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Treating toxoplasmosis

Toxoplasmosis occurs all over the world and is the commonest protozoal infection in England, where 30% of adults have serum antibodies to the parasite (Beattie, 1957). Recently-acquired infection is diagnosed serologically by a significant rise in titre in the Sabin–Feldman dye test, or by the detection of specific IgM using immunofluorescence. While most infections are subclinical some become manifest as painless enlargement of lymph nodes or as 'glandular fever' syndromes. Illnesses of this nature may be prolonged but are nearly always self-limiting.

Much more serious disease may result when the organism attacks either an immunodeficient individual or the unborn baby. CNS toxoplasmosis may arise in patients suffering from lymphoreticular malignancy or connective tissue disorders, particularly if they have received corticosteroids or cytotoxics. In such patients meningo-encephalitis or focal neurological signs may be wrongly attributed to the primary disease (Townsend *et al.*, 1978): the heart, skeletal muscles and lungs may also be involved. Rarely, toxoplasmosis can also cause severe systemic disease in previously healthy subjects.

Maternal toxoplasmosis is not often diagnosed during pregnancy but can lead to transplacental infection and, less frequently, to congenital disease in the foetus. The overall likelihood of foetal death or severe congenital abnormality is low but is greatest when a woman becomes infected between the second and sixth month of pregnancy (Desmonts & Couvreur, 1974). Choroido-retinitis presenting later in life usually has its origins in undetected congenital infection.

For many years pyrimethamine and sulphonamides (usually triple sulphonamides, sulphadimidine or sulphadiazine) have been widely used for the treatment of toxoplasmosis. These agents act synergistically against experimental toxoplasmosis in mice, and also in infected tissue culture systems (Eyles & Coleman, 1953; Nguyen, Stadtsbaeder & Horvat, 1977). Although active against trophozoites they have no effect on tissue cysts (Summers, 1953). A once-daily regime of pyrimethamine-sulphonamides has been employed successfully in all forms of toxoplasmosis including CNS infection and disease in the compromised host (Townsend *et al.*, 1975, Ruskin & Remington, 1975). When used for choroido-retinitis systemic corticosteroids are usually added, especially if vision is threatened (O'Connor, 1974). The main disadvantage of this antimicrobial combination is the inhibitory effect of pyrimethamine on human folate metabolism with the subsequent risk of bone marrow depression: and since patients usually have to be treated for at least four weeks a close watch must be kept on the peripheral blood count. In the event of leucopenia (< 1000 neutrophils/mm^3) or a fall in platelets ($< 100{,}000$/mm^3) the drugs must be stopped and intra-muscular folinic acid substituted. Because of this antifolate activity pyrimethamine-sulphonamide combinations are also potentially teratogenic. Nevertheless their use in maternal toxoplasmosis reduces the risk of transplacental infection (Kräubig, 1966).

The macrolide antibiotic spiramycin is a less toxic alternative agent which has been widely used in continental Europe for some twenty years. It is active against experimental toxoplasmosis, reaches high levels in many

tissues including placenta and seems to be devoid of teratogenic effects at the doses employed in human subjects. In a large controlled trial in Paris, repeated 3-week courses of spiramycin were given to women who acquired toxoplasmosis during pregnancy (Desmonts & Couvreur, 1974). The total incidence of transplacental infection was effectively reduced, but protection against congenital *disease* could not be demonstrated. Spiramycin does not readily cross the placental barrier (Garin *et al.*, 1969) so that it may not cure an already infected foetus. Because it does not depress the bone marrow, spiramycin may be valuable for the treatment of acquired toxoplasmosis in the compromised host; it can also justifiably be used for 'glandular fever' syndromes in other patients if constitutional symptoms are unusually severe or prolonged. However, spiramycin is not the drug of choice for choroidoretinitis: pyrimethamine gives better results (Nolan & Rosen, 1968).

While sulphonamides on their own are active against toxoplasmosis, their effectiveness is greatly enhanced if they are used with other agents, and recently attempts have been made to develop new combined regimes of low toxocity. One approach is to give the customary pyrimethamine component, which has a long half-life, on a weekly basis to minimize unwanted effects. Fansidar (Roche products) is a combination of pyrimethamine and sulphadoxine which is used for malaria prophylaxis: once-weekly Fansidar has also been employed, after the first trimester of pregnancy, in an attempt to prevent congenital toxoplasmosis (Barbosa & Ferreira, 1977). Conclusions about the effectiveness of Fansidar in toxoplasmosis must await further clinical trials.

Toxoplasmosis may also come within the therapeutic range of cotrimoxazole. Although trimethoprim alone is ineffective against experimental murine toxoplasmosis its activity is greatly potentiated by the addition of sulphamethoxazole (Grossman, Krahenbuhl & Remington, 1977; Nguyen, Stadtsbaeder & Horvat, 1977). Clinical experience with cotrimoxazole in toxoplasmosis is very limited, although a small controlled study in Sweden has shown evidence of benefit from three months' treatment (Norrby *et al.*, 1975). Cotrimoxazole could be particularly useful in toxoplasmic meningitis since both its components readily enter the CSF when the meninges are inflamed.

Finally, tetracyclines have been used for treatment (Fertig, Selwyn & Tibble, 1977) although their efficacy is disputed (Grossman & Remington, 1977). Both cotrimoxazole and tetracyclines have practical advantages such as low toxicity, widespread use and easy availability: if found to be effective they might well complement or even supersede the older-established agents. Whatever drug is chosen, however, chemotherapy controls rather than eradicates this infection; prevention of recurrent disease depends upon host defences, particularly cell-mediated immunity.

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Automation for sensitivity testing

It is obvious that some form of mechanization might help to bring about a much desired improvement in the standardization of sensitivity testing with antimicrobials. In this context there are now available three machines the MIC 2000 (Dynatech), Autobac (Pfizer) and MS2 (Abbott), each with interesting possibilities. As all are sufficiently expensive to make the microbiologist pause for thought it seems opportune to discuss their potentialities and possible deficiencies.

The MIC 2000 is essentially a mechanical aid to the determination of MIC values. It uses the versatile Microtitre tray into which it can rapidly and accurately dispense solutions of antibacterials. Following inoculation and incubation the result is read by observation of growth with a magnifying mirror. Should MBC values be required, automated subculture into replica plates without added antibacterials may be performed using a multi-point inoculator. The machine is designed for batch use and as such will be of little interest to the laboratory requiring occasional MIC tests. However it does offer considerable convenience to the investigator who has to undertake a large number of such tests. Users praise its capabilities highly and despite some complaints about mechanical unreliability the MIC 2000 merits serious consideration in its rather specialized field.

The Autobac (Praglin, Curtiss, Langhenry & McKie, 1975) and MS2 machines are for the semi- or fully-automated performance of routine sensitivity tests. Both utilize a multi-chambered disposable cuvette cartridge into which the various antibacterials are introduced in the form of elution discs. In the semi-automatic Autobac the cuvettes are incubated in a separate unit from which they must be removed when the operator deems that they are ready for reading by the photo-electric growth detector. Sensitivity or resistance is inferred by comparison of the growth index of the control with that achieved in the test well. A computer interprets results as S, I or R, 11 drugs being tested simultaneously.

The MS2 (Spencer, Stockert, Wilborn & Price, 1977), though similar in concept to Autobac is fully automated. Organisms are inoculated into an upper growth chamber in the cuvette which is inserted into the machine. The culture is later transferred into the test wells when the photo-electric detector system indicates that logarithmic growth rate has been achieved. Thereafter a growth curve is constructed for the control well and each test well by passing information derived from readings made every 5 minutes to a computer. The machine decides whether organisms are S or R by reference to regression lines from the growth curves. Intermediate results are expressed as MIC values.

The working capacity for Autobac is approximately 32 organisms daily. The MS2 equipped with 2 incubator modules has a similar capability which is increased by the possibility of overnight use and minimal operator involvement. At present neither machine is recommended for use with anaerobes or particularly excavating aerobes. Typical analysis time is 3½ h.

Autobac, though little seen in the U.K., has been in routine use in some laboratories in the U.S. and elsewhere for the past three years. Published information (Butler & Gavan, 1977) indicates that overall reproducibility is similar to that of the Bauer-Kirby technique and agreement between the two methods is approximately 91%. Further, the correlation of Autobac or Bauer-Kirby with a third test (ICS agar-dilution) is very similar at 91·1 and 90% respectively. Needless to say these respectable figures conceal a number of interesting descrepancies. Problem organisms include *Enterobacter* spp. staphylococci and enterococci, and drugs such as penicillin, ampicillin and nitrofurantoin often produce discrepant results. Some of these are readily explained. Ampicillin, for example, suffers from poor quality control of the disc content, a fact commented upon by early evaluators and recently confirmed by the writer. Strains of