Progress and Prospects in the Chemotherapy of Nematode Infections of Man and Other Animals[1]

W. C. CAMPBELL[2]

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Having worked with nematodes and antinematodal drugs for some time, I welcome the opportunity to gain a new perspective on the subject by exchanging viewpoints with those who work on the chemical control of quite different categories of nematode. Some of you work with free-living nematodes and I should tell you that, as a parasitologist, I regard worms without hosts as somehow underprivileged. Many among you work with nematodes that parasitize plants; such worms have shown a laudable degree of upward mobility. This paper concerns worms with higher, or at least hotter, hosts; i.e., nematodes that parasitize man and domestic animals. The important thing, however, is that we have in common not only nematodes but nematode ecology. Worms must be studied in relation to their environment, regardless of whether that environment be animal, vegetable, or mineral. I begin with a brief summary of the major current drugs and their uses, followed by a cursory review of the modes of action of those drugs. Attention is then directed to the question of whether we can reasonably ask for better drugs, and, if the answer be yes, to the question of how we should go about getting them.

DRUGS AND THEIR USES

My initial response to the invitation to consider the distinction between intestinal and extraintestinal nematodes was to sketch out tables of drugs active against worms of either kind, in various host species. It quickly became evident that the most revealing approach lay in a simple listing of major drugs active against intestinal or extraintestinal worms, regardless of whether the host be man, sheep, cattle, horse, swine, or dog (Table 1). The results are quite remarkable. The first three compounds are common to both lists, and they are, by any standard, drugs of major consequence.

It is commonly held that intestinal nematodes are easy to destroy because a narcotic or immobilizing effect will result in their expulsion, whereas extraintestinal parasites are trapped in their various niches and can recover from nonlethal effects and resume their parasitic activity. The classic "intestinal" example (popularized by H. L. Gordon) is to be found in the treatment of *Ascaris* infection. Consider an *Ascaris* worm in the small intestine of a pig given piperazine. The worm becomes stuporous; and by the time it recovers, the pig has gone. One of the attractions of this viewpoint is that drugs against intestinal worms do not need to be absorbed from the gut and therefore offer advantages in terms of safety and tissue residues. But the situation is, for once, simpler than it seems.

It is probably a mistake to think of intestinal nematodes as creatures sloshing around in gut contents (perhaps the pinworm is an exception). The worms and their hosts are on intimate terms, and in most, if not all, cases, the worms are potentially vulnerable to both absorbed and nonabsorbed drugs. Nonabsorbed drugs do have certain advantages; but the spectrum of activity of current nonabsorbed drugs is either narrow (e.g., pyrvinium) or (as in the case of pyrantel) not so wide as that of absorbed drugs. This is important because, in most situations, the advantage conferred by nonabsorption is outweighted by that conferred by breadth of spectrum. It should be noted that among the "intestinal only" compounds in Table 1, many have a spectrum that is narrow even within the context of the gut; whereas those with broad intestinal spectrum generally have activity against extra-intestinal nematodes too.

Extra-intestinal worms, too, may be affected by temporary immobilization. This

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[2]Merck Institute for Therapeutic Research, P.O. Box 2000, Rahway, NJ 07065.

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Table 1. Drugs of current significance in the treatment of nematode infections.

Nematode dwelling site	
Gastro-intestinal	Extra-intestinal
benzimidazoles*	benzimidazoles*
levamisole	levamisole
ivermectin	ivermectin
phenothiazine	suramin
organo-phosphates	arsenicals
piperazine	diethylcarbamazine
pyrantel/morantel	
pyrvinium	
nitroscanate	
bephenium	

*Including the pro-drugs, thiophanate and febantel.

is exemplified in trematode infection by the failure of schistosomes to regain the mesenteric veins one they have been swept into the liver by the action of certain drugs. The same may be true of lungworm in ruminants and heartworm in dogs, although the situation is by no means clear and probably varies from drug to drug.

Of the drugs listed in Table 1 as effective against extra-intestinal worms, three (suramin, organo-arsenic, and diethylcarbamazine) are used for such worms only; yet even within that narrow context, those drugs have limited applicability. They are used almost exclusively for worms of the order Filaroidea. It seems to me, therefore, that in general we should avoid thinking of parasites as intestinal or extra-intestinal. Drug susceptibility undoubtedly depends upon habitat and feeding habit, but habitats should not be categorized simply as intestinal or extra-intestinal. Subtle differences among a wide range of microhabitats, and subtle metabolic differences imposed by phylogenetic heritage are likely to be more important determinants of drug susceptibility.

MODES OF ACTION

It was afterwards . . . when the remedies had already been discovered, that men began to discuss the reason for them: therapy was not a discovery following upon reasoning, but after the discovery of the remedy, the reason for it was sought out (Celsus, 30 A. D.)

For most, if not all, of these drugs, experimental attempts have been made to discover their antinematodal mechanism. These studies may readily be found in the scientific literature, and the findings have been reviewed (5). For the present purpose it will suffice to merely recapitulate the modes of action that have been postulated (Table 2). As might be expected, the weight of evidence varies from drug to drug; in any case, a proper Popperian pru-

Table 2. Biochemical actions which are likely to account for, or contribute to, the antinematodal effect of drugs.*

Drug	Action
benzimidazoles	Inhibition of tubulin polymerization; inhibition of fumarate reductase
levamisole, pyrantel, morantel, methyridine	Depolarization of nerve-cell membranes, through cholinergic agonist action
bephenium, thenium	Depolarization of nerve-cell membranes, through choline-receptor binding
organo-phosphates	Depolarization of nerve-cell membranes, through inhibition of acetylcholinesterase
piperazine	Hyperpolarization of muscle-cell membranes
avermectins	Potentiation of GABA release and binding, at synapse
dithiazanine	Inhibition of glucose or oxygen uptake, depending on target species
styrylpyridinium, pyrvinium	Inhibition of glucose uptake
organo-arsenic	Inhibition of glycolysis
diethylcarbamazine	Opsonization of nematodes
2,4 dinitrophenol	Uncoupling of electron-transport-associated phosphorylation
suramin	Inhibition of dihydrofolate reductase
nitroscanate	None known
bitoscanate	None known
tetrachlorethylene	None known
phenothiazine	None known

*Compiled in collaboration with Dr. R. S. Rew.

dence compels one to point out that the proposed modes of action represent not hypotheses that have been proven correct, but merely hypotheses that have not been proven wrong.

Benzimidazoles have been shown to inhibit fumarate reductase, and some of them have been shown to inhibit glucose uptake in vitro; both actions have been proposed as primary anthelmintic mechanisms. Many workers, however, now favor the thesis that the antinematodal, antifungal, and antitumor effects of benzimidazoles reside in their inhibition of tubulin polymerization and consequent disruption of microtubule assembly.

Levamisole, too, is an inhibitor of fumarate reductase, but at a much higher in vitro concentration. The drug induces contractions of nematodes in vitro, and there is evidence that it acts as a cholinergic ganglionic agonist.

Ivermectin (one of the avermectins) is believed to act through the mediation of the neurotransmitter *gamma*-aminobutyric acid (GABA). Experiments conducted on *Ascaris* and lobster suggest that the avermectins stimulate presynaptic release of GABA in the inhibitory neuron and enhance the postsynaptic binding of GABA to its receptor. These effects cause the chloride-ion channels to remain open, thereby maintaining the postsynaptic cell in a negatively charged resting state and preventing the induction of electric potentials across the cell membrance. In the case of *Ascaris*, the action is believed to operate at the synapse between interneuron and motorneuron; in the case of the lobster walking leg, it appears to act at the synapse between motorneuron and nerve cell.

Other antinematodal drugs that cause paralysis by interference with neuromuscular transmission are the organophosphates, which inhibit acetylcholinsterase in nematodes; bephenium and thenium, which are cholinomimetics; pyrantel and morantel, which are cholinergic ganglionic agonists; and piperazine, which hyperpolarizes muscle cell membranes.

The narrow-spectrum compounds dithiazine, pyrvinium, and styrylpyridinium inhibit glucose uptake; 2,4-dinitrophenol is thought to act as an uncoupler of oxidative phosphorylation, while suramin appears to act by inhibition of parasite dihydrofolate reductase. Other compounds with antinematodal action include methyridine, a cholinergic agonist; diethylcarbamazine, which may make nematodes more vulnerable to host immune responses; organoarsenic, which may inhibit glycolysis; and bitoscanate, nitroscanate, tetrachlorethylene, and phenothiazine, for which mechanisms have not been proposed.

CURRENT NEEDS

No matter how broad the spectrum of efficacy, or how safe the drug, there is always room for improvement. But modern antinematodal drugs are so impressive in these two respects that it seems more useful to look for other, more specific, weaknesses and opportunities.

Potency: The progressive development of potency in drugs is represented in simplified form in Table 3. The current zenith is represented by the avermectins, with avermectin B_1a being active in vitro against *Angiostrongylus cantonensis* and *Metastrongylus elongatus* at 3.6×10^{-18}M (6) and ivermectin being fully active against preadult *Dirofilaria immitis* in dogs when given as a single oral dose at 0.003 mg/kg (4). Since this was the lowest dosage tested, it remains to be determined how closely

Table 3. Increasing potency in the evolution of modern broad-spectrum anthelmintics. A simplification based on the approximate dosage required to give optimum efficacy (for that drug) when given to sheep as a single oral dose.

Time of major market introduction	Compound or class	Dosage (mg/kg)
Early 1940s	phenothiazine	600
Late 1950s	organophosphates	50–100
Early 1960s	thiabendazole	45
Mid 1960s	pyrantel	25
Late 1960s	tetramisole	15
Early 1970s	morantel	10
Early 1970s	levamisole	7.5
Mid 1970s	new benzimidazoles*	5–10
Early 1980s	ivermectin	0.2

*Includes albendazole, fenbendazole, mebendazole, oxfendazole, oxibendazole and benzimidazole pro-drugs. Benzimidazoles of intermediate potency (cambendazole, parbendazole) were introduced between the introduction of thiabendazole and the new benzimidazoles.

one can approximate the point of having efficacy against *D. immitis* in dogs without giving any drug at all!

Extreme potency is not necessarily advantageous to a patient, a livestock owner, a salesman, or a manufacturer. For all of them, a pill with a large amount of some active ingredient may be more (or less) attractive than a pill with a smaller amount of some other drug. The potential payoff of potency lies in the realm of special methods of drug delivery.

Drug resistance: Resistance has been a relatively minor problem in the control of nematode infections in domestic animals and is not known to be a problem at all in the treatment of nematode infections in man. Nevertheless, there are (in domestic animals) nematode strains that are resistant to benzimidazoles, levamisole, and pyrantel/morantel. It is almost impossible to assess the seriousness of the problem in terms of livestock productivity, but it is a recognized, if regional and sporadic, problem in anthelmintic commerce. We lack a sound knowledge of the mechanisms of resistance; therefore, stratagems to minimize the emergence of drug resistance cannot readily be devised.

Specific parasites: Anthelmintics are available that are highly effective against virtually all of the important nematodes of sheep, cattle, swine, and horses. The same cannot be said for man and dog. In human trichinosis, mebendazole appears to be as satisfactory as one could expect a trichinosis drug to be; in addition, that drug and pyrantel are excellent for the common intestinal nematodes of man. But a good treatment is sorely needed for the invasive form of *Strongyloides stercoralis*. A new drug is needed for *Dracunculus* infection in man, although it is hoped that the current "International Water Supply and Sanitation Decade" will minimize that need. Good treatments are needed for certain relatively rare diseases, such as those caused by tissue stages of *Angiostrongylus* and *Toxocara*.

In both dog and man, it is the filarial group of nematodes that represent the greatest need for better drugs. In the dog, treatment for adult heartworm (*Dirofilaria immitis*) usually consists of multiple intravaneous injections of organo-arsenic. On grounds of safety, economics, and convenience, this is a very unsatisfactory treatment. In man, adult *Onchocerca volvulus* can be killed by multiple intravenous injections of suramin; but on the same grounds, the treatment is highly unsatisfactory. Treatment of the preadult and microfilarial stages of these worms is currently unsatisfactory, but recent studies with ivermectin, mebendazole, and, to some extent, levamisole are very promising.

Drugs are also needed for other filariases of man, since the current treatment of bancroftian and brugian filariasis is far from satisfactory. The primary need right now is for efficacy against the lymph-dwelling adult worms. As with all filarial infections in man, chemoprophylaxis remains a goal for the future.

Delivery systems: Probably the best opportunity for the future, with respect to antinematodal drugs, lies in the area of delivery devices. Almost all anthelmintic treatments are given orally or by intramuscular or subcutaneous injection, but we also have drugs that can be absorbed when applied to a patch of skin and so exert an effect on endoparasitic nematodes. Practical use of this method is currently limited to levamisole, but organophosphates are commonly used in this way to provide systemic efficacy against ectoparasites. It can be expected that other drugs will be used in this way in the future.

Sophisticated delivery systems generally will require great potency, because the physical constraints of the system will generally require the use of very small quantities of drug. Nowhere is this more evident than in the case of controlled-release systems, where the objective is to provide prolonged or repeated treatment with only a single administration of drug to the host. The desirability of such a delivery system may arise from the cost, inconvenience, or impracticability of multiple drug administrations to a group of beasts or people. The approach is exemplified by the recent introduction of morantel in the form of a slow-release bolus for the control of gastrointestinal nematodes in cattle (1). An example still in the experimental stage may be found in studies with ivermectin in cattle (3). Further increases in anthelmintic potency may make it possible to

use parenteral controlled-release devices. Regardless of anatomical location, devices could conceivably be designed to release drug in either a continuous or pulsatile manner.

While controlled-release devices appear to offer a major opportunity for the future, they also constitute one of the greatest areas of concern. Subjecting parasites to a sustained, and sometimes suboptimal, drug level may exacerbate the problem of drug resistance. A minor problem could be made major, and our current inability to predict such consequences only emphasizes the need for research on the mechanisms of drug resistance in nematodes.

NEW DRUG DISCOVERY

I am indeed so disgusted with learned quackery, that I take some interest in honest, humane and strong-minded empiricism . . . (Benjamin Waterhouse, 1825)

An argument renewed: I have on another occasion taken a stand in favor of the empirical approach to the discovery of new drugs for infectious diseases (2). The paucity and misdirection of opposing arguments prompt me to recapitulate my viewpoint and to comment on statements by others on the subject.

The argument is made within a very specific context, indicated by the key words *probability, infection,* and *totality* (PIT).

- Probability. A fundamental objective of drug discovery programs is the adoption of an approach that has a high probability of success. A low-probability approach might pay off handsomely, giving its sponsors cause for celebration, but not entitling them to congratulations on intellectual grounds. A scientific attitude usually demands adoption of the method with the highest perceived probability of success.
- Infection. The argument applies only to infectious diseases. The situation with respect to the discovery of new drugs for metabolic disorders is probably quite different. It may also be different with respect to agents for free-living nematode and arthropod pests, although the intimate relationship between pest and microhabitat provides some similarity to the situation under present consideration.
- Totality. The argument deals with the probability of meeting the total objective (i.e., the discovery of a drug that will be clinical and/or commercially successful) not just the discovery of new active compounds.

The probability of success for a particular method of new drug discovery cannot be measured, but we have the historical record to guide us. All successful classes of anthelmintic, antibacterial, and antiprotozoal drugs, with the possible exception of ethopabate, seem to have been discovered as the result of empirical testing or chance observation. None was discovered as the result of biochemical studies on the parasite. Drugs currently under development may change that picture, but the generalization appears to be true at this writing. Empirically discovered drugs or modes of action have been rationally exploited in the development of superior members of a particular drug class, but that point is tangential to the present argument. It seems to me that an appeal to precedent is not unscientific.

Once discovered, a new drug has a low probability of reaching the medical or agricultural marketplace. Of all the factors contributing to the nonintroduction of a new drug, failure to find an active lead compound is only one; matters such as safety, stability, registration costs, and manufacturing costs add up to an obstacle much more formidable than that posed by the need to find an active compound. That is why we must look at the total probability of success. That is why it is important to discover new leads as quickly and cheaply as possible. Newly discovered leads are abandoned frequently and routinely in a big screening program. It is, however, no easy matter to abandon a lead produced as the result of a long and costly piece of basic research.

The rational approach, in simplified terms, is predicated on the discovery, in a parasite, of a biochemical pathway or event that might be blocked without harm to the host. The host may escape harm because of quantitative or qualitative differences from the parasite with respect to the biochemical mechanism in question. The term "rational" has been retained here because it has become a useful convention and accu-

rately describes the concept of the biochemical or other nonempirical approach. The actual use of such an approach in a given situation may or may not be rational (i.e., intelligent), and we should not imply that the choice of the empirical approach in a given situation is irrational. There is a fairly good chance of finding or devising a chemical structure that will block any biochemical mechanism that has been discovered in a parasite and selected as a target. But what is the probability that the chemical will do all the other good things (in terms of stability, absorption, degradation, excretion, etc.) and none of the bad things (in such matters as mutagenicity, lethality, illegality, staining, and stinking)? Surely it is intellectually arrogant to suppose that in the foreseeable future we will be able to predict all biochemical consequences of a hitherto unknown chemical. For the rational approach, as for the empirical, the probability of success cannot be measured.

There has always been a spectrum of rationality in scientific research as there is a spectrum of creativity in the arts. A photograph may be created almost entirely by mechanical operations and chance events. The artistic component of a photograph is a function of the degree of control exercised by the photographer (*sensu latu*). Where there is little or no control, the photograph, no matter how beautiful it is thought to be, is not a work of art; where the degree of control is high, the photograph is art no matter how ugly it may be perceived to be. Similarly the "scientific" component of a new drug discovery depends upon the control exercised by the discoverer. In the initial discovery of an active compound, the element of chance may be large (as in random screening) or medium (as in the semirational approach, the "enlightened empiricism" of Hitchings) or small (as in the yet-to-be-attained design of an antiparasitic drug with all of the attributes of success). However, the selection or creation of an empirical screen is not a matter of chance, and the subsequent process of bringing a drug to the point of practical utility involves both chance and design. The end result is a genuine scientific achievement, and its empirical components need no apology. If our objective is truly to discover new antiparasitic drugs (as distinct from the perfectly understandable objective of impressing our peers with how brilliantly we look for them), then we should worry more about probability and less about rationality.

One would like to think that it might be taken as axiomatic that a large target is easier to hit than a small one. Yet this seems to be the most overlooked aspect of the empirical vs. rational controversy. The testing of compounds against a whole parasite means aiming at a target consisting of thousands upon thousands of known and unknown biochemical processes. The rationalist wants to select one or two. The justification is that in so doing he will achieve differential toxicity; i.e., specificity of action against the parasite. And so he may—but he will have greatly reduced the size of the target. As mentioned above, hitting the target in the sense of finding an active compound, even one with differential toxicity, does not usually lead to the development of a successful drug. We should therefore strive for as many hits as possible and so should not aim at small targets.

A colleague recently devised a biochemical anthelmintic assay based on the mode of action of one of the leading anthelmintic compounds, on the ground that he was seeking a new anthelmintic agent with a unique mode of action. His assay may yield compounds with desirable properties of one kind or another, but it will virtually preclude the discovery of compounds with a unique mode of action. This points up another weakness of the biochemical as opposed to the empirical approach. Since we have learned more about parasites from drugs than vice versa, there is an understandable tendency to base biochemical assays on known modes of action. Such assays may yield better drugs, but those drugs are likely to have much in common with existing drugs, and the assays are unlikely to yield breakthrough treatments.

It does not follow that we should always select the largest possible target. One could seek agents for control of liver fluke by seeking flukes in animals that had been treated in the preinoculation and postinoculation phases. In such as assay, active compounds would include those that had

blocked excystment of the metacerciae in the host gut. But if one sought *only* compounds with that sort of action, then one might want to conduct random screening for compounds that would block excystment in vitro. In this particular case, the natural target event takes place in what is biologically the "outside" of the host; i.e., the lumen of the gut. Similarly, one might want to screen against molting or mating or site selection in nematodes, or cell-wall synthesis in bacteria, or any number of relatively narrow targets. The point here is that an understanding of the biochemical processes of excystment, molting, etc., may help in devising a screen, but such an understanding is not essential. If at all possible, the screen should be based on the whole event of excystment, molting, etc., not on one biochemical component of it.

There is another aspect of empirical screening that tends to be overlooked for reasons of professional unpalatability rather than philosophical unsoundness. Ideally there should be no preselection of the compounds being tested. In practice it is usually impossible to test all the compounds available, so some selection must be made. Such selection tends to be made on the basis of the perceived likelihood that a given structure will be active and safe. Medicinal chemists are highly skilled in this regard, but it is important that they use this skill judiciously and only rarely exclude compounds from an assay on the grounds of predictable unsuitability. The objective of the preselection process should not be to pick likely winners, but to ensure diversity of chemical structure.

Proponents of the rational approach abound, and while they are quick enough to disparage empiricism, they rarely meet the issue head on. It is not enough, for example, to point out biochemical differences between parasite and host and to allege that the differences would be suitable targets for chemotherapeutic attack. What is needed is evidence, or argument on theoreical grounds, that hitting those targets would lead to a useful new drug. It has, too, been alleged that the rational approach would be less costly and less wasteful than the empirical approach, and would provide new drugs more quickly. The cost of discovering new drugs by the empirical approach is certainly high, both in money and in time, but I do not see how it can be compared to the cost incurred by the rational approach until such time as useful drugs are discovered by the rational approach.

The elucidation of biochemical targets can be of value in providing an understanding of the mode of action of drugs, in promoting the most effective use of drugs, and especially in making possible the semirational process by which empirical observations are transformed, embellished, and exploited to yield useful drugs. In the long run, the proposed strategy might even provide totally new and successful rationally designed drugs—so I am not suggesting that such work should not be done. What the strategy will almost certainly not do, is yield useful new drugs inexpensively or quickly; nor can it be relied upon to shorten the time between discovery and clinical trial to the less than 5 years that Cohen considers expeditious.

There is in fact a telling argument against continued reliance on the empirical approach. It is sometimes said that empirical screening was all very well in its day, but it is played out—the supply of untested compounds has dwindled to the point at which there is low probability of success. There is much force in that argument, but it applies more forcibly to some infections than to others. In the case of poultry coccidiosis, where vast numbers of compounds have been tested directly in the target species, empirical screening may have reached the point of diminishing returns. In the case of nematodes, hundreds of thousands of compounds have been tested in vitro, with truly breathtaking lack of success, and similar huge numbers have been tested in vivo—but not in the target hosts and not against certain important nematode groups such as the filariids. For any given infection, however, the question is not whether the empirical method is as good as it was—the question is whether there is anything better. With respect to parasitic nematodes, I see no evidence that there is.

L'ENVOI

We have excellent drugs for most nematode infections of man and his domestic animals. The exceptions are few but important. There is a need for better drugs

for use against certain nematode species, especially those species responsible for filariasis in its various forms. There is an opportunity, if not a need, for new and improved drugs to complement or replace those in current use. The greatest opportunity for improvement probably lies in the area of drug delivery systems.

The discovery of new antiparasitic drugs is generally approached from either the point of view of empirical screening or of biochemical ("rational") design. Each approach has protagonists who have faith in its future success, with empiricists being able to boast of past success. Those who actually face the task of discovering new drugs know that it serves no purpose to espouse the middle ground, important though semirational approaches might be. Nor is it very daring or helpful to say that we should have both approaches—for who does not wish to hedge a bet? Who does not applaud good basic research regardless of its short-term applicability to everyday affairs? Who would deny the possibility of valuable but unpredictable spinoff from such basic studies? It is easy to say we need both empirical and biochemical approaches. But we cannot apply maximum effort in two directions. We can allocate our resources equally or unequally, but the choice must still be made.

The trouble with the empirical approach is that it is intellectually humiliating no matter how successful. The trouble with the rational approach is that it is intellectually irresistable no matter how unfruitful.

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