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Review

Toxoplasmosis of rats: a review, with considerations of their value as an animal model and their possible role in epidemiology

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Abstract

We critically review and summarize information on the prevalence of *Toxoplasma gondii* infections in rats, mainly *Rattus norvegicus*, and their possible role as a source of infection for larger carnivores and omnivores. We also review information on immunology and natural resistance, contributing to the model value of rats in the analysis of human infection. Rats can be successfully infected with oocysts (sporozoites), tissue cysts (bradyzoites), and tachyzoites. Even adult rats, that are resistant to clinical toxoplasmosis, can be infected orally with a few oocysts or tissue cysts. Infections with tachyzoites of the RH strain are highly variable. Congenital transmission of *T. gondii* occurs at a high rate when rats are infected during pregnancy. Congenitally infected rats can harbor viable *T. gondii* in the absence of detectable antibodies to *T. gondii* and rats with low antibody titers may harbor few or no organisms. The isolation of viable *T. gondii* by bioassay is the only reliable means to determine persistence of chronic *T. gondii* infection in feral rats. No evidence was found for maintenance of *T. gondii* in rats by vertical transmission in the absence of cats. © 1998 Elsevier Science B.V.

Keywords: *Toxoplasma gondii*; Toxoplasmosis; Rats; *Rattus norvegicus*; Prevalence; Epidemiology; Tissue cysts; Oocyst infectivity; Pathogenicity

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1. Introduction

Toxoplasma gondii-infected rats are considered important in the epidemiology of toxoplasmosis because they can serve as reservoirs of infection for pigs, dogs, and possibly for cats. Infected rats have also been suggested as animal models for human toxoplasmosis because toxoplasmosis in both species is often subclinical. Much of the literature on toxoplasmosis in rats is 30 to 50 years old and unknown to contemporary workers. There are many misconceptions regarding the resistance of rats to *T. gondii*. This review summarizes information on the prevalence of *T. gondii* infections in rats, mainly *Rattus norvegicus*, their possible role in the epidemiology of toxoplasmosis, and available information on immunity and resistance contributing to the model value of rats in the analysis of human infection.

2. History of recognition of toxoplasmosis in rats

T. gondii-like parasites were first found in the lung of an albino laboratory rat in Italy (Sangiorgi, 1915). The rat was found dead and it had not been experimentally infected. If it had toxoplasmosis, the infection was probably contracted from oocysts shed by cats, which used to be kept in animal colonies to catch stray and escaped mice. Perrin et al. (1943) first reported, well-documented *T. gondii* infection in wild rats from Georgia, USA. During a study of typhus fever, pools of two to eight brains of 1943 trapped rats were inoculated into two pairs of guinea pigs. Some of the guinea pigs inoculated with rat brains died of acute toxoplasmosis. *T. gondii*, as indicated by guinea pig mortality was found 94 times; 63 times in both inoculated guinea pigs and 31 times in only one of the pairs. *T. gondii* was found in 14 of 160 (8.8%) rat brains as evidenced by development of toxoplasmosis in guinea pigs inoculated with individual rat brains. Tissue cysts of *T. gondii* were seen in histologic sections of 7 of 10 rat brains examined. It should be noted that not all *T. gondii* isolates are fatal to guinea pigs, nor do small numbers of *T. gondii* kill guinea pigs. Hence, the percentage of infected rats may have been greater than indicated by guinea pig mortality. No practical serologic tests to diagnose toxoplasmosis were available at that time.

Eyles (1952) was the first to search for antibodies by means of the newly developed dye test in wild rats trapped in Tennessee, USA. He found 8–20% seropositivity and isolated *T. gondii* from 1 of 100 rats by bioassay in mice, and in 5 of 18 guinea pigs each injected with five rat brains.

3. Prevalence

Serologic data in rats from different countries are summarized in Table 1. When different tests were used and different antibody titers considered to indicate *T. gondii*

Table 1
Prevalence of *T. gondii* antibodies in rats

Country	Reference	Species	No.	Test and cut-off titer	Percent positive	Titers <16	16–64	128–512	≥ 1004
Africa	de Roever-Bonnet (1972)	*R. rattus*	61	DT (40)	8				
Australia	Cook and Pope (1959)	*R. rattus*	117	C.F. (8)	3	1	3		
Queensland		*R. norvegicus*	41	C.F. (8)	7	1	2		
		Rattus assimilis	30	C.F. (8)	9		3		
		Rattus conatus	11	C.F. (8)	8		1		
		Hydromys chrysogaster (water rat)	23	C.F. (8)	91	1	20		
China (People's Republic)	Lin et al. (1990)	rat (unspecified)	955	IHA (64)	1		9		
Costa Rica	Chinchilla (1978)	*R. norvegicus*	23	DT (4)	30	2	4	1	
	Ruiz and Frenkel (1980)	*R. norvegicus*	107	DT (2)	21	7	15		
Czech Republic	Zástěra et al. (1966)	*R. norvegicus*	519	DT (4)	9	11	25	7	6
Egypt									
Giza	El Nahal et al. (1982)	*R. norvegicus*	60	IHA (64)	13		1	7	
		Rattus alexandrinus	12	IHA (64)	0				
Cairo	Rifaat et al. (1971)	*R. norvegicus*	100	DT (16)	21	13	7	14	
	Rifaat et al. (1973)	*R. alexandrinus*	110	DT (16)	28	16	25	6	
Finland	Grönroos and Salminen (1955)	*R. norvegicus*	108	DT (4)	12	11	2		
France	Doby et al. (1974)	*R. rattus*	40	DT (10)	2.5				
		R. norvegicus	4	DT (10)	25				
Germany	Laven and Westphal (1950)	*R. norvegicus*	34	DT (16)	15		5		
India									
Haryana	Mir et al. (1982)	*R. norvegicus*	186	IHA (64)	0				
Italy	Zardi et al. (1983)	*R. rattus*	32	IFA (?)	16		5		
Terramo		*R. norvegicus*	152	IFA (?)	22		34		
Monte		*R. rattus*	70	IFA (?)	17		12		
Argentario Baccinello		*R. rattus*	147	IFA (?)	37		54		
Mantova	Genchi et al. (1991)	*R. norvegicus*	20	IFA (40)	70		14		

Table 1 (continued)

Country	Reference	Species	No.	Test and cut-off titer	Percent positive	Titers			
						<16	16–64	128–512	≥ 1004
Japan									
Osaka	Izutani (1958)	*R. rattus*	42	DT (16)	2		2		
		R. norvegicus	116	DT (16)	6		7		
Osaka	Jyono (1960)	*R. norvegicus*	100	DT (16)	12		12		
		R. rattus	40	DT (16)	0				
Tokyo	Katsube et al. (1968)	*Rattus* sp.	14	DT (16)	0				
Niigata	Maitani (1970)	*Rattus* sp.	62	DT (16)	0				
Osaka	Iseki et al. (1972)	*R. norvegicus*	300	HA (256)	8			25	
		R. rattus	26	HA (256)	15			4	
Kobe	Murata (1987)	*R. norvegicus*	15	LAT (16)	0				
Kuwait	Bezjak and Thorburn (1982)	*R. norvegicus*	142	HA (64)	3		4		
Mexico	Varela (1955)	*R. norvegicus*	360	DT (32)	23				
		R. rattus	39	DT (32)	69				
Micronesian atoll	Wallace et al. (1972)	*R. rattus*	238	DT (8)	3		5	2	
		R. exulans	420	DT (8)	10	2	3	9	
Panama	Frenkel et al. (1995)	*R. norvegicus*	226	MAT (60)	23	29	52		
Poland	Dymowska et al. (1955)	Unspecified	150	DT (?)	0				
	Slowakiewicz et al. (1967)	*R. Norvegicus*	646	DT (?)	9				
Saudi Arabia	Morsy et al. (1994)	*R. norvegicus*	142	IHA (64)	14		8	12	
Riyadh		*R. rattus*	24	IHA (64)	29		1	6	

UK									
England	Webster (1994a)	*R. norvegicus*	235	LAT (10)	35				
Scotland	Hay et al. (1983)	*R. norvegicus*	46	DT (10)	11		2	3	
	Jackson et al. (1986)	*R. norvegicus*	65	DT (10)	7		2	3	
USA									
Florida	Burridge et al. (1979)	*R. rattus*	38	IHA (64)	13		5		
		R. norvegicus	8	IHA (64)	12		2		
Georgia	Lubroth et al. (1983)	*R. norvegicus*	2	IHA (64)	100				
Hawaii	Wallace (1973)	*R. rattus*	476	DT (16)	8	10	9	17	
		R. exulans	85	DT (16)	7	5	0		
		R. norvegicus	73	DT (16)	1	0	0	1	
Illinois	Dubey et al. (1995a)	*R. norvegicus*	95	MAT (25)	6		6		
Maryland	Childs and Seegar (1986)	*R. norvegicus*	109	IFA (32)	50		54		
Mississippi	Eyles et al. (1959)	*R. norvegicus*	25	DT (4)	0				
New York	Feldman and Miller (1956)	*R. norvegicus* (Laboratory)	54	DT (4)	0				
Tennessee	Eyles (1952)	*R. norvegicus*	100	DT (16)	8	92	6	1	1
	Eyles et al. (1959)	*R. norvegicus* (Laboratory)	74	DT (16)	0				

DT = Dye test.
MAT = Modified agglutination test.
HA = Hemagglutination.
IHA = Indirect hemagglutination.
CF = Complement fixation.
LAT = Latex agglutination test.

Table 2
Prevalence of *T. gondii* organisms in tissues of rats

Country	Reference	Species	No. examined	No. positive (%)
Australia				
Queensland	Pope et al. (1957)	*R. norvegicus*	15	1
		R. rattus	7	0
		R. assimilis	12	2
Queensland	Cook and Pope (1959)	*R. rattus*	16	0
		R. conatus	12	0
		Rattus villosissimus	27	0
		H. chrysogaster (water rat)		
Queensland, New South Wales, Tasmania	Smith and Munday (1965)	*H. chrysogaster* (water rat)	16	11 (68.7)
		Rattus spp.	13	0
Costa Rica	Chinchilla (1978)	*R. norvegicus*	23	0
	Ruiz and Frenkel (1980)	*R. norvegicus*	120	15 (12.5)
Czech Republic	Hejlíček et al. (1997)	*R. norvegicus*	84	1
Egypt				
Cairo	Rifaat et al. (1971)	*R. norvegicus*	25 (pools of 5 brains each)	2
	Rifaat et al. (1973)	*R. alexandrinus*	64 (in 17 pools)	6 (35.3)
India	Mir et al. (1982)	*R. norvegicus*	91	0
Italy	Genchi et al. (1991)	*R. norvegicus*	25	19[a]
Japan				
Fukushima	Tsunematsu et al. (1958)	*R. norvegicus*	63	0
Hokkaido	Tsunematsu et al. (1958)	*Rattus* sp.	100	1
Niigata	Maitani (1970)	*Rattus* sp.	72	0
Osaka	Nakajyo et al. (1957)	*R. rattus* and *R. norvegicus*	105	2
Osaka	Jyono (1960)	*R. rattus*	48	0
Osaka	Iseki et al. (1972)	*R. norvegicus*	11	1[b]

Tokyo	Matsubayashi and Tazaki (1954)	*Rattus* sp. *R. rattus*	104	0
Tokyo	Tazaki (1954)	*Rattus* sp.	50	0
Tokyo	Katsube et al. (1968)	*Rattus* sp.	63	0
Kuwait	Bezjak and Thorburn (1982)	*R. norvegicus*	12	0
Panama	Frenkel et al. (1995)	*R. norvegicus*	23	1[b]
Republic of China (Taiwan)	Yeh (1966)	*R. norvegicus*	15	1
Sri Lanka	Kulasiri (1962a)	*R. norvegicus*	12	1
		R. rattus	26	2
		Hooded rat	15	1
UK				
England	Lainson (1956)	*R. norvegicus*	99	1
Scotland	Hay et al. (1983)	*R. norvegicus*	46	2[c] (4.3%)
USA				
Georgia	Perrin et al. (1943)	*R. norvegicus*	160	14[d] (8.7%)
Georgia	Lubroth et al. (1983)	*R. norvegicus*	2	1[e]
Illinois	Dubey et al. (1995a)	*R. norvegicus*	107	1
Mississippi	Eyles et al. (1959)	*R. norvegicus*	25	0
Tennessee	Eyles (1952)	*R. norvegicus*	100	1[f]
		R. norvegicus	90 (18 × 5)[g]	5[h]
Tennessee	Eyles et al. (1959)	*R. norvegicus*	11	0

[a] In sections of brain; not confirmed by bioassay.
[b] Only tissues from seropositive rats were bioassayed.
[c] Tissue cysts in rat brains.
[d] In tissue sections of rat brains.
[e] Inoculated mice developed antibodies to *T. gondii* but parasite not reported.
[f] The rat was dye test negative in undiluted serum.
[g] Pools of five brains inoculated in guinea pigs.
[h] One of the donor group of rats was dye test negative in undiluted serum.

infection, findings are difficult to compare. However, all data are included in the table for completeness.

None of the serologic tests have been critically evaluated for the diagnosis of latent *T. gondii* infection in rats. For most hosts, antibody titers specific for *T. gondii* infection are 1:64 for the latex agglutination test (LAT) and the indirect hemagglutination test (IHAT), 1:16 for the dye test and indirect fluorescent antibody test (IFAT), and 1:25 for the modified agglutination test (MAT). No serologic test can be definitive in individual rats because *T. gondii* has been isolated from tissues of rats and humans without antibodies even in a 1:2 dilution of serum, and *T. gondii* could not be recovered from many rats with higher antibody titers.

Parasitologic data are summarized in Table 2. *T. gondii* was recovered from as many as 68% of rats sampled. *T. gondii* was isolated from five of seven water rats (*Hydromys chrysogaster*) but not from 28 domestic rats from the same area from Australia (Cook and Pope, 1959; Smith and Munday, 1965). Although unknown at the time of the study, in view of other water-borne epidemics of toxoplasmosis, we can now suspect contamination of water by feline feces as the source of infection for those water rats (Bell et al., 1995). Several factors such as the rate of shedding of oocysts by cats in the environment, and climate affecting the survival of oocysts may account for the different prevalence rates of *T. gondii* in rats. For example, the high, (15 of 120, 12.5%) prevalence of *T. gondii* in rats in Costa Rica (Ruiz and Frenkel, 1980) may be due to greater contamination of the environment with oocysts in Costa Rica. A high percentage of young cats in Costa Rica were found to be shedding oocysts (Ruiz and Frenkel, 1980). The moist, temperate climate and density of cats in an area also contribute to the environmental survival of *T. gondii* oocysts.

Farm management practices and hygiene might have affected results compiled in Table 2. For example, the low prevalence (0.9%) in 1993–1994 in Illinois (Dubey et al., 1995a) compared with the high prevalence (8.8%) of *T. gondii* in rats in Georgia, USA (Perrin et al., 1943) may be because of more hygienic farm practices which led to a decrease of *T. gondii* infection in pigs in Illinois, USA (Dubey et al., 1995a). Similarly, better hygiene and increased consumption of frozen meat (which kills most bradyzoites) probably led to a decline from 14.4% to 9.5% antibody prevalence between 1962 and 1989 in a cross-section of US military recruits (Smith et al., 1996).

The rate of isolation of *T. gondii* also varied with the antibody titer in the rat. For example, *T. gondii* was not isolated from rats in Costa Rica with dye test antibody titers of $\leq$ 1:64 (Ruiz and Frenkel, 1980), and isolation was accomplished from only 1 of 23 seropositive (titers of 1:60 to 1:162,000 in MAT) rats in Panama (Frenkel et al., 1995); the rat in which infection was parasitologically proven had an antibody titer of 1:162,000.

The method for sampling is also important. For example, pooling of brains from several rats (Perrin et al., 1943; Rifaat et al., 1973; Eyles, 1952) provided only qualitative data. It is also important to verify results by bioassay because identification of *T. gondii* in brain smears or sections is not as sensitive (Dubey and Beattie, 1988). Therefore we cannot be certain that in the report by Genchi et al. (1991), the high seroprevalence (19 of 25 rats, 76%) of *T. gondii* in Italy reflects persistent infection.

4. Host–parasite relationship

4.1. Infectivity of different stages of the parasite

Infection and clinical disease can vary with the isolate, the stage, and the route of inoculation of *T. gondii*. We review infections according to the stage inoculated.

4.1.1. Infection with tachyzoites

There are numerous reports of tachyzoite-induced *T. gondii* infections in rats. Most of the data were derived with tachyzoites of the RH strain. Because infection with the RH strain is always fatal in mice, unless moderated by chemoprophylaxis, rats which develop chronic infection without therapy have been used to maintain the parasite in an animal host. The RH strain of *T. gondii* was isolated in 1939 and since then it has been maintained essentially in mice by twice weekly passages. It is used worldwide, and is the main source of antigen for all serologic tests for *T. gondii*. Jacobs and Jones (1950) reported that adult rats (*R. norvegicus*) inoculated intraperitoneally (i.p.) with RH strain tachyzoites harbored virulent *T. gondii* for 7 months, and Ruchman and Fowler (1951) found that parasites survived in rat brain up to 2 years after i.p. inoculation. However, other investigators reported different results with the RH strain and with other strains. For example, Callot and Puech (1952) could not recover *T. gondii* from tissues of rats only weeks after inoculation with tachyzoites of a Dutch isolate and similar results were obtained by Van Thiel (1956) with other isolates. Parasites were rarely found in histologic sections of rats chronically infected with the RH strain (Hellbrügge et al., 1953, 1956).

The RH strain of *T. gondii*, or other strains, can be fatal to rats depending on the route of infection and dose used. For example, rats inoculated intracerebrally with large numbers of tachyzoites of a human isolate died of toxoplasmosis, whereas those given smaller inocula survived (Ruchman and Johansmann, 1948). The variability of results obtained in rats may in part be related to the changes in the RH strain that occurred during the prolonged passage in mice, since 1939, and the development of different sublines of the RH strain, some even without persistence of the tissue cyst.

The passage of mouse-pathogenic strains of *T. gondii* through rats has given insight into the variability of the *Toxoplasma* genome. Using analysis of Restriction Length Fragment Polymorphism (RFLP) and Random Amplified Polymorphic DNA (RAPD), 13 schizodemes could be distinguished in 14 cloned strains of *T. gondii* (Ambroise-Thomas and Okay, 1993). Mouse-pathogenic strains were relatively uniform, however nonpathogenic strains showed a great diversity in DNA patterns. In addition to inter-strain variations, intrastrain variations were observed after passage of the cloned mouse-pathogenic RH strain though Fischer or Wistar rats which rendered it non-pathogenic for mice, in which it gave rise to chronic infection, with tissue cysts and changed genomic DNA patterns. Additional DNA profile changes were observed in newborn rats after intrauterine infection, with differences in genomic profiles in different rat pups and organs from which isolations were performed (Ambroise-Thomas and Okay, 1993). The genomic drift of *T. gondii* as observed by a number of investigators was reviewed and discussed by Frenkel and Ambroise-Thomas (1997) concluding that

mutations occur with some frequency in *T. gondii* and that passage through immunocompetent rats, especially after intrauterine infection, selects certain of these mutants. After passage in immunosuppressed rats or certain cell cultures, *T. gondii* reverted to become mouse-pathogenic with the typical DNA pattern of other mouse-pathogenic *T. gondii*.

4.1.2. Tissue cyst-induced infections

Rats, like other hosts, become infected by ingesting tissue cysts (Weinman and Chandler, 1954). Tissue cyst-induced infections have been generally subclinical in immunocompetent rats (Henry and Beverley, 1977; Piekarski et al., 1978; Witting, 1979; Dubey and Shen, 1991; Zenner et al., 1993). Even athymic rats have been shown to survive infection with 100 tissue cysts (Schlüter et al., 1995).

4.1.3. Oocyst-induced infections

After the discovery in 1970 of oocysts, the resistant enteric stage of *T. gondii* shed in cat feces, investigators began to study their infectivity. Infections initiated with oocysts are usually accompanied by more lesions than those initiated with tachyzoites or tissue cysts (Dubey and Frenkel, 1973; Dubey and Beattie, 1988). Oocysts can be counted easily and they can be stored at 4°C for 12 months with little loss of infectivity and they are not likely to have been modified as the RH strain by prolonged passage (Dubey and Beattie, 1988). Miller et al. (1972) fed an unspecified number of oocysts to five Sprague–Dawley rats. All rats developed dye test antibodies (1:128). Three rats died and *T. gondii* was isolated from liver and spleen. Two rats were killed and *T. gondii* was isolated from adrenal gland and brain.

Wallace (1973) reported on oocyst-produced infections in laboratory raised and wild rats (*R. norvegicus*). Four young laboratory rats fed 400 oocysts of the M-7741 strain remained subclinically infected until 26 days after inoculation (DAI) when they were killed. The rats had dye test titers of 1:256 and tissue cysts were found in their brains. In another experiment 27 adult wild rats of two species were fed 30 or 60 oocysts of the WC-306 strain. All nine *Rattus exulans* fed 30 oocysts became seropositive (dye test titers of $\geq$ 1:128) by 21 DAI but only 4 of the 10 *Rattus rattus* fed the same dose of oocysts became seropositive ($\geq$ 1:16). Three of these four rats were challenged with 3×10^4 oocysts 22 to 23 DAI; they were bled 3 weeks later and dye test antibody titers were 1:256, 1:16 and 1:4. All eight *R. rattus* fed 60 oocysts became seropositive by 21 DAI, indicating that the infecting dose may modify outcome of infection.

Ito et al. (1975) fed 15 Wistar rats 1.4×10^4 to 1.4×10^5 *T. gondii* oocysts of five isolates, three rats for each isolate. All rats seroconverted but none developed clinical signs. *T. gondii* was later demonstrated by bioassay in several tissues of these rats, most often the brain.

Guerrero et al. (1995) fed 1-, 5-, 10-, 15- and 30-day-old Sprague–Dawley rats with 10^4, 10^5, 10^6 and 10^7 *T. gondii* oocysts per 100 g body weight, in order to examine age-related resistance. All rats survived 30 days. More tissue cysts were found in rats inoculated at 5 and 10 days of age than in those inoculated when 1, 15 and 30 days old (Guerrero et al., 1995). At necropsy, the authors did not find any important lesions in

Table 3
Effect of dose on the number of tissue cysts in brains of rats fed *T. gondii* oocysts[a]

No. of oocysts fed	No. of infected rats survived	No. of tissue cysts			
		Brain homogenate[b]		Tissue sections[c]	
		Range	Average	Range	Average
10^6	2[d]	1380–1920	2650	11–20	15.5
10^5	5	600–2880	1200	9–30	20.6
10^4	5	300–540	396	3–11	6.8
10^3	5	120–1860	600	5–28	10.4
10^2	5	120–1680	528	3–10	6.4
10	5	60–480	180[e]	1–10	5.0
1	3[f]	180–480	300[e]	1–15	6.0

[a] From Dubey (1996).
[b] Homogenate of 1/2 brain from each injected animal.
[c] Per 1 coronal section.
[d] Three rats died.
[e] Identical procedure was performed with mice. Mice surviving inoculation with 1 or 10 oocysts averaged 256 and 430 tissue cysts in homogenate of 1/2 brain, respectively. All other groups of mice died prior to development of tissue cysts.
[f] The remaining two rats in this group were not infected.

tissues of these and another group of rats fed 10^5 oocysts (Guerrero and Chinchilla, 1996–1997).

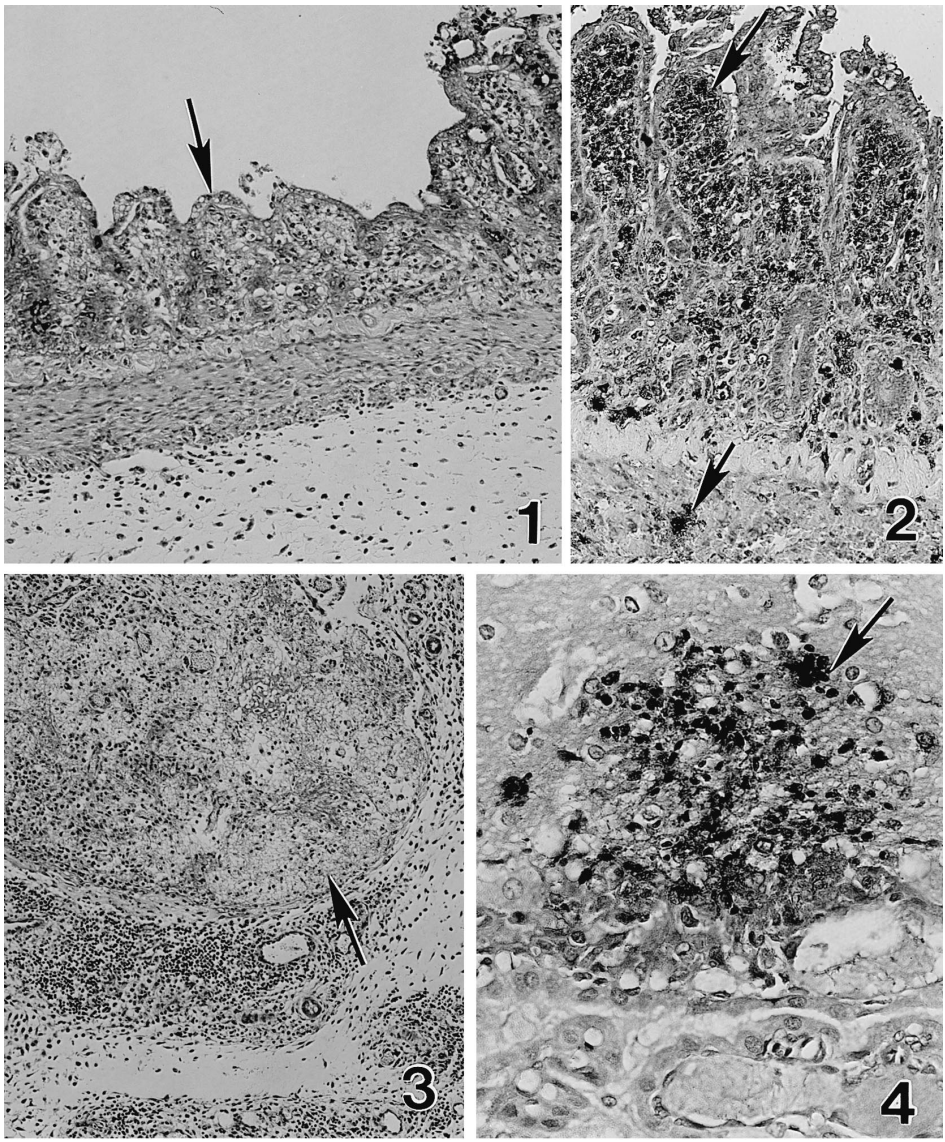
Until recently, it was not known whether a few *T. gondii* were infective to rats. Mice have been traditionally used to test the infectivity of *T. gondii*. Dubey (1996) compared infectivity and pathogenicity of oocysts in rats and mice. Sprague–Dawley ($n = 40$) female rats (130 g) and Swiss Webster ($n = 40$) white female mice (20–25 g) were fed graded doses varying from 1 to 10^6 VEG strain oocysts (five animals for each dose). Rats fed 10^5 or 10^6 oocysts became ill (diarrhea, depression) and three of the five rats fed 10^6 oocysts died between 6 and 9 DAI. The remaining rats receiving lower doses remained healthy (Table 3). The threshold of infection was identical in rats and mice; the rats developed subclinical infection whereas mice became sick and died. The total number of tissue cysts in brains of rats and mice that survived infection with 1 or 10 infective oocysts was comparable. Tissue cysts were detected in histologic sections of brains of all infected rats (Table 3).

Occasionally adult rats fed 10^5 or 10^4 oocysts died with acute toxoplasmosis with lesions and parasites (Figs. 1–8) similar to those seen in mice (Dubey, 1996).

4.2. Immune response of the host

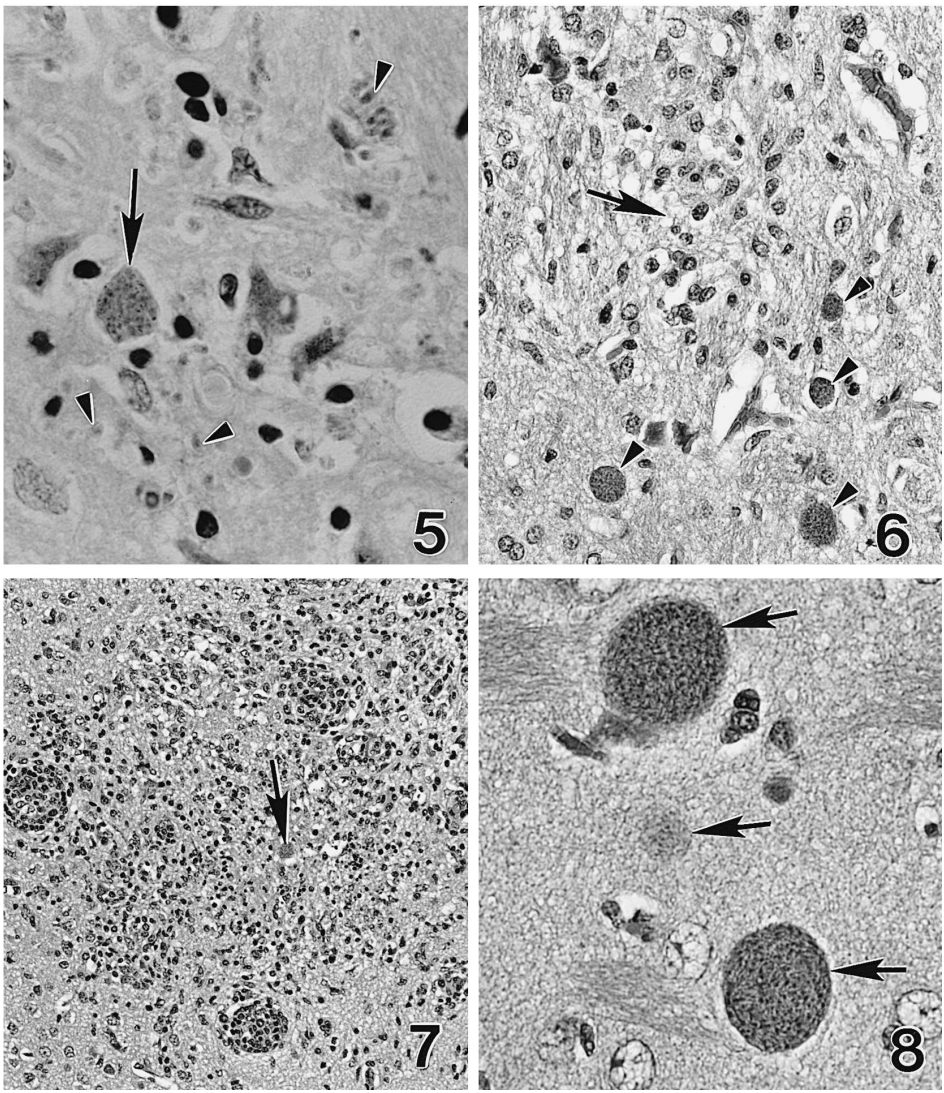
4.2.1. Innate resistance

Rats are considered to be one of the most resistant hosts to *T. gondii* with respect to clinical toxoplasmosis and this natural resistance has been known for 40 years (Lainson, 1955; Dymowska et al., 1955; Lewis and Markell, 1958; Nakayama and Hoshiai, 1960; Kramář and Vrabec, 1960; Suzuki et al., 1971; De Meuter, 1972; Omata et al., 1974;



Figs. 1-4. Lesions and *T. gondii* tachyzoites in tissues of a rat that died 7 DAI with 100,000 *T. gondii* oocysts. (1) Small intestine with short villi and flattened epithelial cells (arrow). Tachyzoites are not visible at this magnification. H and E stain. ×150. (2) Small intestine after immunohistochemical staining (IHC) with anti *T. gondii* serum. All dark black areas (arrows) represent tachyzoites. ×150. (3) Necrosis in mesenteric lymph node (arrow) H and E stain. ×150. (4) Outer cerebral cortex with numerous tachyzoites (arrow) in a necrotic focus. IHC stain. ×750.

Omata and Suzuki, 1975a,b; Fujii et al., 1983; Pettersen, 1988; Hamadto et al., 1989; Shalaby et al., 1993; Benedetto et al., 1996). Lainson (1955) reported that 21-day old rats were resistant to *T. gondii* but newborn rats were susceptible. These results were



Figs. 5-8. Lesions and *T. gondii* in cerebrum of rats fed 100,000 oocysts. (5) Cerebrum from rat that died 7 DAI. Note a necrotic focus with numerous tachyzoites (arrowheads) and a tissue cyst (arrow). H and E stain. ×750. (6) Glial proliferation (arrow) with several tissue cysts (arrowheads) towards the periphery of the lesion, 21 DAI. H and E stain. ×300. (7) Cerebrum with an inflammatory focus with perivascular cuffs in a rat 21 DAI. Note a tissue cyst in the center of the lesion (arrow). H and E stain. ×150. (8) Two well-developed and a small tissue cyst (arrows) in the brain of a rat 29 DAI. H and E stain. ×650.

confirmed by Lewis and Markell (1958), Kulasiri (1962b), Chinchilla et al. (1981), and by others. All of the hooded-rats inoculated i.p. with large numbers of RH strain tachyzoites became infected, their survival rate increased markedly by 23 days of age (Kulasiri, 1962b).

Pettersen (1988) reasoned that the innate resistance to *T. gondii* in rats was not dependent on the nonspecific complement-mediated killing by animal sera (*Toxoplasma* hostile factor, THF), although rats, guinea pigs and rabbits have comparable levels of THF, rabbits and guinea pigs often die, whereas rats survive inoculation with the RH strain tachyzoites.

Resistance to *T. gondii* can be modified by immunosuppressive reagents and diet. Rats given tachyzoites and treated with anti-inflammatory corticosteroids died of acute toxoplasmosis (Giroud et al., 1962; Benedetto et al., 1993; Brun-Pascaud et al., 1996a,b,c,d). Rats fed low protein diet (3% casein) for 2 weeks also died after RH strain inoculation (Kadziolka et al., 1970).

4.2.2. Serologic response, and passive protection

Rats can develop high titers of *T. gondii* antibodies detectable by the dye test, but the magnitude of the serologic response varies with the strain and stage of *T. gondii* inoculated (Remington et al., 1958, 1961a,b; Lunde and Jacobs, 1963; Omata et al., 1974; Suzuki et al., 1974; Pettersen, 1988). In 150 to 250 g Osborne–Mendel and Sprague–Dawley rats inoculated i.p. with $\geq 10^4$ tachyzoites of the RH strain, dye test antibodies were detected as early as 3 to 5 DAI and titers peaked between 1:4000–1:16000 as early as 9 DAI (Lunde and Jacobs, 1963; Remington and Hackman, 1965). Dye test titers were approximately 4-fold lower in rats inoculated i.p. with similar numbers of tachyzoites of other strains of *T. gondii* (Lunde and Jacobs, 1963). Most rats remained seropositive for months. However, some rats (*R. norvegicus*) inoculated with the RH strain became serologically negative (Eyles, 1954). After adult rats were inoculated s.c. with 100 tissue cysts of a mouse-avirulent isolate, dye test antibodies were not yet detected at 9 DAI, titers peaked at 1:220 on day 23, and had declined to $<$ 1:50 in 20 of 32 rats by 86 DAI; *T. gondii* was not reisolated in mice from any of the 20 rats with dye test titers of $<$ 1:50 (Henry and Beverley, 1977). The dye test antibodies in rats were in the gamma globulin fraction and gamma globulins increased during both acute and chronic infections (Remington and Hackman, 1965; Wildführ et al., 1957).

Suzuki et al. (1973) found dye test antibodies with IgM fraction on days 5 and 7, and in the IgG fraction on day 7 and hereafter. IgG was transferred to the fetus and newborn and disappeared after 35 days. Antibody appeared in the dye test after 6 days in Wistar rats, after 9 days in mice and guinea pigs and after 12 days in rabbits following the i.p. injection of 200 bradyzoites of strain 178 (Pettersen, 1988).

Indirect hemagglutination test (IHAT) titers to *T. gondii* have been shown to be erratic and inconsistent in rats, probably varying with the isolate of *T. gondii* used (Lunde and Jacobs, 1963). For example, when rats were inoculated i.p. with 10^4 RH strain tachyzoites, they became positive with the IHAT in 3 weeks but rats infected with a similar number of tachyzoites of the 113-CE isolate did not become seropositive until 10 weeks (Lunde and Jacobs, 1963). Some in the latter group never became seropositive in the IHAT.

Antibody responses to *T. gondii* measured with the complement fixation test have also shown to be dose-dependent; 3×10^6 tachyzoites elicited higher titers than 3×10^4,

whereas little or no response was elicited by inoculation of rats with as few as 3×10^2 tachyzoites (Bozděch et al., 1965).

In rats, synthesis and the dynamics of different classes of antibodies was studied by Godard et al. (1990) who fed 10-week old Fischer rats tissue cysts of the 76 K isolate and showed an early and simultaneous rise in IgA and IgM. The IgA peaked around the 40th DAI, together with an intense IgE response against the major surface tachyzoite antigen, P30 (Godard et al., 1990). Rats were utilized by Darcy et al. (1989) to study IgG, IgM, IgE and IgA responses to infection or after immunization with excreted–secreted antigens of *T. gondii* tachyzoites.

Adult rats developed *T. gondii* antibodies after ingesting even a few oocysts (Dubey, 1996). Antibodies to *T. gondii* were present at 29 DAI in sera of all infected rats by all three agglutination tests (MAT, IHAT, and the latex agglutination test, LAT). The antibody titers by IHAT and LAT were $\geq$ 1:512 in infected rats and $<$ 1:64 in uninfected rats. Antibody titers by MAT were 1:1600 or 1:3200 in infected rats and $<$ 1:25 in uninfected rats. Antibody titers in the MAT increased up to 8-fold between 29 and 75 DAI.

Congenitally infected rats appear to respond to *T. gondii* antigens differently than their dams. Of the 16 congenitally infected female rats, MAT antibodies ($\geq$ 1:500) were found in the sera of all when bled on the day of weaning (day 18–26) (Dubey et al., 1997). However, the MAT antibody titers had declined in 15 of the 16 female congenitally infected rats by 87 days of age. *T. gondii* was found in brains of all 16 congenitally infected rats when tested $\geq$ 2 months of age. At that time, sera of 5 of these 16 rats were found to be negative by the dye test (1:4 dilution) and three of these were also seronegative by MAT ($\leq$ 1:16). By LAT, 7 rats had titers of $<$ 1:64. By IHAT, only 4 rats had titers of $\geq$ 1:64. One rat was negative by all serologic tests (Dubey et al., 1997). What proportion of *T. gondii*-infected rats have no detectable antibodies in nature is not known. The isolation of *T. gondii* from a rat without detectable dye test antibodies by Eyles (1952) may have been due to congenital infection.

Lewis and Markell (1958) first reported that newborn rats born to chronically infected Wistar rats were more resistant to *T. gondii* than newborn rats from uninfected mothers, and Sakurai et al. (1983) made similar observations. Two day old Wistar rats were inoculated with 4×10^4 to 5×10^4 RH tachyzoites. Twenty-one of thirty-seven neonates from uninfected mothers died within 2 weeks whereas only 2 of 37 neonates from chronically infected dams died, indicating some form of passive immunity (Sakurai et al., 1983). These observations were further studied in athymic (nude) Fischer rats by Ridel et al. (1988). Passively transferred serum antibodies from *T. gondii*-infected rats significantly extended the survival time of nude rats infected with *T. gondii* compared with animals not injected with immune serum. It had been found by Suzuki et al. (1973) that IgG antibody was transferred to the fetal and newborn rat, and disappeared after 35 days.

4.2.3. Cellular immune response, adoptive cell transfer, and immunoprophylaxis

Rats infected with *T. gondii* develop good cellular and humoral immune responses within a short time (Wildführ et al., 1957; Remington and Hackman, 1965; Suzuki et al.,

1971; Omata et al., 1974; Omata and Suzuki, 1975b; Piotrowski, 1984; Romero-Piffiguer et al., 1987). One mechanism of killing RH strain tachyzoites in adult Sprague–Dawley rats has been studied in vitro. Macrophages from rats were more resistant to parasitization than macrophages from hamsters and guinea pigs (Chinchilla et al., 1982, 1986). Peritoneal macrophages from newborn rats ingest and kill *T. gondii* to the same extent as do macrophages from adult Sprague–Dawley rats (McCabe and Remington, 1986).

Utilizing nude Fischer rats which do not resist infection with 10^3 tachyzoites of the RH strain of *T. gondii*, whereas euthymic Fischer rats survived 10^7 tachyzoites, Santoro et al. (1987) showed that they can be protected by the adoptive transfer of T lymphocytes from immune isogeneic rats, a technique which had previously been used to protect irradiated hamsters (Frenkel, 1967). This was confirmed by Darcy et al. (1989) who again using nude Fischer rats protected them by reconstitution with 10^6 – 10^7 T nonspecific cells, or with 10^4 T-lymphocytes of rats immunized with excreted–secreted (ES) antigens. While adoptive T-cell transfer protected nude rats so that they survived, passive transfer of antisera of rats immunized with viable or irradiated tachyzoites, merely prolonged their survival time after infection. This study also identified the antigens of *T. gondii* tachyzoites and bradyzoites which were recognized by antiserum of immune rats, or rat immunized with ES antigens. Again, these studies were confirmed by Duquesne et al. (1990) who protected nude Fischer rats with adoptively transferred antigen-specific T helper cells, propagated in vitro for 1 month, employing several doses. They showed that these nude rats could now mount a specific antibody response and they characterized the antigens against which antibodies were directed.

The intracerebral immune response to *T. gondii* was studied by Schlüter et al. (1995) using euthymic and nude Lewis rats studied for 35 days. DX, a *T. gondii* isolate of low pathogenicity was used, and none of the rats had died by 3 months after infection. However, the athymic rats showed more tissue cysts of *T. gondii* in the brain. By a combination of flow cytometric and histochemical analysis of intracerebral leukocytes populations of $\alpha\beta$ TCR +, CD4 + and CD8 + T cells, macrophages, and natural killer cells were identified in euthymic rats. In nude rats, the intracerebral inflammatory exudate consisted of $\gamma\delta$ TCR + CD8 + and CD3 + T cells. These findings were interpreted as indicating a major role of $\alpha\beta$ TCR + T cells in the intracerebral immune response. In addition microglia were strongly activated in both groups of rats with simultaneous upregulation of major histocompatibility class I and II antigens and CD4. Activation of microglia was most prominent in athymic rats demonstrating that the athymic state does not preclude an upregulation of these molecules, including the human immunodeficiency virus receptor CD4 on microglial cells.

4.2.4. Persistence of chronic infection with immunity (premunition)

The persistence of the RH and other strains, beyond 1 month after inoculation in rats varies greatly in different reports (Ruchman and Fowler, 1951; Eyles and Jones, 1955; Jacobs and Melton, 1957; Remington et al., 1958, 1961a,b). The RH strain persisted in the brain longer than in any other tissue (Ruchman and Fowler, 1951). These differences

may be related in part to the strain of rats, the infecting dose, the subline of the RH strain used, and even the number of rats used. For example, Pettersen (1988) inoculated eight Wistar rats with 3×10^4 (two rats), 3×10^5 (two rats) and 3×10^6 (four rats) tachyzoites of his RH strain. After 6 months, he failed to isolate organisms from brains of the two rats inoculated with $\leq 3 \times 10^5$ tachyzoites but recovered it from one of four brains of rats inoculated with 3×10^6 tachyzoites. He isolated *T. gondii* from one of two rats inoculated with 3×10^6 tachyzoites and killed at 12 months; in the positive rat, only one of the five mice inoculated with rat brain became infected indicating that only a few *T. gondii* organisms were present in the donor rat. However, this study is based on only eight rats and a different conclusion might have been drawn if more rats had been used. Unfortunately, cats, which are more sensitive than mice for bioassay cannot be used to detect tissue cysts of the RH strain because this strain does not form oocysts in cats (Frenkel et al., 1976). Pettersen (1988) believes that the organisms persisted as tachyzoites, not bradyzoites, because the organisms were not pepsin-resistant. The type of tissue and the amount of tissue sampled may also influence the stages isolated because there may be only a few organisms in chronically infected rats and they may be present in extraneural tissues. Pettersen (1988) also observed the occurrence of sterile immunity in Wistar rats 12 weeks after the primary inoculation of 10^5 RH tachyzoites and challenge after 6 weeks with the less pathogenic strain 119. *T. gondii* could not be recovered from rat brains bioassayed in mice 6 weeks after infection with the RH strain and 6 weeks after challenge. This sterile immunity, the only one in a small laboratory animal, depended on the use of Wistar rats and a viable RH strain inoculum.

It has been debated whether the RH strain and other long passage lines of *T. gondii* encyst in rat tissues. However, this problem should be analyzed quantitatively. For example, Benedetto et al. (1996) failed to histologically identify tissue cysts in brains of Fischer rats inoculated with the RH strain. However, when rats were treated with corticosteroids or irradiation, they developed clinical toxoplasmosis and had a small number of tissue cysts, indicating that the subline of the RH strain used, still formed tissue cysts.

Lecomte et al. (1992) reported an unusual finding in Fischer rats infected with the RH strain. After a single passage in rats, the RH strain lost pathogenicity for the mouse and persisted as bradyzoites in tissue cysts during chronic infection. In more recent studies, De Champs et al. (1997) also observed some attenuation of the RH strain after passage through rats, and only low numbers of tissue cysts/bradyzoites were observed.

Wallace (1973) fed six young rats an unspecified number of oocysts of the WR-211 strain. One month later all six rats had dye test titers of 1:256. The dye test titers of the same rats 22 months later were 1:8, 1:128, 1:128, 1:512, 1:5028, and 1:2048; *T. gondii* was isolated from only three of the six rats with titers of 1:512 and not from the three rats with titers of $\leq$ 1:128.

In rats fed oocysts of a recent isolate, *T. gondii* was found in many organs 240 DAI with VEG strain (10^5 oocysts) and 443 DAI with the GT-1 strain (10^4 oocysts); the pepsin digestion and mouse bioassay were used to detect organisms (Dubey, 1997a,b).

It appears that after prolonged passage in the tachyzoite stage fewer bradyzoites/tissue cysts are produced. Some sublines of the RH strain may have lost tissue cyst forming capacity as in the *ts-4* mutant (Waldeland et al., 1983). Because passage

through rats may change the bradyzoite forming behavior of some strains of *T. gondii*, the cyst-forming capacity should be reexamined in mice after passage through rats.

4.3. Transplacental transmission in rats

4.3.1. Transmission during acute infection of maternal rat

Transplacental toxoplasmosis in rats inoculated during pregnancy was reported in the early 1950s (Schultz and Bauer, 1952; Hellbrügge and Dahme, 1953; Hellbrügge et al., 1953; Hellbrügge, 1955, 1957). Hellbrügge and associates studied *T. gondii* infection in pregnant rats after intravenous inoculation of 10^6 tachyzoites of the RH strain and found that parasitemia lasted for 18–22 days. In animals killed before the 16th day, *T. gondii* was present in the placenta, but never in the fetus. In animals sampled on the 17th and 18th day, the fetus was also infected. Placental colonization preceded fetal infection (Schultz and Bauer, 1952; Hellbrügge, 1955).

Transplacental transmission of *T. gondii* during primary infection in the rat was confirmed by others (Thiermann, 1957; Remington et al., 1961a; Omata and Suzuki, 1975b; Mayer et al., 1979). Remington et al. (1961a) inoculated 10^6 RH strain tachyzoites into four rats on the 10th day of pregnancy. Maternal parasitemia, and fetal and placental infections were found in rats killed on the 14th day (three rats) and 18th (one rat) day of gestation.

After a period of about 30 years, interest in the rat model of congenital toxoplasmosis was revived and two groups of researchers reported congenital infections in the offspring of rats fed oocysts (Dubey and Shen, 1991) or tissue cysts (Zenner et al., 1993) during pregnancy. Six pregnant Sprague–Dawley rats were inoculated orally (Group A), or subcutaneously (S.C.) (Group B) with 10^4 *T. gondii* oocysts of the CT-1 strain on the 15 day of gestation and two rats were inoculated s.c. with 10^4 bradyzoites of the same strain after 10 or 14 days of gestation (Group C). The percentage of infected pups in group A to C was 91%, 82%, and 44%, respectively (Dubey and Shen, 1991). In another experiment, four pregnant Sprague–Dawley rats were each fed 10^4 oocysts of the VEG strain. *T. gondii* was recovered from 33%, 55%, 83%, and 57% of rats (F1) when dams were inoculated at 6, 9, 12, and 15 days of gestation, respectively (Dubey et al., 1997).

Zenner et al. (1993) fed 28 rats with tissue cysts of the 76 K strain (six rats) or the Prugniaud strain (22 rats) at 8 to 12 days of gestation. Higher numbers of rats were infected congenitally with the Prugniaud strain (63 to 75%) than with the 76 K strain (35%). They also reported that after exposure to the RH strain, 58.2% of fetuses were congenitally infected. Rats infected congenitally with *T. gondii* appeared to be healthy.

4.3.2. Attempted transmission during chronic infection of maternal rat

In most animals studied, chronic *T. gondii* infection persists with immunity beyond primary infection. Hellbrügge (1955) proposed that under certain circumstances *T. gondii* can be transmitted to the fetus from chronically-infected mothers. He found that rats infected with 3×10^6 tachyzoites transmitted *T. gondii* congenitally, but not those infected with 3×10^3 tachyzoites. He believed that reactivation of *T. gondii* infection

Table 4
Congenital transmission of *T. gondii* from chronically infected rats

Reference	Strain rat[a]	No. of dams	*T. gondii* strain	Total offspring examined	No. infected
Thiermann (1957)	St/Pl, CM (cortisone 1 to 2 mg/day)	34 (infected ≥ 30 days)	?	465	2[b]
Remington et al. (1958)	SD	22	RH	140	3[c]
Remington et al. (1961a)	SD, OD, BR, HR	38	RH	278	0
	SD	15	S-6	134	0
	SD	12	Beverley	69	3[d]
Omata and Suzuki (1975b)	WI	20	RH	20	0
Dubey and Shen (1991)	SD	3	CT-1	36	0
Zenner et al. (1993)	Fisher	6	RH	66	0
		7[e]	RH	66	0
		10	Prugniaud	84	0
		9[e]	Prugniaud	90	0
Dubey et al. (1997)	SD	15	VEG	155	1

[a] SD = Sprague–Dawley, OD = Osborne–Mendel, BR = Black rat, HR = Holtzman rat, WI = Wistar–Imamichi.
[b] During the third pregnancy, 20 mothers were given cortisone during pregnancy.
[c] From 1 of 22 litters.
[d] From 3 different litters of 24 born.
[e] Chronic infection plus reinfection with tachyzoites i.p.

occurred during pregnancy, resulting in parasitemia and infection of the fetus. In experiments conducted by Remington et al. (1958, 1961a,b), parasitemia was not found in rats inoculated 2 to 11 months earlier with several *T. gondii* strains. Remington et al. (1958, 1961a) found *T. gondii* infection in 6 of 481 offspring from 87 litters of rats (see Table 4). In 1 experiment, reinoculation of 32 previously infected rats with the RH or Prugniaud *T. gondii* isolates during a second pregnancy did not lead to congenital infection (Zenner et al., 1993). Even the administration of cortisone to chronically infected rats led to repeat congenital infection in only 2 of 465 offspring (Thiermann, 1957). Except in rare instances, when unnaturally high doses were used, *T. gondii* was not transmitted from chronically infected rats to fetuses, irrespective of the route of inoculation, stage, strain or size of inoculum (Table 4).

Recently, Dubey et al. (1997) studied congenital transmission of *T. gondii* during chronic infections. A total of 15 congenitally infected female rats (F1) from four litters were mated and their offspring were examined for *T. gondii*. *T. gondii* was recovered from tissues of 1 of 155 rats (F2) born to congenitally infected dams. None of the original four dams that had given birth to congenitally infected rats produced congenitally infected offspring during the second pregnancy. Thus, evidence for repeated congenital transmission of *T. gondii* in the rat was found in $< 1\%$ of cases.

In summary, contrary to the situation in mice in which *T. gondii* is transmitted repeatedly during chronic infection (Beverley, 1959), *T. gondii* is rarely transmitted vertically in rats.

5. Rat as models of pathogenesis in toxoplasmosis in humans

With respect to clinical course and in utero transmission, toxoplasmosis in rats and humans are similar and the infection in rats can serve as a model for human toxoplasmosis. However, one should consider what stage of *T. gondii* is transmitted and by what routes, in the infection to be modeled.

When designing infections that are intended to serve as some kind of model, one should consider what magnitude of dose may be naturally involved. If that is unknown, comparison of the effects of different titrated doses is safest. However, it appears biologically irrelevant to use inocula of several million organisms; this would correspond to consuming several grams of feces of an oocyst-shedding cat or of many infected mouse brains.

Unfortunately, the RH strain of *T. gondii* is still often used for experiments, although its biological behavior was changed by continuous mouse passages of tachyzoites since 1939; at present it does not produce oocysts in cats and some lines do not produce tissue cysts. It is essential that laboratory isolates of *T. gondii* are passaged simulating natural infection, either by using tissue cysts (from rat brains) or by oocysts (from the feces of infected cats). This is performed more easily in rats in which *T. gondii* forms tissue cysts without use of chemoprophylaxis which is often necessary in mice (Dubey and Frenkel, 1973, 1976). Alternatively, an isolate should be maintained in the frozen state after freezing it slowly to -80°C and later rapid thawing (Cotty et al., 1996).

5.1. Pathogenesis of toxoplasmic encephalitis

Toxoplasmic encephalitis (TE) is the most common manifestation of toxoplasmosis in AIDS patients. Depending on the geographic region, 3 to 30% of AIDS patients develop toxoplasmic encephalitis (Luft and Remington, 1992). Schlüter et al. (1995) have described chronic toxoplasmosis in athymic rats which resembles somewhat the pathogenesis of human TE, which is the result of recrudescence, not primary infection. Six- to eight-week-old female athymic and immunocompetent Lewis rats were fed approximately 100 tissue cysts of an isolate with low pathogenicity for mice. Athymic rats developed chronic TE without marked neurologic signs. Rats were killed 35 DAI and examined histologically. A large number of tissue cysts and inflammation were seen in the brains of athymic rats, however, without large areas of necrosis as seen in immunosuppressed humans (Bertoli et al., 1995). Observation of rats till they became ill or died might have been more informative. Only a few tissue cysts were seen in immunocompetent rats accompanied by small inflammatory foci. Because unlike athymic mice which die of acute toxoplasmosis, athymic rats develop chronic toxoplasmosis, the role of different lymphocyte subsets, particularly (CD4 + , CD8 +) cells, natural killer cells and activated microglial cells in the pathogenesis of TE can now be studied in rats where the course of infection simulates that seen in human beings (Schlüter et al., 1995).

5.2. The effects of chemoprophylaxis on toxoplasmosis in rats immunosuppressed with corticosteroids

The corticoid sensitivity of rats, mice, and hamsters has been compared (Frenkel and Havenhill, 1963). This showed that from a metabolic point of view, rats tolerated the hypercorticoid state best and hamsters the least. Recently, a model of acute toxoplasmosis was described in Wistar rats immunosuppressed with cortisone acetate (or hydrocortisone), 25 mg twice weekly s.c., fed a 8% protein diet for 5 weeks, and then injected i.p. with 10^7 tachyzoites of the RH strain of *T. gondii* (Brun-Pascaud et al., 1994, 1996a,b,c,d). In 1 experiment, subgroups were treated prophylactically with dapsone and a dihydrofolate reductase/thymidilate synthase inhibitor. After 7 weeks all rats were killed and the degree of drug action was assessed by determining the parasite burden in brain, liver, lung, spleen and pleural fluid using a quantitative cell culture method. Pyrimethamine, PS-15, a biguanide, and epiroprim combined with dapsone effectively prevented toxoplasmosis and pneumocystosis (present in most rat colonies), which developed during the period of immunosuppression in the controls (Brun-Pascaud et al., 1996a).

Subsequently, Brun-Pascaud et al. (1996b,c,d) tested the efficacy of other anti-*T. gondii* drugs for their preventive and curative effects in immunosuppressed rats. Combination of three drugs, Rifabutin (200 mg/kg), Atovoquone (100 mg/kg) and cotrimoxazole (1 mg/kg TMP and 5 mg of SMX) were shown to have suppressive effects against *T. gondii* and *Pneumocystis*, both common infections in AIDS patients (Brun-Pascaud et al., 1996b). Different dose ratios of trimethoprim and sulfamethoxazole (TMP–SMX) were tested in the immunosuppressed rat model because the half life of trimethoprim in mice is short compared to that in humans, the half life in rats was of

interest and, in addition there is a need to find other anti-toxoplasmal drugs because of toxicity/sensitivity of some AIDS patients to sulfonamides. Most of the antitoxoplasmic activity of TMP–SMX was found to be due to SMX. To achieve synergistic effects against *T. gondii*, 20 mg/kg of TMP and 100 mg/kg of SMX were shown to be the optimal ratios.

5.3. Genetic models of immunodeficiency in rats

The availability of genetically immunodeficient rats provides another means of studying mechanisms of protection against *T. gondii* in that host. Although it is known that immunity to *T. gondii* is largely cell-mediated (Frenkel, 1967), the interaction of different immune cells in killing *T. gondii* has not been clarified in rats. Athymic (nude) rats usually succumb to infection with the RH strain, however they can be protected by transfer of lymph node cells from immunocompetent rats (Santoro et al., 1987). It has also shown that the transfer of induced helper T cells stimulated by excreted–secreted *T. gondii* antigen provided protection against *T. gondii* infection in nude Fischer rats (Darcy et al., 1989; Duquesne et al., 1990).

Hisaeda et al. (1993) found that immune protection in rats was associated with expression of heat shock proteins (HSP). The HSP are a group of proteins stimulated by microbial infections and other metabolic stresses, such as exposure to heat; T cells contribute to expressions of HSP. Hisaeda et al. (1993) found that one-half of a group of LEC rats, genetically deficient in CD4 + T cells, were not resistant to *T. gondii* and also had low HSP levels.

5.4. T. gondii infection and carcinogenesis

The fact that rats develop strong immunity to *T. gondii* encouraged studies on the possible inhibition of chemical carcinogenesis in Fischer rats infected with *T. gondii*. These studies were performed because *T. gondii* is considered an immunomodulator, it resided in the brain, and provided resistance to implanted tumors of the central nervous system (CNS) (Conley, 1980). Chronic *T. gondii* infection had no effect on the carcinogenicity of ethylnitrosourea in the CNS (Conley, 1980) but had some inhibitory effect on carcinogenicity of 3′-methyl-dimethylaminobenzene in the liver (Frenkel and Reddy, 1977).

6. Role of rats in the epidemiology of toxoplasmosis

T. gondii infection in rats may be of epidemiologic importance because rats can serve as sources of tissue cysts for pigs, dogs, and possibly cats. Pigs, dogs, and cats are known to eat live or dead rats (Murrell et al., 1984; Childs, 1986). It has been known for over 40 years that pigs can become infected by eating *T. gondii*-infected rat tissues (Weinman and Chandler, 1954) and the parasite was thought to be widely prevalent in pigs and rats (Weinman and Chandler, 1956). On a farm where pigs were fed garbage in Connecticut, USA, 50% of 33 pigs had dye test titers of $\geq$ 1:64, and 24% of an undefined number of rats, which ran wild among the pigs, were infected with *T. gondii*

(Weinman and Chandler, 1960). In the USA, the cooking of garbage began in 1954 as a part of the campaign to eradicate vesicular exanthema in pigs and was intensified in 1962 as an adjunct to the hog cholera eradication program. The 1983 Swine Health Protection Act of the US Congress stipulates that all biological garbage must be boiled for 30 minutes in a licensed facility before being fed to swine but these provisions do not apply to small farmers who slaughter pigs at the farm (Murrell, 1985). The management of swine herds in the US has become industrialized during the last 40 years, and perhaps as a consequence, the prevalence of *T. gondii* in swine and in rats is declining (Dubey et al., 1995a). Of 107 rats trapped on medium to large swine farms in Illinois, only 6 of 95 (6.3%) examined serologically had antibodies to *T. gondii*, which could be isolated from tissues of only 1 of 107 rats. However, in a recent study of 25 rats caught on a pig farm in Mantova, Central Italy, 19 rats (76%) had *T. gondii* tissue cysts in their brains and 14 of 20 rats (70%) were seropositive by IFAT (11 had titers of 1:40, two had titers 1:1280, and one had a titer of $>$ 1:5120) (Genchi et al., 1991). The high prevalence of *T. gondii* in rats on the farm in Italy was based on direct microscopic examination of rat brains for tissue cysts, however the identity of the parasite as *T. gondii* was not confirmed by bioassay. Judging from the data in Table 1, the prevalence of antibodies to *T. gondii* in rats is generally $<$ 5–10% (Rifaat et al., 1973; Chinchilla, 1978; Ruiz and Frenkel, 1980; Frenkel et al., 1995).

Antibody to *T. gondii* was absent in humans on Pacific Islands inhabited by rats but not by cats (Wallace et al., 1972), but when cats were also present, *T. gondii* antibody was found in humans and presumably in rats. On some Kuna islands in Panama, despite the presence of rats, and in some cases with cats, no *T. gondii* antibody was found in a small number of children (Etheredge and Frenkel, 1995; Etheredge, 1996, unpublished). It is probable that *T. gondii* is brought to such islands by migratory birds, and that only in the presence of cats shedding oocysts the infection is amplified and can become established in the animals. The consumption of rats as a delicacy by some of the human population was postulated as source of *T. gondii* infection in humans in a study from Nigeria (Olusi et al., 1994). However, data from a population without this habit and from rats were not available.

A recent study by Webster (1994a) reported a high (35%) prevalence of *T. gondii* in wild rats from farms in England. She proposed that *T. gondii* can be maintained in rats without the presence of cats and oocysts. These provocative results need reevaluation and comment. Webster (1994a) sampled 235 rats. The rats were killed, and serum was examined for *T. gondii* antibodies with the latex agglutination test (LAT) at a 1:10 dilution. Confirmation of positive samples was sought by IgG-ELISA and by direct microscopic examination of the rat brains for *T. gondii* tissue cysts. What percentage of sera and brains were so checked was not indicated. It appears that the bulk of the data are based on antibody titer determination using a 1:10 serum dilution in the LAT. Utilizing antibody prevalence, Webster (1994a) found no statistically significant differences in rats from farms where cats were present (47%) or absent (35%) and in a colony of captive rats maintained in a cat-free environment (44%). The mean antibody titers in the three groups were 1:83, 1:18, and 1:15. Cannibalism was discounted as the main route of transmission because there were no differences in prevalence rates with respect to age of the rats.

It is unfortunate that such an extensive survey was based on serology using a very low titer and a serologic method (LAT) untested in rats. There are no published data with respect to the sensitivity and specificity of the LAT for the diagnosis of toxoplasmosis in rats. Using the isolation of *T. gondii* at a serum dilution of 1:64 as the standard, the LAT had a low (45.9%) sensitivity in pigs (Dubey et al., 1995b). The manufacturer of the commercial LAT kit that Webster used, recommends using a serum dilution of at least 1:32. Therefore, the significance of low LAT titer of 1:10 for the diagnosis of toxoplasmosis in any animal is not known. As indicated earlier, rats experimentally infected with even a few oocysts developed LAT titers of $\geq$ 1:512 (Dubey, 1996). Moreover, there are *T. gondii*-related organisms that can produce cross-reactivity with *T. gondii* antigen.

Hammondia hammondi is a coccidian very similar to *T. gondii* that cycles between cats and rodents, rabbits and pigs as intermediate hosts (Frenkel and Dubey, 1975; Eydelloth, 1977). Rats inoculated with *H. hammondi* developed dye test antibodies to *T. gondii* (Frenkel and Dubey, 1975). Although cross reactivity between *T. gondii* and *H. hammondi* in rodent sera in the LAT is unknown, mice infected with *H. hammondi* developed antibodies to *T. gondii* in the IHAT (Wallace, 1975), the ELISA, and the complement fixation test (Weiland et al., 1979). There may be other antigens that may cross react with *T. gondii* in wild rats. Cross reaction may be one reason why *T. gondii* was isolated from only a small proportion of seropositive rats. As has been mentioned [Section 4.2.3.] rats can develop a sterile immunity to *T. gondii* (Pettersen, 1988). In a study from Panama, Frenkel et al. (1995) isolated *T. gondii* from the brain and heart of only 1 of 23 seropositive rats; the parasitologically confirmed rat had an antibody titer of 1:162 000 in the MAT and the other 22 seropositive rats had antibody titers of $>$ 1:60. In addition, *T. gondii* has been isolated from brains of rats with no demonstrable dye test antibodies even in undiluted serum (Eyles, 1952). Therefore, serology alone is not sufficiently specific upon which to base important epidemiologic hypotheses. The only definitive way to distinguish *T. gondii* and *H. hammondi* is to make subinoculations of the organism. *H. hammondi* has an obligatory 2-host life cycle, is transmitted by carnivorism from rodents to cats, and by fecal contamination from cats (soil) to rodents (Frenkel and Dubey, 1975). Bradyzoites or tachyzoites of *H. hammondi* are not infective to mice whereas such stages of *T. gondii* are readily transferred from mouse to mouse. Although *H. hammondi* tissue cysts are more frequent in muscle than in the brain of mice, this character alone is not enough to distinguish these two related organisms because tissue cysts in the brains of animals are similar.

The hypothesis proposed by Webster (1994a,b) that *T. gondii* can be maintained in rats in the absence of cats is also based on the assumption that *T. gondii* can be vertically propagated in chronically infected rats. However, the paper cited in support of vertical propagation refered to mice (Beverley, 1959), showing vertical propagation through successive generations in mice, and repeated transmission from the same mouse. As described earlier, there is overwhelming evidence (see Table 4) that in *R. norvegicus* with which Webster worked, *T. gondii* is rarely transmitted transplacentally from chronically infected dams to their offsprings. Recently, it was found that even congenitally and chronically infected rats, rarely produced congenitally infected offspring (Dubey et al., 1997).

Webster and her associates also proposed that *T. gondii* infected rats were more prone to predation by cats than uninfected rats. Because of the complex nature of their study and its proposed biologic and epidemiologic significance, we analyze their findings in detail. The investigators sought to study how *T. gondii* modifies the behavior of infected rats and whether this makes them more susceptible or resistant to predation by cats. Webster (1994b), Webster et al. (1994), and Berdoy et al. (1995a,b) compared behavior in Lister-hooded laboratory rats inoculated with *T. gondii* and in uninoculated controls. Webster (1994b) used two groups of infected rats. Group 1 rats (15 males, 15 females) had been fed 20 tissue cysts of the Beverley strain of *T. gondii*. Group 2 were 30 (15 males, 15 females) congenitally infected rats. Both groups of infected rats showed greater activity levels than uninfected rats. Webster et al. (1994) compared the reaction of rats to human smell associated with food, to a novel food bowl and to a novel food preparation. Rats were ranked by the number of nights required for infected rats to reach the behavior of uninfected rats. The diagnosis of infection status was made at necropsy by a $>$ 1:16 serologic reaction using the LAT, and the ELISA. Webster et al. (1994) reported that seropositive rats showing the least neophobic indices (were least afraid of changes) which they believe to favor transmission of *T. gondii*.

Berdoy et al. (1995a,b) also tested susceptibility to trapping of rats in a large enclosure and found that the rats trapped first had higher antibody prevalence than the rats trapped later. However, no difference in *T. gondii* seroprevalence was found in rats trapped first or later, on farms. Berdoy et al. (1995a,b) found that *T. gondii*-infected rats were more exploratory in approaching a human observer than uninfected rats. They concluded that *T. gondii* infection may enhance the likelihood of infected rats being preyed upon by cats. However no observations were made concerning the exploratory behavior of rats vis-a-vis cats, or whether cats even predated rats weighing between 302 and 467 g which were studied (Berdoy et al., 1995a). As discussed earlier, the evidence presented and derived hypotheses are clouded also by the serologic methods employed to identify *T. gondii*-infected rats.

We cannot be certain what animals, with the exception of pigs, become infected from rats. In a study on the predation of cats, Childs (1986) observed that cats killed rats only up to 200 g, at which weight only about 10% of rats had antibody to *T. gondii* (Childs and Seegar, 1986). Older rats, with a higher antibody prevalence (up to 70%), could be moderately efficient in transferring infection to other rats which cannibalized them.

Unfortunately, gaining an understanding of the role of rats in the epidemiology of *T. gondii* infection is more complicated than previously assumed. Demonstration even of credible antibody titers is not enough. Validation of serologic data by bioassay is essential, as detailed in Section 5. Only chronically infected rats are likely to be epidemiologically important. Infected rats make up a small proportion of the serologically positive rats.

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