A New Look at Infectious Diseases

Toxoplasmosis

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Toxoplasma gondii, the causal agent of toxoplasmosis, was first found in a North African rodent called *gondi*.¹ It is an unusual parasite in that it is found in most parts of the world and it has little host specificity. It can infect any warm-blooded animal, including birds, and frequently does so. The prevalence of infection in man, as judged by antibody tests, varies from as low as 7% in Navajo Indians² to 94% in Guatemala.³ In England the prevalence among adults varies from area to area but on average is about 30%.⁴ Similar variations in prevalence are found in domestic and semi-domestic animals.

Infection becomes established in any animal when toxoplasma trophozoites penetrate and multiply in the cytoplasm of a nucleated host cell, most often a reticuloendothelial cell. After repeated multiplication of the parasites, the host cell becomes distended and finally ruptures, liberating 16 or more toxoplasms each capable of invading another host cell. Repetition of this process causes microscopic foci of damage. Spread may be local, by the blood stream, by the lymphatics, or across body cavities. Small foci are commonly found in the brain, lungs, heart, liver, and skeletal muscle. Multiplication and spread continue until the host develops immunity or, very rarely, dies. Immunity is partly due to antibodies and partly to sensitized reticuloendothelial cells. Reactive changes in lymph nodes and spleen are thought to be concerned with the development of this immunity.

As immunity develops extracellular parasites are killed, intracellular multiplication is slowed down, and another stage in the life cycle of the parasite develops: the tissue cysts. While these are small, up to 100 μ in diameter, each may contain thousands of toxoplasma zoites which are similar to, but smaller than, trophozoites. The cyst wall screens the zoites from the tissues and the host's defence mechanisms, as well as the tissues from the action of the zoites. Multiplication occurs within a cyst but at a much reduced rate. Cysts persist for years, possibly for the lifetime of the host. They are found most commonly in the brain, heart, and skeletal muscle. It is thought that occasionally a cyst may rupture and precipitate a local inflammatory reaction.⁵

Until recently little was known of how infection was transmitted from one host to another. Transplacental transfer from mother to fetus and accidental laboratory infections were known, as was infection of carnivores and predators by eating uncooked flesh, and of man by undercooked meat.⁶ How infection was transmitted to herbivores and vegetarians was not known since both trophozoites and zoites in cysts are very susceptible

to drying, heat, and changes in tonicity. Then, Hutchison and his colleagues^{7,8} reported the discovery of intestinal stages in the life cycle of toxoplasma occurring in cats. After a meal of flesh infected with toxoplasma, schizogony, gametogony, and oocyst formation were found in the epithelial cells of villi. Oocysts, shed into the lumen of the gut, were passed in the faeces and within 48-72 hours were found to become infective by the development of sporocysts and sporozoites. Many others, working on similar lines at about the same time, came to like conclusions. Sporulated oocysts (faecal cysts) are much more resistant to adverse conditions than are tissue cysts and trophozoites. They are resistant to the action of many chemicals and will survive for many months at room temperature. Dubey *et al.*⁹ have shown that they will survive in moist soil and are transported by earthworms. Feeding or inoculation of oocysts has produced toxoplasma infection in all the animal species in which this has been attempted. So far as is known, gametogony and oocyst formation occur only in the cat family.

While infection is very common, clinically evident infection is comparatively rare. Concomitant infections, extremes of age, exposure, poor nutrition, pregnancy, lactation, blood diseases, concomitant malignancy, and immunosuppressive drugs may be factors which predispose to the severity of an infection becoming sufficiently high to give rise to clinical manifestations.

Clinical Manifestations

These may conveniently be classed as due to congenital or to acquired infections. The former were the first to be recognized and so are probably better known at present. The latter are proving to be the more common.

CONGENITAL TOXOPLASMOSIS

For congenital toxoplasmosis to occur a woman must have a primary infection during pregnancy. This rarely gives rise to clinical illness other than perhaps undue fatigue or muscle pains; occasionally it may cause lymphadenopathy. Even in subclinical infection there may be a temporary parasitaemia leading to placental infection and thence fetal infection. Prospective studies have shown that fetal infection follows about one-third of primary infections of expectant mothers and that only one-third of infected fetuses actually develop disease.¹⁰

The outcome of infection depends on the virulence of the infecting strain and the age of the fetus at the time of infection. Infection in early pregnancy may lead to abortion, later to miscarriage, a little later to a stillborn child with evidence of disease, and still later to a live-born child with clinical manifestations. If infection occurs near the end of pregnancy an apparently healthy child may be born which then develops disease in the early weeks of life.

Infection in the fetus or neonate is at first generalized and there may be hepatosplenomegaly, with or without jaundice, lymph node enlargement, myocarditis, anaemia, oedema, and exudates in the body cavities. When infection occurs in the latter half of pregnancy this stage is usually survived. Then parasites are cleared from the viscera but become localized in the central nervous system.

Eye Infection

By far the commonest site of congenital disease is the eye. Occasionally the whole of the globe is involved producing a useless microphthalmic eye, which is noticed at or very soon after birth. Usually the disease is confined to the choroid and retina. One or both eyes may be affected and the lesions are frequently multiple even when only one eye is affected. Often by the time an ophthalmoscopic examination is made the process is no longer active. An irregular white patch of sclera is visible through a thin atrophic scar in the choroid and retina (see figure). Lesions are often alongside blood vessels and irregular patches of choroidal pigment are usually found, mainly at the edges of scars but sometimes as strands straddling a lesion.

The signs and the age at which ocular disease is first noticed depend on the size of the choroidoretinal lesions and their site. A large white scar in the fundus will cause a white instead of a red reflex when a light shines in the eye. This may be noticed by an observant mother or midwife and lead to an early examination. A small lesion affecting the macula may be the cause of a squint usually first noticed at the age when the child should be developing binocular vision. If the macula of each eye is affected, instead of a squint there is likely to be a searching nystagmus. A lesion near the macula may not be found until early school age when impaired vision is suspected and leads to an ophthalmoscopic examination. Other lesions may not be found until the late 'teens or early twenties, when reactivation of a previously inactive scar occurs and causes inflammatory exudation with accompanying haziness of vision. Still others may not be found until the presbyopic age when an ophthalmoscopic examination is made for the first time or when a complication occurs such as detachment of the retina.

Lesions in the Nervous System

Other parts of the central nervous system may be affected, causing meningoencephalitis—usually more encephalitis than meningitis. The cerebral cortex is more frequently affected than the basal ganglia and brain stem. Focal lymphocytic

infiltrations of varying size occur. The larger ones may undergo central necrosis and at a later stage become calcified, and they may be so numerous as to become confluent—particularly in the layer of tissue just beneath the ependyma of the lateral ventricles. Calcifications may occur to such an extent that they are seen in x-ray films of the head. When in the deeper part of the cortex they are of irregular shape while thin plaques of calcified tissue in the walls of a ventricle show as curvilinear streaks in "end on" views.

Occasionally shreds of necrotic tissue are shed into the lateral ventricles and pass in the cerebrospinal fluid to block the aqueduct, or lesions may develop in the wall of the aqueduct. In either case an obstructive hydrocephalus develops.

Convulsions may occur during the stage of active meningoencephalitis. Intracranial calcifications, convulsions, and hydrocephalus occurring in the newborn and due to toxoplasmosis are nearly always accompanied by choroiditis. Nevertheless, mild infections may give rise to epilepsy, psychomotor retardation, palsies, or paraesthesiae but not until later childhood. The smaller the damage the longer it will be before it causes signs or symptoms. In these circumstances there may be no choroidoretinitis and the condition is known as oligosymptomatic toxoplasmosis.¹¹

Acquired Toxoplasmosis

Acute acquired toxoplasmosis may present in three main ways—simple lymphadenopathy, lymphadenopathy with involvement of another organ, and generalized toxoplasmosis. By far the commonest of these, lymphadenopathy, was first reported by Siim,¹² who, has since dealt with many hundreds of such patients in Denmark. The severity may range from a pyrexial illness requiring lengthy convalescence of 1½–2 years, to the accidental finding of a solitary enlarged lymph node. The number of affected nodes may vary from one to a score or more. Any node or group of nodes may be enlarged, most commonly the upper deep cervical, least often the inguinal and then usually as part of a very generalized lymphadenopathy. The nodes are rarely painful but are often tender and commonly 1.5–2.0 cm in length, sometimes twice this size. They remain discrete, never break down, and gradually return to a normal size but may take several weeks to do so. Relapses are prone to occur when the same nodes or other ones become enlarged. The spleen is rarely palpable. Polymorphonuclear leucocytosis is rare but a mild lymphocytosis is common. While abnormal leucocytes are often found in the blood, the Paul-Bunnell test is always negative.

The table shows that lymphadenopathic toxoplasmosis occurs mainly in children and young adults. Why males should be more frequently affected at younger ages and females at older ones is not clear.

Sometimes, when resolution is slow, a lymph node is removed for examination as possible Hodgkin's disease or from the axillary tail of the breast as a possible carcinoma. Only after histological examination is toxoplasmosis considered. At other times even lymphadenopathy may not be recognized until a laparotomy for "an acute abdomen" discloses enlarged mesenteric lymph nodes or an x-ray examination on account of chest symptoms shows enlarged hilar nodes. Then further investigation reveals the toxoplasmic origin of the condition.

Occasionally lymphadenopathic toxoplasmosis is complicated by involvement of one other organ such as the brain, heart, lung, liver, or skeletal muscles. The signs and symptoms are then mainly due to the particular diseased organ. The first pointer to the toxoplasmic aetiology is usually finding the enlarged lymph nodes.

Generalized toxoplasmosis may occur after accidental laboratory infections or more usually in patients with immunological deficiency states secondary to such conditions as Hodgkin's disease, lymphosarcoma, leukaemia, or in those patients undergoing immunosuppressive treatment.

Age and Sex Distribution of Toxoplasmic Lymphadenopathy

Age Group	Males	Females	Total
0-4	7	1	8
5-14	20	10	30
15-24	13	13	26
25-34	3	10	13
35-44	0	5	5
45-54	0	7	7
55 or more	0	1	1
Total	43	47	90

Age of six patients was not known (three of each sex).

While most ocular toxoplasmosis is due to congenital infection, in a few instances it is known to have succeeded acquired infection. It usually runs a chronic course. Cerebral granulomata are even more rare.

Laboratory Diagnosis

Since a diagnosis on clinical grounds alone is rarely certain, laboratory confirmation should be sought. The surest proof of infection is isolation of the parasite but this is rarely feasible except from tissues obtained by biopsy or at necropsy. As the parasite will grow and multiply only in living cells, isolation can be done only by inoculation of susceptible animals, embryonated eggs, or tissue cultures. Isolation is most commonly made by inoculation of tissue emulsions into mice.

Histological examination of tissues may indicate toxoplasmosis, as when reactive changes are found in lymph nodes or focal necroses in non-lymphoid organs. *Toxoplasma* can be identified with certainty in sections only when a cyst is found. In lymph nodes these are rare and search for them, even in many sections, is usually fruitless.

It follows therefore that serological tests are the mainstay of diagnosis. There are many of these, the chief being the dye test of Sabin and Feldman.¹³ This is difficult to perform and the need for a safe, easy, and reliable test is shown by the great number and variety of other tests which have been introduced. The search for such a test still continues. As with all antibody tests, proof of recent infection can be obtained only by testing paired samples and showing a rise in titre. Nevertheless, often the titre is already maximal when the first sample is taken. Then finding a titre well above the levels usually seen in the normal population is a strong pointer to recent infection. Antibody titres rise rapidly in the first 6-8 weeks after infection, are maintained for a few more weeks, and then fall steadily over the next year or so, when they eventually sink to the levels commonly found in normal people and assumed to be the result of past subclinical infection. This means that in longstanding infections, such as congenital ocular toxoplasmosis in persons over the age of 5-10 years, an antibody test rarely gives a clear-cut answer. All that one can then say is that a positive test with a low titre is compatible with a longstanding infection, whereas a negative test excludes a diagnosis of toxoplasmosis.

Treatment

A synergic combination of sulphonamides and pyrimethamine has been shown to be effective in experimental toxoplasma infections of animals¹⁴ and by many people in some human infections. Likewise, spiramycin has also been shown to be effective in animals.¹⁵ A combination of triple sulphonamide (3.0 g daily) with pyrimethamine (25 mg daily) when given to expectant mothers who became infected during pregnancy, reduced the frequency of congenital infection to a third of that which occurred in an untreated group.¹⁶ In another therapeutic trial, spiramycin (2.0 g daily) caused a similar reduction in the

frequency of congenital infection.¹⁷ Rapid control of active ocular toxoplasmosis is highly desirable—particularly when this is in the perimacular area. Both treatments are effective in these circumstances and their action is helped by the concurrent use of steroids such as prednisolone.

Treatment has had dramatic effects, as in patients with disabling myositis or even been lifesaving, as in those with meningoencephalitis. Nevertheless, neither treatment has an effect on lymphadenopathic toxoplasmosis beyond controlling pyrexia. Pyrimethamine is a folic-acid antagonist and daily doses of 25 mg may cause a folic-acid deficiency in some patients. Thus repeated haematological checks during its use are advisable. If lymphopenia or thrombocytopenia occur, as they occasionally do, pyrimethamine should be stopped and folic acid given. On doing so the blood counts soon return to normal. The need for haematological control is irksome to the patient, and, if only on this account, spiramycin may eventually be found to be preferable.

Epidemiology

The frequency of clinically apparent toxoplasmosis is not known. Reports from the Public Health Laboratory Service¹⁸ show a steady rise in patients for whom a suspect clinical diagnosis of toxoplasmosis was found to be highly likely—from 609 in 1967 to 1,071 in 1971. This rise most probably reflects an increased awareness on the part of clinicians rather than an increased incidence. About one-half of the patients had ocular toxoplasmosis and one-third had lymphoglandular toxoplasmosis or pyrexia of undetermined origin.

Prospective studies in Gottingen,¹⁹ Paris,¹⁰ and New York²⁰ indicate that congenital toxoplasma infection—whether clinically manifest or not—occurs in 57, 12, and 7.5 per 10,000 pregnancies in these cities respectively. Similar studies in Amsterdam, Berlin, London, and Stockholm are in progress and others are about to begin.

The role of oocysts from cats in human infections is currently being assessed. Human infection may be acquired directly from oocysts, possibly by swallowing or by inhaling them. The high frequency with which the upper cervical lymph nodes are affected in lymphadenopathic toxoplasmosis suggests that the point of entry may be the upper respiratory tract. The results of a survey by Price²¹ suggest that cat contact is a significant factor in human infection. On the other hand, man may acquire infection from cats indirectly—that is, as a result of eating the flesh of other animals which have been infected by oocysts from cats.

Whether in confirming clinical suspicions in individual patients, in performing prospective studies, or in assessing the role of animals in human infections, antibody tests are essential. As has been mentioned earlier the dye test is both difficult to do and expensive in man-hours. Should a safe, simple, reliable, and inexpensive test become available, it would give a great impetus to epidemiological work. Kwantes *et al.*²² have recently reported on a latex-agglutination test which holds promise of fulfilling these requirements. Using this antigen as a screening test over four months on sera from 160 patients suspected of having glandular fever, Colquhoun²³ has found four patients who, on subsequent dye tests, were confirmed as having recent toxoplasma infections. If the manufacturers of this commercially available antigen are able to standardize and control its sensitivity, then we may have the test for which we have been waiting so long.

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Reorganization—1974 or 1984?

Three Doctors' Dilemmas

FROM A SPECIAL CORRESPONDENT

Continuing the discussion among the three doctors I started last week, the subject turned to that of the community physician—the new medical man (or woman) described in the Hunter report. All three thought that this job could be exciting—for the district community physician could be the key person in the whole reorganization. He would be the one who would know which committee was doing what, what the health care planning teams were up to, what the district or area management team's recommendations were, and what the area health authority thought about them. At district level he could get to know all the hospital doctors and general practitioners personally. In the first instance, he would probably have been in the public health service and would therefore be familiar with local authority health services. Dr. Shaw insisted that the district management team would not be "his" team but, as the full-time medical person, the district nursing officer would naturally look to him. If he saw eye to eye with the district administrator it could be "their" team. Dr. Smith thought that this would put the sort of "old boy net" he had always found to work well on to an official basis. Some doctors, he said, had expressed fears that the district management team would be "snoopers", but this was a politician's view, and most G.P.s were only too glad to be consulted—especially if the information was being collected for the benefit of the general practitioner service.

Dr. Shaw thought that "monitoring" was an equally inappropriate term. A community physician could talk to G.P.s for specific reasons—for example, to say that only 60% of vaccinations had been achieved and what could be done about it? He had been amazed by the spirit of co-operation that could be obtained. Perhaps the community physician could not do everything; would the district administrator be equally at home with G.P.s? Dr. Smith could not see why not. He and his partners were moving from a group practice to a health centre, and had wanted two big rooms for teaching. The official design guide said that that was impossible but both local and national administrators had accepted reasoned arguments that they should be provided—as well as many other modifications to the health centre.

Cynicism and Pessimism

Mr. Crombie agreed with these views but wondered rather cynically if they would really work. He was one of two ophthalmological advisers to the regional board who had visited all six ophthalmological units in the region. He had been amazed on occasions to find out how little the board knew of what went on in some of these units and, though the advisers had made numerous recommendations for each unit—and hoped to visit these units again soon—they did not expect many of their recommendations to have been even considered let alone carried out. The regional health authority might well be just as out of touch. Mr. Crombie continued that in his hospital (the teaching hospital) management in the form of the Cogwheel system had been introduced, but there was frustration at the level of the divisional executive committees, as much of their hoped-for power had not been delegated to them as yet. The hospital staff committee (all of the consultants) had had talks on reorganization but had found it all very confusing and had had little help from the administrators. Their main fear was of even less voice under the new system. Already it was proving difficult to have meaningful communications with administrators at all levels, and the general feeling was that very often these administrators were out of touch. Mr. Crombie was rather pessimistic about administrators, in that few of them offered very much in the way of constructive help but were interested when doctors undertook administrative changes themselves and they actually worked. These people were concerned with a flat administrative horizon. If anything disturbed this horizon their job was to pat it down, step on it, suck away its foundations and preserve its level qualities. The N.H.S. had perhaps not had the best administrators, not only at board level but also at the Department. It seemed to be an established fact that D.H.S.S. did not figure very highly in the hierarchy of Civil Service appointments.

On the other hand, he thought, the management approach could help in non-medical areas. There was no integrated personnel service in the health service so that it fell down, for example, on labour disputes, but Mr. Crombie doubted whether