EDITORIAL

IN VITRO MODELS FOR DRUG EVALUATION

One of the articles in this issue of the journal is on *in vitro* evaluation of benzimidazoles on cystic larvae of three cestode parasite models and the editorial focuses on this topic.

Parasitic diseases constitute a major health problem among human beings, particularly in tropical countries. Common ones include trypanosomiasis, leishmaniasis, schistosomiasis and helminthiasis. For a long time, progress in research and development of suitable antiparasitic drugs has been hampered by lack of suitable *in vivo* and *in vitro* laboratory models. This is in great contrast to the bacterial diseases where such models abound. Thus the safety and efficacy of many anti-parasitic agents at the point of clinical trial is often based on minimum data. The cestodes, like many other parasites such as schistosomes, trypanosomes and leishmania among others undergo several metamorphic stages before reaching the adult stage. This is further compounded by the fact that these parasites are dependent on two or more hosts. In the case of cestodes one of the hosts is man, the other an animal. The five types of cestodes that infect humans are *Taenia saginata* (beef), *T. solium* (pork), *Diphyllobothrium latum* (fish), *D. caninum* (dog), *Hymenolepis nana* (dwarf tapeworm). Larvae are found in animal hosts, while the adults are found in humans. However, there are two species, *Echinococcus granulosus* and *E. multicularis*, where this is reversed such that adult worms infect animals and larvae infect humans giving rise to *Echnicoccosis* or hydatid disease.

The problem is compounded further by the fact that the parasites inhabit different tissues of the host, and for this reason getting the drug to the required site in adequate concentration becomes a major challenge which cannot be predicted from laboratory models. This is certainly true of hydatid disease where surgery rather than chemotherapy is the rule rather than the exception. In the case of *Ascaris lumbricoides* (nematode), the eggs hatch in the intestine, larvae travel through hepatic vassels to the lungs where they develop, then come down the oesophagus to the intestine to complete the cycle. While it is easy for the antihelmintics to act on the adult worm in the intestine, it is not easy to act on the larvae stage in the lungs. Formulation of antihelmintics into suitable dosage forms using suitable vehicles (like DMSO) and adjuvants may improve absorption from the gastrointestinal tract. However, such a vehicle is not absorbed into systemic circulation in significant amounts and therefore is unlikely to influence the distribution of the drug in various body compartments such as liver, lungs and CNS. Other factors such as physicochemical properties of the drug and its metabolites are important determinants.

Recent advances in *in vitro* techniques have made it possible to study actions of drugs on many parasites. Until recently it was generally accepted that parasites which depend wholly on the hosts could only be studied in animal models. The new techniques include immunocytochemistry, *in vitro* culture and scanning electron microscopy. High performance liquid chromatography (HPLC) analysis of vesicle fluids shows how the drugs are taken up by the parasite. Similarly, transmission electron microscopic investigations of parasite tissue show the cell structure changes brought about by the drug.

Despite these advances in investigational techniques our basic knowledge on how these drugs act is still limited. For example we would expect that drugs belonging to a homologous series and which show a common structure would have the same mode of action. Yet literature indicates that the three benzimindazoles, albendazole, mebendazole and thiabendazole act differently. Albendazole and its metabolites albendazole sulfoxide and albendazole suphone inhibit microtubule synthesis thus impairing glucose uptake while thiabendazole inhibits the enzyme fumarate reductase in the Krebs cycle.

In studying the antiparasitic effects of drugs, several factors must be considered and the *in vitro* techniques only serve a limited purpose in predicting possible outcome in both primary and secondary

hosts. Why is it that the cestode worm is never acted upon by the intestinal enzymes/juices in humans yet as soon as it dies, the body digests it in much the same way as it does any other proteins? What is the role of *Taenia solium* excretory/secretory polypeptides? It is also known that onions, pumpkin seeds and garlic weaken the worm so that it is easily dislodged and expelled, yet these can hardly be called anthelmintics. Most of the anthelmintics were discovered through simple observations. Man at the hunter/gatherer stage of development could hardly fail to appreciate the anthelmintic effect of *Myrsine africana* seeds when he/she observed worms in the stool soon after ingesting the seeds. For the naturally occurring plant material often referred to as "generally recognized as safe" (GRAS) the need for *in vitro* tests is less. The need arises when synthetic chemicals have to be screened for anthelmintic effect.

Editor-in-Chief