxe, 1997).

Additional factors contribute to the difficulties in diagnosing neurological disease from FBPIs. These include confusing symptoms (requiring a high level of suspicion and multi-level evaluations), long latency, and relatively low incidence. Causes are often multifactorial with unequal contributions derived from heredity, environment, and nutrition. It is therefore notoriously difficult to establish strict proof of causality between a specific pathogen and a specific human disease (Cassell, 1998). As an example, a serious brain inflammation like mesenchymalencephalitis associated with L. monocytogenes infection may present with nonspecific symptoms. This requires a combination of imaging, clinical, laboratory, and pathologic studies for accurate diagnosis (Soo et al., 1993).

Due to the low prevalence of foodborne neurotoxicity, the sample size within any one jurisdiction is often small; this reduces the statistical power of associations and can lead to a type II error (Gross, 1984). In addition, most existing experimental studies have not taken a system-wide approach to investigate the role of the NIES in FBP disease. The numerous regulatory mediators in this system exhibit pleiotropic, redundant, and bi-directional characteristics. This may require both the temporal and spatial analysis of multiple components in this complex network. Analysis of a limited number of mediators may only confound the interpretation (Licinio, 1997). For these reasons, we suggest the need for rigidly controlled animal studies that can avoid the bias often found in observational data. This experimental work is needed to provide a better understanding of the pathogenesis, evaluate the dose-response characteristics, identify cause-effect relations, and develop strategies for prediction, prevention, and early intervention (Joh, 1997). The diagnostic difficulties may also require careful evaluation for subtle but biologically important neurotoxic sequelae, such as chronic (possibly silent) neurodegenerative or behavioral change (Ozonoff and Longnecker, 1991).

Possibly due to the difficulties in linking infections with the development of chronic sequelae, only recently has evidence suggested the possible role of human pathogens in the development of disorders (see Table III) that were previously considered to result from a non-infectious etiology (Fauci, 1998). Foodborne Salmonella, Shigella, Listeria, Yersina, Campylobacter, Escherichia, Streptococci, and Staphylococci genera (Hamano et al., 1992; 1993; Ephros et al., 1996; Mead et al., 1999), and Cysticercus (Ostrofsky-Zeichner, 1996) may play a role in neurotoxic sequelae. H. pylori (Vaira et al., 1992; Hopkins et al., 1993) has been linked with cardiovascular disease. We speculate that the NIES model of neuroimmunotoxicity will help
evaluate the potential role of FBPIs as unidentified causes of neurological disorders.

Cause and Effect Relations

Epidemiologists are unable to utilize the gold standard, i.e. the prospective, double-blind, placebo controlled, randomized clinical trial, when evaluating the association of neurological effects with FBPIs. Virtually all of the human data linking FBPIs with neurological disease, therefore, come from clinical observations. These include case reports and case-control studies or cohort studies of disease outbreaks and sporadic illnesses. Case-control and cohort studies are not conducted under controlled experimental conditions and therefore may be unable to account for confounding variables (Gross, 1984).

The case-control results, usually with bacteriological or serological confirmation, however, do represent a substantial amount of information that is supported by limited animal studies. Anecdotal information may complement but cannot substitute for formal research evidence (Enkin and Jadad, 1998). The information reviewed here supports a potential link between neurological manifestations and FBPI disease; however, the observed associations from these kinds of studies cannot be used to prove a cause and effect relation. They do indicate that FBPI, under some poorly understood conditions, may be a risk factor for autoimmune and neurological disorders and may therefore have sufficient public health implications to warrant specific study. Although the risk of neurological manifestations to any single individual appears to be low, the high incidence of enteric FBPI produces a large group that is at risk. Repeated exposure may also be a key factor in the development of neurotoxicity; this has been shown experimentally for L. monocytogenes (Altimira et al., 1999). This may be compounded by the long-term manifestations of some neuroinflammatory processes such as that reported for hypoxia/ischemic (Bona et al., 1999). Neurological effects are often associated with genetic, life-style, age, or health related predispositions, and the subpopulation with these risk factors is growing (Mead et al., 1999). Neurological manifestations can also be severe, and the prognosis is often poor even with prompt diagnosis and treatment; therefore, prevention is a better option than treatment.

POTENTIAL IMPLICATIONS OF IMMUNE INDUCED NIES EFFECTS FOR FETAL DEVELOPMENT AND NEURODEGENERATION

Evidence supports the suggestion that FBPIs, as activators of the NIES, may have a particularly adverse impact on both the beginning and ending phases of life, i.e. the developing brain and the aging brain.

Fetal Brain Development

As early as 1919 it was observed that severe systemic illness in pregnant animals and humans could cause abortion, perinatal mortality, and fetal resorption (Bland, 1919; Graeff et al., 1973; Coid et al., 1976 and 1978). Bacterial LPS, possibly by its cytokine effects, is a potent teratogen in experimental animals (Lanning et al., 1983; Au-Jensen and Heron, 1987; Tartakovsky and Ben-Yair, 1991; Glockner et al., 1992; Collins et al., 1994). It is associated with altered development of embryos and decreased pregnancy rates in humans (Randall and Gantt, 1990), adverse pregnancy outcomes (Romero et al., 1989), and neurological and behavioral damage in fetally exposed mice (Haesaert and Ornoy, 1986). Ornoy and Altshuler (1976) reported that E. coli LPS given to pregnant rats produced fetal anomalies and a 10-fold greater incidence of fetal CNS damage.
Few studies have investigated the developmental effects of mild or subclinical maternal illness (Reul et al., 1994). Subclinical infections are able to activate the APR; this is the primary justification for low-level antibiotic treatment of farm animals (Johnson, 1997). Appropriate production of cytokines is especially critical for processes that regulate normal fetal brain development. The brain has the most stringent requirements of all tissues for specific cellular, cytokine, and chemokine interactions (Rezaie and Male, 1999). At physiological levels they are essential for normal cell development, especially in the brain (Gadient and Otten, 1994) and the heart. At elevated levels cytokines are associated with neurological disorders (Merrill, 1992; Zhao and Schwartz, 1998). Cytokines are potent and critical physiological mediators of early fetal development (Tartakovsky and Ben-Yair, 1991). They have primary regulatory functions in neural cell migration, proliferation, differentiation, cellular maturation, and inflammatory responses of both the periphery and CNS (Mehler and Kessler, 1997). Potential toxicogenic mechanisms include increased sensitivity of developing neurons to glutamate toxicity (Conroy and Gruol, 1997), induced iNOS activity (Sato et al., 1995; Chao et al., 1996; Ding et al., 1997), overproduction of reactive oxygen species (ROS) (Chao et al., 1995), elevated prostaglandin levels (Bauer et al., 1997), altered BBB permeability (Banks et al., 1999), induced infiltration of activated lymphocytes (Calvo et al., 1996; McManus et al., 1998; Weiss et al., 1999), and activated resident brain microglia (Delgado et al., 1998). Over-production of cytokines has also been shown to adversely affect implantation (Sharkey, 1998), trophoblast proliferation, embryo development, and fetal survival (Shaarawy and Nagui, 1997) with persistent or permanent effects on the reproductive axis and immune system (Hall et al., 1992). In humans, elevated levels of PICks in amniotic fluid are associated with increased risk (four- to sixfold) of decreased birth weight, decreased age at birth, white matter lesions, cerebral palsy, and early death (Yoon et al., 1997). Low birth weight, as a marker for adverse intrauterine exposure, is associated with increased human neuroendocrine dysfunction, perinatal morbidity, mortality (Mantzoros et al., 1997), and several chronic adult diseases (Curhan et al., 1996). Infectious diseases may also be linked to mental illness (McSweeney, 1998), and in rats, altered NIES activity affects the sexual dimorphism of brain structures (Henry et al., 1996). The degree to which FBPIs may cause similar adverse effects in humans under clinically relevant conditions has not been studied. However, the similarities from both direct infection and modification of the maternal/fetal NIES by NFBPs and FBPs leads to speculation that similar adverse effects may occur if the fetus is exposed to sufficiently high levels of inflammatory mediators at critical periods of development.

Foodborne bacteria clearly initiate inflammatory processes that involve immune cells and nerve cells in animals and humans (Fiser et al., 1973; Wilcock and Olander, 1977; Silva et al., 1980; Stroud and Roelke, 1980; Heyes et al., 1988; Hou et al., 1989; Dunn, 1992; Breder et al., 1994; Huang, 1996; Lloret et al., 1996; Lu et al., 1997). The structures of these nerve cells are known to change during and after acute inflammation (Theodorou et al., 1996). Structural changes that occur during sensitive periods of nervous system development, in response to NIES mediators, may become permanent, and this response may help to explain a variety of deficits in immune, behavioral, and cognitive function of both young and mature organisms including humans (Reul, 1994; Ember, 1998). Therefore, as a consequence of this integrated peripheral and central NIES, neurotoxicity is suggested as a possible sequela of FBPI.

Chronic Neurodegenerative Disease

Although the etiological basis of chronic neurodegenerative diseases is unresolved,
animal and human studies strongly suggest that chronic neuroinflammation significantly contributes to the pathogenesis of AD (Griffin et al., 1989; Bauer et al., 1991; McGeer and McGeer, 1997; Akiyama et al., 2000), AIDS dementia (Benveniste et al., 1995; Vitkovic et al., 1995; Rafalowska, 1998), Parkinson's disease, MS, and prion disorders (Forster and Lal, 1990; Aisen and Davis, 1994; Singh, 1994; Campbell et al., 1994; Koka et al., 1995; Brugg et al., 1995; Singh, 1996; Campbell et al., 1997; Popovic et al., 1998; Nath et al., 1999; Gahtan and Overmier, 1999; Kim et al., 2000). As a component of brain inflammation, reactive gliosis has been found to occur in virtually all neurological disorders. A NIES mechanism has been postulated for PD (Kuhn et al., 1995). There is no evidence for a link between FBPs and AD; however, FBPs can activate the central NIES and could theoretically contribute to neuroinflammatory processes. AD lesions co-localize with immune components in the brain. These include major histocompatibility complex II (MHCII) antigens, receptors for complement, and T lymphocytes that have infiltrated into the CNS (McGeer et al., 1994). Abundant immunologically active microglia associate with senile plaques; these are one of the classic pathological hallmarks of AD. Microglia can be stimulated by β amyloid peptide, in vitro, to produce nitric oxide that is known to be cytotoxic via an oxidative mechanism when present in excess of physiological levels (Lii et al., 1996). Alzheimer’s brains contained elevated levels of IL-1, IL-6, S-100, and α-2-macroglobulin; these are indicative of an APR (Griffin et al., 1989; Bauer et al., 1991). Most recently, studies of CNS inflammation induced by LPS produced AD-like neurodegenerative lesions in a rat model. This provided experimental evidence that supports the observations seen in human patients (Hauss-Wegrzyniak et al., 1998a,b; 1999a,b). We suggest that experimental attention should be given to the possibility that activation of the NIES by any or all of the primary homeostatic stressors mentioned in this paper could contribute to overproduction of inflammatory and immune mediators. In this manner FBPIs and other stressors may contribute to the promotion, if not the initiation, of neurodegenerative diseases in susceptible people, i.e. those with certain genetic mutations (Marx, 1998).

CONCLUSION

There is extensive epidemiological and experimental evidence to suggest that neurotoxicity can be an important consequence of some bacterial foodborne illnesses. Many steps are needed, however, to transverse from this hypothesis to an understanding of the possible relationships between the non-enteric manifestations of FBPI and the pathophysiology of the NIES. This severely limits the conclusions to be drawn from the existing data. It is not possible at this time to unambiguously determine the extent and the severity of all neurological manifestations caused by foodborne disease in the human population. There are too many unidentified agents of foodborne disease, too many unrecognized and unreported cases of foodborne and autoimmune disease, and too few controlled clinical and experimental research results with foodborne transmission. Speculation, based on physiological and pathophysiological mechanisms that have been identified, indicates that at least some microbes have the potential to make significant neurological contributions to the disease burden from foodborne transmission. This speculation is consistent with the growing number of suggested links between pathogens and chronic inflammatory disorders that had been previously attributed to a non-infectious etiology. Assessing the possibility that neuroimmunotoxicological sequelae may be causally related to FBPIs will require carefully controlled experimental studies in animal models. Biomarkers identified in animal studies may then be useful for detecting potential neurotoxic effects.
in humans. The effectiveness of these efforts can be maximized with a better understanding of the full spectrum of health effects produced by FBPs.

**Acknowledgements**

The authors gratefully acknowledge the efforts of Jan Johannessen, Darcy Hanes, Maryann Principato, Sue Ann Assimon, and especially Carolyn Jeletic for reviewing the manuscript and providing many helpful suggestions and thoughtful comments.

**References**


Alcocer-Varela, J., Aleman-Hoey, D. and Alarcon-Segovia, D. (1992) "Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local T cell activation markers", Lupus 1, 111–117.


cytokines in the central nervous system", Molecular Psychiatry 2, 125–129.


Eckmann, L., Frier, J. and Kagnoff, M.F. (1996) "Genetically resistant (Ityr) and susceptible (Ity+) congenic mouse strains show similar cytokine responses following infection with *Salmonella dublin*," *Journal of Pathology* 156, 2894–2900.


immune responses”, *Advances in Pharmacology* 42, 583–587.


genic mice expressing interleukin-6 in the brain", Proceedings of the National Academy of Sciences, USA 94, 1500–1505.


Kanoh, Y. and Ohtani, H. (1997) "Levels of interleukin-6, CRP and alpha 2 macroglobulin in cerebrospinal fluid (CSF) and serum as indicator of blood-CSF barrier damage", Biochemistry and Molecular Biology International 43, 269–278.


properties, and epitope presentation by multiple DR alleles". *Immunology* 164, 1529–1537.


Urbanovitch, P.P. (1975) "Listeriosis in agricultural animals (problems of the epizootiology, pathological anatomy and pathogenesis)", *Arkhiv Patologii* 37, 88–90.


