Review Article

Anthelmintic agents: some recent developments and their clinical application*

G.C. Cook

Department of Clinical Sciences, Hospital for Tropical Diseases, St Pancras Way, London, NW1 0PE, UK

Introduction

Until the 1960s, the chemotherapy of human intestinal and systemic helminthiasis was extremely unsatisfactory;¹ piperazine compounds, bephenium hydroxynaphthoate and pyrantel embonate were, for example, widely used for the former, and diethylcarbamazine (DEC), niridazole, and bithionol for the latter. Table I summarizes some important agents which have recently become available. The first of the benzimidazole compounds, thiabendazole (which had formerly been widely used in veterinary medicine and which has many undesirable side effects) was introduced into clinical medicine in the early 1960s; others soon followed, and the most recently introduced is albendazole. This group of compounds is of value in the management of many intestinal and systemic nematode infections.^{2–4} Praziquantel (introduced during the 1970s) has proved of immense value in many cestode and trematode (flake) infections; numerically it has been most extensively used in the human schistosomiasis.^{2,3,5,6} Ivermectin, which had also been widely used in veterinary medicine first became available in clinical medicine in the early 1980s,^{7,8} as well as being effective in a wide range of intestinal nematode infections it has proved to be a valuable and safe microfilaricidal agent in onchocerciasis (see below).

In addition to these 3 agents, oxamniquine and metrifonate have been introduced into clinical medicine for *Schistosoma mansoni* and *S. haematobium* infections, respectively (see below). They have the advantage that in most countries they are

cheaper than praziquantel; however, both are species specific and the latter compound is often cheaper to administer, overall, in areas where mixed *S. mansoni* and *S. haematobium* infections are common.

The benzimidazoles

Table II summarizes the helminthiasis which are susceptible to this important group of compounds. Clinical application has mostly been in the context of intestinal, and to a lesser extent systemic, nematode infections;⁴ recently, use in some systemic cestode infections has also received a great deal of attention (see below). Success rates of up to 100% have been documented in small-intestinal (hookworm, *Ascaris lumbricoides*, and *Strongyloides stercoralis*) and colorectal (*Trichuris trichiura* and *Enterobius vermicularis*) infections.^{9–11} A high degree of efficacy has also been reported in *Capillaria philippinensis* infection.^{12,13} Two recent outbreaks of trichinellosis (trichinosis) – a systemic nematode infection – in France, which were caused by ingestion of infected horse-meat, apparently responded satisfactorily to albendazole.¹⁴ Recent unpublished evidence from Thailand indicates a good response in *Gnathostoma spinigerum* infection.⁴ While cutaneous larva migrans is rapidly cured with albendazole chemotherapy, visceral larva migrans responds far less favourably (see below).

The usual daily dose(s) of the benzimidazole compounds in the intestinal nematodiasis is:⁴ mebendazole 100 mg twice daily (3–4 days), albendazole 400 mg daily (1–3 days), and thiabendazole 1.5 g twice daily for 3 days; longer courses have been used for *C. philippinensis* infection. Significantly higher doses (and longer regimens) are recommended for systemic nematodiasis, and this applies especially to mebendazole – which is poorly absorbed from the small-intestine.

*Based on a paper read at a Tripartite meeting on 'Tropical diseases, immunity and chemotherapy' organised by The Royal Society of Tropical Medicine & Hygiene, the Society for Drug Research, and the Society of Pharmaceutical Medicine, held on 31st May 1990 at the Royal Postgraduate Medical School, London
Correspondence: G.C. Cook, M.D., D.Sc., F.R.C.P., F.R.A.C.P., F.L.S.

Table I Anthelmintic agents (including cost in the UK) introduced into clinical medicine in the 1960s and after

	Chemotherapeutic agent	Manufacturer	Cost of treatment in the UK
Benzimidazoles	Thiabendazole	(MSD)	9 × 100 mg £0-78 (+ VAT)
	Mebendazole	(Janssen)	6 × 100 mg £1-57 (+ VAT)
	Albendazole*	(SKB)	-
	Praziquantel	(Bayer)	6 × 100 mg £11-75 (+ VAT)
	Ivermectin*	(MSD)	-
	Oxamniquine	(Pfizer)	8 × 250 mg £4-85 (+ VAT)
	Metriphosphate*	(Bayer)	-

*Named patient basis only; not readily available in the UK.

Table II Some human helminthic infections which are susceptible to one or more of the benzimidazole compounds

Helminth	Thiabendazole	Mebendazole	Albendazole
Intestinal nematodes:			
Small-intestinal	hookworm	±	+
	<i>Ascaris lumbricoides</i>	+	+
	<i>Strongyloides stercoralis</i>	+	+
	<i>Capillaria philippinensis</i>	+	+
	<i>Angiostrongylus costaricensis</i>	±	±
Colorectal	<i>Trichuris trichiura</i>	±	+
	<i>Enterobius vermicularis</i>	±	+
Systemic nematodes:			
	<i>Trichinella spiralis</i>	+	±
	<i>Gnathostoma spinigerum</i>	±	±
	<i>Angiostrongylus cantonensis</i>	±	±
	cutaneous larva migrans	+	±
	visceral larva migrans	±	±
	<i>Onchocerca volvulus</i>	±	±
Systemic cestodes:			
	<i>Echinococcus granulosus</i>	±	+
	<i>E. multilocularis</i>	±	+
	neurocysticercosis (<i>Taenia solium</i>)	-	+

+, Good evidence exists for efficacy; -, present evidence indicates that this agent is ineffective.

Praziquantel

Table III summarizes those helminthiasis which are susceptible to this compound. Prior to its introduction into clinical medicine in the 1970s, the management of human cestode and trematode infections was difficult. Intestinal cestodes - *Taenia solium*, *T. saginata*, *Diphyllobothrium latum*, *Dipylidium caninum*, and *Hymenolepis nana* - all respond to a single dose of praziquantel 10-25 mg/kg.^{6,15,16} However, intestinal trematode infections

require a higher dose-regimen; in the case of *Fasciolopsis buski* and *Heterophyes heterophyes* 25 mg/kg three times on a single day is usually effective.⁶ This compound also gives satisfactory results in tissue trematode infections: *Clonorchis sinensis*, *Opisthorchis* sp.,^{17,18} and *Paragonimus* sp.;¹⁹ a satisfactory dose-regimen consists of 25 mg/kg three times daily for 1-2 days.⁶ This is in fact, the first satisfactory chemotherapeutic strategy in pulmonary paragonimiasis,^{19,20} a parasitosis which is usually caused by ingestion of *P. westermani*.

Table III Some human helminthic infections which are susceptible to praziquantel

Intestinal cestodes:	<i>Taenia solium</i> <i>T. saginata</i> <i>Diphyllobothrium latum</i> <i>Dipylidium caninum</i> <i>Hymenolepis nana</i>
Systemic cestodes:	<i>Taenia solium</i> (cysticercosis)
Systemic trematodes:	<i>Schistosoma mansoni</i> <i>S. haematobium</i> <i>S. japonicum</i> <i>S. mekongi</i> <i>S. intercalatum</i>
Biliary and pulmonary trematodes:	<i>Clonorchis sinensis</i> <i>Opisthorchis</i> sp. <i>Paragonimus</i> sp.
Intestinal trematodes:	<i>Heterophyes heterophyes</i> <i>Fasciolopsis buski</i>

infected shell-fish in south-east Asia.

The major impact of praziquantel chemotherapy has, however, undoubtedly been related to schistosomiasis,²¹ a parasitosis which is becoming increasingly common in the 'Third-World' countries of Africa, southern America and the Middle-east; one estimate puts the number of infected individuals at 200 million, of whom 100 million suffer from hepatosplenic disease. Numerous reports have now documented impressive results in *S. haematobium*,^{22,23} *S. mansoni*^{24–26} and *S. japonicum*²⁷ infections. Of all the schistosomicides which have been produced to date, it offers the most attractive combination of efficacy, broad-spectrum activity and low toxicity. Unlike the formerly used agents, there is now good evidence that praziquantel reduces hepatosplenomegaly and portal hypertension in schistosomiasis;²⁸ ultrasonographic studies also indicate a reduction in Symmer's pipe-stem fibrosis.²⁹ Although an improvement in the bladder-lesions of *S. haematobium* infection has been documented, praziquantel does not, unfortunately, reverse the obstructive features associated with this infection – hydroureter and hydronephrosis.³⁰ Recommended dose regimens vary for the different species; in *S. haematobium* and *S. intercalatum* infections 40 mg/kg as a single dose is usually effective, whereas there is good evidence with *S. mansoni*, *S. japonicum* and *S. mekongi* infections that 20 mg three times daily during a single day gives superior results.⁶ Side effects associated with praziquantel administration are almost always mild;³¹ fits have been documented rarely.³²

Ivermectin

The slow recognition of the value of ivermectin in clinical medicine, which followed extensive use in

veterinary medicine over many years represents an excellent example of the low level of cooperation between these two major disciplines, and a lack of extrapolation in application of chemotherapeutic regimens from animals to man. Following its introduction in 1983,⁷ it was rapidly shown to be active against the intestinal nematode infections.^{33,34} However, a far more important observation was that *Onchocerca volvulus* microfilariae are also highly susceptible to its action; when administered at a dose of 100–200 µg/kg it exerts a microfilaricidal action which lasts for 6–12 months.^{35–41} Annual re-treatment must be provided, however, until the adult worms are dead. Furthermore, the severe side effects – manifested in both anterior and posterior chambers of the eye – which were associated with the formerly used compound DEC (2–3 mg/kg three times daily for 21 days) are very unusual.^{42–47} Those reactions which have been reported are of minor importance; the most common is a temporary aggravation of pruritus and rash. (When macrofilaricidal activity is required, suramin is still used but has potentially serious side effects.)

Oxamniquine and metrifonate

The advantage of these two agents over praziquantel is one of cost (Table I). Many studies have compared the efficacy of oxamniquine (a quinolone compound) with praziquantel in *S. mansoni* infection; most document comparable cure-rates and similar rates of reduction in the faecal egg-excretion.^{48–51} The optimal dose-regimen varies with the geographical region in which the *S. mansoni* infection was acquired. Rarely oxamniquine produces fever and/or epileptic fits. A significant problem has emerged, however – in Kenya, Liberia and Brazil, there is evidence of

oxamniquine-resistant *S. mansoni*. Evidence that metrifonate (an organophosphorous compound) produces comparable cure-rates, and reduction in urinary *S. haematobium* egg-excretion when compared with praziquantel has also been produced.⁵² Because it reduces the plasma cholinesterase concentration it should be used with caution in individuals who are likely to be frequently exposed to organophosphorous insecticides.

Some outstanding problems for the 1990s

Table IV summarizes some of the human helminthiases for which there is as yet no ideal chemotherapeutic agent, or regimen.

Systemic nematode infections

Unfortunately there are few published reports on the use of ivermectin in the human filariases apart from onchocerciasis (see above). Encouraging results have, however, been documented (using dose-regimens similar to those used for *O. volvulus* infection) in *Loa loa* infection in Gabon;⁵³ unfortunately, other studies have not confirmed these observations.³ Mebendazole has been used but with very limited success in loaiasis.⁵⁴ Therefore, DEC is still widely used as a microfilaricide. As with onchocerciasis there is no satisfactory macrofilaricide. There are no published reports of the use of ivermectin in the lymphatic filariases; apart from DEC, metrifonate 10–15 mg/kg administered at 14 day intervals, is the only agent which has been shown to produce a significant reduction in the peripheral blood microfilarial concentration. Although there is now some evidence that DEC (and possibly metrifonate also) has limited properties as a macrofilaricidal agent; this requires further investigation. In dracontiasis (guinea-worm disease) a satisfactory chemotherapeutic agent simply does not exist; this fact is reflected in the numerous regimens which have been used – of which none is of proven

efficacy. These include: metronidazole (400 mg daily for 10–20 days), niridazole (25 mg/kg daily for 10 days), thiabendazole (25 mg/kg daily for 3 days), and mebendazole (300–800 mg daily for 6 days).³

Toxocara canis (and *T. cati*) infection is important in childhood; visceral larva migrans and more importantly ocular larva migrans produce significant morbidity, including blindness. The infection(s) is conveyed by dog (and cat) faeces; this is accidentally ingested whilst, for example, playing in a public recreation ground.⁵⁵ Recently, a clinical trial comparing albendazole with thiabendazole produced evidence that the former agent (10 mg/kg daily for 5 days) is of value in toxocariasis;⁵⁶ however, confirmatory evidence is required. Other regimens which remain in use are: DEC (as for filariasis), thiabendazole (25 mg/kg twice daily for at least 5 days), and fenbendazole (250 mg twice daily for 10 days).

A good deal of evidence has recently been accumulated indicating that albendazole is at least as effective as thiabendazole against intestinal *S. stercoralis* infection (see above).^{4,57} However, its use in the 'hyperinfection syndrome' (which is usually associated with immunosuppression)³ seems less satisfactory. This syndrome consists of widespread dissemination of larvae throughout most, or all, organs; severe dyspnoea caused by pulmonary infiltration, and paralytic ileus are common accompaniments. In addition, the migrating larvae transfer enterobacteriaceae (from the caecum and colon) to blood and central nervous system and this results in a subsequent bacteraemia and meningitis – the cerebrospinal fluid may in fact contain both *S. stercoralis* larvae and coliform bacteria. Unless satisfactory chemotherapy (which should include a suitable antibiotic) is immediately initiated as soon as a diagnosis is made, death ensues. The most effective of the benzimidazole compounds is probably cambendazole;^{58,59} however, this agent has never been officially released for human use. Thiabendazole (25 mg/kg twice daily for 15 days) is of proven value; albendazole (400 mg daily for 15 days) has been studied to a far lesser extent. Ivermectin³⁴ and cyclosporin A have not been adequately evaluated.

Some of the other human nematode infections also remain difficult to treat. Very few data exist on *Angiostrongylus costaricensis* and *A. cantonensis* (limited evidence suggests that thiabendazole is at least partly effective), and *Anisakis* sp. infections for example; with the latter infection (which is acquired by ingestion of raw or undercooked fish – sushi and sashimi – and is common in Japan, and can be contracted in fish-bars in the USA and Europe), there is no satisfactory published evidence on the efficacy of any anthelmintic agent.

Table IV Some outstanding unsolved clinical problems in the 1990s

Nematodes:	The filariases Toxocariasis Strongyloidiasis Angiostrongyliasis Anisakiasis
Cestodes:	Hydatidosis Neurocysticercosis Coenuriasis
Trematodes:	Fascioliasis

Systemic cestode infections

Although major advances have been made in the chemotherapy of hydatidosis (caused by *Echinococcus granulosus* and *E. multilocularis*) and neurocysticercosis (which results from a *T. solium* infection), ideal chemotherapeutic agents have not yet emerged. Coenuriasis is of far less importance numerically, but is clinically similar to neurocysticercosis; here too, treatment remains unsatisfactory.

Hydatid disease involves the liver in 60% of cases, the lungs in 25% and other organs in 15%; in approximately 80% of cases infection consists of a solitary-cyst. *In vitro* evidence has clearly demonstrated cyst penetration and protoscolicidal activity of albendazole (sulphoxide) in both *E. granulosus* and *E. multilocularis* infections.^{60,61} Problems in assessing therapeutic efficacy *in vivo* include difficulty in: (i) assessing cyst-viability before chemotherapy, (ii) assessment of cure,^{3,62} and (iii) comparison of small series^{63,64} with different organ involvement. Recently, Horton⁶⁵ has reviewed the results of albendazole chemotherapy in 253 cases of *E. granulosus* and 35 of *E. multilocularis* infection; these patients received 10–15 mg/kg daily for 30 days, and this 'cycle' was repeated after 14–15 days at least 4 times. Whereas 72 of the 253 with *E. granulosus* infection were subsequently considered cured, 46 were unchanged, and 6 became worse; of the 35 with an *E. multilocularis* infection, 2 were cured, 25 were unchanged and 4 became worse. While these results give room for optimism, they provide no grounds for complacency. When surgery is required, pre-operative albendazole chemotherapy (for one month) kills most protoscolices and probably renders the risk of recurrence significantly less.^{4,66} Recently, praziquantel (given at high dose) has also been shown to possess antiscolicidal action *in vitro*,^{61,67,68} this compound has been used alone,⁶⁹ in conjunction with albendazole, and also in an intermittent (sequential) regimen with the latter compound, but there are as yet no published results of controlled trials. It seems likely overall, however, that praziquantel + albendazole will prove to be superior to either of those agents when used alone. (While an *in vitro* study has suggested a superior effect when a combination regimen is used,⁷⁰ this was not borne out by an experimental *in vivo* study⁷¹.)

Neurocysticercosis, like hydatidosis, was until recently untreatable medically; surgery offered the only approach in management. Praziquantel has been widely used with considerable success in neurocysticercosis during the last decade.^{3,72,73} It is important, however, to give a corticosteroid 'cover' to prevent the 'central nervous system reaction syndrome' (which results from cyst-death); this complication of chemotherapy causes significant

morbidity⁷² and occasional mortality. The usual dose-regimen consists of 50 mg/kg daily for 15 days,³ and long-term follow-up studies have yielded encouraging results.⁷⁴ However, not all cases respond well to praziquantel, and surgery is still necessary in some cases: (i) intraventricular cysts, (ii) chiasmatic cysts, (iii) spinal cysts, and (iv) when chemotherapy has failed. Albendazole has also been used in neurocysticercosis (15 mg/kg daily for 30 days), and has been claimed by some investigators to be more effective than praziquantel,^{75,76} however, comparative clinical trials suggest similar success-rates using the two compounds.⁷⁷ (Recently, a higher dose regimen, the safety of which is untested: 20–30 mg/kg has been used successfully). Metrifonate (7.5 mg/kg daily for 5 days) has also been used to good effect.³ Coenuriasis – which is caused by *T. multiceps* – is an intestinal infection of various carnivores, especially dogs; this cestode occasionally produces human disease. Praziquantel has been claimed to be effective; support for this is limited however, and comes from the successful treatment of this infection in a spectacled langur.⁷⁸

Systemic trematode infections

Overall, praziquantel has proved of great value in intestinal and systemic trematode infections (see above); however *Fasciola hepatica* responds poorly to this agent.^{79,80} The benzimidazole compound, triclabendazole (at a dose of 10 mg/kg) has recently been used successfully;⁸¹ this observation requires confirmation.

Conclusions

The last 2–3 decades have seen significant advances in the management of human helminthiasis. The benzimidazoles, oxamniquine and metrifonate are sold at reasonable cost, and, with the exception of the poorest Third-World countries, are now widely available. Praziquantel remains a relatively expensive chemotherapeutic agent in most (but not all) countries. Albendazole, ivermectin, and metrifonate are available but only on a named-patient basis in the UK (Table I). Despite these major advances, there are, however, several nematode, cestode and trematode infections for which safe and effective chemotherapy is still required; meanwhile the older agents (and also surgery) must still be employed.

An ideal broad-spectrum anthelmintic remains a long way off. Such a compound would be: (i) effective against *all* intestinal and systemic helminths, (ii) 100% effective when given as a single-dose, (iii) safe in pregnancy and infancy as well as in

healthy adults, (iv) stable at high (and low) ambient temperatures, and (v) low in cost.

There is, therefore, no room whatsoever for

complacency in the chemotherapy of human helminthiasis in the years ahead.

References

- Janssens, P.G. Chemotherapy of gastrointestinal nematodiasis in man. In: Vanden Bossche, H., Thienpont, D., Janssens, P.G. (eds) *Chemotherapy of Gastrointestinal Helminths*. Springer-Verlag, Berlin, Heidelberg, 1985, pp. 183–406.
- Goldsmith, R.S. Recent advances in the treatment of helminthic infections: ivermectin, albendazole, and praziquantel. In: Leech, J.H., Sande, M.A., Root, R.K. (eds) *Parasitic Infections*. Churchill Livingstone, New York, Edinburgh, 1988, pp. 327–347.
- Cook, G.C. *Parasitic Disease in Clinical Practice*. Springer-Verlag, London, Berlin, 1990, p. 272.
- Cook, G.C. Use of benzimidazole chemotherapy in human helminthiasis: indications and efficacy. *Parasitol Today* 1990, 6: 133–136.
- Mahmoud, A.A.F. Praziquantel for the treatment of helminthic infections. *Adv Intern Med* 1987, 32: 193–206.
- King, C.H. & Mahmoud, A.A.F. Drugs five years later: praziquantel. *Ann Intern Med* 1989, 110: 290–296.
- Campbell, W.C., Fisher, M.H., Stapley, E.O., Albers-Schönberg, G. & Jacob, T.A. Ivermectin: a potent new antiparasitic agent. *Science* 1983, 221: 823–828.
- Campbell, W.C. Ivermectin: an update. *Parasitol Today* 1985, 1: 10–16.
- Campbell, W.C. The chemotherapy of parasitic infections. *J Parasitol* 1986, 72: 45–61.
- Cook, G.C. The clinical significance of gastrointestinal helminths – a review. *Trans R Soc Trop Med Hyg* 1986, 80: 675–685.
- Cook, G.C. Parasitic infections of the gastrointestinal tract: a worldwide clinical problem. *Curr Opinion Gastroenterol* 1989, 5: 126–139.
- Youssef, F.G., Mikhail, E.M. & Mansour, N.S. Intestinal capillariasis in Egypt: a case report. *Am J Trop Med Hyg* 1989, 40: 195–196.
- Cross, J.H. Intestinal capillariasis. *Parasitol Today* 1990, 6: 26–28.
- Fourestié, V., Bounoux, M.E., Ancelle, T. et al. Randomized trial of albendazole versus tiabendazole plus flubendazole during an outbreak of human trichinellosis. *Parasitol Res* 1988, 75: 36–41.
- Campos, R., Bressan, M.C.R.V. & Evangelista, M.G.B.F. Activity of praziquantel against *Hymenolepis nana*, at different development stages, in experimentally infected mice. *Rev Inst Med Trop São Paulo* 1984, 26: 334–340.
- Fan, P.C., Chung, W.C., Chan, C.H., Chen, Y.A., Cheng, F.Y. & Hsu, M.C. Studies on taeniasis in Taiwan. V. Field trial on evaluation of therapeutic efficacy of mebendazole and praziquantel against taeniasis. *Southeast Asian J Trop Med Publ Hlth* 1986, 17: 82–90.
- Jong, E.C., Wasserheit, J.N., Johnson, R.J. et al. Praziquantel for the treatment of *Clonorchis*/*Opisthorchis* infections: report of a double-blind, placebo-controlled trial. *J Infect Dis* 1985, 152: 637–640.
- Pungpak, S., Sornmani, S., Suntharasamai, P. & Vivatanasesth, P. Ultrasonographic study of the biliary system in opisthorchiasis patients after treatment with praziquantel. *Southeast Asian J Trop Med Publ Hlth* 1989, 20: 157–162.
- Udonsi, J.K. Clinical field trials of praziquantel in pulmonary paragonimiasis due to *Paragonimus uterobilateralis* in endemic populations of the Igwu Basin, Nigeria. *Trop Med Parasitol* 1989, 40: 65–68.
- Johnson, R.J., Jong, E.C., Dunning, S.B., Carberry, W.L. & Minshew, B.H. Paragonimiasis: diagnosis and the use of praziquantel in treatment. *Rev Infect Dis* 1985, 7: 200–206.
- Davis, A. Recent advances in schistosomiasis. *Q J Med* 1986, 58: 95–110.
- Mott, K.E., Dixon, H., Osei-Tutu, E., England, E.C. & Davis, A. Effect of praziquantel on hematuria and proteinuria in urinary schistosomiasis. *Am J Trop Med Hyg* 1985, 34: 1119–1126.
- King, C.H., Wiper, D.W., Stigter, K.V. de et al. Dose-finding study for praziquantel therapy of *Schistosoma haematobium* in Coast Province, Kenya. *Am J Trop Med Hyg* 1989, 40: 507–513.
- Sukwa, T.Y., Boatín, B.A. & Wurapa, F.K. A three year follow-up of chemotherapy with praziquantel in a rural Zambian community endemic for schistosomiasis mansoni. *Trans R Soc Trop Med Hyg* 1988, 82: 258–260.
- Farid, Z., Woody, J. & Kamal, M. Praziquantel and acute urban schistosomiasis. *Trop Geog Med* 1989, 41: 172.
- Friis, H. & Bysskov, J. The effect of praziquantel against *Schistosoma mansoni* – infections in Botswana. *Trop Geog Med* 1989, 41: 49–51.
- Minggang, C., Xiangjin, H., Mingjie, W., Rongji, X., Changbao, Y. & Shoubai, J. Dose finding double-blind clinical trial with praziquantel in schistosomiasis japonica patients. *Southeast Asian J Trop Med Publ Hlth* 1985, 16: 228–233.
- Stephenson, L.S., Latham, M.C., Kinoti, S.N. & Oduori, M.L. Regression of splenomegaly and hepatomegaly in children treated for *Schistosoma haematobium* infection. *Am J Trop Med Hyg* 1985, 34: 119–123.
- Homeida, M.A., Fenwick, A., DeFalla, A.A. et al. Effect of antischistosomal chemotherapy on prevalence of Symmers' periportal fibrosis in Sudanese villages. *Lancet* 1988, ii: 437–440.
- Devidas, A., Lamothe, F., Develoux, M., Mouchet, F. & Sellin, B. Ultrasonographic assessment of the regression of bladder and renal lesions due to *Schistosoma haematobium* after treatment with praziquantel. *Ann Soc belge Méd trop* 1989, 69, 57–65.
- El Masry, N.A., Bassily, S. & Farid, Z. A comparison of the efficacy and side effects of various regimens of praziquantel for the treatment of schistosomiasis. *Trans R Soc Trop Med Hyg* 1988, 82: 719–720.
- Torres, J.R., Noya, O., Noya, B.A. de & Mondolfi, A. Seizures and praziquantel. A case report. *Rev Inst Med Trop São Paulo* 1988, 30: 433–436.
- Freedman, D.O., Zierdt, W.S., Lujan, A. & Nutman, T.B. The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989, 159: 1151–1153.
- Naquira, C., Jimenez, G., Guerra, J.G. et al. Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989, 40: 304–309.
- Editorial. Ivermectin in onchocerciasis. *Lancet* 1984, ii: 1021.
- Awadzi, K., Daddie, K.Y., Schulz-Key, H., Gilles, H.M., Fulford, A.J. & Aziz, M.A. The chemotherapy of onchocerciasis. XI A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Ann Trop Med Parasitol* 1986, 80: 433–442.
- Aziz, M.A., Chemotherapeutic approach to control of onchocerciasis. *Rev Infect Dis* 1986, 8: 500–504.
- Editorial. Ivermectin vs. Onchocerciasis. *Parasitol Today* 1986, 2: 233–235.
- White, A.T., Newland, H.S., Taylor, H.R., Erttmann, K.D., Williams, P.N. & Greene, B.M. Controlled trial and dose finding study of ivermectin for treatment of onchocerciasis. *Trop Med Parasitol* 1986, 37: 96.

40. Albiez, E.J., Walter, G., Kaiser, A. *et al.* Histological examination of onchocercomata after therapy with ivermectin. *Trop Med Parasitol* 1988, **39**: 93–99.
41. Larivière, M., Beauvais, B., Aziz, M. *et al.* Étude en Côte-D'Ivoire (1985–1987) de l'efficacité et de la tolérance de l'ivermectine (Mectizan) dans l'onchocercose humaine. *Bull Soc Path Exot* 1989, **82**: 35–47.
42. Greene, B.M., Taylor, H.R., Cupp, E.W. *et al.* Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *N Engl J Med* 1985, **313**: 133–138.
43. Larivière, M., Vingtain, P., Aziz, M. *et al.* Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet* 1985, **ii**: 174–177.
44. Taylor, H.R., Murphy, R.P., Newland, H.S. *et al.* Treatment of onchocerciasis: the ocular effects of ivermectin and diethylcarbamazine. *Arch Ophthalmol* 1986, **104**: 863–870.
45. Dadzie, K.Y., Bird, A.C., Awadzi, K., Schulz-Key, H., Gilles, H.M. & Aziz, M.A. Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis. *Br J Ophthalmol* 1987, **71**: 78–85.
46. Rothova, A., Lelij, A. van der, Stijlma, J.S., Wilson, W.R. & Barbe, R.F. Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989, **i**: 1439–1441.
47. Taylor, H.R., Semba, R.D., Newland, H.S. *et al.* Ivermectin treatment of patients with severe ocular onchocerciasis. *Am J Trop Med Hyg* 1989, **40**: 494–500.
48. Katz, N. & Rocha, R.S. Double-blind clinical trial comparing praziquantel with oxamniquine in *Schistosomiasis mansoni*. *Rev Inst Med Trop São Paulo* 1982, **24**: 310–314.
49. da Silva, L.C., Zeitune, J.M.R., Rosa-Eid, L.M.F. *et al.* Treatment of patients with *Schistosomiasis mansoni*: a double-blind clinical trial comparing praziquantel with oxamniquine. *Rev Inst Med Trop São Paulo* 1986, **28**: 174–180.
50. Polderman, A.M., Gryseels, B. & de Caluwe, P. Cure rates and egg reduction in treatment of intestinal schistosomiasis with oxamniquine and praziquantel in Maniema, Zaire. *Trans R Soc Trop Med Hyg* 1988, **82**: 115–116.
51. Taddese, K. & Zein, Z.A. Comparison between the efficacy of oxamniquine and praziquantel in the treatment of *Schistosoma mansoni* infections on a sugar estate in Ethiopia. *Ann Trop Med Parasitol* 1988, **82**: 175–180.
52. Pugh, R.N.H. & Teesdale, C.H. Single dose oral treatment in urinary schistosomiasis: a double blind trial. *Br Med J* 1983, **286**: 429–432.
53. Richard-Lenoble, D., Kombila, M., Rupp, E.A. *et al.* Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infections. *Am J Trop Med Hyg* 1988, **39**: 480–483.
54. Burchard, G.D. & Kern, P. Failure of high dose mebendazole as a microfilaricide in patients with loiasis. *Trans R Soc Trop Med Hyg* 1987, **81**: 420.
55. Cook, G.C. Canine-associated zoonoses: an unacceptable hazard to human health. *Q J Med* 1989, **70**: 5–26.
56. Stürchler, D., Schubarth, P., Gualzata, M., Gottstein, B. & Oettli, A. Thiabendazole vs. albendazole in treatment of toxocarosis: a clinical trial. *Ann Trop Med Parasitol* 1989, **83**: 473–478.
57. Pungpak, S., Bunnag, D., Chindanon, D. & Radmoyos, B. Albendazole in the treatment of strongyloidiasis. *Southeast Asian J Trop Med Publ Hlth* 1987, **18**: 207–210.
58. Grove, D.I. & Northern, C. The effects of thiabendazole, mebendazole and cambendazole in normal and immunosuppressed dogs infected with a human strain of *Strongyloides stercoralis*. *Trans R Soc Trop Med Hyg* 1988, **82**: 146–149.
59. Grove, D.I. Treatment. In: Grove, D.I. (ed.) *Strongyloidiasis: a major roundworm infection of man*. Taylor & Francis, London, New York, 1989, pp. 199–231.
60. Morris, D.L., Chinnery, J.B., Georgiou, G., Stamatakis, G. & Golematas, B. Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987, **28**: 75–80.
61. Taylor, D.H. & Morris, D.L. *In vitro* culture of *Echinococcus multilocularis*: protoscolicidal action of praziquantel and albendazole sulphoxide. *Trans R Soc Trop Med Hyg* 1988, **82**: 265–267.
62. Wilcox, M.H., Morris, D.L. & Bailey, J.W. Serology in patients treated with albendazole for hydatid disease. *J R Soc Med* 1988, **81**: 714–717.
63. Wilson, J.F., Rausch, R.L., McMahon, B.J., Schantz, P.M., Trujillo, D.E. & O'Gorman, M.A. Albendazole therapy in alveolar hydatid disease: a report of favorable results in two patients after short-term therapy. *Am J Trop Med Hyg* 1987, **37**: 162–168.
64. Todorov, T., Vutova, K., Petkov, D. & Balkanski, G. Albendazole treatment of multiple cerebral hydatid cysts: case report. *Trans R Soc Trop Med Hyg* 1988, **82**: 150–152.
65. Horton, R.J. Chemotherapy of *Echinococcus* infection in man with albendazole. *Trans R Soc Trop Med Hyg* 1989, **83**: 97–102.
66. Morris, D.L. Pre-operative albendazole therapy for hydatid cyst. *Br J Surg* 1987, **74**: 805–806.
67. Richards, K.S., Riley, E.M., Taylor, D.H. & Morris, D.L. Studies on the effect of short term, high dose praziquantel treatment against protoscolices of ovine and equine *Echinococcus granulosus* within the cyst, and *in vitro*. *Trop Med Parasitol* 1988, **39**: 269–272.
68. Taylor, D.H., Morris, D.L. & Richards, K.S. *Echinococcus granulosus*: *in vitro* maintenance of whole cysts and the assessment of the effects of albendazole sulphoxide and praziquantel on the germinal layer. *Trans R Soc Trop Med Hyg* 1989, **83**: 535–538.
69. Henriksen, T.-H., Klungsoyr, P. & Zerihun, D. Treatment of disseminated peritoneal hydatid disease with praziquantel. *Lancet* 1989, **i**: 272.
70. Taylor, D.H., Morris, D.L. & Richards, K.S. Combination chemotherapy of *Echinococcus granulosus* – *in vitro* studies. *Trans R Soc Trop Med Hyg* 1988, **82**: 263–264.
71. Taylor, D.H., Morris, D.L., Richards, K.S. & Reffin, D. *Echinococcus multilocularis*: *in vivo* results of therapy with albendazole and praziquantel. *Trans R Soc Trop Med Hyg* 1988, **82**: 611–615.
72. Moodley, M. & Moosa, A. Treatment of neurocysticercosis: is praziquantel the new hope? *Lancet* 1989, **i**: 262–263.
73. Sotelo, J. Praziquantel for neurocysticercosis. *Lancet* 1989, **i**: 897.
74. Sotelo, J., Torres, B., Rubio-Donnadieu, F., Escobedo, F. & Rodriguez-Carbajal, J. Praziquantel in the treatment of neurocysticercosis: long-term follow-up. *Neurology* 1985, **35**: 752–755.
75. Escobedo, F., Penagos, P., Rodriguez, J. & Sotelo, J. Albendazole therapy for neurocysticercosis. *Arch Intern Med* 1987, **147**: 738–741.
76. Quintero-Rodriguez, E. Praziquantel vs. albendazol for cysticercosis. *Neurosurgery* 1988, **23**: 128.
77. Sotelo, J., Escobedo, F. & Penagos, P. Albendazole vs praziquantel for therapy for neurocysticercosis: a controlled trial. *Arch Neurol* 1988, **45**: 532–534.
78. Price, T.C., Dresden, M.H., Alvarado, T., Flanagan, J. & Chappell, C.L. Coenuriasis in a spectacled langur (*Presbytis obscura*): praziquantel treatment and the antibody response to cyst antigens. *Am J Trop Med Hyg* 1989, **40**: 514–520.
79. Knobloch, J., Delgado, E., Alvarez, A., Reymann, U. & Bialek, R. Human fascioliasis in Cajamarca/Peru I. Diagnostic methods and treatment with praziquantel. *Trop Med Parasitol* 1985, **36**: 88–90.
80. Farid, Z., Kamal, M. & Woody, J. Treatment of acute toxæmic fascioliasis. *Trans R Soc Trop Med Hyg* 1988, **82**: 299.
81. Markwalder, K., Koller, M., Goebel, N. & Wolff, K. Infektion mit *Fasciola hepatica*: Erfolgreiche therapie mit triclabendazol. *Schweiz med Wschr* 1988, **118**: 1048–1052.