Toxoplasmosis in the perinatal period

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Summary
Although many of the fundamental biological features of toxoplasmosis are today well appreciated, the practical problem of prevention of its most serious consequence—disabling congenital disease, remains unsolved. The reasons vary in different communities, but are concerned with detection of the chief mode of spread, assessment of incidence, delineation of vulnerable antenatal women in latently infected populations, and assessment of the risks of therapeutics. The results of some of the approaches to these problems in Scotland are reported and discussed.

Introduction
This may be an appropriate time to review perinatal toxoplasmosis for it is almost exactly the thirtieth anniversary of Bamatter's (1946) first description of congenital toxoplasmosis of infants in Europe and his successful isolation of the causative agent.

The three decades following his discovery witnessed an enormous interest in toxoplasmosis and much experimental work at the great centres of European medicine, Geneva and Leiden, Paris and Vienna, Scandinavia and this country. Together with major contributions from the U.S.A. this work culminated in the resolution of many of the basic biological features of toxoplasmosis, an essential prerequisite for the understanding and management of the perinatal disease. Numerous problems remain; some fundamental, but many at an applied level, although this does not imply that they afford of any easier a solution.

To gain perspective a brief summary of some of the basic features of this zoonosis is now given: the pathogen is a parasite with sexual and asexual reproductive phases, where the former is accomplished in the feline intestine and the latter in tissues of most warm blooded animals including man. Primary infection acquired in the adult, from one of these sources, is associated with an active period of parasite proliferation at the site of entry during which dissemination by the lymphatics and blood stream occurs. Intracellular parasitic growth, if unrestricted, leads eventually to cell death and further dissemination. This phase is succeeded by host reaction during which the number of parasites is much reduced, humoral antibody becomes detectable and tissue cyst formation takes place. In nature the parasite is well adapted to its host, so that asymptomatic parasitaemia and subsequent latency is common and disease rather rare. The parasite is antigenically complex and the antibody produced equally diverse. Since the parasite is large and mainly intracellular some of its antigen may not be accessible to the lymphocyte system, and the parasite itself may be sequestrated from the effects of sensitized cells and antibody. If primary infection occurs during pregnancy the parasite may cross the placenta to infect the fetus, and the subsequent fate of the conceptus is probably intimately connected with the fetal age at the time of infection.

Since France has a high incidence of toxoplasmosis and devoted considerable resources to its study concepts have been strongly influenced by the French School. Desmonts and Couvreur (1969) in their large prospective survey of 30 000 antenatal women were convinced that congenital toxoplasmosis was the result of an acute infection in a pregnant woman. Since, in their experience, not a single case of fetal infection occurred if maternal infection took place before conception they saw the problem basically as the differentiation of primary from latent infection in the pregnant woman.

The question as to whether chronic infection can ever under any circumstances be associated with congenital transmission is an important one, and not fully settled. Toxoplasmas can apparently readily persist and be recovered from uterine tissue in latently infected women (Remington, Melton and Jacobs, 1960). Cases of congenital infection in an apparently chronically infected woman have been reported (Engelbrecht, 1971) but these appear to be exceptional cases and the weight of present evidence is that congenital toxoplasmosis is the result of primary infection of the mother during pregnancy.

The diagnosis in the neonate is best made from a consideration of the maternal antibody status during
pregnancy as well as, and including the findings in cord serum. Such ideal conditions are not likely to occur very often unless deliberate antenatal testing is undertaken, as in some centres in France. It is impractical to dye-test large antenatal populations; but tests which are more susceptible to mechanical help, e.g. the complement fixation, haemagglutination and direct agglutination tests, can under certain conditions be used for screening and selecting patients for dye test. Patients who sero-convert during pregnancy, who present with or develop high titres of dye test antibody, and a smaller number who develop clinical disease, e.g. lymphadenitis or hydramnios, delineate the susceptible group. The recommendations of the Lyon Conference (1975), which surveyed the current French experience on toxoplasmosis in the pregnant woman, suggested that two tests designed to detect IgG and IgM respectively should be employed and that suspects should be assiduously followed-up. They suggested the dye test and the complement fixation test in which IgG antibody would participate and the Remington fluorescent test and agglutination with and without 2-mercapto-ethanol (2-ME) for IgM antibody detection.

Desmonts and Couvreur (1974) showed that maternal infection acquired during pregnancy was not transmitted to the infant in more than 50% of the cases and even when transmission occurred it was most often subclinical. The risk to the fetus was closely related to the time when maternal infection occurred. Infection in the first trimester yielded fewer infected infants but when it did occur fetal damage was often severe. Infection of the mother in the last trimester more often resulted in transmission of the parasite to the fetus but infection was likely to be subclinical in the newborn. But the infection can be devastating. In Eichenwald’s (1960) series of 150 infants with congenital toxoplasmosis the mortality rate was 12%, and 90% of the survivors were mentally retarded, 75% developed convulsions and 50% had impairment of vision. The severe cases with central nervous system involvement, or those presenting at birth with the generalized form of the disease, with jaundice, hepatomegaly or splenomegaly, will be readily detected and the parasite sometimes can be successfully isolated by intraperitoneal inoculation of mice with neonatal blood but in the subclinical cases diagnosis is entirely by serological means and is based on high dye-test titres, the presence of Toxoplasma-specific IgM antibody and in a consideration of the IgG Toxoplasma antibody level in the infant (which declines in titre rapidly in uninfected infants but which fails to do so in infected infants). The test to show specific IgM by immunofluorescence may be negative owing either to delay in transmission of the parasite from the placenta to the fetus or to high levels of specific IgG antibody transmitted transplacentally from the mother which can inhibit the secretion of specific IgM by the infant. Specific IgM anti-Toxoplasma antibody may not therefore be detectable until complete disappearance of maternal antibody has occurred so that the follow-up of such infants may have to be prolonged before maternal antibody can be excluded (Desmonts and Couvreur, 1975).

Alford and his group (1969) successfully used the method of screening cord sera for increased IgM levels in 2916 deliveries and found elevated values in 123. Of the 123, forty-two were shown to have infections and in six of the forty-two Toxoplasma was responsible—an incidence of 1 : 486 or roughly 2/1000. He also reported a study of 7000 infants in which the indirect fluorescent IgM test for Toxoplasma antibodies was used in a Negro population and infection was detected in fourteen infants—an incidence of 1 : 644 or 1·6/1000 (Alford, 1973).

There are inherent difficulties in getting accurate figures of the actual incidence of congenital toxoplasmosis in a community and the incidence may change as a result of emigration or changes in socio-economic circumstances. Remington (1973) cites estimated rates of congenital infection in Austria as 6 to 7/1000 infants, and in Germany, France and Sweden 5, 3 and 0·2/1000 respectively. In the U.K. the incidence has been estimated as somewhere between 1 : 4000 and 1 : 14 000 (Fleck, 1974).

Pregnant women could be protected from infection with more confidence if the pathways of infection could be more clearly defined. In communities not given to the consumption of raw meat the resistant oocyst shed in cat faeces may be specially important. In this context Dubey’s (1976) recent report on the resheding of Toxoplasma oocysts from chronically infected cats may be important. Cats with antibody and hitherto thought not to be a hazard can be induced to reshed toxoplasma oocysts when subsequently infected with Isospora felis or I. rivolta—common feline parasites.

The question of therapy is particularly difficult. Pyrimethamine and sulphonamide in combination are the most effective therapeutic agents but potentially too dangerous to give indiscriminately to pregnant women. Nevertheless pyrimethamine is widely used for the control of malaria and toxoplasmosis and is administered during pregnancy (Bottura and Coutinho, 1965; Hentsch, 1971). Desmonts and Couvreur (1974) found that maternal spiramycin reduced the number of infected offspring from 51% in an untreated group to 23% in a treated group of infected pregnant women if given in a dosage of 3 g/24 h for 6 weeks.

The pressing questions associated with perinatal toxoplasmosis appear to be: (a) What is the
incidence of infection, especially primary infection in antenatal women? (b) How is the disease being transmitted? (c) Are efficient screening procedures available, and if so should they be used to detect these patients? (d) What measures can be taken in pregnant women if these cases are detected? (e) How should the neonate be treated if grossly infected, or if subclinically infected? The author does not believe that there are clear-cut answers to these questions, nor that every community will give them similar significance. Accurate data on which to proceed in some will depend on the painstaking study of epidemiological data. Some of these data for Scotland are given below.

Results and discussion

Table 1 shows the background position in northern Scotland—an overall rate in the Highland region of 27-6% of the population with antibody to Toxoplasma. There are detectable regional differences, e.g. in the islands off the west coast of Scotland the rate drops to 17%, and in marked contrast the incidence in the Shetland Islands in the north at about 10% compares with an incidence on the Orkney Islands of around 40%. The economy of Orkney is quite different from that of Shetland; Orkney has a highly developed intensive agricultural industry, whereas Shetland, over the period these figures were obtained, depended almost entirely on the fishing industry. Table 2 shows the incidence of dye-test Toxoplasma antibodies in three antenatal populations—London, Inverness and Glasgow—from data obtained between 1970 and 1975, with a slightly lower incidence of antibody in the Scottish communities.

Table 1. Incidence of Toxoplasma antibodies—general population

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highland region</td>
<td>27-6</td>
</tr>
<tr>
<td>Hebrides</td>
<td>17-7</td>
</tr>
<tr>
<td>Orkney</td>
<td>45-1</td>
</tr>
<tr>
<td>Shetland</td>
<td>8-3</td>
</tr>
</tbody>
</table>

Table 2. Incidence of Toxoplasma antibodies—antenatal patients

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>London* (%)</th>
<th>Inverness (%)</th>
<th>Glasgow (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–20</td>
<td>15</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>21–25</td>
<td>27</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>26–30</td>
<td>33</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>31–35</td>
<td>34</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>36–40+</td>
<td>36</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Overall</td>
<td>22</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

* Ruoss & Bourne.

Table 3 shows some of the data of a prospective survey of antenatal women attending the Royal Maternity Hospital in Glasgow from the beginning of 1975. In this survey, an automated complement fixation (CF) technique was employed to screen sera which were also tested by a direct haemagglutination (HA) test for comparative purposes, and samples positive by either test were submitted for dye testing, sixty-five attaining a titre of 512 or greater. The comparative results on approximately 9500 (Table 4) sera involving 4160 women show that fifty-three of those sixty-five sera were detected by both the CF test and the HA test. Nine such sera were missed by the CF test and three by the HA test. However, since at least two specimens of serum were obtained from the majority of patients, it was possible to establish that only one patient would have been missed by the automated CF alone, and none by the HA test. Of the 4160 antenatal patients, 585 (14%) had antibody at the first visit, and eleven seroconverted during pregnancy (Table 5). An attempt is being made to follow-up fifty infants from a total of 2478 where cord serum was available; the serological status of the mothers is shown in Table 6. One infant with definite clinical signs and overt serological evidence has been detected; follow-up of this group of infants is being continued.

In toxoplasmosis, pyrimethamine with sulphonamide are the most effective therapeutic drugs available, but are generally held to be too dangerous.

Table 3. Serology (Glasgow Antenatal Survey 1975)

<table>
<thead>
<tr>
<th>CF</th>
<th>HA</th>
<th>Neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg.</td>
<td>8630</td>
<td>Pos.</td>
</tr>
<tr>
<td>8137</td>
<td>Pos.</td>
<td>1122</td>
</tr>
<tr>
<td>1615</td>
<td>Pos.</td>
<td>1831</td>
</tr>
<tr>
<td>32</td>
<td>512</td>
<td>65</td>
</tr>
<tr>
<td>32</td>
<td>1059</td>
<td>1059</td>
</tr>
</tbody>
</table>

CF, complement fixation; HA, haemagglutination; DT, dye test; Neg, negative.

Table 4. Evaluation of screening methods

<table>
<thead>
<tr>
<th>DT titre</th>
<th>HA.</th>
<th>CF.</th>
<th>HA.</th>
<th>CF.</th>
<th>HA.</th>
<th>CF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32</td>
<td>192</td>
<td>365</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32/128</td>
<td>604</td>
<td>324</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>256</td>
<td>53</td>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 512</td>
<td>365</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>906</td>
<td>709</td>
<td>216</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CF, complement fixation; HA, haemagglutination; DT, dye test; Pos., positive; Neg., negative.
for the treatment of pregnant women. The diamino-
pyrimidines are folic acid antagonists whose \textit{in vitro}
effects can be assessed on cultures of separated
phytohaemagglutinin (PHA)-stimulated human
lymphocytes. The activities of a number of these
drugs have been examined by Dr A. C. Stevenson
using the distribution of nuclear diameters, the
proportion reaching metaphase, chromosomal dam-
age and the protective effects offered by calcium
folinate and thymine for the assessment of cell
damage. These experiments have demonstrated a
range of activity and toxicity to human cells together
with protective effects by calcium folinate and
thymine. It is in this group that potential therapeutic
agents are likely to be found.

Toxoplasmosis in the mother is capable of causing
severe damage to the embryo; the most effective
treatment yet available is likewise subject to similar
risks. These factors are relevant where the manage-
ment of maternal toxoplasmosis is concerned and
especially so when legislation to protect the rights of
the unborn child is contemplated.

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\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Condition} & \textbf{Incidence} \\
\hline
\textit{With antibody} & 585 \\
Rising titre & 4 \\
Stable high titre & 24 \\
\hline
\textit{Without antibody} (at risk) & 3575 \\
Appearance of Ab at low titre (≤128) & 93 \\
Seroconversion (≥256) & 11 \\
Total number of patients & 4160 \\
\hline
\end{tabular}
\caption{Incidence of \textit{Toxoplasma} antibody in Glasgow antenatal patients}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Serological status} & \textbf{No. of mothers} \\
\hline
Seroconversion & 6 \\
Rising titre & 4 \\
Stable high titre & 24 \\
Single high titre & 16 \\
\hline
\end{tabular}
\caption{Fifty infants; the serological status of their mothers (Glasgow antenatal survey)}
\end{table}
Toxoplasmosis in the perinatal period.

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