The evolution of tissue migration by parasitic nematode larvae

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SUMMARY

Migration by nematode larvae through the tissues of their mammalian hosts can cause considerable pathology, and yet the evolutionary factors responsible for this migratory behaviour are poorly understood. The behaviour is particularly paradoxical in genera such as *Ascaris* and *Strongylus* in which larvae undergo extensive migrations which begin and end in the same location. The orthodox explanation for this apparently pointless behaviour is that a tissue phase is a developmental requirement following the evolutionary loss of skin penetration or intermediate hosts. Yet tissue migration is not always necessary for development, and navigation and survival in an array of different habitats must require costly biochemical and morphological adaptations. Migrating larvae also risk becoming lost or killed by the host. Natural selection should therefore remove such behaviour unless there are compensating benefits. Here we propose that migration is a selectively advantageous life-history strategy. We show that taxa exploiting tissue habitats during development are, on average, bigger than their closest relatives that develop wholly in the gastrointestinal tract. Time to reproduction is the same, indicating that worms with a tissue phase during development grow faster. This previously unsuspected association between juvenile habitat and size is independent of any effects of adult habitat, life-cycle, or host size, generation time or diet. Because fecundity is intimately linked with size in nematodes, this provides an explanation for the maintenance of tissue migration by natural selection, analogous to the pre-spawning migrations of salmon.

Key words: larval migrans, life-history, natural selection, nematode larvae, tissue phase.

INTRODUCTION

'*On release within the intestine, the larvae undergo a migration so remarkable that it is difficult to believe it is not a phylogenetic reminiscence, the parasite reliving its life cycle in a once intermediate but now definitive host.*' (Smyth 1994, p. 403)

A paradoxical behaviour exhibited by some nematodes is the bizarre migration undertaken by larvae through their hosts. Frequently these end where they began. *Strongylus vulgaris* larvae, for example, penetrate the intestinal wall, travel through the submucosal, caecal and colic arteries to the anterior mesenteric arteries and then return by the same route to the intestinal lumen to breed. *Ascaris* larvae burrow through the gut wall, enter the vascular system and are carried via the liver to the heart and lungs before ascending the trachea to be swallowed back into the gut. These larval migrations can cause considerable host pathology including lesions, thrombosis, embolism, severe inflammatory responses, and allergy (Muller, 1975; Coles, 1985; Urquart *et al.* 1987; Vercruysse, Taraschewski & Voight, 1988; Crompton & Stephenson, 1990; Wilson, 1990), both during the normal course of infection (e.g. *Strongylus vulgaris* in horses; Ogbourne & Duncan, 1985) and when larvae undergo aberrant migration in atypical hosts (e.g. visceral and cutaneous larva migrans in humans). On an evolutionary scale, the behaviour has had a number of consequences, apparently allowing, for example, some species to exploit novel infection routes such as those associated with carnivory and pre-natal and transmammary transmission (e.g. within the Ascaroidea, Anderson (1992).

The evolutionary factors responsible for larval migration are poorly understood. Numerous authors have discussed the apparent meaninglessness of the behaviour; Rothschild & Clay (1952 p. 180) even likened it to the charge of the Light Brigade ('hundreds set out on their apparently pointless mission but only a few come back'). The prevailing explanation for its existence is that it is an evolutionary legacy (Rothschild & Clay, 1952; Sprent, 1962; Beaver, 1969; Read, 1970; Noble & Noble, 1976; Adamson, 1986; Anderson, 1988, 1992; Schmidt & Roberts, 1989; Smyth, 1994), a view apparently first advanced by Fülleborn. He interpreted the tissue phase of *Ascaris lumbricoides* as a necessary requirement for development because the parasite was descended from ancestors whose larvae

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penetrated the skin (Fülleborn, 1920 in Sprent, 1954) or utilized an intermediate host (Fülleborn, 1927, 1929). Similarly, the extensive tissue migration by *Strongylus* larvae is thought to be a developmental necessity which is a legacy from their skin-penetrating ancestors (Anderson, 1992).

However, on its own, this explanation is at best incomplete. First, a tissue phase need not be an obligatory requirement for development. Many nematode species remain in the gastrointestinal tract throughout their development, even in taxa thought to be ancestrally skin penetrating or heteroxenous (e.g. *Uncinaria stenocephala* and *Toxascaris leonina*; Sprent, 1962; Beaver, 1969; Anderson, 1992). And in some species which normally migrate, individuals can under appropriate experimental conditions successfully mature without migrating (e.g. dog hookworms, *Ancylostoma* spp. (reviewed by Behnke (1990)). Second, tissue migration must involve a range of complex and presumably costly biochemical and morphological adaptations associated with the ability to move and orientate through the body and survive in an array of different habitats (Chappell, 1993). Third, migration is frequently energetically expensive. *S. vulgaris* larvae, for example, migrate up to several metres against the flow of arterial blood. Finally, several authors have pointed out that migration is hazardous and there are numerous anecdotal reports of migrating larvae becoming encysted in organs en route or failing to relocate the gastrointestinal tract (Rothschild & Clay, 1952; Muller, 1975; Crompton & Pawlowski, 1985; Ogbourne & Duncan, 1985; Urquart *et al.* 1987; Schmidt & Roberts, 1989). Below we review experimental data on adult establishment rates which show that for a given infective dose, orally infecting gastrointestinal worms are more likely to establish as adults in naive hosts if they do not migrate. In addition, migrating larvae elicit host responses that are effective against subsequent larval invasion (concomitant immunity; Cox (1993 p. 208)); non-migrating larvae would presumably avoid this.

These observations argue against the idea that migratory behaviour is just evolutionary baggage: natural selection eliminates unnecessary, costly and risky behaviour. There must therefore be fitness benefits associated with migration, and tissue migration might profitably be viewed as a selectively advantageous life-history strategy. If so, it should be possible to identify these fitness benefits. Observing that larval migration elicits an effective immune response directed against larvae in subsequent infections, Cox (1993) recently suggested that larval migration has evolved in order to prevent overcrowding in the gastrointestinal tract, thus increasing adult fecundity. Such a strategy would, however, be evolutionarily unstable, since individuals which did not migrate would have an advantage.

Instead, we suggest the following. Considerable growth and development occurs during tissue migrations (Anderson, 1992). An obvious fitness benefit would accrue if tissue migration allows more rapid growth and consequently greater size and/or more rapid maturation. As with many invertebrates (Blueweiss *et al.* 1979; Sibly & Calow, 1986), there is abundant evidence that bigger nematodes are more fecund, both within species (e.g. Michael & Bundy, 1989; Szalai & Dick, 1989; Sinniah & Subramanian, 1991; Goater, 1992) and across species (Skorping *et al.* 1991). Furthermore, larger bodied nematode species probably have longer reproductive life-spans (Skorping *et al.* 1991). Thus, larval migration by nematodes could be maintained in a manner analogous to the pre-spawning migrations of salmon to the sea: a behaviour favoured by natural selection because it enables greater growth, despite the inherent costs.

This idea presupposes that there are growth advantages associated with developing outside the gastrointestinal tract. Here we test this idea using mammalian nematodes. A variety of nematode life-cycles incorporate a tissue phase prior to reproduction. In some cases, infection routes (e.g. skin penetration, vector-borne) or adult breeding site necessarily result in a tissue phase. In other cases, larvae actively migrate out of the gastrointestinal tract following oral infection and subsequently breed either in the tissues or back in the gut. We exploit this diversity to examine whether development in the tissues *per se* is associated with earlier maturation or greater size. We then examine whether any such advantages accrue to larval migration by orally infecting worms that return to breed in the gastrointestinal tract, where the existence of a tissue phase is apparently most superfluous. Finally, in order to confirm the anecdotal reports of larval loss during migration reviewed above, we gathered data on the establishment rates of orally infecting gastrointestinal nematodes for species in which larvae migrate and those where they do not.

MATERIALS AND METHODS

Nematode life-history

Data. Life-history data were collected from the literature for species of mammalian nematodes for which the adult and juvenile habitat in the definitive host (here defined as the mammal in which production takes place) could be ascertained. We omitted members of the genus *Trichuris* because their shape differs dramatically from that of other nematode taxa, making meaningful size comparisons difficult. Habitats were dichotomized as either *gastrointestinal* (gut lumen or gut wall) or *tissues*. *Adult habitat* is defined as that where reproduction takes place; *larval habitat* as that habitat in the definitive host in which larvae are normally found following natural infection and prior to reproduction. Species whose larvae are found in locations outside the gastrointestinal tract or gut wall at any stage during normal development were classified as having a *larval tissue phase*. Thus, all species with tissue-dwelling adults have, by definition, tissue-inhabiting juveniles; species reproducing in the gastrointestinal tract can have either tissue-inhabiting juveniles (if they infect via skin penetration or have a tissue migration following oral infection) or gastrointestinal juveniles (oral-infecting species with no tissue migration).

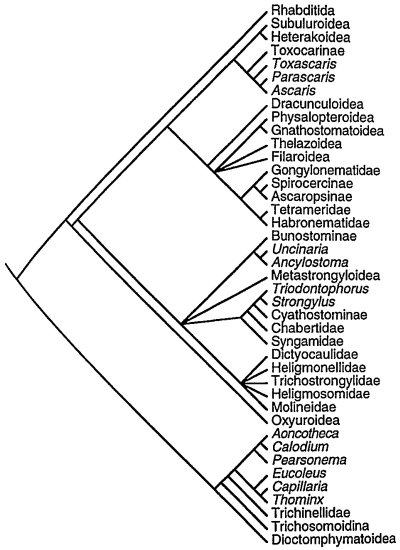

Fig. 1. Phylogenetic relationships of nematode taxa used in our analyses, deduced from the sources listed in text. For clarity, we have resolved the tree to include only the highest nodes relevant to the derivation of the sister taxa comparisons used here. Branch lengths arbitrary.

For each nematode species, the following life-history data were collected or calculated: *female length* (where given as an average, otherwise calculated as the mid-point of the maximum and minimum recorded), *female width* (where given as an average, otherwise calculated as the mid-point of the maximum and minimum recorded), *female volume* (using the formula given by Andrassy (1956)), *pre-patency period* (minimum time from infection to first observation of the production of eggs or larvae), *patency period* (maximum recorded period of egg or larval production by a female), *fecundity* (estimated as the average number of eggs produced/female worm in 24 h), *mean egg length*, *mean egg width*, and *egg volume* (calculated from the egg length and width data, assuming an ellipsoid shape), and *growth rate* (mm^3/day, calculated from female volume and pre-patency). Note that pre-patencies may differ slightly between worms breeding in the tissues and gastrointestinal tract, because eggs and larvae from the former may take longer to leave the body. However, if this bias is detectable across species, our conclusions below would be strengthened. In addition to the data on nematodes, the following were collected on their definitive hosts: *body weight* (average adult female weight), *age at maturity* and *maximum recorded longevity*. Hosts were categorized as carnivores, omnivores or herbivores.

Most of the nematode data were taken from Skrjabin (1953–1971), Soulsby (1968), Levine (1980) and Anderson (1992); data on hosts come from sources given by Read & Harvey (1989).

Analysis. It is well known that nematode taxa differ in their life-cycles and mode of development, but that these traits are frequently conserved within taxa (e.g. Anderson, 1992). Simple cross-species analyses are thus inappropriate (Harvey & Pagel, 1991). What is required are comparisons of taxa which are as similar as possible but which differ in their site of development. If larval habitat affects nematode life-histories, then comparisons of taxa with larval tissue phases and their most closely related intestine-dwelling taxon should reveal any differences. Thus, for each life-history variable, we compared the average value within a tissue-dwelling taxon with the equivalent value for the most closely related intestinal-dwelling taxon for which we had life-history data. These sister-taxon comparisons can be used in conventional statistical tests for differences between matched pairs. When nothing was known of the phylogenetic affinities within a taxon containing both intestinal and tissue nematodes, the average value for each habitat was compared. Once used in a comparison, taxa were excluded from the calculation of higher taxa means, ensuring that paths through the phylogeny linking taxa in each comparison do not cross and therefore that sister taxon comparisons are independent. For further details of this approach, see Felsenstein (1988), Pagel & Harvey (1988) and Burt (1989); for examples of its use, see Mitter, Farrell & Wiegmann (1988) and Read (1991).

All comparative analyses are based on hypotheses about phylogenetic relationships of the groups involved. Cladistic or molecular phylogenies are unavailable for most taxa of mammalian nematodes, so we have attempted to construct a consensus from morphological systematics. Phylogeny was inferred from the taxonomies in the *CIH Keys to Parasitic Nematodes* (Anderson *et al.* 1974–83; Anderson, 1992); additional resolution was derived from the phylogenetic hypotheses of Skrjabin (1949–1953, 1953–1971), Lichtenfels (1979), Butterworth & Beverley-Burton (1980), Moravec (1981, 1982), Anderson (1984, 1988), Barus & Libosvarsky (1984), Durette-Desset (1985),

Table 1. Sister taxa used in comparisons of the life-history differences associated with a tissue phase during development

(Maximum number of species for which at least some life-history data were available given in parentheses; for many variables, less data were available and hence geometric means for some taxa were estimated from fewer species. Note that the categories assigned to each taxon are that of the constituent species used in our analyses (Appendix) and is not necessarily that of all extant species in that group. Pair code is that used in Fig. 2 and Appendix. i, indirect life-cycles; d, direct life-cycles; g, breed in the gastrointestinal tract; t, breed in the tissues; o, oral infection, s, skin penetration, v, vector-borne.)

Pair code	No tissue development	Juvenile tissue phase
A	*Toxoascaris* (1) d&i, g, o	*Ascaris* + *Parascaris* (3) d, g, o
B	Subuluroidea + Heterakoidea (20) d&i, g, o	Toxocarinae (1) d&i, g, o
C	Physalopteroidea (1) i, g, o	Gnathostomatoidea (2) i, g, o
D	Ascaropsinae (2) i, g, o	Spirocercinae (1) i, g, o
E	*Triodontophorus* (4) d, g, o	*Strongylus* (3) d, g, o
F	*Uncinaria* (1) d, g, o	*Ancylostoma* (4) d, g, s
G	*Aoncotheca* (1) i, g, o	*Calodium* (1) i, t, o
H	Trichinellidae (1) d&i, g, o	*Pearsomena* + *Capillaria* + *Thominx* + *Eucoleus* (7) d&i, t, o
I	Habronematidae (2) i, g, o	Tetrameridae (3) i, t, o
J	Gongylonematidae (1) i, g, o	Filaroidea + Thelazoidea (61) i, t, v
K	Oxyuroidea (72) d, g, o	Bunostominae + Dracunculoidea + Metastrongyloidea (51) d&i, t&g, s&o
L	Cyathostominae + Chabertidae (22) d, g, o	Syngamidae (6) d&i, t, o
M	Heligmosomidae + Molineidae + Trichostongylidae (12) d, g, o	Dictyocaulidae + Heligmonellidae (5) d, t&g, o&s

Adamson (1986) and Moravec, Prokopic & Shlikas (1987). The phylogeny we derived from these authors is given in Fig. 1. Future improvements in nematode phylogenetics will alter our results only if the sister taxa we have compared prove not to be monophyletic; whether this would affect our conclusions would of course depend on the detail of any revisions.

All data were log transformed prior to analysis. For the most part, we are testing predicted directions of differences between sister taxa (e.g. in body size), so that one-tailed *P*-values are justified. However, for some variables no direction is predicted and so for consistency we report two-tailed *P*-values throughout. Non-parametic tests are used throughout; *z*-scores are from the Wilcoxon signed-rank test; binomial *P*-values are from a sign test taking as the null hypothesis that differences between paired taxa are equally likely to be negative or positive.

Establishment rates

To assess whether larval migration has any effect on larval survival, we reviewed experimental data on adult establishment rates of migratory and non-migratory orally infecting gastrointestinal nematodes. Helminth establishment rates are generally negatively density dependent (Anderson, 1993), so we searched the literature for experiments in which a known dose of infective larvae was administered to immunocompetent, previously unexposed natural mammalian hosts by the normal transmission route, and in which the number of worms surviving to reproduce determined relatively soon after infections became patent. Where class of host was varied as an experimental treatment (e.g. sex, age, genotype), we calculated the across-group average weighted by sample size. In many cases, infective dose was varied as an experimental treatment, but we have also included experiments where a single dose was administered. Our literature review was not exhaustive, but we attempted to gather data from a range of nematode and host taxa, and from a range of laboratories. In principle, it would be possible to get data on adult establishment rates of migrants and non-migrants in previously exposed hosts. However, the protection afforded by acquired immunity is dependent on both the size of the primary dose and exposure regime as well as on the size of the challenging dose (Quinnell & Keymer, 1990) and we have been unable to find sufficient comparable data.

Table 2. Comparison of nematode sister taxa with and without a tissue phase during development in mammalian host (A) Size and life-histories of nematodes. (B) Size and generation time of their hosts.

(Tabulated are the number of sister taxon comparisons listed in Table 1 for which relevant life-history data were available, the number of such comparisons in which the geometric mean for taxon with a tissue phase (T+) was greater than that of its sister taxon remaining in the gastrointestinal system (T−), the test statistic (*z*) for the Wilcoxon ranked sign test (*n* as in first column) and associated probability value (*P*). Thus, there were sufficient data on female length to make 13 independent comparisons of taxon with a larval tissue phase and its sister taxon lacking a tissue phase; in 11 of these, females were on average longer in the tissue-developing taxon.)

	No. of possible sister-taxon comparisons	No. where T+ > T−	*z*	*P*
(A) Nematodes				
Female length	13	11	2·83	0·005
Female volume	12	11	2·82	0·005
Male length	13	10	2·34	0·019
Male volume	12	11	2·43	0·015
Egg volume	12	5	0·31	0·75
Pre-patency	10	5	1·07	0·28
Patency	4	3	1·46	0·14
Fecundity	1	1	—	—
Female growth rate	9	8	2·55	0·011
(B) Hosts				
Adult body size	11	5	0	1
Age to maturity	10	7	1·58	0·11
Maximum longevity	11	7	1·42	0·15

RESULTS

Amongst the 700 species of mammalian nematodes for which we have at least some relevant life-history data, there are 13 taxa with a tissue phase during development which have a sister group developing only in the gastrointestinal tract (Fig. 1, Table 1). These taxa include 288 species for which we have at least some life-history data; these species are listed in the Appendix. Not all comparisons could be used in all analyses (Table 2) because we were unable to find values for some sister taxa for some life-history variables.

With few exceptions, taxa developing in the tissues are larger bodied as adults than their closest relatives developing only in the gastrointestinal tract (Table 2A, Fig. 2). On average, females in taxa utilizing host tissues during development have a body volume about 25 times that of their closest relatives who develop only in the gastrointestinal tract. This greater size is apparently achieved by faster growth: time until first eggs or larvae are released into the environment (pre-patent period) is no greater in taxa with a tissue development phase. There is no evidence that egg size is affected by juvenile habitat. In addition, those few data available reveal no effect of a tissue phase on reproductive life-span (patency). Too few data were available to investigate any effects on fecundity.

Many species moving through the tissues during development remain to breed in the tissues. If greater size and faster growth rate are a consequence of a tissue phase prior to reproduction rather than an adaptive strategy associated with breeding in the tissues, then amongst nematodes breeding only in the gastrointestinal tract, those with a tissue phase should be larger than those which remain in the gut. This is indeed the case: amongst the 13 sister-taxon comparisons in Table 1, 6 consist of taxa which differ in their juvenile habitat but which all reproduce in the gastrointestinal tract, either following oral ingestion or skin penetration. In all 6, nematodes with tissue phases during development are still bigger (Fig. 2 comparisons A–F; binomial $P = 0{\cdot}031$; for both sexes: $z = 2{\cdot}20$, $P = 0{\cdot}028$). This is probably

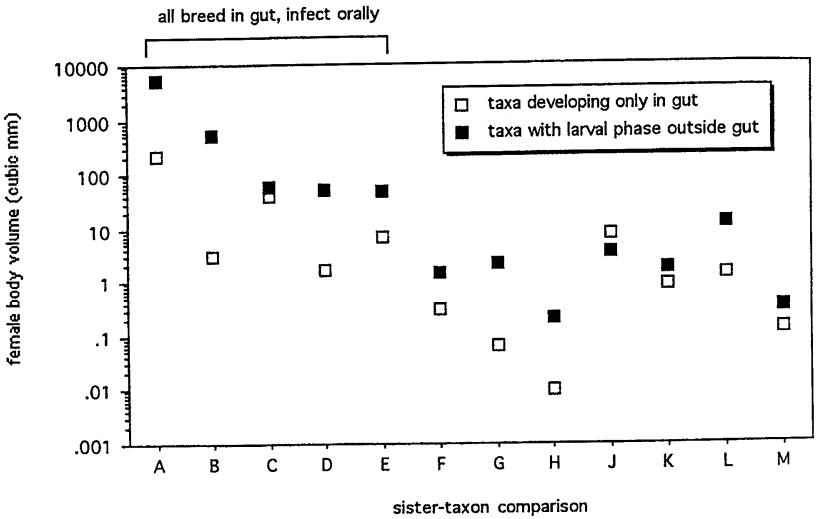

Fig. 2. Geometric mean female body size of nematode taxa developing in the tissues compared with their gastrointestine-dwelling sister taxon. In 11 out of 12 comparisons, females are bigger in taxa developing in the tissues than in closely related taxa developing only in the gastrointestinal tract. Plotted points are geometric means. Letters refer to the comparisons in Table 1. The first 5 comparisons are of orally-infecting taxa reproducing in the gastrointestinal tract with and without larval migration; species comparison F all breed in the gastrointestinal tract but sister taxa differ in their route of infection, species in other comparisons vary in route of infection and/or breeding habitat. We have no data on the female volume of any Habronematidae (comparison I).

associated with higher growth rates, but we have been able to obtain sufficient data for only 4 of the 6 comparisons. In all 4, growth rates of taxa with a tissue phase are higher, but not quite significantly so ($z = 1{\cdot}83$, $P = 0{\cdot}068$). There is no hint of differences in pre-patency amongst the 5 comparisons for which we have data ($z = 0{\cdot}67$, $P = 0{\cdot}50$).

Anderson (1992) suggested that nematode species with intermediate hosts can have accelerated larval growth. If so, the effect of tissue development on worm size could arise if taxa utilizing intermediate hosts are more likely to have tissue phases during development, as is so for vector-borne nematodes, for example. However, a life-cycle difference cannot underlie the association between the tissue phase and greater worm size. Of the sister-taxon comparisons in Table 1, 9 for which we have size data consist either of taxa with the same type of life-cycle (direct or indirect), or where the taxon developing only in the gastrointestinal tract has an indirect life-cycle and its sister taxon a direct life-cycle. In 8, adult female body volume is bigger in the tissue-developing taxon (binomial $P = 0{\cdot}039$; $z = 2{\cdot}43$, $P = 0{\cdot}015$). Of the subset of comparisons where the life-cycle of sister taxa is of the same type ($n = 7$), female volume is still bigger in taxa with a juvenile tissue phase ($z = 2{\cdot}03$, $P = 0{\cdot}043$).

Mammalian hosts of nematodes differ widely in their size and generation times. However, nematodes with tissue phases during development are no more likely to occur in bigger or longer lived hosts (Table 2B). Host diet also differs widely and may affect the relative frequency of oral and skin infection routes and hence the relative frequency of tissue-migrating nematodes in different hosts (Adamson, 1986). In 11 of the 13 comparisons in Table 1, sister taxa exploit hosts with different diets. However, in two comparisons host diet is the same, and in a further 6 a single diet category is shared by at least some members of each sister taxon. Excluding species within those taxa not sharing that diet, nematodes with tissue development are bigger than their wholly gastrointestinal sister taxa ($z = 2{\cdot}10$, $P = 0{\cdot}036$). Thus, differences in host diet cannot account for size differences of nematodes in different juvenile habitats.

The above analyses show that nematodes with a tissue phase during development grow faster and are larger as adults. Are worms which actively burrow out of the gut only to return to breed bigger than those that do not? Five of the cases in Table 1 involve comparisons of orally infecting gastrointestinal worms with and without larval migration. In all 5, female volume is larger in the migratory taxa

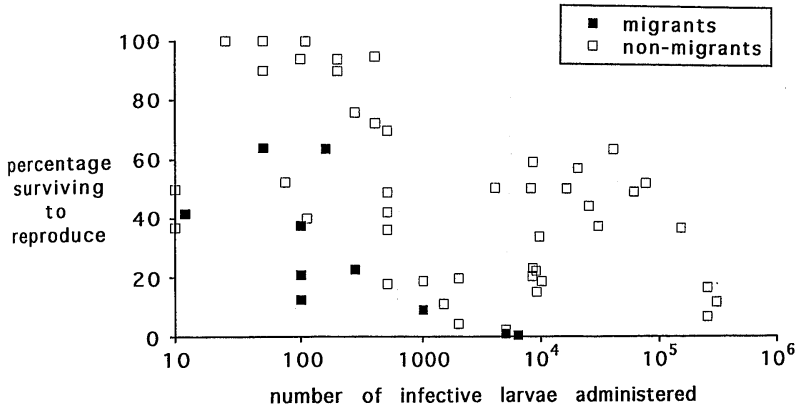

Fig. 3. Proportion of infective larvae reaching adulthood in experimental infections with orally infecting, gastrointestinal worms. Data are from the following species and studies: *Parascaris equorum* (Clayton & Duncan, 1977), *Ascaris suum* (Andersen *et al.* 1973; Galvin, 1968; Tromba, 1978), *Gnathostoma doloresi* (Wenceslao-Ollague *et al.* 1988), *G. spinigerum* (Imai *et al.* 1989), *G. hispidium* (Akahane & Mako, 1986), *Oesophagostomum columbianum* (Dobson, 1974; Dash, 1981), *O. venulosum* (Dash, 1981), *Ostertagia ostertagi* (Herlich, 1959; Anderson & Michel, 1977), *Trichostrongylus colubriformis* (Gregg & Dineen, 1978; Dineen & Windon, 1980), *T. axei* (Herlich, 1959; Goldberg, 1973), *Nematodirus battus* (Lumley & Lee, 1981), *Heligmosomoides polygyrus* (Dobson, Sitepu & Brindley, 1985; Robinson *et al.* 1989; Maema, 1986 (quoted by Anderson & May, 1991)), *Haemonchus contortus* (Altaif & Dargie, 1978; Barger & LeJambre, 1988), *Trichuris muris* (Wakelin, 1974, 1975*a*, *b*) and *Trichinella spiralis* (Murrell, 1985).

(Fig. 2 comparisons A–E; $z = 2{\cdot}02$, $P = 0{\cdot}043$). Unfortunately we have too few relevant pre-patency data to determine whether they, like other nematodes with tissue phases, grow faster.

The data we have gathered on establishment rates in naive hosts are shown in Fig. 3. For the most part, fewer adults establish when infective doses are larger, but for a given density, establishment rates are typically lower for species with larval migration. Given the variability involved, and that well-studied parasites represent rather few taxa, the data in Fig. 3 should be treated with some caution. Nevertheless, there is certainly no evidence that migration in naive hosts enhances establishment.

DISCUSSION

These analyses support our contention that there should be selective advantages associated with larval migration. Nematodes that develop in the tissues of their hosts are bigger and grow faster than their closest relatives developing only in the gastrointestinal tract. This previously unsuspected association between larval habitat and size is independent of any effects of adult habitat, worm life-cycle or host size, generation time or diet, and provides an obvious selective advantage to migration because body size is intimately linked with fecundity in nematodes (Skorping *et al.* 1991).

Why are worms growing faster when they develop outside the gastrointestinal tract? Presumably they do so because they can. This might be possible for several reasons. First, chemical demands in tissues are less severe. Worms in the gastrointestinal tract live in an organ specialized for breaking down organic material, and are consequently bathed in gastric acid, bile and a battery of digestive enzymes (Castro, 1990). Second, physical demands are less severe. Intestines are highly motile, the gut mucosa is frequently sloughed off, and the movement of gut contents is a constant threat. In contrast, the risk of dislodgement and the severity of its consequences are less in the tissues. For example, many anthelmintic drugs (e.g. piperazine) act by temporarily paralysing worms. This leads to rapid expulsion of gastrointestinal worms. These drugs also affect the ability of tissue stages to remain *in situ* against the movement of blood or lymph but, unlike gastrointestinal worms, dislodged tissue worms can frequently regain their original positions (Mansour, 1979). Third, the less aerobic environment of the gut lumen restricts respiration below that of the oxygen-rich tissues (Tielens, 1994). The tissue environment is also characterized by a constant supply of pre-processed nutrients. Four, host responses in the tissues and in the gastrointestinal tract differ both qualitatively and quantitatively. For example, gastrointestinal effector mechanisms are frequently non-specific, and include inflammatory responses over large areas and drastic changes in gut motility and

mucosal structures (Rothwell, 1989; Moqbel & MacDonald, 1990). Tissue responses are more typically specific and localized, perhaps because major trauma in organs other than the gastrointestinal tract would reduce host fitness more than would a few nematodes living in them. The host may also be able to use more severe oxidative bursts by leucocytes and macrophages to attack worms in the gastrointestinal tract: the anaerobic conditions make reactive oxygen intermediates less stable and consequently less damaging to the host itself.

Obviously, none of the difficulties posed by growth in the gastrointestinal system is insurmountable, and nematodes have a battery of effective defence strategies (Behnke, Barnard & Wakelin, 1992; Maizels *et al.* 1993). But these are unlikely to be costless. The more resources that have to be diverted into, for instance, the secretion of antioxidant enzymes, thickening of teguments, and moving from regions of inflammation, the slower growth will be. Thus, the harsher environment of the gastrointestinal tract may reduce growth rates below that possible in the tissues. Migrants avoid this, but run the risk of getting lost or trapped in inappropriate host tissues.

Many of these difficulties are largely associated with life in the gut lumen and could be avoided by larvae burrowing deep into the tissues of the gastrointestinal wall. Indeed, larvae of many of the species we have classified as gastrointestinal, such as many of the spirurids and trichostrongyles, do just that. Yet their relatives developing outside the gastrointestinal system still grow larger. Perhaps the most likely difficulty which might impede growth in the gastrointestinal system as a whole arises from the different nature of host responses in that organ relative to those in the tissues.

The idea that host tissues are a more benign habitat in which to grow explains a number of other phenomena. Orally infecting worms that are going to develop in the tissues do so very shortly after they arrive in the gastrointestinal tract, with little development occurring prior to migration (Anderson, 1992). Most skin-penetrating gastrointestinal worms undergo considerable development in the tissues before proceeding to their breeding site. No nematodes which breed in the tissues travel to the gastrointestinal tract to develop first. Carnivore-transmitted infective stages are inevitably found in the tissues of prey (Anderson, 1992); if growth is easier in the tissues, maintenance is also likely to be easier. Juvenile stages living in tissues are typically able to survive and even develop in hosts other than those they normally infect, but they are rapidly expelled from inappropriate gastrointestinal tracts. Finally, so far as we are aware, normally free-living nematodes are capable of some growth and development in the tissues (e.g. the rhabitiform *Micronema delatrix* in horses (Urquhart *et al.* 1987)), but not in the gastrointestinal tract, even though accidental ingestion must occur frequently.

Whatever the cause – and we are only too aware of the speculative nature of our discussion about the particular mechanisms involved – we have nevertheless demonstrated that, for some reason, taxa which escape the gastrointestinal tract during development are larger bodied. We suggest that this is sufficient to explain the existence of migratory behaviour. But if tissue migration is selectively advantageous because it allows greater growth, why don't all gastrointestinal nematodes migrate? Whether any behaviour is evolutionarily stable depends at least in part on the balance of costs and benefits; these are likely to vary in different taxa. In addition, as numerous authors have pointed out, migratory behaviour is apparently found in taxa which were ancestrally skin penetrating or heteroxenous (see Introduction section). If so, it may be that selection was more easily able to take advantage of the growth benefits of migration in taxa preadapted to penetrate or survive in tissues. In principle, it should be possible to investigate this using modern techniques of phylogenetic analysis and character state reconstruction (e.g. Maddison & Maddison, 1992), but we have resisted the temptation to do so because that requires considerably more information on non-mammalian nematodes and more accurate phylogenetic information than is currently available.

Our hypothesis that migration is selectively favoured because of associated growth advantages is open to further testing. Similar analyses could be done for the nematodes of other vertebrate groups, and some species of *Ancylostoma*, for example, have a tissue phase following skin penetration but not following oral infection. It should also be possible to investigate directly how resource allocation decisions affect growth in parasitic nematodes in different habitats. For instance, do larvae in the gut produce more antioxidant enzymes for their body size? In addition direct experimentation would be possible in species where migration following oral infection is facultative. We know of no such species, but suggest they might exist. For example, the development of concomitant immunity should alter the benefits of migration, so that in previously exposed hosts, larvae might avoid migration or limit their time in tissues. This may be especially so for male nematodes, where the fitness benefits of size may be less than for females.

Our results may be of more than just theoretical interest. Much of medical and veterinary intervention is likely to affect worm survivorship differently during gastrointestinal and tissue phases of migratory species. The different consequences of paralysis-inducing drugs in the two habitats discussed above is one such example; stage-specific vaccines and site-specific drugs are others. If, as we have argued, migration is maintained by natural selection, widespread use of some intervention strategies could select for prolonged tissue migration, with the consequence of producing larger (and more fecund) worms, as well as increasing pathology associated with more tissue migration. This possibility deserves theoretical and empirical investigation.

Finally, and more generally, our results suggest that we should view the host as a series of habitats within which the costs and benefits of particular life-history strategies will vary. The idea that habitat is a templet for life-history evolution (Southwood, 1977) has been pervasive in ecology, and there has been a proliferation of schemes attempting to classify habitats likely to generate similar life-histories (reviewed by Begon, Harper & Townsend, 1990). However, it has proved remarkably difficult to show that interspecific variation in life-histories of free-living organisms is associated with habitat variation, probably because of the difficulties of relating habitat to the age-specific mortality schedules which are believed to underpin life-history evolution (Charlesworth, 1980; Harvey, Read & Promislow, 1989; Stearns, 1992). This may be easier to do in host–parasite interactions, and viewing the host as a mosaic of habitats has the potential to explain variation in parasite traits such as migration routes (e.g. many tissue-dwelling nematodes develop in immunological havens such as the central nervous system), as well as site-specific variation in host responses and consequently in parasite defence strategies. We have, for example, already mentioned that the relative costs to a host of inflammatory responses and oxidative bursts are likely to vary between organs. More generally, it is likely that the optimal balance for hosts between the costs of parasitism and the costs of anti-worm responses (Behnke *et al.* 1992) depends on the location of the parasites. Such costs are likely to underlie much parasite diversity, as well as determine both the short-term and long-term consequences of particular intervention strategies.

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APPENDIX

Species represented in analysis

(Bold letters represent codes of sister taxon comparisons used in Table 1 and Fig. 2.)

A Juv. tissue phase
Ascaris lumbricoides, A. suum, Parascaris equorum
No tissue phase
Toxascaris leonina

B Juv. tissue phase
Toxocara canis
No tissue phase
Subulura andersoni, S. distans, S. elongata, S. hindi, S. indica, S. interrogans, S. jacchi, S. lanigeri, S. linstowi, S. neodistans, S. ortleppi, S. otolicini, S. perarmata, S. sarasinorum, S. schebeni, S. trinitatis, S. ungulatus, S. vulpis, S. funambulensis, Heterakis spumosa

C Juv. tissue phase
Gnathostoma spinigerum, G. hispidum
No tissue phase
Physaloptera praeputialis

D Juv. tissue phase
Spirocerca lupi
No tissue phase
Ascarops strongylina, Mastophorus muris

E Juv. tissue phase
Strongylus equinus, S. edentatus, S. vulgaris
No tissue phase
Triodontophorus serratus, T. minor, T. tenuicollis, T. brevicauda

F Juv. tissue phase
Anclysostoma caninum, A. braziliense, A. tubaeforme, A. duodenale
No tissue phase
Uncinaria stenocephala

G Juv. tissue phase
Calodium hepatica
No tissue phase
Aonchotheca erinacei

H Juv. tissue phase
Capillaria felis, C. splenacea, Eucoleus tenuis, E. aerophilus, Pearsonema mucronata, P. plica, Thominx longicauda
No tissue phase
Trichinella spiralis

I Juv. tissue phase
Crassicauda anthonyi, C. giliakiana, Placentonema gigantissima
No tissue phase
Draschia megastoma, Habronema muscae

J Juv. tissue phase
Thelazia rhodesi, T. californiensis, T. callipaeda, T. erschowi, T. gulosa, T. lacrymalis, T. leesei, T. skriabini, Oyspirura conjunctivalis, Pneumospirura hainanensis, P. capsulata, Metathelazia massino, M. multipapillata, M. petrovi, M. skrjabini, Vogeloides oesophagea, V. servalis, V. massinoi, V. ramanujacharii, Dipetalonema reconditum, D. dracunculoides, D. perstans, Wuchereria bancrofti, Brugia malayi, B. pahangi, B. patei, B. ceylonensis, Mansonella ozzardi, Litosomoides carinii, Ackertia burgosi, Edesonfilaria malayensis, Deraiophoronema evansi, Loa loa, Dirofilaria immitis, D. repens, D. tenuis, Onchocerca lienalis, O. armillata, O. gibsoni, O. cervicalis, O. volvulus, Elaephora poeli, E. schneideri, E. boehmi, Cordophilus sagitta, Stephanofilaria stilesi, S. dedoesi, S. assamensis, S. kaeli, S. zaheeri, Setaria cervi, S. digitata, S.

africana, S. marshalli, S. congolensis, S. bernardi, S. thomasi, S. equina, Suifilaria suis, Parafilaria bovicola, P. multipapillosa

No tissue phase

Gongylonema pulchrum

K Juv. tissue phase

Bunostomum phlebotomum, Acheilostoma moucheti, Gaigeria pachyscelis, Necator americanus, Grammocephalus varedatus, G. hybridatus, Metastrongylus apri, M. elongatus, M. salmi, M. pudendotectus, M. madagascariensis, Protostrongylus rufescens, P. boughtoni, P. brevispiculum, P. cameroni, P. skrjabini, P. unciphorus, P. raillieti, Spiculocaulus leuckarti, S. austriacus, S. kwongi, Cystocaulus ocreatus, C. nigrescens, Neostrongylus linearis, Varestrongylus pneumonicus, Muellerius capillaris, Elaphostrongylus rangiferi, Parelaphostrongylus tenuis, P. odocoilei, P. andersoni, Filaroides milksi, F. martis, F. hirthi, Oslerus rostratus, Angiostrongylus vasorum, A. cantonensis, A. abstrusus, Didelphostrongylus hayesi, Gurltia paralysans, Andersonstrongylus captivensis, Crenosoma vulpis, C. mephitidis, C. petrowi, C. goblei, C. taiga, C. hermani, Troglostrongylus subcrenatus, Skrjabingylus lutrae, S. chitwoodorum, S. nasicola, Dracunculus medinensis

No tissue phase

Oxyuris equi, O. karamoja, Auchenacantha galeopteri, A. hoeppli, Enterobius vermicularis, E. anthropopitheci, E. bipapillatus, E. brevicauda, E. buckleyi, E. lemuris, E. lerouxi, E. trypanuris, E. apapillus, E. callithricis, E. deserti, E. interlabiata, E. microon, E. minutus, E. nycticebi, E. sciuri, Passalurus ambiguus, P. abditus, P. assimilis, P. nonannulatus, Protozoophaga obesa, Syphacia obvelata, S. lahorea, S. montana, S. nigeriana, S. peromyscus, S. thompsoni, S. tineri, S. venteli, S. pallaryi, S. transafricana, Citellina dispar, C. alatau, C. levini, C. marmotae, C. petrovi, C. schulzi, C. skrjabini, C. triradiata, Evaginuris evaginata, Helminthoxys urichi, Skrjabinema ovis, S. oreamni, S. parva, S. rupicaprae, S. tarandi, Heteroxynema cucullatum, H. wernecki, Dentostomella translucida, Dermatopallarya baylisi, Aspiculuris tetraptera, A. ackerti, A. americana, A. asiatica, A. kazakstanica, A. schulzi, Dermatoxys veligera, D. getula, D. polyoon, D. proboscidiphora, D. romerolagi, D. rufucaudata, D. vlakhaasi, Cephaluris ochotonae, C. andrejevi, C. coloradensis, Labiostomum naimi, L. vesicularis

L Juv. tissue phase

Mammomonogamus laryngeus, M. auris, M. ierei, M. megaughei, M. dispar, Stephanurus dentatus

No tissue phase

Cyathostomum coronatum, C. longibursatum, C. carandicum, C. catinatum, C. labiatum, C. minutum, Cylicocyclys brevicapsulatum, Cylicostephanus hybridus, C. leptostomum, C. bidentatum, C. asymmetricum, Cylindropharynx brevicauda, C. intermedia, C. rhodesiensis, Cylicodontophorus bicoronatus, C. mettami, C. ornatum, Chabertia ovina, Oesophagostomum radiatum, O. columbianum, O. venulosum, O. dentatum

M Juv. tissue phase

Nippostrongylus brasiliensis, Heligmostrongylus hepaticum, Dictyocaulus viviparus, D. filaria, D. arnfieldi

No tissue phase

Trichostrongylus axei, T. retortaeformis, T. colubriformis, Ostertagia ostertagi, Cooperia curticei, C. pectinata, C. punctata, Haemonchus contortus, Nematodirus filicollis, N. battus, N. helvetianus, Heligmosomoides polygyrus.

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