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Gastrointestinal Tract Abnormalities in Autism, Inflammatory Bowel Disease and Many Other Clinical Entities May Be Due To *T. Gondii* infection

Joseph Prandota*

Department of Social Pediatrics, Faculty of Health Sciences, University School of Medicine, Wroclaw, Poland

Abstract

Several studies demonstrated various gastrointestinal tract (GT) disturbances in children with autism, including active/chronic inflammation of the GT and development of ileo-colonic lymphoid nodular hyperplasia. Emerging evidence now indicates that autism and many congenital and acquired GT abnormalities and their intensity, including Hirschsprung's disease, may be due to prenatal and/or postnatal damage of the enteric nervous system associated mainly with peroral infection with *T. gondii,* its genotype, virulence/antigenicity, number of oocysts/sporozoites/ bradyzoites/ tachyzoites, part of GT tract infected, and the host innate prenatal and postnatal immunity. Maternal and fetal microchimerisms and physiologic swallowing of amniotic fluid by the fetus probably play an important role in early dissemination of the parasite as a Trojan horse and development of these abnormalities. Mast cells are vital in sustaining gut inflammation because they are infected with the parasite, secrete chemotactic factors able to recruite neutrophils, macrophages and lymphocytes when the parasite reaches the lamina propria, and finally reduce survival and cause death of myenteric neurons. Lactoferrin, a component of the breast milk, plays an important role in the host defense against *T. gondii* infection and dissemination, therefore it should be included into therapeutic assets used for treatment of GI tract disturbances caused by the parasite both in young and adult patients.

Keywords: *T. gondii* infection, Autism spectrum disorders, Gastrointestinal tract pathology, Ileocolonic nodular hyperplasia, Enteric nervous system, Myenteric neurons, Inflammatory bowel disease, Necrotizing enterocolitis, Lactoferrin.

Gastrointestinal Disturbances in Patients with Autism Spectrum Disorders (ASD)

Autistic children frequently develop several gastrointestinal (GI) symptoms including pyrosis (heart burn), regurgitations, excessive salivation, vomiting, constipation, fecal impaction, chronic diarrhea, abdominal discomfort and pain, gaseousness, and distention [1-11]. Recent review by Buie et al. [12] based on 11 studies reported that the prevalence of GI symptoms, such as constipation, diarrhea, bloating, belching, abdominal pain, reflux, vomiting and flatulence, in children with ASD range widely from 9 to 91%, averaging 44%.

Horvath et al. [8] found reflux esophagitis in 60% of an autistic sample, duodenal inflammation in 67%, low carbohydrate digesting enzymes (lactase) in 58%, and abnormal pancreatic response to secretin in 75% of the individuals. Gonzales and his group [10,11] reported that 100% of their 45 ASD children had chronic inflammation and lymphoid nodular hyperplasia (LNH) in the colon compared with 66.66% of the 57 developmentally normal controls, reflecting a high background rate of infectious enterocolitis in Venezuelan young patients. Gastrointestinal endoscopy showed that these children had also reflux esophagitis (88.88% vs. 48.71%, $P < 0.001$) and eosinophilic esophagitis, nonspecific gastritis (55%) with micro- and macronodularity in the gastric body and antrum, nonspecific inflammation of the small intestine (37%), including chronic active duodenitis with LNH, and intestinal villus alterations [10,11].

Ingested foreign antigens enter the gut mucosa through the microfold (M) cells in the Peyer's patches or through damaged epithelium, and are taken up by antigen presenting cells, most likely dendritic cells (DCs). DCs move to Peyer's patches and mesenteric lymph nodes, where they interact with naive lymphocytes and initiate adaptive immune response that result in activation of T and B memory cells, and proliferative response and cytokine release, finally leading to GI inflammation [13,14]. Enhanced density of dendritic T cells was observed in the colon of ASD children with GI tract disturbances compared to controls [6]. (Nb. it should be noted that the host-endoplasmic reticulum-parasitophorus vacuole interaction provides a route of entry for antigen cross-presentation in *T. gondii*-infected DCs [15]). Chronic inflammation in the gut can damage the epithelial cell layer, and D'Eufemia et al. [5] showed abnormally increased intestinal permeability in 9 out of 21 analyzed autistics (43%) but in none of the 40 controls [8]. de Magistris et al. [16] also reported abnormally high intestinal permeability in their sample of patients with ASD and their first-degree relatives compared with controls (36.7% and 21.2% vs. 4.8%, respectively).

In several autistic patients Ashwood and Wakefield [9] reported increased levels of proinflammatory cytokines TNF-α and IFN-γ, and reduced levels of regulatory IL-10 cytokine in peripheral blood and mucosal lymphocytes. PBMCs from ASD children stimulated with LPS produced higher levels of TNF-α than controls regardless of dietary interventions [17]. In PBMCs from ASD children with positive GI symptoms, Jyonouchi et al. [17] found a positive association between TNF-α levels produced by LPS and those with cow's milk protein. In the unrestricted diet group, GI positive ASD PBMCs produced higher IL-12 than controls and less IL-10 than GI negative ASD PBMCs with LPS. Furthermore, some studies suggested an association between gut

***Corresponding author:** Joseph Prandota, Department of Social Pediatrics, Faculty of Health Sciences, University School of Medicine, Wroclaw, Poland, E-mail: jozef.prandota@am.wroc.pl

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inflammation and NO-dependent oxidative injury [18]. Recently, it was shown that NO metabolite S-nitrosogluthatione, a novel potent inducer of intestinal barrier function in human colon [19] is secreted by enteric glia cells [20]. It is possible that the increased NO levels in autism may also be responsible for the gastrointestinal abnormalities observed in some individuals with autism [21]. This is in line with the finding that patients with autism have increased NO levels and glutathione peroxidase activity in red blood cells ($P < 0.0001$) [22], and the incubation of sodium nitroprusside (SNP) with Caco-2BBe intestinal epithelial monolayers resulted in time-, and concentration-dependent decreases in transepithelial resistance [23]. Electron microscopy study revealed that SNP widened tight junctions. NO reduced cellular ATP levels and reversibly increased permeability of tight junctions in cultured Caco-2Bbe cells [23]. Moreover, Unno et al. [24] demonstrated that incubation of cultured human intestinal epithelial monolayers Caco-2BBe cells with IFN-γ resulted in upregulation of NO biosynthesis and a marked increase in permeability of intestinal epithelial monolayers.

Wakefield et al. [3] reported prominent ileal LNH and ileocolitis called "autistic enterocolitis", in an uncontrolled study of 12 autistic children. Mucosal lesions manifested as chronic ileocolonic LNH were characterized by lymphocyte infiltration, complement deposition, and cytokine production. This inflammatory condition was associated with eosinophilic infiltrate lesions on the intestinal wall, in the upper gastrointestinal tract [18]. It was found [25] that the prevalence of LNH was significantly greater in ASD children compared with controls in the ileum (90 vs 30%, $P < 0.0001$) and colon (59 vs 23%, $P = 0003$). The severity of ileal LNH was markedly greater in ASD children compared with controls, with moderate to severe ileal LNH present in ASD children (68 vs15%, $P < 0.0001$). Severe ileal LNH was associated with co-existent colonic LNH. The presence and severity of ileal LNH was not influenced by either diet or age at colonoscopy and hyperplastic lymphoid follicles were significantly more prevalent in the ileum of ASD children compared with controls (61 vs 9%, $P < 0.0001$). The authors suggested that ileo-colonic LNH was a characteristic pathological finding in children with ASD and gastrointestinal symptoms, associated with mucosal inflammation [25]. It is interesting that Kokkonen & Karttunen [26] analyzing a consecutive series of 140 children with persistent and severe gastrointestinal symptoms revealed that among the whole study group 46 subjects also had LNH, and 26% could be defined as having food allergy. This expression of mucosal immune response on the mucosa of the colon or terminal ileum, the authors considered as common but not an innocent bystander, which may be related to food allergy but also to other immunologically active disease states [26].

In ASD children, histopathologic examination showed lymphocytic colitis, although less severe than in classical inflammatory bowel disease (IBD) [3]. Basement membrane thickness and mucosa gamma cell density were significantly increased as compared with controls, inlcuding IBD. Intraepithelial lymphocyte numbers and CD3, plasma cell, and CD8 cell counts were also markedly increased [3]. The authors concluded that IBD was a lymphocytic enterocolitis in ASD, probably skewed in the T_H2 dominant direction [3]. Torrente et al. [7] also analyzed duodenal biopsies in 25 children with regressive autism and found increased number of enterocytes and Paneth cells, duodenal lining demonstrated increased lymphocytic proliferation, crypt cell proliferations, and more T cells. Also, the increased IgG deposition on the epithelial cell surfaces accompanied by complement C1q have been found [7]. The authors believed that this pattern was characteristic for autism. The serum levels of complement C3/C4 proteins and α1-antichymotrypsin (both these biomarkers are positive acute phase proteins in blood that facilitate immunological and inflammatory responses) were found to be markedly higher in children with autism than in their unaffected siblings [21,27,28]. Duodenal biopsies performed by Kushak et al. [29] showed that frequency of lactase deficiency was 58% in autistic children ≤ 5 yrs old and 65% in older patients. However, only 6% of autistic patients had intestinal inflammation, and it was suggested that lactase deficiency may contribute to abdominal discomfort, pain and observed abnormalities in behavior of those children [29].

The presence of LNH has been found also in normally developing children with autism and gastrointestinal symptoms [6]. Histologic studies demonstrated lymphocytic colitis less severe than in IBD. Basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of subjects with Crohn's disease, IBD, ulcerative colitis (UC), and children with LNH. $CD8^+$ density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups. CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial glycosaminoglycans were disrupted, but the epithelium was HLA-DR (-), suggesting a predominantly T_H2 response [30]. It is interesting that glucosamine, a naturally-occurring amino monosaccharide, has been shown to exhibit an antiinflammatory action by inhibiting neutrophil functions. Moreover, this monosaccharide suppressed IL-8 production and ICAM-1 expression by TNF-α-activated human colonic epithelial cell line HT-29 cells [30], as well as it inhibited TNF-α-induced phosphorylation of p38MAPK and NF-κB p65, and nuclear translocation of NF-B in intestinal epithelial cells, which may confirm its antiinflammatory activity [30]. Wang et al. [31] found that IL-6 receptors are present in intestine epithelia in a polarized fashion, and basolateral IL-6 and, to a lesser extent, apical IL-6 induced activation of the NF-κB pathway. IL-6 induced polarized expression of ICAM-1, an adhesion molecule shown

Biomarker of neuroinflammation	References
Activation of microglia and astroglia	[36]
Brain IL-6	[36]
Brain MCP-1	[36]
Brain GFAP[a]	[37]
Cerebrospinal fluid GFAP	[38]
GM-CSF ↑	[39[b]; 40[c]]
Serum IFN-γ	[34]
TNF-α ↑	[41, 42]
TGF-β	[43]
IL-1β ↑	[36]
IL-10 ↓	[42]
IL-6 ↑	[36, 41]
IL-8 ↑	**[39]**
IL-4 ↑	[44]
IL-5 ↑	[44]
IL-12 ↑	[34]
IL-13 ↑	[44]
NO ↑	[45, 46]

GFAP: Glial Fibrillary Acidic Protein; MCP-1: Macrophage Chemoattractant Protein-1. GM-CSF: Granulocyte, Monocyte-Colony Stimulating Factor [a]It should be noted that proinflammatory cytokines (IL-1β, TNF-α) and LPS increased GFAP expression also in enteric glia [47], and the expression of GFAP and glial-derived neurotrophic factor (GDNF) in the mucosal plexus was highly increased in the inflamed colon of patients with UC and CD [20]. [b]It was a trend showing higher plasma GM-CSF in children with ASD compared with typically developing and developmental delay patients. [c]GM-CSF was markedly increased in the brain of autistic patients.

Table 1: Elevated biomarkers of neuroinflammation in autism (acc. to Rossignol [35]; with own modification).

to be important in the neutrophil-epithelial interactions in IBD. ICAM-1 induction by IL-6 required activation of NF-κB. They demonstrated that overexpression of SOCS-3, a protein known to inhibit STAT activation in response to IL-6, down-regulated IL-6-induced NF-κB activation and ICAM-1 expression [31]. These are important informations because patients with ASD have systemic manifestions of the immune deregulation/chronic inflammatory condition with elevated levels of several proinflammatory cytokines, including IFN-γ [32], TNF-α [33], IL-6, IL-8, IL-12 [34], NO and other biomarkers (Table 1). An ongoing relevant inflammatory response in children with autism has been suggested by the elevated macrophage product neopterin found in these individuals [48]. Otherwise, it must be noted that astrocytes secretion of IL-1 and IL-6 upon infection was triggered by *T. gondii* bradyzoites and tachyzoites in a time-, and dose-dependent manner [49,50]. In addition, IL-6 may enhance *T. gondii* intracellular multiplication also in a dose-dependent manner [51,52] therefore these activities may drive local and systemic inflammatory reactions. Moreover, inhibited production of antiinflammatory cytokines, such as IL-10 [42] and TGF-β [43] found in children with autism suggested also a deficiency of natural feedback inhibitor mechanisms, albeit it must be emphasized that TGF-β is a potent deactivator of PMN and macrophages since it suppresses the production of ROS, RNI and IL-1, as well as impair expression of L-selectin on PMN known to be essential for PMN recruitment [53], and increases *T. gondii* replication also significantly enhancing TGF-β production [54].

Finally, Medical Research Council [55] suggested that LNH could also be a secondary phenomenon, related to infections or infestations. The histological appearances of the ileal biopsies commonly included reactive follicular hyperplasia, marked expansion of lymphoid tissue, and acute cryptitis; ileitis, eosinophil infiltration and an increase in intraepithelial lymphocytes (IELs) were unusual [56]. In the colon, biopsies showed appearances that were similar to, but less severe than those seen in children with established ulcerative colitis, being perhaps more reminiscent of the features of lymphocytic colitis, as seen in adults [57]. It is of interest, given the proposed association of autism with gluten intolerance, that colonic inflammation has been also described in adults with celiac disease [56,58].

Morphometric Abnormalities of the Enteric Nervous System (ENS) in Experimental Animals Caused by *T. Gondii* Infection may be also At Least in Part Responsible for Development of Gastrointestinal Tract Dysfunction Reported in Patients with Autism and Individuals with IBD

Development of the ENS

The ENS is an independently acting nerve network within the walls of the gastrointestinal tract that controls secretion, motility, blood flow, uptake of nutrients, immunological and inflammatory processes in the gut [59]. Two main cell populations are represented in the ENS, enteric glial cells (EGCs) and neurons, the former being up to 4-fold more abundant than neurons [60,61]. Glial cells are found encapsulating neuronal cell bodies within the enteric ganglia and also surrounding the neurons that project from this plexi to innervate the intestinal mucosa and submucosa [62]. In humans, the ENS is subdivided into several plexuses (subserous, longitudinal muscle, myenteric, circular muscle, deep muscle, muscularis mucosae, and mucosal) [63]. Ganglionated plexuses are present in the submucosa (Meissner's and Henle's plexuses) and in the septum between the circular and longitudinal layers of the muscularis propria (Auerbach's plexus) [64]. EGCs are small cells with a "star-like" appearance containing intracellular arrays of 10 nm filaments made up of glial fibrillary acid protein (GFAP) [65,66]. Most EGCs are found within the ganglia, and are also present in the interconnecting nerve strands of the ganglionated and in all non-ganglionated plexuses [67,68]. In the ganglia, EGCs are very tightly packed around neurons [69,70]. The ENS has many interneurons and intrinsic microcircuits [71]. The ultrastructure of the ENS is different from those of sympathetic or parasympathetic ganglia, enteric neurons are supported by glia rather than by Schwann cells, enteric ganglia lack internal collagen, and the ENS resembles the CNS more than it resembles other regions of the peripheral nervous system [72-74].

The ENS comprises the neurones and glia that are found in the wall of the gastrointestinal tract [75-79]. Its ganglia contain primary afferent neurones, interneurones and motor neurones, i.e. the neural components necessary for complex reflex circuitry [71,75,76]. The gastrointestinal tract is also home to the largest component of the immune system in the body, which serves to defend the host from viral, bacterial, or parasitic invasion, and to limit the consequences of the antigenic stimulus caused by the digestion of food. The submucosal and myenteric plexuses of the ENS contain a large number of neurones, but enteric neurones are outnumbered by enteric glia [79,80]. Glial cells in the ENS appear to be very similar in origin, gross morphology and ultrastructure to astrocytes of the CNS and bear similar relationships with neuronal cell bodies and processes to peripheral Schwann cells [60]. Enteric glia are connected to one another and to enteric neurones via gap junctions, and their processes ensheat enteric neurones and can project to blood vessels and the mucosa [60,81]. Enteric glial cells (but not neurones) contain L-arginine immunoreactivity, suggesting that that NO precursor is supplied to enteric neurones by glial cells [82]. In addition to enteric neurons, enteric glia express the GABA reuptake transporter GAT-2, which suggests the participation of enteric glia in the removal of released neurotransmitters from the synaptic cleft [83].

Neuronal loss associated with aging

Studies in rats showed a correlation between small intestine length with body weight [84]. On the other hand, Schäfer et al. [85] believed that the intestinal length and muscular layer thickness were related to the development of the intrinsic innervation, and the increase in these parameters would provoke changes in neuronal density. Recently, Marese et al. [86] suggested that both these observations are correct, emphasizing the importance of the relation of intestinal length to neuronal density with more advanced age (Table 2). Investigations in animal models showed striking neuroplasticity in the ENS associated with aging [86-88]. A linear decrease in neurons number with age in all small intestine segments, being the presented in duodenum up to 30% [86,88] (Table 3). A probable cause of this reduction was attributed

Animal age (days)	Body weight (gm)	Length of small intestine (cm)	Thickness of the external muscular tunica (μm)
21	49.7 ± 2.07 e	61.9 ± 6.93 c	101.9 ± 4.87 a
60	245.5 ± 18.91 d	114.6 ± 10.21 a	109.1 ± 6.96 a
90	389.2 ± 26.25 c	118.9 ± 11.29 a	99.8 ± 34.22 a
210	447.0 ± 45.82 a,b	121.2 ± 6.12 a	86.3 ± 21.43 a
345	463.7 ± 25.38 b	103.3 ± 18.84 b	118.0 ± 30.90 a
428	521.1 ± 65.80 a	94.3 ± 16.17 b	119.3 ± 21.06 a

The results are expressed as means ± SD. Means followed by letters in the same column indicate statistically significant differences (Tuckey test, P < 0.05).

Table 2: Body weight, length of small intestine and thickness of the external muscle tunica of the duodenum of rats of different ages (acc. to Marese et al. [86]; with own modification).

Animal age	Giemsa		Myosin-V	
(days)	Mean no. of neurons (per 14.832 mm²)	Neuronal density (per cm²)	Mean no. of neurons (per 14.832 mm²)	Neuronal density (per cm²)
21	13250 ± 1362 a*	89 335	8805 ± 587.2 a	59 364
60	7092 ± 1069 b*	47 814	4537 ± 223.2 b	30 291
90	6064 ± 931.5 b*	40 885	4303 ± 220.4 b	29 010
210	4474 ± 341.2 c*	30 164	3359 ± 288 c	22 646
345	3418 ± 91.2 c*	23 046	2447 ± 96.2 d	16 499
428	1935 ± 173.3 d*	13 047	1526 ±115.4 c	10 287

The results are expressed as mean ± SD. Means followed by small letters in the same column indicate statistically significant differences (Tuckey test, $P < 0.05$). Means followed by asterik in the same line indicate marked differences (Student's *t* test, $P < 0.05$). It must be noted that the Giemsa technique represent methylene blue affinity for acidic cell structures, the rough endoplasmic reticulum and free ribosomes, while the Myosin-V technique is restricted to the neurons cytoplasm, including cellular bodies and nerve fibers, being a marker for myenteric neurons [86].

Table 3: Neuronal quantification by the non-histochemical Giemsa and the Myosin-V immunohistochemical techniques (n = 10) in an area of 14.832 mm² of the duodenum of rats, and values converted into cm² (acc. to Marese et al. [86]; with own modification).

to the reduction in the integrity of the extrinsic vagal innervation, which may make the intrinsic network more susceptible to the effects of the advance of age, and approximately 20% of the myenteric neurons of the duodenum have afferent vagal innervation [86]. Neurons number reduction of the ENS related to age were also observed in the gastrointestinal tract of humans [89,90]. Moreover, some neurons can be more susceptible than others [91], and this may be related to the increase in ROS production [92]. It appeared that positive NADPH-diaphorase neurons, which express NO activity (nitrergic neurons) are less vulnerable to the process of aging than cholinergic neurons [93-95]. Phillips et al. [94] showed that myenteric neurons in the large intestine of rats were significantly larger at 24 months and numerous NADPH-diaphorase positive axons were swollen. In younger animals (21 and 60 days old), Marese et al. [86] demonstrated a predominance of neurons with a smaller area (0-200 μm²), while neurons with a larger area of the cellular profile (200-300 μm²) predominated in animals of higher age groups. These changes probably were responsible for maintenance of ganglionic organization in all the age groups possibly because the larger neurons have a higher capacity of synthesis (reflected by Giemsa technique) and transport (Myosin-V) [86] (Table 4).

Damage of enteric glia caused by peroral prenatal infection with T. gondii may be, at least in part, responsible for development of necrotizing enterocolitis in young infants

Hirschsprung's disease is the most visible congenital birth defect of the ENS, in which ganglia are totally absent from variable lengths of the terminal bowel [96]. It must be noted that the ENS is responsible for the integrative control of behavior [97,98], and vagus nerve stimulation can be employed to affect epilepsy [99,100], treat depression [101,102], and even to improve learning and memory [103]. Serotonin may be a late acting growth factor promoting the development of subsets of enteric neurons and muscle/interstitial cells of Cajal (ICCs), and enteric serotonergic neurons are an example of neuron that might well cause a sublethal disorder of intestinal motility when they develop abnormally [104].

Schreiner et al. [105] suggested that it would be interested to investigate wheather oral infection with *T. gondii* is associated with IBD in humans. Until now, a slightly but significantly higher seropositivity rate based on Sabin-Feldman dye test results has already been observed in a small cohort of patients with Crohn's disease over age 40 in Israel [106].

An important role for EGCs in gastrointestinal tract inflammation may be supported by the studies performed in two transgenic mouse models in which the ablation of enteric glia led to fulminant and ultimately fatal small and large intestinal inflammation that was unrelated to bacterial overgrowth [107,108]. One cannot therefore exclude that an exaggerated inflammatory response [109-112] mounted abnormally by the immature intestinal cells of the premature infants to gastrointestinal injury and caused by prenatal oral *T. gondii* infection sustained in the neonatal period resulted in development of necrotizing enterocolitis. Abnormal bacterial colonization, genetic predisposition [113-115], and various milk formulas [116] may be important contributing factors.

Glia in the CNS react to inflammatory insults with proliferation, increased cytokine secretion, and expression of GFAP, a phenomenon known as reactive gliosis [79]. The expression of GFAP has been reported to be higher in enteric cells compared with CNS glia [117]. In the CNS, proinflammatory cytokines, such as IL-1β and TNF-α have been shown to elicit astrocyte proliferation [118-120], whereas the anti-inflammatory cytokine IL-10 has been found to inhibit astroglial reactivity in vivo [121-123]. The proliferation rate of enteric glia also can be modulated by cytokines, for example IL-1β significantly and dose-dependently suppressed EGCs proliferation, while IL-10 had a biphasic effect, suppressing cell proliferation at lower concentrations and augmenting it at higher concentrations [124]. EGCs may act as "receptors" for cytokines and they themselves produce IL-6 and IL-1β [125,126], and express iNOS and L-arginine, the machinery for the time-delayed and micromolar release of NO [85,127]. Stimulation with TNF-α also involved in intestinal inflammation, did not affect glial IL-6 mRNA expression, while IL-1β stimulated IL-6 mRNA and protein synthesis in a time-, and concentration-dependent fashion [125].

It must be noted that children with ASD have evidence of neuroinflammation [36,37,128] and marked activation of microglia and astroglia with elevation of IL-6 and macrophage chemoattractant protein-1 (MCP-1) were found in autistic brain samples and cerebrospinal fluid [36]. In addition, some autistic children have increased GFAP in brain samples and CSF [37,38] (Table 1). It should be noted that studies of Matowicka-Karna et al. [129] performed in women with peripheral lymphadenopathy due to acute infection with *T. gondii* (IgM index > 0.7, specific anti-*T. gondii* IgG titer exceeded 300 IU/ml, low avidity) also showed highly significant increase of serum IL-5, IL-6, and IL-10, while TNF-α level was not changed. All these findings may at least in part suggest that there was a link between oral infection with *T. gondii* and the development of ileo-colonic LNH in children with ASD [25].

Abnormalities of the ENS reported in IBD

There is increasing evidence implicating enteric nerves in the

Animal age (days)	Giemsa	Myosin-V
21	142.9 ± 6.37 c	151.3 ± 15.87 c,A
60	219.0 ± 9.23 b	225.6 ± 19.32 b,A
90	247.3 ± 19.16 a,b	244.5 ± 17.67 b,A
210	232.1 ± 14.61 a,b	261.3 ± 25.11 a,b,A
345	237.6 ± 20.25 a,b	238.3 ± 21.89 b,A
428	254.0 ± 21.14 a	295.3 ± 37.87 a,A

The results are expressed as means ± SD. Means followed by small letters in the same column indicate statistically significant differences (Tuckey test, $P < 0.05$). Means followed by capital letters in the same line also denote marked differences (Student's *t* test, $P < 0.05$).

Table 4: Area of the myenteric neuronal cell body profile (m²) estimated by Giemsa and Myosin-V techniques (n = 10) (acc. to Marese et al. [86]; with own modification)

Parameters	Crohn's disease	Ulcerative colitis	Non specific colitis normal/ controls	References
Routine microscopy (H&E) - TEM				
Nerve fibers				
Hypertrophy (mucosa/ submucosa)	+++	–	–	[139-145]
Hyperplasia	++	+	–	[143,145-148]
Axonal damage	++	+	+	[148-154]
Neuronal cell bodies				
Normal				[155]
Hypertrophy	++	+	–	[155]
Hyperplasia	++	+	–	[141-145,149,156-158]
Damage	+	+	–	[146,153,159,160]
Glial cells				
Hyperplasia	++	?	?	[140]
Immunochemistry				
Nerve fibers				
Mucosa				
Antisynaptophysin	+	+	?	[143]
Nerve growth factor receptor (CD27)	+	–	+	[143]
CD56 (Leu 19)	+	+	–	[147]
VIP increase, abnormal, decrease	+			[158,159,161-164]
VEGF	+	+	–	[165]
NO synthase increase	+			[159]
PACAP increase	+			[159]
Submucosa				
Nerve growth factor receptor (CD27)	+			[143]
CD56 (Leu 19)	+			[147]
Neuronal cell bodies				
NO synthase	+			[159,165]
Glial cells				
GFAP[a]	+	+		[20,47]
GDNF[a]	+	+		[20,47]
MHC class II HLA DR	++	-/+	-/+	[166,167]
MHC class II HLD--DP/DQ	+			[166,167]
Nerve growth factor receptor (CD27)	+			[143,168]

H&E, hematoxylin and eosin; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; PACAP, pituitary adenylate cyclase activating peptide; VEGF, vascular endothelial growth factor (a glycoprotein with potent angiogenic, mitogenic and vascular permeability-enhancing activities specific for endothelial cells); VIP, vasoactive intestinal peptide. [a]GFAP and GDNF as signs of activated enteric glia cells (EGC) are increased in the mucosal plexus in the colon of patients with UC and infectious colitis, and although these biomarkers content are increased in CD, it is significantly less, which may suggest a diminished EGC network in this disease [20].

Table 5: Structural abnormalities of the enteric nervous system in inflammatory bowel disease (acc. to Geboes et al. [134]; with own modifications).

pathogenesis of IBD [130]. Full-thickness biopsy of the jejunum revealed inflammation and myenteric ganglioneuritis in severe IBS (low-grade infiltration of lymphocytes in the myenteric plexus, which had peri- and intraganglionic location, intraepithelial lymphocytosis with cytotoxic T-cell predominance, hyperplasia and hypertrophy of Cajal cells, neuron degeneration, and the longitudinal muscle layer thickened) [131,133]. Structural abnormalities of the ENS and even outside the ENS have consistently been observed in CD and, less frequently, in UC [134]. Recently, Villanacci et al. [135] demonstrated a marked increase for neuronal cell bodies, enteroglia and ICCs in deep muscular plexus in CD while in uninvolved areas the number of enteroglial cells was decreased. In UC an increase of ICCs in the muscular propria and enteroglial cells was found in the diseased tissue. Myenteric plexitis was observed in 75% of CD (transmural disease), and 56% of patients with UC (mucosal disease) [143] even in macroscopically normal intestinal segments [136]. Ohlsson et al. [136] found enteric ganglioneuritis in 11 of 19 studied patients with CD and in 5 of 11 with UC, and only individuals with CD had ganglioneuritis in the small intestine. Moreover, in CD the ICCs in the small bowel showed atrophy and vacuolar degeneration, along with the significantly reduced number of cells ($P = 0.005$); in UC, the colonic ICCs were hyperplastic ($P = 0.05$) without signs of degeneration [136]. Ultrastructural abnormalities of ICCs in these clinical entities, such as swelling of mitochondria, decreased electron density autophagosomes and partial depletion of cytoplasm, were also described in previous studies [137,138]. Structural abnormalities of the ENS and neurochemical changes in IBD patients are presented in Tables 5 and 6.

Vasculitis, granulomatous arteritis and lymphangitis are not uncommon in CD [179,180]. Enteroglial cells surrounding the nerves innervating mucosal blood vessels show MHC class II expression during inflammation [166]. Disturbances of the cellular components of the ENS found in CD and UC included hyperplasia or an increase in the number of neuronal cell bodies, mainly in the ganglia of the submucosal plexuses, neuronal cell damage, and neuronal hypertrophy. Hypertrophy of neurons with the appearance of prominent organelle, including numerous strands of rough endoplasmic reticulum has been identified in tissue samples obtained from patients with CD [152,155]. Neuronal hypertrophy in Meissner's plexus seemed to be more common in UC than CD, while hyperplasia of neuronal cell bodies was a more frequently observed and constant finding than neuronal hypertrophy [142,145,146,156]. A 3-fold increase in the number of ganglion cells of the ileal myenteric plexus was recorded in a series of 24 cases with CD. The increase was also present in areas not actively involved in the inflammatory process [157]. Increased numbers of

Neurons and nerve fibers	Effects	References
Neurotransmitters/Neuromodulators		
SP	↑	[170]
CGRP		[171]
VIP	↑/↓	[159,163,172,173]
NOS	↑	[159]
PACAP		[159,172]
Inflammatory mediators		
COX-2	↑	[174]
Receptors and channels		
NK-1, NK-2	↑	[175]
IK1		[176]
ASIC-3	↑	[177]
P2X3		[178]

IK1, intermediate potassium channels; SP, substance P (neurokin-1); CGRP, calcitonin gene-related peptide; NK, neurokinin receptors; PACAP, pituitary adenylate cyclase-activating polypeptide; VIP, vasointestinal peptide; ASIC, acid-sensitive ionic channels; P2X3, one of ATP-gated purinergic cation channels expressed on sensory neurons; NOS, nitric oxide synthase; COX, cyclooxygenase; IK1, potassium channel.

Table 6: Neurochemical changes in inflammatory bowel disease (acc. to Vasina et al. [169]; with own modification).

ganglion cells were reported for the submucosal plexuses in CD when compared with control samples [158]. Neuronal hyperplasia of the myenteric plexus was also reported for UC, but the data sometimes may have been confused by difficulties in the differential diagnosis between granulomatous colitis and genuine UC [153,181].

In CD, a relative increase in NO positive neurones has been demonstrated in the submucosal and myenteric plexuses [159,165]. The increase in myenteric neurones containing NOS and also vasoactive intestinal peptide (VIP) and PACAP might cause persistent relaxation of smooth muscle of the affected segment(s) [159]. An increase in number, size and immunostain and an abnormal pattern of VIP-containing fibers have been reported in CD [158,161,162]. The increase was found in histologically normal bowel, in areas with pathology both in specimens of the ileum and colon. In addition, an increase in the number of VIP immunostained ganglion cells in the submucosus plexus with 6-8 immunoreactive cell bodies in the ganglia in the CD samples and 0-2 in controls was noted. Numbers of immunoreactive neurones in the myenteric ganglia were 7-89 for VIP in CD compared to 2-45 in controls and 7-65 compared to 4-73 for NOS [159]. A marked decrease in V nerve fibers was found in the lamina propria and submucosa in both UC and CD, and in the lamina propria the variation in decrease was significantly associated with the severity of the disease [163,164].

Ultrastructural changes in the nerve elements in Crohn's disease

Ganglion cell and axon degeneration and necrosis has been demonstrated in the small bowel autonomic nerve plexus of patients with Crohn's disease [149,150], and it was suggested that this feature may be useful in differential diagnosis of Crohn's disease from other conditions, especially ulcerative colitis [150]. Brewer et al. [151] also found considerable numbers of abnormal, very small axons, and concluded that axonal damage is common in chronic IBD, but is not specifically related to Crohn's disease. In animal model, Bradley et al. [183] showed that inflammation did not stimulate appearance of new myenteric neurons of the guinea-pig ileum but stimulated mitosis in myenteric glia. Electron microscopic examinations showed a markedly decreased number of synapses in the wall of small intestine in Crohn's disease [184]. In the ileum, the numbers of nerve terminals were decreased, as well as that of the vesicle population in the remaining nerve terminals. Some of the nerve processes were degenerating, and the number of the lysosomes in the nerve cell bodies increased. Inflammatory cells, such as lymphocytes, plasma cells, and mast cells were demonstrated in tola submucosa and in the mucous membrane, and their number was also increased. It was suggested that these immune cells and their bioproducts were responsible for these neuronal abnormalities in the small intestine in Crohn's disease [184].

Enteric glial cells (EGCs) and intestinal inflammation

Animal studies showed that ECGs may play an important role in intestinal inflammatory processes [185-187], and that initiation and/or progression of IBD (especially Crohn's disease) might be ascribed to an immune-mediated damage of enteric glia [108]. The finding that EGCs functionally interact with lymphocytes [125], respond actively to inflammation process, and become activated as antigen-presenting cells [188] attracting immune cells to the ENS [60,185] suggests that this cell population is likely involved in inflammatory processes in the gut. Studies performed in patients with IBS showed the presence of inflammatory infiltrates closely associated with the enteric plexuses and mucosal activation of the immune system [131,189], and some individuals with intestinal dysmotility and megacolon have a lymphoplasmacellular infiltrate within the myenteric plexus that likely accounts for their symptoms [132].

Development of the Gastrointestinal Tract Immunity in Newborns and Young Children

Newborns and young infants suffer increased infectious morbidity and mortality as compared to older children and adults. There are qualitative and quantitative age-specific changes in innate immune reaction in response to various stimuli. Neonatal B cells do not respond to polysaccharide antigens to produce antibodies required for neutralization, opsonization, phagocytosis and complement activation (Tables 7 and 8). This may explain why young children are particularly vulnerable to infections caused by encapsulated bacteria. However, the conjugation of polysaccharides to protein carriers allows T-cell recruitment and renders the polysaccharides immunogenic in early infancy [195,196].

It was reported that neonatal innate toll-like receptor (TLR)-mediated responses are distinct from those of adults [197]. In response to most TLR ligands, neonatal innate immune cells, including monocytes and conventional and plasmacytoid dendritic cells, produced less IL-12p70 and IFN-α (and consequently induced less IFN-γ), moderately less TNF-α, but as much or even more IL-1β, IL-6, IL-23, and IL-10 than adult cells. Corbett et al. [198] summarized the innate TLR responses of human blood mononuclear cells and found that:

Age	B cell response	
	T cell dependent	T cell independent
Birth	B cell receptor diversity. Priming for B cell memory	Absent
2 months	Effective B cell response to most antigens	Minimal or no response to polysaccharide antigens
17-18 months	Mature B cell differentiation and homing patterns[b]	Minimal response to polysaccharide antigens[a]
4-6 years	Effective response	Effective responses. Marginal B cell zones in lymph nodes

[a]Based on data provided by Wilson et al. [191].

Table 7: Age related functional characteristics of systemic B cell (antibody) response in early childhood[a] (acc. to Ogra [190]; with own modification).

	Age	Cellular characteristics (MacDonald & Spencer [192,193])	Peyer's patches Mean number (± range) (Cornes [194])
Fetal-prenatal	10-11 weeks	Rudimentary patches HLA DR^+ cells, $CD4^+$ cells	
	11-16 weeks	$CD8^+$ cells surface IgM^+, IgD^+ B cells	
	16-18 weeks	$CD5^+$ B cells, IgA^+ B cells	
	20-40 weeks	Visible Peyer's patches appearance from B and T cell zones	60 (45-70)
	At birth		60 (50-90)
Postnatal	24 hrs to 6 weeks	Formation of germinal center after mucosal antigen exposure	94 (70-150)
Adolescents	12-15 yrs		295 (185-325)
Adults	20 yrs		180 (100-285)
Aging	90 yrs		100 (60-170)

based on data from MacDonald & Spencer [192,193], and Cornes [194]; with own modification).

Table 8: Age-related development of cellular characteristics of human Peyer's patches (acc. to Ogra [190].

1. T_H17 adaptive immune responses (IL-23, IL-6) peaked around birth and declined over the following 2 years only to increase again by adulthood;

2. antiviral defense (IFN-α) reached adult level function by 1 year of age;

3. T_H1 type immunity (IL-12p70, IFN-γ) slowly rose but remained far below adult responses at 2 years of age;

4. IL-10 production steadily declined from from a high around birth to adult levels by 1 or 2 years of age; and

5. production of TNF-α or IL-1β varied by stimuli [198].

These changes support T_H17- and T_H2-type immunity promote defense against extracellular pathogens, and have a reduced capacity to reinforce T_H1-type responses, which promote defense against intracellular pathogens [197]. In this context, it must be noted that TLR9 expressed by a variety of cells, including epithelial cells, B cells, and dendritic cells, is required for the gut-associated effective development of lymphoid tissue T_H1-type immune response following oral infection with *T. gondii* [199]. Murine mesenteric lymph node dendritic cells also showed protective mucosal T_H2 immune response against the parasite, including a production of specific secretory IgA [200]. In addition, innate recognition by TLR4 was involved in protective mechanisms against peroral infection with *T. gondii* ME49 [201]. Furthermore, the parasite was able to block the response of macrophages to LPS antigens [202], and also actively down-regulated of MHC class II molecules and was unable to up-regulate class I molecules in murine macrophages. These properties may represent an important strategy for evasion from the host's immune response and for its intracellular survival [203].

GI segment	Length (cm)		Width (cm)		Area (cm^2)	
	CG	EG	CG	EG	CG	**EG**
Duodenum	8.4 ± 0.7	7.0 ± 0.5[a]	0.8 ± 0.1	0.8 ± 0.0	6.6 ± 0.3	5.6± 0.4[a]
Jejunum	105.3 ± 4.1	102.6 ± 7.5	1.2 ± 0.1	0.9 ± 0.1	126.1 ± 13.5	96.4 ± 18.3
Ileum	1.7 ± 0.6	1.7 ± 0.4	1.1 ± 0.2	0.9 ± 0.1	2.0 ± 1.1	1.6 ± 0.5
Proximal colon	8.3 ± 0.5	5.6± 0.5[a]	1.3 ± 0.1	1.1 ± 0.2	11.8 ± 1.2	6.7 ± 0.6[a]
Distal colon	9.0 ± 1.0	7.0 ± 2.0	1.2 ± 0.1	1.1 ± 0.2	11.7 ± 2.0	8.6 ± 3.3

GI: Gastrointestinal; CG: Control Group; EG: Experimental Group
Results represent mean ± SD. [a]Values significantly different compared with controls (P < 0.05).

Table 9: Length, width and area of specific segments of the gastrointestinal tract in rats intraperitoneally infected with 10^6 tachyzoites of T. gondii type I (BTU IV strain) and examined 6 days post inoculation (acc. to Silva et al. [204]; with own modification).

Segment of GI tract	Group of animals	Length (cm)	Width (cm)	Area (cm^2)
Ileum-jejunum	CG	107.25 ± 2.36	1.40 ± 0.08	150.10 ± 8.27
	AEG	102.75 ± 3.77	1.38 ± 0.15	141.23 ± 15.77
	CG	109.16 ± 5.62	1.68 ± 0.08	183.33 ± 11.92
	CEG	100.94 ± 3.31[a]	1.50 ± 0.12[a]	151.18 ± 9.26[a]
Total colon	CG	15.45 ± 1.32	2.15 ± 0.37	33.11 ± 5.74
	AEG	14.88 ± 2.78	1.73 ± 0.30	26.15 ± 9.38
	CG	15.86 ± 1.18	2.16 ± 0.29	34.31 ± 5.84
	CEG	16.08 ± 3.13	2.10 ± 0.30	33.93 ± 8.54

CG: Control Group; AEG: Acute Experimental Group; CEG: Chronic Experimental Group; GI: Gastrointestinal
Values are presented as means ± SD. [a]Statistically significant results compared with respective controls (P < 0.05).

Table 10: Length, width and area of the ileum-jejunum and the total colon in rats with acute and chronic *T. gondii* type III infection (acc. to Sugauara et al. [205]; with own modification).

Bioparameter	30 DPI		60 DPI	
	CG	EG	CG	EG
Intestinal wall (μm)	561.0 (476.5; 623.0)	489.4 (419.2; 562.1)[a]	530.0 (465.7; 594.5)	657.9 (561.1; 774.4)[a]
External muscle (μm)	243.9 ± 47.2	185.6 ± 35.7[a]	280.0 (235.6; 340.3)	332.2 (270.4; 404.5)[a]
Mucosa (m)	253.2 (190.2; 329.6)	272.2 (207.8; 329.6)	197.3 ± 70.8	260.5 ± 81.0[a]
Villous height (μm)	377.7 ± 130.1	414.4 ± 121.2[a]	328.6 ± 116.4	370.8 ± 120.4[a]
Enterocyte height (μm)	42.9 ± 8.6	44.1 ± 8.4	37.0 (32.6; 41.5)	40.2 (34.6; 45.1)[a]
Enterocyte nucleus (μm)	8.0 (7.0; 8.8)	7.8 (6.8; 8.6)	6.8 1.3	6.6 ± 1.3

CG: Control Group; EG: Experimental Group; DPI: Days Post Inoculation
Results represent mean ± SD or median and P25, P75 percentiles. [a]Values significantly different compared with respective controls (P < 0.0001).

Table 11: Thickness of the total wall, external muscle, mucosa, villous and enterocyte height in the jejunum of pigs orally infected with *T. gondii* type III (M7741 strain) and examined 30 and 60 days post inoculation (acc. to da Silva et al. [206]; with own modification).

Peroral *T. Gondii* Infection Causes Development of Various Pathologic Changes in the Gastrointestinal Tract of both Experimental Animals and Humans

Animal studies

Development of GI tract inflammation following oral infection with *T. gondii* has been reported in a large number of different animal species belonging to two classes, mammalia and aves, and the most frequently affected organs were the liver (93.9% of the cases) and small intestine (57.6%) [105]. Additional sites affected with less frequency were the stomach, large intestines, and mesenteric lymph nodes. In most cases of experimental infections with the parasite, an inoculum of $\geq 10^2$ and 40-100 tissue cysts of *T. gondii* type II and III (ME49 strain) were fed orally by the animals, and the small intestines (95%) and liver (85%) were the organs affected most frequently. In the majority of cases, small intestinal pathology was characterized by a complete loss of the villous architecture. In mice, the small intestines showed formation of edema between the epithelial layer and the lamina propria, secretion of fluid from the epithelial layer into the gut lumen, mild desquamation of epithelial cells, and moderate to severe necrosis [105]. Pathological abnormalities were most prominent in the distal part of the ileum, and intracellular parasites can be detected in large numbers in its lamina propria, while parasite numbers in the liver were smaller. It was suggested that the strain of *T. gondii*, the infectious inoculum, and the host genetic features affect development of intestinal pathology and severity of its course [105]. Specifically, in animals with acute and chronic infection peroral inoculation with various numbers of the parasite oocysts or tachyzoites caused significant changes in length, width and area of specific segments of the GI tract. In addition, it affected thickness of the intestinal wall, external muscle, mucosa, villous and enterocyte height, decreased numbers of various neurons in myenteric ganglions, and resulted in markedly changed proportions between the cell body, nucleus and cytoplasm of the intestinal neurons (Tables 9-13).

Alves et al. [209] showed that chronic subclinical infection of rats with *T. gondii* (confirmed by the presence of serum anti-*T. gondii* antibodies but no manifestations or signs of the infection were observed) resulted in a 14.73% decrease in the mean stomach weight when compared with control animals, and both the small and large gastric curvature regions of the glandular areas showed respectively 27.56% and 25.25% decrease of myenteric neurons population density

Neurons	NADPHd-p		NADHd-p	
	CG	EG	CG	EG
Total number	1020.6 ± 130.5	1168.0 ± 259.2	1532.7 ± 69.5	862.3 ± 116.5[a]
Number per ganglion	8.5 ± 0.6	11.0 ± 1.4[a]	20.0 ± 1.1	10.7 ± 1.5[a]

CG: Control Group; EG: Experimental Group; NADHd-p: Dihydronicotinamide Adenine Nucleotide Diaphorase Positive; NADPHd-p: Dihydronicotinamide Adenine Dinucleotide Phosphate Diaphorase Positive
[a]Values significantly different compared with respective controls (P < 0.05).

Table 12: Mean ± SD of the number of NADPHd-p and NADHd-p neurons in 100 myenteric ganglions of the jejunum in pigs orally infected with oocysts of *T. gondii* type III (M7741 strain) and examined 30 days post inoculation (acc. to Odorizzi et al. [207]; with own modification).

Group of rats	Cell body area (μm²)	Nucleus area (μm²)	Cytoplasm area (μm²)	Nucleus/cell body area ratio
CG	165.49 (131.12; 203.42)	55.31 (42.81; 69.17)	108.26 (83.90; 139.67)	0.33 (0.28; 0.39)
EG	170.24[a] (129.60; 221.68)	53.30[a] (39.90; 67.74)	116.99[a] 85.87; 157.35)	0.30[a] (0.26; 0.36)

CG: Control Group; EG: Experimental Group
[a]Values significantly different compared with respective controls (P < 0.05).

Table 13: Median and P25, P75 percentiles of the cell body, nucleus and cytoplasm areas, and the nucleus/cell body ratio of NADH diaphorase-positive neurons in the jejunum of rats orally infected with 500 oocysts of *T. gondii* type III (M7741 strain) and examined 24 hrs post inoculation (acc. to Pereira et al. [208]; with own modification).

Gastric region	Group of rats	Number of neurons	Cell body area (μm²)
Greater curvature	CG	2495 ± 91.6	334 (264.4; 389.5)
	EG	1865 ± 221.4[a]	300 (246.7; 390.7)
Lesser curvature	CG	3248 ± 135.9	236 (165.7; 308.0)
	EG	2353 ± 45.0[a]	251 (139.0; 340.0)

CG: Control Group; EG: Experimental Group
Number of neurons is presented as mean ± SD, and the values of body cell area represent median and P25, P75 percentiles. [a]Statistically significant results compared with respective controls (P < 0.05).

Table 14: Population density and the cell body area of myenteric neurons of glandular stomach in rats orally infected with 104 tachyzoites of *T. gondii* type III (BTU II strain) and examined 30 days post inoculation (acc. to Alves et al. [209];with own modification).

(Table 14). Those authors [209] reported that no form of the parasite was been observed in the neurons studied. However, as the parasite needs nucleated cells to survive, one cannot exclude that at least some residues of *T. gondii* and/or its parasitophorus vacuole remained in the myenteric neurons because Pereira et al. [208] demonstrated that the only class of the rat jejunum neurons markedly decreased following oral inoculation with 500 oocysts of *T. gondii* type III (M7741) strain (examined 24 hrs after inoculation), was perikarion nerve cells between 151 and 200 μm², thus large enough to eventually harbor various forms of the parasite, including parasitophorus vacuole and/or its remnants [210]. Enlarged the cell body, cytoplasm, and nucleus areas were also observed in the myenteric neurons of the ileum of rats acutely infected with the *T. gondii* type II (Table 15) [211]. On the other hand, Sugauara et al. [205] administered the parasite genotype III and found these cell bioparameters in the rat descending colon during acute infection decreased (Table 16), and Soares et al. [212] demonstrated augmentation of the cell body and cytoplasm areas in myenteric neurons of descending colon in rats chronically infected with *T. gondii* type I. Therefore, it seems that these quantitative and morphometric changes of the myenteric neurons are depending on acute or chronic infection, dose of inoculum required to induce intestinal pathology, genotype of the parasite used, and animal species infected [105]. Moreover, recent studies of Berenreiterova et al. [213] showed that the distribution of *T. gondii* cysts in the brain of a mouse with latent toxoplasmosis had no well targeted tropism although some brain regions were consistently more infected than others.

It must be noted that *T. gondii* genotype I strains are considered highly virulent in laboratory animals [214]. The *T. gondii* population in Europe and North America consists of three clonal strains, types I, II, and III [215]. However, in South America, Asia, and Africa, these clonal strains are less dominant, and recombinant and exotic strains are more common. Some of these atypical strains have been associated with the development of toxoplasmosis also in immunocompetent individuals [216,217]. In the Northern hemisphere genotype II and III strains have been presenting low virulence that promotes development of chronic infection with formation of tissue cysts in the central nervous system [215,218,219]. The virulence of genotype III Brazilian strains found in South America was different from those of the Northern hemisphere [220] and the strain M7741 isolated in the U.S. in 1958 was thought to have low virulence [221]. Recently, it was found that virulence of *T. gondii* is associated with distinct dendritic cell responses and reduced numbers of activated $CD8^+$ T cells [222]. During acute infection,

Segment of GI tract	Group of animals	Cell body area (μm²)	Nucleus area (μm²)	Cytoplasm area (μm²)	Nucleus/cell body area ratio
Terminal ileum	CG	238.9 (134.2; 826.5)	95.3 (47.8; 330.2)	145.3 (79.9; 466.0)	0.39 (0.31; 0.49)
	EG	309.2 (142.3; 900.0)[a]	119.7 (55.3; 326.0)[a]	191.9 (85.5; 544.2)[a]	0.38 (0.31; 0.47)
Descending colon	CG	135.0 (98.3; 183.4)	69.9 (50.7; 94.6)	60.9 (42.8; 94.2)	0.52 (0.44; 0.59)
	EG	132.1 (88.3; 216.4)	69.4 (46.7; 101.2)	60.2 (36.4; 121.6)	0.52 (0.42; 0.61)

GI: Gastrointestinal; CG: Control Group; EG: Experimental Group
[a]Values significantly different as compared with controls (P < 0.05)

Table 15: Median and P25, P75 percentiles of the cell body, nucleus, and cytoplasm areas, and the nucleus/cell body area ratio of myenteric neurons in the terminal ileum and descending colon of rats orally infected with tissue cysts of *T. gondii* type II (ME-49 strain) and examined 24 hrs post inoculation (acc. to Sugauara et al. [211]; with own modification).

Segment of GI tract	Group of animals	Cell body area (μm²)	Nucleus area (μm²)	Cytoplasm area (μm²)	Cell body/ nucleus area ratio
Terminal ileum	CG	238.9 (134.2; 826.5)	95.3 (47.8; 330.2)	145.3 (79.9; 466.0)	0.39 (0.31; 0.49)
	AEG	258.4 (134.3; 828.2)	99.0 (48.6; 290.8)	155.2 (78.9; 496.2)	0.38 (0.29; 0.48)[a]
	CG	333.2 (164.4; 845.2)	123.81 (58.4; 309.5)	207.7 (100.0; 511.8)	0.37 (0.30; 0.46)
	CEG	161.5 (95.7; 515.8)[a]	56.4 (33.2; 202.5)[a]	104.2. (58.7; 289.5)[a]	0.36 (0.29; 0.45)
Descending colon	CG	135.0 (98.3; 185.40)	69.8 (50.7; 94.6)	60.9 (42.4; 94.2)	0.52 (0.44; 0.59)
	AEG	124.4 (87.6; 170.1)[a]	62.9 (43.8; 84.8)[a]	57.7 (39.7; 88.7)[a]	0.50 (0.42; 0.58)[a]
	CG	120.2 (74.1; 182.9)	60.5 (38.0; 86.1)	55.8 (34.9; 93.9)	0.49 (0.41; 0.57)
	CEG	157.3 (115.8; 209.9)[a]	74.8 (55.3; 97.8)[a]	75.4 (50.8; 114.3)[a]	0.49 (0.40; 0.57)

CG: Control Group; AEG: Acute Experimental Group; CEG: Chronic Experimental Group; GI: Gastrointestinal Values are presented as median and P25, P75 percentiles. [a]Values significantly different compared with respective controls (P < 0.05).

Table 16: Cell body, nucleus and cytoplasm areas, and nucleus/cell body area ratio of the myenteric neurons of terminal Ileum and descending colon in rats with acute and chronic infection with *T. gondii* type III (acc. to Sugauara et al. [205]; with own modification).

Cell components	NADPHd-p		NADHd-p	
	CG	EG	CG	EG
Cell body area (μm^2)	633.1 (475.0; 837.4)	714.2 (543.9; 921.2)[a]	392.1 (265.1; 557.5)	388.9 (270.3; 566.4)
Nucleus area (μm^2)	144.8 (99.5; 207.5)	180.1 (130.4; 263.1)[a]	101.7 (78.3; 126.1)	94.3 (73.1; 120.0)[a]
Cytoplasm area (μm^2)	473.9 (342.3; 643.5)	516.5 (393.2; 669.9)[a]	282.0 (174.5; 441.8)	286.4 (183.7; 459.8)[a]
Nucleus/cell body area ratio	0.24 (0.17; 0.31)	0.27 (0.21; 0.32)[a]	0.26 (0.19; 0.35)	0.24 (0.17; 0.32)[a]

CG: Control Group; EG: Experimental Group; NADHd: Dihydronicotinamide Adenine Nucleotide Diaphorase Positive; NADPHd-p: Dihydronicotinamide Adenine Dinucleotide Phosphate Diaphorase Positive

The animals from the EGs started to present diarrhea and had positive serum antibodies against *T. gondii* from day 13 to day 30 post infection. [a]Values significantly different compared with respective controls ($P < 0.05$).

Table 17: Median and P25, P75 percentiles of the cell body, nucleus, and cytoplasm areas, and the nucleus/cell body area ratio of NADHd-p myenteric neurons of the jejunum in pigs orally infected with oocysts of *T. gondii* type III (M7741 strain) and examined 30 days post inoculation (acc. to Odorizzi et al. [207]; with own modification).

Cell components	NADPHd-p		NADHd-p	
	CG	EG	CG	EG
Cell body x nucleus	0.56	0.73	0.62	0.54
Cell body x cytoplasm	0.93	0.95	0.98	0.98
Nucleus x cytoplasm	0.29	0.51	0.48	0.40

CG: Control Group; EG: Experimental Group; NADHd-p: Dihydronicotinamide Adenine Nucleotide Diaphorase-Positive; NADPHd-p: Dihydronicotinamide Adenine Dinucleotide Phosphate Diaphorase-Positive

Table 18: Degree of correlation between the cell body, nucleus and cytoplasm areas of NADPHd-p and NADHd-p myenteric neurons of the jejunum in pigs orally infected with oocysts of *T. gondii* type III (M7741 strain) and examined 30 days post inoculation (acc. to Odorizzi et al. [207]; with own modification).

Technique	Number of neurons		
	Mesenteric segment	Intermediate segment	Antimesenteric segment
Giemsa	2144.40 ± 161.05[a1]	1790 ± 128.24[b1]	1647.00 ± 76.67[c1]
NADH-d	1657.80 ± 88.23[a2]	1265 ± 41.17[b2]	981.80 ± 68.04[c2]
NADPH-d	473.80 ± 19.62[a3]	371.30 ± 27.84[b3]	298.50 ± 22.75[c3]
AchE	905.25 ± 22.40[a4]	770.25 ± 33.12[b4]	704.50 ± 69.38[b4]

AchE: Acetylcholine Esterase; NADH-d: Dihydronicotinamide Adenine Dinucleotide-Diaphorase Positive; NADPH-d: Dihydronicotinamide Adenine Dinucleotide Phosphate-Diaphorase Positive.

Mesenteric ileal segment: 0º-60º and 300º-360º, antimesenteric segment: 120º -240º and intermediate segment: 60º -120º and 240º -300º, considering the mesenteric attachment as Oº. The numbers of neurons are presented as means ± SD. The means followed by different letters in the same row are significantly different ($P < 0.05$). The means followed by different numbers in the same column are significantly different ($P < 0.05$)

Table 19: Neuronal density (mean ± SD) in myenteric plexus of the mesenteric, intermediate and antimesenteric ileal segments in rats aged 7 months, estimated by different techniques of neuronal staining (acc. to Miranda-Neto et al. [232]; with own modification).

effective presentation of parasite proteins to $CD8^+$ T-cells appeared to be a consequence of active protein secretion by *T. gondii* and escape from the parasitophorus vacuole, rather than degradation of phagocytosed parasites or parasite's bioproducts [223]. It must be added that type I strains replicate slightly faster than type II strains *in vitro* [217], and type I strains also have better migratory ability across biological barriers, including the lamina propria and submucosa [224]. Moreover, *T. gondii* type I strains interfere with NF-B activation and induce less IL-12 from infected macrophages *in vitro* than type II strains, suggesting that the parasite may be able to modulate the host immune response in a strain-specific manner [222,225,226]. Gut commensal bacteria also direct a protective immune response against the human pathogen *T. gondii* [227].

Studies performed in animals showed that oral infection with *T. gondii* resulted in different plastic changes in myenteric plexus neurons. For instance, in rats no changes in the population or density of these cells were observed [205,212,228], while there was an intense myenteric plexus neuronal cells death and atrophy reported in chicken [229]. On the other hand, in pigs orally infected for 30 days with oocysts of *T. gondii* III (M7741 strain) Odorizzi et al. [207] showed that the number of nitrergic NADPHd-p neurons per ganglion markedly increased, and the cells became hypertrophic through the augmentation of the cell body by 12.8% ($P < 0.0001$), and specifically through the increase of the nuclear area by 24.8% ($P < 0.0001$) (no change was observed in the distribution among different classes of neuronal cell sizes) (Tables 17 and 18). Because NO plays an important role in resistance of the host cells against *T. gondii* infection [230], it was suggested [207] that the cell hypertrophy may be indicative of the increased generation of biochemical mediator(s) with antiparasitic activity that may simultaneously exert a detrimental effect on tissue cells containing parasites [229,231]. Therefore, one may suggest that markedly different distribution of nitrergic neurons found in different ileal rat segments (Table 19) [232] is, at least in part, responsible for predominant dispersion of the gastrointestinal tract pathology and its intensity reported in both IBD and necrotizing enterocolitis in humans. Moreover, the marked decreases (and the recovery phase of $CD8^+$ T cells) of T-lymphocyte subsets during proliferative response of mesenteric and splenic T

Cellular immune responses	Relative % of T cells	fluorescent $CD4^+$	Cells $CD8^+$	CD4/CD8 ratio
Mesenteric lymph nodes cells				
Control	74.4 ± 0.4	45.4 ± 0.3	38.8 ± 2.9	1.17
Day 6 PI	24.0 ± 3.3	2.5 ± 0.9	10.2 ± 2.9	0.24
Splenic cells				
Control	49.1 ± 3.2	23.4 ± 6.1	17.7 ± 2.8	1.32
Day 28 PI	22.5 ± 0.3	4.5 ± 0.7	11.7 ± 3.3	0.38
Day 56 PI	34.6 ± 2.8	10.6 ± 5.4	22.2 ± 3.5	0.47

PI: Post Inoculation

A lymphocyte suspension was prepared from two mice and relative percentages of T, $CD4^+$, and $CD8^+$ fluorescent cells were determined from cytofluorometric analyses collected on 10 000 cells. Data are expressed as mean ± SD

Table 20: Phenotypic analyses of the mesenteric and splenic T-lymphocyte subsets from C57BL/6 mice orally infected with 40 cysts of *T. gondii* strain 76K at the time of T-cell proliferative response (acc. to Chardes et al. [233]; with own modification).

Antigen	Immunogen concentration	Mouse strain C57BL/6	BALB/c	CBA/J
BSA	40.00 g/ml	0.32 ± 0.16	0.67 ± 0.13	1.42 ± 0.05
TSo	40.00 µg/ml	4.04 ± 0.16	13.38 ± 3.95	23.10 ± 3.93
SAG1	3.12 µg/ml	0.39 ± 0.32	1.05 ± 0.14	11.53 ± 6.23
	0.78 g/ml	0.42 ± 0.07	1.46 ± 0.73	6.02 ± 4.36
	0.19 µg/ml	0.53 ± 0.30	0.62 ± 0.01	5.60 ± 4.33
GRA4	1: 50	0.48 ± 0.22	2.26 ± 1.29	6.92 ± 1.63
	1: 200	0.43 ± 0.09	1.33 ± 0.58	2.46 ± 2.17
	1: 800	0.30 ± 0.05	0.60 ± 0.11	2.08 ± 0.69
229-242 peptide	25.00 µg/ml	0.38 ± 0.21	0.55 ± 0.13	11.56 ± 0.61
	6.25 µg/ml	0.36 ± 0.02	0.52 ± 0.15	3.69 ± 1.93
	1.56 µg/ml	0.41 ± 0.07	0.37 ± 0.04	1.93 ± 0.02

Responder lymphocytes were cultured with irradiated antigen presenting cells for 5 days in the presence of different immunogens at various concentrations. *Toxoplasma* sonicate (TSo) and bovine serum albumin (BSA) were used as positive and negative controls, respectively

Table 21: SAG1, GRA4 and 229-242 peptide-induced lymphocyte proliferation of mesenteric T cells from three inbred mouse strains orally infected with 40 cysts of *T. gondii* (76K strain) and collected on day 6 post inoculation. (acc. to Chardes et al. [233]; with own modification).

lymphocytes demonstrated in mice orally infected with 40 cysts of the parasite strain 76 K (Table 20), as well as the variations in cytokine response profiles to diverse *T. gondii* antigens in the three different mouse strains studied (Tables 21-24) [233], may at least partly explain large variability of signs, symptomes and histopathologic changes observed during clinical course of IBD in humans. This reasoning is supported by the finding that T_H1 and T_H2 cytokines have opposing effects on gastrointestinal motility in gastrointestinal disorders via 5-HT signaling, i.e. T_H1 cytokines downregulate CPI-17 (C-kinase potentiated protein phosphatase-1 inhibitor, m.w. = 17 kDa) and L-type Ca^{2+} channels and upregulate regulators of G protein signaling 4, which contributes to hypocontractibility of inflamed intestinal smooth muscles, and conversely, T_H2 cytokines cause hypercontractibility via signal transducer and activator of transcription 6 or mitogen-activated protein kinase signaling pathways [234].

In rats infected with *T. gondii* genotype III (M7741 strain), morphometric analysis showed increased cell body and cytoplasm areas, and decreased nuclear area of the myenteric neurons [208]. The high degrees of the correlation value (Table 25) found between the subcellular structures of the jejunum neurons suggest that the observed hypertrophy of metabolically active neurons were related to the augmentation of the cytosol and/or organelles in the cytoplasm [208]. One cannot exclude that these cellular changes may be associated with the intracellular proliferation and metabolism of *T. gondii* tachyzoites/bradyzoites/parasitophorus vacuole). Otherwise it was found that in the small intestine, the lymphoid tissues were represented by Peyer's patches, which formed dome-like anatomic structures consisting of lymphocytes and dendritic cells [235]. The early *Toxoplasma* sonicate-induced mucosal T-cell proliferation occurred in the mesenteric lymph nodes and Payer's patches with a peak responsivenes on day 6 post inoculation and rapidly reached background levels on day 7 post infection in Peyer's patches and on day 8 post inoculation in mesenteric lymph nodes [233]. Subsequently, splenic cellular blastogenesis was observed from day 28 after infection and persisted throughout the experiment (day 91) [233].

Antigen	Immunogen	Mouse strain		
	concentration	C57BL/6	BALB/c	CBA/J
BSA	40.00 g/ml	0.18 ± 0.03	0.48 ± 0.12	0.49 ± 0.04
TSo	40.00 µg/ml	6.60 ± 1.29	12.22 ± 1.90	24.04 ± 0.86
SAG1	3.12 µg/ml	0.32 ± 0.01	0.99 ± 0.04	3.97 ± 0.01
	0.78 g/ml	0.27 ± 0.02	1.15 ± 0.71	2.16 ± 017
	0.19 µg/ml	0.17 ± 0.03	0.77 ± 0.26	1.68 ± 0.38
GRA4	1: 50	0.61 ± 0.03	2.40 ± 0.70	2.91 ± 0.34
	1: 200	0.36 ± 0.05	1.17 ± 0.47	2.49 ± 0.20
	1: 800	0.19 ± 0.01	0.34 ± 0.09	0.72 ± 0.05
229-242 peptide	12.50 µg/ml	0.23 ± 0.05	0.57 ± 0.15	2.21 ± 1.42
	3.12 g/ml	0.18 ± 0.01	0.72 ± 0.06	1.90 ± 1.05
	0.78 µg/ml	0.11 ± 0.01	0.59 ± 0.02	0.46 ± 0.01

Responder lymphocytes were cultured with irradiated antigen presenting cells for 5 days in the presence of different immunogens at various concentrations. Toxoplasma sonicate (TSo) and bovine serum albumin (BSA) were used as positive and negative controls, respectively

Table 22: SAG1, GRA4 and 229-242 peptide-induced lymphocyte proliferation of spleen T cells from three mouse strains orally infected with 40 cysts of *T. gondii* (76K strain), and collected on day 42 post inoculation. (acc. to Chardes et al. [233]; with own modification).

Antigen	Cytokine				
	IFN- (ng/ml)	IL-2 (U/ml)	IL-4 (U/ml)	IL-5 (pg/ml)	IL-6 (pg/ml)
BSA	< 1	< 0.10	< 0.10	< 20.0	< 1.0
TSo	3590	0.24	1.09	68.8	81.2
SAG1	157	< 0.10	< 0.10	< 20.0	< 1.0
GRA4	193	< 0.10	< 0.10	48.9	7.5
229-242 peptide	121	< 0.10	< 0.10	38.0	5.5

Cells were harvested on day 6 post inoculation. Toxoplasma sonicate (TSo) and bovine serum albumin (BSA) were used as positive and negative controls, respectively

Table 23: Cytokine response profile of *T. gondii* antigen-specific mesenteric T lymphocytes from CBA/J mice orally infected with 40 cysts of *T. gondii* (76K strain) (acc. to Chardes et al. [233]; with own modification).

Antigen	Cytokine measured		
	IFN-γ (ng/ml)	IL-2 (U/ml)	IL-6 (pg/ml)
BSA	< 1	< 0.10	< 1.0
TSo	2580	6.25	150.5
SAG1	89	0.25	< 1.0
GRA4	< 1	< 0.10	5.5
229-242 peptide	< 1	< 0.10	< 1.0

BSA, bovine serum albumin; GRA4, *T. gondii* dense granule protein 4 (m.w. 40-41 kDa) released after host cell invasion and recognized by mucosal IgA antibodies; TSo, *Toxoplasma* sonicate; SAG1, *T. gondii* surface antigen (m.w. 30 kDa); the 229-242 peptide (S-V-S-T-E-D-S-G-L-T-G-V-D) derived from the deduced amino acid sequence of GRA4

Table 24: Cytokine response profile of *T. gondii* antigen-specific spleen T lymphocytes from CBA/J mice orally infected with 40 cysts of the parasite strain 76K (acc. to Chardes et al. [233]; with own modification).

Group of rats	Cell body x nucleus	Cell body x cytoplasm	Nucleus x cytoplasm
CG	0.73	0.94	0.48
EG	0.78	0.96	0.60

Table 25: Degree of correlation between the cell body, cytoplasm, and nucleus areas of the jejunum neurons in rats orally infected with 500 oocysts of *T. gondii* type III (M7741 strain) and examined 24 hrs post inoculation (acc. to Pereira et al. [208]; with own modification).

After *T. gondii* infection, the host cells release a plethora of neuroimmune mediators that can seriously affect enteric nerves, including many cytokines and NO, to provide and regulate proper immune defense against the invading intracellular parasite [202]. Peroral *T. gondii* infection induced a significant decrease in the relative percentage of the T-cell population and the CD4/CD8 ratio, wheather it was on day 6 post inoculation with MLN cells ($P < 0.01$) or on days 28 and 56 post inoculation with splenic cells ($P < 0.01$ and $P < 0.05$, respectively) (Table 20) [233]. In the high responder CBA/J model, the mesenteric T-lymphocyte blastogenesis induced by *Toxoplasma* sonicate was associated with significant IFN-γ, IL-4, IL-5 and IL-6 production and little IL-2 secretion, whereas *Toxoplasma* sonicate-specific splenic T cells only generated IFN-γ, IL-6 and a higher level of IL-2. These findings suggested that mice orally infected with *T. gondii* induced a predominant mesenteric T_H2-type cytokine response and a major spleen T_H1-type response [233].

Finally, Bonapaz et al. [229] showed that chicken from the experimental group infected with oocysts of *T. gondii* type III (M7741 strain) and examined after 60 days had diarrhea, inflammatory infiltrates in the tunica mucosa, and duodenum layers atrophy (decreased thickness of all the studied bioparameters) (Table 26), as well as a marked increase in the number of caliciform cells. There was also about 70% loss of myenteric neurons, and the remaining cells presented a reduction of about 2.4% of the pericarion and 40.5% of the nucleus ($P < 0.05$) (Table 10). It was found that the intestinal mucosa goblet cells marked with PAS, which estimates glycoconjugates components of mucins and indicates a neutral mucus, increased 29.66% ($P < 0.05$) and the cells marked by AB, which estimates acid mucus, increased

Group of birds	Total wall (μm)	Muscular tunic (μm)	Muscularis mucosa (μm)	Mucosal tunic (μm)
CG	556.85 (530.78; 582.35)	293.55 (270.70; 313.33)	25.95 ± 3.26	294.40 (268.78; 332.73)
EG	404.20[a] (374.60; 444.70)	233.30[a] (216.60; 250.73)	18.73 ± 2.70[a]	205.30[a] (189.70; 219.33)

Results represent median and P25, P75 percentiles, and means ± SD. [a]Values significantly different compared with respective controls (P < 0.05)

Table 26: Thickness of the duodenal total wall, muscular and mucosal tunics, and muscularis mucosa in chicken orally infected with 1000 oocysts of the *T. gondii* type III (M7741 strain) and examined 60 days post inoculation (acc. to Bonapaz et al. [229]; with own modification).

Group of chicken	PAS	AB pH 2.5	AB pH 1.0
CG	967.75 ± 249.93	1134.15 ± 84.10	1169.5 ± 125.96
EG	1254.83 ± 90.67[a]	1156.07 ± 61.58[a]	1319.38 ± 77.64[a]

PAS: Periodic-Acid-Schiff; AB: Alcian Blue
Values represent mean ± SD. [a]Statistically significant results compared with respective controls (P < 0.05)

Table 27: Number of goblets cells estimated by different histochemical techniques for glycoconjugates (components of mucins) in a 0.96 mm^2 area of the duodenum tunica mucosa in chicken orally infected with 1000 oocysts of *T. gondii* type III (M7741 strain) and examined 60 days post inoculation (acc. to Bonapaz et al. [229]; with own modification).

only 12.8% (P < 0.5). These changes suggested that the duodenal mucus became denser, thus providing protection intestinal epithelium from potential damage due to recurrent diarrhea [229] (Table 27). It must be noted that *T. gondii* sporozoites cross the intestinal mucosa either through the enterocytes or the caliciform cells [236], and the parasite was found in caliciform cells of the guinea pig conjunctiva minutes after inoculation [236,237].

Humans: In immunosupressed individuals, gastric abnormalities caused by *T. gondii* infection included ulcerations, thickening of gastric wall and folds, thickening and necrosis of tunica mucosa, as well as inflammatory infiltrates, were reported [238-240].

In patients with AIDS, *T. gondii* infection has been identified in the stomach, small intestine, colon, and esophagus in both biopsy specimens and during postmortem examinations [238,241,242]. Those patients, both men and women 22 to 39-yrs-old, presented with mild-to-severe abdominal pain, nausea, vomiting, anorexia, weight loss, fever, and diarrhea. Endoscopic findings included ulcerated lesions and thickening of gastric folds and gastric wall, edema (the histologic correspondent of thickened gastric folds), focal necrosis, and sometimes narrowing of the antrum. The antrum and fundus appeared to be the main sites of involvement. The pathologic findings were variable acute and chronic cell infiltrates and the presence of tachyzoites, bradyzoites, and pseudocysts [242,243] identified in the lamina propria, endothelial cells, cytoplasm of the epithelial cells, and smooth muscle cells [243].

In AIDS patients with diarrhea and sometimes with lower GI tract bleeding [244-246] biopsy specimens of colonic/small intestine mucosa showed the presence of *T. gondii* tachyzoites, and endoscopy revealed multiple ulcers with raised margins [246,247].

Animals: *T. gondii* infection caused gastric lesions in several animal species [108], and inflammatory changes, necrosis of the gastric wall, as well as eosinophilic fibrosing gastritis [105,209,248-251]. Histopathologic, immunohistochemical and ultrastructural studies showed the parasite inside the epithelial, muscle, endothelial cells and macrophages [238], and in intracellular vacuoles in glandular cells on gastric wall [240]. Alves et al. [209] found that in rats *T. gondii* type III, tachyzoites were capable of resisting the gastric juice and crossed the GI tract barrier, reaching systemic circulation, because they documented the presence of anti-*T. gondii* antibodies in serum of the animals despite lack of clinical signs of the infection. There was a marked decrease in the population density of myenteric neurons of both the small and the large gastric curvatures (P < 0.012) with no change in the cell body area (Table 14). In addition, a decrease of the stomach area and its weight were also found [209]. Other authors also reported neuronal hypertrophy of duodenum and descending colon [205], whereas marked decreases in the nucleus and cell areas [205,253] occurred in the jejunum and ileum, respectively, demonstrating that myenteric plexus had been the subject of *T. gondii* infection [205,253-255]. It is interesting that no tissue cysts were found in the neurons of the gastric myenteric plexus evaluated by Alves et al. [209], but Montoya & Remington [241] suggested that these structures of the parasite have been diffusively and heterogeneously formed considering all tissues in the body. The lack of a blood-brain barrier and the absence of microglial cells in the ENS ganglions as compared with the central nervous system may result in augmented vulnerability of its neurons to *T. gondii* infection.

It was found that a single immunodominant surface antigen SAG1 exclusively expressed on the tachyzoite of *T. gondii* can elicit lethal inflammatory process in experimental model of pathogen-driven ileitis [256] through a robust B and T cell-specific response. SAG1 induces the dominant antibody response during infection [257,258] and a strong, systemic T_H1-like T cell response characterized by high titer IFN-γ production by CD4 and CD8 lymphocytes [259]. Intestinal inflammation and tissue damage are distinguished by an exaggerated immune response mediated by both TNF-α and IFN-γ [260] and heightened sensitivity of intestinal epithelial cells to TNF-α [261-263]. IFN-γ is the cytokine mediator associated with intestinal inflammation following oral infection with *T. gondii* [255]. Moreover, recent studies showed that the parasite expresses serine and cysteine proteases that are critical for the assembly and trafficking of organellar content proteins [264], host cell invasion, replication and nutrient acquisition [265], finally at least in part affecting severity of the intestinal inflammation process.

In vitro stimulation of mesenteric T cells with three different *T. gondii* antigens resulted in secretion of IL-5 and IL-6 (except for SAG1) and IFN-γ, whereas no detectable IL-2 or IL-4 was observed (Table 23). It seems that mice orally infected with the parasite induced a predominant mesenteric T_H2 cytokine response and a major spleen T_H1 reaction [266], similarly as it was reported with other intestinal parasite infections [267,268]. Also miniature pigs fed with 1000 oocysts of the *T. gondii* VEG strain responded to the infection by simultaneously inducing proinflammatory cytokines, such as IFN-γ mRNA expression early post inoculation, and IL-12p35, as well as anti-inflammatory cytokine IL-10 later to provide a balance between controlling parasite growth and avoiding host pathology mediated by cytokine toxicity. In addition, a significant increase in the percentage of $CD8^+$ cells was observed in the second week of infection [269].

Effect of Oral *T. Gondii* Genotype III M7741 Strain Oocysts Infection in Rats on Nadph-Diaphorase Positive (Nitrergic) and Nadph-Diaphorase Negative (Cholinergic) Myenteric Neurons

Nitrergic neurons

The morphometric analysis of the NADPH-d+ (nitrergic) myenteric neurons performed by Hermes-Uliana et al. [270] showed atrophy for both the 30 DPI (19%) and 90 DPI (12.1%) rats as compared

Bioparameter	Giemsa			NADPHd-p		
	CG	DPI30	DPI90	CG	DPI30	DPI90
Cell body area (μm²)	144.0 (109.0; 87.0)	129.0[a] (102.0; 172.0)	154[a] (108.0; 207.0)	200.5 (164.6; 247.5)	162.4[a] (135.1; 202.0)	176.3[a] (143.8; 216.6)
Nucleus area (μm²)	38.0 (27.0; 51.0)	34.0[a] (25.0; 47.0)	43.0[a] (30.0; 57.0)	58.5 (46.8; 71.6)	50.9[a] (39.8; 62.9)	53.4[a] (42.1; 66.0)
Cytoplasm area (μm²)	104.0 (77.7; 137.0)	97.0[a] (72.0; 128.0)	109.0[a] (74.0; 152.0)	142.1 (112.6; 179.1)	112.2[a] (89.3; 144.5)	121.8[a] (98.5; 154.8)
Nucleus/cell body area ratio	0.27 (0.22; 0.33)	0.26[a] (0.1; 0.32)	0.28[a] (0.22; 0.34)	0.29 (0.24; 0.34)	0.30[a] (0.26; 0.36)	0.30[a] (0.25; 0.35)

CG: Control Group; DPI: Days Post Inoculation (experimental group); NADPHd-p: Dihydronicotinamide Adenine Dinucleotide Phosphate Diaphorase-Positive
Values significantly different compared with respective controls ($P < 0.05$)

Table 28: Median and P25, P75 percentiles of the cell body, nucleus and cytoplasm areas, and the nucleus/cell body area ratio of the neurons stained with Giemsa and NADPHd-p in the jejunum of rats orally infected with 500 oocysts of *T. gondii* type III and examined 30 and 90 days post inoculation (acc. to Hermes-Uliana et al. [270]; with own modification).

with control animals. However, the comparison of the neurons in the 30 DPI with those in the 90 DPI demonstrated hypertrophy in the latter (8.6%), which perhaps indicated a recovery phase of the cellular area (Table 28). At 30 DPI, an increase in the population of smaller (101-150 μm²) neurons (new young cells?) and a decrease in the population of the larger (201 to > 301 μm²) neurons (old, infected with the parasite and undergoing apoptosis cells?) were observed [270].

The high degree of the correlation between the area of the cell body and cytoplasm in these cells subpopulation suggested that the morphological changes resulted mainly from the changes in the cytoplasm of those cells ($r = 0.95$, $P < 0.001$) [260]. It seems that rapid reduction of the excessive generation of NO in the inflamed intestinal tract tissue cells by mitochondria, and reversible inhibition of mitochondrial respiration by NO [271] may, at least in part, serve as an explanation of these subcellular changes.

After ingestion of contaminated food and water containing *T. gondii* cysts or sporulated oocysts [272], the bradyzoites released from the cysts first invade intestinal epithelial cells (IECs) leading to parasite dissemination throughout different organs. In response to the parasite infection, IECs and enterocytes released a plethora of cytotoxic mediators, such as for example NO, and up-regulated production of proinflammatory cytokines and chemokines such as MCP-1 (CCL2), MIP-2 (CXCL2), and IP (CXCL10), RANTES (CCL5), MCP-3 (CCL7), and CXCL9 [273-275]. Moreover, during *T. gondii* infection, it has been shown that commensals, such as *E. coli*, activated macrophages, dendritic cells and neutrophils through TLR4 engagement thus contributing to the parasite-associated intestinal inflammation [276]. Enteric bacteria were also found to induce cell death in porcine myenteric neurons via LPS, as a consequence of intestinal inflammation [277]. Experimental studies showed that bacteriotoxin LPS, acting via TLR4 activation and driving the T_H1-type intestinal inflammatory process [278], caused delayed gastric emptying [279,280], intestinal dysmotility [280,281], and sphincter dysfunction [282], thus unraveling its damaging interaction with myenteric neurons [277]. It should be noted that the immune recognition by TLR4 also was involved in the protective mechanisms against peroral infection with *T. gondii* ME49 strain [201]. These are important findings because several investigations about the pathogenesis of inflammatory bowel disease adapted the view that the disease is due only to a fundamental abnormality in bacterial microflora of the gut [283].

Important Role Of Nitric Oxide During *T. Gondii* Infection

The role of NO in parasitic diseases is very important [284]. Normally NO production is necessarily under tight control, but excessive NO can lead to development of immunopathology (diabetes, liver cirrhosis, rheumatoid arthritis). A number of cytokines, including IL-4, IL-10 and TGF-β, can downregulate induction of NO synthase in macrophages [284]. Also NO can reduce the activity of NO synthase by feedback inhibition, and inhibits the production of IFN-γ by T_H1 cells with the regulatory pathways involving tyrosine kinase and protein kinase C [284]. NO (and IFN-γ) plays an important role also in upregulation of VEGF gene expression [285], the factor known to be markedly increased in the cerebrospinal fluid of patients with ASD [36].

NO is a cytotoxic effector molecule produced by macrophages [286] that acts by inhibiting essential mitochondrial and nuclear enzymes [287], and results in iron mobilization from tumor target cells, which inhibits DNA synthesis and mitochondrial respiration. Mitochondria may contain NO synthase and can produce significant amounts of NO to regulate their own respiration. This function may therefore be important for physiological and pathological (because of a known overproduction of NO in autism) regulation of energy metabolism [288-290] in gastrointestinal tract.

NO is known to affect the development and function of the central nervous system, such as neurite growth [291], synaptogenesis [292], neurotransmitter release [293], memory processing and learning (learning was dose-dependently affected) [294, 295], and macrophage-mediated cytotoxicity [286]. The expression of iNOS and production of NO also affect inflammatory processes [296], for example peroxynitrite (a product of NO and superoxide anion) generated by iNOS synthase and NADPH oxidase mediated microglial toxicity to oligodendrocytes [297], and NO exerted a dose-dependent biphasic regulatory effect on the activity of matrix metalloproteinase-9 secreted from murine macrophages [298]. Recently, it was reported that human enteric glial cells directly responded to proinflammatory stimuli by changing their expression profile and by proliferating, and were able to increase production of NO through release of glial proteins, such as S100B [299,300]. S100B is specifically and physiologically expressed by enteric glial cells and its overexpression is associated with the onset and maintenance of intestinal inflammation because it has a proinflammatory activity, which gain access to the extracellular space especially at immune-inflammatory reaction sites in the gut [66]. NO also modulated T-lymphocyte migration in Peyer's patches and in nonlymphoid villous submucosa of rat small intestine through a significantly increased rolling and adherence of lymphocytes in postcapillary venules of Peyer's patches and submucosal venules without markedly decreasing red blood cell velocity [301]. Thus, *T. gondii* infection may be, at least in part, responsible for development of gastrointestinal symptoms and intestinal entropathy, including the characteristic ileo-colonic LNH, increased enterocyte and Paneth cell numbers reported in autistic children [3,6,7,25,302]. The increased number of cells per ganglion, hypertrophy of NADPH diaphorase-positive (nitrergic) neurons, the decrease of the cellular number, as well as their nuclear area in these nitrergic (metabolically more active) neurons [207,208,270], and the significant increase of the villous and enterocyte height [206] found in the laboratory animals following oral inoculation

with the parasite, are in agreement with the above-presented reasoning. It must be noted that in mice infected by the VEG strain of *T. gondii*, great amounts of parasites were found in the mesenteric lymph node, 48 hrs post infection [303]. In this context, the ileo-colonic LNH observed in some autistic children may therefore reflect an enhanced immune response [26] to chronic phase of oral *T. gondii* infection. This may be supported by the fact that lactoferrin administered orally improved gastrointestinal morphology in growing calves because it enhanced size of Peyer's patches in the ileum and decreased villous size in the jejunum [304]. Moreover, these changes are in line with the intestinal morphometric abnormalities reported in animals orally infected with oocysts of *T. gondii* type II or type III strains [205,206,208,211,270]. In the experimental animals, PCR analysis showed the presence of *T. gondii* only in the mucosa and submucosa, which may indicate that the finding in the myenteric plexus occurred as a result of an indirect action of the parasite via cytokines and other immune biomediators released [305,306]. Myenteric neurons are target cells for paracrine secretions from the immunocytes at the intestinal wall [307] or even the myenteric ganglions themselves [173] because neurons within this plexus are closely associated with the immune system [308]. It must be added that mast cell-nerve interactions play a key role in intestinal inflammation because mast cells secrete chemotactic factors able to recruite neutrophils, macrophages and lymphocytes when the parasite reaches the lamina propria [309], finally reducing survival of myenteric neurons [310].

The genotype II strains of *T. gondii* have low virulence in mice and high cystogenic capacity and the positive serologic anti-*T. gondii* titers found by Hermes-Uliana et al. [270] ensured that the animals have been successfully infected with the parasite. However, the authors did not find tissue cysts of the parasite in the myenteric neuron samples evaluated and this is in agreement with the observation of Dubey et al. [272] that intestinal cysts are rarely found. In addition, the maintenance of the same number of neurons reported by Hermes-Uliana et al. [270] was similar to the findings reported by other authors [205,211,212] in the small and large intestine of animals infected orally with *T. gondii* tachyzoites or bradyzoites. Moreover, the myenteric neurons of the total population became atrophic in the 30 DPI animals and experienced recovery followed by hypertrophy 90 DPI, independently of the class studied. Both, the atrophy and hypertrophy of these cells resulted mainly from the changes in cytoplasmic area, and the area of nucleus changed proportionally to these alterations [270]. Preliminary studies in rats showed atrophy in the myenteric neurons of the ileum 30 DPI after infection with tachyzoites from another genotype II strain [211]. In contrast, *T. gondii* genotype III [205] and genotype I infection [212] caused neuronal hypertrophy in the large intestine of rats 30 DPI. Thus, it seems that changes in enteric neurons found after peroral infection of animals with *T. gondii* depend on the parasite genotype used, infecting material and its virulence/antigenicity, part of gastrointestinal tract infected, animal species used, and their innate immunity.

Cholinergic neurons

After *T. gondii* infection, the number of cholinergic neurons in rats showed no changes in the population density and remained as the predominant subpopulation of the cells in comparison with the nitrergic neurons [270,311], in spite of the fact that cholinergic neurons are considered vulnerable to neuronal death [312]. This finding may be important for controlling intensity of intestinal inflammation in the animals infected with the parasite because in mice cholinergic stimulation of macrophages reduced their production of TNF-α through a mechanism involving nicotinic receptor activation [313]. It must be noted that in the cortex of autistic patients, the cholinergic receptors known to be sensitive to NO toxicity were found to be decreased [314]. However, it was found that the treatment with cholinergic agonists improved behavioral abnormalities in those individuals [315,316]. These beneficial therapeutic effects may be explained by the finding that proinflammatory cytokine levels and excessive inflammation can be regulated by specifically augmenting cholinergic signaling via the efferent vagus nerve and/or applying selective cholinergic modalities targeting the 7 subunit-containing nicotinic acetylcholine receptor [317,318].

Gastrointestinal Tract Disturbances in Autistic Patients May Be At Least in Part Caused By Mast Cell Activation During Peroral *T. Gondii* Infection Associated with Reduced Surivival of Myenteric Neurons

Several children with ASD suffer from "allergic-like" symptoms [319-321], and many of them may be consistent with chronic idiopathic or chronic autoimmune urticaria [322]. A case-control study of Croen et al. [323] showed that prevalence of maternal psoriasis, asthma, hay fever and atopic dermatitis during the second trimester of pregnancy correlated with > 3-fold elevated risk of ASD development in their children. Recently, a strong link between allergies and autism has been also suggested [324].

Inflammatory cells release an array of cytokines and inflammatory mediators that affect enteric nervous system. Mast cells are ascribed a central role in mediating hyperexcitability and neuron depolarization via their release of histamine, prostaglandins, leukotrienes and tryptase [325,326]. The elusive mast cells increase in number in several gastrointestinal disorders, including infectious diseases, food allergy, IBD, and IBS [310,327]. Crohn's disease associated dysmotility has been attributed to fibrosis and damage to enteric nerves and interstitial cells of Cajal (ICC) [137]. Ultrastructural injury to ICC was patchy and ICC-Auerbach's plexus showed damage more frequently, i.e. swelling of mitochondria, decreased electron density, autophagosomes and partial depletion of cytoplasm. Electron microscopy showed mast cells exhibiting piecemeal degranulation and making frequent and selective membrane-to-membrane contact with all types of injured ICC, which suggested chronic release of granule content [137]. Nb. it must be added that mercury used as a preservative in vaccines also induced inflammatory mediators release from human mast cells [328], and recently DeLong [329] demonstrated a positive and statistically significant relationship between the proportion of children who received the recommended vaccines by age of 2 years and the prevalence of autism or speech/language impairment across the U.S. population.

In pigs orally infected with oocysts of *T. gondii* type III (M7741 strain), Silva et al. [206] demonstrated hypertrophy of the intestinal wall (the increases in the villous and enterocyte heights, mucosal and external intestinal muscle thickness) of jejunum 60 days post inoculation. It must be noted that at 30 days post inoculation, there was atrophy of the intestinal wall with a decrease in the external muscle and increase in villous height [206]. Chickens infected with oocysts of the same strain of the parasite also showed mucosal atrophy in both the duodenum [330] and ileum [331]. Mice fed with oocysts of *T. gondii* VEG strain had great amounts of parasites in the mesenteric lymph nodes [331]. The studies of Silva et al. [204] in rats intraperitoneally infected with 10^6 tachyzoites of *T. gondii* type I (BTUIV strain) showed that approximately 14.9% of the myenteric neurons in the jejunum died ($P < 0.05$) and the cellular response of myenteric neurons to the infection was heterogenous depending on the small and large intestinal

segment (Table 29). In the neurons of control animals jejunum, the nucleus occupied 52% of the cell body and the infection caused its reduction to 48% ($P < 0.05$) (Table 30), which suggested decreased nuclear [204] and increased cytoplasmic metabolism. In the jejunum of pigs orally inoculated with oocysts of *T. gondii* type III (M7741 strain) there was also an increase in the cytoplasmic area in NADH-diaphorase positive neurons that are considered more metabolically active, while the area of the cell body did not change markedly (Table 17) [207]. The morphometric alterations in the intestine wall probably have been caused by the proliferation and/or higher recruitment of immune cells to the lamina propria as a result of *T. gondii* invasion because, for example, mast cells activation results in secretion of chemotactic factors that attract neutrophils, macrophages and lymphocytes [333,334]. It was found that the mast cells found in the ileum submucosa 48 hrs post intraperitoneal inoculation with 10^5 tachyzoites contained *T. gondii* (Table 31) and also showed significant morphological alterations, including an increase in the amount of their cytoplasmic projections in the contact area with the parasites, as well as cytoplasmic granules with flocculent material and electron lucid halo, granule fusions, outlining wide intracytoplasmic channels, possibly due to the intense degranulation process, probably in response to the discharge of the granule contents from mast cells, such as cytotoxic leukotrienes on the parasites present in this compartment [333,335]. Mast cells were found to interact with other parasitized cells, including macrophages. [Nb. it must be noted that proliferation rate of intracellular *T. gondii* tachyzoites varies depending on the cell type affected (Table 32)]. In experimental animals free tachyzoites with morphological alterations and parasitophorus vacuoles inside mast cells were demonstrated within one hour after intraperitoneal inoculation [333]. These findings may be responsible for the enteroglial-sustained intestinal inflammation in IBD because they are similar to the *perpetuum mobile*-like biomachinery probably responsible for the persistent neuroinflammation in patients with autism and other neurodegenerative diseases recently proposed by Prandota [210], in which host-endoplasmic reticulum-parasitophorus vacuole interaction provides a route of entry for antigen cross-presentation in *T. gondii*-infected dendritic cells [15].

GI tract segment	Number of neurons per 1 cm^2		Projection of the number of neurons to total area of each segment of the GI tract	
	CG	EG	CG	EG
Duodenum	1484722.2 ± 17361.6	1593386.2 ± 54598.2	9890064.8 ± 1616305.4	8927671.9 ± 803645.2
Jejunum	888095.2 ± 37079.2	1001719.5 ± 120774.7	111783148.2 ± 10184710.7	95103015.9 ± 838908.5[a]
Ileum	2484920.6 ± 905208.3	3648280.4 ± 349612.2	5505142.8 ± 4148995.7	5813023.8 ± 1918374.8
Caecum	508184.5 ± 34679.0	446130.9 ± 13200.5[a]		
Proximal colon	1482539.6 ± 166102.1	1853174.6 ± 54086.3[a]	17611660.0 ± 3255913.9	12469669.3 ± 1502820.6
Distal colon	1344047.6 ± 79884.2	1445238.0 ± 109044.7	1678276.4 ± 445923.3	12430335.9 ± 4705535.1

Results represent mean ± SD. [a]Values significantly different compared with respective controls ($P < 0.05$)

Table 29: Neuron population density per 1 cm^2 of specific segments of the gastrointestinal tract and projection of these numbers to the total area of each segment of intestine in rats intraperitoneally infected with 10^6 tachyzoites of *T. gondii* type I (BTU IV strain) and examined 6 days post inoculation (acc. to Silva et al. [204]; with own modification).

Important role of mast cells in gastrointestinal inflammation

Mast cells are important in allergy and inflammation [321,353] because they contain histamine, proteoglycans, and neutral proteases in various compositions. Lipid-derived mediators include the metabolites of arachidonic acid by cyclooxygenase and lipogenase, various cytokines (IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, TNF-α, TNF-β) and chemokines (MIP-1, MCP-1) are synthesized and secreted early after contact with antigen [354]. Mast cells play also a regulatory role in the innate and acquired immune responses because they influence T and B cell functions, present antigen to T cells, and can directly stimulate IgE synthesis in B cells [354]. Mast cells are attracted to the molecules secreted by the enterocytes in the basolateral region of the intestinal crypts [206,275], finally inducing NF-κB, which plays a key role in the regulation of the inflammatory, immune and antiapoptotic response in the host infected with *T. gondii* [355]. Interestingly, on the basolateral enterocyte surface of autistic children with gastrointestinal disturbances, deposition of IgG1 and IgG4, co-localizing with complement C1q, was shown to be accumulated compared to healthy controls [7]. It must be noted that *T. gondii* penetrates intestinal epithelial cells, and either develops within them, or exits through the basolateral side and burrows across the basement membrane [224,356]. Buzoni-Gatel et al. [357] showed that the intensity of experimental ileitis after infection with the parasite was controlled by TGF-β-producing intraepithelial lymphocytes (IELs), since primed IELs reduced production of inflammatory chemokines by the infected enterocytes, and IFN-γ by splenocytes. Finally, a striking mast cell-induced myenteric neuronal cell death in culture (probably mediated via PAR_2 activation, IL-6 and prostaglandin D_2) was demonstrated [310].

Segment of GI tract	Group of animals	Cell body area (μm^2)	Nucleus area (μm^2)	Cytoplasm area (μm^2)	Nucleus/cell body area ratio
Duodenum	CG	217.8 (170.6; 297.1)	91.3 (70.1; 121.4)	127.2 (89.6; 188.7)	0.41 (0.33; 0.50)
	EG	167.8 (130.7; 229.4)[a]	74.8 (55.1; 97.3)[a]	94.8 (68.8; 135.7)[a]	0.42 (0.35; 0.51)[a]
Jejunum	CG	195.4 (155.5; 242.5)	99.7 (82.2; 121.8)	91.5 (66.5; 125.5)	0.52 (0.44; 0.59)
	EG	188.4 (149.9; 236.7)	90.0 (74.1; 109.2)[a]	95.9 (68.0; 134.3)[a]	0.48 (0.41; 0.56)[a]
Ileum	CG	159.2 (120.9; 205.3)	66.0 (48.0; 90.1)	89.5 (65.0; 122.7)	0.42 (0.34; 0.49)
	EG	102.5 (77.6; 136.7)[a]	41.0 (28.9; 56.6)[a]	59.3 (44.2; 81.4)[a]	0.40 (0.33; 0.48)[a]
Caecum	CG	229.2 (164.3; 321.5)	89.4 (60.6; 129.2)	133.3 (93.8; 199.0)	0.38 (0.30; 0.47)
	EG	259.5 (189.5; 365.2)[a]	92.1 (63.6; 128.8)	160.5 (107.9; 244.6)[a]	0.34 (0.26; 0.45)[a]
Proximal colon	CG	225.9 (168.4; 299.0)	91.9 (62.4; 126.3)	130.1 (87.9; 189.2)	0.42 (0.31; 0.52)
	EG	180.9 (136.1; 244.3)[a]	76.8 (52.3; 107.6)[a]	101.2 (72.6; 144.6)[a]	0.41 (0.32; 0.52)
Distal colon	CG	232.1 (169.4; 315.8)	89.4 (64.6; 125.7)	133.5 (95.8; 202.9)	0.38 (0.30; 0.47)
	EG	209.0 (161.7; 286.8)[a]	92.7 (65.0; 124.8)	119.8 (84.9; 170.3)[a]	0.42 (0.34; 0.50)[a]

Results represent median and P25, P75 percentiles. [a]Values significantly different compared with respective controls ($P < 0.05$)

Table 30: The cell body, nucleus and cytoplasm areas, and the nucleus/cell body area ratio of myenteric neurons of specific segments of the gastrointestinal tract in rats intraperitoneally infected with 10^6 tachyzoites of *T. gondii* type I (BTU IV strain) and examined 6 days post inoculation (acc. to Silva et al. [204]; with own modification).

Time after infection	Group of animals		% Mean (± SD)		
(hrs)		Lymphocytes	Macrophages	Mast cells	Neutrophils
1	EG	91.3 ± 5.7	3.6 ± 3.7	3.7 ± 3.7	1.3 ± 2.2
	CG	93.3 ± 1.2	1.0 ± 1.7	4.8 ± 1.7	0.9 ± 1.6
3	EG	90.3 ± 3.7	2.6 ± 2.9	5.2 ± 1.1[a]	2.0 ± 2.0
	CG	93.5 ± 1.4	0.7 ± 1.1	3.6 ± 2.0	2.3 ± 2.2
6	EG	92.8 ± 0.8	2.9 ± 1.0	3.1 ± 0.4	1.2 ± 0.2
	CG	94.7 ± 2.3	1.6 ± 0.5	2.8 ± 0.9	0.9 ± 1.5
12	EG	81.1 ± 5.5	7.0 ± 1.9	4.1 ± 0.9[a]	7.9 ± 2.9[a]
	CG	97.5 ± 0.6	1.1 ± 0.0	1.1 ± 0.0	0.3 ± 0.6
24	EG	63.2 ± 7.5	4.7 ± 1.6	1.1 ± 0.3	31.0 ± 6.8[b]
	CG	97.1 ± 0.9	0.5 ± 0.9	1.7 ± 0.1	0.6 ± 1.0
36	EG	57.5 ± 12.5	12.5 ± 3.9	7.4 ± 1.3[a]	22. 6 ± 7.3[b]
	CG	92.4 ± 5.9	3.7 ± 4.4	2.8 ± 2.8	1.1 ± 1.8
48	EG	72.3 ± 3.9	5.7 ± 3.7	6.3 ± 3.2[a]	15.7 ± 0.9[b]
	CG	93.8 ± 2.9	2.5 ± 2.2	2.6 ± 2.3	1.1 ± 1.9

Values statistically significant when compared with controls, [a]($P < 0.05$), [b]($P < 0.01$)

Table 31: Relative numbers of lymphocytes, macrophages, mast cells and neutrophils from peritoneal cavity of the wild mouse *Calomys callosus* intraperitoneally infected with 10^5 tachyzoites of *T. gondii* RH strain, from 1 to 48 hrs post inoculation, when compared with uninfected animals (acc. to Ferreira et al. [333]; with own modification).

Cell type	Parasite division rate		**Mechanism**	References
	Unprimed	IFN-γ primed		
Hematopoietic				
Lymphocyte	S			[336]
Neutrophil	S			[336-338]
Adherent monocyte	S			[338-342]
Nonadherent monocyte	R	R	ROS; not TS	[336,343]
Dendritic cell	R			[336]
Alveolar macrophage	R	S	Partly TS	[342]
Peritoneal macrophage	R	S		[344]
Monocyte-derived macrophage	R	S	ROS; not RNI	[339,341,342,344, 345]
Nonhematopoietic				
Neuron	S			[346]
Foreskin fibroblast	R	S	TS	[347,348]
Umbilical vein endothelial cell	R	S	TS or ROS; not RNI	[347,349]
Retinal pigment epithelal cell	R	S	TS	[350]
Fetal astrocyte	R	S	RNI	[346,351,352
Fetal microglial cell	R	R		[352]

R: Rapid; S: Slow; RNI: Reactive Nitrogen Intermediates; ROS: Reactive Oxygen Species; TS: Tryptophan Starvation

Table 32: Division rate of intracellular *T. gondii* tachyzoites in primary human cells in vitro (acc. to Channon et al. [336]; with own modification).

Serum Antineutrophil Cytoplasmic Autoantibodies (ANCA) in Patients with Inflammatory Bowel Disease (IBD) may be Generated by Chronic Oral *T. Gondii* Infection

Lidar et al. [358] demonstrated that titers of anti-IgM (7.5 vs. 1%) and anti-IgG (33 vs. 26.9%) antibodies toward *T. gondii,* hepatitis C virus (HCV) and *Saccharomyces cerevisiae* were markedly higher in sera of IBD patients (80 with CD, 39 with UC) than in controls (98 healthy individuals). The higher prevalence of IgM antibodies resulted from a significantly increased frequency in CD patients (13.5 vs. 1%, $P < 0.001$). They suggested that whereas an excess of anti-HCV may be the result of immunosuppression from the inflammatory disease, the parasite has an initiating role in the etiopathogenesis of human IBD, especially CD, thus corroborating the murine model [276,358]. Although Lidar et al [358] did not cite or discuss this finding in their later publications, they believed that certain infections via for example molecular mimicry could generate an immunological environment that confers protection from certain autoimmune conditions, such as CD [358,359]. Most recently, Egan et al. [360] also proposed that *T. gondii* acts as a trigger setting into motion a series of events culminating in loss of tolerance in the intestine and emergence of pathogenic T cell effectors. This suggestion was based on the finding that oral infection of certain inbred mouse strains with the parasite caused inflammatory pathology resembling lesions seen during human IBD, in particular CD [360].

Perinuclear ANCA has been found consistently in serum of children and adults with IBD, and occurs significantly more often in UC than in CD [361-365]. The presence of ANCA may be associated with peroral *T. gondii* infection of those individuals because Rattan et al. [106] demonstrated a higher incidence of positive Sabin-Feldman dye test to the parasite among patients with Crohn's disease over the age of 40 ($P < 0.05$). This finding is in line with the increased seropositivity to *T. gondii* infection along with age reported by Hinze-Selch et al. [366] (Table 33). [Nb. the seroprevalence of anti-Toxoplasma IgG antibodies and IgG titers was found to be significantly higher in patients with abdominal hernia repair than those without hernia, and in ≥ 50 years old individuals than those < 50 yrs old [367]. This is also in agreement with the above-presented reasoning that the parasite causes damage to myenteric neurons and markedly affects the cell body, nucleus and cytoplasm areas and nucleus/cell body ratios depending on acute or chronic infection (Tables 13-18,25,28,30). It should be noted that the parasite has the ability to infect every type of nucleated cell in mammals, including neutrophils, and Ferreira et al. [367] demonstrated a remarkable increase in the influx of neutrophils toward the peritoneal cavity of infected experimental animals already 12 hrs post infection (Table 31). It was reported that mast cell-deficient mice displayed a

Percent *T. gondii* positive	Age (yrs)											
	18-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75
100												100
80									80		80	
60							58	58		60		
40		35	32	40	39	38						
20	19											
0												

In the control individuals 45 yrs or younger recruited from the same geographical region as the psychiatric patients admitted to the hospital, serofrequency of *T. gondii* infection ranged between 20 and 40% without any systematic age effect, whereas in the individuals older than 45 yrs serofrequency systematically increased with age from about 40% to almost 100% [366]

Table 33: Percentage of *T. gondii* positive individuals among 214 nonpsychiatrically affected controls depending on age analyzed during a large epidemiologic study of 869 psychiatric patients [366]).

Erythropoietin
IL-1, IL-6, IL-8
Nitric oxide synthase-2
Heme oxygenase-1
Ornithine decarboxylase; hexokinase 2
Phosphofructokinase L; phosphoglycerate kinase-1
Pyruvate kinase M; glucose transporter-1, -3
Lactate dehydrogenase A
Glyceraldehyde-3-phosphate dehydrogenase
Insulin-like growth factor-2; enolase 1
Aldolase A, C; adenylate kinase 3
Pituitary adenylate cyclase-activating polypeptide
Transforming growth factor β_3
Vascular endothelial growth factor

Table 34: Hypoxia-inducible gene expression [380].

		No of	cases			
		T. gondii	type			
Clinical findings	Time of maternal infection, weeks	I	II	III	Atypical	Total
Fetal death	2-11[a]		6			6
Newborn death	Unknown	1	2			3
Severe toxoplasmosis	7-17	2	16		3	21
Asymptomatic or benign toxoplasmosis	15-38		43	2		45
Child not infected, placenta positive	14-20[b]	4				4
No clinical data available	10-31		6		1	7
Total		7	73	2	4	86

[a]One reactivation during AIDS. [b]One reinfection or reactivation

Table 35: Clinical characteristics of fetus and newborns with *T. gondii* infection, and relationship with the main genotypes of the parasite (acc. to Ajzenberg et al. [385]; with own modification).

significant defective ability to recruit PMNs during early infection by *T. gondii,* which suggested that these cells served as a major effector cell type involved in neutrophil recruitment, and CXCR2 was required for this process [368]. Finally, recently Prandota [210] suggested that the increased generation of antibodies directed against brain proteins in patients with autism and their families may be caused by *T. gondii* infection and emphasized possible important role of maternal and fetal microchimerisms in these processes.

Prenatal and Postnatal Oral *T. Gondii* Infection May Cause Development of Necrotizing Enterocolitis and Inflammatory Bowel Disease in Newborns, Children and Adults

Necrotizing enterocolitis (NEC)

NEC, an inflammatory disease of the terminal ileum, cecum, and ascending colon, is the most common gastrointestinal disease of infancy, afflicting 5-15% of all infants born at less than 30 weeks gestational age or < 1500 gm birth weight. However, up to 10% of all neonates who develop NEC are born at term [369,370]. NEC occurs principally in premature infants after the introduction of artificial oral feeding [371]. Pathophysiology of NEC in term infants is often associated with congenital heart disease, a recent "bypass" operation, hypoxemic-ischemic events, polycythemia [115,372]. There is also strong evidence that the initial bacterial colonization of the newborn intestine plays a pivotal role in the development of NEC [114,373,374]. Pathologic microorganisms, particularly Gram-negative bacteria, such as, Enterobacter, Enterococcus Clostridia, and Staphylococcus, are predominant fecal bacterial species with very little colonization with Bifidobacteria [115,375]. LPS interaction with enterocytes via TLR-4 involves activation of NF-κB to stimulate generation of various proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, IL-18 [115], and for instance, IL-8 stimulates migration of neutrophils from intravascular to interstitial and luminal sites [374]. It was found that immature human enterocytes react with excessive proinflammatory cytokine production, and IL-8 activity was noted predominantly in villous and crypt epithelium but also in a few immunoresponsive lymphoid cells [376]. In addition, there was a pronounced TLR-4 expression documented in fetal human intestine [377] and in formula-fed and hypoxia-stressed rats [115,378]. In this context, it must be emphasized that *T. gondii* activates hypoxia-inducible factor 1 (HIF1) already at physiologically relevant oxygen levels and requires HIF1 for growth and survival [379], and HIF1 activates gene expression of several proinflammatory cytokines (including NO synthase-2), various enzymes, and biologic substances (e.g. erythropoietin) (Table 34). [Nb. erythropoietin is a breast milk and amniotic fluid component that plays an important role in intestinal development, cell migration, and intestinal restitution [381,382].] It must be noted that hypoxia as a risk factor of NEC development and its intensity is in line with recent suggestion that migraine associated with patent foramen ovale may be caused by reactivation of cerebral toxoplasmosis triggered by arterial blood oxygen desaturation [380], and also with hypoxemic-ischemic events associated with clinical course of other congenital heart diseases [372]. Finally, hypoxia may also impair function of the CO_2, aquaporin 1 (AQP1), and AQP4 gas channels, thus enhancing neuroinflammation in children with NEC, especially those with RhAG phenotype of the red blood cells, as it was suggested in autistics [383]. Recently, in the U.S. Olariu et al. [384] reviewed clinical data and laboratory profiles of 164 infants with congenital toxoplasmosis whose mothers had not been treated for the parasite during gestation and found that 84% of the infants had one or more severe clinical manifestations, including eye disease (92.2%), brain calcifications (79.6%), and hydrocephalus (67.7%). In 61.6% of the infants, these abnormalities were present concurrently. It appeared that *T. gondii*-specific IgM, IgA, and IgE antibodies were demonstrable in 86.6%, 77.4%, and 40.2% of the infants, respectively. The authors emphasized that these results contrast remarkably with several European investigators who rarely observe severe clinical signs in infants with congenital toxoplasmosis [384], and one cannot exclude that *T. gondii* genotype as well as various diagnostic methods used estimating only certain parasite antigens may be at least in part responsible for the difference (Tables 35-37). It is now apparent that many atypical genotypes exists besides the typical 3 genotypes that can differ in pathogenicity and transmissibility from the typical genotypes used so far in scientific research, thus changing paradigm of congenital toxoplasmosis [388].

	Successful pregnancies	Unsuccessful pregnancies	Total pregnancies
Number of pregnancies	119	2	121
PCR-positive pregnancies	24	0	24
Percentage congenital transmission	20.1 ± 7.2	0 ± 0	19.8 ± 7.1

SAG1 PCR was used to measure infectivity of human umbilical cord samples with the parasite. Unsuccessful pregnancies were defined as involving the loss of one or more baby during birth. Percentages are supplied with 95% confidence levels (±). It must be noted that SAG1 is exclusively expressed only on the tachyzoites (and not on bradyzoites!) and induces the dominant antibody response during infection [257,258]

Table 36: Congenital transmission of *T. gondii* in humans. (acc. to Hide et al. [386]; with own modification).

Gestational age (weeks)	Vertical transmission (%)	Morphological abnormalities (%)
6-20	21	11
21-30	63	4
> 30	89	0

Table 37: Risk of *T. gondii* vertical transmission and frequency of morphological abnormalities of fetus with increasing gestational age [387].

Ajzenberg et al. [385] studied the influence of *T. gondii* genotypes on the severity of human congenital toxoplasmosis (asymptomatic, benign, or severe infection of newborn or fetal death) and showed that type II isolates were largely predominant (84.88% of 74 different genotypes and 96.49% in 57 consecutive cases) (Table 35). Type I and atypical isolates were not found in asymptomatic or benign congenital toxoplasmosis, and in 4 cases *T. gondii* was isolated from placenta [385], which may suggest that these children after all were infected with the parasite via maternal microchimerism.

Development of NEC may be due to prenatal or postnatal peroral infection with the parasite because, for example Bonapaz et al. [229] showed that chicken infected with oocysts of *T. gondii* type III (M7741 strain) and examined after 60 days had diarrhea, inflammatory infiltrates in the tunica mucosa, and duodenum layers atrophy (decreased thickness of all the studied bioparameters) (Table 26), as well as about 70% loss of intestinal myenteric plexus neurons. These alterations of the intestinal wall and myenteric plexus of hen duodenum leading to diarrhea irreversibly impair acquisition of nutrients and gastrointestinal tract motility, finally resulting in death of animals. One cannot exclude that similar sequence of pathophysiological events plays an important role also during development of NEC in young infants. This reasoning may be supported by the morphologic alterations of the ENS and deficiency of non-adrenergic non-cholinergic (NANC) inhibitory innervation reported in neonatal NEC [389,390]. The deficiency in NANC inhibitory innervation may contribute to the formation of functional obstructions following acute NEC [389]. Examination of the myenteric plexus and external submucosal plexus by whole-mount immunohistochemistry revealed a marked reduction in glial cells concomitant with gradual deterioration of nerve cells, both abnormalities predominating in antimesenteric intestinal circumference, where ischemic lesions tended to appear first [390]. The most severe damage of nervous tissue was found in the plexus mucosus and submucosus internus. The destroyed ganglia appeared like "empty baskets" (residual tangles) and housed both glial and nerve cells with various stages of cell deterioration and the formation of central lesions within the myenteric ganglia [389,390]. It must be noted that neurons of the ENS are intimately associated with enteric glial cells that share many similarities with astrocytes of the CNS, and acute loss of enteric gial cells induces massive pathological changes with similarities to NEC and early Crohn's disease [391]. In this context, it must be emphasized that reduction of Purkinje cell size (by 24-50%), number, and cerebellar volume, particularly of the posterior lobe, was reported in the patients with autism [392,393]. Recently, Arndt et al. [394] suggested that these findings may be explained by the finding that the Purkinje cell body is wrapped by processes of the neighboring basket cells therefore the late loss of Purkinje cells is characterized by the presence of "empty baskets". Prenatal exposure of rats to valproic acid also reproduced the cerebellar anomalies associated with autism [395]. Interestingly, gastrointestinal symptoms, such as nausea, vomiting, dysphagia, constipation, diarrhea, and heartburn, were highly common adverse effects of valproate in intractable epileptic patients treated with valproate for a long-time [396,397].

Finally, pathognomic of NEC pneumatosis intestinalis creating characteristic indentations sometimes seen radiographically and endoscopically [398,399] may be caused by heme oxygenase-1 system activation leading to generation of CO, which plays an important protective role during acute and chronic gastrointestinal inflammation and oxidative injury [400-402]. Otterbein et al. [401] demonstrated that CO inhibits production of proinflammatory cytokines (TNF-α, IL-1β, macrophage inflammatory protein-1β) and stimulates synthesis of the antiinflammatory cytokine IL-10.

Cytomegalovirus-Associated Nec and Other Gastrointestinal Tract Abnormalities May Be Rather Caused by *T. Gondii* Infection Comorbidity

Gastrointestinal manifestations of post-natally acquired cytomegalovirus (CMV) in preterm neonates can vary from mild diarrhea to severe NEC. CMV has been detected in breast milk in 32 to 96% of CMV seropositive mothers and the rate of transmission was 37% [403]. Gessler et al. [404] reported a development of NEC in a preterm twin after breastfeeding and his CMV serology tests determined at the 5th, 13th, and 27th week of gestation were IgG 85, 92, ad 94 U/ml (positive), respectively, and the IgM negative. However, the child was also *Toxoplasma*-IgG seropositive (IgG 39 U/ml, IgM negative), which may suggest chronic infection. CMV was detected also during acute NEC [405], as well as during the proliferative stage of stricture development after NEC [406-408], and ileal perforations and gastrointestinal beeding have been reported even in elderly immunocompetent individuals [409-413]. The clinical and endoscopic features of 20 cases with gastrointestinal CMV disease showed that many patients were immunocompromised, and the endoscopic abnormalities involved inflammatory mucosa alone (3/20), ulceration alone (7/20), inflammatory mucosa associated with ulcer (9/20), and submucosal tumor with ulcer (1/20), and the most common abnormality were multiple ulcers with at least one large ulcer [414]. Rafailidis et al. [415] analyzed 89 articles reporting on severe CMV infection in 290 apparently immunocompetent adults and found that the gastrointestinal tract (colitis) and the CNS (meningitis, encephalitis, and transverse myelitis) were the most frequent sites of infection. Constant seroprevalence of *T. gondii* and CMV infection reported among pregnant women (anti-Toxoplasma IgG antibody vs anti-CMV IgG, 48.3%-69.3% vs. 76.6%-96.4%, respectively) [416-418], as well as the common comorbid pathology of HIV-infected patients (CMV infection vs cerebral toxoplasmosis, 10.1% vs. 9.2%, respectively [419], may suggest that the gastrointestinal abnormalities found in CMV seropositive children and adults were at least in part due to concomitant *T. gondii* infection.

Chronic Constipation may be due to Post-Inflammatory Damage to the Enteric Nervous System by Prenatal or Postanatal Oral *T. Gondii* Infection

Chronic constipation with megarectum is frequently reported in children with autism [420]. It is known that malformations or lesions of the ENS may lead to a severely prolonged intestinal transit time resulting in chronic constipation resistant to conservative treatment. The most recognized intestinal innervation disorder

represented aganglionosis (Hirschsprung's disease) characterized by the absence of intramural nerve cells and the hypertrophy of the nerve fiber bundles within the affected intestinal segment [421]. Non-aganglionic intestinal innervation abnormalities include intestinal neuronal dysplasia (IND), hypoganglionosis and heterotopic ganglia [422]. At present, the pathogenesis of intestinal neuronal malformations

is mainly attributed to developmental disorders of the ENS, in part caused by genetic defects, and until now no unified pathophysiological concept has been established to explain the ENS sustained damage during the postnatal period [421]. Histologic study of Tomita et al. [423] performed in children (aged 2-15 years) with chronic refractory constipation, such as Hirschsprung's disease, hypoganglionosis, and IND, showed that the incidence of hypoganglionosis was significantly greater than that of hypoganglionosis and IND ($P < 0.01$, $P < 0.001$, respectively). Both these entities could be diagnosed by full-thickness rectal mucosal biopsies, especially by NADPH-diaphorase and acetylcholinesterase staining [423,424]. Wester et al. [425] investigated specimens obtained from postmortem small bowel and colon in 20 children (aged one day to 15 years) with IND and found that the density of ganglion cells in the myenteric plexus decreased significantly with age during the first 3-4 years of life at all levels of small bowel, colon, and rectum. The meshwork of fibers also becomes sparser during that time. The histological features of IND are mainly confined to the submucosus plexus [425]. However, Meier-Ruge [426] also found hyperplasia of the myenteric plexus, and rarely, isolated hyperganglionosis of the myenteric plexus with no submucous abnormalities has been described [427]. It appeared also that the NADPH diaphorase positive (nitrergic) subpopulation represented about 34% of all neurones in the myenteric plexus [425]. In adult patients with slow-transit constipation and megacolon, the intramuscular networks of the interstitial cells of Cajal showed a significantly reduced density (nb. interstitial cells of Cajal contribute markedly to the mediation of intestinal motility by generating "slow wave" activity) [424]. All these marked postnatal alterations in the myenteric plexus, and huge variations between these reports analyzed by Wester et al. [425] may be in part explained by various *T. gondii* genotypes and numbers of oocysts/sporozoites/bradyzoites/tachyzoites affecting different parts of the gastrointestinal tract of patients with IND. This suggestion is supported by the morphological changes in the cecal myenteric neurons depending on the genotype I (BTU IV) or III (BTU II) *T. gondii* strains [428]. The parasite dose of 10^5 tachyzoites administered orally in rats tested later positive for the presence of IgG

Region	CG	EG1	EG2
AA	212.8 ± 32.4	312.0 ± 58.3[a]	269.4 ± 21.7
AB	213.8 ± 85.0	305.2 ± 50.1	189.6 ± 65.1
MA	307.4 ± 63.7	344.8 ± 45.4	231.2 ± 34.2
NA	330.4 ± 133.0	432.2 ± 58.1	336.2 ± 97.8
AA + AB + MA + NA	1064.4 ± 300.2	1394.2± 117.4	1026.4 ± 184.2

AA: Antimesenteric Apical Region; MA: Mesenteric Apical Region; AB: Antimesenteric Basal Region; NA: next to the Cecal Ampulla; AA + AB + MA + NA = Entire Cecum, [a]$P < 0.05$

Table 38: Myenteric neuron population density in the four regions of the cecum and the entire organ of control rats (CG) and rats inoculated with the genotype I (EG1) and genotype III (EG2) strains of *T. gondii* (mean ± SD) (acc. to Zaniolo et al. [428]; with own modification).

Region	CG	EG1	EG2
AA	77.4 (55.2; 98.8)	68.7 (37.4; 98.8)[a]	90.3 (65.8; 129.6)[a]
AB	79.5 (57.6; 106.2)	60.9 (39.0; 93.6)[a]	98.7 (66.4; 137.2)[a]
MA	80.3 (51.9; 112.0)	81.3 (45.1; 103.1)	96.9 (66.1; 130.8)[a]
NA	72.6 (52.0; 96.1)	59.1 (37.0; 91.7)[a]	87.8 (61.3; 120.7)[a]
AA + AB + MA + NA	78.1 (54.7; 102.8)	65.0 (38.9; 98.4)[a]	92.5 (64.2; 129.9)[a]

EG: Experimental Group; AA: Antimesenteric Apical Region; MA: Mesenteric Apical Region; AB: Antimesenteric Basal Region; NA: next to the Cecal Ampulla; AA + AB + MA + NA = Entire Cecum. [a]$P < 0.05$

Table 39: Nuclear area of myenteric neurons in the four regions of the cecum and the entire organ of control rats (CG) and rats inoculated with the genotype I (EG1) and genotype III (EG2) strains of *T. gondii* (median and percentiles 25; 75) (acc. to Zaniolo et al. [428]; with own modification).

Region	CG	EG1	EG2
AA	176.3 (109.0; 256.9)	179.5 (85.2; 317.0)	188.3 (115.3; 298.4)
AB	228.8 (138.0; 394.0)	134.9 (81.8; 239.5)[a]	195.5 (117.9; 315.0)[a]
MA	216.1 (115.1; 357.5)	170.9 (92.1; 207.0)[a]	185.9 (119.6; 295.4)
NA	164.1 (102.1; 279.6)	129.8 (79.7; 207.0)[a]	158.8 (97.2; 258.6)
AA + AB + MA + NA	193.4 (114.1; 321.7)	148.5 (84.0; 271.2)[a]	181.3 (111.7; 290.4)[a]

EG: Experimental Group; AA: Antimesenteric Apical Region; MA: Mesenteric Apical Region; AB: Antimesenteric Basal Region; NA: next to the Cecal Ampulla; AA + AB + MA + NA = Entire Cecum. [a]$P < 0.05$

Table 40: Cytoplasmic area of myenteric neurons in the four regions of the cecum and the entire organ of control rats (CG) and rats inoculated with the genotype I (EG1) and genotype III (EG2) strains of *T. gondii* (median and percentiles 25; 75) (acc. to Zaniolo et al. [428]; with own modification).

Region	CG	EG1	EG2
AA	256.5 (167.1; 342.5)	249.7 (126.3; 422.8)	287.2 (190.6; 419.7)[a]
AB	310.7 (199.3; 503.4)	199.5 (130.7; 344.2)[a]	298.1 (187.8; 460.6)
MA	297.7 (169.0; 452.6)	254.2 (147.6; 447.0)	290.4 (186.6; 422.5)
NA	238.8 (162.4; 375.7)	198.6 (122.8; 290.0)[a]	251.1 (165.3; 386.5)
AA + AB + MA + NA	275.1 (172.0; 426.9)	221.0 (130.7; 376.5)[a]	280.7 (178.8; 417.7)

EG: Experimental Group; AA: Antimesenteric Apical Region; MA: Mesenteric Apical Region; AB: Antimesenteric Basal Region; NA: next to the Cecal Ampulla; AA + AB + MA + NA = Entire Cecum. [a]$P < 0.05$

Table 41: Cell body area of myenteric neurons in the four regions of the cecum and the entire organ of control rats (CG) and rats inoculated with the genotype I (EG1) and genotype III (EG2) strains of *T. gondii* (median and percentiles 25; 75) (acc. to Zaniolo et al. [428]; with own modification).

against *T. gondii* caused different effects on the population density and morphometry of myenteric neurons within the four regions of the intestine investigated (Tables 38-41) [428]. Moreover, it was found that although *T. gondii* RH and Ankara strains had dense protein bands between 60 and 70 kDa and at 15 kDa, TS-4 strain had different and fewer bands [429]. This may at least partly serve as an explanation for the differences in molecular weights of antibodies and autoantibodies against brain proteins reported in various autistic individuals [210].

Headache, Abdominal Migraine, Recurrent Abdominal Pains and Development of IBD

A link between recurrent headache/migraine and gastrointestinal disorders has been confirmed by many clinical observations and epidemiologic studies [430-434].

Abdominal migraine (AM) occurs in 1-4% of children and represents 4-15% of pediatric gastroenterology patients followed for idiopathic non-colicky abdominal pain [435-437]. Pallor, anorexia, nausea, vomiting, photophobia, or headache may be associated with the episodes, and a family history of migraine headaches often is noted. AM emerges between the ages of 3 and 10 years [438], and evidence suggests its evolution into migraine headaches, being a "precursor of migraine" [439]. Carson et al. [437] found that it was 4 times more likely for a patient with recurrent abdominal pain to have AM if they also had migraine headache ($P < 0.024$), and an esophagoduodenoscopy performed as part of their diagnostic evaluation ($P < 0.008$). Frequently reported clinical features among suspected AM patients included nausea ($P < 0.001$), vomiting ($P < 0.038$), and anorexia ($P < 0.001$). The nonabdominal pain has been reported as periumbilical (63% of patients), midline (11%), and poorly localized (5%) [438]. In preschool-age children recurrent abdominal pain epidemiology showed a prevalence ranging from 0.3% to 19% (median 8.4%) higher in females [441,442].

Endoscopic examination performed in a consecutive series of 31 children (median age 12 yrs) with recurrent abdominal pain

Drug	Solvent	ID_{50}[a] (μg/ml)	TD_{50}[b] (μg/ml)	TI[c]
Valproic acid	ethanol	4.5	62.4	13.9
Sodium valproate	ethanol	4.1	52	12.7
Carbamazepine	ethanol	72	100	1.3
Lithium carbonate	1 N HCl	> 100	> 100	
Haloperidol	ethanol	5.6	103	18.4
9-OH-Risperidone	tartaric acid	20.1	134	6.7
Risperidone	tartaric acid	74	129	1.7
Fluphenazine HCl	Toxo CGM	3.5	17.9	5.1
Clozapine	ethanol	5.8	20	3.4
Olanzapine	DMSO	33.2	100	3.0
Chlorpromazine HCl	DMSO	2.6	6	2.3
Quetiapine fumarate	DMSO	18.6	33	1.8
Trimethoprim	DMSO	5.3	63.8	12.1

[a]Median inhibitory dose, a measure of tachyzoite inhibition. [b]Median toxicity dose, a measure of cytotoxicity. [c]Therapeutic index, a measure of efficacy determined by TD_{50}/ID_{50} ratio. DMSO, dimethylsulfoxide; Toxo CGM, Toxoplasma cell growth medium. Valproic acid at a concentration of 1 μg/ml inhibited 7% of the tachyzoites and trimethoprim at 3.2 μg/ml produced 2% inhibition, but the combination of these two compounds at those concentrations resulted in a potentiating effect inhibiting 55% of the tachyzoites

Table 42: Drugs tested for in vitro activity against *T. gondii* (acc. to Jones-Brando et al. [450]; with own modification).

and suffering from migraine with (n = 21) or without (n = 10) aura demonstrated that 41.9% of them had esophagitis, 51.6% - gastritis of corpus, 38.7% - antral gastritis, and 87.1% had duodenitis [432].

In one neurologic study, functional gastrointestinal disorders were reported in 69% of patients with migraine in periods between the attacks (eg. diarrhea in 16-20%), and specifically IBS in 43% of them [443]. Watson et al. [430] found that frequent headaches were noted by 50% of 90 patients with IBS and only 18% of controls (447) ($P < 0.001$). In the IBS group, the headaches were age-related, the prevalence being greatest (65%) in women 16 to 30 years of age and diminishing with advancing age. Investigations based on a questionnaire performed in general population (1620 persons) showed that migraine was present in 32% (112 questioned individuals) of patients with IBS compared with 18% (229) ($P < 0.01$) of those without the syndrome [431].

Finally, it must be noted that the recurrent headache/migraine attacks have been reported in several infants, children, adolescents, and adults with markedly increased serum anti-*T. gondii* IgG antibody levels, and pharmacological treatment directed against the parasite was successful in those individuals [444-446]. These findings may be indirectly supported by the fact that intravenous valproic acid, a drug used for migraine prophylaxis, has been on occasion administered with apparent success in cases of abdominal migraine [447-449], and *in vitro* studies showed its high activity against *T. gondii* (Table 42) [450].

Development of Metabolic Syndrome in Patients With IBD may be due to *T. Gondii* Infection

Metabolic syndrome (MetS) is a chronic inflammatory disease characterized by abdominal obesity, impaired glucose metabolism, dyslipidemia with elevated triglycerides, low high density lipoproteins, and hypertension [451]. Nagahori et al. [452] showed that in their cohort of 107 quiescent IBD patients (76 with UC, 31 with CD; 21.1% of males, 12.9% females) the prevalence of MetS was comparable to that of the general population. Yorulmaz et al. [453] reported frequent occurrence of MetS with increasing age in 177 patients with IBD (62 had CD and 115 UC), especially in UC than in CD (29.5 vs. 17.7%, $P < 0.01$). MetS was diagnosed in 10.3% of patients with IBD, under 45 yrs of age, and in 55% of patients over 45 yrs of age ($P < 0.0001$) [452,453].

Intestinal inflammation in IBD may arise primarily from intraepithelial cells dysfunction due to unresolved endoplasmic reticulum (ER) stress caused by the accumulation of misfolded or unfolded proteins within the ER [454-456]. Impairment of proper ER stress resolution in highly secretory Paneth and, to lesser extent goblet cells within the epithelium, can primary lead to intestinal inflammation [454,457,458]. The range of environmental factors possibly leading to ER and development and/or perpetuation of intestinal inflammation include those associated with bacteria, metabolic factors, drug effects, hypoxia, and inflammation itself [455]. It must however be emphasized that congenital or acquired oral *T. gondii* infection should also be included in these environmental factors because the host cell ER-parasitophorus vacuole interaction provides a route of entry for the parasite antigens cross-presentation in *T. gondii* -infected dendritic cells [15]. Recently, Prandota [210] proposed to term this close relationship a "*perpetuum mobile*-like machinery" because the parasite or its fragments remain in the host cell permanently, thus being a constant source of various antigens. C-reactive protein has been shown to be an objective marker of intestinal inflammation and fecal lactoferrin important for the innate defense against *T. gondii* infection (sic!) and calprotectin may be helpful in differentiating patients with IBD from those with functional disorders and to predict clinical relapse [459].

Similarities between MetS in IBD and Clinical/Metabolic Changes Found in Patients With ASD as well as These in the Host Cell Proteome Caused by *T. Gondii* Infection

Children with autism had a serious prevalence of at-risk-for overweight and overweight [460-463]. Xiong et al. [460] found that among 380 boys and 49 girls with ASD, the prevalence of at-risk-for or being overweight were 31.8% and 17% in 2-5 years old group, and 37.9% and 21.8% in 6-11 years old group. Other authors reported [461] that the prevalence of at-risk-for-overweight was highest in the 12-17.9 years old group, and in a large study of 20,031 Japanese children and adolescence with mental retardation that included 413 children with autism, the prevalence of obesity was 22% in boys and 11% in girls [463]. Proinflammatory cytokines, such as IL-1, TNF-α, sTNFR-1 and sTNFR-2 have been shown to be elevated in obese patients/animals and to decline with weight loss [464,465], in general population [452], as well as in obese prepubertal children [466,467]. In those children statistically significant positive correlations were found between serum leptin and IL-2, IL-1β, IL-6 or TNF-α concentrations [466]. There was also a significant negative correlation between leptin and IL-2 serum concentrations [466]. Wiest et al. [468] showed significantly changed plasma fatty acid profiles in children with autism, including phosphatidylcholine and phosphatidylethanolamine, and suggested that the function of perioxosome and the enzymes of the perioxosome involved with fatty acid metabolism may be affected in this clinical entity.

T. gondii infection induced lipid metabolism alterations in the murine host [469]. A significant decrease in plasma HDL and total cholesterol concentrations was first noted at day 14 and persisted to day 42 after inoculation by oropharyngeal gavage with 8 cysts, and at day 42 serum LDL levels correlated with the brain cysts counts of above 300 (44% of the infected mice), while the change in HDL between days O and 42 correlated with both the overall mean cyst count and cyst counts above 300 [469]. The parasite can synthesize lipids *de novo*, as

Environmental factors	UC	CD
Smoking	↓↓↓	↑↑↑
Appendectomy	↓↓	0
High-level public health in childhood	0	↑↑
Sugar intake	0	↑
Infection in delivery	?	↑
Breast feeding	↓?	?
Oral contraceptives	↑?	?

Table 43: Possible effect of some environmental factors on clinical course of UC and CD [475].

well as actively scavenge specific lipids and sterols from the extracellular milieu, lipid bodies, and mitochondria [464,470-473]. It appeared that *T. gondii* employs host low-density lipoprotein receptor (LDLr) to acquire cholesterol and favor its growth, and in the presence of hypercholesterolemia the parasites are able to acquire cholesterol-rich lipoproteins through an alternative host receptor, and overcome LDLr deficiency, favoring host parasitism and impairing lipid loading of foam cells [465]. It must be also noted that mast cells, like macrophages and T lymphocytes, are inflammatory cells that participate in the pathogenesis of inflammatory diseases such as cardiovascular complications and metabolic disorders, including involvement in insulin resistance and type 2 diabetes, therefore playing an important role in development of MetS [474]. Mast cells are also believed to play an important role in development of ASD [320,321,353].

Studies of Nelson et al. [472] showed that the host cell proteome responds in a dramatic way to *T. gondii* invasion, in terms of both protein expression changes and protein modification, and revealed a complex and intimate molecular relationship between host and parasite. Modulation of the host metabolism was intrinsic to the cell response to infection, and overall out of 30 affected proteins 16 proteins were downregulated, with only 10 being upregulated and the remaining 4 modulated [472]. Each of the 4 proteins directly involved in lipid and sterol metabolism identified by Nelson et al. [472] (carbonyl reductase 1, vigilin, cargo selection protein TIP47, and LRP protein) was downregulated in response to infection. Also, several proteins involved in glycolysis, amino acid metabolism, and other aspects of intermediary metabolism essential to lipid synthesis exhibited marked changes [472].

Differences in Susceptibility of the Cholinergic and Adrenergic Myenteric Neurons to Damage Caused by *T. Gondii* Infection may be Partly Responsible for Some Distinct Pathophysiological Features Characteristic for CD and UC

Hibi et al. [475] suggested that several environmental factors differently affect clinical course of IBD, with cigarette smoking identified as the strongest agent (Table 43). Interestingly, nonsmoking, appendectomy, and breastfeeding may even exert a beneficial effect on clinical course of UC (a disease largely of nonsmokers and former smokers), while smoking has a detrimental influence on CD. They believed that the potential mechanisms involved in this dual relationship include changes in humoral and cellular immunity, cytokine and oxygen free radicals production [475]. These observations are in agreement with the fact that the control of *T. gondii* infection in a variety of host cells is mediated through production of various cytokines, including IFN-γ, TNF-α, IL-1β, NO, and reactive oxygen/nitrogen species [476,477]. One cannot therefore exclude that differences in the feces transit time through the small and large intestines, and different numbers of tachyzoites, bradyzoites, and/or oocysts finally reaching these parts of the gastrointestinal tract may be partly responsible for development of some characteristic clinical features of UC and CD.

It must be noted that nicotine causes dose-dependent superoxide anion generation by human neutrophils [478], and production of reactive oxygen/nitrogen species is one of six important mechanisms that control *T. gondii* survival in both phagocytic and non-phagocytic cells [477]. It must be noted that treatment with cholinergic agonists improved behavioral abnormalities in autism [315,316]. Moreover, recently Ghia et al. [479,480] demonstrated the protective, antiinflammatory function of the vagus nerve in murine models of acute and chronic relapsing colitis and a role for nicotinic receptors and macrophages in mediating this function. Beneficial therapeutic effects of smoking observed in patients with UC and summarized by Hibi et al. [475] may therefore be explained by the fact that proinflammatory cytokine levels and excessive inflammation can be regulated by specifically augmenting cholinergic signalling via the efferent vagus nerve and/or applying selective cholinergic modalities targeting the α7 subunit-containing nicotinic acetylcholine receptor [317,318,481]. Furthermore, it seems that because proliferation of *T. gondii* in inflammatory macrophages *in vivo* is associated with diminished oxygen radical production [482], the enhanced tobacco smoke exposure potentiated superoxide anion generation by human neutrophils [483] appeared to be advantageous for the UC patients infected with the parasite. On the other hand, nicotine was found to inhibit production of proinflammatory mediators in human monocytes [481]. The nicotine action might be at least in part responsible for the detrimental effects of smoking reported in patients with CD (Table 43), whose inflammatory processes probably generate less neutrophils locally and in the systemic circulation than in UC individuals. Moreover, there was a relationship between NO toxicity and cholinergic receptors in the brain of patients with ASD. In the cortex of autistic patients, the cholinergic receptors known to be sensitive to NO toxicity were found to be decreased [314]. (Nb. age-related cell loss in the small and large intestines of rats occur exclusivelly in the cholinergic subpopulation, but it appeared from the somatic hypertrophy and the presence of swollen axons that the nitrergic neurons were not completely spared from the effects of age [94]). Zoroğlu et al. [45] and Sweeten et al. [46] reported elevated plasma nitrite (a metabolite of NO) levels in autistic subjects, and Sogut et al. [22] found increased NO levels in red blood cells of patients with autism. A positive correlation was found between nitrates and IFN-γ concentrations, indicating that elevated plasma NO may be related to IFN-γ activity in ASD [46]. This is not surprising because the induction of iNOS is mediated by some cytokines, namely IFN-γ, TNF-α and IL-β1 [484], and autistic individuals have persistent neuroinflammation [39,41,44]. Finally, it should be noted that IBD is associated with a differential expression of VIP and nNOs neuronal subpopulations whithin the two major enteric plexi, likely due to phenotypic switch [485]. In pediatric patients with CD the sumbucosal plexus of inflamed regions showed significant increase in density of VIP immunoreactive neurons, while in the myenteric plexus, there was a significant increase in the percent of NOS neurons. Boyer et al. [485] suggested that these changes might contribute to the pathogenesis of IBD and ongoing symptoms even in quiescent disease. Nb. development of human enteric nervous system has been characterized by the early (between 9 and 12 weeks' gestation) appearance of adrenergic and cholinergic nerves, and by 12 weeks' gestation nitrergic neurons had appeared in the myenteric ganglia and had begun plexus formation [486]. By 23 weeks' gestation nitrergic innervation has matured and the onset and pace of development of nitrergic innervation are similar to adrenergic and cholinergic innervatiuon and occur before peptidergic innervation,

thus NO has a pathophysiological role in development of gut motility disorders [486].

Disturbances in the carbohydrate metabolism due to *T. gondii* invasion might be at least in part responsible for the reported link between the increased sugar intake and development/worsening of IBD clinical course, especially in Crohn's disease [475,487] (Table 43). Studies on the modulation of the host cell proteome by the parasite showed that six proteins were involved in carbohydrate metabolism (aldose reductase, aldehyde dehydrogenase 1A3, aldehyde dehydrogenase X, hexoaminidase B, phosphoenoylpyruvate carboxykinase, and 6-phosphogluconolactonase) [488]. The glycolytic pathway also exhibited considerable modification during such infection with six enzymes showing either an increase or modulation (aldolase A and B, enolase, glyceraldehyde 3 phosphate dehydrogenase, phosphoglycerate kinase, and pyruvate kinase) and only one of which showed a decrease in expression (triose phosphate isomerase) [488] Table 44 presented some changes in the proteomes of human foreskin fibroblasts proteins caused by infection with the parasite and proteomic expression of some similar biomarkers reported also in the rat model of IBS due to mothball odor.

In individuals with UC oral contraceptives may enhance intensity of clinical course [475]. Deleterious effects of estrogen and progesterone derivatives contained in contraceptive preparations may be associated with modulation of the innate and acquired immunity of the host resulting in disturbances of immune balance between the immunocompetent host and latent *T. gondii* infection [477]. Estrogen

Protein name	Change in expression in HFF	Microarray experiment	Change in IBS	Bioactivity
Protein disulfide isomerase A3[b]	↑	↑	↑	catalytic
Peroxiredoxin 6[b]	M		↑	antioxidant
Cathepsin S				catalytic
Cathepsin B	↓	↓		
Cathepsin D preprotein	M			
Carbonyl reductase 1	↓			
Enolase 1	M	↑		
Glyoxalase I				catalytic
Cytokeratin 8			↑	structural support
Heterogenous nuclear ribonucleoprotein F				
Eukaryotic translation initiation factor				
Alpha-enolase			↓	catalytic
Transgelin	↓		↓	protein binding
Transgelin 2	↓			
Serpin peptidase inhibitor B5			↓	protein binding
Cardiac alpha-actin 1			↓	
40S ribosomal protein SA			↓	signal transduction

Host cell proteins were designated as being downregulated in expression (↓), upregulated (↑), or modulated (M). [a]The host cell proteins changed expression also in the brains of patients with mild cognitive impairment, early AD, or AD [491]. [a]Protein disulfide isomerase become unfosforylated following infection with *T. gondii* [488]. [b]It must be noted that *T. gondii* peroxiredoxin promotes altered macrophage function, caspase-1-dependent IL-1β secretion enhances parasite replication that highlights the role of *T. gondii* derived redox enzymes as important immune modulators [492]

Table 44: Selected changes in the proteomes of human foreskin fibroblasts (HFF) caused by *T. gondii* infection (acc. to Nelson et al. [488]; with own modification), and proteomic expression analysis of colonic mucosa in a rat model of IBS established by a special odor of mothball as a conditional stimulation (Ding et al. [489,490]; with own modification).

significantly increased IFN-γ and IL-2 mRNA in concavalin-A activated thymocytes, splenic lymphocytes, and in enriched splenic T cells [493], regulated transcription factors STAT-1 and NF-κB to promote inducible NO synthase and inflammatory responses [494], and dysregulated T- and B-cell balance by inducing selective T-cell hypoactivity and B-cell hyperactivity [495]. Moreover, progesterone-induced blocking factor (PIBF), a molecule with inhibitory effects on cell-mediated immune reactions, by acting on the phospholipase A2 enzymes interfered with arachidonic acid metabolism, induced a type 1 to type 2 cytokine shift by upregulating the production of type 2 cytokines, and controlled NK activity modulated cytokine production by lymphocytes [496-499].

Finally, possible beneficial effects of breastfeeding on clinical course of UC summarized by Hibi & Ogata [475] may be associated with strong anti-*T. gondii* activities of Lf contained in the breast milk.

T. Gondii Transmission in Eukaryotic Cells Acting as a "Trojan Horse"

T. gondii transmission may occur by eating uncooked or undercooked meat, contaminated vegetables, cat feces [500], blood transfusion [501-503], materno-fetal transmission [504] during transplacental passage of blood cells [505], via various solid organs allografts [506], bone marrow transplantation [507], allogeneic stem cell transplantation [508], sputum [509], breast milk [510,511], and semen [512]. *T. gondii* can invade and multiply inside any nucleated cell type including epithelial cells and blood leukocytes [513,514]. A preference to infect and multiply inside myeloid cells in vitro has been reported [336] and several studies indicate that dendritic cells and monocyte/macrophages function as systemic parasite transporters (Trojan horses) during infection in mice [514-519]. The parasite can be transmitted from infected dendritic cells to NK cells [520]. NK-cells and T-cells have been suggested to contribute to parasite dissemination via a sequestering mechanism [520-522].

Maternal-Fetal Microchimerisms and Transmission of *T. Gondii*

The risk of infection with *T. gondii* is 0.1% to 1% of all pregnancies [523], and the risk of intrauterine infection of the fetus increases during pregnancy from 10-20% after primary maternal infection in the first trimester to about 59-90% in the third trimester [387,524-526] (Table 37). Tachyzoites can invade and multiply within placental trophoblastic cells [527], and are located directly at the interface between maternal and fetal compartments. Therefore, cytotrophoblasts play a key role in the maternal-fetal transmission of the parasites, especially that the fetus is swallowing the amniotic fluid, up to 1 liter per day (about every 30 min at 24 weeks of gestational age, every 40 min at 32 weeks, and every 80 min at term) [528,529].

The prenatal transfer of nucleated maternal cells into the fetal circulation can occur as early as the 13th week of gestation [530]. This prenatal cell trafficking is a potential mechanism for the mother to affect the development of the immune system of the fetus. In one study, overall 33% (10/30) subjects had at least one source of microchimerism in CD66b$^+$ cells [532]. Maternal microchimerism was found to be more common than fetal microchimerism, 40% vs. 15%, respectively ($P = 0.05$) and was present at higher levels ($P = 0.03$) [531]. Studies of Jonsson et al. [532] showed that the maternal cells of lymphoid and myeloid lineages and hematopoietic progenitors were widely distributed in the second-trimester fetuses. It must be noted that the second-trimester histopathological placental findings in maternal-fetal inflammatory response syndrome showed 65.3% acute inflammatory response of the

354 placentas and in 98.7% of the cases, inflammation was classified as maternal inflammatory response and in 49.8% as fetal inflammatory response analyzed [533]. Microchimerism of maternal origin persists well into adult life [534]. This may also provide a possible route for the prenatal transmission of infectious agents, such as the intracellular parasite *T. gondii*, from the mother to the fetus [530]. It must be emphasized that fetal-maternal and maternal-fetal microchimerisms involve the colonization of different organs and tissues, and therefore may play an important role in *T. gondii* trafficking as a "Trojan horse" in eukaryotic cells.

Maternal Microchimerism during Physiologic Swallowig of Amniotic Fluid by the Fetus May Cause Development of Serious Gastrointestinal Tract Pathology Before and After Birth

Recently, it was reported that unrecognized ingestion of *T. gondii* oocysts leads to congenital toxoplasmosis and causes epidemics in North America [535]. Moreover, studies showed that the inflammatory bowel syndrome has origins in the childhood socioeconomic environment [536,537].

Physiologic swallowing of amniotic fluid by the fetus may have pivotal pathophysiological consequences because in neonates inflammatory lesions involving esophagus, stomach, and duodenum, as well as gastro-esophageal reflux, are frequent findings with unknown etiology [538-540]. It must be noted that chronic ulcerative colitis [541-544], and Crohn's disease [545-548] have been reported already in newborn infants. Among patients with UC, 20% are younger than 20 years of age and 1% are infants [549,550]. It was found that the early onset of Crohn's disease may be at least in part explained by markedly reduced intracellular T_H1 IFN-γ levels in peripheral blood of children with this entity compared with controls ($P < 0.006$) [551]. It must be noted that in mice following peroral infection with *T. gondii* IFN-γ induced Fas-dependent apoptosis of Peyer's patch T cells causing a remarkable decrease in the numbers of T cells in the Peyer's patches of the small intestines [552]. It was also demonstrated that CD11c- and CD11b-expressing mouse leukocytes from the mouse small intestine transported single *T. gondii* tachyzoites to the brain extravascular space [517]. After intragastric inoculation of cyst-containing parasites in mice, $CD11c^+$ dendritic cells from the intestinal lamina propria, the Peyer's patches, and the mesenteric lymph nodes were parasitized, while in the blood, parasites were associated with $CD11c^-$ $CD11b^+$ monocytes [517]. These findings are in line with our reasoning that *T. gondii* infection of the fetus may be responsible for early development of the gastrointestinal tract and brain abnormalities because IFN-γ and p47 GTPases, a new family of IFN-γ-induced genes, play a crucial role in the protective immunity against the parasite [477,553,554] and susceptibility of pregnant mice and maternal-fetal transmission of the parasite are type 2-dependent [555,556]. On the other hand, one cannot exclude that virulent *T. gondii* strain RH promotes T-cell-independent overproduction of proinflammatory cytokines IL-12 and IFN-γ and high level apoptosis [557,558], which may be partly responsible for development of NEC in some newborns.

Fetal microchimerism during pregnancy and transmission of T. gondii

The trafficking of fetal cells into the maternal circulation starts very early during pregnancy at approximately 4^{th} to 6^{th} week of gestation [559,560]. A greater number of fetal cells transfer into the maternal circulation than do maternal cells into fetal circulation [505,561]. This traffic of cells is primarily composed by immune cells (T and B-lymphocytes, monocytes, NK cells), including hematopoietic stem cells $CD34^+$ and $CD34^+/38^+$ committed to early B and T-cells with the capacity for multilineage differentiation [562]. The number of fetal progenitor cells circulating in the blood of a pregnant woman, has been estimated to be 0-2 per ml, but it can vary according to the gestational age. In normal second-trimester pregnancies, the number of fetal cells in the maternal circulation was found to be 1-6 cell/ml of maternal venous blood. After delivery, this fraction rapidly decreases, and 30-50% of healthy women have fetal cells in their blood from four weeks to decades postpartum [563]. Pregnancy-associated progenitor cells can survive in the maternal bone marrow representing a long-term reservoir of stem cells [564,565]. The exchange of fetal microchimeric cells between non-HLA identical twins also is a common event [566] and approximately 8% of human twin pregnancies and 21% of triplets are chimeric in their blood cell populations from their siblings [567]. Table 45 presented fetal-maternal cell trafficking involving a broad range of different cell types, including maternal and fetal cells with stem/progenitor phenotype [568,571,572]. Furthermore, trisomy 21 was reported to result in especially high numbers of maternal cells in the infant [573], which may support recent suggestion that *T. gondii* infection is responsible for development of Down syndrome [574].

Possible link between bidirectional transmission of T. gondii and/or its antigens in fetal and maternal cells and development of primary biliary cirrhosis and several other autoimmune diseases

The origins of autoimmunity are still elusive despite marked advances in immunology [575]. Because *T. gondii* can be transmitted bidirectionally in fetal and/or maternal cells, one cannot exclude that the majority of individuals in the group of patients with primary biliary cirrhosis studied by Fanning et al. [576] suffered from the parasite infection. The extracellular mtDNA found by Zhang et al. [577] in serum of autistic children may eventually represent DNA of the parasite since Bidgoli et al. [578] detected *T. gondii* DNA by PCR analysis in a vitreous sample in a 13-year-old immunocompetent patient with toxoplasmic chorioretinitis even with repeated negative serology for *T. gondii*. Possible important role of transplacentally-acquired antibodies to infectious agents as the cause of neuromental disorders proposed by Nahmias et al. [579], also may support this reasoning. Moreover, the markedly increased female to male ratio found in these diseases is in line with our recent finding that females are more susceptible to the parasite infection than males [444].

Extravillous cytotrophoblasts
Nucleated erythroblasts
Platelets
Mesenchymal stem cells
CD34+ hematopoietic stem/progenitor cells
CD34+ and CD38+ lymphoid progenitors
CD19+ and IgM+ B lymphocyte precursor cells
CD8+ T cells
CD4+, CD25high and FOXP3+ regulatory T-cells
CD45+ leukocytes
CD3+ and CD14+ mononuclear cells
CD56+ and CD16+ natural killer cells

The maternal cells [569] and soluble maternal HLA were transferred in breast milk [570]

Table 45: Different types of cells involved in fetal-maternal trafficking (acc. to Klonisch et al. [568]; with own modification).

It is interesting that anti-mitochondrial antibodies directed against various proteins of the outer and inner mitochondrial membrane (AMA-M2) have been clinically detected also in patients with biliary cirrhosis [580]. Moreover, it was found that fetal microchimeric cells are present in high numbers in women with several autoimmune diseases, including primary biliary cirrhosis (Table 46). This is not surprising because Khosrotehrani et al. [562] found that fetal cells have multilineage potential to maternal tissue, and several authors [593,594] provided evidence of maternal microchimerism underlying pathogenesis of biliary atresia (2 X-chromosome and maternal chimeric $CD8^+$ T cells, respectively). It must be noted that no fetal cell microchimerism was demonstrated in the patients with primary biliary cirrhosis [595,596]. These findings are therefore in agreement with our suggestion that maternal and/or fetal cells may serve as a Trojan horse for *T. gondii* dissemination in eukaryotic cells, especially that high levels of IgG antibodies against *T. gondii* were found in the sera of patients with autoimmune thyroid diseases (Hashimoto's thyroiditis and Graves' disease) compared with controls (56.5% vs. 38.0%, $P < 0.02$). Another study performed also in nonautoimmune individuals found that infection with the parasite was associated with a high autoantibody burden.

Amelioration of Experimental Colitis was Found to be Associated with Histone Hyperacetylation. *Toxoplasma Gondii* Expresses a Histone Deacetylase Class I Enzyme Homologous to Human HDAC3, and Valproic Acid, an Antiepileptic Drug and Histone Deacetylase Inhibitor, has Potent Antitoxoplasmal Activity

Recently, Glauben et al. [597] demonstrated that inhibitors of histone deacetylases (HDAC) exerted strong protective effects in various models of experimental colitis by inducing apoptosis and suppressing proinflammatory cytokines. This is an important finding because in Crohn's disease and ulcerative colitis, disease severity can be ameliorated by T_H1 inhibitory strategies, such as infliximab (the neutralizing anti-TNF-α Ab) [598], while for ulcerative colitis, anti-T_H2 means, such as IL-13-neutralizing compounds, are efficacious [599].

HDAC comprise of a family of enzymes that participate in the regulation of chromatin structure, gene expression, and cell signalling in eukaryotes [600]. One of the most important mechanisms in chromatin remodelling is the posttranslational modification of the NH_2-terminal tails of histones by acetylation, which contributes to a "histone code" determining the activity of target genes [601]. Acetylation of histone proteins neutralizes the positive charge on lysine residues and disrupts nucleosome structure, allowing unfolding of the associated DNA, subsequent access by transcription factors (e.g. Mad-1, BCL-6, ETO), and changes in gene expression [602]. Acetylation of core nucleosomal histones is regulated by the opposing activities of histone acetyltransferase and deacetyltransferase HDACs [603]. HDACs catalyze the removal of acetyl groups on the NH_2-terminal lysine residues of core nucleosomal histones, and this activity is generally associated with transcriptional repression [599]. Histone deacetylation and DNA methylation are two major epigenetic modifications that contribute to the stability of gene expression states. Perturbing DNA methylation or disrupting the downstream response to histone deacetylases by genetic or pharmacologic means has revealed a critical requirement for epigenetic regulation in brain development, learning, and mature nervous system stability [604].

Disease	Female/ male ratio	Tissue source	References
Systemic sclerosis	≥ 8:1	Peripheral blood cells	[581,582]
Juvenile idiopathic inflammatory myopathy	3:1	Sorted $CD4^+$ or $CD8^+$ peripheral blood cells	[583,584]
Systemic lupus erythematosus	5:1	Peripheral blood nucleated cells	[585]
Sjögren syndrome	9:1	Peripheral blood whole nucleated cells	[586]
Primary biliary cirrhosis	14:1	Peripheral blood nucleated cells	[576]
Hashimoto's thyroiditis	20:1	Thyroid tissue	[587]
Graves' disease	8:1	Thyroid tissue	[588]
Lichen planus	2:1	Peripheral blood nucleated cells	[589]
Polymorphic eruptions of pregnancy	pregnancy		[590]

Interestingly, maternal microchimerism was found in the peripheral blood of patients with type 1 diabetes and pancreatic islet beta cell microchimerism [591]. It was demonstrated that this bioevent also leads to the production of IL-2, a proinflammatory cytokine, in IL-2 knockout mice [592]

Table 46: Diseases associated with fetal and/or maternal microchimerism (acc. to Klonisch et al. [568]; with own modification).

HDAC inhibitors, such as valproic acid (VPA), a short-chained fatty acid, increase the accumulation of hyperacetylated histones H3 and H4, directly affecting chromatin structure, and thereby, the relationship of the nucleosome and the gene promoter elements [600,605,606]. Inhibition of HDAC *in vitro* was associated with a significant dose-dependent suppression of proinflammatory cytokines, stimulation of apoptosis, and a local increase in histone acetylation [597,607].

VPA is an effective inhibitor of HDAC with an IC_{50} (0.4 mM) well within the therapeutic range of VPA (0.35-0.7 mM in serum). *T. gondii* expresses a HDAC class I enzyme homologous to human hdac3, and VPA inhibited the parasite tachyzoite proliferation at concentrations only a few times greater than its respective IC_{50} [607]. VPA resulted in amelioration of disease in dextran sodium sulfate-induced colitis (a marked reduction in weight loss and histologic signs of the inflammation) associated with suppression of IFN- γ, IL-6, IL-1β, and MIP-2 [600]. In parallel to the beneficial effect observed, a dose-dependent increase in histone 3 acetylation at the site of inflammation was observed under VPA treatment [600]. Also apicidin's (a novel antiprotozoal cyclic tetrapeptide agent) antiparasitic activity appeared to be due to low nanomolar inhibition of histone deacetylase, a key nuclear enzyme involved in transcriptional control, which induces hyperacetylation of histones in treated parasites [608]. Because VPA and its sodium salt inhibited *in vitro* replication of *T. gondii* tachyzoites (Table 42), one cannot exclude that the preparations may be effective also in amelioration of some gastrointestinal signs and symptomes observed in anti-*T. gondii* seropositive patients with ASD and/or other neurodegenerative clinical disorders [574,609], including Alzheimer disease [610]. This reasoning may be supported by the finding that VPA was found to be neuroprotective in experimental cerebral ischemia and the protection mechanisms may involve HDAC inhibition and heat shock protein 70 time-dependent induction [611].

Colonization of the Pouches Formed for Ulcerative Colitis by Sulfate-Reducing Bacteria May Be Associated With a Defense Reaction of the Intestine against *T. Gondii* Infection

Duffy et al. [612] isolated sulfate-reducing bacteria from ulcerative colitis pouches in 8 of their 10 patients with UC. It was found that these bacteria were exclusive to patients with the background of UC because

the levels of Lactobacilli, *Bifidobacterium*, *Bacteroides sp*, *Clostridium perfringens*, enterococci, and coliforms were similar in both pouch groups, i.e. UC and familial adenomatous polyposis [612]. The authors suggested that since sulfate-reducing bacteria are specific to UC pouches, they play a role in the pathogenesis of pouchitis. Further studies of Ohge et al. [613] showed that in active pouchitis, sulfate-reducing bacterial counts were found to be significantly higher than in those who never experienced pouchitis. It was reported that pouch contents of the patients with ileoanal pouches and ongoing pouchitis or an episode within the previous year, released significantly more hydrogen sulfide (a highly toxic gas produced by certain fecal bacteria, which causes tissue injury in experimental animals) than did the contents of patients who never had an attack of pouchitis and those with longstanding inactive disease [613]. In addition, pouch contents from familial adenomatous polyposis patients produced markedly less hydrogen sulfide than did any group of nonantibiotic treated UC patients [613]. These findings may suggest that the colonization of pouches formed for ulcerative colitis by sulfate-reducing bacteria is associated with a defense reaction of the intestine against *T. gondii* infection. This motion may be supported by the fact that electric charges on cell surface play an important role in some cellular processes, including cell-cell interaction, cellular differentiation and endocytosis [614-616]. It was demonstrated that the parasite invaded nearly all types of mammalian cells and it seems that recognition of cell surface sulfated proteoglycans may contribute to such invasion [617]. Cell surface heparan sulfate (HS) and glycans, containing sialic acid have been shown to act as potential receptors for the parasite [617-619]. HS consists of alternating units of N-acetyl glucosamine and glucuronic acid or iduronic acid variously decorated with sulfate residues. The chains are covalently linked to proteoglycan core proteins on the surface of cells and in the extracellular matrix [620,621]. Sialic acids are found on the termini of the glycan chains on glycoproteins or glycolipids. Loss of HS chains or sialic acid from cellular glycoconjugates results in significant reduction of *T. gondii* infection in vitro [618]. *T. gondii* recognizes host cell sulfated proteoglycans by examining a wide range of human cell types, and ligands on the parasite are capable of recognizing both highly sulfated glycans like heparin, consisting of glucuronic or iduronic acid and sulfated glucosamine, and the relatively less sulfated chondroitins, consisting of glucuronic acid and variably sulfated N-acetylgalactosamine [617]. Jacquet et al. [622] demonstrated that the parasite surface antigen SAG3 mediates the attachment of *T. gondii* to cell surface proteoglycans, and it appeared that proteoglycan sulfation was critical for SAG3 adherence to target cells HS proteoglycans. These findings apply also to other microorganisms migration and invasion of host cells, such as Plasmodium sporozoites [623], human cytomegalovirus [624], *Listeria monocytogenes* [625], and herpes simplex virus [626]. Thus, one cannot exclude that the sulfate-reducing bacteria exclusive to patients with ulcerative colitis pouches plays an important role in markedly diminishing attachment of *T. gondii* to the host intestinal cells that results in further dissemination, invasion and proliferation of the parasite inside the host intestinal cells. Moreover, the parasite may, at least in part, be responsible for development of ileal and colonic pouches in patients with UC and Crohn's disease because it causes GI tract inflammation associated with enteric glial cells dysfunction/loss and local damage of myenteric neurones in the intestinal wall [107,150,151,391,627]. Development of acute and chronic diverticular disease also may be caused by post inflammatory damage to the ENS [628] caused by *T. gondii* infection because of marked changes in the intestinal wall morphology reported in experimental animals (Tables 9-13) affecting its integrity.

Development of Celiac Disease May Be Associated With *T. Gondii* Infection

Several studies showed a strong association between celiac disease and various unexplained "soft" neurologic and psychiatric manifestations, such as headache, migraine (in one study tension type headache and migraine had about 40% of children with celiac disease), visual disturbances, cerebral calcifications, developmental delay, hypotonia, learning disorders, cognitive impairment, and attention deficit/hyperactivity disorder, as well as chronic "hard" disorders, such as epilepsy, chorea, chronic neuropathies, cerebellar ataxia, myoclonic ataxia, dementia, depression, and progressive leukoencephalopathy [629-636]. It was believed that neurologic complications of celiac disease could be a nonspecific result of chronic poor nutritional condition or caused by specific nutritional deficiences, such as lowered levels of vitamin B_{12}, E, D, folic acid, pyridoxine, or carnitine [629,633]. At present, however, celiac disease is diagnosed earlier and severe malabsorption is rare, and therefore, it has been suggested that these disorders may result from the fact that the brain is particularly vulnerable to prolonged exposure to gluten with its multisystem immunologic and inflammatory effects [629,633,635].

Celiac disease is characterized by mixed cellular infiltrate of jejunal mucosa by B and T-cell lymphocytes and macrophages or dendritic cells. Gliadin-activated T cells are suggested to play an important role including production proinflammatory cytokines (including IFN-γ and IL-6), increase of cell infiltration and their activation [637,638]. The patients with active celiac disease showed to have higher percentage of samples expressing IL-1β, TNF-α, TNF-β, IL-2, IFN-γ, TGF-β, IL-10 mRNA compared with controls [639]. The expression of both T_H1 (IFN-γ, IL-2) and T_H2 (IL-4, IL-10)-associated cytokine transcripts in the same biopsies and peripheral blood cells of these subjects was implying activation of T_H0 cells [639]. Hansson et al. [637] found, however, that peripheral blood cytokine-producing cells of children with celiac disease secrete cytokines compatible with a type T_H1 response. Increased levels of serum NO have also been reported in such patients, and such sustained high-output NO production occurring in chronic inflammation, may be deleterious to the tissues [638,640]. In addition, food antigens, gluten, gliadin, and their proteolytic fragments activated macrophages (producer of reactive nitrogen oxide radicals) and significantly enhanced TNF-α, IFN-γ, IL-6, NO and iNOS mRNA production [637,638].

MRI revealed unilateral and bilateral white matter lesions of different degrees of intensity, varying between smaller spot and larger flat lesions in one study of 15 children (20%) with neurologic manifestations and biopsy-proven celiac disease (mean age of 11.6 years, 10 girls, 5 boys) [629]. These lesions were hypointense in T2 and fluid attenuated inversion recovery sequences and showed biparietal and left-sided predominance (including periventricular hypodensity) [629]. It was believed that they may be ischemic in origin as a result of vasculitis or caused by inflammatory demyelinetion [629]. In the patients with established celiac disease, epilepsy (with an incidence of 1% to 6%) often associated with bilateral corticosubcortical occipital calcifications, was the most frequent neurologic complication [641-645]. It was suggested that in patients who suffer from celiac disease with migraineous or nonspecific headache, malabsorption did not play a significant role in the pathogenesis of this symptom and inflammatory processes and one should look for other causes, including immunologic mechanisms [633]. Thus, basing on these facts and reasoning one may suggest that all the above-mentioned immune state irregularities of the patients with neurologic manifestations associated with celiac disease could

interfere with the immune state of the host and *T. gondii* in the brain finally causing reactivation of latent cerebral toxoplasmosis. The rapid and concentration-dependent changes in CYP-450 enzyme activities in isolated perfused rat livers due to administration of exogenous NO donors [646], may at least in part, support this suggestion.

The MRI findings in the brain of those subjects, including cerebral calcifications considered as vascular calcified malformations [641], may therefore be a result of chronic subclinical cerebral vasculitis due to *T. gondii* infection/inflammation. The improvement of neurologic symptoms in some patients after introduction of gluten free diet [629,632,633,641,645] (in few children, even hypodense areas in the white matter around calcifications decreased or disappeared after such a diet [631]) may be explained by amelioration of immune irregularities caused by this triggering factor and therefore diminished pathologic interference in the immune state of the host and the parasite in the brain. The above-presented reasoning may be supported by the opinion of Nejad et al. [647] that celiac disease increases the risk of *T. gondii* infection in pregnant women. However, this conception may also be alternatively interpreted that the parasite plays an important role in development of celiac disease. Although Plot et al. [359] reported that the rate of positive anti-*T. gondii* IgG antibodies in their cohort of 90 celiac patients and 297 healthy individuals was similar (23.3% vs. 25.9%, $P = 0.36$), genetic predisposition should be taken into consideration, because the celiac patients also had markedly increased antibodies against other infectious agents, antirubella IgG ($P < 0.05$), anti-CMV IgG ($P < 0.01$), and anti-EBV capsid antigen IgG ($P < 0.01$).

Finally, it was reported that some children with celiac disease suffer with eosinophilic esophagitis concomitantly, and the coexistance of both these clinical entities is more frequent than anticipated [648-650]. It was believed that based on differences in pathophysiology and affected gastrointestinal compartments, a causal relationship between these two clinical entities seems unlikely [650], but one cannot exclude that development of eosinophilic esophagitis in children with celiac disease may be associated with *T. gondii* infection.

Clear Cell Colitis with Presence of Foamy Macrophages May Be Caused by Oral *T. Gondii* Infection

Presence of characteristic foamy macrophages observed in histopathological hematoxylin and eosin-stained specimens is a crucial diagnostic factor in foamy colitis, excludes Crohn's disease and UC, and confirms mild and moderate course of that type of inflammation in children [651-654]. The induction of foamy macrophages packed with lipid bodies have been reported in several clinical pathologic states associated with chronic proinflammatory stimuli, including *T. gondii* [465] and human Mycobacterium tuberculosis infections [655].

Foamy colitis (microscopic colitis) [651,654] may be caused by oral prenatal and/or postnatal infection with *T. gondii*. It was reported that bradyzoites are resistant to gastric digestion and remain orally infective whereas tachyzoites are destroyed by gastric juice within 1 hr [656-658]. However, Dubey [659] showed that tachyzoites occasionally survived at acid peptic digestion for 2 hrs, and the strain of *T. gondii* did not affect the susceptibility of tachyzoites to acid pepsin solution. In orally inoculated animals extracellular tachyzoites were infective, although the infectivity was dose-dependent [659]. One cannot therefore exclude oral infection with *T. gondii* in breastfed infants of infected mothers because it is known that the parasite is disseminated in breast milk [507,508], and postnatally gastric acid secretion displays a biphasic pattern with the lowest gastric acid concentrations between 10 and 30 days of life approaching the lower limit of adult values by 3 months of age [660]. The parasite is disseminating in the body as a Trojan horse in various eukaryotic cells, including macrophages, and division rate of intracellular unprimed *T. gondii* tachyzoites in alveolar, peritoneal or monocyte-derived macrophages is rapid [335]. Successful intracellular replication of tachyzoites and a substantial increase in membrane mass of PV is dependent on diversion and use of lipid resources from its host, especially long-chain fatty acids and cholesterol [468]. *T. gondii* employs host low-density lipoproteins (LDL) receptor to acquire cholesterol [465] and diverts it for cholesteryl ester synthesis and storage in lipid bodies [468,661,662], leading to formation of foam cells [465]. Macrophages convert into foam cells through a dysregulation in the balance between the influx and efflux of LDL particles (containing cholesterol, triacylglycerides and phospholipids) from the serum. It must be emphasized that foamy macrophages are not only the product of an inflammatory response but amplify that response through production of PGE_2 and leukotrienes [663,664], and appear to be a key player in both sustaining persistent bacteria and contributing to development of human tuberculosis granuloma and cavitation [655]. Foam macrophages characteristic for microscopic colitis probably play a similar role.

Enlarged Mesenteric Lymph Nodes Frequnetly Seen at Imaging in Patients with IBD, Children with Abdominal Pain, and in Asymptomatic Children may be Associated with *T. Gondii* Infection

Mesenteric lymphadenopathy is commonly found in patients with IBD, both in CD and UC [665,666], although it is more frequently observed in CD [665,667]. The lymph nodes described as large or prominent may be seen at the mesenteric root, the mesenteric periphery, or the right lower quadrant. Inflammatory changes in the small or large bowel are usually but not always present [667].

Enlarged mesenteric lymph nodes (MLNs) have been frequently reported in children with acute or chronic abdominal pain during abdominal CT or ultrasonographic examination in children with mesenteric lymphadenitis [668-671]. These abnormalities may be found also in asymptomatic children [671-674]. In one study [671], enlarged MLN were detected in 55 of 189 asymptomatic children (29.1%) aged 2 to 10 years and the longitudinal diameter of the lymph nodes ranged between 5 mm and 19 mm. These lymph nodes were arranged in clusters (3 to 9 in number in a cluster) and some children had associated minimal mural thickening of the terminal ileum. It was suggested that this is a non-specific and usually non-pathological finding with the most common location around the iliac vessels [670,671]. Watanabe et al [674] also detected enlarged ileocecal lymph nodes in asymptomatic children examined by ultrasound with similar incidence (26 of the 112 cases, 21%). In patients with mesenteric lymphadenopathy, the clinical presentation is non-specific including abdominal pain, fever and leukocytosis mimicking a broad spectrum of different clinical diagnoses, such as acute appendicitis, infectious enterocolitis and pyelonephritis [668,671,675].

It must be noted however that the above mentioned enlargement of MLNs in young and adult patients and healthy individuals may be caused by toxoplasmosis because: a) toxoplasmosis affects about a third of gobal human population, b) in experimental animals oral *T. gondii* genotype III or II inoculation with oocysts (sporozoites)/tachyzoites/tissue cysts (bradyzoites) also frequently resulted in an increased number of neurons per ganglion and hypertrophy of myenteric neurons [204,205,207,208,211,212,270], and c) oral infection with the parasite

spreads locally to MLNs and distant organs by invasion of lymphatics and blood [676].

Human Milk Lactoferrin (Lf) May Be, At Least In Part, Responsible For the Delayed Onset of ASD in Newborns and Young Infants Because It Plays an Important Role in Host Defense against *T. Gondii* Infection and Dissemination

Important role of breastfeeding and Lf in human milk

Vertical transmission of toxoplasmosis from a chronically infected immunocompetent woman developed probably after maternal reinfection or reactivation of the preexisting disease [677]. Acute toxoplasmosis can be transmitted via breast feeding [678].

Breastfeeding had a protective effect on the incidence of childhood illnesses in the 1st 2 years of life, particularly gastrointestinal disease. Infants who had been partially or fully breastfed initially had significantly lower rates of gastrointestinal diseases at 14-26 weeks, 27-39 weeks, and 40-52 weeks compared to bottle-fed infants and a lower rate of hospital admission [679]. Breastfeeding during the first 13-26 weeks of life conferred subsequent protection against gastrointestinal illness that persisted beyond the period of breastfeeding itself [679,680]. Exclusive breastfeeding for the first 6 months is recommended by the World Health Organization and considered allergy preventive [681]. Saarinen & Kajosaari [682] found that prevalence of eczema at ages 1 and 3 years was lowest in the prolonged (> 6 months) breastfeeding group of infants compared with intermediate (1-6 months), and short or no (< 1 month) breastfeeding. It was reported, however, that prolonged strictly exclusive breastfeeding for more than 9 months was associated with atopic dermatitis ($P < 0.002$) and symptoms of food hypersensitivity ($P = 0.01$) in children with a family history of allergy [681].

Human breast milk has been shown to have antiinflammatory properties and have an immediate and localized salutary action on the gastrointestinal and respiratory tracts of the infant [683]. Human milk, colostrum and bovine milk contain a factor, in part resembling TGF-β activity, which inhibits production of IL-2 [684,685].

Studies performed with milk collected from women 20 to 35 years of age during the first year of lactation showed that the concentrations of Lf, total IgA, and leukocytes fell during the first several weeks of lactation [686]. Afterwards, the levels of Lf and IgA stabilized. Approximately 90% of total IgA in human milk during the first year of lactation was secretory IgA. The concentrations of lysozyme, after falling to a nadir of 20 to 30 μg/ml at 2 to 4 weeks, rose to 200 to 300 μg/ml by six months and remained elevated [685].

Lf is found in large amounts in most secretions, particularly in milk where its concentration may vary from 1-3 g/L (mature milk) to 5-7 g/L (colostrum) [686-688], and in secondary granules of neutrophils [689]. Plasma concentration of Lf may range from 0.4 to 2 mg/L under normal conditions, but increases to up 200 mg/L in septicemia [690]. Pacora et al. [691] found that Lf was also detectable in 85.4% (229/268) of amniotic fluid samples obtained during transabdominal amniocentesis, not detectable in all fluid obtained in the mid trimester, and detectable in all maternal and cord plasma samples. With advancing gestational age, the concentration of Lf was markedly increasing ($r = 0.68$, $P < 0.0001$), and intra-amniotic infection was associated with significant increases in amniotic fluid Lf concentrations in patients with preterm labor [691].

Lf has bacteriostatic and bactericidal activity and plays an important role in the first line of defense against microbial infections, since many pathogens tend to enter the body via the mucosa. Lf can bind with high affinity to a 105 kD receptor on cell membrane, but binding to low affinity binding sites, such as glycosaminoglycans does also occur. The positively charged N-terminus of Lf is responsible for the binding to glycosaminoglycans, such as heparan sulfate, chondroitin sulphate [692]. In addition, the LDL remnant receptor [693] and the 45 kD subunit of asialoglycoprotein receptor [694,695] have been demonstrated to act as receptors for Lf [696]. Binding of Lf to LPS of Gram-negative bacteria prevents priming of neutrophils, leading to an inhibition of ROS production [697].

Spontaneous integrin expression on $CD4^+$, $CD8^+$ and $CD19^+$ lymphocytes at 6 months was significantly lower in breastfed than formula-fed infants ($P < 0.05$) [698]. Before MMR vaccination, lymphocytes of breastfed children had lower levels of blast transformation without antigen ($P < 0.001$), with tetanus toxoid ($P < 0.02$) or Candida ($P < 0.04$), and lower IFN-γ production ($P < 0.03$). Fourteen days after the live viral vaccination, only the breastfed children had increased production of IFN-γ ($P < 0.02$) and increased percentages of $CD56^+$ and $CD8^+$ cells. These findings are consistent with a T_H1 type response by breastfed children, not evident in formula-fed children [698], important also for host defense against *T. gondii* infection.

Beneficial immunomodulatory properties and effects of Lf

Lf is an 80-kD, non-hem iron-binding multifunctional LPS-chelating glycoprotein of the transferrin family, present at the mucosal surface where it functions as a prominent component of the first line host defense against infection and inflammation [687,699]. Lf is also abundant component of the specific granules of neutrophils and can be released into the serum upon neutrophil degranulation. The protein displays a broad antimicrobial spectrum against Gram positive and Gram negative bacteria, fungi and several viruses, because it is an important component of the non-specific immune system. Lf may have protective effects against LPS-mediated intestinal mucosal damage and impairment of barrier function in intestinal epithelial cells [700]. At the cellular level, the glycoprotein modulates the migration, maturation and function of immune cells [701]. It interacts with soluble CD14 and inhibits expression of endothelial adhesion molecules, E-selectin and ICAM-1, induced by CD14-LPS complex, thus modifying activation of endothelial cells [702]. Lf administered orally improved gastrointestinal morphology in growing calves because it enhanced size of Peyer's patches in the ileum and decreased villous sizes in the jejunum [304]. In addition, Lf increased expression and production of several proinflammatory cytokines, such as IL-1β, TNF-, IL-6, IL-8, NO, granulocyte-macrophage colony-stimulating factor [703-706], number and activity of NK cells [707-709], and phagocytosis-enhancing effect [710]. Moreover, up-regulation of antiinflammatory IL-4 and IL-10 cytokines was found after oral Lf administration in rats with colitis [711]. Lf increased also serum IgG levels and the number of peripheral blood leukocytes, and mRNA levels of various cytokines, such as IL-1β, IL-8, IL10, and IFN-γ in those cells, in response to Lf treatment, were enhanced [304]. Haversen et al. [712] found that in monocytic cells Lf down-regulated the LPS-induced cytokine production (expression of TNF-α, IL-6, IL-8 mRNAs, and secretion of IL-10), and the inhibitory mechanism was suggested to involve the interference of Lf with NF-κB activation. It appeared that Lf was internalized into THP-1 and Mono Mac 6 monocytic cell lines and detected in the nucleoli [712]. Additionally, the mRNA expression of proinflammatory cytokines IL-

1β and IFN-γ in blood decreased over 10-week treatment with Lf [304]. It was suggested that immunomodulatory effects of Lf are due, in part, to LPS binding [714] (Table 7). Moreover, orally administered Lf restored humoral immune response in immunocompromised mice [714]. Thus, the immune regulatory properties of Lf may exert beneficial effects in the patients with inflammatory processes of the gastrointestinal tract caused by various microbial pathogens, including *T. gondii*.

Beneficial effects of Lf in inflammatory diseases

Lf is a potent molecule in the treatment of inflammatory diseases and its major activity is related to the scavenging of free iron, which accumulates in inflamed tissues and catalyzing the production of tissue-toxic hydroxyl radicals. Ambruso et al. [715] found that Lf enhances hydroxyl radical production by human neutrophils, neutrophil particulate fractions, and an enzymatic generating system.

Free radical is thought to play a significant role in the pathogenesis of several disease processes in low birth weight preterm infants including NEC [716], partly because iron is a known catalyst in free radical-mediated oxidation reactions. Raghuveer et al. [716] found that before adding medicinal iron to formula or human milk, significantly more ascorbate and alpha-hydroxyethyl radical production and more lipid peroxidation products (*i.e.* thiobarbituric acid reactive substances, malondialdehyde, and halothane) were detected in formula. After addition of medicinal iron to either formula or human milk, further increases were observed in free radical and lipid peroxidation products. The authors believed that the presence of greater concentration of iron and the absence of Lf in formula compared with human milk resulted in greater in vitro generation of free radicals and lipid peroxidation products [716].

Davidsson et al. [717] found that fractional iron absorption was markedly lower from breast milk (11.8%; range 3.4-37.4%) than from Lf free breast milk (19.8%; 8.4-72.8%) ($P < 0.05$). It must be added that iron absorption was higher from human milk than from infant formula or bovine milk [718]. Human fetal small intestinal brush-border membrane receptor for Lf may be responsible for high iron absorption from human milk. The molecular weight of the receptor was 110 kD under nonreducing conditions and 37 kD after reducing circumstances. The binding was pH dependent, with an optimum between pH 6.5 and 7.5. Little binding of bovine Lf or human transferrin to human brush-border membrane vesicles was found [718].

In neurodegenerative diseases where iron deposits contribute to oxidative stress and neuronal death, an upregulated by TNF-α synthesis of Lf by activated microglia in human substantia nigra [719], together with transcytosis of plasma Lf through the blood-brain barrier to limit inflammation processes in the brain, were reported [720]. Lf was found to display antiviral activity against both DNA- and RNA-viruses, including herpes simplex type 1 and 2 viruses (α-herpes virus family), by preventing entry of virus to the host cell, either by blocking cellular receptors, or by direct binding to the virus particles [696]. It appeared that lactoferricin (Lfcin), a residue of 24 aminoacids derived from the N-terminal region of the N-lobe of Lf, also displayed antiviral activity against HSV, but the native protein (Lf) was more potent [721].

Important role of Lf in IBD

During the course of IBD activated leukocytes infiltrate the intestinal mucosa and are detected in feces as they shed into the intestinal lumen. Lf can reflect the activity of neutrophil leukocytes and levels of this iron-binding glycoprotein have been shown to increase dramatically in body fluids during the course of inflammation [722]. Several authors reported that the levels of fecal Lf were markedly higher in IBD patients, especially those with Crohn's disease, than in controls, patients with bacterial infectious bowel disease, or IBS individuals [723-725]. The levels of fecal Lf were markedly higher in the patients with inactive IBD than in individuals with IBS [725]. Therefore, fecal Lf has been used as a specific and sensitive noninvasive biomarker of intestinal inflammation activity with cut-off values between 60 g/g [723] and 240 μg/g for active Crohn's disease and 324 μg/g for active ulcerative colitis [722,724].

Lactoferrin inhibits replication of T. gondii in enterocytes

The oral route is the natural portal of entry for *T. gondii*. Enterocytes are the first cells to be invaded by the parasite when ingested pathogens are released from cysts or oocysts within the gastrointestinal tract [726]. The intestinal epithelium constitutes a unique lymphoid compartment of the gut mucosa immune system, with the presence of intraepithelial lymphocytes that have the ability to lyse *T. gondii*-infected enterocytes and to synthesize IFN-γ in infected mice [727]. The capacity of enterocytes to inhibit *T. gondii* replication after IFN-γ activation through an iron-dependent mechanism may have important implications in the defense against the parasite and its dissemination.

Ingested organisms are released from cysts or oocysts within the gastrointestinal tract and initially invade the intestinal epithelium before disseminating throughout the body. The intestinal epithelium and the underlying mucosal tissues are heavily populated with cells of the local immune system that can make rapid contact with the parasite during intestinal penetration [728]. Intestinal cells have a rapid cell turnover, with a mean cell duration time of 2-3 days *in vivo* and a few hours *in vitro* [729]. *In vivo*, the most prominent expression of secretory component was such in crypt cells [730] and diminished during the maturation of the enterocytes.

T. gondii invaded and proliferated also in cultured primary rat enterocytes. It was found that primary rat enterocytes possess a microbiostatic capacity [728]. Activation of the enterocytes with rat recombinant IFN-γ inhibited *T. gondii* replication through an iron-dependent mechanism [728]. Iron diminished IFN-γ-induced activity against *T. gondii*, and the replication of the parasite was dependent upon the intracellular iron pool. Iron is acquired by enterocytes by a carrier-mediated process, essentially through a transferrin-free form into vesicles [731].

Milk carbohydrate components are interfering with microbial attachment to mucosal membranes

Bout et al. [726] showed that the transcytotic pathway of IgA could interfere with intracellular replication of *T. gondii*. Otherwise, it was demonstrated that incubation of sodium nitroprusside (SNP), a donor of NO molecules, with Caco-2BBe intestinal epithelial monolayers resulted in time- and concentration-dependent decreases in transepithelial resistance, and widened tight junctions in electron microscopy [23]. Also NO reduced cellular ATP levels and reversibly increased permeability of tight junctions in cultured Caco-2Bbe cells [23]. Unno et al. [24] found that incubation of cultured human intestinal epithelial monolayers Caco-2BBe cells with IFN-γ resulted in upregulation of NO biosynthesis and a marked increase in permeability of intestinal epithelial monolayers.

Lf is relatively resistant to degradation by trypsin and chymotrypsin, and stools of breast-fed babies contain considerable amounts of this glycoprotein [732]. To be able to infect host via the mucosal membranes, where most infections occur, the microbes must attach to the mucosal

cells. The process is specific, with different microbes binding to different carbohydrate structures on the cell surface [732]. The carbohydrate components of human milk function as receptor analogues and can therefore prevent microbes from binding to the carbohydrate moiety on the mucosal epithelium to which they are specifically adapted to bind. A similar capacity to prevent microbial attachment to specific mucosal carbohydrate structures has been demonstrated for glycoconjugates in human milk. The milk glycolipid Gb3 prevents binding of *Shigella dysenteriae* and Shiga-like toxin from enterohaemorrhagic *E. coli* [733].

Sisk et al. [734] found that gestational age was the only perinatal factor associated with risk of NEC. It appeared that enteral feeding containing at least 50% human milk in the first 14 days of life was associated with a sixfold decrease in the odds of NEC. Prophylactic therapy with recombinant human Lf and the probiotic, Lactobacillus GG (LGG), acted to enhance defenses against invasive E. coli in the neonatal small intestine [735]. It was suggested that rhLf and LGG were therapeutic agents that may reduce NEC and gut-related sepsis in preterm human infants [735]. Sherman et al. [736] hypothesized that Lf helped terminate bacterial invasion of enterocytes via a detachment-induced apoptosis called anoikis. Death of infected epithelia by anoikis prevents local spread of bacterial pathogens because the bacteria are trapped within the cell. Such infected, apoptotic and sloughed epithelia also cannot infect the lower gastrointestinal tract, and epithelia exit the body with the stool. When neonatal rats were pre-treated with intra-gastric recombinant human Lf, epithelia with anoikis were found in ileal fluid after enteric infection. They believed that Lf might prevent NE in preterm infants who cannot take human milk [736].

Milk Lf exerts a protective effect against murine gastrointestinal T. gondii infection

In experimental murine toxoplasmosis, all mice orally administered 5 mg Lfcin and challenged with cysts of *T. gondii* at a dose of LD_{90} survived 35 days postchallenge [711]. Intraperitoneal administration of 0.1 mg of Lf also prevented death in 100% of treated mice challenged with *T. gondii* cysts, while 80% of untreated mice died of acute toxoplasmosis within 14 days postchallenge [737].

The sporozoites of *T. gondii* preincubated with bovine Lfcin showed decreased activity in penetration of mouse embryonal cells [738]. Mice inoculated with 10^5 sporozoites preincubated with Lfcin showed a higher survival rate than those inoculated with the same number of untreated sporozoites. Rabbits inoculated with 10^5 sporozoites preincubated with Lfcin shed fewer oocysts than these inoculated with the same number of untreated sporozoites [738]. The mechanism of anti-*T. gondii* activity induced by Lf was associated with Lf-induced tyrosine phosphorylation in macrophages [739]. Tanaka et al. [739] found that bovine Lf induced tyrosine phosphorylation of a 30 kDa protein in murine macrophages, which may be associated with inhibition of multiplication of *T. gondii* in the host cells. The density of the specific band of this protein increased dose-dependently and the highest density appeared in the case of mouse peritoneal macrophages incubated with 1,000 μg/mL Lf [739].

Dzitko et al. [740] found that multiplication of the parasite was inhibited by human Lf in human CaCo-2 epithelial cells and in mouse L929 fibroblasts. The intracellular growth of *T. gondii* was not affected when tachyzoites or host cells were only precoated with human Lf. Tanaka et al. [741] also demonstrated that bovine Lf inhibited in a concentration-dependent manner development of intracellular parasites. Supplement of apo-Lf and holo-Lf, but not transferrin, showed similar results. Mouse embryonal cells preincubated with Lf suppressed the intracellular growth of the parasite, while pretreatment of Lf to the macrophages did not show any inhibitory effects [741].

Finally, it must be noted that the trophozoites of *T. gondii* strain RH obtained from peritoneal exudate of infected mice treated with various concentrations of oolong tea and green tea showed that the lowest and effective concentration of tea to kill *T. gondii* completely was 0.5%, but the time necessary to kill the parasites was longer than a half hour [742].

Conclusion

In summary, physiologic swallowing of amniotic fluid containing maternal cells with *T. gondii* by the fetus may play an important role in early development of GT tract disturbances in patients with ASD or other GT diseases. The intestinal inflammation experimentally induced after the parasite infection shares a number of features in common with inflammatory bowel disease and necrotizing enterocolitis. Moreover, it seems that the morphometric abnormalities of the enteric nervous system found in animals caused by oral infection with *T. gondii* may markedly contribute for occurrence of the GT pathophysiology. NKT cells are critical for initiation of inflammatory bowel response against *T. gondii,* and transmission of the parasite from the infected dendritic cells to NKT cells probably plays an important role in this process because the enhanced density of dendritic T cells was demonstrated in the colon of autistic children with gastrointestinal disturbances. The presence of free tachyzoites and parasitophorus vacuoles inside the intestinal mast cells associated with marked morphological alterations in the cells may be responsible for the enteroglial-sustained gut inflammation and death of myenteric neurons in patients with IBD and several other GI tract abnormalities. It must be emphasized that significantly increased titers of anti-IgM and anti-IgG antibodies toward *T. gondii* have already been demonstrated in those individuals compared with controls. The changes in mast cells are similar to the recently proposed perpetuum mobile-like biomachinery causing persistent neuroinflammation in autistics, in which host-endoplasmic reticulum-parasitophorus vacuole interaction provides a route of entry for antigen presentation in *T. gondii*-infected dendritic cells. Mast cells secrete chemotactic factors able to recruite neutrophils, macrophages and lymphocytes when the parasite reaches the lamina propria, and finally reduce survival or cause death of myenteric neurons. The parasite may be also in charge for development of ileal and colonic pouches in patients with ulcerative colitis, Crohn's disease, and in acute and chronic diverticular disease, because it causes post inflammatory damage to the enteric nervous system (ENS). This suggestion may be supported by the findings in laboratory animals that chronic oral/peritoneal inoculation with *T. gondii* genotypes I-III resulted in atrophy or hypoplasia of some segments of the GT and death/hypertrophy of part of myenteric neurons. In addition, perinuclear antineutrophil cytoplasmic autoantibodies found consistently in the serum of children and adults with IBD may be associated with damage to myenteric neurons and marked changes in the cell body, nucleus and cytoplasm areas and nucleus/cell body area ratios depending on acute or chronic parasite infection. Virulence of *T. gondii* has been linked with strain-dependent distinct dendritic cell responses and reduced number of activated $CD8^+$ T cells. Polymerase chain reaction analysis showed presence of the parasite only in the intestinal mucosa and submucosa, which suggested that the quantitative and morphometric alterations found in the myenteric neurons occurred as a result of profuse generation of NO and proinflammatory cytokines by the immune system during the infection. Thus, it seems that many congenital and acquired GI tract abnormalities and their final clinical presentation, including Hirschsprung's disease, may be due to prenatal and/or postnatal damage of the ENS associated with peroral infection

with *T. gondii,* its genotype, virulence/antigenicity, numbers of oocysts/sporozoites/bradyzoites/tachyzoites, part of GI tract infected, and the host innate prenatal and postnatal immune state. On the other hand, it must be noted that lactoferrin (Lf) contained in the breast milk have protective effects against LPS-mediated intestinal mucosal damage and impairment of barrier function in the intestinal epithelial cells observed after oral *T. gondii* infection. Lf has the capacity to enter the nuclei of leukocytes and block the transcription factor NF-κB, which otherwise induces production of IL-1β, TNF-α, IL-6 and IL-8. Lf administered orally improved gastrointestinal morphology in growing calves because it enhanced size of Peyer's patches in the ileum and decreased villous sizes in the jejunum. This effect of Lf and the hypertrophy of intestinal myenteric neurons demonstrated in rats inoculated with *T. gondii* may at least in part be responsible for development of LNH in some children with autism. In addition, Lf have immunomodulatory effects that were partly associated with LPS binding, and this may contribute for the delayed ASD diagnosis until approximately 1.5 to 2 years of age despite the evidence of prenatal morphological changes in the brain. Maturation of the innate immunity to *T. gondii* LPS antigens approximately at this age as compared with much earlier efficacious immune reaction to the parasite peptide antigens may strongly support this reasoning.

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