TOXOPLASMOSIS: WITH SPECIAL REFERENCE TO PROPOSALS FOR REDUCING CONGENITAL INFECTION

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Toxoplasmosis begins with the cat, including in this term all felidae (Hutchison, 1965; Hutchison *et al.*, 1968; Frenkel *et al.*, 1969; Sheffield and Melton, 1969; Dubey *et al.*, 1970). An infected cat sheds oöcysts in its faeces. If these are ingested by another cat, oöcysts may develop in that cat. This is the sexual cycle found only in the cat.

The asexual cycle is found in all species of animals including the cat. It may be initiated by oöcysts from the faeces of the cat or, in the case of carnivores and omnivores, by tissue cysts in animal flesh. In either event zoites are produced and proceed to the formation of tissue cysts. In herbivores and in man it stops at the first infection, but in some species it may pass from animal to animal by cannibalism.

There is one other mode of infection – congenital – when an infected pregnant animal transmits zoites to its fetus. In some species this may happen in successive pregnancies and may pass from generation to generation (Beverley, 1959), but in women it can happen only once and stops at one generation.

Oöcysts are most likely to be shed by young cats and are not immediately infectious when passed but require 1 to 5 days for sporulation. Usually an infected cat shed oöcysts only once in its lifetime and then for 1 to 3 weeks only; but in a single day it may shed up to 10 million, they are very hardy, being able to survive in soil for up to 18 months, especially when there is shade and moisture (Frenkel et *al.*, 1980).

The tissue cyst, although not so hardy, can survive for weeks in meat, and its contained zoites (bradyzoites) resist the action of gastric juice. It is however, destroyed by cooking, smoking and pickling and by efficient cold storage at −20 °C.

The unencysted zoite (tachyzoite) is more delicate and, apart from laboratory accidents (Rawal, 1959a), important only in congenital infection.

The chances of human infection depend on:

(a) number of infected cats, closeness of their association with man, climatic condition, and

(b) prevalence of infection in meat animals and cooking habits.

EXTENT OF INFECTIONS IN CATS

Serological surveys indicate than in the UK about 25% of cats are, or have been, infected and that at any one time 2% shed oöcysts (McColm *et al.*, 1981).

At first this figure may fail to impress but, when it is remembered that in a single day a cat may shed millions of oöcysts and that they can survive for many months, the danger becomes obvious.

EXTENT OF INFECTION IN MEAT

In the UK serological surveys have shown infection in 28% of cattle, 11% to 90% of sheep, and in 12% of pigs (McColm*et al.*, 1981). Of greater importance is the proportion of animals whose flesh contain tissue cysts. Rawal (1959b)

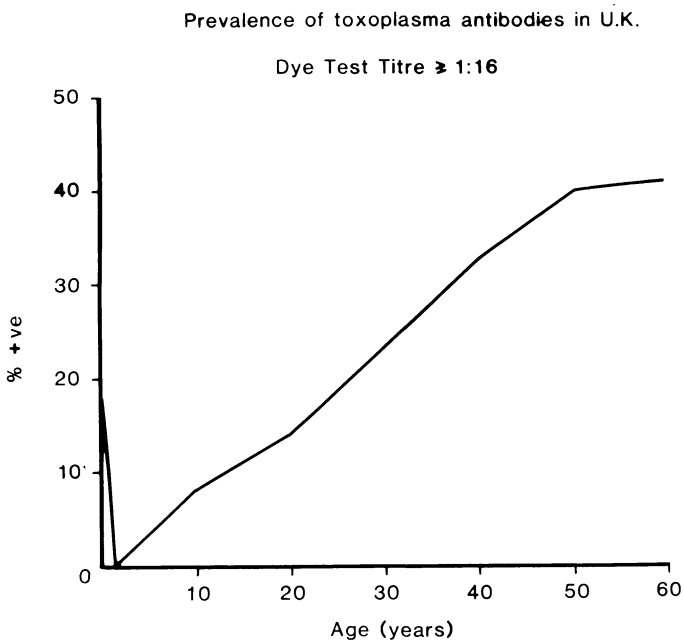

Fig. 1. — Fresh infections to be expected each year – 1/4 million. Adapted from Fleck 1969.

found them in 6 of 21 sheep brains in England. In other countries they have been found in 9% to 23% of sheep (Work, 1971; Jacobs *et al.*, 1960); 12% to 15% of pigs (Work, 1971; Janitschike, 1971) but very rarely in cattle (Work, 1971; Dubley and Streitel, 1976; Čatár *et al.*, 1969); so the danger lies in mutton and pork rather than in beef.

EXTENT OF INFECTION IN MANKIND

Serological surveys show the prevalence of human infection in the UK to be somewhat as shown in figure 1 (Fleck, 1969).

This is the type of curve that would be expected as a result of universal, but infrequent, exposure to an omnipresent source of infection. As the population of

the UK hardly ever eats raw meat, but is in the habit of cooking it well, the main source of infection would seem to be oöcysts in cat faeces. (It is of interest that in France, where raw or undercooked meat is more commonly eaten, the prevalence of infection is much higher than in the UK).

Just as it is more important to know the proportion of cats which sheds oöcysts and of animals whose flesh contains tissue cysts than it is to know the proportion of positive serological reactors, so it is more important to know the amount of human illness than to know the number of persons with antibodies.

REPORTS OF POST-NATALLY ACQUIRED CLINICAL TOXOPLASMOSIS

The Communicable Disease Surveillance Centre (CDSC) receives reports from England, Wales and Northern Ireland.

The results for the years 1976-80 have been published (Bannister, 1982) and, excluding toxoplasmic eye disease, show a yearly average of 260 cases of illness due to post-natally acquired toxoplasma infection. 180 of the cases were of glandular enlargement. Others were of fever of uncertain origin, jaundice or hepatocellular disorder, rashes, eosinophilia, gastro-intestinal disorder, skin and breast nodules and arthralgia.

Surprisingly there were no reports of encephalitis, meningoencephalitis, myocarditis and pneumonitis and in 5 years only 3 of toxoplasmosis during the course of immuno-suppressive disease, or treatment. One of these was related to Hodgkin's disease, one to lymphatic leukaemia and one to organ transplantation.

Since the publication of the reports, however, a case of encephalitis has been reported from Scotland (Howden *et al.*, 1983) and, disturbingly, a case of generalised *Pneumocystis carinii* and toxoplasma infection in a sufferer from the acquired immunodeficiency syndrome (AIDS) (Gransden and Brown, 1983).

REPORTS OF CONGENITAL TOXOPLASMOSIS

Bannister (1982), interpreted the CDSC reports as showing 37 new congenital cases in 1976-80, about 7 a year, and Hall (1983), as showing 34 in 1975-80, about 6 a year. These numbers are obviously too few and suggest insufficient awareness of the many possible manifestations of congenital toxoplasmosis, some of which are shown in table 1.

If the cases of uxeitis reported to the CDSC are transferred from the acquired to the congenital category the number becomes 307, but this may be too many because the serological diagnosis of toxoplasmic eye disease is far from certain and, moreover, some reports may have been on repeated examinations.

SEROLOGICAL SURVEYS TO DETECT CONGENITAL TOXOPLAMA INFECTION

A better idea of the prevalence of congenital toxoplasmosis may be obtained from serological surveys to detect women who develop toxoplasma antibodies *de novo* during pregnancy or who at that time show a significant rise in antibody titre,

TABLE 1. — *Manifestations of congenital toxoplasmosis.*

Neurological Disease 108 patients		Generalised Disease 44 patients
55%	Abnormal C.S.F.	84%
94%	Chorioretinitis	66%
51%	Anaemia	77%
50%	Convulsions	18%
50%	Intracranial calcification	4%
29%	Jaundice	80%
28%	Hydrocephalus	0%
25%	Fever	77%
21%	Splenomegaly	90%
17%	Lymphadenopathy	68%
17%	Hepatomegaly	77%
16%	Vomiting	48%
13%	Microcephalus	0%
6%	Diarrhoea	25%
4%	Eosinophilia	18%
3%	Abnormal bleeding	18%
2%	Hypothermia	20%
1%	Rash	25%
0%	Pneumonitis	41%

especially if it is accompanied by the appearance of specific IgM antibodies. (Ruoss and Bourne, 1972; Williams *et al.*, 1981; Broadbent *et al.*, 1981). Such surveys supplemented by the observations of Desmonts and Couvreur (1974) give the results shown in table 2.

The definitions give by Desmonts and Couvreur (1979), are: "subclinical" – "asymptomatic and no disease related to toxoplasmosis occurred later"; "mild" – "apparently normal and developed normally on follow-up, e.g. no mental retarda-

TABLE 2.

Number of births				650,000
Women infected during pregnancy	0.23%	of	650,000	1,495
No congenital toxoplasmosis	61%	of	1,495	912
Subclinical toxoplasmosis	26%	of	1,495	389
Mild toxoplasmosis	6%	of	1,495	90
Severe toxoplasmosis	4%	of	1,495	60
Neonatal deaths	3%	of	1,495	45

TABLE 3. — *Congenital toxoplasmosis. Major Sequelae.*

	Neurologic Disease	Generalised Disease
(1) Mental retardation	89%	81%
(2) Convulsions	83%	77%
(3) Spasticity and palsies	78%	58%
(4) Severely impaired sight	69%	42%
(5) Hydro- or Microcephalus	46%	7%

Adapted from Eichenwald (1960)

tion or neurological disturbance on later examination, but isolated retinal scars discovered on systematic examination (or in one case, isolated intracranial calcification)"; "severe" – "both chorioretinitis and intracranial calcification (whether or not the child was otherwise clinically normal) or mental retardation or neurological disorder".

It will be seen that the commonest clinical manifestation found by Desmonts and Couvreur were mental retardation, often associated with neurological disorder, and chorioretinitis. The same order was found by Eichenwald (1960). In cooperation with a group of hospitals he examined serum samples from 2208 infants with undiagnosed neurological illness, from 3284 with undiagnosed generalised illness and from 5761 normal infants. Evidence of toxoplasmosis was found in 4.9% of the first group, in 1.3% of the second group and in 0.07% of the third. The relative frequency of the commonest manifestations found by him is shown in table 1.

The major sequelae on "follow-up" 4 years later are shown in table 3.

One might add a syndrome resembling hydrops foetalis and note that prematurity is common. The frequency and severity of congenital disease are related to time of maternal infection. When it occurs in the first trimester congenital infection is least frequent but most severe; when in the third it is most frequent but least severe, and in the second, intermediate. Abortion occasionally occurs, but not repeated abortion.

ATTEMPTS TO REDUCE THE INCIDENCE OF CONGENITAL TOXOPLASMOSIS

In an endeavour to reduce the incidence of congenital toxoplasmosis serological screening of pregnant women is virtually obligatory in Austria (Mutter-Kind Pass, 1978) in France and in the state of Oregon in the U.S.A. (Beach, 1979).

In Austria, women are tested in the first trimester of pregnancy and again in the eighth month. Those found to have been infected are treated with pyrimethamine and sulphonamide (Thalhammer, 1957). In France tests are made every two months, or even every month. Tests for specific IgM antibodies are included and treatment is with spiramycin (Desmonts and Couvreur, 1979).

As serological surveillance and preventive treatment has been advocated for the UK (Wynn and Wynn, 1976) it is sensible to determine its probable cost effectiveness. Detailed calculations of cost effectiveness have been published (Henderson *et al.*, 1983). The method of sensitivity analysis used, gave minimum, central and maximum estimates, but here only the central one is given. Estimates were based on the assumption that the main costs of congenital toxoplasmosis would arise from mental retardation and impaired sight.

The findings of Desmonts and Couvreur indicated that chorioretinitis would be present in all the 150 clinically manifest cases, and other publications (Wolf *et al.*, 1967; Desmonts, 1976a; Roever-Bonnet *et al.*, 1979; Wilson et al., 1980) pointed to its later development in 40% of 390 subclinically infected patients. This gave a figure of 300, but probably only 120 would have serious visual disability. Serious mental subnormality was assumed to be present in 90% of the 60 severely ill and to develop in 8% of the 400 mildly affected or subclinically infected (Wilson *et al.*, 1980; Stern et al., 1969). This, supplemented by consideration of the proportion of mental subnormality due to toxoplasmosis in institutions and in the home, led to a figure of 90. The cost of mental subnormality was estimated at £ 4,380,000 and of visual handicap at £ 503,000. To these sums was added £ 131,000 for initial treatment of babies in hospitals for acute illnes. This gave a total of £ 5,104,000 but, as mental handicap and visual disability are frequently associated, £ 330,000 was deducted for double counting, giving a final total of £ 4,774,000. The cost of screening and treatment was estimated at £ 4.75 million by the method used in Austria and at £ 11.5 milion by that used in France. Assuming a 50% effectiveness the first would show a financial loss of about £ 2.4 million and the second of about £ 9 million.

Of course cost effectiveness should not be the only, or even the main consideration. If universal screening and treatment were practicable in the UK, which is doubtful, they might still be desirable to prevent the misery caused the birth of severely damaged children. Against this, however, must be weighed the anxiety which might be caused in the minds of pregnant women by the knowledge that they were infected with toxoplasma. In other countries this has led to requests for termination of pregnancy which Desmonts (1976b) found to have been unnecessarily performed in 20 of 21 instances in France. In the UK it could be justified in only 60 of 1,500 infected women; with no means of telling which 60. The efficacy of present forms of preventive maternal treatment is not established beyond doubt. In the experience of Desmonts and Couvreur (1979) it was followed by a reduction in congenital infection, but an increase in the proportion of severely affected babies.

POST-NATAL SCREENING AND TREATMENT OF INFECTED BABIES

Instead of pre-natal screening and treatment of infected mothers, Frenkel (1981) has suggested post-natal screening, followed by treatment of infected babies, but the efficacy of this is also debatable. There are, indeed numerous accounts of

success in treatment of toxoplasmosis by pyrimethamine, sulphonamide and folinic acid or by spiramycin, but there are also accounts of failures. There has never been a controlled trial, nor, in view of the rarity of the disease, is it ever likely that there will be one. Eichenwald (1966), from his great experience, wrote "there is as yet no evidence that the use of pyrimethamine and sulfadiazine in neonatal toxoplasmosis offers any measurable benefit to the infant". It is to be hoped that more efficacious medicaments will be found.

VACCINATION OR TREATMENT OF CATS

Another suggestion is that toxoplasma infection should be reduced by vaccinating cats or treating them with toxoplasmicidal drugs (Frenkel and Smith, 1982). This might protect against oöcysts from a person's own cat but not against the multitude of oöcysts liberally distributed by other cats. The British public has a poor record of acceptance of obviously and directly useful methods of immunisation against such common diseases as whooping cough, measles, and rubella. It is inconceivable that immunisation, or treatment, of cats in order, indirectly, to protect babies against a rare disease would be widely accepted, or even understood.

EDUCATION IN HYGIENIC PRECAUTIONS

The best, cheapest and safest method of prevention would be education of pregnant women in hygienic precautions. Preferably they should not keep a cat but, if they do, should arrange for some other member of the household to clean its litter pan and sanatize it with boiling water. They should wear disposable gloves when they do this and when they garden. They should wash vegetables and salads and after preparing vegetables or meat, should wash their hands. They sould never eat raw or undercooked meat. Such recommendations have been followed by a marked reduction in the incidence of toxoplasmosis in Paris (Desmonts G., personal communication).

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