Toxoplasmosis Update and Public Health Implications

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SUMMARY

Toxoplasma gondii has a coccidian life cycle in the intestine of domestic and wild felids that includes a series of asexual and sexual stages and an oocyst stage that is shed in the feces. Oocysts complete their development outside the body, eventually becoming infective for about 350 species of vertebrates including cats and man. The effects of climate on oocyst survival and the physical and biological means of oocyst dispersal are discussed. Infectivity and pathogenicity for livestock species vary. Acute disease results from rapidly multiplying tachyzoites that may be transmitted by carnivorism, transfusion, vertical transmission and other routes. Patent infections may persist for the life of a host as bradyzoites within tissue cysts. Bradyzoites initiate acute infection in other hosts after carnivorism or organ transplantation or in the same host after immunosuppression. Also discussed are: (a) prevalence of *T. gondii* in livestock as determined by digestion and serological techniques, (b) identification in humans as accomplished by isolation, serological and skin test techniques and (c) identification in cats as accomplished primarily by fecal examinations for oocysts infective for mice. Source of human infections, major outbreaks, treatment, effects on mental health and methods for preventing toxoplasmosis in man and livestock are listed.

RÉSUMÉ

Mise à jour sur la toxoplasmose et ses implications en santé publique

Toxoplasma gondii possède un cycle identique à celui des coccidies, dans l'intestin des félidés domestiques et sauvages; ce cycle implique par conséquent une série de stades asexués et sexués, ainsi que l'excrétion d'oocystes dans le fumier. Les oocystes complètent leur développement en dehors du corps et deviennent éventuellement infectieux pour environ 350 espèces de vertébrés, y compris le chat et l'homme. L'auteur commente les effets du climat sur la survie des oocystes, ainsi que les moyens physiques et biologiques de leur dispersion. L'infectivité et la pathogénicité pour les bestiaux varient d'une espèce à l'autre. La toxplasmose aiguë résulte de la multiplication rapide des tachyzoïtes dont la transmission peut se faire par l'ingestion de viande contaminée, par transfusion et de façon verticale ou autrement. Des infections patentes peuvent durer toute la vie d'un hôte, sous la forme de bradyzoïtes, à l'intérieur de kystes tissulaires. Les bradyzoïtes amorcent une infection aiguë, chez d'autres hôtes, après l'ingestion de viande contaminée ou la transplantation d'organes; chez le même hôte, ils le font ordinairement après l'immunosuppression.

L'auteur commente: a) la prédominance de *T. gondii,* au sein du cheptel, d'après les résultats des épreuves sérologiques et digestives; b) son identification, chez l'homme, à l'aide de l'isolement du protozoaire, des épreuves sérologiques et de l'épreuve cutanée; c) son identification, chez le chat, surtout par la recherche, dans les fèces, d'oocystes infectieux pour la souris.

L'auteur énumère aussi les sources de l'infection humaine, les éclosions importantes, le traitement, les effets sur la santé mentale et les méthodes aptes à prévenir la toxoplasmose, tant chez l'homme qu'au sein du cheptel.

LIFE CYCLE

Although the coccidian protozoan *Toxoplasma gondii* has been found as a parasite in most tissues of nearly all vertebrate species, basically it develops in the small intestine of domesticated and wild felids through a sequence of asexual, sexual, and occyst stages (23,31,47,59). Ocelots, margays, bobcats, mountain lions, jaguarundis, and Bengal tigers have been studied, but the most information is available from domestic cats. Cats can become infected by ingesting animals latently infected with tissue cysts that contain asexually produced organisms called cystozoites or bradyzoites, by ingesting acutely infected animals with asexual stages called trophozoites, or by ingesting oocysts from the feces of other cats. See Figure 1 for life cycle stages.

Although several years have now passed since these original observations, the exact sequence of developmental stages is still not known. The documented data are from cats infected with cysts rather than tachyzoites or oocysts. In newborn kittens orally infected with cysts in mouse brains, trophozoites were found in the lamina propria of the small intestine and in the mesenteric lymph nodes, lungs, and brain. They were seen soon after infection and remained for many days thereafter (12). Five asexual stages, described and designated as types A to E, occur in the epithelium of the small and large intestines. The types differ from one another in size,

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number of organisms, method of multiplication, time of development, and location in the intestine. Another investigator, unable to find asexual stages A-C in the intestine of weaned kittens within four days after infection, considers them to result from exceedingly heavy infections (48). He hypothesizes an obligatory extraintestinal pregametogonic stage (EIPS), based on the finding of epithelial stages in cat intestine after intraperitoneal injection of a homogenate of viscera taken from a cat 114 hours after it was fed cysts. A third study was conducted, and types A-C were found in the intestines of a weaned kitten, but the EIPS hypothesis was not confirmed (11). Apparently there is a need for clarification of the asexual stages in the cat.

The sexual stages (gametocytes) are found throughout the small intestine but most often are in the ileum three to 15 days after infection. Fertilized female gametes become surrounded by a protective wall and develop into oocysts, which enter the lumen of the gut and are shed in the feces.

The oocyst shed in the feces is not immediately infective for other hosts but must first undergo internal development (sporulate) for about 48 to 72 hours in an aerobic environment. A sporulated oocyst contains two sporocysts, each with four sporozoites, and is infective for felids and nearly 350 other species of vertebrates, including man (64). A single cat may shed as many as 20 million oocysts per day in about 20 g of feces.

The prepatent period is the length of time from the acquisition of an infection until oocysts are first shed. The prepatent period for cyst induced infection (ingestion of bradyzoites) is three to ten days, with peak oocyst production at five to 18 days; the patent period lasts seven to 21 days. When animals with very early infections are ingested (only tachyzoites are present), the prepatent period is 20 to 40 days, the same as that after ingestion of oocysts (22).

IMMUNITY IN CATS

Unless cats are kept strictly isolated and fed only canned, dry, or well cooked food, they can be expected to be regularly exposed to cysts or oocysts and thereby keep their immunity to *Toxoplasma* active. Although immunity against reinfection may be slightly less effective with heterologous strains than with homologous strains, one investigator (49) believes that under natural circumstances most cats shed oocysts only once in their lifetime. However, the number of times oocysts are shed in nature is not known (10). At any given time as little as 1% to as much as 41% of domestic cat populations have been found shedding oocysts (10). In most instances the oocysts are shed after weaning, when the cats have lost any passive immunity transferred by their mother and have started to hunt or eat raw meat. In 12 surveys involving 4226 cats throughout the world, most spontaneous shedding was found in cats less than four to six months of age. Oocysts are rarely shed by old cats. However, cats that are severely ill from other causes, especially those with enteritis, may reshed large numbers of oocysts due to reactivation of a latent infection or from a newly acquired infection. Reactivation and reshedding of *Toxoplasma* oocysts have been reported (4) to result from superimposed infections with *Isospora felis* and other coccidia, but this phenomenon is thought to be infrequent (49). It is known that cysts may rupture from physical trauma, or stress, or following treatment with corticosteroids, and that bradyzoites within the cysts may revert to tachyzoites, which initiate acute infection. But it is not known whether these stages enter the intestine and develop into stages leading to oocysts.

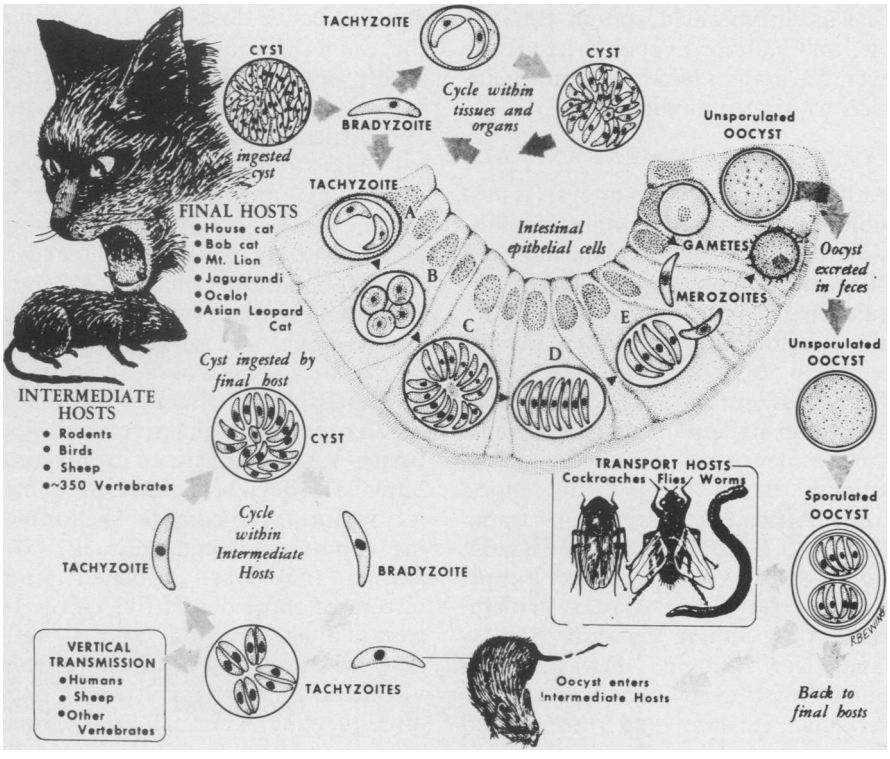

FIGURE 1. Life cycle stages of *Toxoplasma* in Felidae.

PATHOLOGY, DIAGNOSIS, AND TREATMENT OF CATS

After ingestion of cysts, newborn kittens may develop enteritis, hepatitis, myocarditis, myositis, pneumonitis, and encephalitis and become moribund by nine days. Kittens two weeks old and older may develop enteritis, myocarditis, encephalitis, and myositis but often survive. Adult cats usually remain asymptomatic. Cysts develop in the heart as early as nine to ten days after infection and develop later in the brain.

Toxoplasma infection in cats can be diagnosed by identifying oocysts in the feces or by sequential serological studies. Oocysts can be identified by microscopically examining a droplet from the surface of a suspension of cat feces mixed with high specific gravity solutions of sugar or zinc sulfate (21). *Toxoplasma* oocysts are 10x13 μm

and are distinguishable in cat feces from those of *Isopora felis, I. rivolta, Besnoitia,* and *Sarcocystis* but indistinguishable from those of *Hammondia hammondi*. Oocysts suspected of being *Toxoplasma* must be fed to mice or other test animals to confirm development into tachyzoites or cyst stages. Because many cats have latent or asymptomatic *Toxoplasma* (40-60% of the total cat population in the United States) serological identification of current infection is not recommended routinely (21). At least two sera taken a week or two apart should be compared in the same test run, and an eightfold or greater increase in titer is presumptive evidence of current toxoplasmosis (21).

Toxoplasmosis in cats can be treated by oral administration or injection of sulfadiazine at 100 mg/kg/day divided into four doses, and if possible, with pyrimethamine at 1 mg/kg/day for one to two weeks (21). Folinic acid and baker's yeast relieve the side effects of pyrimethamine. Oocyst shedding sulfadiazine alone at 60 to 120 mg/kg or both drugs at 60 mg/kg and 0.5 mg/kg, respectively, with cat food; most clinical signs should be controlled within a week, and oocyst shedding, within a few days. Either 2-sulfamoy 1-4, 4-diaminodiphenylsulfone (SDDS) at 160 to 1000 mg/kg or clindamycin at 100 or 250 mg/kg will also reduce oocyst shedding (15). However, because no medication completely inhibits oocyst shedding, cat feces should be handled carefully.

DISPERSAL AND SURVIVAL OF OOCYSTS

The site of deposit of cat feces greatly influences the subsequent dispersal of oocysts. Oocysts of *Toxoplasma* are small and therefore easily dispersed by wind, rain, and fomites. In addition, oocysts in cat feces deposited in fields, pastures, or lawns may be dispersed by machinery, shoes, or feet of animals. Those deposited in barns or animal feed storage facilities (51,52) may be distributed on the soiled bodies of rodents, birds, or other small animals or by the movement of feed. Oocysts in cat feces buried in gardens, sand boxes, or play areas may be dispersed by cultivation or digging. Those in city or suburban streets may be dispersed through storm sewers to streams, lakes, or bays. Biological dispersal may also occur when slugs, cockroaches, earthworms, flies, or isopods (sow bugs) ingest oocysts at one location and either deposit them at another location or get eaten by birds (25,66,67).

Although oocysts of *Toxoplasma* have been reported to survive as long as 13 to 18 months (25,28,69), climatic factors affect the length of survival and infectivity of all coccidial oocysts. Unsporulated oocysts are more susceptible than sporulated oocysts to damage from extremes in temperature, to decreased relative humidity, and to exposure from sunlight. Unsporulated oocysts do not become infective after a day at -21 C, whereas sporulated oocysts survive at that temperature for 28 days. Unsporulated oocysts are killed after a day at 37°C, whereas sporulated oocysts remain infectious for ten months at that temperature (25,69).

Disinfection of *Toxoplasma* in cat feces is best accomplished by heating feces with boiling water or with dry heat to over 170°F (76.7°C) for five minutes, preferably within 24 hours after feces are shed, while oocysts are still unsporulated (21). Oocysts are quite resistant to even harsh chemicals such as chromic acid, sodium hydroxide, and sodium hypochlorite. However, 5% ammonium hydroxide disinfects within ten minutes (10).

TOXOPLASMA IN MEAT ANIMALS

Although transmission by cysts is possible among carnivores, only transmission by oocysts can explain infection of herbivorous meat animals. The prevalence of *Toxoplasma* in meat animals, therefore, is a reflection of the distribution of oocysts in cat feces. Numerous surveys have been conducted on six continents to determine the prevalence of *Toxoplasma* in meat animals. Based on 38 to 50 reports from Africa, Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Czechoslovakia, Denmark, Egypt, France, Germany, Great Britain, India, Italy, Japan, Malaysia, Netherlands, New Zealand, Norway, Philippines, Russia, Singapore, Spain, Switzerland, Taiwan, and the United States, the worldwide prevalence of latent infections in cattle, sheep, and pigs have been calculated. The method of determining infection was not given in all reports, but methods given included isolation of organisms from tissues and serological tests. The serological tests included indirect fluorescent antibody (IFA), indirect hemagglutination (IHA), Sabin-Feldman dye test (SFDT), complement fixation (CF), and direct agglutination. Of 16 293 cattle, 9654 sheep, and 17 499 pigs examined, the prevalence ranged from lows of 0, 0 and 1% to highs of 99, 96 and 98%, respectively. The average rates of infection for cattle, sheep, and pigs were 25, 31 and 29%, respectively. The great range of prevalence indicates an uneven distribution of exposure to *Toxoplasma* within each host species from one sampling site to another but an overall similarity in the percentage of cattle, sheep, and pigs exposed. By extrapolation it might appear that persons who eat raw or undercooked meat run a similar risk of acquiring toxoplasmosis from beef, lamb, or pork, but this has not been demonstrated.

Although the percentage of cattle, sheep, and pigs with antibody to *Toxoplasma* may be similar, marked differences have been observed in the response of each of these hosts to infection with *Toxoplasma.* Given equal infective doses of *Toxoplasma,* the serum antibody titer becomes most highly elevated and remains elevated longest in sheep, pigs are intermediate, and cattle are lowest. Similarly, clinical illness and abortion from *Toxoplasma* are most often observed in sheep, somewhat less frequently in pigs, and rarely in cattle. Under experimental conditions, marked differences have been observed in pathogenicity, serology, and survival of *Toxoplasma* with various parasite strains in bovine tissues (17). Because the ability of *Toxoplasma* to survive in bovine tissues is a prerequisite to its infecting humans through beef or beef products, it is important to consider the following. A poorly adapted strain of *Toxoplasma* (46) was reisolated from viscera of three out of five calves 14 weeks after infection, and a well-adapted strain (5) was reisolated from viscera of five calves 69 to 107 days after infection. Although *Toxoplasma* has been isolated from various organs of sheep, pigs, and cattle, it is approp-

riate to note that parasites have been recovered from lamb, and pork but not beef (14,33). Perhaps it is these differences in host response and recovery of parasites that foster the generally held view that cattle are innately resistant to *Toxoplasma* infection. Indeed, one investigator (46) concluded that this resistance permits cattle to graze heavily contaminated pastures that are unsafe for sheep and that rare steak should be a safer dish than undercooked lamb chop. This latter conclusion is contradictory to reports of humans who supposedly acquired *Toxoplasma* by eating raw beef (2,27).

TRANSMISSION BY TACHYZOITES

During acute toxoplasmosis tachyzoites are distributed throughout the body. They are found in tears, nasal secretions, saliva, milk, vaginal secretions, semen, urine, and feces. They remain infectious for days and can penetrate mucous membranes (58).

Toxoplasma tachyzoites have been isolated from milk of cows, goats, sheep, pigs, dogs, cats, rabbits, guinea pigs, and mice with natural or experimental infections (34). Unpasteurized goat milk supposedly containing tachyzoites has been reported as a source of human infection (55). Tachyzoites have also been transmitted to a human via an arthropod vector, the tick (40).

Toxoplasma has been demonstrated by mouse inoculation in semen of three goats as early as seven days after oral inoculation with oocysts and continuing for as long as 52 days (13). Although tachyzoites have been isolated from semen of experimentally infected rams, and disseminated infections in ewes have resulted from vaginal inoculation, actual sexual transmission has not yet been documented in sheep (60). Nor does epidemiological evidence suggest that sexual transmission plays a role in human toxoplasmosis, although organisms have been isolated from human semen. The transmission potential of tachyzoites is probably very low compared with that of oocysts and cysts.

PREVALENCE IN HUMANS

It has been estimated that one half billion people throughout the world have antibody to *Toxoplasma*. It is also apparent from Table I that the prevalence of infection varies greatly among and within the countries and cities surveyed. Because the prevalence of antibody in humans increases with age, some variation seen in Table I may be biased by the age of the people sampled. Local fauna, environmental conditions, cultural habits, and social and economic patterns also influence the prevalence of human infection. No consistently significant difference has been found in the prevalence of antibody in males versus females.

As with herbivorous animals, only transmission by oocysts can explain the relatively high prevalence of *Toxoplasma* antibody in strict vegetarians, as was found in the United States and India (33,53). In this regard, although actual transmission has not been confirmed, it has been suggested that the high prevalence of *Toxoplasma* antibody in Costa Ricans may be partially explained by the finding of infected cat feces in false attics (ceilings) of houses; material from the attic may enter the living area below, where it could be inhaled or ingested (57).

A 13 year study of over 11 000 sera from ten Canadian cities revealed a six year cycle of high disease prevalence, and because oocyst survival is favored by moisture, positive reactors decreased each fall after dry summer conditions (65).

A person's immediate environment is often determined by his job, duties, or profession, and that, in turn, may place him or seem to place him at a greater risk of acquiring *Toxoplasma*. Of the many groups studied for potential risk by serological or skin test surveys, three interesting groups are agricultural workers, abattoir workers, and veterinarians. Agricultural workers in California who are in close contact with the soil were found to be at greater risk than county employees or cattle feedlot employees (19). Abattoir workers, butchers, and meat inspectors in either Brazil or Japan were found to be at risk, but abattoir workers in Egypt and Ghana were not (7,54). Neither veterinarians nor veterinary students in general from California, Illinois, Iowa, Minnesota, or New York were found to be at risk (18,70). However, within some of these studies a subgroup of students who had spent more than 70% of their life on a farm was found to be at greater risk than the others. Therefore, general exposure to animals or animal products does not appear to present as great a risk as does exposure to soil or the handling of fresh animal tissues without gloves, as in some abattoirs as opposed to postmortem facilities.

Cultural habits involving food greatly influence the transmissioin of parasites. Jewish women in New York City who purchased live fish at market to prepare minced, boiled fish patties known as gefilte fish became infected with larvae of the fish tapeworm *Diphyllobothrium latum* by sampling the fish until it was cooked just right (9); likewise, a significantly greater percentage of *Toxoplasma* positive reactors was found among Russian women in Kiev who tasted raw, minced meat while cooking than among those who did not taste the meat (45). In Hawaii, where Hawaiians and Filipinos are known to enjoy raw meat (especially pork) and to have a high prevalence of infection, Caucasians and Japanese tend to cook meat and have a lower prevalence (67). Of 1125 hospitalized children in France, 204 acquired infection during hospitalization (8). The infection rate of 4.8% per month increased to 9.0% per month when the customary ration of raw or very undercooked meat was increased. This finding was in agreement with the observation that the prevalence of *Toxoplasma* infection in France is greater than that in other countries of similar climate and culture because of eating habits regarding cooking of meat. An unexpected finding related to culture and socioeconomics was found in New York City, where a greater percentage of affluent whites than poor blacks had antibody to *Toxoplasma*. It was suggested that this difference reflected a greater preference for raw ground meat (steak tartare) among the affluent whites (34).

EPIDEMICS OF TOXOPLASMOSIS

Only a few *Toxoplasma* outbreaks have been recorded in which groups of persons became infected. Such outbreaks are due to much the same causes as individual infections: the ingestion of undercooked meat and the contamination of the environment with oocysts or tachyzoites. Acute

TABLE 1
WORLD WIDE HUMAN INFECTION WITH *TOXOPLASMA*

	No. Examined	% Positive	Serological Test[a]
AFRICA			
Egypt	395	27-37	IFA
Ethiopia	99	48	SFDT
Ghana	255	50	SFDT
Ivory Coast	25	51	SFDT
Kenya	901	45	SFDT
Liberia	159	50	SFDT
Malawi	32	75	SFDT
Niger	62	65	SFDT
Senegal	600	45	IFA
Tanzania	57	40	SFDT
Transvaal	806	37	IFA
Uganda	94	12	SFDT
AMERICA (NORTH)			
Canada			
B.C.	596	28	SFDT
Que.	1 516	27	IFA
Ont.	650	26	SFDT
Mexico	?	29	?
U.S.A.			
Alaska	1 572	28	IFA
Alaska, (Pt. Barrow)	21	0	SFDT
California	66	44	IHA
Iowa	250	26	IFA
Louisiana, (New Orlean)	270	31	SFDT
Minnesota-Illinois-Iowa	775	18	Skin
Missouri, (St. Louis)	184	26	SFDT
Military	2 680	14	SFDT
Military Caucasians	2 162	14	IHA
Blacks	209	21	IHA
N.Y.	4 048	32	SFDT
Oregon	95 929	8	IHA
Oregon, (Portland)	293	17	SFDT
Pennsylvania	144	35	SFDT
Washington, (Seattle)	369	19	IFA
AMERICA (SOUTH)			
Argentina	123	0-52	Skin
Brazil	1 410	61	IFA
Brazil,			
(Para)	?	83	?
(Sao Paulo)	?	67	?
Colombia	?	30	SFDT
Costa Rica	156	89	SFDT
Cuba	?	29	?
French Guiana	345	63	IFA
Guatemala	?	50-100	?
Paraguay	123	33	SFDT
ASIA			
Borneo	1 050	10-51	SFDT
Caroline Islands	281	77	SFDT
India	57	23	SFDT
Israel	7 506	35	SFDT
Japan	?	25	?
Kashmir	68	22	SFDT
Pakistan E.	22	23	SFDT
Pakistan W.	38	11	SFDT
Papua-New Guinea	315	7-63	SFDT
Russia	252	34	?
AUSTRALIA			
NSW, Sydney	396	34	IHA
NSW, Camberra	100	28	IFA
SA, Bedford Park	523	33	IFA
Tasmania	9 037	6	IFA
EUROPE			
England	3 169	22	SFDT
Germany, (Berlin)	850	73	SFDT
Greece	480	44	SFDT
Hungary	10 496	53	Skin
Norway, Military	1 577	22-39	SFDT
Oslo	11 677	13	SFDT
Scotland	10 736	15	?

[a]SFDT: Sabin-Feldman dye test; IFA: indirect fluorescent antibody; IHA: indirect hemagglutination.

toxoplasmosis was diagnosed in 30 of 81 persons at a seminary in Brazil, but the cause of infection could not be determined (41). Five medical students who had all eaten undercooked hamburgers at a Cornell University dormitory snack bar on the same night developed acute toxoplasmosis eight to 13 days later (35). It is important to note that the type or types of meat present in the hamburger were never conclusively determined. Similarly, acute toxoplasmosis was found at a university in Brazil, where 110 persons were affected over a ten week period after they ate undercooked meat (42). Again, the specific meat(s) were not conclusively determined. Four of 19 people who ate a Syrian dish called "kibee nayee" made of raw beef had clinical toxoplasmosis beginning ten to 38 days later (2). Acute toxoplasmosis was diagnosed in six of seven family members seven to 11 days after they ate undercooked lamb (44). Acute toxoplasmosis was diagnosed in a Canadian farmer, and serological evidence of latent infection was found in ten family members and three cats that were all accustomed to eating cornflakes from the same table (56). Acute toxoplasmosis was diagnosed in 37 persons at a riding stable in Atlanta, Georgia (63). No common meals were consumed, and dietary history eliminated meat as a source of infection. Cats and mice at or near the stable were found positive for *Toxoplasma.* Because the highest rate of infection was found in patrons who spent most of their time at the end of the stable where a cat defecated and in those who visited the stable daily rather than less frequently, the oocyst stage was considered to be the source of infection. Oocysts may have been inhaled and swallowed after they were stirred up in the dust by horses or after direct or indirect contamination of food or beverages. Acute toxoplasmosis was diagnosed in 30 United States Army troops five to 18 days after they completed jungle training in Panama (3). The dietary history eliminated meat as a source of infection. All affected troops shared a common water source — a pool adjacent to a small jungle creek. Several months later water was collected from this pool and examined microscopically. It contained a variety of helminth eggs and eimerian and

isosporan oocysts, including some resembling those of *Toxoplasma*. Pica (geophagia) is considered the primary source of an outbreak of toxoplasmosis involving ten of 30 members of an extended family in Alabama (61). The outbreak was confined largely to preschool aged children who remained at the home of one family member five days a week and played in a part of the yard described as "a natural sandbox." The family cat had been allowed to defecate at random in the yard and had an elevated IHA titer to *Toxoplasma*. Although several cases of laboratory related infections with *Toxoplasma* are known, only one laboratory epidemic of toxoplasmosis has been documented. Seven of 14 employees in the department of genetics in a regional hygiene station in Czechoslovakia developed acute toxoplasmosis within a period of four months (43). All infected persons were women who worked with cell cultures or washed tissue culture glassware. It was hypothesized that *Toxoplasma* originating from infected fetuses or maternal tissues had contaminated and proliferated in various cell cultures and then served as a source of infection for those handling the cultures. Whether such infections resulted from aerosols produced during centrifugation, from mouth pipetting, or from other means was not discussed.

CLINICAL SIGNS, DIAGNOSIS AND TREATMENT

In animals and man *Toxoplasma* has been found in nearly all organs. During acute infection, lesions resulting from intracellular multiplication have produced dermatomyositis, encephalitis, enteritis, hepatitis, lymphadenitis, myocarditis, placentitis, pneumonitis, retinochoroiditis, skeletal myositis, tenosynovitis, tonsilitis, vasculitis, anemia, and fever. Diagnosis is based on epidemiological history, tissue sections, smears, paired serological tests with rising titers, and isolation of organisms. *Toxoplasma* would be implicated based on contact with cats, eating of undercooked meat, known chronic infection, blood transfusion from an infected person, or maternal infection during pregnancy. Tissue sections and smears should contain *Toxoplasma*. Antibody titer should reflect disease states. Serological tests include the SFDT, IFA, IHA, CF and direct agglutination test, of which the first two are most useful. However, factors are present in chicken and bovine sera that interfere with the SFDT, rendering it unreliable for these species. The best method of isolating the organisms is to concentrate them via pepsin-HCl digestion of cysts in host tissue (32) and then inoculate the suspect material intraperitoneally into mice known to be free of *Toxoplasma* antibody. Tachyzoites may be found in mouse peritoneal exudate four to six days or more after inoculation. Antibody may be present in the mice two to three weeks after inoculation. Cysts may be present in the brain a month or more after inoculation as confirmation of transmission.

Either sulfadiazine, sulfamerazine, sulfamethazine, or triple sulfa in divided doses at 2 g per day plus pyrimethamine in a single dose at 25 mg per day is usually the medication of choice (22). Folic acid is given to counter the side effects of pyrimethamine on bone marrow. Because of the potential teratogenicity of this combination for pregnant women clindamycin is recommended at 600 to 900 mg per day.

INFECTION

Natural or experimental transplacental transmission of *Toxoplasma* has been documented in man, sheep, pigs, dogs, rats, mice, guinea pigs, hamsters, and cats (34). It is most severe in sheep and man.

In Europe, congenital toxoplasmosis ranges in frequency from 1 to 6% of the newborn population and is probably the most serious form of *Toxoplasma* infection (62). The fetus is thought to become infected via the placenta as a consequence of parasitemia in the mother, with a primary infection of the lymph node type (62). Although congenital infection is rare in more than one child of the same mother, it has been hypothesized that cysts in the uterus wall could burst during pregnancy, causing relapse and thus active infection in subsequent pregnancies. Some investigators claim that organisms are rarely isolated (26). One investigator (38) who claimed to have isolated *Toxoplasma* from 23 of 70 women with repeated miscarriages, premature or stillbirths, or from their fetuses, later indicated that he had actually found pollen grains that were indistinguishable from *Toxoplasma* cysts. Although association between chronic toxoplasmosis and abortion is statistically significant, a cause and effect relationship has not been demonstrated. Therefore chemotherapy was withheld from 21 habitual aborters with *Toxoplasma* antibody, of these, 17 were reported to have had healthy births (36). Infection acquired during pregnancy is transmitted to the fetus approximately 40% of the time; of those infected, approximately 40% have clinical illness; of those with clinical illness, approximately 40% are severe or lethal. The earlier in pregnancy that infection is acquired, the greater the extent of lesions in the fetus. In actual numbers of infected children, the following Dutch study (37) is similar to others in Europe: of 1821 births, only 12 children acquired *Toxoplasma,* and only one of these had clinical signs of infection or squinting, at least ten and probably all 12 infections were primary. Based on these findings, these authors do not recommend routine examination for all pregnant women in the Netherlands to detect infection that may be dangerous to the child. In contrast, studies in the United States have shown that about 3000 babies are born with the disease each year; of these, 5 to 15% die, 8 to 10% have brain and ocular lesions, 10 to 13% have visual damage, and the 58 to 72% who are normal at birth later develop active infections (19). The annual cost of this neonatal toxoplasmosis in the United States is estimated at US $31 to US $40 million for hospitalization, institutionalization, and special education (20). Therefore, maximal, minimal, and compromise prevention plans have been recommended (26). Maximally, serological tests would be made on all prospective obstetric patients in advance of pregnancy. Those with negative tests would be advised to avoid cats, soil, raw meat, and other sources of infection and to be retested early in pregnancy, at any time during pregnancy if there was an illness suggestive of toxoplasmosis, and at parturition. Minimally, all obstetric patients would be advised to avoid the sources of *Toxoplasma,* and serological tests would not be given.

TOXOPLASMOSIS AND IMMUNOSUPPRESSION

Patients with malignant neoplasms often die with infections that healthy people can control. *Toxoplasma,* therefore, is especially important among such patients because latent infections are so common and primary infections are continually acquired. Experimental evidence from animal studies indicates that *Toxoplasma* infection is held in check by cellular immunity; such immunity disappears and clinical illness results when corticosteroids are administered. Thus, immunosuppression is suggested as the mechanism responsible for toxoplasmic lesions produced in cancer patients. Concurrent toxoplasmosis and immunosuppression has been reviewed (24).

How much of the immunosuppression results from the underlying lymphoreticular neoplasm and how much is due to treatment? A few untreated patients with lymphoma or leukemia acquired primary *Toxoplasma* infections via blood transfusion and developed generalized infections, not preponderantly involving the central nervous system. Other untreated patients have had widespread involvement of the lymphoreticular tissue for several years without evidence of toxoplasmosis. Corticosteroids alone, and some cytostatic drugs, can suppress immunity to *Toxoplasma* in humans; this has been shown with leukemia and lymphoma patients in remission and in corticosteroid treated patients without tumors, who develop toxoplasmic lesions of the central nervous system (CNS).

The foregoing observations lead to the conclusions that occasionally neoplasms alone may permit the persistence of primary generalized toxoplasmosis, resulting in death, and that cytostatic agents or corticosteroids lead to recrudescence of latent infections, resulting in CNS lesions that lead to death. It is not known with certainty why the lesions of recrudescent toxoplasmosis in humans are limited to the brain.

It is important that immunosuppressive drugs used for controlling neoplasms and other diseases such as lupus erythematosus and those used for transplant patients do not affect immunity to *Toxoplasma* infection in those patients at risk. Experimental and clinical evidence suggests that corticoids, cyclophosphamide, and extensive radiation interfere with immunity to *Toxoplasma,* whereas nitrogen mustard (mechlorethamine) and urethane do not.

As in pregnancy, nothing can be done to eliminate latent infections, but immunosuppressed patients should avoid primary *Toxoplasma* infection. Early diagnosis of *Toxoplasma* could avoid fatalities because chemotherapy is effective even in immunosuppressed hosts. Diagnosis is based on serology, patient history, and isolation of organisms, but treatment should not wait for results of animal inoculation. Treatment is by sulfadiazine and pyrimethamine, with folinic acid and baker's yeast as antagonists to prevent thrombocytopenia and leukopenia.

INFLUENCE ON MENTAL HEALTH

Although much attention has been given to the physical pathology resulting from toxoplasmosis, much less attention has been given to mental health implications, probably because they are so difficult to document. *Toxoplasma gondii* gives rise to a variety of acute neurological disorders as well as latent asymptomatic infections in the CNS. Although documentation is still scant, latent brain infections probably influence the behavior and mental ability of many undiagnosed persons. Personality changes, including speech disorders, slowness, apathy, and mental retardation, from *Toxoplasma* infection have been observed in children (50). In Germany, 30% more institutionalized brain damaged children and adolescents than normal individuals were serologically positive for *Toxoplasma* (16). Similarly, in Norway, within a group of 510 functionally handicapped children and adolescents, the frequency of serologically positive individuals varied from 71% among slow learners to 44% among those with behavioral disorders, a significantly greater proportion of reactors than that within the general population (39). In Cuba, that was a significantly greater number of skin test positive reactors among 300 hospitalized mentally handicapped patients than among the general population (6). Many cases have been recorded to date which indicate that toxoplasmosis, especially congenital toxoplasmosis, impairs the mental development of children; whether postnatal toxoplasmosis leading to a latent infection of the CNS affects behavior and learning is not known (68). Only a few observations of infection in man substantiate the assumption that latent *Toxoplasma* affects the CNS. Average intelligence quotients (I.Q.) were lower among latently infected children than among uninfected children of the same social group; congenitally infected children treated with pyrimethamine-sulfadiazine and later tested had normal I.Q. levels (1).

A limited number of animal tests tend to confirm what is suspected in latent human infections. In maze tests rats and mice with a latent avirulent *Toxoplasma* strain had reduced learning ability proportional to the number of brain cysts; they also exhibited poor memory (68). Specific behavioral abnormalities have also been observed in experimentally infected mice (29). One group of investigators, noting differences in responsiveness between infected and uninfected mice, suggests that if infection with *Toxoplasma* does indeed impair response to stimuli, then infected mice are more likely to be taken by predators and thus pass on their *Toxoplasma* (30).

PREVENTION AND CONTROL

The following preventive measures apply to all persons, but because toxoplasmosis is most severe in the perinatal period, they should be emphasized for pregnant women and young children.

1. Avoid contamination with oocysts from cat feces by:
   a. Feeding cats dry, canned, or thoroughly cooked food.
   b. Preventing cats from hunting birds and rodents.
   c. Emptying litter boxes daily, before oocysts sporulate.
   d. Wearing gloves or thoroughly washing hands after working in the garden or with soil and before eating or touching the face.
   e. Covering children's sandboxes when not in use.
   f. Preventing aerosols in the laboratory during centrifuga-

tion of potentially infected biological samples.

g. Boiling drinking water from streams, ponds, or lakes frequented by cats.

2. Avoid ingestion of tissue cysts by cooking meat to over 66C and washing hands after handling raw meat.

The following preventive measures apply to farms and other animal rearing facilities. Avoid contamination of feed or water with oocysts in cat feces by:

a. Using rodenticides and traps to prevent cats from hunting rodents.

b. Covering, closing, or locking feed storage facilities to prevent cats from entering and defecating.

c. Promptly removing cat feces from buildings, stalls, or cages, and flushing, burning, or burying them to destroy oocysts.

d. Providing adequate dry, canned, or thoroughly cooked food and separate water to prevent cats from sharing facilities used by other animals.

REFERENCES

1. ALFORD, C.A., S. STAGNO and D.W. REYNOLDS. Toxoplasmosis: silent congenital infection. Bull. N.Y. Acad. Med. 50. 1974.
2. ANONYMOUS. Toxoplasmosis-Pennsylvania. Morbid. Mortal. Wkly. Rpt. 24: 285-286. 1975. In Abstr. Hyg. 52: 1521. 1977.
3. BENENSON, M.W., E.T. TAKAFUJI and S.M. LEMON. A toxoplasmosis outbreak occurring in U.S. soldiers undergoing jungle training in the Canal Zone. Personal communication. 1979.
4. CHESSUM, B.S. Reactivation of toxoplasma oocyst production in cat by infection with *Isospora felis*. Br. vet. J. 128: 35-38. 1972.
5. COSTA, A.J., F.G. ARAUJO, J.O. COSTA, J.D. LIMA and E. NASCIMENTO. Experimental infection of bovines with oocysts of *Toxoplasma gondii*. J. Parasit. 63: 212-218. 1977.
6. DELGADO, G.G. Results of the intradermal test using toxoplasmin during a survey done among mentally handicapped patients admitted to the October 10th Clinical Surgical Teaching Hospital in Havana, Cuba. Revta. cubana Med. trop. 31: 67-72. 1979.
7. DE ROEVER-BONNET, H. Toxoplasmosis in tropical Africa. Trop. geogr. Med. 24: 7-13. 1972.
8. DESMONTS, G., J. COUVREUR, F. ALISON, J. BAUDELOT, J. GERBEAUX et M. LELONG. Étude epidémiologique sur la toxoplasmose: de l'influence de la cuisson des viandes de boucherie sur la fréquence de l'infection humaine. Revue fr. Étud. clin. biol. 10: 952-958. 1965.
9. DESOWITZ, R.S. On New Guinea tapeworms and Jewish grandmothers. Natural History 8: 22,24,26. 1978.
10. DUBEY, J.P. *Toxoplasma, Hammondia, Besnoitia, Sarcocystis* and other tissue cyst-forming coccidia of man and animals. *In* Parasitic Protozoa. Volume 3. J.P. Kreier, Ed. pp. 101-237. New York: Academic Press. 1977.
11. DUBEY, J.P. Direct development of enteroepithelial stages of *Toxoplasma* in the intestines of cats fed cysts. Am. J. vet. Res. 40: 1634-1637. 1979.
12. DUBEY, J.P. and J.K. FRENKEL. Cyst-induced toxoplasmosis in cats. J. Protozool. 19: 155-177. 1972.
13. DUBEY, J.P. and S.P. SHARMA. Prolonged excretion of *Toxoplasma gondii* in semen of goats. Am. J. vet. Res. 41: 794-795. 1980.
14. DUBEY, J.P. and R.H. STREITEL. Prevalence of *Toxoplasma* infection in cattle slaughtered at an Ohio abattoir. J. Am. vet. med. Ass. 169: 1197-1199. 1976.
15. DUBEY, J.P. and R.A. YEARY. Anticoccidial activity of 2-sulfamoyl-4,4-diaminodiphenylsulfone, sulfadiazine, pyrimethamine and clindamycin in cats infected with *Toxoplasma gondii*. Can. vet. J. 18: 51-57. 1977.
16. ELIAS, M.I. and T. PORSCHE. Beitrage zum Problem der Toxoplasmose: Serologische Untersuchungen an Normalen und Hirngeschadigten, Sowie an Hunden. Z. ges. inn. Med. 15: 93-94. 1960.
17. FAYER, R. and J.K. FRENKEL. Comparative infectivity for calves of oocysts of feline coccidia: *Besnoitia, Hammondia, Cystoisospora, Sarcocystis,* and *Toxoplasma*. J. Parasit. 65: 756-762. 1979.
18. FOX, J.G. and L.H. CAMPBELL. Serological survey of toxoplasmosis in selected populations of veterinarians in California. Calif. Vet. 28: 32-35. 1974.
19. FRENCH, J.G., H.B. MESSENGER and J. McCARTHY. A study of *Toxoplasma gondii* in farm and nonfarm groups in the same geographic location. Am. J. Epidem. 91: 185-191. 1970.
20. FRENKEL, J.K. *Toxoplasma* in and around us. BioScience 23: 343-352. 1973.
21. FRENKEL, J.K. Toxoplasmosis in cats and man. Feline Practice 5 (1): 28-41. 1975.
22. FRENKEL, J.K. Toxoplasmosis. *In* Pathology of Tropical and Extraordinary Diseases, Volume 1. C.H. Binford and D.H. Connor, Eds. pp. 284-300. Washington, D.C.: Armed Forces Institute of Pathology. 1976.
23. FRENKEL, J.K., J.P. DUBEY and N.L. MILLER. *Toxoplasma gondii:* fecal stages identified as coccidian oocysts. Science 167: 893-896. 1970.
24. FRENKEL, J.K., B.M. NELSON and J. ARIAS-STELLA. Immunosuppression and toxoplasmic encephalitis. Human Path. 6: 97-111. 1975.
25. FRENKEL, J.K., A. RUIZ and M. CHINCHILLA. Soil survival of *Toxoplasma* oocysts in Kansas and Costa Rica. Am. J. trop. Med. Hyg. 24: 439-443. 1975.
26. FUCHS, F., A.C. KIMBALL, B.H. KEAN. The management of toxoplasmosis in pregnancy. Clin. Perinatol. 1: 407-422. 1974.
27. HOLLINS, P.J., B.I. HOFFBRAND and I.M. HAFFAJEE. *Toxoplasma* encephalitis in a raw steak eater. Post-grad. med. J. 48: 384-385. 1972.
28. HUTCHISON, W.M. The nematode transmissions of *Toxoplasma gondii*. Trans. R. Soc. trop. Med. Hyg. 61: 80-89. 1967.
29. HUTCHISON, W.M., P.P. AITKEN and B.W.P. WELLS. Chronic *Toxoplasma* infections and familiarity — novelty discrimination in the mouse. Ann. trop. Med. Parasit. 74: 145-150.
30. HUTCHISON, W.M., M. BRADLEY, W.M. CHEYNE, B.W.P. WELLS and J. HAY. 1980. Behavioral abnormalities in *Toxoplasma*-infected mice. Ann. trop. Med. Parasit. 74: 337-345. 1980.
31. HUTCHISON, W.M., J.F. DUNACHIE, J.C. SIIM and K. WORK. Coccidian like nature of *Toxoplasma gondii*. Br. med. J. 1: 142-144. 1970.
32. JACOBS, L., J.S. REMINGTON and M.L. MELTON. The resistance of the encysted form of *Toxoplasma gondii*. J. Parasit. 46: 11-21. 1960.
33. JACOBS, L., J.S. REMINGTON and M.L. MELTON. A survey of meat samples from swine, cattle, and sheep for the presence of encysted *Toxoplasma*. J. Parasit. 46: 23-28. 1960.
34. JONES, S.R. Toxoplasmosis: A review. J. Am. vet. med. Ass. 163: 1038-1042. 1973.
35. KEAN, B.H., A.C. KIMBALL and W.N. CHRISTENSON. An epidemic of acute toxoplasmosis. J. Am. med. Ass. 108: 1002-1004. 1969.
36. KIMBALL, A.C., B.H. KEAN and F. FUCHS. Congenital toxoplasmosis: a prospective study of 4048 obstetric patients. Am. J. Obstet. Gynec. 11: 211-218. 1971.
37. KOPPE, J.G., G.J. KLOOSTERMAN, H. deROEVER-BONNET, J.A. ECKERT-STROINK, D.H. LOEWER-SIEGER and J.I. de BRUIJNE. Toxoplasmosis and pregnancy, with a long-term follow-up of the children. Eur. J. Obstet. Gynecol. Reprod. Biol. 4/3: 101-110. 1974.
38. LANGER, H. Repeated congenital infection with *Toxoplasma gondii*. Obstet. Gynecol. 21: 318-329. 1963.
39. LANGSET, M., E. AANDAHL, T. OMLAND and T. MIDTVEDT. The frequency of positive *Toxoplasma* dye test in children and adolescents with physical and mental handicaps. NIPH (Nat'l Inst. Public Health) Ann. (Oslo) 1: 13-19. 1978.
40. LECCHINI, P., G. DIOLOSA and F. CORDELLI. Toxoplasmosi trasmessa de zecca. Min. Ped. 31: 576-577. 1979.
41. MAGALDI, C., H. ELKIS, D. PATTOLI, J.C. de QUEIROZ, A. COSCINA and J.M. FERREIRA. Surto de toxoplasmose em um seminario de Braganca Paulista (Estado de Sao Paulo). Aspectos clinicos, sorologicose epidemio-

logicos. Rev. Saude Publ., S. Paulo 1: 141-171. 1968.
42. MAGALDI, C., H. ELKIS, D. PATTOLI and A.L. COSCINA. Epidemic of toxoplasmosis at a university in Sao-Jose-dos-Campos, S.P. Brazil. Revta lat.-am. Microbiol. Parasit. 11: 5-13. 1969.
43. MARKVART, K., M. REHNOVA and A. OSTROVSKA. Laboratory epidemic of toxoplasmosis. J. Hyg. Epidem. Microbiol. Immun. 22: 477-484. 1978.
44. MASUR, H., T.C. JONES, J.A. LEMPERT and T.D. CHERUBINI. Outbreak of toxoplasmosis in a family and documentation of acquired retinochoroiditis. Curr Ophthal. 24: 133-134. 1979.
45. MELNIK, M.N., N.A. IOVA, L.N. PUKHTEEVA, I.D. NETREBKO. Raw meat as a factor in the transmission of toxoplasmosis. Problemy Parazit. Materialy VIII Nauch. Konfer. Parazit. UKSSR. Chast. Kiev, USSR "Naukova Dumka." 22-24. (Russian) 1975.
46. MUNDAY, B.L. Bovine toxoplasmosis: experimental infections. Int. J. Parasit. 8: 285-288. 1978.
47. OVERDULVE, J.P. The identity of Toxoplasma Nicolle and Manceaux, 1909 with *Isopora* Schneider, 1881 (I). Akad. (Amsterdam) Proc., Series C 73: 129-151. 1970.
48. OVERDULVE, J.P. Studies on the life cycle of *Toxoplasma gondii* in germ free, gnotobiotic and conventional cats. I and II. Proc. K. ned. Akad. C 81: 19-59. 1978.
49. OVERDULVE, J.P. Excretion of *Toxoplasma gondii* by nonimmunized and immunized cats; its role in the epidemiology of toxoplasmosis. Proc. K. ned. Akad. C 81: 1-18. 1979.
50. PAUL, J. Untersuchungen mit dem Serofarbtest auf Toxoplasmose bei Kindern I-III. Teil. Monatsscht. Kinderheilkd. 10: 228-235, 281-288, 403-410. 1956.
51. PENKERT, R.A. Possible spread of toxoplasmosis by feed contaminated by cats. J. Am. vet. med. Ass. 162: 924. 1973.
52. PLANT, J.W., N. RICHARDSON and G.C. MOYLE. *Toxoplasma* infection and abortion in sheep associated with cat feces. Aust. vet. J. 50: 19-21. 1974.
53. RAWAL, B.D. Toxoplasmosis. A dye test survey on sera from vegetarians and meat eaters in Bombay. Trans. R. Soc. trop. Med. Hyg. 53: 61-63. 1959.
54. REIMANN, H.P., P.C. BRANT, D.E. BEHYMER and C.E. FRANTI. *Toxoplasma gondii* and *Coxiella burnetti* antibodies among Brazilian slaughterhouse workers. Am. J. Epidem. 102: 386-393. 1975
55. REIMANN, H.P., M.E. MEYER, J.H. THEIS, G. KELSO and D.E. BEHYMER. Toxoplasmosis in an infant fed unpasteurized goat milk. J. Pediatr. 87: 573-576. 1975.
56. ROSSIER, E., S.F. FLORIAN and J.A. McKIEL. Toxoplasmosis in a farmer's family. Can. J. publ. Hlth 65: 66-67. 1974.
57. RUIZ, A. and J.K. FRENKEL. Isolation of Toxoplasma from cat feces deposited in false attics and homes in Costa Rica. J. Parasit. 63: 931-932. 1977.
58. SAARI, K.M. and S.A. RAISANEN. Transmission of toxoplasmosis by trophozoites. Lancet 2: 1077. 1977.
59. SHEFFIELD, H.G. and M.L. MELTON. *Toxoplasma gondii*: The oocyst, sporozoite, and infection of cultured cells. Science 167: 892-893. 1970.
60. SPENCE, J.B., C.P. BEATTIE, J. FAULKNER, L. WILSON, W.A. WATSON. *Toxoplasma gondii* in the semen of rams. Vet. Rec. 102: 38-39. 1978.
61. STAGNO, S., A.C. DYKES, C.S. AMOS, R.A. HEAD, D.D. JURANEK, and K. WALLS. 1980. An outbreak of toxoplasmosis linked to cats. Pediatrics, Springfield 65: 706-712.
62. TERRAGNA, A. Present perspectives of toxoplasmosis in pediatrics. Paediatrician 4: 138-154. 1975.
63. TEUTSCH, S.M., D.D. JURANEK, A. SULZER, J.P. DUBEY and R.K. SIKES. Epidemic toxoplasmosis associated with infected cats. New Engl. J. Med. 300: 695-699. 1979.
64. TIMOFEEV, B.A. and A.K. AKULOV. Life cycle of toxoplasmas and their epizootic dangers for animals. Sel.-khoz. Biol. 10: 257-263. 1975.
65. TIZARD, I.R., N.A. FISH and J.P. QUINN. Some observations on the epidemiology of toxoplasmosis in Canada. J. Hyg., Camb. 77: 11-21. 1976.
66. WALLACE, G.D. Experimental transmission of *Toxoplasma gondii* by cockroaches. J. infect. Dis. 126: 545-547. 1971.
67. WALLACE, G.D. The prevalence of toxoplasmosis on pacific islands and the influence of ethnic group. Am. J. trop. Med. Hyg. 25: 48-53. 1976.
68. WITTING, P.A. Learning capacity and memory of normal and Toxoplasma infected laboratory rats and mice. Z. Parasitenkd. 61: 29-51. 1979.
69. YILMAZ, S.M. and S.H. HOPKINS. Effects of different conditions on duration of infectivity of *Toxoplasma gondii* oocysts. J. Parasit. 58: 938-939.
70. ZIMMERMAN, W.J. Prevalence of *Toxoplasma gondii* antibodies among veterinary college staff and students, Iowa State University. Publ. Hlth Rpts. 91: 526-532. 1976.