Small intestinal inflammation following oral infection with *Toxoplasma gondii* does not occur exclusively in C57BL/6 mice: review of 70 reports from the literature

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Small intestinal immunopathology following oral infection with tissue cysts of Toxoplasma gondii *has been described in C57BL/6 mice. Seven days after infection, mice develop severe small intestinal necrosis and succumb to infection. The immunopathology is mediated by local overproduction of Th1-type cytokines, a so-called "cytokine storm". The immunopathogenesis of this pathology resembles that of inflammatory bowel disease in humans, i.e., Crohn's disease. In this review, we show that the development of intestinal pathology following oral ingestion of* T. gondii *is not limited to C57BL/6 mice, but frequently occurs in nature. Using a Pubmed search, we identified 70 publications that report the development of gastrointestinal inflammation following infection with* T. gondii *in 63 animal species. Of these publications, 53 reports are on accidental ingestion of* T. gondii *in 49 different animal species and 17 reports are on experimental infections in 19 different animal species. Thus, oral infection with T. gondii appears to cause immunopathology in a large number of animal species in addition to mice. This manuscript reviews the common features of small intestinal immunopathology in the animal kingdom and speculates on consequences of this immunopathology for humankind.*

Key words: *Toxoplasma gondii* - gastrointestinal tract - inflammation - necrosis - animal

Within eight days of peroral infection with *Toxoplasma (T.) gondii*, susceptible C57BL/6 mice develop severe ileal inflammation resulting in necroses of mucosal villi and complete tissue destruction. Ileitis is caused by a Th1-type immunopathology and is characterized by a $CD4^+$ T cell-mediated increase in pro-inflammatory mediators, including interferon (IFN)-γ, tumor necrosis factor (TNF)-α and nitric oxide (NO) (Liesenfeld et al. 1996, 1998). Activation of IFN-γ and TNF-α are initiated by production of IL-12 and IL-18 (Vossenkaemper et al. 2004). IL-10 and TGF-β have been identified as counter-regulatory cytokines in the inflammatory cascade (Suzuki et al. 2000, Buzoni-Gatel et al. 2001). Recently, we have shown that the ileal bacterial flora, i.e., LPS derived from *Escherichia coli* and *Bacteroides/ Prevotella* spp., contributes to the immunopathology (Heimesaat et al. 2006, 2007). Thus, *T. gondii*-induced ileal immunopathology resembles a large number of inflammatory mechanisms that operate during the acute phases of human inflammatory bowel diseases (IBD) (Liesenfeld 2002, McGovern & Powrie 2007). IBD are characterized by chronic intestinal inflammation with acute episodes (Basset & Holton 2002, Podolsky 2002). Ulcerative colitis is restricted to the colon, whereas Crohn's disease more frequently affects the small intestines, including the terminal ileum. In this article, we review current knowledge on the development of intestinal pathology following oral ingestion of *Toxoplasma* in different hosts throughout the animal kingdom and discuss consequences for intestinal pathology in humans.

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MATERIALS AND METHODS

Two separate PubMed searches were conducted on June 1, 2008 using the following search terms: (1) (*Toxoplasma* OR toxoplasmosis) AND (gastrointestinal OR intestinal OR intestine OR enteritis OR ileitis OR gut OR bowel); (2) (disseminated OR acute OR systemic) AND toxoplasmosis. We excluded the following articles: articles about infections in humans, mice, or genetically modified organisms; articles involving experimental treatment of animals; articles without descriptions of inflammation or necrosis in at least one of the following organs: gastrointestinal tract, mesenteric lymph nodes or liver; and articles describing merely isolation of *T. gondii* out of one of the above mentioned organs without noting inflammatory changes or necrosis.

The search retrieved 2,654 articles published between 1960-May 2008. Using the exclusion criteria, 70 articles remained and these were included in the analysis. Articles about experimental infections and observations were analyzed separately. The animal species identified in the articles were then grouped according to their taxonomic classes. Lesions were analyzed for the following organ systems: small intestines, other gastrointestinal tract locations, mesenteric lymph nodes and liver. Characteristics of lesions were further separated to distinguish between necrosis and inflammatory changes without necrosis.

TABLE I

Observational reports on the development of gastrointestinal inflammation in animal species following oral ingestion of *Toxoplasma gondii*

Class	Sub/ infraclass	Superorder	Order	Suborder	Infraorder	Parvorder	Family	Subfamily
AVES		Neognathae	Anseriformes				Anatidae	
							Anseranatidae	
			Galliformes				Phasianidae	Meleagridinae
								Perdicinae
			Strigiformes				Strigidae	
MAMMALIA	EUTHERIA	Euarchontoglires	Lagomorpha				Leporidae	
			Primates	Haplorrhini	Simiiformes	Platyrrhini	Aotidae	
							Cebidae	Callitrichinae
								Saimiriinae
							Pitheciidae	Callicebinae
								Pitheciinae
				Strepsirrhini	Lemuri-formes		Lemuridae	
			Rodentia	Hystricognathi			Erethizontidae	
				Sciurognathi			Castoridae	
							Sciuridae	Sciurinae
								Xerinae

Species	Small intestine	Gastrointestinal tract (other)	Mesenteric lymph nodes	Liver	Reference
nene geese [*Branta (Nesochen) sandvicensis*]	n			n	Work et al. 2002
magpie geese (*Anseranas semipalmata*)				n	Dubey et al. 2001
turkey (*Meleagris gallopavo*)		n (colon, oesophagus)		n	Howerth & Rodenroth 1985
Erckel's francolin (*Francolinus erckelii*)				n	Work et al. 2002
barred owl (*Strix varia*)				n	Mikaelian et al. 1997
rabbit (*Oryctolagus cuniculus*)				n	Dubey et al. 1992
owl monkey (*Aotus trivirgatus*)	n		n	n	Seibold & Wolf 1971
golden lion tamarin (*Leontopithecus rosalia*)	n			n	Pertz et al. 1997
				n	Dietz et al. 1997
	n		n	n	Juan-Sallés et al. 1998
cotton-top tamarin [*Saguinus (Oedipomidas) oedipus*]	n			n	Dietz et al. 1997
				n	Benirschke & Richart 1960
red-chested mustached tamarin (*Saguinus labiatus*)	n			n	Dietz et al. 1997
squirrel monkey (*Saimiri sciureus*)	i			n	Inoue 1997
			n	n	Anderson and McClure 1982
	n	i (stomach)	n	n	Cunningham et al. 1992
titi (*Callicebus moloch*)				n	Seibold & Wolf 1971
white-faced saki (*Pithecia pithecia*)				n	Dietz et al. 1997
ring tailed lemur (*Lemur catta*)	i			n	Spencer et al. 2004
	n		n	n	Dubey et al. 1985
Mexican hairy dwarf porcupine [*Sphiggurus (Coendou) mexicanus*]				n	Morales et al. 1996
American beaver (*Castor canadensis*)		n (large intestine)			Forzán & Frasca 2004
American red squirrels (*Tamiasciurus hudsonicus*)				i	Bangari et al. 2007
gray squirrels (*Sciurus carolinensis*)	i		n	n	Dubey et al. 2006
woodchuck (*Marmota monax*)				n	Bangari et al. 2007

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Class	Sub/ infraclass	Superorder	Order	Suborder	Infraorder	Parvorder	Family	Subfamily
MAMMALIA	EUTHERIA	Laurasiatheria	Carnivora	Caniformia			Canidae	
							Mustelidae	Mustelinae
							Otariidae	
				Feliformia			Felidae	Acinonychinae
								Felinae
							Pantherinae	
							Herpestidae	
			Cetacea	Odontoceti			Delphinidae	
			Artiodactyla	Ruminantia	Pecora		Bovidae	Antilopinae
								Caprinae
				Suina			Suidae	Suinae

Species	Small intestine	Gastrointestinal tract (other)	Mesenteric lymph nodes	Liver	Reference
dog (*Canis lupus familiaris*)	n	n (stomach)		n	Pimenta et al. 1993
				n	Baba & Rotaru 1983
fennec fox (*Fennecus zerda*)	n	n (stomach)			Kottwitz et al. 2004
gray fox (*Urocyon cinereoargenteus*)	n		n	n	Dubey & Lin 1994
arctic foxes [*Vulpes (Alopex) lagopus*]				n	Sørensen et al. 2005
Blanford's fox (*Vulpes cana*)	n			n	Dubey & Pas 2008
red fox (*Vulpes vulpes*)	i[a]	i[a] (stomach)		n	Reed & Turek 1985
				n	Dubey et al. 1990a
black-footed ferrets (*Mustela nigripes*)		i (large intestine)		n	Burns et al. 2003
California sea lion (*Zalophus californianus*)		n (stomach)			Migaki et al. 1977
cheetah (*Acinonyx jubatus*)				n	Lloyd & Stidworthy 2007
Pallas' cat [*Felis (Octolobus) manul*]	n		n	n	Dubey et al. 1988
		n (stomach)		n	Kenny et al. 2002
Pallas' cat (postpartal) [*Felis (Octolobus) manul*]				i	Basso et al. 2005
domestic cat (*Felis catus*)			n	n	Last et al. 2004
	n		i[a]	n	Dubey & Carpenter 1993
	n			n	Dubey et al. 1990b
domestic cat (postpartal) (*Felis catus*)				n	Dubey et al. 1989
lion (*Panthera leo*)	n		n	n	Ocholi et al. 1989
slender-tailed meerkats (*Suricata suricatta*)	n	n (stomach)	n	n	Juan-Sallés et al. 1997
Risso's dolphin (*Grampus griseus*)	i	n (stomach, oral)		n	Resendes et al. 2002
spinner dolphin (*Stenella longirostris*)		n (oral)		n	Migaki et al. 1990
dik-dik (*Madoqua guentheri*)	n	n (large intestine), i (rumen)	i	n	Dubey et al. 2002
domestic goat (*Capra aegagrus hircus*)	n	n (abomasium)		n	Mehdi et al. 1983
domestic pig (postpartal) (*Sus scrofa domestica*)	n		n	n	Jolly 1969
				n	Hansen et al. 1977
	n		n	n	Dubey et al. 1979

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Class	Sub/ infraclass	Superorder	Order	Suborder	Infraorder	Parvorder	Family	Subfamily
MAMMALIA			Xenarthra				Bradypodidae	
	METATHERIA		Dasyurimorphia				Dasyuridae	
							Myrmecobiidae	
			Diprotodontia	Macropodiformes			Macropodidae	
				Phalangeriformes			Phalangeridae	
				Vombatiformes			Phascolarctidae	
							Vombatidae	
							Petauridae	
			Peramelemorphia				Peramelidae	
							Thylacomyidae	
	PROTOTHERIA		Monotremata				Tachyglossidae	

a: no histopathological proof; i: (only) inflammatory cell infiltrate; n: necrosis.

Species	Small intestine	Gastrointestinal tract (other)	Mesenteric lymph nodes	Liver	Reference
three-toed sloth (*Bradypus tridactylus*)	n			n	Túry et al. 2001
dasyurids	n	n (stomach)	n	n	Canfield et al. 1990
numbat (*Myrmecobius fasciatus*)	n	n (stomach)	n	n	Canfield et al. 1990
red-necked wallabies (*Macropus rufogriseus*)	i		i	i	Basso et al. 2007
		n (stomach)	n	n	Adkesson et al. 2007
macropods	n	n (stomach)	n	n	Canfield et al. 1990
possums	n	n (stomach)	n	n	Canfield et al. 1990
koala (*Phascolarctos cinereus*)	n	n (stomach)	i	n	Canfield et al. 1990
	n	n (stomach)	i	n	Hartley et al. 1990
common wombat (*Vombatus ursinus*)	i	n (stomach)	i	i	Canfield et al. 1990
sugar gliders (*Petaurus breviceps*)	n				Barrows 2006
bandicoots	n	n (stomach)	i	i	Canfield et al. 1990
bilby (*Macrotis lagotis*)	n	n (stomach)	i	i	Canfield et al. 1990
echidna (*Tachyglossus aculeatus*)				i	McOrist & Smales 1986

TABLE II

Reports on experimental oral infection with *Toxoplasma gondii* resulting in the development of gastrointestinal inflammation

Class	Sub/ infraclass	Superorder	Order	Suborder	Infraorder	Parvorder	Family	Subfamily	Species	Strain	Dose (oral oocysts unless otherwise noted)
AVES		Neognathae	Galliformes				Odontophoridae		bobwhite quail (*Colinus virginianus*)	ME-49, GT-1	ME-49: 10^4, 10^5; GT-1: 10^4, 10^5
							Phasianidae	Perdicinae	japanese quail (*Coturnix japonica*)	ME-49, GT-1	ME-49: 10^3, 10^5;
									red-legged partridge (*Alectoris rufa*)	OV-51/95	10^1, $5x10^1$, 10^2, 10^3, 10^4
								Phasianinae	pheasant (*Phasianus colchicus*)	ME-49, GT-1	ME-49: 10^4, 10^5; GT-1: 10^3, 10^5
			Psittaciformes				Psittacidae		budgerigars (*Melopsittacus undulatus*)	VEG	10^2, 10^3, 10^5
MAMMALIA	EUTHERIA	Euarchontoglires	Lagomorpha				Leporidae		brown hare (*Lepus europaeus*)	K7	10, 10^3, 10^5
									mountain hare (*Lepus timidus*)	Tg-SweF1	$5x10^1$
									rabbit (*Oryctolagus cuniculus*)	Tg-SweF1 K7	$5x10^1$ 10, 10^3, 10^5
			Primates	Haplorrhini	Simiiformes	Platyrrhini	Cebidae	Callitrichinae	cotton-top tamarin [*Saguinus* (Oedipomidas) *oedipus*]	DX, K65, MB, ALT, KA, BK, Witting, Weiß	8-666 (BK-strain: 10^5 trophozoites intraperitoneally)
								Saimiriinae	squirrel monkey (*Saimiri sciureus*)	ME-49	1,1 - 2,1 x 10^3
			Rodentia	Sciurognathi			Cricetidae	Sigmodontinae	large vesper mouse (*Calomys callosus*)	RH	10^2 - 10^6 tachyzoites intraperitoneally
		Laurasiatheria	Artiodactyla	Ruminantia	Pecora		Antilocapridae		pronghorn (*Antilocapra americana*)	GT-1	10^2, 10^4
							Bovidae	Bovinae	domestic cow (juvenile) (*Bos bovis*)	GT-1	10^5
								Caprinae	domestic goat (juvenile) (*Capra aegagrus hircus*)	GT-1	10^3, 10^4, 10^5

Small intestine	Gastro intestinal tract (other)	Mesenteric lymph nodes	Liver	Comments	Reference
i			n	lesions only with GT-1 strain	Dubey et al. 1993
i			i	all animals from GT-1 group had lesions; only 4 out of 12 animals from ME-49 group had lesions (1 fed with 10^3, 3 fed with 10^5 oocysts)	Dubey et al. 1994a
n			n	lesions only in 2 out of 30 animals, which died due to the infection (fed with 5 x 10^1 and 10^4 oocysts, respectively); others had yellowish diarrhea	Martínez-Carrasco et al. 2005
n				lesions only in 1 out of 5 animals from GT-1 group	Dubey et al. 1994b
n			i	lesions in 4 out of 4 birds fed with 10^5 oocysts; 3 out of 4 fed with 10^3; 0 out of 4 fed with 10^2	Dubey & Hamir 2002
n		n	n	milder lesions in animals infected with 10^1 or 10^3 oocysts	Sedlák et al. 2000
n		n	n		Gustaffson et al. 1997
i		i	i i		Gustaffson et al. 1997 Sedlák et al. 2000
n	n (large intestine)	i[a]	n[a]	no pathologic changes with BK-strain	Werner et al. 1969
n		n	n	horizontal transmission among cagemates could be documented serologically and via PCR; cagemates remained, however, clinically normal and had no histopath changes	Furuta et al. 2001
oa			oa		Favoreto-Júnior et al. 1998
n		n	n		Dubey et al. 1982
n		n	i		Dubey 1983
n	i (oesophagus, rumen)	n	n		Dubey 1989

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Class	Sub/ infraclass	Superorder	Order	Suborder	Infraorder	Parvorder	Family	Subfamily	Species	Strain	Dose (oral oocysts unless otherwise noted)
MAMMALIA	EUTHERIA	Laurasiatheria	Artiodactyla	Ruminantia	Pecora		Cervidae	Odocoileinae	mule deer (*Odocoileus hemionus*)	GT-1	10^5
									reindeer (*Rangifer tarandus*)	ME-49	$5x10^3$, $5x10^4$
				Suina			Suidae	Suinae	domestic pig (postpartal) (*Sus scrofa domestica*)	GT-1	10^4
	METATHERIA		Diprotodontia	Macropodiformes			Macropodidae		Tammar wallabies (*Macropus eugenii*)	ME-49, PT-12	ME-49: $5x10^2$, 10^3, 10^4; PT-12: 10^3
			Perameles-morphia				Peramelidae		eastern barred bandicoots (*Perameles gunnii*)	P89/VEG	10^2

a: no histopathological proof; i : (only) inflammatory cell infiltrate; n: necrosis; oa : only "organ affection" stated.

RESULTS AND DISCUSSION

The Pubmed-based search revealed 70 publications on inflammatory changes in the gastrointestinal tract caused by infection with *T. gondii*. These publications were subdivided into observational reports and experimental infections. Table I provides an overview of all observational reports on gastrointestinal inflammation caused by *T. gondii* infection. There were 66 publications that reported the development of inflammatory changes in the gastrointestinal tract. Animals affected belonged to two classes (Mammalia and Aves) and 51 different species. Among the latter, inflammatory changes were most frequently reported in the orders carnivora and primates. Of all gastrointestinal organs reported to be affected, the liver (93.9% of cases) and small intestines (57.6%) were most frequently affected. Additional sites affected with less frequency were the stomach, large intestines and mesenteric lymph nodes. The parasite could be detected in a large number of these studies. Interestingly, the suborder Feliformia, the definite host for *T. gondii*, was also reported to develop intestinal pathology. Domestic cats, cheetahs, Pallas cats, meerkats and lions were the species reported from that suborder. Gastrointestinal pathology, independent of the species, was characterized by small intestinal necrosis with loss of the physiological villus architecture. Since these publications were observational reports, often from zoos, no information is available regarding source of infection (tissue vs. oocyst), strain or dose of infection.

Table II summarizes results from 20 publications on experimental infections. As in observational studies shown above, these experiments include infections in aves and mammals. In most cases, oocysts were fed orally to animals, doses ranged from 10^1 to 10^5 oocysts and type II and III strains were used in most cases. The small intestines (95%) and liver (85%) were the organs affected with highest frequency. In most cases, small intestinal pathology was characterized by a complete loss of the villous architecture and was similar to the pathology described in observational studies discussed above.

Since pathological changes were also similar to changes observed following experimental infection of mice with tissue cysts, the pattern observed appears to be a common feature of oral infection with *T. gondii*. In mice, the small but not the large intestines show formation of oedema 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. Pathological changes are most prominent in the distal part of the ileum, but the duodenum and jejunum are usually not affected. In the liver, foci of inflammation can be observed around vessels and in the parenchyma. Intracellular parasites can be detected in large numbers in the lamina propria of the ileum; parasite numbers in the liver are smaller. Intestinal pathology may lead to death in susceptible mice and other animals. The publications reviewed here suggest that the strain of *Toxoplasma*, the infectious inoculum and the host genetics may impact the development of intestinal pathology. It remains to be investigated whether humans also develop intestinal pathology after oral infection. Intestinal pathology has not been reported thus far, however, the parasite was detectable in AIDS-patients with reactivated disease, intestinal pathology and diarrhoea (Liesenfeld 1999). One reason for the lack of intestinal pathology in humans may be due to the dose required for the development of pathology. In animals, an inoculum of $\geq 10^2$ oocysts and 40-100 tissue cysts (ME49 strain) are required to induce intestinal pathology. Consumption of raw and undercooked meat or ingestion of contaminated environmental sources (i.e., water) may not harbour sufficient numbers of parasites to induce pathology. In this regard, it will be of inter-

Small intestine	Gastro intestinal tract (other)	Mesenteric lymph nodes	Liver	Comments	Reference
n		i			Dubey et al. 1982
n	i (abo-masum)	n	n	Only 1 reindeer fed with $5x10^4$ oocysts died and was necropsized; reindeer 2 fed with $5x10^3$ oocysts had haemorrhagic faeces	Oksanen et al. 1996
n		n	n		Dubey et al. 1984
n		n	n	2 animals were treated with *Hammondia* oocysts prior to *Toxoplasma* infection and survived	Reddacliff et al. 1993
n		n	n		Bettiol et al. 2000

est to investigate whether oral infection with *T. gondii* is associated with IBD in humans. It is tempting to speculate whether the strong local and/or systemic immune response during the acute or latent phase of the infection may contribute to an imbalance in the homeostasis of mucosal immune responses in humans with IBD. As a first step, the prevalence of antibodies against *T. gondii* could be determined in patients with IBD compared to well-selected control populations; a slightly but significantly higher seropositivity rate (based on Sabin-Feldman dye test results) has been observed previously in a small cohort of Crohn's patients over the age of 40 in Israel (Rattan et al. 1986). Results of studies that include larger patient numbers should be especially interesting since an association of *T. gondii* infection (based on the presence of IgG antibodies) with psychiatric disorders has been suggested (Yolken & Torrey 2008).

In conclusion, development of small intestinal pathology following oral infection with *T. gondii* is not uncommon in the animal kingdom and the association of infection with *T. gondii* and gastrointestinal pathologies, including IBD in humans, deserves further investigation.

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