TRENDS IN THE DEVELOPMENT OF CHEMOTHERAPY FOR PARASITIC DISEASES

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INTRODUCTION

The predominant trend in the chemotherapy of parasitic diseases is a re-emphasis of the need to continue to search for and develop new drugs. The importance of chemotherapy in the management of parasitic diseases is obvious. The need to continue to look for more effective and less toxic drugs is accepted even by those who correctly maintain that control or eradication of these diseases will only result from measures such as vector control, immunization and improvement in public health and sanitation practices.

There are a large number of parasitic diseases and it is not possible to mention them all individually nor is it appropriate to discuss them under the all embracing term "parasitoses". Therefore, attention will be directed first to malaria since this disease still represents the greatest problem among the tropical illnesses and is a significant problem in Southeast Asia. Reference will then be made to amoebiasis which has been estimated to affect up to 10% of the world's population; to schistosomiasis and filariasis which affect over 400 million people; and to the intestinal helminths such as *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm which together affect probably more than 1,400 million people throughout the world.

MALARIA

It is now apparent that the hope firmly held for many years that malaria would be eradicated by programmes involving the elimination of the anopheline mosquito vector has not been realized. Although obvious progress has been made in some areas, the disease has not yet been controlled, let alone eradicated in malarious regions of Africa, South America and Southeast Asia. In fact, malaria is returning in India where it had almost been eliminated several years ago (Bruce-Chwatt, 1974). The World Health Organization (WHO), although continuing to emphasize the absolute necessity for mosquito control, also insists that antimalarial drugs will be of great importance in the management of this disease in the near and even distant future (W.H.O., 1976).

The overall trend is therefore to support research that is directed to the finding of new chemotherapeutic agents, which is made even more necessary by the emerging resistance throughout the world of *P. falciparum* to chloroquine. This problem of chloroquine resistance has increased the intensity of the search for more effective and less toxic agents since quinine is the only drug presently available for serious and complicated cases of chloroquine resistant falciparum malaria. It is also the only parenteral drug readily available in this situation.

The trend in chemotherapy of malaria was therefore away from the use of chloroquine (except in Africa), and instead a complex and often toxic regimen was used. This consisted of quinine three times daily for 10-14 days with pyrimethamine daily for 3 days plus dapsone daily for as long as one month (Sheehy *et al.*, 1967). A much more simple and less toxic regimen of four doses of quinine and a single dose of either a single drug (mefloquine) or a combination product, pyrimethamine with sulfadoxine (Fansidar)

has recently been mentioned as the treatment of choice (Hall, 1976). This regimen has resulted from basic research and clinical studies performed under the direction of the U.S. Army Antimalarial Drug Development Programme.

Other studies have shown that combining an antibiotic, such as tetracycline or clindamycin, with quinine is also effective in treating chloroquine resistant falciparum malaria, but the response is slow and recrudescence occurs (Hall, 1975b).

Several institutes are involved in the synthesis and testing of new anti-malarial compounds, such as the WHO Collaborating Centre in Liverpool, England; a few pharmaceutical companies and the U.S. Army Antimalarial Drug Development Programme at the Walter Reed Army Institute of Research in Washington D.C. The testing of new drugs will be carried out at the clinical facilities of WHO Tropical Diseases Research Centre at Ndola, Zambia, within the framework of the Special Programme for Research and Training in Tropical Diseases; and in many other centres in countries through-out the world. One of the most important and productive field trial centres is in Thailand, namely, the U.S. Army Medical Component of the Armed Forces Research Institute of Medical Sciences (formerly the medical research laboratory of the South East Asia Treaty Organization).

Since the U.S. Army effort is the most ambitious and productive and many of the actual field studies are done in Thailand it is appropriate to describe their programme in more detail.

The U.S. Army Antimalarial Drug Development Programme was organized in 1963 with the aim of developing drugs for the prevention and treatment of malaria due to chloroquine resistant strains of *P. falciparum*. The approach was a comprehensive one which included the screening of all available chemicals from various sources as well as the synthesis of new compounds. With the emergence of chloroquine resistance in Southeast Asia, more specifically in Vietnam, the U.S. Army faced a serious military problem and the Drug Programme received an added impetus. Well over 200,000 compounds have been tested. About 3% were active in primary screening tests and 170 of the most active compounds went on for advanced testing in monkeys. Pre-clinical pharmacological and toxicological studies were performed on 36 selected compounds. Investigational new drug applications were submitted to the U.S. Food and Drug Administration for 27 of these. Thirteen compounds have been or are being studied in clinical trials and several have also undergone field evaluation (Canfield and Rozman, 1974).

The most promising of all these compounds was WR 142,490 or, as it is now called, mefloquine. The history of this drug is interesting. Over 30 years ago a large number of 4-quinolinemethanols were investigated for their antimalarial activity. The agent with the greatest activity, SN 10,275, was tested in volunteers. Phototoxic side-effects prevented its general use although it was an effective blood schizonticidal agent with a long duration of activity. A derivative of this compound, WR 30,090, was recently found to be highly effective in man against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*. This 4-quinolinemethanol showed only slight evidence of phototoxicity but demonstrated a short duration of action. Mefloquine hydrochloride (WR 142,490) is an analogue of SN 10,275 and WR 30,090. Preclinical studies revealed that this drug was more effective than WR 30,090, had the long duration of action characteristic of SN 10,275 and showed no evidence of phototoxicity (Trenholme *et al.*, 1975).

Extensive clinical testing of the drug under field conditions has been done and it has been concluded by Hall (1977) that mefloquine in association with quinine is the most effective treatment for patients with chloroquine-resistant falciparum malaria, including those with severe or complicated disease. Mefloquine has also been shown to be effective when used alone as a single-dose treatment of mild falciparum malaria; moreover, it has a prophylactic suppressant action against *P. vivax* and *P. falciparum*, but relapse occurs with *P. vivax* several weeks after cessation of treatment (Clyde *et al.*, 1976). Unfortunately, the drug is not commercially available. A parenteral form of mefloquine would be a very useful alternative to quinine but local intolerance to the injection is delaying development of this formulation at the moment.

A few pharmaceutical companies have been involved in the search for new antimalarials and the combination of pyrimethamine with sulfadoxine (Fansidar) is now widely accepted and used for the treatment and prophylaxis of falciparum malaria. In fact, the combination of this product with quinine maybe the best available treatment for moderate and severe chloroquine resistant falciparum malaria presently available (Hall *et al.*, 1975 a). Fansidar is also recommended for prophylaxis (WHO, 1976) and is an advantage over presently available drugs since it can be given either weekly, every two weeks or even monthly.

WHO (1976) has recommended that particualr attention should be given to the development of long-acting formulations providing optimum bio-availability of the drugs. This therefore is another trend and a promising compound of this sort, cycloguanil embonate, has been developed by Parke-Davis.

As regards resistance, the trend now is to use more than one drug at a time in the hope of preventing the development of resistance to single agents (Peters, 1975). Hence there was the initial concurrent use of three drugs, quinine, pyrimethamine and dapsone or a sulphonamide (Sheehy *et al.*, 1967). This combination was also used because it was more effective than any of the drugs used alone in preventing recrudescence. This complex approach has been much simplified by the sequential use of quinine with the fixed drug combination of pyrimethamine and sulfadoxine.

The combination of pyrimethamine with the long acting sulphonamide, sulfadoxine, is effective when given alone as a single-dose treatment, especially in mild cases, but because there are some cases of recrudescence and concern about resistance developing, it is recommended that quinine be given as well.

There is a parenteral form of the pyrimethamine sulfadoxine combination available and studies have shown this to be of value in severe malaria, including the cerebral form, but comparative studies with quinine have not been done. However, Fansidar, is clearly an important and useful alternative to parenteral quinine.

Although the major emphasis and trend has been to develop drugs against *P. falciparum* there has been a recent shift of emphasis to the development of drugs with exoerythrocytic activity, since the only one available at present is primaquine. A compound, WR 171,952, from the U.S. Army Antimalarial Drug Programme, found to be effective in animal studies, was not successful in human volunteers infected with *P. vivax* (Canfield and Rozman, 1974). New drugs with exoerythrocytic activity in animal models are being discovered but it will be several years before clinical trials in humans will be completed.

AMOEBIASIS

This parasitic infection is common in many parts of the world and although the intestinal

form appears to be a less serious disease in Southeast Asia than in Africa, it causes a significant amount of morbidity.

The trend in chemotherapy for amoebiasis has been away from the complicated use of a combination of several drugs given at the same time. This treatment approach was not an attempt at preventing the development of resistance, as in the case of malaria, but was necessary because of the varying degrees of effectiveness of the available drugs at the sites where the amoebae may be located. That is, in the bowel lumen, the wall of the bowel or in the liver. The development of new drugs that are highly active at all these sites is simplifying treatment and changing the belief that complete cure of amoebiasis requires several drugs and often repeated courses of treatment.

Previously it was necessary to think of drugs as belonging to different categories, such as those that act on amoebae in the bowel lumen (direct-acting or luminal), those acting on amoebae in the lumen and in the bowel wall (indirect acting), and those that act on the amoebae in the liver and the bowel wall (tissue amoebicides). Direct-acting or luminal amoebicides include the hydroxyquinolines and the arsenical derivatives. Indirect-acting drugs comprise the tetracycline group of antibiotics; while tissue amoebicides include emetine and dehydroemetine and chloroquine which is effective only on amoebae in the liver. In the past, therefore, for liver and intestinal involvement it was necessary to give emetine and chloroquine for the liver amoebae, diiodohydroxyquinoline for the luminal amoebae and tetracycline for amoebae in the bowel wall and lumen.

New drugs effective at all sites are now available and the present trend in the chemotherapy of amoebiasis is to use a single drug for a very short period of time. Metronidazole (Flagyl), a nitroimidazole derivative was first successfully used in the mid 1960s (Powell *et al.*, 1966) and until recently was the drug of choice if given for a period of 5-10 days. Ornidazole (Tiberal) and tinidazole (Fasigyn) are newer nitroimidazole derivatives and studies have shown that ornidazole, for example, given only for 3 days is effective in treating intestinal amoebiasis (Lasserre, 1978; Adjung *et al.*, 1978). For amoebic liver abscess the single dose or single day therapy first shown to be effective with metronidazole (Aswapokee *et al.*, 1974; Bunnag *et al.*, 1975), is also true with ornidazole, but at a lower dosage of 2 gm instead of 2.4 gm (Lasserre, 1978). Concurrent aspiration of the abscess is recommended.

In the Western world where metronidazole is mainly used for the treatment of trichomoniasis, a non-serious, non-fatal disease, the recent concern about the carcinogenicity of metronidazole in rodents and its mutagenicity in bacteria has led to a restriction of its use. In amoebiasis it has been suggested that the drug be reserved for the moderate to seriously ill patient and that diiodohydroxyquin with paromomycin or tetracycline be used for the asymptomatic or mild case (Medical Letter, 1976). In those parts of the world where amoebiasis is a serious problem it becomes a matter of balancing priorities and risks and most people treating the disease would not hesitiate to use the nitroimidazole derivatives in the management of all cases of amoebiasis.

SCHISTOSOMIASIS

Schistosomiasis, like malaria, presents enormous problems to be overcome in order to bring about its eradication. While intensive efforts at vector control must be continued there is also an obvious need to find better drugs to treat patients who have the disease. The trend in chemotherapy is to find more effective and less toxic drugs which can

be used for individual and mass treatment. There is also a current trend to use drugs prophylactically since re-infestation is frequent in areas where the disease is prevalent and transmission is high. The development of new schistosomicidal drugs has been slow due to the marked interspecies variation in susceptibility to infection and to the poor correlation between *in vitro* and *in vivo* tests (McMahon, 1976).

Schistosoma haematobium

A new drug, metrifonate (Bilarcil) an organophosphorous compound, is safe and effective in treating infections with *S. haematobium* but is ineffective against *S. mansoni*. When given as a single, spaced-dose oral medication (every two weeks) it has also been found in initial studies in children to be an effective prophylactic drug since it protected them against *S. haematobium* infection (Jewsbury and Cooke, 1976).

The treatment of *S. haematobium* is also successful with niridazole (Ambilhar) which acts against *S. mansoni* and *S. japonicum* as well, but less effectively. This drug given in a low dose may inhibit egg production thereby limiting pathological changes and transmission while maintaining immunity. If mass treatment is given every 3 or 4 years to the population affected transmission of the disease may cease (Roux *et al.*, 1975).

Schistosoma mansoni

The recent drug of choice for *S. mansoni* was stibophen (Fuadin) but as with other antimony agents such as antimony potassium tartrate, it must be given parenterally in a complicated schedule for several weeks. The trend in chemotherapy therefore, is to use a new drug, oxamniquine (Mansil) a hydroxytetrahydroquinoline derivative. This drug when given as a single oral dose treatment has fewer side-effects than when given intramuscularly (Katz *et al.*, 1977).

Schistosoma japonicum

The antimonial drugs given parenterally are effective although severe side-effects and the parenteral mode of administration restrict these drugs to individual treatment. Niridazole can be used for *S. japonicum*, especially for children since the severe side-effects of this drug are less frequent in patients under 14 years of age (Blas, 1978), and its administration is less complicated than that of the antimony compounds.

An isoquinoline-pyrazoline derivative, praziquantel (Embay) is presently undergoing clinical trials and appears to be effective against all three schistosomes. Roche has two new compounds, Ro 11-0761 and Ro 11-3128, which are being tested in phase I clinical trials in schistosomiasis. However, it will be several years before these drugs could be generally available.

With the older more standard drugs there are certain difficulties, mainly related to side-effects, but a recent long-term follow-up (13 years) of antimony-treated *S. mansoni* infected patients showed that 23% (7 of 30) still had active infections (Hedman and Bengtsson, 1977). Whether this will also be a problem with the newer drugs is impossible to say at this stage.

Hycanthone has been shown to be a useful drug and in a single intramuscular dose is a convenient treatment for mass campaigns against *S. mansoni* if the dose is kept low since large doses cause toxicity and possible liver damage (Cook *et al.*, 1976). But the known mutagenicity of hycanthone in bacterial tests and in cytogenetic assays is of concern, especially when a metabolite with three times the mutagenic activity of hycanthone has been found at the site of an intramuscular injection eight months later (Bueding, 1975).

FILARIASIS

There is little to report concerning trends in the chemotherapy of filariasis. The standard drug diethylcarbamazine (Hetrazan) is still the best one available although it is expensive, not completely effective and has troublesome side-effects. Early clinical trials with levamisole are encouraging (Moreau *et al.*, 1975) but late relapse occurs with short treatment courses (Mak, pers. comm.). The mode of action of levamisole is a direct effect against the microfilariae and adult worms, but whether it works also through its T-cell immunopotentiating properties is not yet known.

A new compound Radanil, a nitroimidazole derivative, is effective in Chagas disease (*Trypanosoma cruzi*). It has also shown *in vitro* micro and macro filaricidal activity. At the moment this drug is being tested in animal models of filariasis at the Institute of Medical Research in Kuala Lumpur. If the results are encouraging, clinical studies in patients will be carried out in Malaysia and Indonesia.

Two trends, however, using diethylcarbamazine are of interest. A recent study concluded that mass treatment of the population in highly endemic areas is better than selective treatment of only those with microfilaraemia (Partono and Borahima, 1978). This is in keeping with another study that showed in a closed population that the use of common salt medicated with diethylcarbamazine resulted in clinical cure or improvement in patients with filariasis and in the control of the disease in the rest of the population. This was demonstrated by a significant reduction in the microfilarial rate and microfilarial density in patients and a reduction in the infection rate and larval density in the mosquito vector (Fan *et al.*, 1978).

HELMINTHIASIS

Parasitic worms or helminths are estimated to affect a very large number of people around the world. This number is probably increasing rather than decreasing as a result of the increased agricultural use of land and artificial irrigation.

Effective drugs are available that will bring about a cure in most instances. Considerable advances have been made in the last few years in discovering drugs that are an improvement on older remedies both in selectivity of action and in relative lack of toxicity. The trend has been away from drugs such as aspidium, hexylresorcinol and gentian violet, which are now obsolete and also away from more recent discoveries such as pirvinium pamoate and tetrachlorethylene in favour of more broad-spectrum activity drugs such as pyrantel pamoate (Combantrin) and mebendazole (Vermox) (Hutchison *et al.*, 1975). Although tetrachlorethylene is still considered an effective low-cost treatment for hookworm (Senewiratne *et al.*, 1975).

Pyrantel is a depolarizing neuromuscular blocking agent which causes spastic paralysis of the worm. It is effective against *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma duodenale* and *Necator americanus*. Mebendazole acts by irreversibly inhibiting glucose uptake by the nematode. It is effective against the above and also *Trichuris trichiura*, and has few side effects (Davis, 1973).

A methyl-thienyl analogue of pyrantel, morantel, has been introduced as a veterinary nematocide with claims of greater tolerability. Since pyrantel pamoate was first introduced as a veterinary drug several years before it was studied in man it is probable that morantel will also undergo human trials.

FUTURE TRENDS

Trends in the chemotherapy of parasitic diseases which are as yet little explored, include the use of compounds to stimulate the cellular and humoral defence mechanisms of

the human host. Also under consideration is the use of antibodies as pure substances; but the "purification" of large protein molecules, which is necessary to reduce further antigen-antibody production and consequent side-effects, is extremely difficult.

Since chemical synthesis of new compounds is becoming increasingly more difficult and more expensive and the obtaining of useful products from plants has already been explored, the search for new chemotherapeutic agents has turned to the sea. The Roche Institute of Marine Pharmacology in Australia is looking at substances isolated from living organisms found in the ocean. A compound kainic acid obtained from a red alga, digenea simplex, has shown anthelminthic activity and this may be the beginning of a new era in the never-ending search for improved drugs in man's struggle against disease.

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