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Review article

Longevity and ageing in parasitic and free-living nematodes

David Gems
Department of Biology, University College London, 4 Stephenson Way, London NW1 2HE, UK
(e-mail: dgems@galton.ucl.ac.uk)

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Abstract

In the developing field of biological gerontology, rapid advances have recently been made in the genetics of ageing in the nematode *Caenorhabditis elegans*. The aim of this work is to develop an understanding of the general mechanisms determining the ageing process. Within the last decade the prospect of actually achieving this somewhat hubristic aim has begun to look startlingly real. In this context, knowledge of every aspect of the biology of ageing in nematodes is of added interest. Here the patterns of ageing observed among parasitic and free-living nematodes are surveyed and compared. Like insects, nematode species exhibit enormous differences in the rate of ageing, with maximum life spans varying over more than a 1000-fold range, from three days in free-living *Rhabdias bufonis* adults, to at least 15 years in the filarial parasite *Loa loa*. The possible evolutionary and mechanistic causes of such differences in ageing are discussed.

Introduction

The mechanistic basis of ageing remains essentially an unsolved mystery, although there are a number of theories for which there is some empirical support (Rose 1991; Finch 1990). An experimental approach that may succeed in revealing the nature of ageing is the use of short-lived model organisms for genetic studies (Jazwinski 1996). Work using the free-living nematode *Caenorhabditis elegans* has been particularly fruitful (Kenyon 1997; Hekimi et al. 1998; Gems 1999). Many dozens of genes have been identified where mutation increases life span, and the molecular pathways and processes that determine the rate of ageing are being revealed. Given the intense effort currently being invested into the study of ageing in *C. elegans*, it is interesting to compare its pattern of ageing with what is know about those of other nematode species, both free-living and parasitic. The following survey, which is drawn from the extensive parasitological and nematological literature covering a period of over a century, is far from being exhaustive. Its principal aim is to give a general comparative overview of ageing in the phylum Nematoda, and to examine how ageing varies with other aspects of life history, and ecology. A further aim is to identify nematodes with interesting patterns of ageing that warrant further gerontological investigation. This survey largely excludes the extensive work carried out on ageing in *C. elegans*, and the other nematode model species *Caenorhabditis briggsae* and *Turbatrix aceti*, which is reviewed elsewhere (Zuckerman 1980; Kenyon 1997; Gems 2000).

Nematodes exhibit a remarkable diversity of life histories, which includes considerable variation in adult life span and rate of ageing. Life histories are sometimes divided into two sorts according to the reproductive schedule. In semelparous life histories, a single bout of reproduction is followed fairly rapidly by death. By contrast, in iteroparous life histories, multiple rounds of reproduction occur (Finch 1990). Longer-lived species are typically iteroparous, with some exceptions, such as the century plant, *Agave americana*. Iteroparous species are generally

those that reproduce seasonally over successive years. Among nematodes, the species with the longest-lived adults are parasitic, for example the hookworm *Ancylostoma duodenale*, which live for up to 15 years (Hyman 1951). Here reproduction is continuous rather than intermittent, probably the consequence of the continuous availability of host nutrients. By contrast, the reproductive life span of the human pinworm *Enterobius vermicularis* is only a few weeks. Such species have been referred to as iteroparous and semelparous, respectively (Morand 1996). Yet in the absence of intermittent or seasonal reproduction in iteroparous species, the distinction is unclear between a short-lived iteroparous species and one that is semelparous.

Problems of observing nematode ageing

Measuring ageing in nematodes can be difficult for several reasons. Firstly, it can be hard to determine whether morbidity or death results from ageing or from extrinsic causes, e.g. in the case of parasitic nematodes, attack by the host immune system. One characteristic feature of ageing is an exponential increase in the rate of mortality with increasing age (Finch 1990). Unfortunately, accurate age-specific mortality measurements have only been made on a small number of free-living species, and estimating age-specific mortality in parasitic nematodes is problematic. In fact, as was once observed, "... there is no proof that infections of the very long lived parasitic nematodes are limited by senescence" (Finch 1990). In the relatively few nematode species where ageing has been examined, all that is typically available is survival data from small ageing cohorts, or estimates of maximum life span.

In the case of free-living nematodes, several factors confound estimates of ageing and potential longevity, and comparisons between species-specific rates of ageing. Firstly, as in other ectothermic organisms, nematode life span depends on the ambient temperature such that longevity is greater at lower temperatures, within the physiological temperature range (Zuckerman et al. 1971; Klass 1977; Suzuki et al. 1978). Secondly, in survival studies it is not always clear whether animals are dying as the consequence of ageing, or some other cause, e.g. non-optimal culture conditions, or effects of bacteria. Thirdly, longevity is affected by various aspects of reproduction, such as mating, which shortens life span (Honda 1925; Suzuki et al. 1978; Gems and Riddle 1996).

Observing ageing in parasitic nematodes is especially problematic. Here, estimates of longevity and the rate of ageing must be derived from the patency period (the duration of the parasitic infection). This can be measured either by observing the continued appearance of progeny, indicating the persistence of adults, or by carrying out experimental infections and periodically examining the infected host, e.g. by dissecting out the gut. However, when inferring the longevity of adult parasitic nematodes from patency periods, several factors have to be taken into account. Firstly, the patency period may merely reflect the efficiency of host immunity rather than nematode life span potential. However, some parasitic nematodes possess efficient immune evasion mechanisms, such that maximum observed life spans may approximate life span potential as limited by ageing, e.g. in *Onchocerca volvulus*, the filarial nematode which causes river blindness in humans (Remme et al. 1990; Plaisier et al. 1991). In some parasitic nematodes where the patency period is usually limited by host immunity, a better idea of potential longevity may be obtained either by using immunocompromised hosts (Wakelin and Selby 1974; Gemmill et al. 1997), or levels of infection too low to provoke a host immune response (Graham 1938). Measurements of the patency period can, at the very least, give a lower estimate of the life span potential.

Secondly, the length of patency will only be a good indicator of adult longevity if the host does not get reinfected, either by the progeny of the infecting parasites within the body (autoinfection), or by further infection from the environment. In infections of humans with some parasitic nematode species, it is possible to estimate longevity by following the course of infections in individuals who have moved away from endemic regions (Sandground 1936). In other parasitic species, nematode life span is impossible to measure, either due to the occurrence of autoinfection, as in the human parasite *Strongyloides stercoralis* (Schad 1989), or because not all infecting nematodes develop directly into adults, but instead arrest development for variable periods, as in the rabbit stomach worm *Obeliscoides cuniculi* (Watkins and Fernando 1986). All these problems of observation and comparability have to be borne in mind when surveying longevity and ageing among nematode species.

Table 1. Adult longevity in parasitic nematodes.

Species	Maximum adult life span[a]	Class of life span estimate[b]	Host[c]	Reference
SECERNENTEA				
Strongylida (hookworms)				
Ancylostoma braziliense	>32 weeks	D (C)	Cats	Sarles (1929b)
A. caninum	100 weeks	D (C)	Dogs	Sarles (1929a)
A. duodenale	15 years	(A)	Humans	Hyman (1951)
Haemonchus contortus	>2 years	D (C)	Sheep	Adams (1981)
Heligmosomoides polygyrus	114 days	A, E	Mice	Kerboeuf (1982)
Necator americanus	14 years	(A)	Humans	Palmer (1955)
Nippostrongylus brasiliensis	16 days	C	Rats	Mayberry (1985)
Oslerus osleri (Filaroides)	4–5 months	D	Dogs	Pillers (1935)
Trichostrongylus	8 years	(A), E	Humans	Sandground (1936)
Uncinaria lucasi	< 3 months	D	Fur seals	Olsen (1965)
U. stenocephala	30 weeks	D	Dogs	Sarles (1929)
Spirurida (filarial nematodes)				
Brugia malayi	6–7 years	(A)	Humans	Wang (1994)
B. pahangi	7–8 years	(A)	Humans	Wilson (1971)
Dipetalonema viteae	25 months	D	Jirds	Johnson (1974)
Dirofilaria immitis	7 years	(A)	Dogs	Sandground (1936)
Dracunculus insignis	36, 47 weeks, F, M	D, E (males)	Ferrets	Brandt (1990a, b)
*Litomosoides sigmodontis*4	3 years	D	Cotton rats	Olsen (1974)
Loa loa	17–20 years	(A)	Humans	Coutelen (1935)
Onchocerca volvulus	13–14 years	A	Humans	Plaisier (1991)
Wuchereria bancrofti	6–8 years	(A)	Humans	Leeuwin (1962) Mahoney (1970)
Ascaridida (roundworms)				
Ascaris lumbricoides	1–2 years	D	Humans	Croll (1982)
Pseudoterranova decipiens	2–3 weeks	D (C)	Seals	des Clers (1990)
Toxocara canis	3–6 months	D (C)	Dogs	Lloyd (1993)
Strongyloididae				
Rhabdias bufonis	5, 3 days, F, M	—	FL	Spieler (1995)
	3 months	D, E	Amphibians	Goater (1991)
R. fuscovensa	9 months	D, E	Snakes	Chu (1936)
Strongyloides fuelleborni	15, 9 days, F, M	—	FL	Augustine (1940)
S. ratti	2 weeks, F, M	—	FL	Gemmill (1997)
	55 weeks	B, E	Rats	Graham (1938)
S. simiae	12 days	—	FL	Augustine (1940)
S. stercoralis	>2 days, F	—	FL	Yamada (1991)
Oxyuridae (pinworms)				
Enterobius vermicularis	2 months	D (C)	Human	Sandground (1936)
Heterakis spumosa	>10 months	D	Mouse	Sandground (1936)
ADENOPHOREA				
Trichocephalida (whip-worms)				
Trichinella spiralis	3 months	D (C)	Rats	Finch (1990)
	5 weeks	D (C)	Guinea pigs	McCoy (1932)
Trichuris muris	10 weeks	B	Mice	Wakelin (1974)

Table 1. Continued.

Species	Maximum adult life span[a]	Class of life span estimate[b]	Host[c]	Reference
Mermithidae				
Agamermis decaudata	>18 months	—	Insects, snails	Christie (1929)
Dioctophymoideae				
Dioctophyma renale	3 years	D	Dogs	Olsen (1974)

[a]F, females; M, males.
[b]The degree to which maximum reported life span of parasitic species reflects the life span potential of the species (i.e., longevity as limited by ageing) varies between species. To give an indication of the reliability of maximum reported life span as an indicator of ageing estimates are classified to five groups. (A) Species with effective host immune evasion mechanisms, where maximum life span is not limited by host immunity. (B) Species where patency is usually limited by host immunity, but where adult parasite survival data has been obtained from immunocompromised hosts or trickle infections. (C) Species where reported life span is likely to reflect host immunity alone. (D) Species where relative contribution of host immunity and nematode ageing to nematode life expectancy is unclear. In (A) and (B) species maximum reported life span is a better indicator of life span potential than in (C) and (D) species. (E) Species where maximum life span estimation was limited by the length of the observation period. Parentheses indicate tentative designation.
[c]FL, free-living form.
[d]Prevously *L. carinii.*

Ageing in parasitic nematodes

Parasitic nematodes which infect vertebrates fall broadly into two groups: those that reproduce in the alimentary canal, and tissue-dwelling species. Intestinal parasitic nematodes include the strongylids (e.g. hookworms), the ascarids (roundworms), some of the Strongyloididae, and the trichocephalids (whipworms). Tissue-dwelling species of medical and veterinary importance are largely members of the Spirurida (filarial worms), for example, *Wuchereria bancrofti*, which causes lymphatic filariasis (elephantiasis). Maximum life span estimates of parasitic nematodes are summarised in Table 1.

The Strongylida

This is an order of parasitic species that live in the gut of vertebrate species, and includes the hookworms. Recent phylogenetic analysis using small subunit ribosomal DNA sequences indicates that the order Strongylida is most closely related to the suborder Rhabditina (Blaxter et al. 1998), which includes the laboratory model species *C. elegans*. Thus, ageing in strongylids is of particular relevance to the study of ageing.

Estimates of longevity in hookworm species that parasitise humans are derived from two main approaches: the survey of levels of infection among inmates of institutions such as prisons and mental hospitals, and experimental self-infections by investigators. For example, Mhaskar (1920) studied the levels of *Ancylostoma duodenale* infection among prisoners in Trichinopoly Jail in Madras, India, where the sanitary conditions largely precluded reinfection. Comparing prisoners whose period of incarceration ranged from a few days to 16–17 years, infection levels were found to decline with increasing length of stay. After five years most infections had cleared, but occasional worms were found even after 16 years. Similar results were obtained from a study in Alipore Jail in Calcutta, of *A. duodenale* and *Necator americanus*: egg output by infected prisoners was reduced by 90% after four years, and by 95% after eight years (Chandler 1925). The percentage of infected individuals only declined appreciably after five years, with occasional instances of infection being found even after 20 years of incarceration. From this it was inferred that the majority of hookworms are lost from the gut before reaching the limit of their life spans; that infections found after 20 or even 10 years probably result from reinfection; and that the maximum life span of the hookworm is 6–7 years. These conclusions are supported by a study from the Georgia State Sanatorium, USA, where the percentage of patients infected with hookworms remained steady during the first six years of residence, and then dropped markedly (Willets 1917).

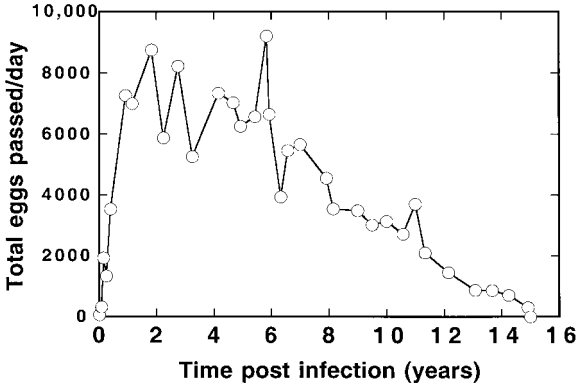

Figure 1. Egg output in a case of *Necator americanus* infection. Evidence from an experimental infection demonstrates the maximum fecundic life span of *N. americanus* to be at least 15 years. Data derived from Palmer (1995).

The Trichinopoly jail study also examined infections with *N. americanus*, which largely ceased after about seven years, with no worms detected after 12 years. However, a much higher estimate of longevity in *N. americanus* was derived from an experimental infection by Palmer (1955), presumably of himself. Egg production reached a plateau by 11 months post-infection, which lasted six years, and then gradually declined until the 14th year (Figure 1). The rapid drop in the intensity of infection observed among the Indian prisoners was not seen in the Palmer study. This is unlikely to be due to a lower intensity of infection in the latter, whose initial worm burden was estimated to be around 200 adults. Similarly, egg production was high, approximately 3,000–9,000 eggs/gram of faeces during the infection plateau (Palmer 1955), compared to approximately 1,000 eggs/gram (average) in 27 new, hookworm-infected prisoners at Alipore Jail, falling to 290 eggs/gram after only a few months (Chandler 1925). Thus, it is unclear whether the maximum life span of *N. americanus* is 6–7 years or 14 years. Two other light self-infections with *Necator* by parasitologists persisted in one case for over four years, and in the other, less than six months (Chandler and Read 1961). Another experimental self-infection with hookworm involved a species of *Trichostrongylus* originating from Zimbabwe (possibly *T. colubriformis*). In this study, no reduction of egg-production was observed at 8.5 years post-infection (Sandground 1936).

What is known of the life spans of animal-parasitic strongylid nematodes is largely derived from experimental infections. These are typically cleared relatively quickly as the result of host immunity. For example, experimental infections of young dogs with *Ancylostoma caninum* were cleared within 43–100 weeks (Sarles 1929a). The rate of egg-production decayed exponentially with time, due to a constant rate of loss of adults from the gut. Most adult worms were expelled within a few months. Experimental infections of dogs and cats with *Ancylostoma braziliense* gave similar results: most adults survived less than two weeks in a young cat, but a few survived for up to 32 weeks (Sarles 1929b). This infection probably did not end as the result of nematode ageing, since the one female adult worm recovered from the host after autopsy was found to contain fertilised eggs. The constant rate of loss of adults from the gut also supports this conclusion. *A. braziliense* survive up to 30 weeks in dogs. In conclusion, minimum estimates of potential life span in *A. caninum* and *A. braziliense* are 100 weeks and 32 weeks, respectively.

Haemonchus contortus is the twisted wireworm of sheep and other ruminants. Here the patency period depends on the intensity of infection. Heavy infections are cleared within five months (Stoll 1929, cited in Sandground 1936). In the absence of reinfection, infections of sheep can last for more than two years (Adams and Beh 1981). In one experimental infection of a cow, *H. contortus* egg production had almost ceased by 15 months post infection (Mayhew 1942).

One animal parasitic strongylid where infections are not always cleared by host immunity is the laboratory model nematode *Heligmosomoides polygyrus* (*Nematospiroides dubius*). In one study involving infections of mice, adult population size showed no decline after 114 days, although there was a drop in fertility (Kerboeuf 1982). In a study of a second laboratory model nematode, the trichostrongylid *Nippostrongylus brasiliensis*, which infects rodents, infections were cleared by 16 days after inoculation (Mayberry et al. 1985). However, in low level infections this nematode can survive for a much longer period (R.M. Maizels, personal communication).

The Ascaridida

By comparison with the hookworms, ascarid nematodes (roundworms) have relatively short patency periods. The life expectancy of *Ascaris lumbricoides*, which live in the intestinal lumen of humans, ranges from a few weeks to a month (Croll et al. 1982). Estimates of *A. lumbricoides* longevity range from less

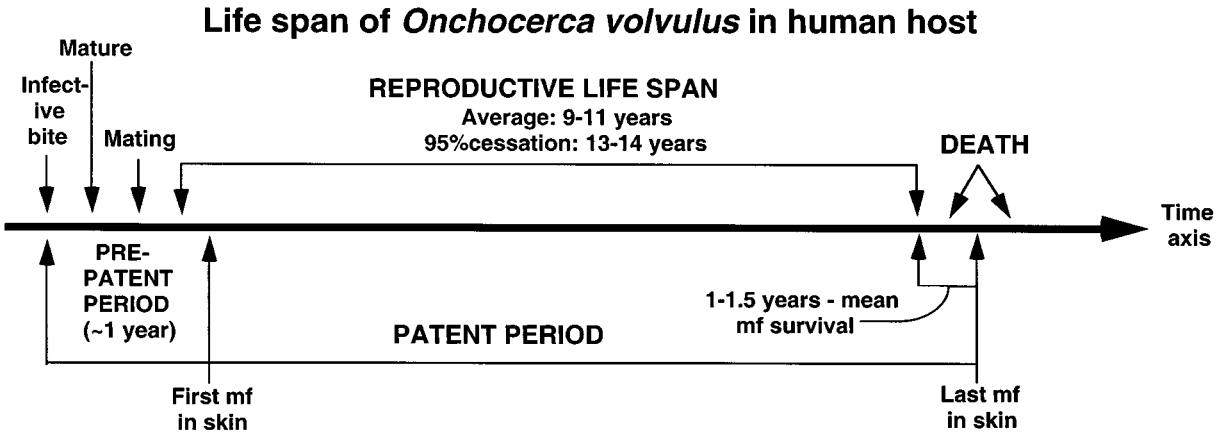

Figure 2. Life history of *Onchocerca volvulus* in the human host. mf = microfilariae. Adapted from Remme et al. (1986).

than a year (Keller 1931; Otto 1932) to 1–2 years (Croll et al. 1982). One possibility is that the failure to persist of *A. lumbricoides* is due to the lack of a fully effective mechanism for adult worms to anchor themselves within the gut and avoid expulsion resulting from peristalsis (Otto 1932). By contrast, hookworms anchor themselves firmly to the gut by burrowing their head into the intestinal mucosa. Trichocephalid nematodes (whip-worms) anchor themselves to the gut wall in a similar fashion by means of the whip-like anterior end of the body (although the trichocephalids appear relatively short-lived, see below). Other estimates of life span in ascarid species include 2–3 weeks for the seal-worm *Pseudoterranova decipiens*, and 279 days (life expectancy) for *Parascaris equorum*, which infects horses (Mozgovoy 1953, cited in Morand 1996). Adult *Toxocara canis* occur in lactating bitches, and puppies (Lloyd 1993). Adult worms are cleared from the gut of puppies within 3–6 months of birth. In conclusion, not much is known at all about ageing in this important nematode group.

The Spirurida

The filarial parasitic nematodes include a number of very long-lived species, particularly among those that infect humans. Estimates of the longevity of adult filarial worms in human infections are largely derived from studies of infected individuals after extended periods during which no reinfection could occur. Since autoinfection does not occur in filarial nematodes, the longevity of the infection reflects either the intrinsic longevity of the adult worms, or the gradual effects of host immunity.

The filarial nematode species which has been best characterised in terms of ageing is *Onchocerca volvulus*, which causes river blindness in humans. In a number of areas endemic for onchocerciasis, reinfection has been prevented by eradication of the secondary host vector, the blackfly (*Simulium* species), which transmits the infective third stage larva of *O. volvulus*. Adults produce developmentally arrested first stage larvae (microfilariae), which are able to survive for up to about 1.5 years. In an early study carried out in Kenya, *O. volvulus* microfilariae (mfs) were observed in human hosts 9 and 11 years after blackfly eradication, but not after 18 years (Roberts et al. 1967).

The most detailed analysis of ageing in *O. volvulus* comes from studies of infected individuals after vector eradication by the W.H.O. Onchocerciasis Programme in West Africa. Data on the declining prevalence of mfs and adults was incorporated into an epidemiological model of *O. volvulus* infection, taking into account a number of variables affecting the course of infections, including parasite reproductive life span, which limits the period of infection (Remme et al. 1990; Plaisier et al. 1991). Model predictions and field data indicated that the mean reproductive life span of *O. volvulus* is 9–11 years, with 95% of animals ceasing reproduction by 13–14 years of age (Plaisier et al. 1991) (Figure 2). Variation in adult life span was modelled in terms of the Weibull equation, which is often used to described the mortality rate accelerations accompanying ageing. Significantly, at the end of infections, 12–14 years after vector eradication, the prevalence of infection declined at an accelerated rate (Remme et al. 1990). This is consistent with the

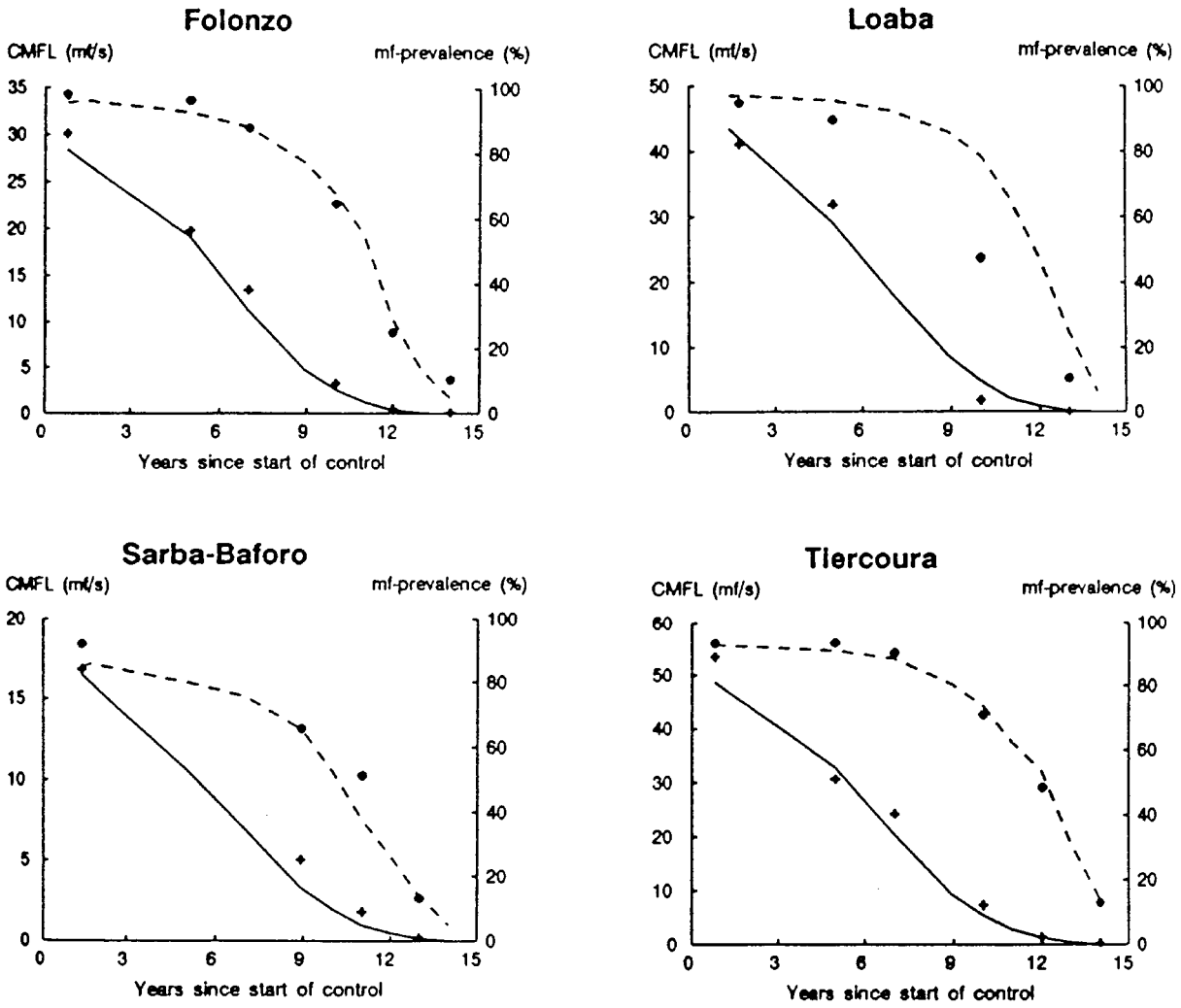

Figure 3. Simulated and observed treads in *Onchocerca volvulus* mf (microfilariae) prevalence and CMFL (Community Microfilarial Load) in four West African villages. Symbols: filled circles = mf prevalence observed; broken line = mf prevalence simulated; + = CMFL observed; unbroken line = CMFL simulated. CMFL is expressed as the mean number of mfs per biopsy (skin snip) for all individuals over 20 years of age. The decline of mf-prevalence reflects the declining fertility and survival of adult *O. volvulus*. Reproduced with permission from Plaiser et al. (1991).

occurrence of senescence in *O. volvulus* adult populations, and is the only case where clear evidence exists for ageing in a parasitic nematode. Figure 3 gives some examples of the pattern of decline of prevalence of *O. volvulus* mfs with time after blackfly eradication. *O. volvulus* reproductive life span has also been estimated in chimpanzee hosts (Duke 1980). This study yielded shorter estimates of life span, with mfs disappearing from four animals after 6–9 years.

Extensive studies have also been carried out on excised ageing *O. volvulus* adults, or macrofilariae. These are largely found in sub-dermal nodules (onchocercomata), which contain between one and several dozen worms. To study ageing in *O. volvulus* adults, nodules were surgically excised from populations at varying intervals after blackfly eradication. Increasing numbers of macrofilariae from populations 7–10 years after vector eradication showed apparent signs of ageing. Young adult worms were largely transparent, and had an almost clean cuticle. By contrast, older worms became increasingly opaque, and brownish in colour (Karam et al. 1987), and accumulated an iron

pigment in the body wall and the uterus (Büttner et al. 1983). They also exhibited large numbers of iron-containing spherules in the intestinal epithelium, uterine muscles, and to a lesser extent the uterine epithelium, visible under the electron microscope (Franz and Büttner 1983). As adult females aged, increasing amounts of collagenase-resistant incrustations were seen on most parts of the cuticle, and whitish inclusions accumulated in the body fluid, and within the muscular layer of the body wall (Schulz-Key et al. 1980). The final stage of these changes was body calcification and death.

It is likely that these changes to some extent represent the cumulative effects of interactions with the host resulting from the sessile habit of female worms: male worms, which are more motile (going in search of females), retained a clean, smooth cuticle (Schulz-Key et al. 1980). Males are also less subject to calcification: in one survey of adult worms in an endemic area, 8% of females but only 0.5% of males were calcified (Albiez et al. 1984). This suggests that calcification is not a senescence-specific form of deterioration. This possibility is supported by the fact that a dramatic increase was seen in the number of calcified worms after treatment of onchocerciasis sufferers with a nematocidal drug (Wolf et al. 1980).

In nodules from endemic areas, females outnumber males by approximately 1.5 : 1 (Albiez et al. 1984; Karam et al. 1987). In ageing populations of *O. volvulus*, this ratio decreases, suggesting that male life expectancy may exceed that of females (Karam et al. 1987). This is consistent with the observation that males exhibit a lower level of cuticular incrustations and calcification (Schulz-Key et al. 1980; Albiez et al. 1984). However, an alternative explanation is that males merely become less peripatetic with increasing age, and therefore appear in nodules with higher frequency.

Adult *O. volvulus* fecundity remains constant for eight years and then gradually drops (Remme et al. 1990). This reduction in fertility may to some extent result from a decrease in the frequency of mating, as suggested by the observation that with increasing age an increasing proportion of males contained undelivered sperm (Karam et al. 1987). A few males with brownish bodies and empty testes were also found, and were taken to be senescent. Among female worms from individuals in endemic areas, the uterus was empty in 21% of females (Karam et al. 1987). By contrast, 9–10 years after blackfly eradication this had increased to 47%. These results are consistent with the occurrence of senescence in both sexes in *O. volvulus*.

The filarial nematodes which cause lymphatic filariasis (including elephantiasis) in humans, such as *Loa loa*, *Wuchereria bancrofti* and *Brugia malayi*, are also very long-lived. There are several early reports of the duration of *L. loa* infections involving Westerners returning from the tropics with filariasis infections (reviewed in Coutelen 1935). *L. loa* adults migrate around the body and have the unsettling habit of emerging unexpectedly from under the eyelids of their host. In one report, an infected doctor describes drawing six *L. loa* adult females from his own eyes, by tying a silk thread around the end of each worm. This he did at intervals over a period of 10 years, the last one 15 years after leaving an area endemic for *L. loa* (Eveland et al. 1975). Earlier reports describe *L. loa* infections lasting 15 years (Knabe 1932) 17 years (Manson-Bahr 1925), and even 20 years (Connal 1923, cited in Coutelen 1935).

As in *O. volvulus*, lower estimates of mean reproductive life span of *W. bancrofti* were derived from studies of infected populations in India after programmes of eradication of the secondary host (in this case, a mosquito). These were 10.2 years (Vanamail et al. 1990), 5.4 years (Vanamail et al. 1989), and 5.0 years (Vanamail et al. 1996). Case histories of infected individuals moving from endemic areas have given a similar range of estimates of maximum life span for *W. bancrofti*: 5 years (Bancroft 1879; Guptavanij and Harinasuta 1971), 6 years (Jachowski et al. 1951), 7.5 years (Conn and Greenslit 1952), and 8 years (Leeuwin 1962; Mahoney and Aiu 1970). Given that mfs may survive several years, this suggests a conservative estimate of maximum reproductive life span of *W. bancrofti* of around 6–8 years. However, several reports suggest much higher estimates of *W. bancrofti* longevity (Manson-Bahr 1959; Trent 1963; Carme and Laigret 1979).

Another unpleasant filarial parasite is *Brugia malayi*. From studies of human populations in areas previously endemic for the periodic form of this nematode after eradication of the mosquito vector, the mean fecundic life span was estimated at 3.5 years (Krishnamoorthy et al. 1991; Sabesan et al. 1991). A considerably higher value was obtained from a study where a researcher experimentally infected himself and two members of his family with periodic *B. malayi*, and remained microfilaremic for up to 8.5 years (Wang et al. 1994). From the report of this work it is painfully clear that this investigation caused

considerable suffering to its subjects. In a further two cases of individuals infected with *B. malayi* in Southeast Asia who left endemic areas, circulating mfs disappeared in one case after seven years, while the other was still microfilaremic after seven years (Guptavanij and Harinasuta 1971). Taken together, this suggests a lower estimate of *B. malayi* maximum reproductive life span of approximately 6–7 years.

Estimates of adult life span in animal parasitic filarial nematodes are generally lower than in species that infect humans. In infections of dogs with *Dirofilaria immitis* (dog heartworm), mfs were observed seven years after infections (Fülleborn 1929, cited in (Sandground 1936). However, (Olsen 1974) estimates the reproductive period of adult *D. immitis* to be only 2–5 years. In infections of cotton rats with *Litomosoides sigmodontis* (previously *L. carinii*) the majority of adult worms died within the first year, with a minority surviving for about three years (Olsen 1974). Adults of another rodent parasitic species, *Dipetalonema viteae* survived for up to two years in jirds (*Meriones unguiculatus*) (Johnson et al. 1974). One 25-month-old female was found to contain mfs in the uterus, and spermatozoa in the seminal vesicle, suggesting that she was not yet senescent.

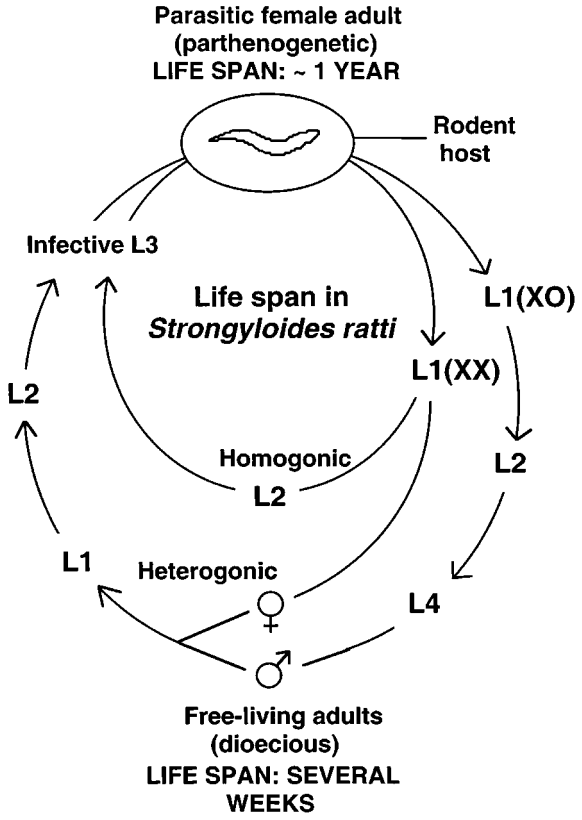

Figure 4. Life cycle and life span in *Strongyloides ratti*. Adapted from Harvey (1999). L denotes larval stages.

The Strongyloididae

Most species in this group have both parasitic and free-living adult forms. In terms of the biology of ageing, the Strongyloididae are particularly interesting since the parasitic adult forms appear to be intrinsically much longer lived than the free-living adult forms of the same species. Two major genera are *Strongyloides* and *Rhabdias. Strongyloides* species infect vertebrate hosts ranging from mammals and birds to reptiles and amphibians (Speare 1989), while *Rhabdias* species infect reptiles and amphibians alone. *S. stercoralis* causes human strongyloidiasis (Cochin China diarrhoea) which can be fatal in frail patients. Infections of infants with *S. fuelleborni kellyi* can also result in fatality (Ashford and Barnish 1989).

Strongyloides ratti has been used extensively as a laboratory model (Viney 1999). In this species parthenogenetic female adults reproduce in the intestinal mucosa of rodents. The resulting eggs hatch, pass out with the faeces, and then develop through one of two routes. Direct (homogonic) development leads to formation of infective filariform third stage female larvae (iL3s). Indirect (heterogonic) development leads to free-living rhabditid males and females (Figure 4). These mate and produce filariform progeny only (Bolla and Roberts 1968). As in *S. ratti*, the free-living adults of the human parasitic species *S. stercoralis* give rise only to filariform larval progeny. However, other species have been maintained through numerous free-living generations, e.g. *S. simiae* (14 generations), *S. fuelleborni* (Augustine 1940), and *S. planiceps* (9 generations) (Yamada et al. 1991). Infections of immunocompetent rodents with *S. ratti* are cleared rapidly from the gut: within around 10 days in mice, or in rats from 16 days (Dawkins 1989) to 3–6 weeks (Sheldon 1937; Gemmill et al. 1997). However, the potential life span of *S. ratti* parasitic adults appears to be much greater. Infections of immunodeficient hypothymic (nude) rats were found still to be patent after 46 weeks, although a decline in progeny production occurred after 31 weeks, dropping from over 10,000 larvae/night to less than 100 larvae/night by 46 weeks. (Gemmill et al. 1997). In immunocompetent rats infected with single *S. ratti* adults, a small proportion of infections were still

patent after 55 weeks (Graham 1938). This suggests that the maximum life span of *S. ratti* parasitic adults may be over a year. It is not possible to estimate the life span of the parasitic adults of *S. stercoralis* due to the occurrence of autoinfection (hyperinfection), where infective larvae reinfect the host from within the gut (this does not occur in *S. ratti*). However, long- lived, non-reproductive *S. stercoralis* parasitic females are believed to persist in occult infections, giving rise to recrudescing strongyloidiasis upon immunosuppression (Mansfield et al. 1996).

Free-living strongyloidid adults exhibit a very different pattern of ageing. Estimates of the maximum life span of free-living adult *S. ratti* range from 3–4 days at 25 °C, to 2 weeks at 13 °C (Gemmill et al. 1997) (S. Harvey and M. Viney, personal communication). It remains unclear whether free-living adults die as the consequence of ageing, especially since no age- specific mortality data is available. However, certain observations are consistent with the occurrence of senescence in these forms. For example, animals show reduced movement and become increasingly opaque with increasing age (S. Harvey and M. Viney, personal communication). They also exhibit pharyngeal pumping, suggesting that they do not die of starvation. Only a small proportion of mated females die as the consequence of internal hatching of larvae. In contrast to free-living adults, filariform iL3s can survive and for up to two months at 13 °C, during which time they retain infective ability (Gemmill et al. 1997). In several respects they resemble the long-lived, diapausal dauer larva stage of *C. elegans* (Riddle and Albert 1997).

Very short life spans have been observed in free-living adults of several other species of *Strongyloides*. In a study of four species, including *S. fuelleborni* and *S. simiae*, free-living adult males lived 4–9 days, and virgin free-living females up to 15 days (Augustine 1940). In a different study of *S. fuelleborni*, first and second free-living generations of adult males and females died within four days (Hansen et al. 1969). One observation could be consistent with the occurrence of rapid senescence in *S. stercoralis* free-living adults: after 48 h they became sluggish and exhibited poor movement and darkly pigmented intestinal walls (Yamada et al. 1991).

Rhabdias bufonis parasitic adult hermaphrodites infect several types of amphibian, including frogs and toads, where they are found in the lungs. In contrast to *Strongyloides*, larval development occurs entirely by the indirect route (Spieler and Schierenberg 1995). Parasitic hermaphrodites grow to around 10 times the length of the free-living female, and lay thousands of eggs. By contrast, free-living females lay, on average, only 3 eggs each, and possess a vulva too small for eggs to pass through (Spieler and Schierenberg 1995). In one laboratory study, free-living, rhabditid males started to degenerate on day one of adulthood, 80% had died by day 2, and all had died by day 3 (Spieler and Schierenberg 1995). All free-living females died after only a few days, whether they carried eggs or not. By contrast, the lower estimate of the maximum life span of *R. bufonis* parasitic adults is three months (Goater 1991). Similarly, adults of *R. fuscovensa* var. *catanensis*, maintained in snakes under conditions precluding reinfection or autoinfection, were still reproductively active after nine months (Chu 1936).

Taken together, these data indicate that in strongyloidid species, free-living adults age much more rapidly than parasitic adults of the same species. In some cases (e.g. *R. bufonis*), the free-living adult life span is so short as to suggest the possibility that death results from a degenerative process more rapid and catastrophic than ageing.

The parasitic Adenophorea

The previously discussed nematode orders all belong to the class Secernentea. There is even less information on longevity and ageing in the other major nematode class, the Adenophorea. Host immunity generally clears infections of the intestinal parasitic genera *Trichuris* (whip-worms) and *Trichinella* within weeks or months. *Trichuris muris* infections are cleared within approximately three weeks, although in immunocompromised hosts (cortisone-treated), fertile adults can persist for 7–10 weeks after reaching sexual maturity (Wakelin and Selby 1974). The life span of female *Trichinella spiralis* has been estimated at three months (A. Maggenti, cited in Finch 1990). *T. spiralis* infections of rats, and guineas pigs last 2–3 weeks, and around five weeks, respectively (McCoy 1932).

Agamermis decaudata is one of the Mermithidae, which parasitise snails and insects. *A. decaudata* eggs are laid in the soil, where they hatch and develop into infective larvae. These invade grasshopper nymphs, where they develop into adults in the hemocoele (Hyman 1951). *A. decaudata* adults are aphagous, surviving entirely on food stored in intestinal trophosomes, which make their bodies opaque (Christie 1929). In one study, adult females when mated after 14 months were found still to be fertile, and virgin

females were "apparently in good condition" after 18 months (Christie 1929). Mated females exhibited shorter life spans, and grew less opaque during the egg-laying period. This was interpreted as the result of the depletion of their stored nutrients (Christie 1929).

Ageing in free-living nematodes

Comparisons of life span values between species can only give an approximate idea of the relative differences in the rate of ageing, due to differences between laboratories in culture conditions, e.g. the food source and handling methods. Furthermore, lowering of temperature, food availability and reproductive activity can all increase life span. As far as possible, such factors have been taken into account in the following survey. A summary of species-specific life span is shown in Table 2. Maximum life span is shown, since at a given temperature, where culture conditions are not highly deleterious to survival, differences in the optimality of culture conditions are likely to cause greater variation in mean than maximum life span, and the latter at least represents a lower estimate of potential life span (Finch 1990).

One of the earliest reports of ageing in free-living nematodes describes 12 species, nine of which are hermaphroditic and three parthenogenetic (Maupas 1900). A minor problem with this study is that while the temperatures at which the rate of development was measured are given (ranging from 12–27 °C), the extent to which temperature varied during the life span measurements is unclear. Temperature variation clearly did occur during life span measurements, since it is stated that day to day variation in egg laying in *Cephalobus dubius* could have been due to temperature variation (Maupas 1900). The temperatures given in the following account of the Maupas study are those at the start of each trial. In most cases animals were maintained in drops of water containing ground meat as the food source.

Rhabditis elegans, later renamed *Caenorhabditis elegans*, is the first species described. Hermaphrodites lived 10–12 days (20 °C), or 7–9 days from the onset of egg-laying, a very low estimate when compared to later studies of this species. Life span estimates of a similar magnitude for eight other hermaphroditic species are given in Table 2. Three parthenogenetic species are also described, of which *Rhabditis schneideri* was German, and *Cephalobus dubius* and *C. lentus* Algerian. *R. schneideri* was short-lived, surviving 18–19 days (12–13 °C) or approximately 15–16 days from the onset of egg-laying; or 8–9 days (19–20 °C), or 6–7 days from the onset of egg-laying. By contrast, the two Algerian species proved to be much longer-lived. For these Maupas took the approach of picking a single egg and giving a detailed biography of the resulting worm. In the case of *C. dubius*, this individual survived for approximately 150 days (20 °C), or around 138 days from the onset of egg-laying, until finally, to Maupas' evident chagrin, it was "*. . . devenu d'une inertie presque absolue, et s'éteignit d'épuisement senile*". During the first four months of its life it laid 450 viable eggs, after which it continued to lay non-viable eggs. In the case of *C. lentus*, a single female survived 105 days (26–27 °C), or 84.5 days from the onset of egg laying. It laid 315 viable eggs and was sterile during the last 40 days of its life.

Another parthenogenetic cephalobid is *Acrobeloides nanus*. Here, longevity was observed to vary with temperature and nutrition. On ample nutrients adults survived 23–27 days at 13 °C and 15–21 days at 21 °C. Under conditions of dietary restriction (25% of ample nutrient levels), life span was extended to 21–42 days (13 °C) or 12–30 days (21 °C) (Sohlenius 1973). Interestingly, under dietary restriction, the daily reproductive rate was reduced, but the reproductive period was lengthened, so that life time reproductive output was unchanged. Similar results were obtained for *Aphelenchus avenae* and *Tylenchus emarginatus* (Fisher 1969; Gowen 1970). By contrast, in *Mesodiplogaster biformis*, the rate of reproduction, the life time reproductive output and the life span were all reduced when dietary restriction was imposed (Sohlenius 1969).

One nematode in which ageing has been studied extensively is the vinegar eelworm *Turbatrix aceti*, which is a dioecious cephalobid. In one study, median life span of solitary males and females was found to vary with temperature, from 104 days (211 maximum) at 15 °C to 13 days (37 maximum) at 36 °C (Vogel 1974). Estimates of median life span in *T. aceti* vary, from 55 days (25 °C) (Vogel 1974), to 25 days, either at 27 °C (Kisiel and Zuckerman 1972), or 30 °C (Gershon 1970), to 35–40 days (30 °C) (Zeelon et al. 1973). This variation may be due either to difference in culture conditions or to strain variation. In each case animals were cultured in liquid axenic medium (with no other organisms present), which may increase life span relative to growth on bacteria. *T. aceti* males and females exhibit similar mean life spans:

Table 2. Variation of life span with temperature in free-living and plant-parasitic nematodes.

Species	Sex[a]	Culture conditions[b]	Maximum life span (days) 15 °C	20 °C	25 °C	30 °C	Reference
Caenorhabditis elegans	H	Mo, S	32 (16 °C)	19	11 (25.5 °C)	—	Klass (1977)
C. briggsae (G16)	H	Mo, S	—	21	—	—	Gems (unpublished)
C. briggsae	H	Ax, L	30.0[c] (17 °C)	30.8[c] (22 °C)	26.2[c] (27 °C)	—	Zuckerman (1971)
Caenorhabditis species[d]	F	Mo, S	—	38	—	—	Gems (unpublished)
C. remanei[e]	F	Mo, S	—	58	—	—	Gems (unpublished)
Rhabditis tokai	F	Mo, S/L[f]	—	193	145	92	Suzuki (1978)
	M	Mo, S/L[f]	—	—	—	70	Suzuki (1978)
Rhabditis terracoli[g]	F	Mo, S	12	12 (22 °C)	—	—	Sohlenius (1968)
	M	Mo, S	7	7 (22 °C)	—	—	Sohlenius (1968)
Mesodiplogaster biformis	H	Mo, S	—	7.9[c] (21–22 °C)	—	—	Sohlenius (1969)
Rhabditis marionis	H	Ax, L	—	27.5 (31)[h]	—	—	Maupas (1900)
R. duthiersi	H	Ax, L	—	19 (23)[h]	—	—	Maupas (1900)
R. guignardi	H	Ax, L	22.5 (28)[h] (14 °C)	—	—	—	Maupas (1900)
R. viguieri	H	Ax, L	—	4 (6)[h] (22 °C)	—	—	Maupas (1900)
R. dolichura	H	Ax, L	—	—	11.3 (14)[h] (23–24 °C)		Maupas (1900)
R. schneideri	P	Ax, L	16 (19)[h] (12–13 °C)	6–7 (9) [h] (19–20 °C)	—	—	Maupas (1900)
Diplogaster robustus	H	Ax, L	—	12.5 (16)[h]	—	—	Maupas (1900)
D. minor	H	Ax, L	12 (16)[h] (17 °C)	—	—	—	Maupas (1900)
D. aerivora	F	Ax, L	—	—	68 (21–25 °C)	—	Honda (1925)
	M	Ax, L	—	—	71 (21–25 °C)	—	Honda (1925)
Cephalobus dubius	P	Ax, L	—	138 (150)[h]	—	—	Maupas (1900)
C. lentus	P	Ax, L	—	84.5 (105)[h]	—	—	Maupas (1900)
Acrobeloides nanus	P	Mo, S	—	21 (21 °C)	—	—	Sohlenius (1973)
Turbatix aceti	M, F[i]	Ax, L	211	137	123	70	Vogel (1974)
	M, F	Ax, L	—	—	60.5 (27 °C)	—	Kisiel (1972)
Panagrellus redivivus	F	Ax, L	—	—	29.2–36.4[c]	24.5[c]	Abdulrahman (1975)
	M	Ax, L	—	—	21.0–29.3[c]	20.9[c]	Abdulrahman (1975)
Ditylenchus triformis	F	FC, S	—	—	124 (24–26 °C)	—	Hirschmann (1962)
	M	FC, S	—	—	145 (24–26 °C)	—	Hirschmann (1962)
Tylenchus emarginatus	P	C, S	128	66	60	—	Gowan (1970)
Aphelencus avenae	P	FC, S	—	48	37	32	Fisher (1969)

[a] M, male; F, female; H, self-fertilising hermaphrodite; P, parthenogenetic female.
[b] Ax, axenic culture; FC, fungal culture; L, liquid medium; Mo, monoxenic culture (*E. coli*); PC, plant cell culture; S, solid medium (agar).
[c] Mean life span.
[d] Previously referred to as *C. remanei*. Strain CB5161.
[e] *C. remanei* ssp. *vulgaris*, strain EM464. Previously referred to as *C. vulgaris*.
[f] Agar plates overlayed with 0.1 ml M9 buffer to reduce burrowing.
[g] Identification as *R. terracoli* in question (Sohlenius 1968).
[h] From the onset of egg laying; life span including pre-adult development in parenthesis.
[i] Summed data from population of solitary animals, 40% males and 60% females.

66 and 73 days, respectively (Kisiel and Zuckerman 1974). In axenic medium, mating did not significantly reduce life span in either sex (Kisiel and Zuckerman 1974).

Another well-studied dioecious cephalobid species is *Panagrellus redivivus*. Here, as in most nematodes, females were observed to live longer than males, with mean life spans of 36 and 29 days, respectively (axenic medium, 25 °C) (Abdulrahman and Samoiloff 1975). The frequency of death from hypotonic shock (i.e. bursting when dropped into distilled water) also increased more rapidly with age in males than females. Mating generally reduced life span in both sexes, e.g. in females and males to 32 and 26 days, respectively, under the conditions described above. However, under nutritional conditions that slightly reduce life span in

virgin animals, the effect of mating on survival was reduced or non-existent (Abdulrahman and Samoiloff 1975). In studies of *P. redivivus* grown at 25 °C on *E. coli* on agar plates, maximum life span of females and males was 20 days and 6 days, respectively (Duggal 1978a, b). In these studies, mating shortened life span in females, but increased it in males.

Mating was also found to reduce the mean life span of females of the dioecious species *Diplogaster aerivora* from 52 days (range, 33–68 days) to 25 days (range, 11–54 days) (Honda 1925). Similarly, in males mating also reduced mean life span from 43 days (range, 15–71 days) to 33 days (range, 10–54 days) (Honda 1925). Here, animals were maintained in axenic liquid culture at 21 °C until the end of egg laying, after which temperature varied from 22–25 °C.

Ditylenchus triformis is a tylenchid nematode with three sexes: males, females and an intersex form that behaves as a female (Hirschmann 1962). Propagated on a fungal culture at 24–26 °C, life span was found to range from 31–124 days (mean, 63 days) in females, and 33–145 days (mean 74 days) in males. The life span of the intersex was intermediate. Females were sexually functional for about 75% of their life span, and showed retarded movement and anatomical changes in later life (Hirschmann 1962). Another tylenchid species, *Tylenchus emarginatus*, feeds on plant root cells. Here again, life span varied with temperature, from a mean of 128 days (range 72–128 days) at 15 °C, to 46 days (range 22–66 days) at 20 °C, to 33 days (range 12–60 days) at 25 °C (Gowen 1970). In this study it was again observed that while the rate of egg laying varied with temperature, lifetime fecundity did not. From this the unusual conclusion was drawn that longevity depends on the rate of reproduction, which is reduced at lower temperatures, or where food supply is reduced (Gowen 1970). *Aphelenchus avenae* is a parthenogenetic aphelenchid nematode that feeds on fungi. This is a relatively short-lived species, with maximum life spans of 48, 37, 32 and 21 days at 20, 25, 30 and 35 °C, respectively (Fisher 1969).

C. elegans is by far the best characterised of the free-living rhabditid nematodes. The mean life span of unmated hermaphrodites grown on *E. coli* varies from a mean of 9 days (25.5 °C) to 35 days (10 °C) (Klass 1977). Hermaphrodite life span in the standard laboratory strain Bristol (N2) is also affected by genetic variation between different laboratory lines, with median life span (20 °C) varying from 11 days to 17 days (Gems and Riddle 2000a). Dietary restriction increases life span and reduces life time fecundity in this species: reducing bacterial concentration increases mean life span from 16 to 26 days (20 °C), and reduced mean brood size from 273 to 63 (Klass 1977). Under conditions of full nutrition, hermaphrodite reproduction by self-fertilisation does not reduce life span: sterile *fer-15* and *fog-2* mutants are not longer-lived (Friedman and Johnson 1988; Gems and Riddle 1996), nor are sterile animals in which precursor cells of the germ-line and somatic gonad have been ablated with a laser microbeam (Kenyon et al. 1993). However, mating with males reduces hermaphrodite median life span from 17 to 8 days (20 °C) (Gems and Riddle 1996). This appears to be due to the effect of copulation per se rather than an increase in egg production. In comparisons of groups of males and hermaphrodites, males are shorter-lived. For example, on *E. coli* lawns on agar plates male and hermaphrodite median life spans are 17 and 10 days, respectively 20 °C (Gems and Riddle 1996). However, isolation of males increases life span up to 20 days, indicating that male-male interactions shorten life span (Gems and Riddle 2000b). Many other aspects of the biology of ageing in *C. elegans* have been extensively studied, and are reviewed elsewhere (Kenyon 1997; Hekimi et al. 1998; Gems 2000).

Caenorhabditis briggsae is also hermaphroditic. In axenic culture, mean life span of *C. briggsae* hermaphrodites was measured at 30, 31, and 26 days at 17, 22 and 27 °C, respectively (Zuckerman et al. 1971). In a limited study of the *C. briggsae* G16 strain, maintained in *E. coli* on agar plates at 20 °C, life span was found to be similar to that of *C. elegans*, with median and maximum life spans of 14 and 21 days, respectively (B. Fletcher and D. Gems, unpublished results).

The free-living rhabditid nematode *Rhabditis tokai* was isolated from mud in a rice farm in Southern Japan (Suzuki et al. 1978). This species is unusual in that it is dioecious, but has a male: female ratio of around 1:15. Female life span was found to range from 92–97 days at 20 °C (maximum: 151–193 days) to 30 days at 35 °C (maximum 63 days) (Suzuki et al. 1978). Virgin males were shorter-lived than virgin females, with mean life spans of 38 days and 58 days, respectively (30 °C). Mating with males reduced mean female life span from 92–97 days to 64 days (20 °C). When females were exposed to males after 100 days (20 °C) (slightly beyond average life span), 33% produced eggs (Suzuki et al. 1978).

R. terracoli, a Swedish soil nematode, proved to be much shorter lived, with virgin females living only up to 12 days, and males from 5–7 days, suprisingly at both 15 °C and 22 °C (Sohlenius 1968). In another Swedish species, hermaphrodites of the rhabditid species *Mesodiplogaster biformis* exhibited a mean adult life span of only 8 days (21–22 °C) (Sohlenius 1969). Animals were maintained on *E. coli* lawns on agar drops. The unusually short life spans of both of these species suggests either that free-living nematodes from Sweden are unusually short-lived, or that the culture conditions employed in these studies were not optimal for survival. *M. biformis* is potentially a good model organism for the study of ageing, given that its life span appears to be approximately half that of *C. elegans*. This species and also forms dauer larvae in response to overcrowding and reduced nutrients.

The determinants of longevity and ageing in nematode species

Within the Nematoda, maximum life span varies from three days in the case of free-living *R. bufonis* females to at least 15 years in the case of *L. loa*, representing a variation in longevity over three orders of magnitude. Potentially, much may be learned about the determinants of ageing and longevity by studying their biological and ecological correlates in comparisons between nematode species. While the evolutionary theory of ageing provides a sound explanation for why ageing occurs, its mechanistic basis remains essentially an unsolved riddle.

In evolutionary terms, ageing appears to be the consequence of the inability of natural selection to eliminate mutations with effects detrimental to survival that are expressed at an age when, under natural conditions, most individuals will have already succumbed to extrinsic causes of mortality (e.g. predation, disease or starvation). By this view, ageing reflects the accumulation of late-acting deleterious mutations (Medawar 1952), and is therefore in essence a form of late onset genetic disease. According to this interpretation, ageing is an entirely non- adaptive biproduct of evolution, and its evolutionary origin may be thought of as akin to the atrophy of the eyes of blind cave-dwelling fish. In the absence of active maintenance by natural selection, biological structures will atrophy and disappear, whether they are individual organs in individuals of all ages, as in the human appendix, or the entire body at advanced ages.

Since a given gene may affect many different aspects of the biology of an organism, gene mutations may produce different pleiotropic effects at different times in the life history. In such cases, the earlier that the effects of such pleiotropic mutations are expressed, the greater their effects are likely to be on overall fitness. In theory, a pleiotropic mutation causing an early increase in reproductive fitness, but a reduction in life span, may actually increase overall fitness (Medawar 1952; Williams 1957; Partridge and Barton 1993). Thus, decreases in life span potential may evolve as a consequence of antagonistic pleiotropy. For a detailed account of the evolutionary theories of ageing, see Rose (1991), Partridge and Barton (1993).

Parasitic nematodes

A key prediction of the evolutionary theory of ageing is that the maximum life span that a particular species may attain under optimal conditions (e.g. in the laboratory) will be correlated with the life expectancy of that species in the wild, where mortality is entirely due to extrinsic causes. Among parasitic nematode species are many whose life span potential greatly exceed those of any free-living nematode. This is consistent with the evolutionary theory of ageing. A number of factors are likely to contribute to the evolution of increased longevity in parasitic nematodes: (a) the assured supply of nutrients from the host; (b) the ability to evade host immunity; (c) the lack of intraspecies competition; (d) the protected nature of the host environment; (protected, e.g. from environmental disturbance, pathogens and predators); and (e) the longevity of the host. All of the above may reduce the extrinsic mortality in the parasite, and allow natural selection to act on the effects of genes at later ages, leading to increases in fitness and viability at later ages.

One interpretation of the apparent contrast in the rate of ageing between parasitic and free-living adults of strongyloidid species such as *Strongyloides ratti* is that the relatively low rate of extrinsic mortality of parasitic adults has resulted in the evolution of greater longevity, while high levels of extrinsic mortality among free-living adults has given rise to accelerated ageing. Thus, the parasitic adults resemble ascarid or strongylid nematodes in their relative longevity, while the free-living adults resemble short-lived, free-living nematodes such as *C. elegans*. In the case of *S. ratti*, it has been demonstrated that free-living and parasitic females are karyotypically identical (Harvey 1999).

Thus, an approximately 50-fold difference in life span appears to result from differences in gene expression in development and adulthood, resulting in a more enduring and better maintained organism in the case of parasitic adults.

Little is known about the mechanistic determinants of the enhanced longevity of parasitic species. Two potential contributory factors are the occurrence of anaerobic rather than aerobic respiration, and increased levels of antioxidant enzymes. A major determinant of ageing appears to be the accumulation of damage caused by reactive oxygen species (ROS) (Harman 1956; Sohal and Weindruch 1996). The principal source of ROS in the cell is thought to be the mitochondria, which produce superoxide ($O_2 \cdot$-) as a biproduct of oxidative phosphorylation. Adults of many parasitic nematode species respire anaerobically, and in many cases atmospheric levels of oxygen are toxic (Barrett 1981). In principal, a reduction in oxidative metabolism could result in a reduction in ROS production, resulting in slowing of the rate of ageing.

Defense within the cell against ROS is provided by antioxidant enzymes such as the superoxide dismutases (SODs), catalase and the glutathione peroxidases. In *C. elegans*, long-lived *age-1* and *daf-2* mutants have been shown to be resistant to oxidative stress, and possess elevated levels of SOD and catalase activity (Larsen 1993; Vanfleteren 1993; Adachi et al. 1998). Several long-lived parasitic nematodes also exhibit elevated expression of antioxidant enzymes. However, this is likely to function as a defense against host immunity, e.g. oxidative burst from host activated leukocytes. For example, Cu/Zn SOD is secreted by adult *O. volvulus* (Henkle-Dührsen et al. 1997) and *Brugia malayi* (Ou et al. 1995a). Protection against the H_2O_2 produced by SOD activity varies between filarial species. While a protein homologous to glutathione peroxidase is secreted by several filarial nematodes (Cookson et al. 1992; Cookson et al. 1993), the enzyme is actually a lipid peroxidase and inactive against H_2O_2. However, *Brugia malayi* secretes catalase, and is resistant to H_2O_2, while *O. volvulus* and *Dirofilaria immitis* are not (Ou et al. 1995b). While it has been suggested that the difference in catalase levels in *B. malayi* microfilariae and adults could contribute to their differences in longevity (Ou et al. 1995b), the high level of production of antioxidant enzymes in these species does not appear to be consistently correlated with their slow intrinsic ageing. For example, *O. volvulus* adults, which can live over 14 years, are highly sensitive to H_2O_2 (Ou et al. 1995b).

Free-living nematodes

These exhibit more than a 10-fold variation in life span between species (20 °C), from the short-lived *M. biformis* (mean hermaphrodite life span, 8 days) to the long-lived *R. tokai* (mean female life span, 92–97 days) (Table 2). This variation is likely to be due in part to variation between culture conditions. For example, in *C. elegans*, life span is increased in axenic liquid culture by up to 40% relative to culture on *E. coli* on agar plates (Croll et al. 1977; Mitchell et al. 1979). Furthermore, life span potential may be greatly reduced by non-optimal culture conditions. Nonetheless, it must be assumed that much of the variation in life span shown in Table 2 is due to variation in the genetically-determined life span potential, which has evolved as the result of differences in species ecology.

One factor that may lead to the evolution of accelerated ageing is protandrous hermaphroditism (production of sperm before eggs). Here, in the absence of mating with males, hermaphrodites become non-reproductive after the depletion of self-sperm. Studies of the protandrous species *C. elegans* suggest that the evolution of timing of the switch from sperm to egg reproduction is determined by a trade-off between the advantages of an early switch, which reduces generation time, but reduces self-brood size, and that of a later switch, which increases brood size, but increases generation time. The *tra-3(e2333)* mutation, which delays this switch and increases brood size by 50%, actually decreases the intrinsic rate of population growth, thus presumably reducing fitness (Hodgkin and Barnes 1991). A consequence of evolution for rapid population growth rate is a reduction in the reproductive period. In the absence of mating with males, the evolutionary theory of ageing suggests that this might result in the evolution of reduced longevity. In this context, it may be significant that the longer-lived species shown in Table 2 are generally dioecious or parthenogenetic rather than hermaphroditic. This issue was addressed experimentally by comparing life spans of four species of *Caenorhabditis*: *C. elegans* and *C. briggsae*, which are hermaphroditic and *C. remanei* and *Caenorhabditis species*, which are dioecious. The longevity of females of the latter species greatly exceeded those of the hermaphrodites (Table 2) (B. Fletcher and D. Gems, unpublished results).

Another possibility suggested by this survey is that nematodes species from latitudes closer to the poles may be shorter-lived. For example, the very short-lived *R. terracoli* and *M. biformis* were isolated from woods in Sweden, while the long-lived *R. tokai* was isolated from a rice field in Southern Japan, and *C. dubius* and *C. lentus* from Algeria. A possible explanation for this observation is that it is due to the effect of temperature on the rate of living. Suppose that two species, one from a cold climate and another from a hot one, have the same life expectancy in the wild, and as a consequence evolve at their native temperatures to have similar life span potentials. If the longevity of these two species were compared at the same temperature, one would expect that the species from the warm climate would be longer-lived.

Conclusions

Consistent with the great variety seen among the life histories of nematode species, adult nematodes exhibit a remarkable degree of variation in life span. This evolutionary plasticity in the rate of ageing is mirrored by the ease with which life span can be altered in the nematode *C. elegans*, where mutations in dozens of genes and various environmental manipulations have been shown to alter life span. Much may be also learned from comparative studies of ageing among nematode species. Currently, the ageing process in the nematode seems best to be explained by the evolutionary theory of ageing and the free radical hypothesis. Both ideas may be investigated using comparative approaches.

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