Parasites

part 8 Nematode biology- boring but very successful

Enterobius vermicularis
rectal nematode

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Origins of this article

Since childhood I am fascinated by creepy organisms. I gave talks to medical trainees about spotted fevers and the ticks that spread them. I volunteered in West Africa in 2004, sometimes treating malaria and other tropical diseases. For the past decade I use old microscopes as a hobby, and now I contribute to *Micscape* magazine.

Parasites being so damn interesting and me being so curious makes for long articles. I will write about the biology of parasites, go off on tangents, and eventually relate my own and other true stories about patients with parasites. I have a collection of vintage microscope slides of parasites, allowing me to illustrate some kinds.

Disclaimers

I am a doctor of general internal medicine but **nothing in this article should be used to diagnose or treat medical conditions**. Medical Parasitology is a subspecialty of both deep knowledge and judgement calls. The few times I encountered parasites locally, I consulted the US CDC website and the state health department.

Ideally, science is an iterative process that self corrects using nature as its arbitrator. Science is never all correct or complete; it advances by adapting models as new evidence accumulates. **Be skeptical** and investigate for yourself if something seems unlikely. You can learn a lot from the internet, or be fooled by it.

Think you have parasites? Consult your doctor. If you live in the USA or Western Europe having serious parasites is unlikely, so the doctor may dismiss your self diagnosis and offer you $100 of anxiety pills. An alternative healer might order $200 of questionable parasite tests and sell you a useless $200 parasite cleanse. Serious human parasites are now rare in wealthy nations. Soap, shoes, flush toilets, clean water and cooked food are generally your best bets against parasites.

Disclaimer to the disclaimer
Immigrants or travelers returning from the tropics and patients on certain medications really could have life threatening parasites, which most US doctors now know little about. Remind the doctor about travel or immunocompromise to lessen the chance of becoming a medical error in these special cases.

Cover page photomicrograph

Enterobius vermicularis, vintage Ward's (no relation) slide. The human pinworm lives in the rectum of perhaps a billion people worldwide, mostly young children. Apart from causing itching, it's harmless. *E. vermicularis* is unique to man but many other animals have their own pinworm species.
10X objective, sl. cropped, dark field illumination, image about 1 mm wide and worm ~ 4 mm long

Other illustrations

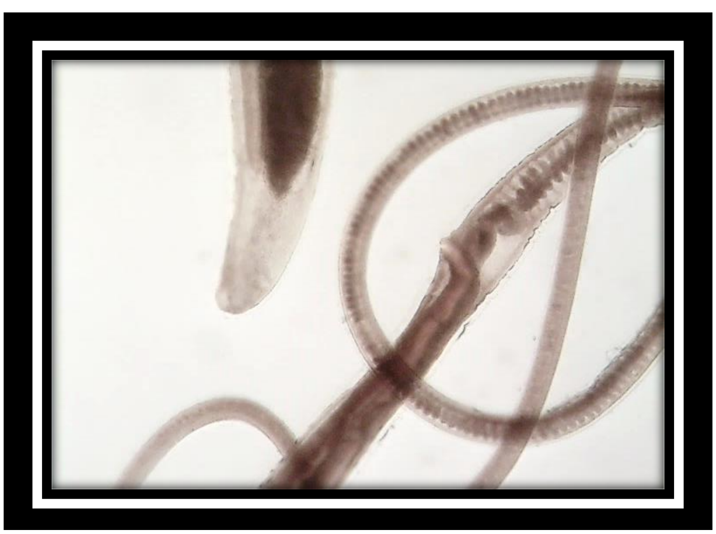
If not noted otherwise, photomicrographs are mine, taken with AO/Reichert microscopes and USB camera with 0.5X reducer (added late 2017). My 2.5X objective images are about 5 mm across, the 4X about 3 mm, 10X about 1.2 mm, 40X about 0.3 mm (300 microns), 63X 190 microns, and 100X about 120 microns across. Brightness may be adjusted. Some patient photos of mine from West Africa are also included.

Contents

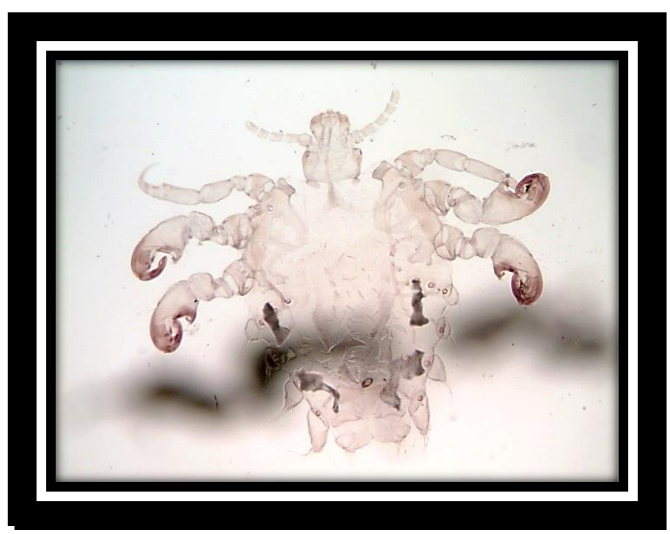
Parasites, a general summary

Life penetrates every nook and cranny where it might survive, including inside and outside the bodies of animals. Those bodies turned out to be very comfy and tasty. So evolution produced and adapts many endoparasites (like intestinal worms) and ectoparasites (like lice). Most wild animals have parasites, as did most humans in the past. Most individuals are not harmed, but hosts are sometimes injured by heavy infestations or complications. In poor and tropical areas many people are still harmed or killed, including about 600,000 annual deaths from malaria. Some ectoparasites also act as vectors to spread bacteria and viruses that cause Lyme disease, encephalitis, plague and other illness. Nearly half of humans still have parasites, most commonly helminths (worms) and hidden toxoplasmosis, but they don't make most of us sick. Parasites come from many different branches of life, but especially from protozoans, flatworms, roundworms, and arthropods (including ticks, crustaceans, insects). I mostly discuss three main kinds of parasites of humans: protozoan parasites, helminths (worms), and ectoparasites.

Today parasites do the most harm in poor areas of the world. We need to continue life saving efforts to control malaria, worms, and other neglected tropical diseases. Still, most of you reading this need not fear parasites. Anxiety about parasites is far more common than parasitic disease in the developed world. Parasites may be the majority of animal species in the wild, and the balance of nature might be hurt if we continue to extinct parasite species faster than we can discover them.



Trichuris trichura, human whipworm, female adult with thin anterior, thick posterior end, 4X objective, image 3 mm wide



Pediculus pubis human pubic louse, antique slide unknown maker, 4X object., body ~1.5 mm long

Part 8 Biology of nematode parasites

Worms that are parasites are called **helminths**, the big two kinds being flatworms and roundworms. Tapeworms and flukes, the parasitic members of Phylum Platyhelminthes (flatworms), were discussed previously. Today I cover the biology of Phylum Nematoda, aka roundworms. Compared to previous worms, the biggest new inventions of nematodes were a butthole and tough skin. Although most are microscopic, in terms of numbers of individuals nematodes are the most common animals on earth. Most nematodes are tiny, free living in soil and water and look much alike, rather boring. The many parasitic nematodes are mostly bigger, more diverse and some appear beautiful. With the exception of latent (silent) toxoplasmosis more human parasitic diseases are caused by nematodes than by any other kind of parasite. Before the 21st century, over half of all humans carried intestinal roundworms.

Nematode Taxonomy

Kingdom Animalia

Phylum Nematoda

A 2022 genomic taxonomy scheme:

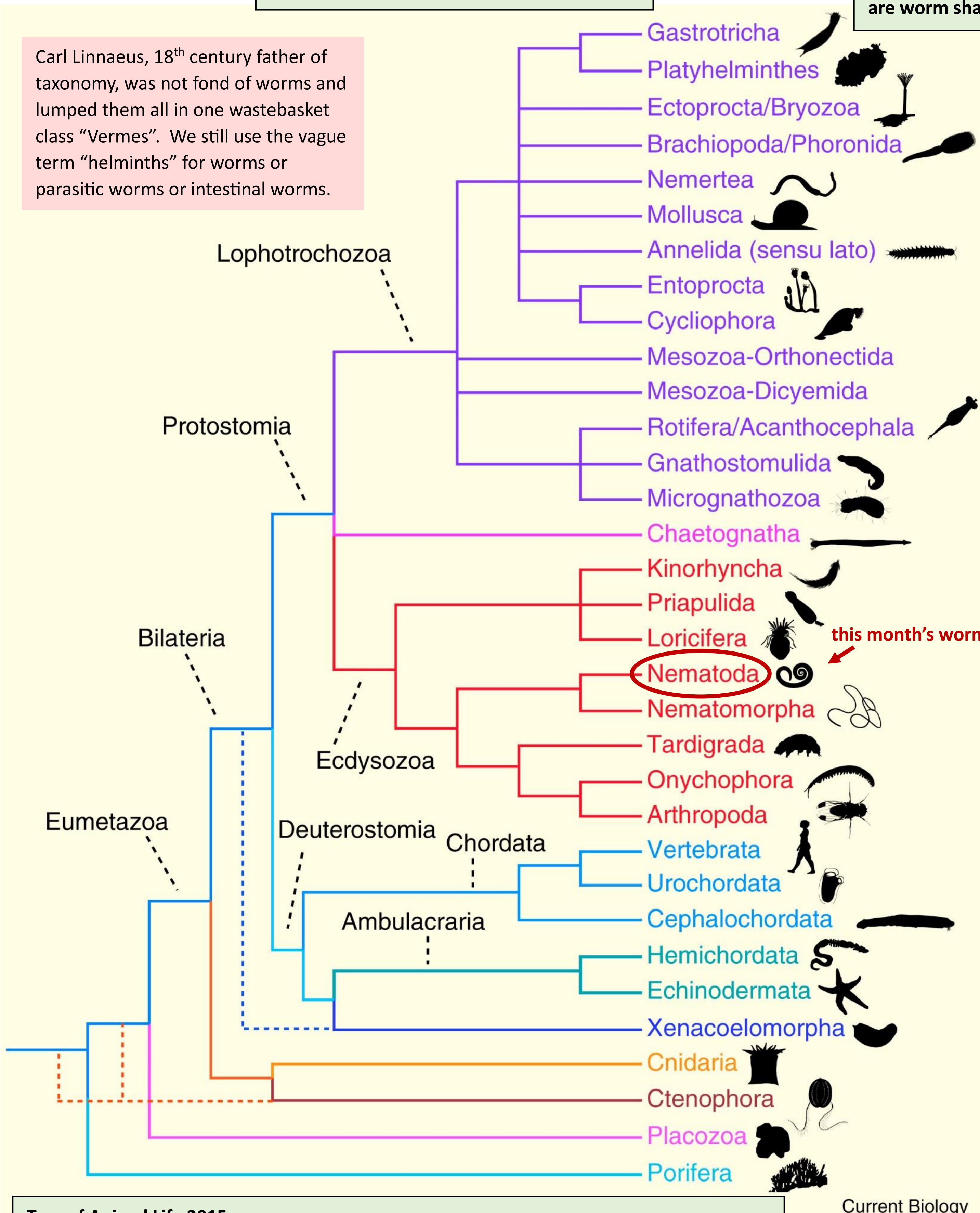
Class Enoplea	2297 species, all or almost all marine and free living (Trichinellids may belong to Enoplia or Dorylaimea)
Class Dorylaimea	4917 species, freshwater and in soils, many free living and many parasitic
Class Chromadorea	21317 species, widely varied habitats and life styles
	____________
	28537 species total (some unclassified) in 3 classes, 32 orders, 303 genera
	species numbers from Hodda's 2022 census

Not discussed yet are other less common helminths: Acanthocephala, Nematomorpha, etc.

Worms on a tree of animal life

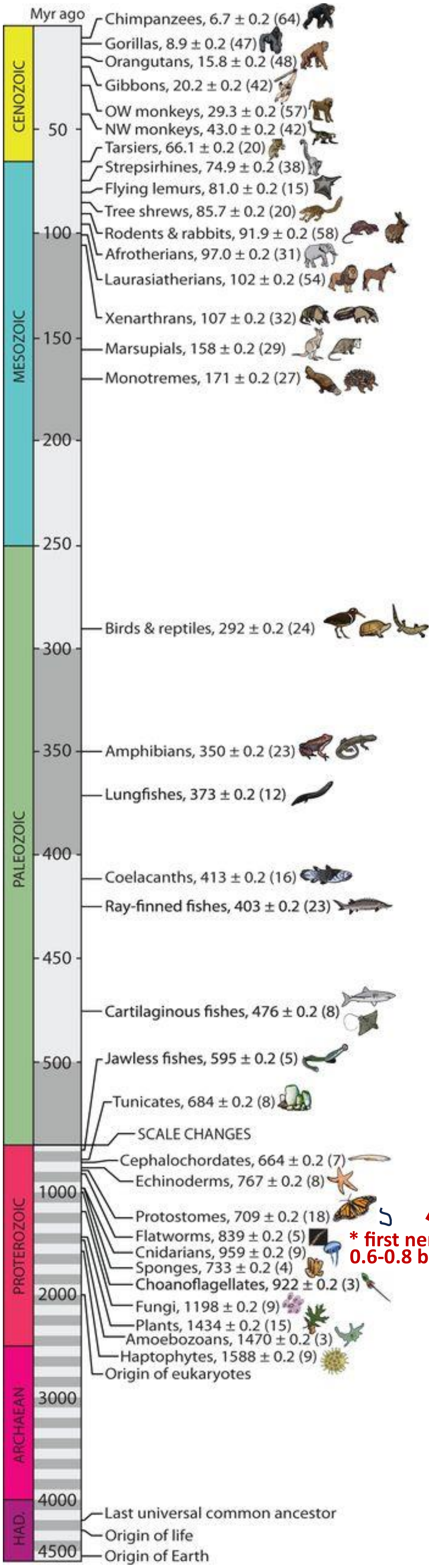
Note how many animal outlines are worm shaped

Carl Linnaeus, 18th century father of taxonomy, was not fond of worms and lumped them all in one wastebasket class "Vermes". We still use the vague term "helminths" for worms or parasitic worms or intestinal worms.



Tree of Animal Life 2015
Best estimate of the phylogenetic relationships of major animal phyla. Major clades named. Some alternative possible positions are indicated by dashed lines.
Telford, Budd, Philippe. Phylogenomic Insights into Animal Evolution **Current Biology** 2015

Nematodes on a timeline of life*

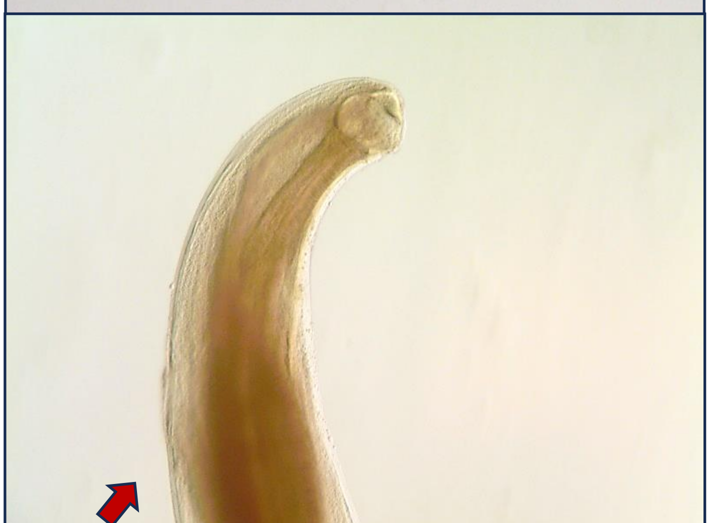


* first nematodes about 0.6-0.8 billion years ago

Times of diversification of select groups, by genomic clocks

Hedges et al Tree of Life Reveals Clock-Like Speciation and Diversification 2015 **Molecular Biology Evolution**

Most nematodes are **free living**, and more live in the soil than anywhere else. This one came from a flowerpot at my house. It is microscopic and pale. with 20X objective, cropped, oblique lighting. Worm about 0.5 mm long, 20 microns in diameter



Necator americanus, aka hookworm, blood eating **intestinal parasite** of man. Vintage slide by Ward's Science (no relation). With 10X objective, oblique lighting, image about 1.2 mm wide. *N. americanus* hookworm adults are typically about 9 mm long.

Worms

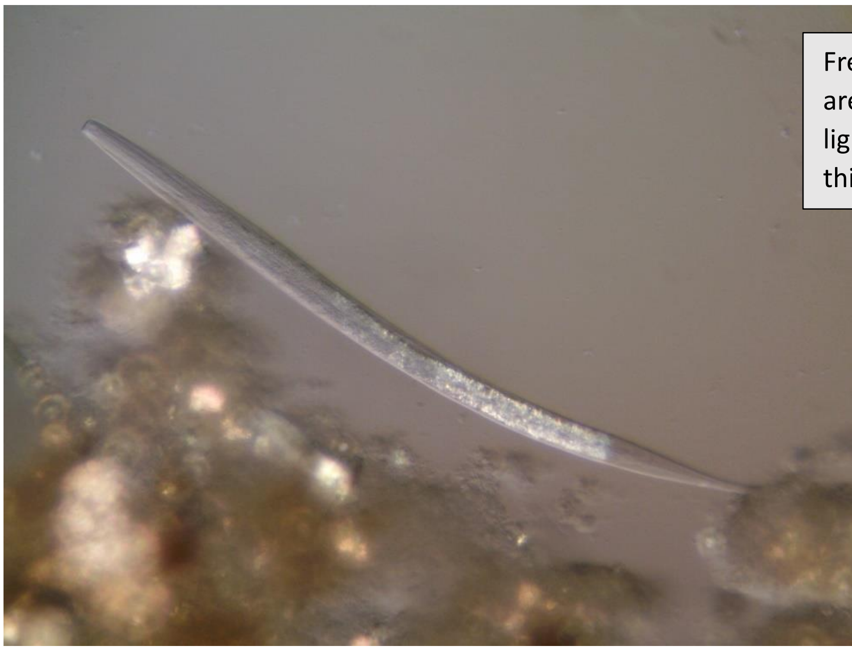
You know what a worm is: a long, thin, wiggly little animal. Being slender and legless is good for moving through granular substrates like dirt. Father of taxonomy Carl Linnaeus lumped all worms together as “Vermes” as they have a similar shape, but we now divide worms among 30 different animal phyla based on body plan and heredity. The big 3 phyla of worms are Platyhelminthes, Nematoda and Annelida: flatworms, roundworms and segmented worms. The most classic of all parasites are intestinal worms. Unlike protozoan parasites, these are multicellular animals and many adults are large enough to be seen without a microscope (free living nematodes are mostly microscopic, but many parasitic nematodes are bigger).

I see lots of soil and fresh water nematodes under my microscope. (I also see many flatworms and annelid worms in pond water samples, and the latter can have visible internal organs and well developed mouth parts and look interesting.) But the free living nematodes are tiny, constantly wiggling and look much alike to me. Nematodes don’t have many interesting or distinguishing parts like antennae or legs. Honestly, I find them boring. But nematodes don’t care what I think. They are one of the most successful animal groups on earth, with more total numbers of individuals than any other kind of animal, even more than insects. Many are parasites of invertebrates, plants, fish and higher vertebrates including humans. Indeed, boring looking, hidden nematode worms are the most common intestinal parasites of man.

Parasitic worms are also called **helminths**. The most common are tapeworms and flukes (both flatworms) and parasitic roundworms (nematodes). The most common parasitic worms of humans are soil transmitted helminths, and the most common big three worldwide are all **nematodes**: roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworm (*Necator americanus* and *Ancylostoma duodenale*). In antiquity probably all humans had worms and even in the last century over half of us were infested. About 2 billion humans (one in four of us, concentrated in poor, tropical areas) are still harboring soil borne helminths, although most infested hosts don’t feel ill.

Nematodes: mostly hidden, boringly successful

Life is dominated by microscopic organisms. Most nematodes are microscopic but some are visible to the naked eye. They are mostly tiny, colorless roundworms that look much alike. Nematodes exist in unimaginably vast numbers in the soil, fresh and salt water and as plant and animal parasites. There are 57 billion mostly microscopic nematode worms for each one of the 8 billion humans on earth, 44 billion trillion total worms. 1 in 4 humans carries nematode parasites in their gut, mostly without any symptoms. Nematodes are the most common animals on the planet, yet few people will ever notice one in the dirt or in themselves.



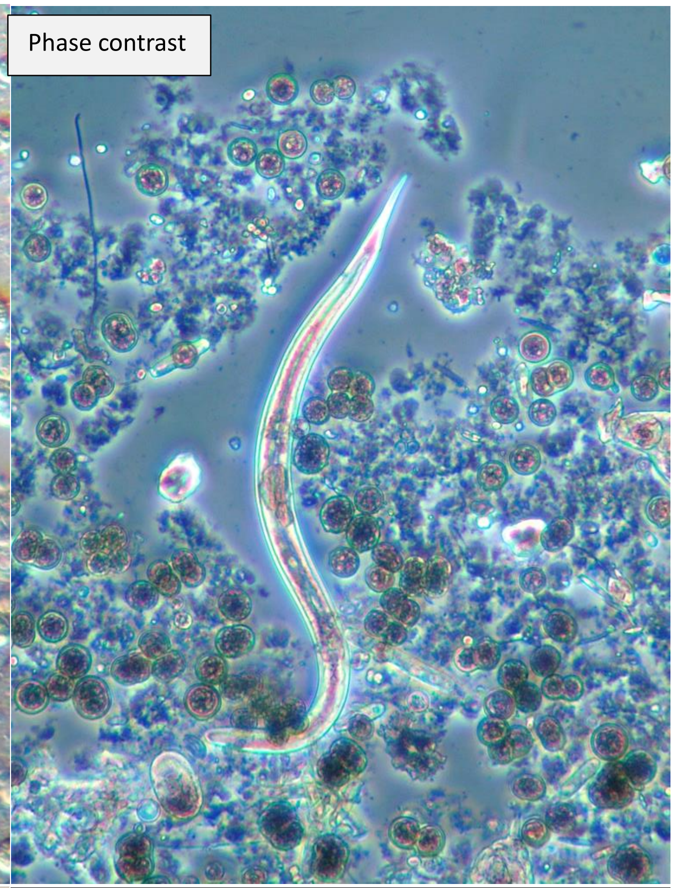
Free living nematode in aquarium debris. Most are microscopic, featureless bacterivores. Polar lighting shows something in the posterior part of this one. 20X objective, worm about 0.6 mm long.

Note the parasitic nematode below is over 600 times longer, colorful and interesting compared to the colorless microscopic free living worm above

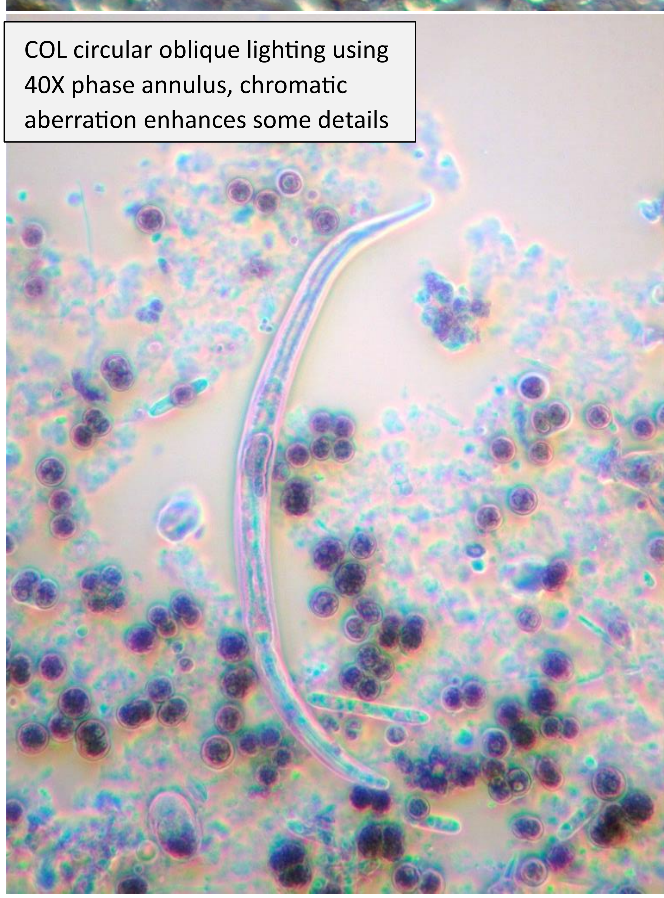
Anterior end of live *Camallanus sp.* parasitic nematode pulled from anus of small fish caught in Minnesota, USA. The 4 cm long female worm was visible to the naked eye, bright red, and a microscope revealed mom was full of thousands of squirming larvae. Parasites can be beautiful. 4X objective, darkfield, image about 3 mm wide, July 2021

Live colorless nematodes benefit from optical contrast methods

strong oblique lighting with “Mathias arrow” in condenser slot



Phase contrast



COL circular oblique lighting using 40X phase annulus, chromatic aberration enhances some details

Dark field using 100X phase annulus

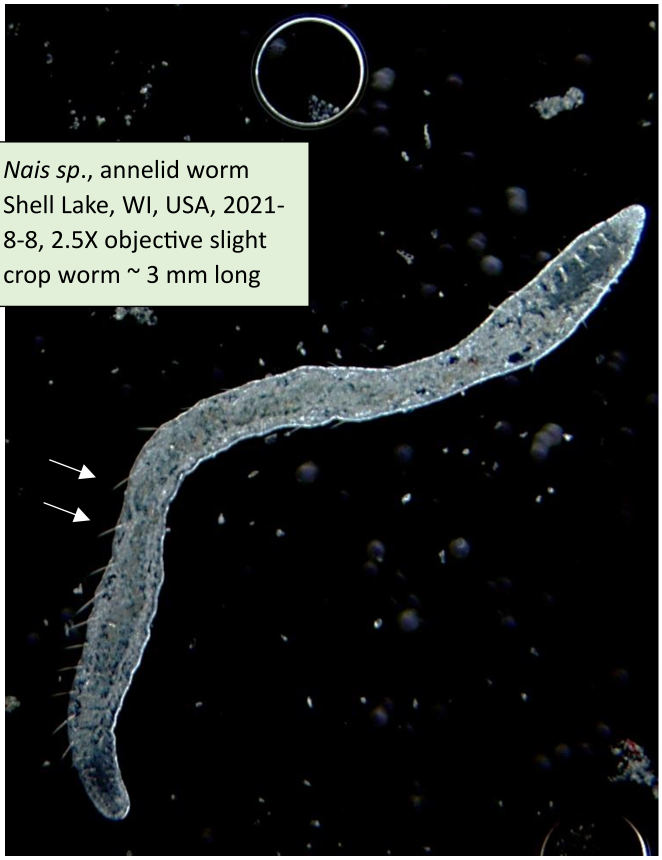
Free living nematode grazing among green algae on wet aquarium lid, 9 Dec 2017
10X objective (no reducer), worm about 0.4 mm long. Plain brightfield showed little.
False color from older American Optical 34 mmm parfocal objective on AO 410 stand.

The place of nematodes among other creepy crawlies

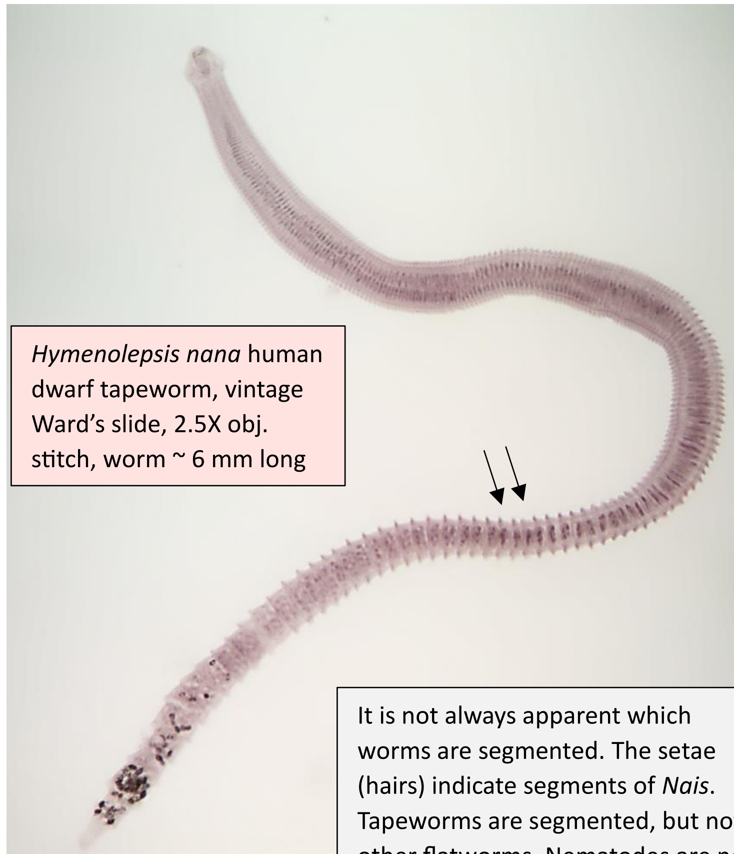
Based on body plan (symmetry, organ systems) scientists classify animals into major groups called phyla. Subsequently genomics has confirmed most of these groupings are correct. Metazoans (multicellular animals) evolved from a eukaryotic single celled ancestor similar to a choanoflagellate protist that lived about 1 billion years ago. The oldest major phyla of animals with members still alive today are Porifera (sponges, filter feeders with asymmetric shapes), Cnidaria (corals, jellyfish, hydra etc., predators with stinging cells, radial symmetry) and Platyhelminthes (flatworms, mobile predators or parasites with bilateral symmetry). Later came Nematoda, aka roundworms, which are also mobile bilaterally symmetric predators (often of bacteria) or parasites. They were the first animals to have a full length gut with an anus, and to have a tough extracellular cuticle secreted by the skin. Having a softer equivalent of an exoskeleton, they grow in stages, molting their cuticle 4 times during larval life. The third phylum of common worms is Annelida, the segmented worms. They are mostly fee living, including earthworms and many marine and freshwater relatives.

When I was in school most scientists believed annelid worms with their more complex body plan (with a true body cavity and an open circulatory system similar to insects) were the ancestors of arthropods (exoskeleton animals including crustaceans and insects). There was even a seeming missing link: onychophorans, soft bodied segmented “velvet worms” with multiple walking legs. But genomics shows nematodes and “penis worms” are more ancestral to the arthropods and their ecdysozoan relatives (including cute, tough little tardigrades). Molting an exoskeleton turned out to be very adaptable by evolution, as over 80% of all known animal species (about 1.2 million described so far) are arthropods. The exoskeleton plan is successful in making many small individual animals and the greatest amount of total animal biomass is comprised of creepy crawly insect arthropods and wiggly nematodes.

Parasitism evolved independently in 15 of 35 animal phyla (Weinstein and Kuris), although not all of these parasites are wormlike. The term “Helminth” includes parasitic worms or worm-like animals from many phyla, although the big 2 are Platyhelminthes (flatworms, discussed in previous chapters) and Nematoda (roundworms). There are also parasitic worms in phyla Annelida (most free living but includes blood sucking leeches), Nematomorpha (horsehair worms, parasites of insects), Acanthocephala (spiny headed worms, exclusively parasitic close relatives of rotifers), Arthopoda (pentastomid “tongue worms”, and some crustaceans and insects are very elongated endo- or ectoparasites) and Xenacoelomorpha (small flattened worms related to echinoderms, some are parasitic). Most authors use “helminth” specifically to refer to intestinal worms, but some use the term more broadly (“sensu lato”) to include all worm-like parasites or even to include all worms both parasitic and free living.

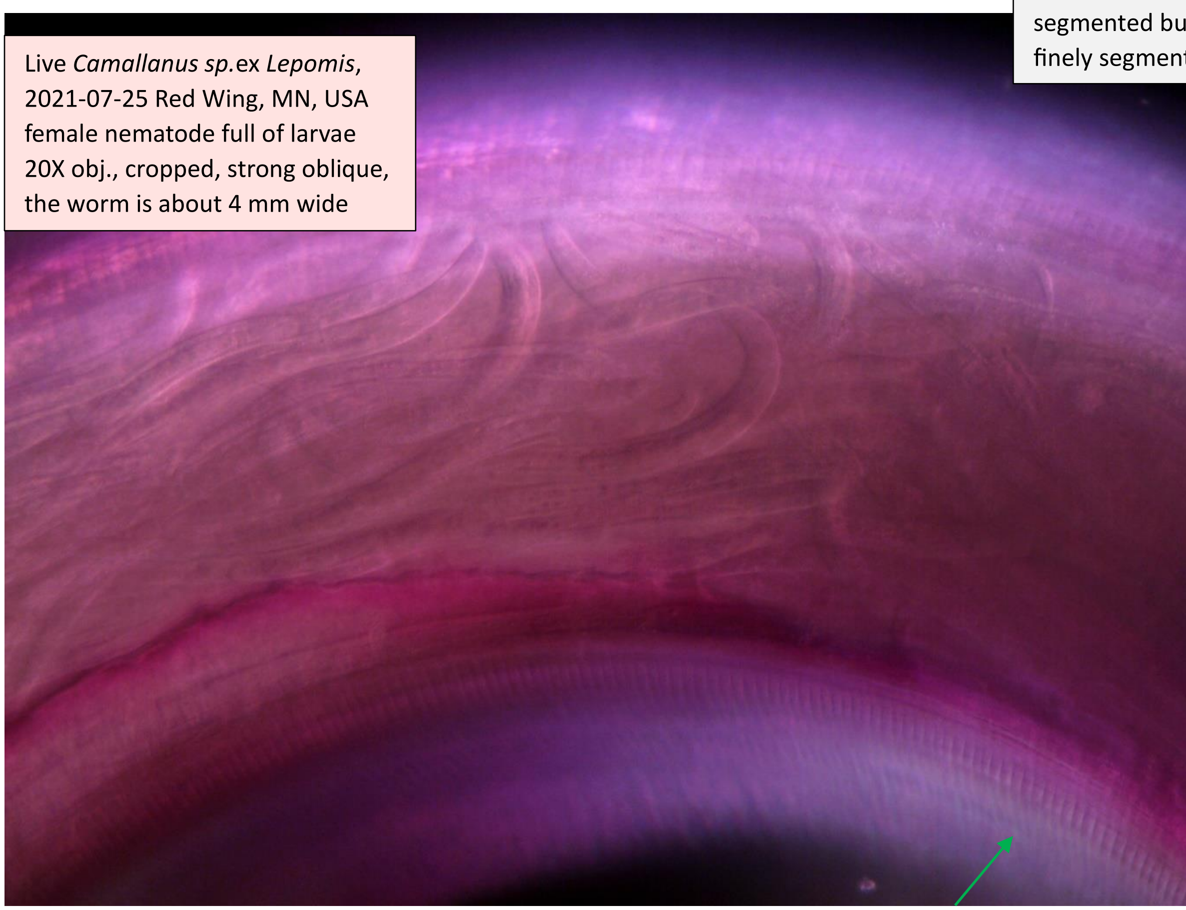


Nais sp., annelid worm Shell Lake, WI, USA, 2021-8-8, 2.5X objective slight crop worm ~ 3 mm long



Hymenolepsis nana human dwarf tapeworm, vintage Ward's slide, 2.5X obj. stitch, worm ~ 6 mm long

It is not always apparent which worms are segmented. The setae (hairs) indicate segments of *Nais*. Tapeworms are segmented, but not other flatworms. Nematodes are not segmented but sometimes appear finely segmented when contracted.



Live *Camallanus sp.*ex *Lepomis*, 2021-07-25 Red Wing, MN, USA female nematode full of larvae 20X obj., cropped, strong oblique, the worm is about 4 mm wide

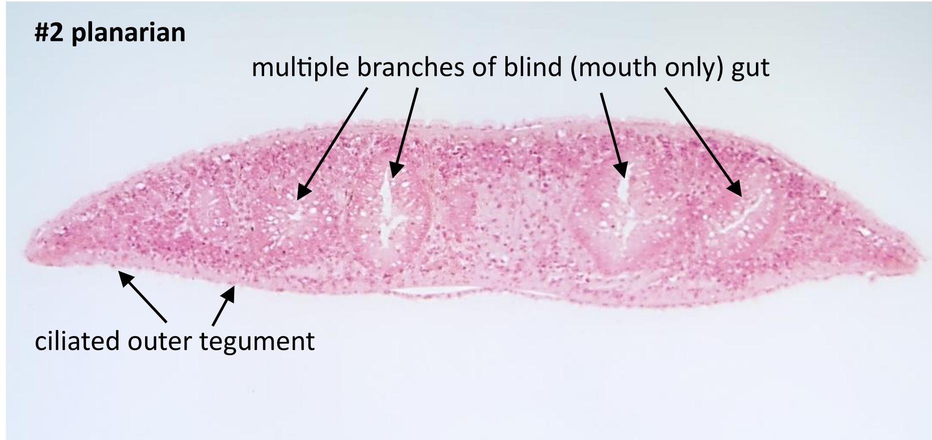
fine corrugations in stiff cuticle improve flexibility

Nematode anatomy and sex

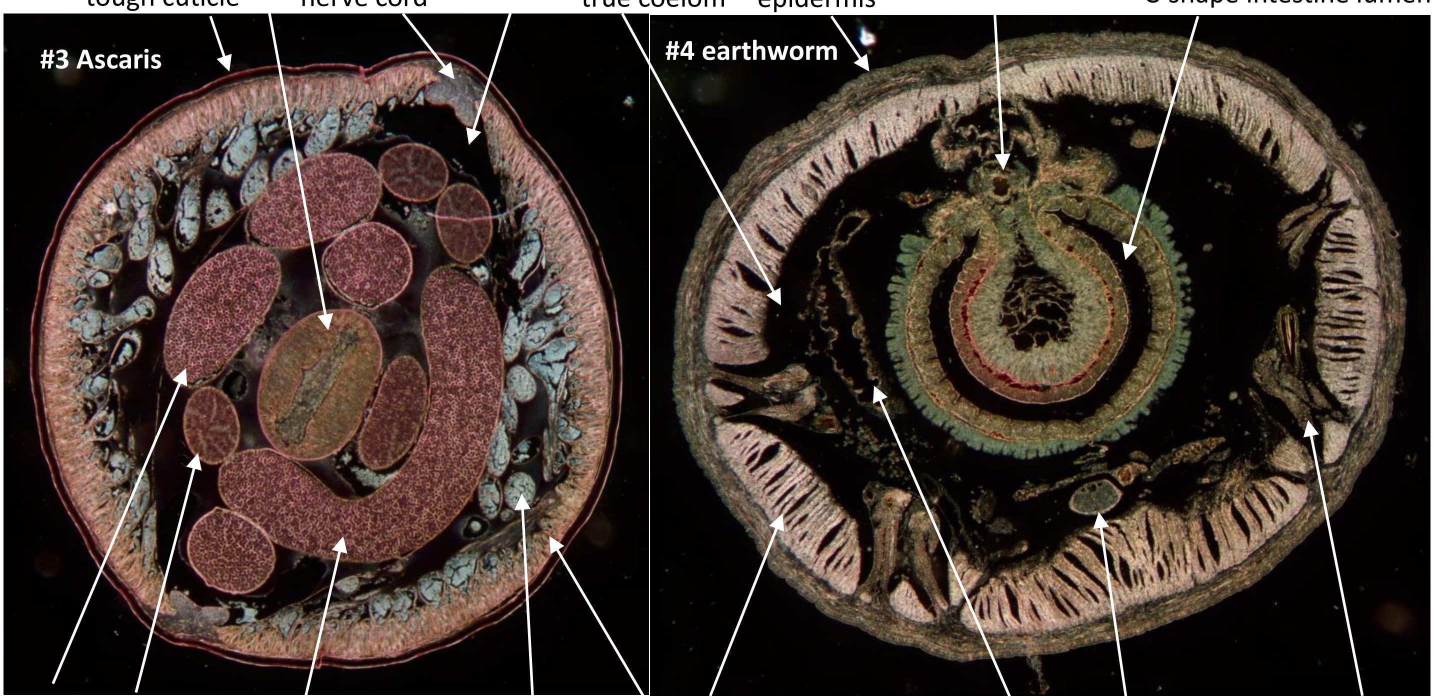
Roundworms comprise their own phylum, **Nematoda**. In the evolution of life, roundworms came along after flatworms. Their two great new inventions were the anus and tough skin. Roundworms can poop out undigested waste out the butt, rather than vomiting it out their mouth like a flatworm. They also have a new tough acellular cuticle (made of collagen plus lipids and glycoproteins) secreted by the hypodermis (a usually multinucleate syncytium also called the outer epidermal cell layer) which is underlaid by a somatic muscle layer. The cuticle is mostly smooth, with a slick glycoprotein outer layer that may hamper host immunity. Nematodes grow in stages called instars, by molting their cuticles (arthropods also grow this way). Nematodes have no legs, but males may have small genital claspers and sometimes the cuticle has scales or very tiny spines (setae). Some nematodes dress up in a coat of bacteria.

Most but not all nematodes are tiny, ranging in adult length from about 0.1 mm (1/250 of an inch) to 8 meters (25 feet). Parasitic nematodes tend to be bigger than the free living species (perhaps they are better housed and fed compared to living in dirt). The longest nematode is *Placentonema gigantissima*, a parasite of sperm whale placentas. All have a simple cylindrical body that is bilaterally symmetric with a top, bottom and sides. Inside the epidermis are four longitudinal cords (ridges) that divide the body into quadrants in a cross section. The anterior (head) end has a mouth, a small ring of neurons as a brain and sometimes tiny eyespots. An intestine runs almost the length of the body; the main organs are gonads (they make lots of eggs but some give live birth). Most nematode species have separate male and female individuals (are dioecious) but some are hermaphrodites and some species have 3 sexes (XO males, XX females and XX hermaphrodites), some (including *C. elegans*) have just males and hermaphrodites, and parasitic *Strongyloides* are all females, reproducing by parthenogenesis. Unusual for animals, they lack any cilia (you have cilia in your lungs, brain ventricles and inner ear). Most nematode sperm are amoeboid, lacking flagella, so they crawl, not swim. Nematodes don't have respiratory or circulatory systems and the excretory system is abbreviated. Long and skinny provides lots of surface area for exchange of oxygen, carbon dioxide and wastes including ammonia, although some have excretory glands to dump excess sodium. Nematodes are triploblastic (three embryonic cell layers- endoderm, mesoderm, ectoderm), acoelomate (no true, membrane lined body cavity) and unsegmented.

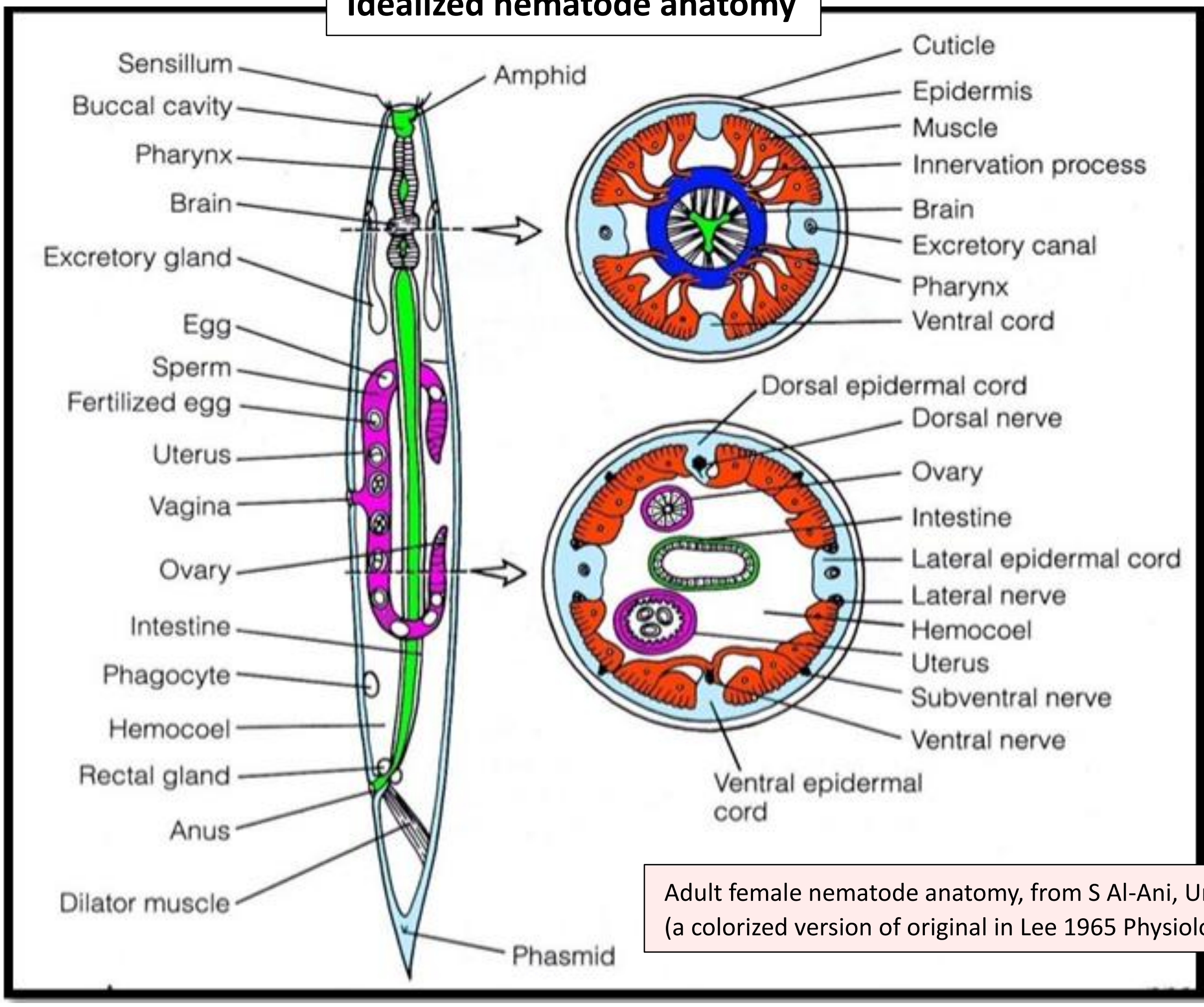
Colors added to the images on following page for clarity. The *Ascaris* slide (a classic among biology teachers) is stained. Most microscopic nematodes are clear, and big ones like *Ascaris* mostly look white. Interestingly, although *Ascaris* looks pale it can secrete hemoglobin to protect itself from host free radicals. But some nematodes (including *Anasakis*, *Camallanus* and others) make and keep hemoglobin in their body fluid and so appear blood red.



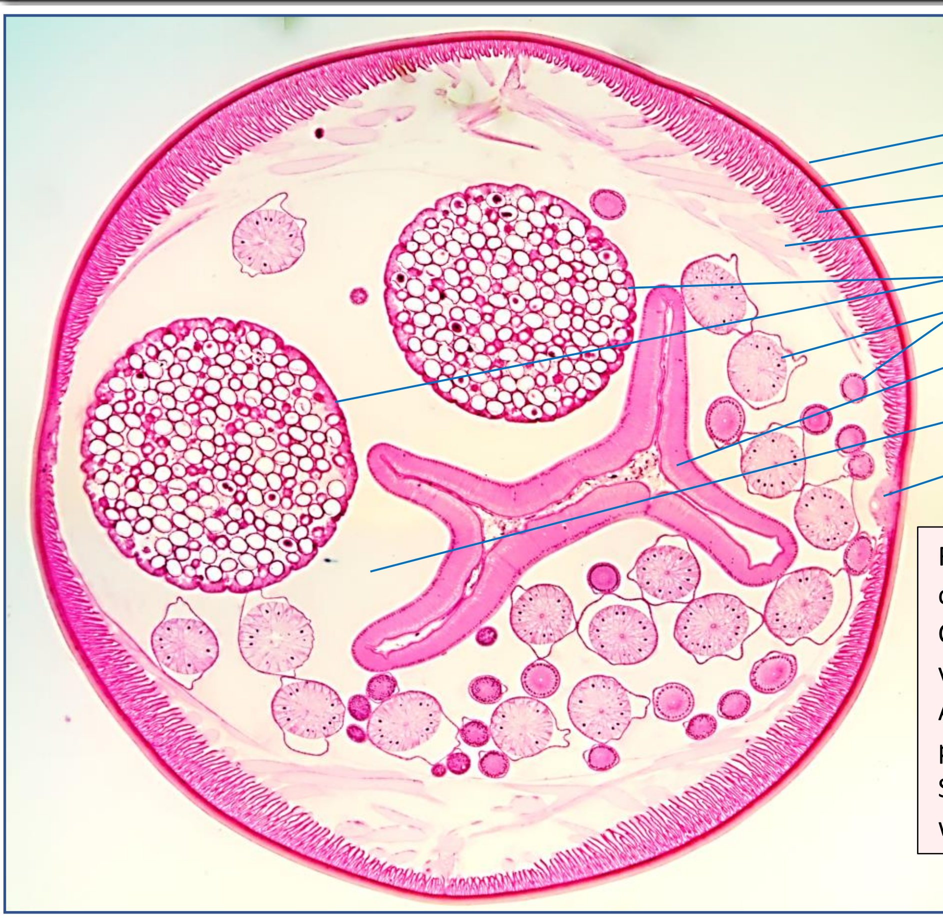
Cross section educational slides of some soft slender animals (planarian bright field, others dark field lighting)
Anemones are not worms. The big 3 worm phyla are flatworms, roundworms and segmented worms
#1 *Metridium sp.* (an anemone body) phylum Cnidaria, vintage Ward's slide, stitched 4X obj., about 3 mm diameter
#2 *Dugesia sp.* planaria flatworm phylum Platyhelminthes, vintage Ward's slide, stitched 10X obj., about 2 mm wide
#3 *Ascaris sp.* male roundworm phylum Nematoda, " Wards-Turtox" slide, 4X objective stitch, about 3 mm diameter
#4 *Lumbricus sp*. earthworm segmented worm phylum Annelida, " Wards-Turtox" 10X obj. stitch, about 5 mm wide



Idealized nematode anatomy



Adult female nematode anatomy, from S Al-Ani, University Anbar, Iraq (a colorized version of original in Lee 1965 Physiology of Nematodes)



Female *Ascaris lumbricoides* cross section, stained.
Classic basic biology subject, vintage Turtox, quality slide.
As in many helminths, egg production is prominent
Stitched using 4X objective, worm about 3.5 mm diameter

Nematode taxonomy

In 1735 Linnaeus threw all 9 worms he named into a grab bag "class Vermes", which was slowly sorted out over the next 2 centuries. In 1919 Cobb suggested the demonstrably different horsehair worms and acanthocephalan worms be removed from phylum Nematoda (which he called simply "Nema", Greek for thread). 19th and 20th century biologists worked on nematodes using morphology, but the big taxonomic advances now come from genomics.

As for most tiny organisms, nematode taxonomy is a bit of a mess, and is being sorted out by ongoing research (commonly sequencing 18S small subunit ribosomal DNA). Nematode data is complicated by bias towards sequencing parasites and model organisms, and by uncertainty regarding which characteristics come from directly from ancient ancestry. Some nematode groups probably moved back and forth between salt and freshwater and between free-living and parasitic lifestyles over the eons. Although it is often the most powerful tool we have to elucidate evolutionary history, DNA sequencing does not magically reveal the full truth. Genomic family tree results depend in part on assumptions and analytical choices made by researchers. The human parasites *Trichinella* and *Trichuris* (whipworm) and the insect parasitic mermithids usually end up low in the nematode family tree. So the first nematode may have been free-living marine or (seemingly less likely) a terrestrial parasite.

The soil nematode *Caenorhabditis elegans* became a model organism for developmental biology (easily cultured, with only 959 or 1031 somatic cells) and then became the first multicell organism to have its whole genome read, in December 1998 (less than 2 years before the first human). Around the same time other nematodes were sequenced in part and 5 clades were found. Every year more roundworms are sequenced, allowing the phylogenetic trees to get ever more complicated, as seen in the 2002, 2013, 2022 and 2023 examples that follow.

We seem to have three classes (or at least clades of some rank) comprising phylum Nematoda:

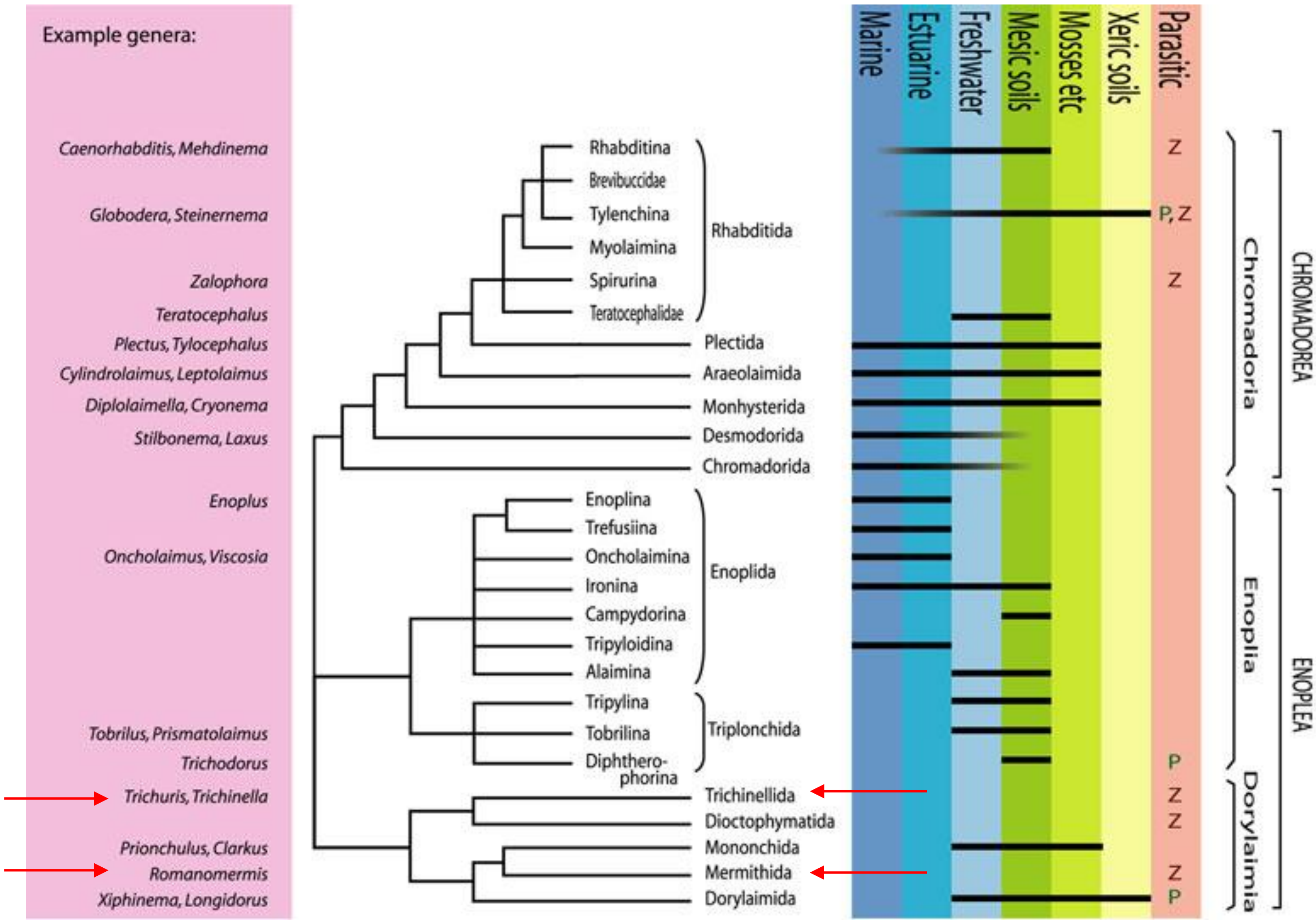
Class Enoplea 2297 species, all or almost all marine and free living
---Trichinellids and Mermithids belong to Enoplia or Dorylaimea (see my red arrows)

Class Dorylaimea 4917 species, freshwater and in soils, many free living and many parasitic

Class Chromadorea 21317 species, widely varied in habitats and life styles

There were a total of 28537 nematode species (some unclassified) in 3 classes, 32 orders, and 303 genera according to Hodda's 2022 (now incomplete) census.

Nematoda family tree as of 2002

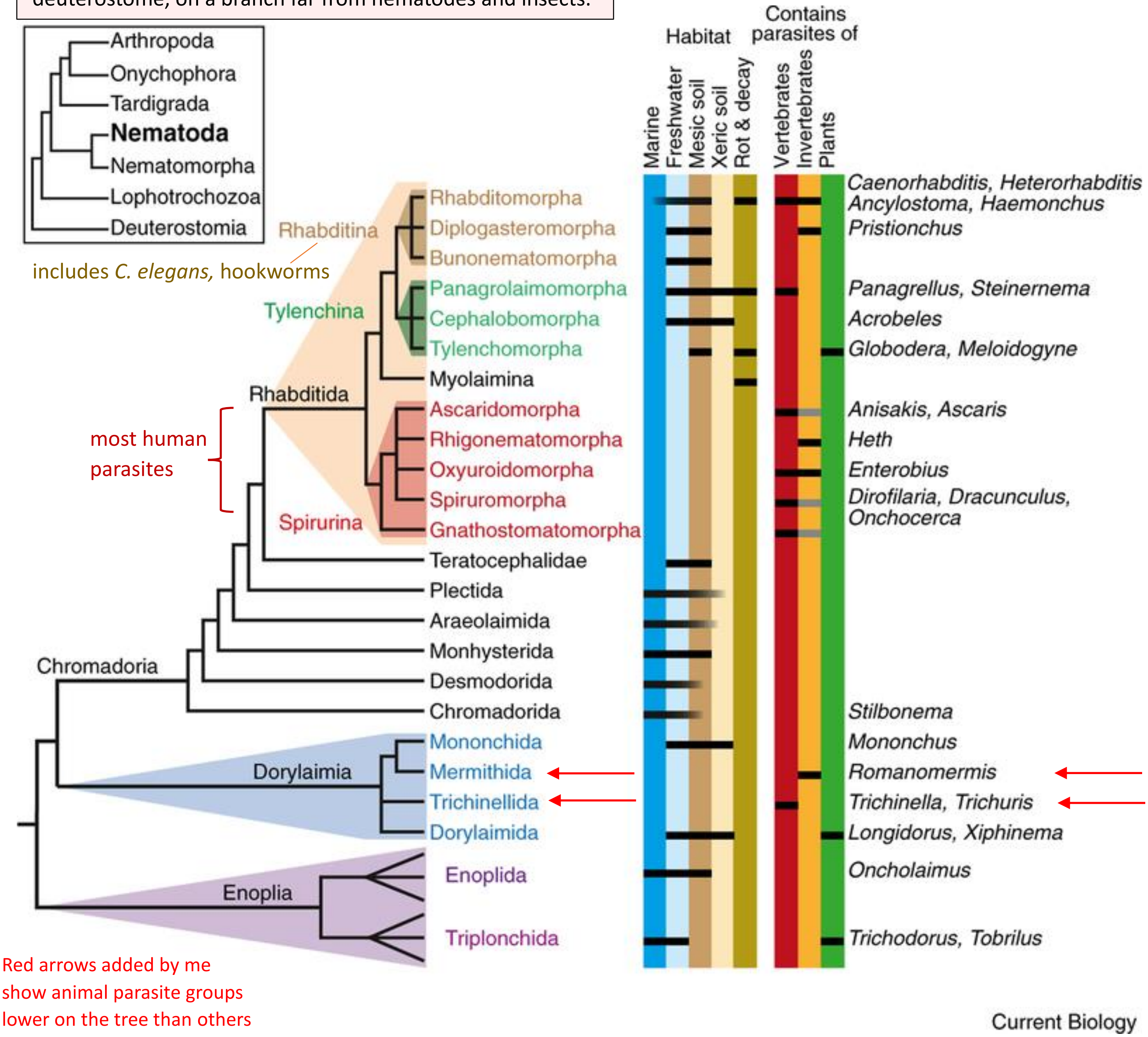


(red arrows added by me, showing some parasites of terrestrial animals near base of tree)

Summary 18S rDNA phylogenetic tree of Nematoda with examples, ecological range and higher classification. Many free living soil nematodes including *C. elegans*, and many human parasites including *Ascaris* are in the large Order Rhabditida. Mesic soils are moderately damp and Xeric soils are dry, P= phytoparasitic, Z= zooparasitic. (De Ley in WormBook 2024, adapted from De Ley et al 2002 based on 53 18S genomes organized by Blaxter et al in 1998).

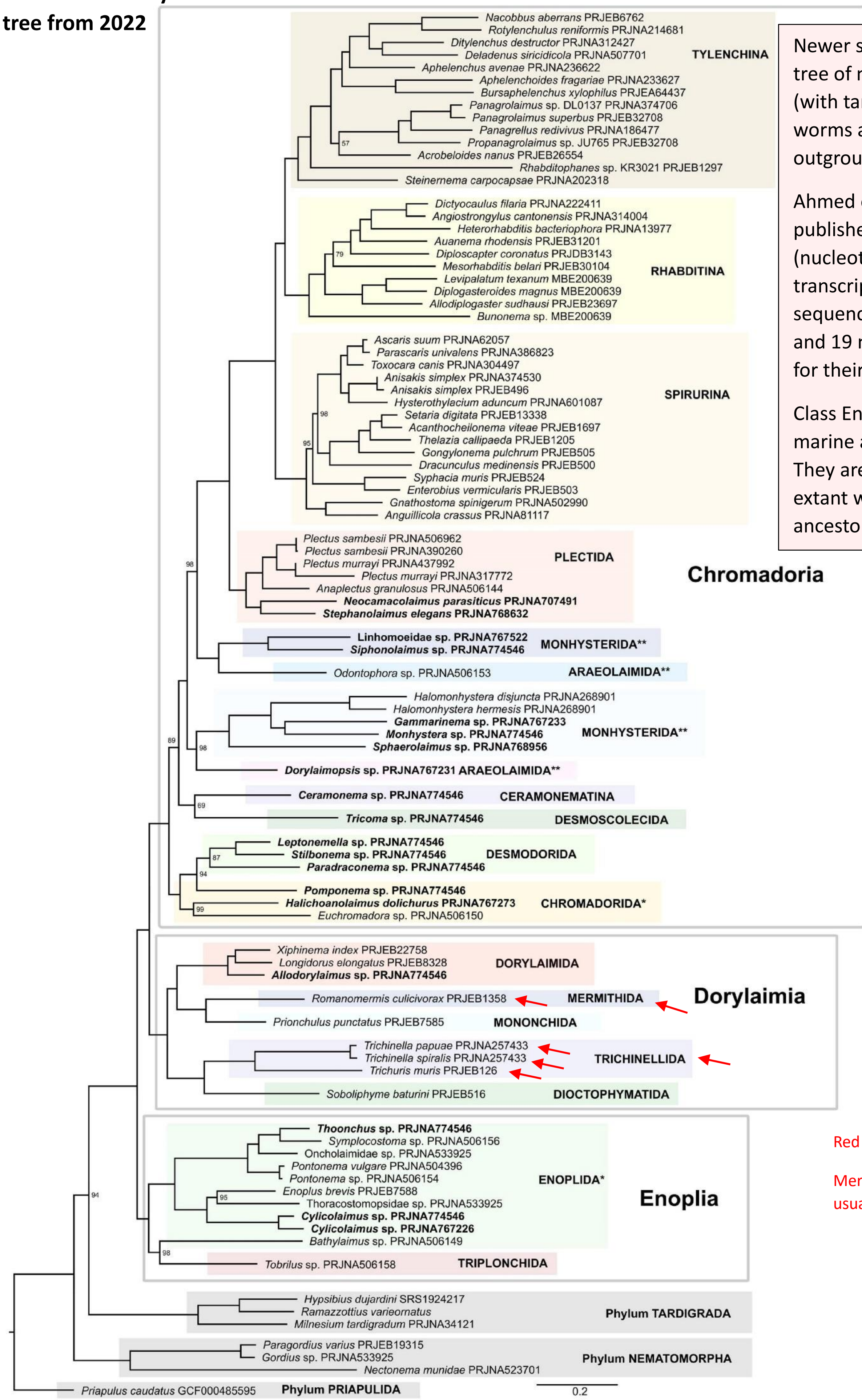
Nematode family tree from 2013

Upper left inset: nematodes in a tree of animal life. You are a deuterostome, on a branch far from nematodes and insects.



Main chart: taxonomy of nematodes as of 2013, well organized, mostly per small-subunit rRNA sequences. Note three large monophyletic groups: mostly marine Enoplia, Dorylaimia including trichinellids and mermithids, and Chromadoria with nematodes of all habitats and life styles (mesic is damp, xeric dry). Most animal parasites belong to Spirurina in Rhabditida, but hookworms (Strongylida) are found in the related Rhabditina. Bars at right indicate hosts of parasitic nematodes (grey intermediate, black definitive hosts). Example genera are listed on far right.
Kiontke, Fitch **Current Biology** 2013, adapted after De Ley 2006 based on 53 18S genomes organized by Blaxter 1998

Nematode family tree from 2022



Newer summary phylogenetic tree of nematodes (with tardigrades, horsehair worms and penis worms as outgroups).

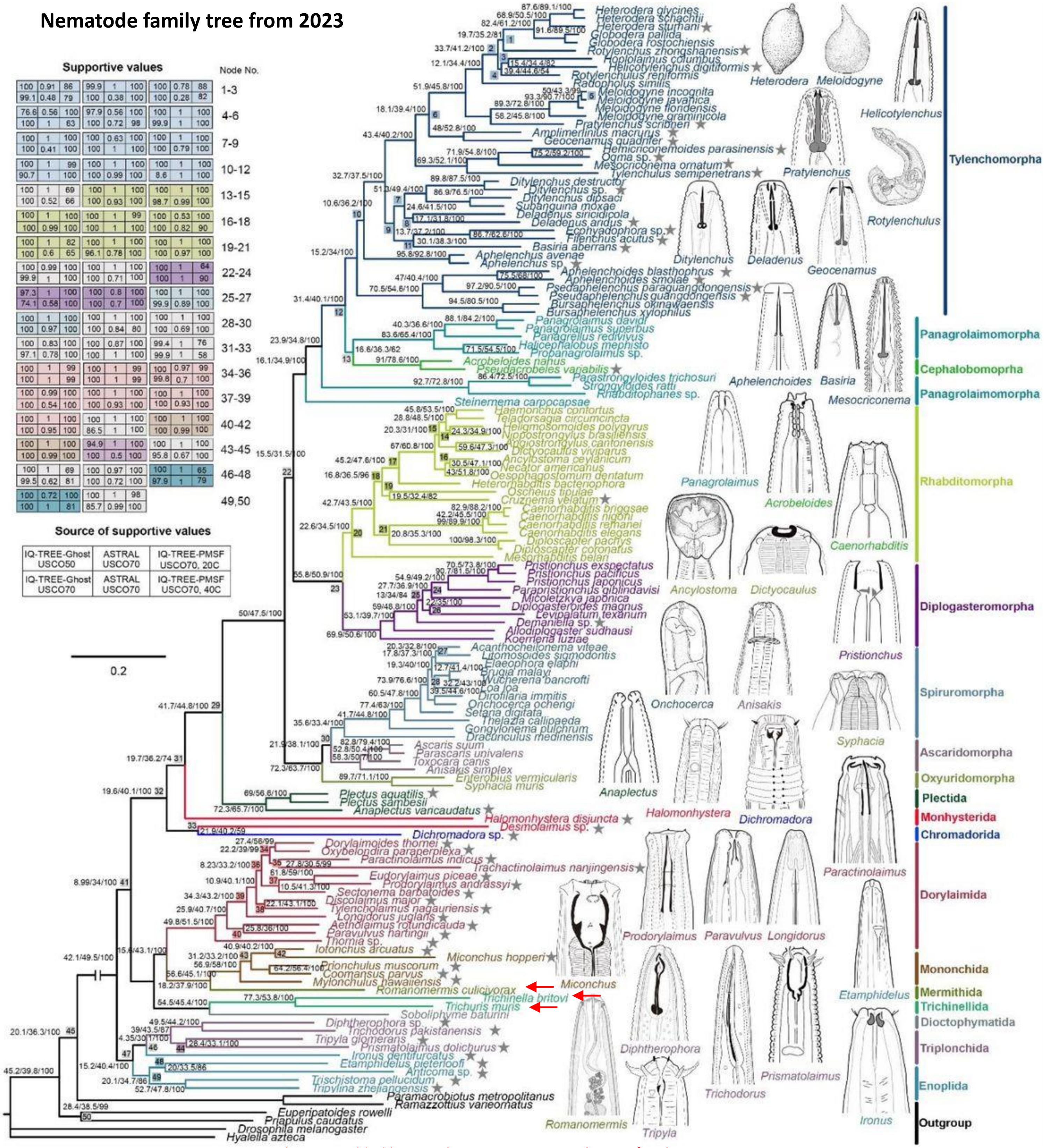
Ahmed et al, 2022 used 286 published genomes (nucleotide sequences) and transcriptomes (amino acid sequences, i.e. "proteomes") and 19 new transcriptomes for their tree.

Class Enopila species are marine and mostly free living. They are likely the closest extant worms to the common ancestor of all nematodes.

Red arrows added by me

Mermithids and Trichinellids usually end up in Dorylaimia

Nematode family tree from 2023



Node No.									
1-3	100	0.91	86	99.9	1	100	100	0.78	88
	99.1	0.48	79	100	0.38	100	100	0.28	82
4-6	76.6	0.56	100	97.9	0.56	100	100	1	100
	100	1	63	100	0.72	98	99.9	1	100
7-9	100	1	100	100	0.63	100	100	1	100
	100	0.41	100	100	1	100	100	0.79	100
10-12	100	1	99	100	1	100	100	1	100
	90.7	1	100	100	0.99	100	8.6	1	100
13-15	100	1	69	100	1	100	100	1	100
	100	0.52	66	100	0.93	100	98.7	0.99	100
16-18	100	1	100	100	1	99	100	0.53	100
	100	0.99	100	100	1	100	100	0.82	90
19-21	100	1	82	100	1	100	100	1	100
	100	0.6	65	96.1	0.78	100	100	0.97	100
22-24	100	0.99	100	100	1	100	100	1	64
	99.9	1	100	100	0.71	100	100	1	90
25-27	97.3	1	100	100	0.8	100	100	1	100
	74.1	0.58	100	100	0.7	100	99.9	0.89	100
28-30	100	1	100	100	1	100	100	1	100
	100	0.97	100	100	0.84	80	100	0.69	100
31-33	100	0.83	100	100	0.87	100	99.4	1	76
	97.1	0.78	100	100	1	100	99.9	1	58
34-36	100	1	99	100	1	99	100	0.97	99
	100	1	99	100	1	99	99.8	0.7	100
37-39	100	0.99	100	100	1	100	100	1	100
	100	0.54	100	100	0.93	100	100	0.93	100
40-42	100	1	100	100	1	100	100	1	100
	100	0.95	100	86.5	1	100	100	0.99	100
43-45	100	1	100	94.9	1	100	100	1	100
	100	0.99	100	100	0.5	100	95.8	0.67	100
46-48	100	1	69	100	0.97	100	100	1	65
	99.5	0.62	81	100	0.72	100	97.9	1	79
49,50	100	0.72	100	100	1	98			
	100	1	81	85.7	0.99	100			

Source of supportive values

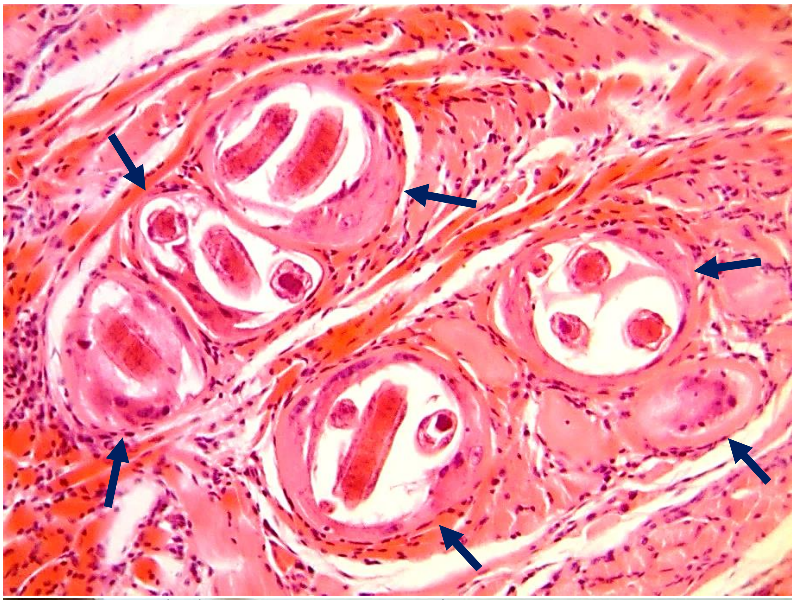
IQ-TREE-Ghost USCO50	ASTRAL USCO70	IQ-TREE-PMSF USCO70, 20C
IQ-TREE-Ghost USCO70	ASTRAL USCO70	IQ-TREE-PMSF USCO70, 40C

Red arrows added by me, show some parasites low on family tree

Recent summary phylogenetic tree of nematodes based on whole genomes. Qing et al, 2023, used 54 newly obtained full genomes, picking out individual worms under a microscope to be chopped up and analyzed. Helpfully, their figure also shows some typical anterior end morphology for some example genera. Parasitic *Trichinella, Trichuris* and *Romanomermis* again end up somewhere between most Enoplida and Dorylaimida

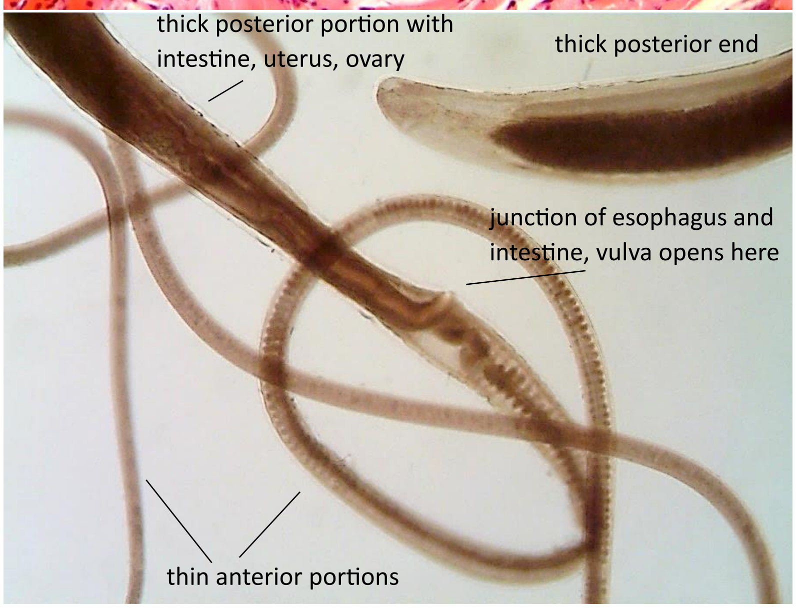
Are trichinellids living fossils?

Probably not. Nematodes likely first appeared in the sea over 0.5 billion years ago, as did all the other major phyla of animals. But surprisingly, trichinellid and mermithid nematodes, all parasites of land animals, appear near the base of nematode genomic family trees. Trichinellids include *Trichinella spiralis* and *Trichuris trichiura* which infect people; closely related nematodes infect mammals, birds and reptiles. Mermithids are important parasites of insects. Life didn't come onto land until the first plants about 470 million years ago. Insects may have come ashore around the same time, but the oldest insect fossil, *Rhyniognatha*, is from the early Devonian Rhynie chert, about 396 million years ago. The oldest land vertebrate fossil is the late Devonian amphibian *Elginerpeton*, about 368 million years old, but fossil records (and all scientific data) are always incomplete.



Trichinella spiralis encysted in muscle of rat tongue, nice 1950's slide by unknown maker. The worms are curled up and transected at various angles. Arrows point to 6 cysts. *T. spiralis* was an important human parasite before meat inspection began in the late 1800's. Owen named *T. spiralis* in 1835 and Virchow figured out the life cycle and preventive measures in the 1860's.

20X objective, H&E stain, image about 0.6 mm wide and worms about 30 microns in diameter



Trichuris trichiura, whole female, Ward's slide. Called whipworm after the body shape, the long thin part is the anterior end, with mouth at the tip. Adult females grow up to 6 cm long and (along with males) live in the colon, passing up to 20 thousand eggs in feces daily. *T. trichiura* is one of the big 3 soil borne human nematode infections.

4X objective, image is about 3 mm wide.

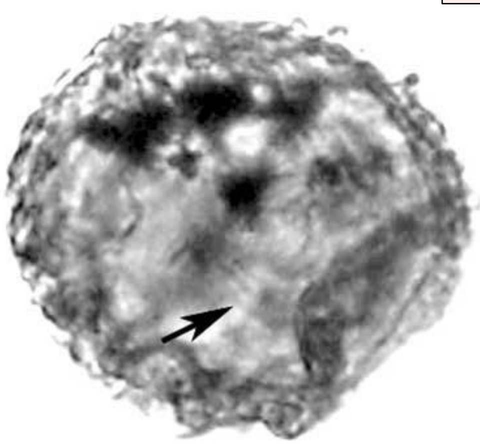
Mermis nigrescens, the grasshopper nematode, can get up to 20 cm long, far longer than its insect host, which is killed by the worm's emergence. The adult female then lives in soil and cements eggs onto grass at night, to be eaten by hosts.

image University of Florida, about life size

Fossil nematode parasites

"DNA clocks" are inexact. Nematodes may have originated 1 billion or just a ½ billion years ago. Ideally genomics is complemented by hard fossil evidence. But the small nondescript bodies of nematodes can make it difficult to be sure what sort of worm a fossil is. Fossilized "worm" burrows can be found in 565 million year old early Cambrian rocks, but we don't know if the makers really were worms or other sediment dwelling animals. The oldest nematode fossil is 396 million year old *Palaeonema phyticus*, found parasitizing an early Devonian land plant.

Parasitic nematode *Palaeonema phyticus* in the stomatal chambers of the land plant, *Aglaophyton major.* Worm about 0.9 mm long and looks much like extant nematodes. Wonderfully preserved in Early Devonian Rhynie Chert of Scotland. Image- G Poinar Jr, who named the fossil nematode



Egg (about 40 microns diameter) of nematode *Ascarites priscus* in coprolite of predatory dinosaur, *Megalosaurus,* from early Cretaceous of Belgium, about 124 million years old. Species named by and image by George Poinar Jr.

Fossil mermithid nematode *Heydenius formicinus* emerging from about 3 mm long male *Prenolepis henschei* flying ant in Baltic amber, Eocene, about 40+ million years old. Image also Poinar.

Professor Poinar is an entomologist and an insects in amber expert who gave the idea of getting dinosaur DNA from mosquitoes in amber to Crichton for Jurassic Park (not feasible in reality).

Late breaking fossil news

On-line on 18 November 2024 Hughes, Evans and Droser published "An Ediacaran bilaterian with an ecdysozoan affinity from South Australia" in Current Biology. They think multiple fish hook shaped 1 cm long fossils about 555 million years old are ancient nematode worms. Could be. They were found in the Ediacaran fossil beds, which reveal a variety of first animals (many are odd vaguely plant like fractal shapes) coming on scene just before the famous Cambrian explosion introduced modern phyla including arthropods, mollusks and echinoderms.

One of the putative Precambrian nematode fossils found by mother and son paleontology professors Droser and Hughes. The worm shaped impression is about 1 cm long.

Nematodes by the numbers: the most abundant animal on earth

Nematodes are well known to most amateur microscopists. Soil is full of microscopic roundworms, as is aquarium or pond detritus. My pond water sample jars often become overrun by bacteria, followed by swarms of nematodes a few days later. Most roundworms are tiny (a mm or less long, microscopic or nearly so, being so slender) and look alike to a nonexpert. The freshwater and soil nematodes I frequently see under the microscope wriggle incessantly and about all I can make out is approximate size and if they have red eyespots.

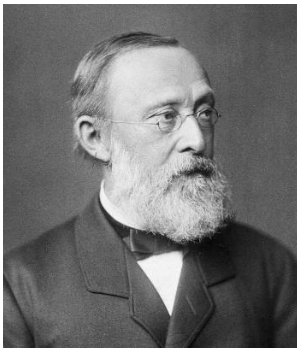
Nematodes live everywhere: marine, freshwater and on land. Evolutionary analyses show they made multiple transitions back and forth between these realms and that parasitism evolved many different times. Soil nematodes live everywhere where there is dirt, from moist tropics, to deserts and the arctic. Many live near the surface but some are far underground. Nematodes are tough. *Panagrolaimus kolymaensis* was brought back to life after being found frozen for 46,000 years in Siberian permafrost 40 meters (130 feet) deep.

In 2019 van den Hoogen and colleagues estimated there are 4.4×10^{22} soil nematodes, making them the most numerous animals on earth in individual numbers (dethroning copepods; in 2004 Boxshall and Halsey had estimated there are 1.4×10^{21} planktonic copepods. There are more roundworms and copepods than insects [$\sim 10^{18}$] in total numbers, but average insects are big enough to see, and so total insect biomass is far greater than nematode or copepod mass). There are about 57 billion nematodes living in the dirt for every single human being. And that estimate leaves out marine nematodes. **3 out of every 4 individual animals on earth is a tiny nematode worm.** The unbelievable abundance of nematodes was calculated and poetically described by Nathan Cobb (2nd quote from 1914 US Dept. Agriculture yearbook):

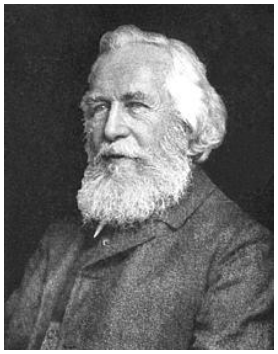
"If the nematodes resident in a single acre of soil near San Antonio, Texas, USA, were to proceed in head-to-tail procession to Washington D.C., some 2000 miles away, the first nematode would reach Washington before the rear of the procession left San Antonio!"

"In short, if all the matter in the universe except the nematodes were swept away, our world would still be dimly recognizable, and if, as disembodied spirits, we could then investigate it, we should find its mountains, hills, vales, rivers, lakes, and oceans represented by a film of nematodes. The location of towns would be decipherable, since for every massing of human beings there would be a corresponding massing of certain nematodes. Trees would still stand in ghostly rows representing our streets and highways. The location of the various plants and animals would still be decipherable, and, had we sufficient knowledge, in many cases even their species could be determined by an examination of their erstwhile nematode parasites."

Nathan Cobb was the "father of nematology" and was a student of racist German zoology genius Ernst Haeckel (a fascinating and flawed figure, who was in turn a student of antiracist Rudolph Virchow, the late 19th century father of both pathology and of social medicine). He died at Johns Hopkins Hospital on the day of his (too rigorous?) annual physical in 1932.



born1821-died1902



born1834-died1919

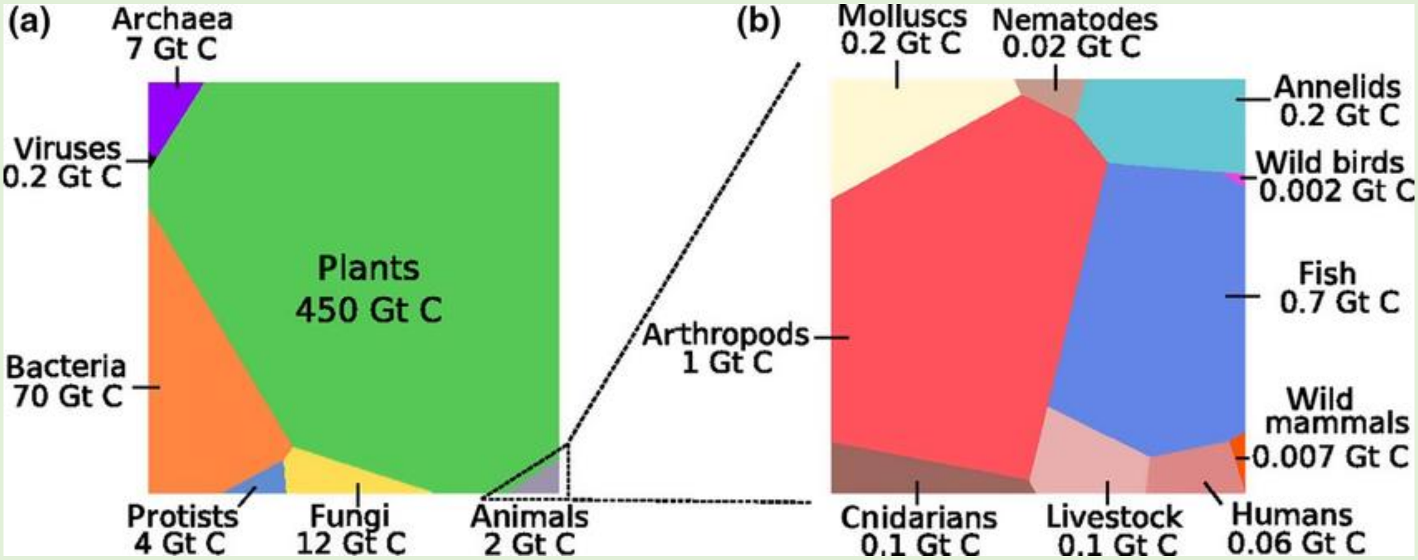
born1859-died1932

Basic scientific and social ideas of our modern world were passed down by stern looking white men such as these.
Left to right:
Rudolph Virchow
Ernst Haeckel
Nathan Cobb
images- Wikipedia

How many nematode species?

A century ago nematologist Nathan Cobb described over 1000 new species and created a morphology based taxonomy for nematodes. Nematodes don't all look alike, but the differences are subtle to a nonexpert. There is no confusion with common names because apart from a few common roundworm parasites, nematodes don't have common names. The US Department of Agriculture remains concerned with nematode pests, funding research on root knot and stem nematodes of food and industrial crops. The number of nematode species continually grows as more research is done, and genomics assists. As of 2022 Hodda tallied 28,537 distinct species of nematodes but like other tiny invertebrates most species are not yet described. The microbial world is still largely an uncharted wilderness. Experts have guessed that the real total number of nematode species is between 500,000 and 10 million. Despite looking all alike to me, nematodes are a varied and diverse group, adapted to many different environments including ocean sediments, freshwater, hot springs, various kinds of soils (with more per gram of soil in artic and temperate soils than in tropical soils), on mosses, plant roots and inside plants and inside invertebrate and vertebrate animals as commensals or parasites. Although Hugot estimated 60% of nematode species might turn out to be parasitic, the majority of nematode species described so far are free living. Genomics shows parasitism on animals or plants arose at least 18 separate times in nematode worms. Most nematode parasites are adapted to a specific host. Humans have discovered 35 nematode species adapted just to us, and about 30% of nematode genera contain vertebrate parasites. Given about 70,000 living vertebrate species (about half fish, half on land) it is likely we have so far discovered only a small minority of the real total extant parasitic nematode species.
(In numbers of species and biomass, insects win; arthropods are the most successful animals).

Life by the numbers chart Bar-on et al PNAS 2018



Size

The smallest prokaryote, *Mycoplasma*, can be 0.15 microns across; blue whales up to 33.6 m (110 feet) long.

Species

Life on earth is wonderfully diverse. Prokaryotic microbes (bacteria and archaea, which lack a nucleus) are the oldest and most abundant life, but only 22,919 species were named as of 2022, while perhaps 4 million extant (living) prokaryotic species exist. The IUCN Red List in 2022 listed 953,434 animal species, 215,644 plants, 43,271 fungi and 16,151 protist species. The about 1.2 million named eukaryotic species are also a vast undercount, especially for tiny ones, and maybe 10 million eukaryotic species are out there.

Individuals

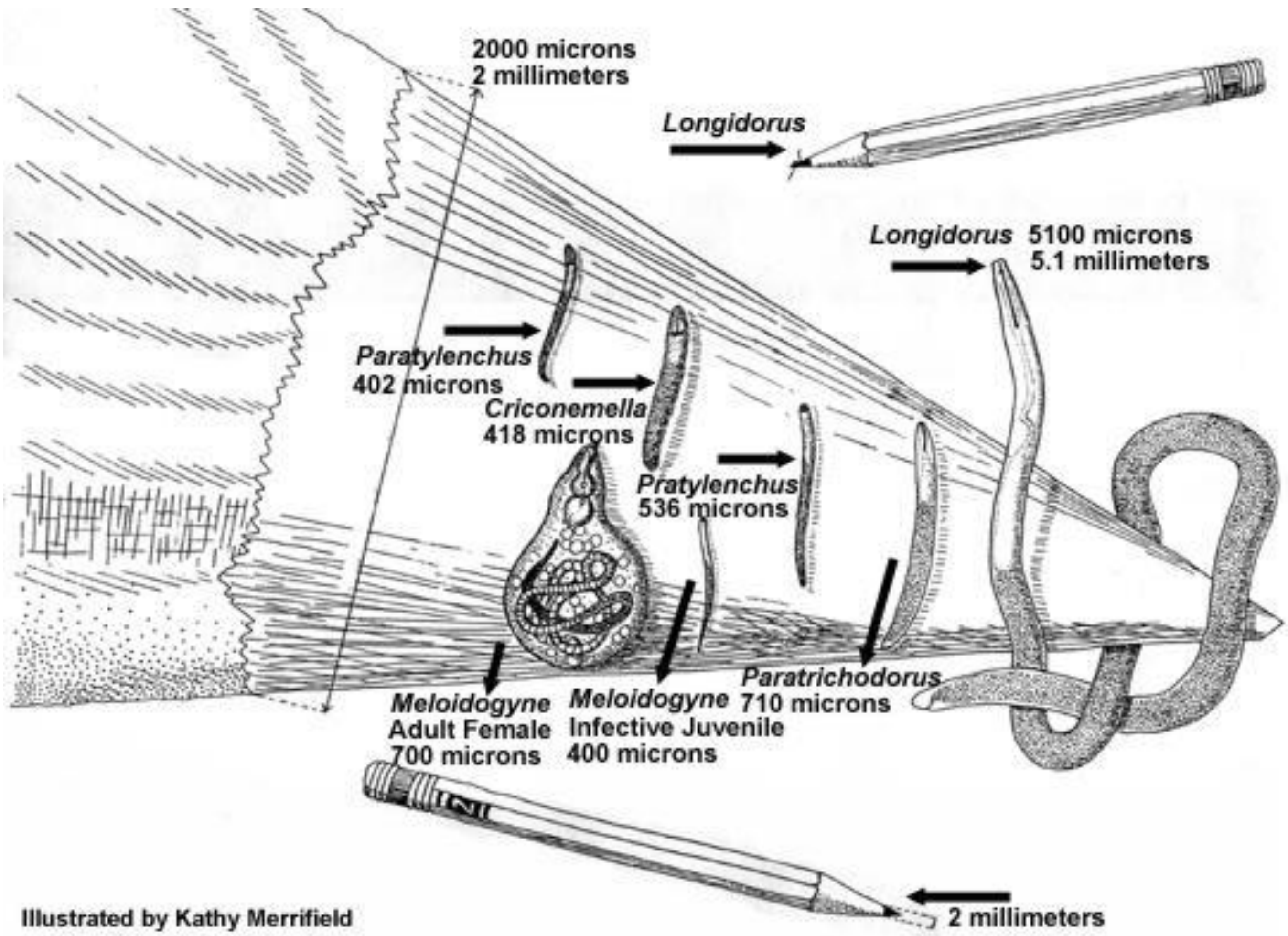
Microscopic viruses and prokaryotes (bacteria and archaea) dominate life by the number of individuals, and nematodes are the most numerous of animal individuals. Best estimates are that there are about 10^{31} virus particles (which straddle the line between living or inanimate) on earth and about 10^{30} to 10^{31} prokaryotic cells. I couldn't find good global estimates of numbers of individual of protists and plants. Soil nematode numbers are estimated at 4.4×10^{22} and marine copepod crustaceans at 1.4×10^{21}. But much life is bigger (macroscopic) and an important way of thinking about the bulk of life is in terms of mass. Most insects are big enough to see with the naked eye so their 10^{18} individuals dwarf nematodes in total mass.

Biomass

You are about 60% water by weight. All organisms are mostly water so scientists often use dry carbon weight to quantify biomass. The chart by Bar-on et al from 2018 lists biomass by giga tons (billions of metric tons) of carbon. Plants (especially trees) dominate global living mass, which makes sense if you look out the nearest window (if not in a manmade urban center). Prokaryotes come in second (impressive for microbes mostly so tiny they need oil immersion microscope objectives to be seen clearly). In terms of total mass, animals are the smallest kingdom of life. Arthropods, especially insects, dominate animal biomass. Most vertebrate mass is fish. All the terrestrial vertebrates put together are just a tiny speck on the earth, well under the gigaton ranges of other life forms. Man and his livestock dominate this tiny bit of terrestrial vertebrate life, having eliminated 98% of wild mammals. *Homo sapiens* is recently out of control. The human population doubled between 1974 and 2023, hitting 8×10^9, using more resources than earth can sustain, making doomsday machines, harming the atmosphere and killing off 2% of other species so far. *H. sapiens* needs to wise up.

Small but powerful

Nematodes' 4 x 10^{22} abundance plus tiny size and slender shape yields lots of surface area, facilitating exchange of molecules with the environment, supporting worm metabolism and enabling a vast amount of ecosystem services. Many nematodes eat bacteria, which would overwise take over the planet more completely than they have already (bacteria and archaea total about 5 x 10^{30} cells on earth). Nematodes cycle nutrients, helping most plants while keeping some others in check as plant parasites. They also keep many insects and themselves in check (some live in the body fluid of insects, and some prey on other nematodes). Soil nematodes live in vast numbers, yet are so small that most humans will never notice one.

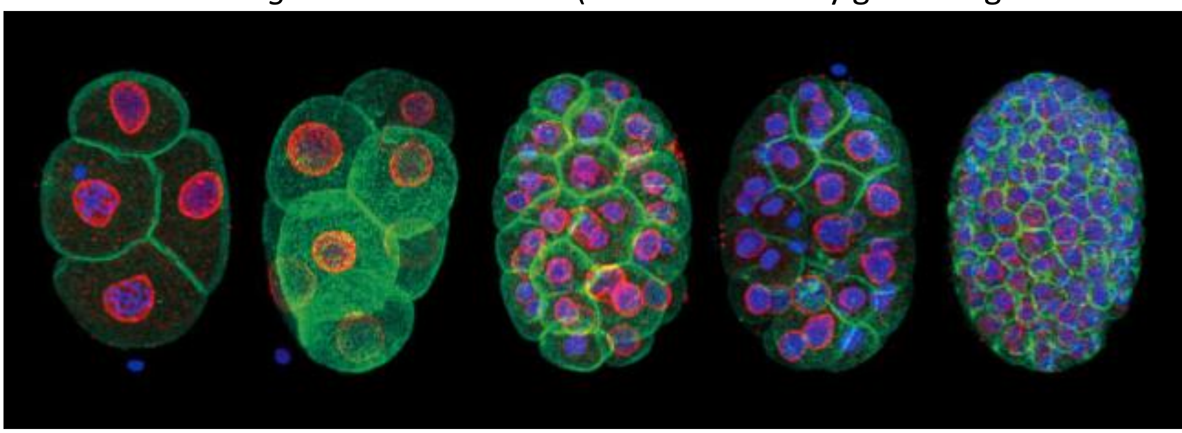


Ingham, Merrifield. 1996. A Guide to Nematode Biology and Management in Mint. Integrated Plant Protection Center, Oregon State University, Corvallis. Pub. No. 996

The old school illustration shows the size of some nematodes that parasitize mint plants. As small as these are, most free living nematodes in soil and water are smaller. Parasitic nematodes tend to be a bit larger than their free-living relatives, all the way up to the giant *Placentonema gigantissima.* One adult female worm from a sperm whale placenta was 8.4 m (27 feet) long and 2.4 cm (an inch) in diameter! Thankfully, most nematodes are much smaller.

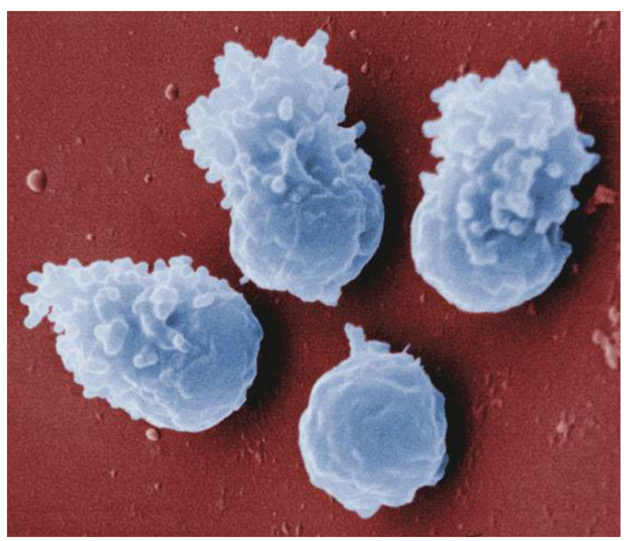
A model organism from dirt

As a group nematodes are relatively neglected, but we know one free living species in great detail, having purposefully made it a subject of intense study. ***Caenorhabditis elegans*** is a pale 1 mm long rhabditiform nematode first found in compost soil in Algeria in 1900. It eats bacteria, smelling them and swimming to them in wriggling movements in tiny amounts of moisture in soil. Most are hermaphrodites and self fertilize, but 1 in 1000 is male. A path of sequential cell divisions from single cell zygote through 4 larval stages always leads to an adult hermaphrodite with 959 somatic cells (or a male with 1031) plus a similar number of germ cells. Convenient for study, it always ends up with the same number of cells (called eutely, seen in some small animals), including 302 neurons. In the late 20th century *C. elegans* become a model organism for developmental biology research, including work leading to Nobel prizes for six scientists. Embryology, brain development, sex determination, meiosis (cell divisions to make sex cells), apoptosis (programmed cell death), RNA interference and gene silencing (epigenetics), aging, sleep cycles and even drug addiction to nicotine have all been studied in the humble *C. elegans* dirt nematode (but how did they get 1 long mm worms to smoke?).



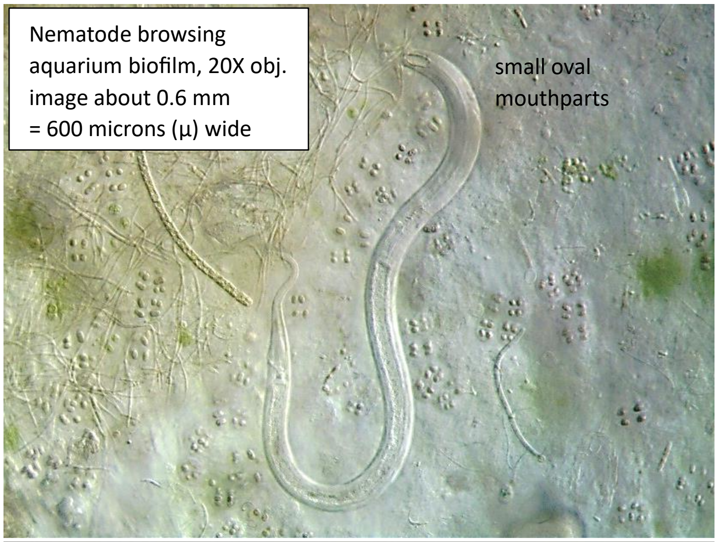
C. elegans early embryos, confocal with 63X objective, by Alyson Ramirez, Harvard.
Nikon Small World contest image of distinction, 2017

Four *C. elegans* spermatozoa. Lacking flagella, they crawl with pseudopods like amoeba, but using MSP (major sperm protein) instead of actin. *C. elegans* sperm vary from about 5 to 15 microns in diameter (about the size of your blood cells), varying by strain and by sex (male sperm are larger than hermaphrodite sperm, and are favored during mating). Colorized SEM image wormatlas.org. Original by S Ward in Nelson et al 1982

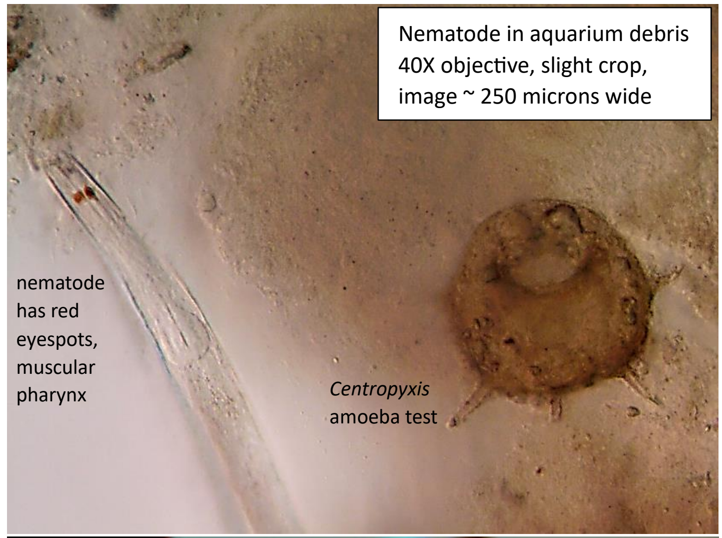


Free living nematodes: boring little worms?

The multitudes of nematodes I find in soil and freshwater samples are usually tiny and colorless. I'm lucky if I get to see some tiny red eyespots (usually in pairs, and may not always be light receptors). Photos from 2022.

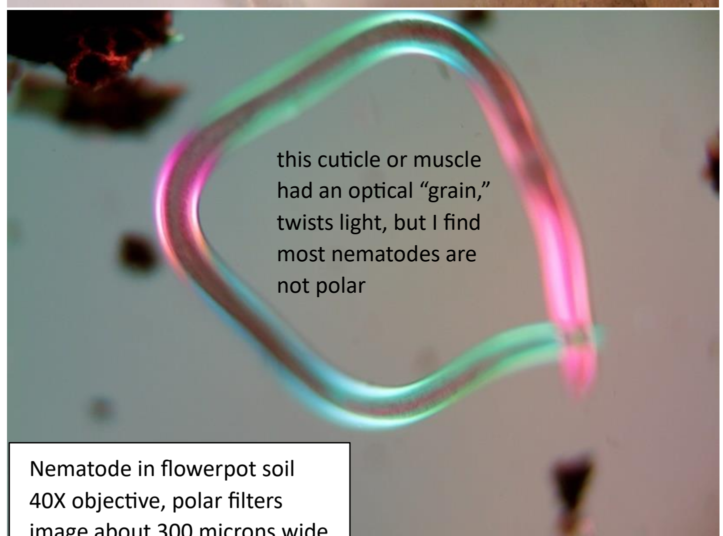


Nematode browsing aquarium biofilm, 20X obj. image about 0.6 mm = 600 microns (μ) wide

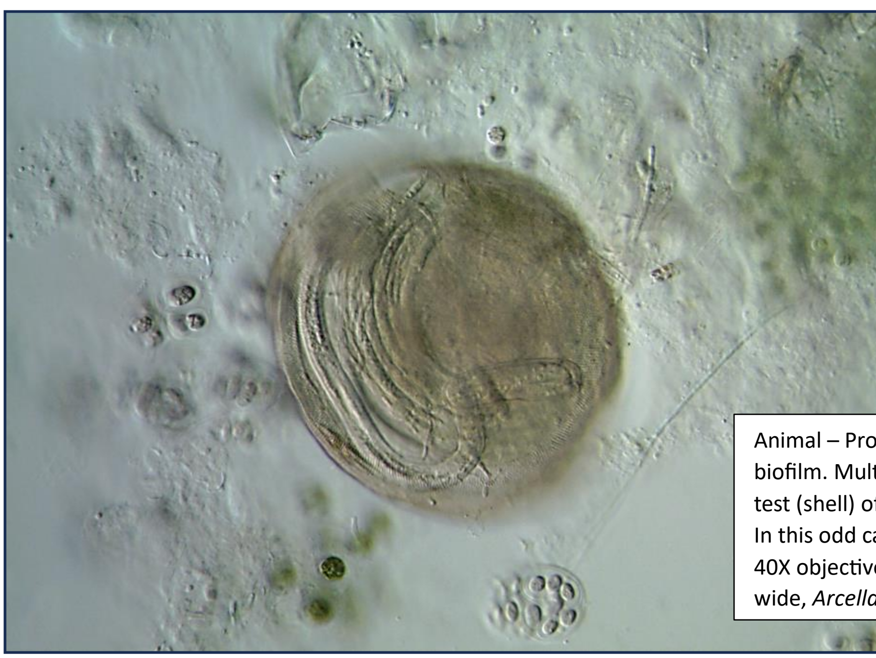


Nematode in aquarium debris 40X objective, slight crop, image ~ 250 microns wide

Nematode in flowerpot soil 20X objective, cropped, image about 300 microns wide



Nematode in flowerpot soil 40X objective, polar filters image about 300 microns wide



Animal – Protist comparison in aquarium biofilm. Multicellular nematodes inside a test (shell) of unicellular amoeba *Arcella.* In this odd case the metazoan is smaller. 40X objective, image about 300 microns wide, *Arcella* test about 100 microns

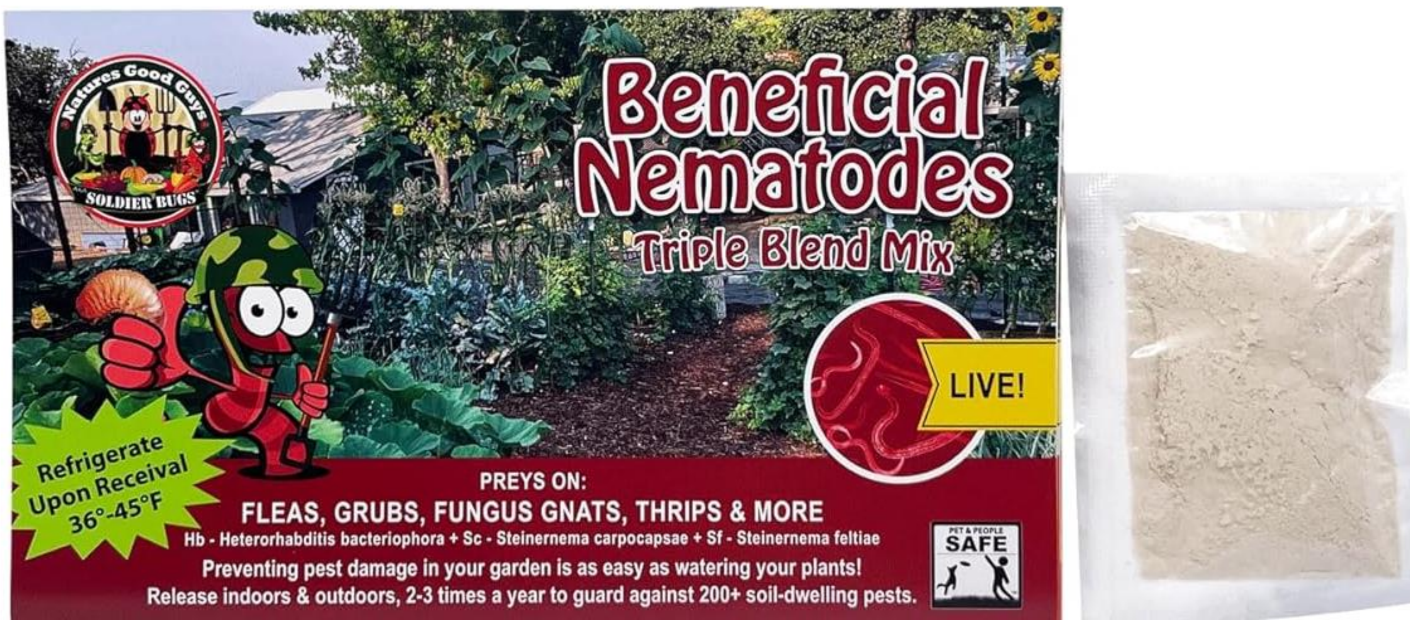
Nematode Lifestyles

Like *C. elegans* **most nematodes are free living** and super abundant, with an average of 3 living in every gram (pinch) of soil on earth. 70 to 85% of described nematode species are free living. One author estimated 60% of nematode species will turn out to be parasites, but others find about 30% or fewer are parasitic (still, only flatworms have a larger proportion as parasites). Nematodes are important in ecosystems as consumers and prey. Most soil nematodes are bacterivores or scavenge organic matter, and some are predators on protists or fellow nematodes. Some are hunted by insects, centipedes, tardigrades or predatory fungi that capture them with snares. Nematodes have many relationships with bacteria, often eating them, sometimes "farming" them on the cuticle for future consumption, sometimes using bacteria against a host (see below) and some live symbiotically with intracellular *Wolbachia* bacteria (as do many insects, although insects tend to be harmed and nematodes helped). Nematodes are an important part of nature's waste management systems. By scavenging the dead and by eating bacteria they break complex organic molecules into smaller chemicals, a key step in many nutrient cycles. Maintaining soil health, their types and numbers are markers of soil health. Nematodes have complex relationships with bacteria, fungi, plants and animals.

Some nematodes are parasites of a large variety of plant and animal hosts. The most studied parasitic nematodes use plants or insects as hosts. Nematodes can be devasting crop and domestic animal pests. Nathan Cobb, father of US nematology, worked for the Department of Agriculture and much nematode research is agriculture related to this day. Harmful root-knot nematodes and cyst nematodes are much studied. But parasites can also be useful as biologic controls on unwanted host populations (the enemy of my enemy is my friend). The nematode *Rhabdias sp,* frog lungworm, was tried (unsuccessfully) against invasive *Rhinella marina* cane toads in Australia (which were originally introduced to control a beetle pest, but multiplied out of control). Nematodes are sold to control insect pests of plants; you can get 5 million tiny live *Heterorhabditis* and *Steinernema spp.* nematodes for $17.25 on Amazon.

Parasitic nematodes have the same basic anatomy and biology as their free living cousins, but live on or inside plants and animals, deriving their nutrition from the host. The nematodes parasitizing animals tend to be bigger than the free living kinds. Perhaps the guts of animals provide easier meals and a comfortable place to hang out. Sometimes mouthparts have become adapted for hanging on, or getting blood. Plant parasites have sharp stylet shaped mouthparts to penetrate the tough cell walls of plant hosts. Parasites are part of the original balance of nature but now humans farm massive amounts of crops and food animals. As of 2022 nematodes caused about 125 billion dollars of global annual damage to our plants.


Root-knot nematode penetrating root of tomato plant
SEM image Wergin, Sayre, false color Ausmus, U.S.D.A.



Many nematodes eat bacteria but some nematodes live in **beneficial symbiosis with bacteria**. *Steinernema carpocapsae* and closely related species are entomopathogenic (insect harming) nematodes widely used commercially to control insect pests. *Steinernema spp.* nematodes harbor bacteria (mostly *Xenorhabdus nematophila* but also *Pseudomonas* and many others) in their gut that do the actual killing work. In a mutualistic relationship the worm synthesizes some nutrients for the bacteria, which then help the worm by turning an insect to worm food. The nematode enters an insect through the mouth or anus and poops out insect killing bacteria. 2 days later the dead insect body is a liquefied feast for 80,000 baby nematodes. Another family of nematodes, filaria, live in obligatory beneficial symbiosis with an intracellular bacteria, *Wolbachia.* The bacteria synthesize certain vitamins for the worm, and in turn get a place to live. The worm controls filarial reproduction and passes itself from parent to offspring inside oocytes (the worm's egg cells). (Important in some human disease control schemes, *Wolbachia* also lives in most arthropods, including many insect vector species).

History of nematode parasitology

Large helminths sometimes pass in stools and were known in ancient Egypt, Greece and Rome. Both Robert Hooke (about 1683) and Anton von Leeuwenhoek (in 1722) saw free living nematodes with their early microscopes. The first nematode parasite discovered was a plant parasite seen by Turbevil Needham in a crushed wheat cockle (aka gall, a tumor like growth caused by infection) in 1743 who described being surprised to see "worms, eels or serpents" under the microscope. Later, tiny parasitic nematodes were found in insects and vertebrates. *Ascaris*, a human roundworm, was named by Linnaeus in 1758. *Trichina* (soon renamed *Trichinella*) worms were discovered in a cadaver by Owen in 1835. Investigations by Virchow in 1859, who revealed a life cycle including larvae ingested in undercooked pork, bringing a scientific understanding and public health prevention measures to human parasitic diseases. Lewis found microfilaria in blood in India in 1872, and 5 years later Patrick Manson had an "Aha!" moment seeing microfilaria in the stomach of a blood fed mosquito. The ensuing decades were a golden era for parasitology and infectious disease study with the transmission cycles of many diseases being worked out by brave scientists all around the world (before antibiotics, Dr. Ricketts died from the *Rickettsia* he discovered). Scientific knowledge and better living standards eventually abolished some parasites from much of the world, but they still cause a lot of human suffering in the tropics. Nematode parasites continue to infect billions, mostly as intestinal species, but some other nematodes travel in our blood to every organ.

Loa loa microfilaria in stained human blood smear, vintage Ward's Science slide. The worm remains endemic in parts of Africa. 40X objective, cropped, image about 150 microns across (red blood cells are about 6 microns diameter).

Burden of nematode parasites of humans

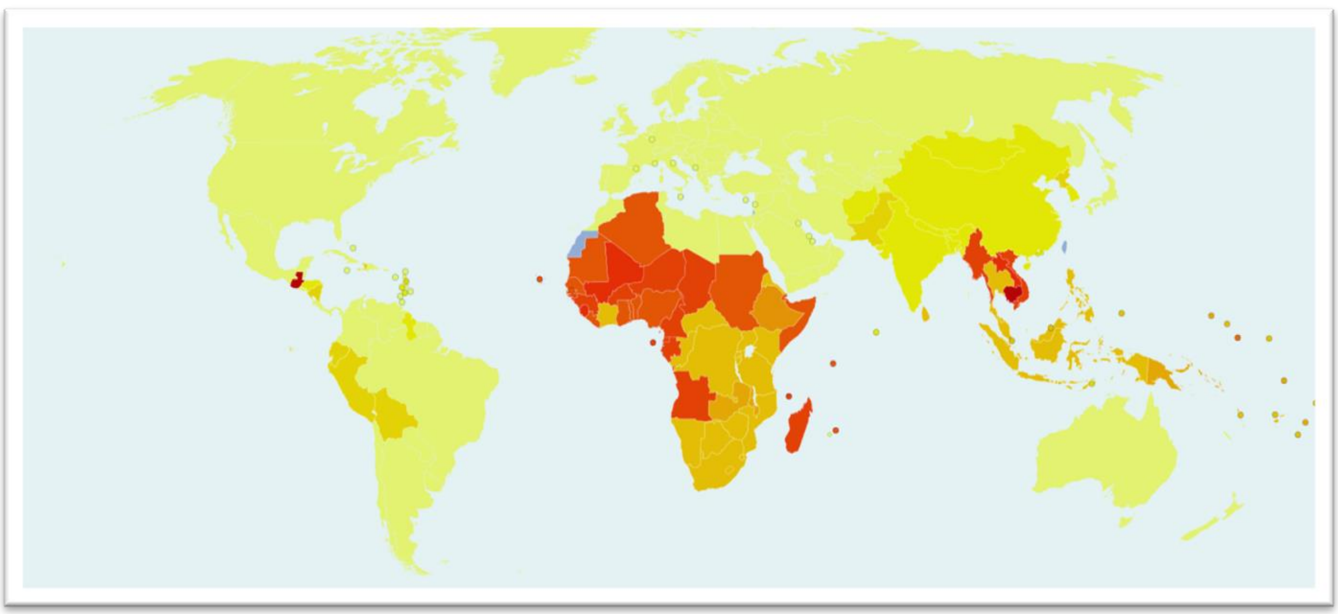
Nematodes are everywhere on the surface of planet earth, including hidden inside of 1 in 4 humans. Most intestinal helminth infections are asymptomatic or nearly so, but they infect more humans than any other kind of parasite. They can kill in rare cases, usually with high parasite load in a host already suffering from malnutrition and poor health from other causes, or sometimes from a complication such as a bowel obstruction. International parasite prevention and eradication programs have had real success, along with better water supplies, public hygiene and billions rising out of the most extreme ($2 a day) poverty. The number of humans with worms dropped from about 3.5 billion (60% of the population) in 2000 to about 2 billion (30% of a growing human population) in 2010. Deaths from helminths were estimated at about 125,000 per year in 2000 but have hopefully also dropped by half or more. Still worms can sicken or disable without outright killing. US scientists a century ago attributed southern US poverty largely to anemia from hookworms leaving people unable to work hard. Globally in 2010 the WHO attributed 5.2 million DALYs (disability adjusted years of life lost) to the big three 3 soil acquired nematodes, with hookworms causing the most disability.

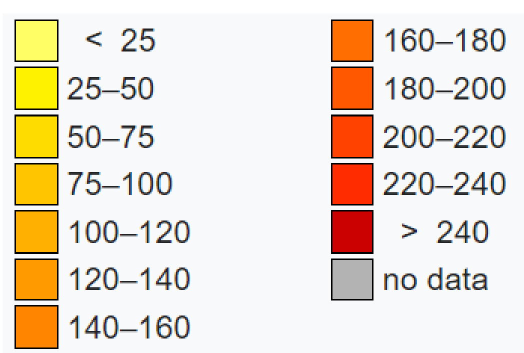
Global human nematode infections at turn of the 21st century (data Crompton 1999)

Species of Nematode	Numbers Infected	Distribution
Ascaris lumbricoides "roundworm"	1,472,000,000	World wide
"hookworms" *Ancylostoma duodenale* and *Necator americanus*	1,298,000,000	World wide
Trichuris trichiura "whipworm"	1,049,000,000	World wide
Enterobius vermicularis	400,000,000	Temperate regions
Strongyloides stercoralis	70,000,000	Temperate regions
Onchocerca volvulus and	17,660,000	Central and South America sub Saharan Africa
Brugia maylayi and *B. timori* India	13,000,000	South Pacific, SE. Asia,
Loa loa	13,000,000	West and Central sub Saharan Africa and Yemen
Dracunculus medinensis	80,000	Sub Saharan Africa, Yemen

(Bracket annotation on the first three rows: the "big three" soil associated helminths)

Sir Manson founded the London School of Hygiene & Tropical Medicine in 1899. Parasitism of people remains a **neglected tropical disease** problem in today's world. We used to all have intestinal worms but then 60% of us got regular access to toilets by the beginning of the 21th century (although only 40% of people have those toilets connected to sewage treatment; much human waste is still piped raw into rivers and the sea). Once the material gains of the industrial revolution were spread to include the workers (an ongoing process), health and comfort climbed in developed western nations over the past 150 years. Today for people in rich countries parasites are no longer a major problem. The burden of parasitic disease is borne mostly by poor people in the tropics, "other people" we seldom think about, even though some of them grow food and make clothes for us (without being paid fairly for their work). The tropics have many natural resources and hosted advanced civilizations before 1492. The tropics being mostly poor and less healthy today is a cruel accident of history. European germs and technologies wiped out much of the population of the Americas 500 years ago and helped establish a system of worldwide economic dominance that persists today. The World Health Organization, UNICEF, Oxfam, the Gates Foundation and others continue to work on health promotion in the less prosperous parts of the world.

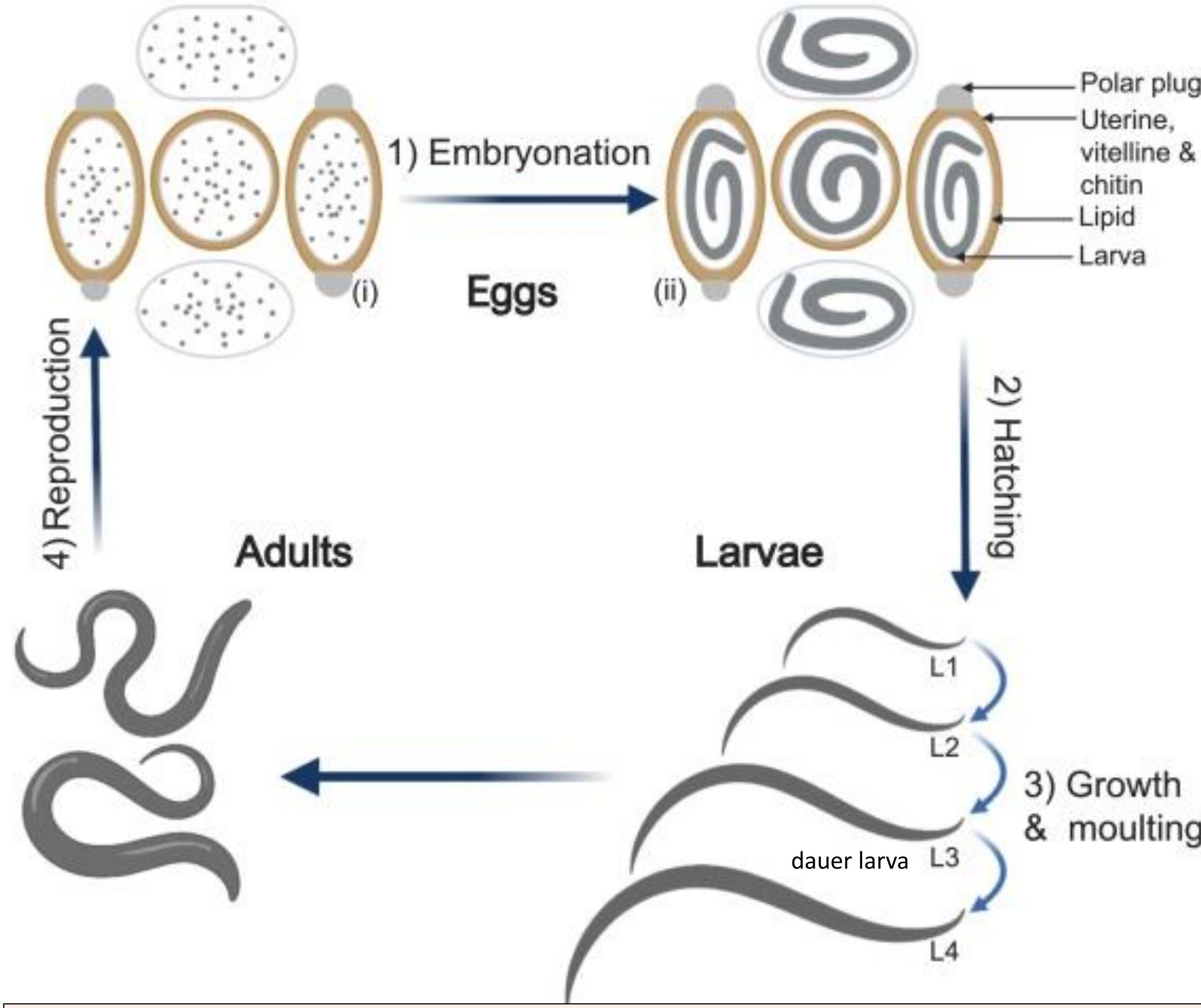




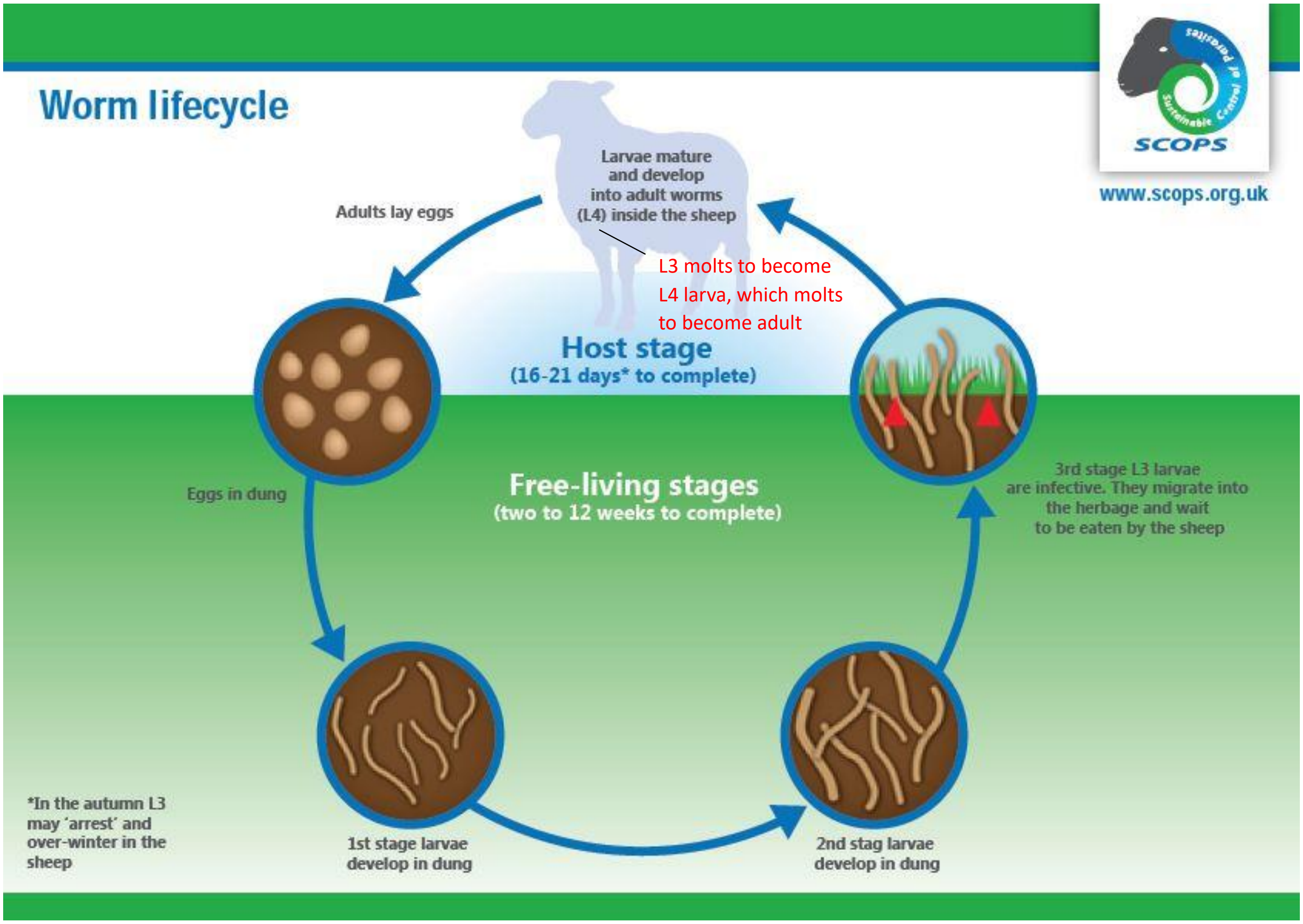
Disability adjusted life years lost to intestinal nematode infections per 100,000 people in 2002
"Lokal Profil" at Wikipedia, WHO data

Nematode parasite life stages and lifecycles

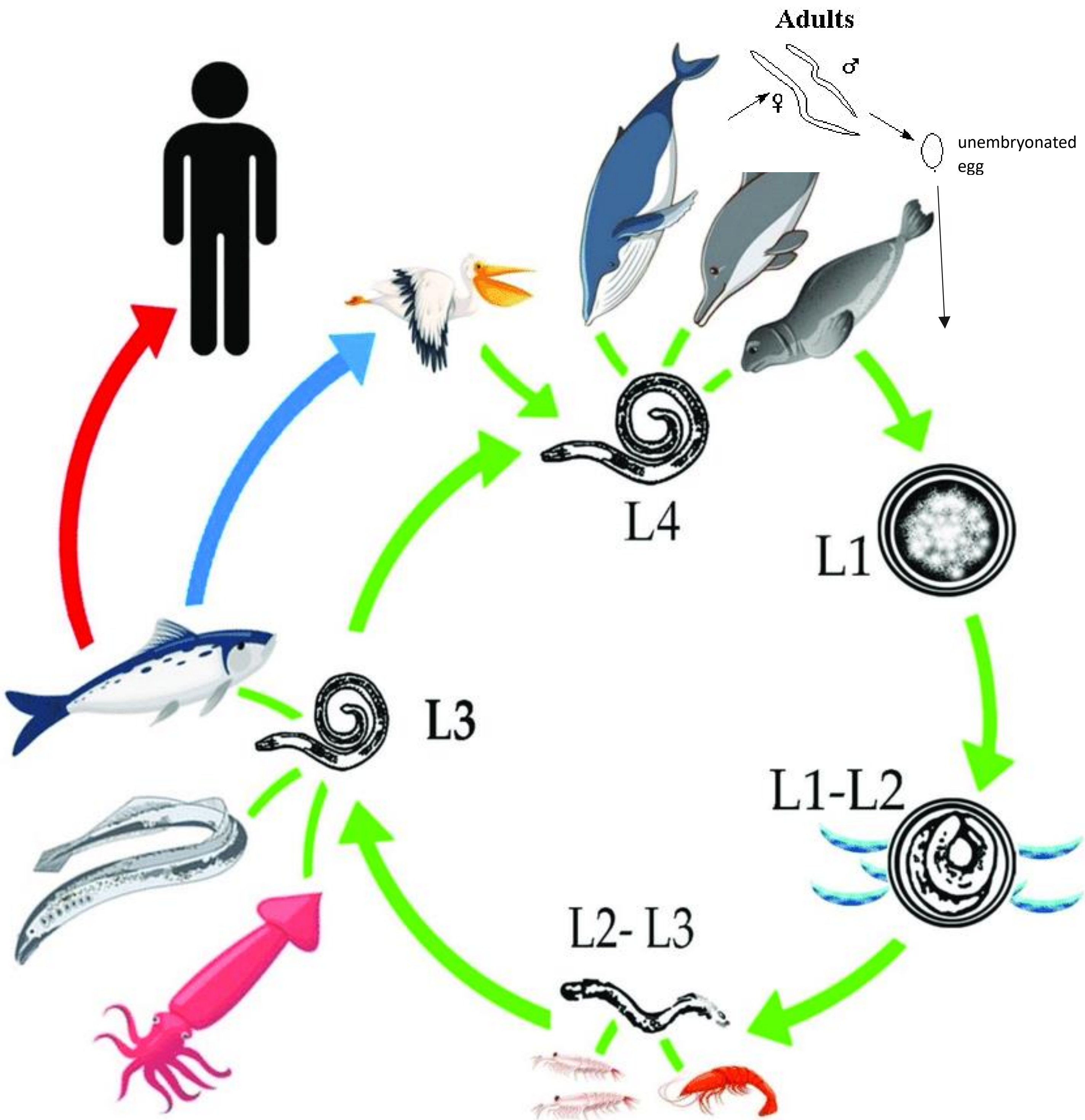
All nematodes have 6 life stages: egg, 4 larval stages, adult. Eggs hatch out the 1st larval stage (usually), then grow through succeeding stages with 4 molts (shedding the cuticle "outer skin"). The stages are equivalent to the instars of insects and other arthropods. Like nematodes, arthropods shed their exoskeleton (chitinous, even tougher than collagenous nematode cuticle) between growth stages. The 4 larval (juvenile) stages are traditionally called J1 to J4 by nematologists working with plant parasites, and L1 to L4 by other nematologists. In order Rhabditida (a large group that includes *C. elegans*, filaria and some other parasitic nematodes) the L3 larval stage is known as the "dauer larva." It is adapted for dormancy to survive harsh conditions, does not feed, and is often a dispersal stage. Nematodes may be oviparous or viviparous: adult females or hermaphrodites lay eggs (that may be 1 cell zygotes or developed into embryos or larvae) or in some species give live birth to L1 or L2 larvae.



Nematodes have 6 life stages: egg, 4 larval stages (L1 to L4 or J1 to J4) then adult. Larvae go through 4 molts on the way to growing into an adult worm. L3 is the dispersal stage in rhabditiform nematodes. Hermaphrodite or female adults may lay unembryonated or embryonated eggs or give birth to live L1 or L2 larvae (*Trichinella* and filiarial worms are viviparous). Image- Mkandawire et al, **Trends in Parasitology**

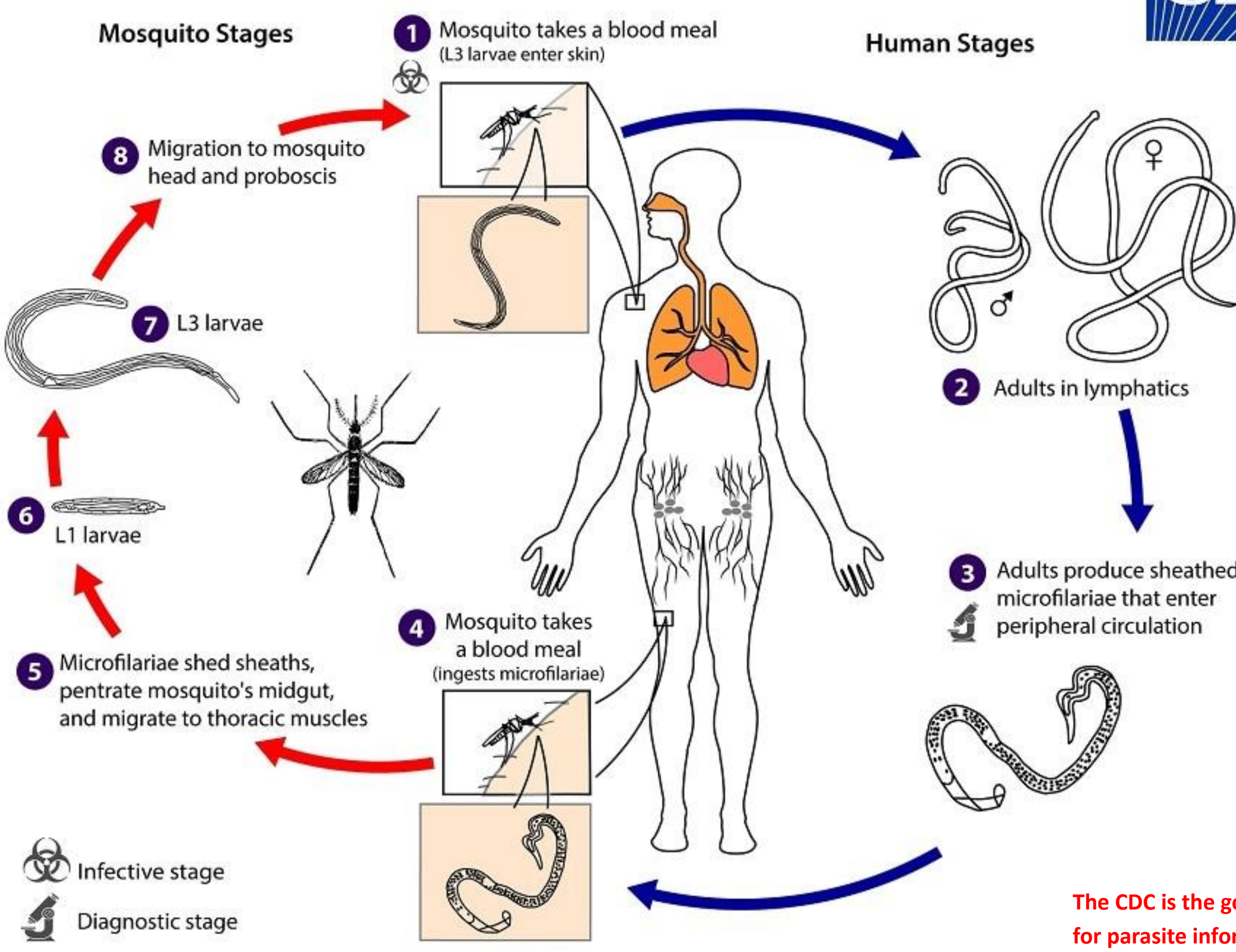


Monoxenous Nematode Parasite Lifecycle (example with an omission some other sources also make)
Generalized life cycle of the 20 species of nematodes that infect the gastrointestinal tract of sheep: Adult females in the sheep lay eggs that pass in the dung and hatch, releasing first-stage larvae (L1) that develop and molt (UK moult) to create second stage larvae (L2). Both of these stages remain in the dung feeding on bacteria. After another molt the third stage larvae (L3) appear and migrate up into grass to be ingested by sheep. They enter the wall of the stomach or intestines and molt to become fourth stage larvae (L4) and then, about 14 days later, go through a final molt to become adult worms. The prepatent period (time between the L3s being eaten by the sheep and the appearance of eggs in the dung) is normally 16-21 days. There is no multiplication of worms within the sheep and the lifecycle is direct (i.e. there is no intermediate host). Adult worms can remain viable within the sheep for several months before dying naturally.



Heteroxenous Nematode Parasite Lifecycle (example with some errors and my correction)
Generalized life cycle of *Anisakis spp.* which can cause human disease. Adult worms (I added) mate in marine mammal definitive hosts and unembryonated eggs pass in feces. L3 larva hatch from matured eggs and are eaten by krill (crustacean) intermediate hosts, which are eaten by fish or squid second intermediate hosts (in which larvae migrate to muscle), which are eaten by dolphin or whale definitive hosts (seals in *Pseudoterranova spp*). In the definitive host the L3 larvae molt twice to become adults. People eating worm contaminated seafood can become dead end hosts, suffering acute abdominal pain and later bowel problems and possible complications from anisakiasis. image Angeles-Hernandez et al

Lifecycle of ***Brugia malayi,*** a filarial nematode



The CDC is the gold standard for parasite information.

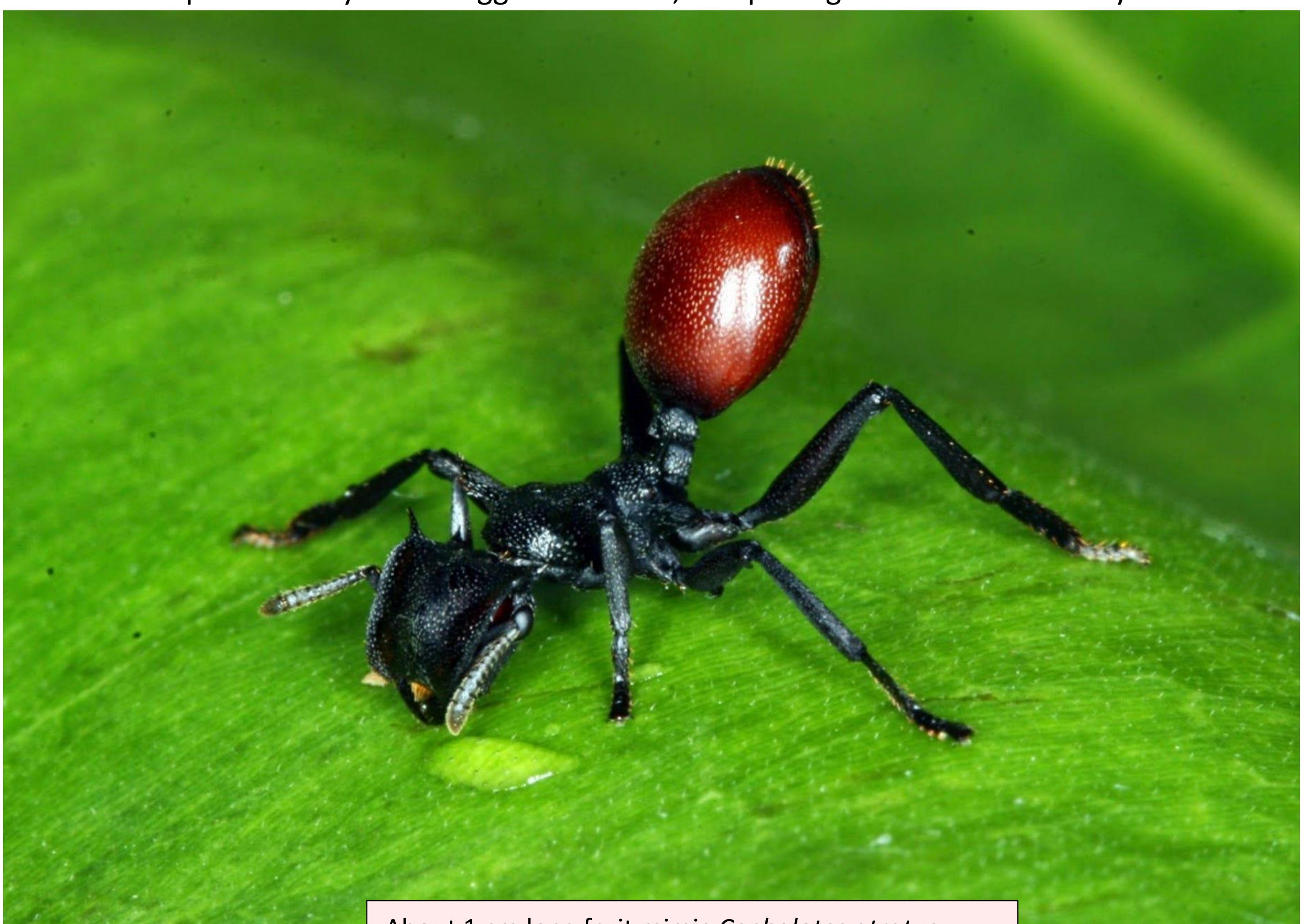
During a blood meal, an infected mosquito (typically *Mansonia* spp. and *Aedes* spp.) introduces third-stage filarial larvae onto the skin of the human host, where they penetrate into the bite wound (1). They molt twice and develop into adults that commonly reside in the lymphatics (2). The adult worms outwardly resemble those of *Wuchereria bancrofti* but are smaller. Female worms measure 43 to 55 mm in length by 130 to 170 µm in width, and males measure 13 to 23 mm in length by 70 to 80 µm in width. Adults produce microfilariae (motile embryos), measuring 177 to 230 µm in length and 5 to 7 µm in width, which are sheathed and have nocturnal periodicity (in some regions *B. malayi* may be sub-periodic, and note that microfilariae are usually not produced in *B. pahangi* infections). The microfilariae migrate into lymph and enter the blood stream reaching the peripheral blood (3). A mosquito ingests the microfilariae during a blood meal (4). After ingestion, the microfilariae lose their sheaths and work their way through the wall of the proventriculus and cardiac portion of the midgut to reach the thoracic muscles (5). There the microfilariae develop into first-stage larvae (6) then subsequently molt twice to develop into third-stage larvae (7). The third-stage larvae migrate through the hemocoel to the mosquito's proboscis (8) and can infect another human when the mosquito takes a blood meal (1).

Nematode tricks?

I remain amazed by the interesting, horrifying host manipulations practiced by parasites. Single celled *Toxoplasma* makes rodents less afraid of cats, getting more of them eaten to continue the parasite's life cycle. Many trematodes including *Dicrocoelium, Leucochlorium* and *Ribeiroia* play all sorts of tricks on intermediate hosts including making zombie ants climb into the grass to be eaten by sheep, turning snail eyestalks into pulsating disco lights to attract birds, and creating frogs hobbled by dangling extra legs. The acanthocephalan parasite *Pomphorhynchus* draws its amphipod *Gammarus* intermediate host to the odor of the predatory fish definitive host. Nematomorpha ("horsehair worms", close relatives of nematodes) drive their cricket hosts to jump into water and drown in oder to to deliver the worms to their breeding sites. Parasite life cycles can be powerful evolutionary drivers of host manipulation.

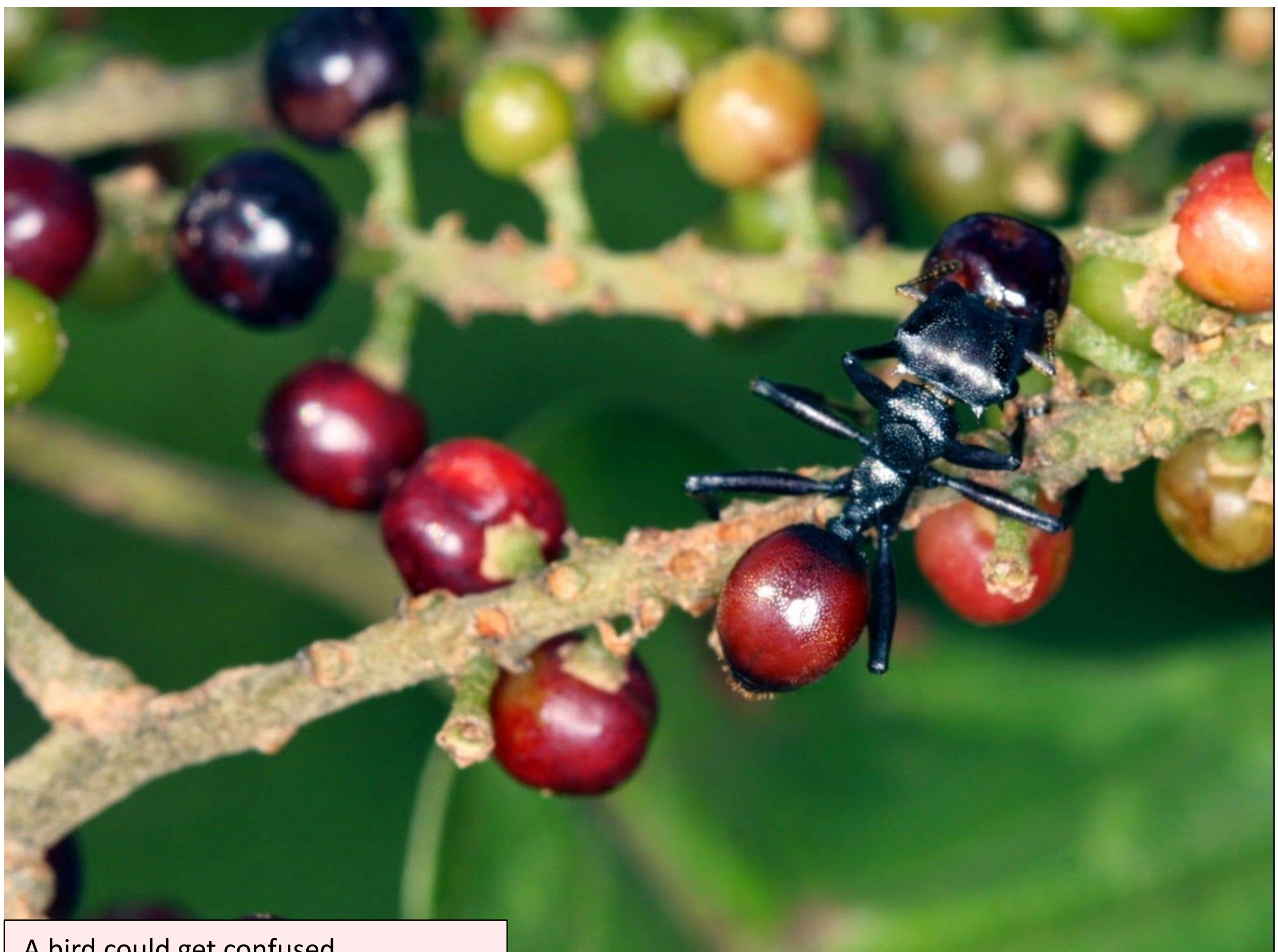
But nematode parasites still seem a bit of a let down. Yes, they are super succesful, but dramatic host manipulation is not found repeatedly, as it has in protist, fungal, trematode and arthropod parasites. There are a few lackluster examples of possible host behavior modification by nematode parasites. The mermithid nematode *Strelkovimermis spiculatus* mostly parasitizes and kills larva of *Culex* mosquitoes but sometimes also the adults. Female adult mosquitoes infected with the worm switch their preference for blood meals to drinking water, assisting dispersal of the parasite. The nematode *Phasmarhabditis hermaphrodita* parasitizes and kills slugs (terrestrial gastropods) leading to use as a commercial slug control agent. Experimentally infected *Deroceras and Arion spp*. slugs were found to spend more time in areas where *P. hermaphrodita* was present. Serotonin blocking drugs abolished the slugs changed behavior. Infection with the lungworm *Rhabdias pseudosphaerocephala* induces the cane toad *Rhinella marina* to seek warmer locations. This could be an illness behavior to hurt the parasite, but evidence shows higher toad body temperatures boosted nematode numbers.

Perhaps the most satisying example of nematode parasite host manipulation I've found is that of *Myrmeconema neotropicum*, a mermithid worm (insect parasites in class Enoplea, order Dorylaimdia) that compels its ant host to mimic ripe fruit. Embryonated eggs are picked up in bird feces by foraging tropical arboreal *Cephalotes atratus* ants that feed them to their larvae. L2 worm larvae mature through 3 more molts and become adults. After the ant larvae molt to become pupae, adult nematodes mate inside them. When the ant pupae molt to become adults, the *M. neotropicum* worms migrate to the gaster (the ants' abdomen), female worms become full of embryonated eggs, and nematode manipulation of the host ensues through several means. The ants' gasters become swollen with thinning of the cuticle (skin), turning bright red (the nematodes look red through the ants' skin). The ants also act sluggish (their metabolism is reduced 37% by the parasite) and thrust their gasters upward as they walk, looking much like a small red berry. The nematode has made the ant a fruit mimic. This results in the ant being eaten (not yet directly observed) by a fruit eating bird (birds seldom eat ants) which will disperse embryonated eggs in its feces, completing the nematode life cycle.



About 1 cm long fruit mimic *Cephalotes atratus* worker ant infected by *Myrmeconema neotropicum* image Yanoviak at grrlscientist.medium.com

A) uninfected *C. atratus* ant B) infected with *M. neotropicum*
Scale bar about 2 mm. Yanoviak, Kaspari, Dudley, PoinarJr. 2008



A bird could get confused
Yanoviak at grrlscientist.medium.com

Despite the example of a nematode worm making an ant mimic a berry, overall the evidence for host manipulation by nematodes is less compelling than for other phyla of parasites. But the rather mundane day to day life cycles of most nematodes are super successful. Nematodes are very good at living in or just hanging out as microscopic eggs in soil. The dirt under your feet has millions to billions of tiny free living nematodes. Some parasitic nemades are heteroxenous with complex life cycles including 1 or 2 intermediate hosts, but the most successful helminths of people are monoxegenous with plain old direct transmission. Three soil borne nematodes (*Ascaris, Trichurus* and hookworm) parasitize more people than any other kinds of worms. During the worm's life *Ascaris* and some other nematodes navigate multiple host organ sytems like a master anatomist. Yet few victims even know they are infected. This may be in part to nematode worms tamping down host immunity, including tamping down the type 2 immune responses they cause in hosts, which typically includes eosinophils and T helper cells. Similar pathways are involved in allergies and in inflammatory bowel disease (Chrohn's and ulcerative colitis) and nematodes are being investigated as possible alternatives to standard care with up to $20,000 a year injectable medications that can cause dangerous side effects. Nematodes would seem to be more skilled micro-anatomists and immunomodulators than all but a very few humans (see the following pages).

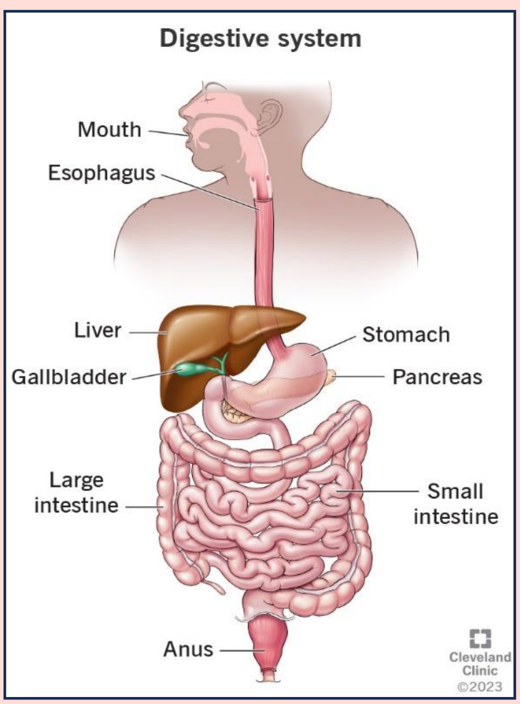
What a worm knows about your internal anatomy

Helminth parasites take epic journeys through animal bodies during their complex life cycles. How can they do that? Flatworms have a simple nervous system including a pair of nerve cords and 2 cerebral ganglia (little brains). The two ganglia and connections between have about 80 cells in *Triaenophorus nodulosus*, the pike tapeworm, compared to about 80 billion in your brain. Worms also have peripheral nerves including sensory neurons for chemicals (taste), pressure and temperature (plus free-living flatworms have eyes, although most parasitic flukes do not). Trematodes have muscles to move and suckers to hold on with. With limited information and a billion times less neurons than you have, flukes wriggle from one organ to another in your body, eventually laying eggs and continuing the life cycle.

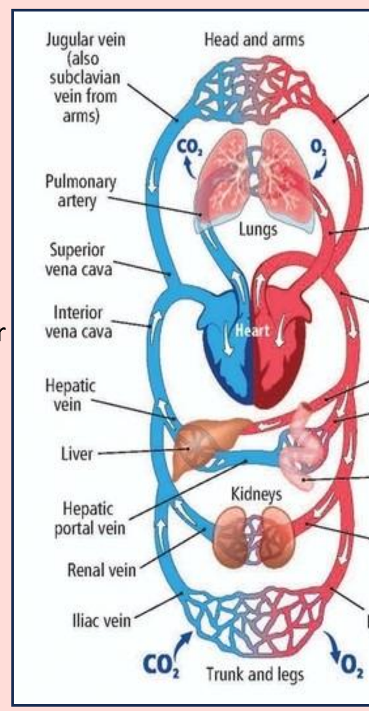
C. elegans brain has about 100 neurons in a ~ ½ mm diameter nerve ring around its throat. 2 cells connect it to the 200 neurons in the body. Colorized reconstruction from electron microscopy of 8 worms. Image- Mei Zhen and Witvliet et al

Despite having very few neurons, tiny worms navigate the human body. Nematodes bore through tissue and blood. Schistosomes live in specific blood vessels as adults while other flukes get into the intestines, liver or lungs. After a hard journey several times around a human body, each parasite is adapted by eons of evolution to settle into hanging on in a blood vessel or being bathed in digested food or caustic bile or being exposed to air. Life prevails.

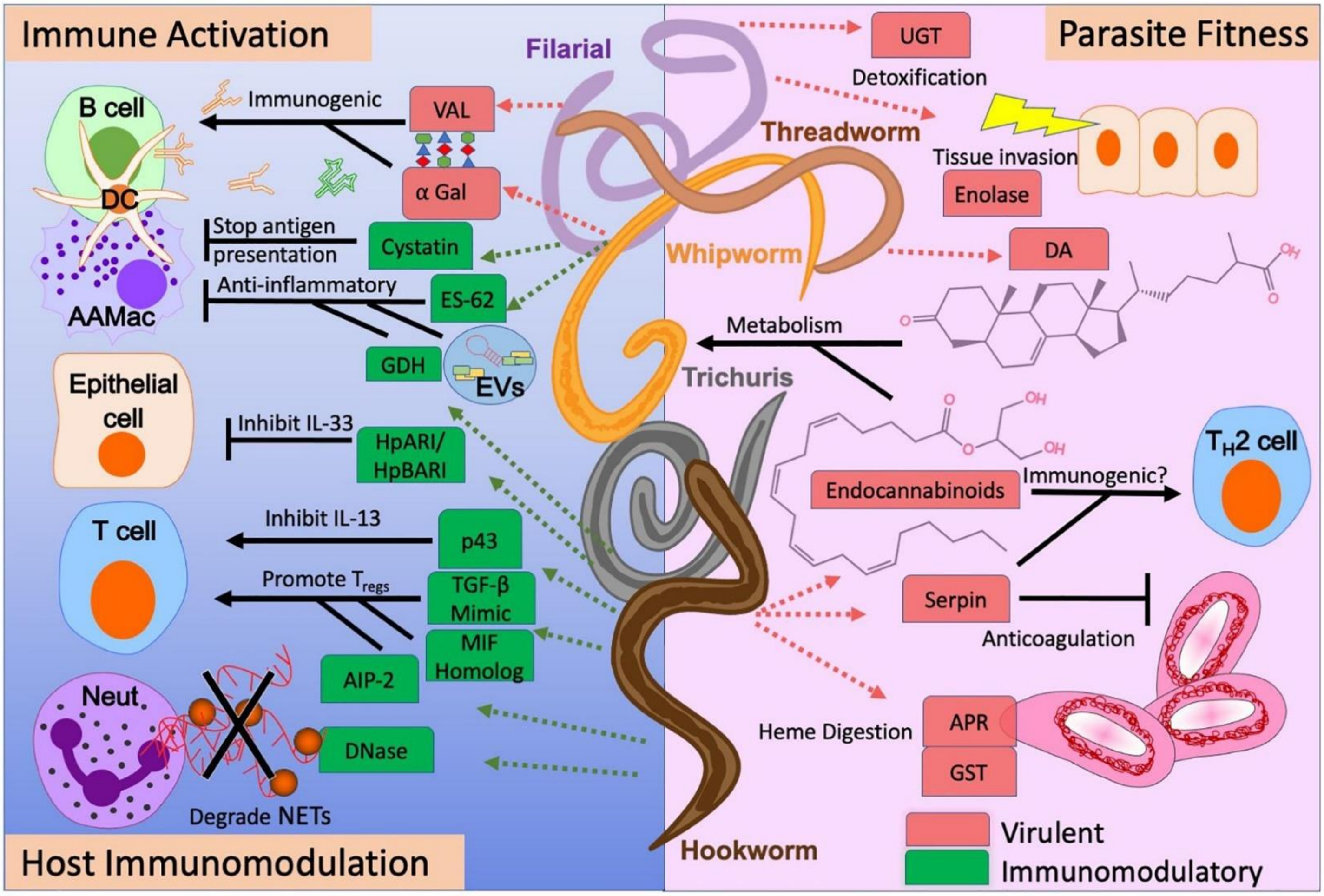
Oversimplified, the human gut is simple, a long coiled up tube about 9 meters (30 feet) long. A small side branch goes to the liver and pancreas. The bigger main bile ducts and gallbladder are under the liver, which is full of tiny bile ducts. Worms can use chemical clues to crawl through the GI system. By contrast the adult circulatory system contains about 60,000 miles (!) of vessels, going every which way. The heart and arteries distribute oxygen and nutrients, and veins help move wastes. Arteries branch smaller and smaller until ending in capillaries about 5 microns wide, where blood exchanges molecules with cells. Downstream of this veins merge becoming bigger as they return to the heart. Then all the blood is pumped through the lungs and their pulmonary capillaries. The gut has an extra venous system; the portal vein branches out and ends in about 10 micron wide liver sinusoids, then venules merge into a hepatic vein.



Somehow, juvenile schistosomes and nematodes are programmed to use pressure and chemical signals to know which capillaries to exit. After entering skin capillaries schistosomulae go through lungs and heart and exit into the liver. *Ascaris* larvae enter gut capillaries and exit in the lungs, mature, and later exit into the alveoli (air sacs). Even single celled plasmodia (malaria parasites) migrate from skin vessels to liver and back into the blood. Evolution invented some amazing parasites as life pushed into every chance opportunity.



human circulation
Pletsch ubc.ca



Parasitic nematodes use many proteins to enhance infection (virulence) or modulate immunity (mostly downregulating, avoiding detection but sometimes immune activating, causing symptoms in the host). Bobart et al **Front Microbiol** 2020

steroidal hormone dafachronic acid (DA)   venom allergen-like proteins (VAL)   Serine protease inhibitors (serpins)
ES excretory proteins   cysteine protease inhibitors (cystatins)   UGT Glucuronosyltransferase

Enolase is a glycolytic metalloenzyme (Mg, Zn or Mn ions are cofactors)
galactose-alpha-1,3-galactose carbohydrate on glycoproteins of mammals except old world monkeys and apes
APR (aspartic haemoglobinase) and GST (glutathione-S-transferase) help hookworm *Nectar americanus* digest blood
Transforming growth factor beta (TGF-β) helps regulate cell growth, differentiation, and apoptosis (programmed death)

ES-62 secreted product of the rodent filarial nematode *Acanthocheilonema viteae* and a homologue of excretory–secretory (ES) products produced by human filarial pathogens (*Brugia malayi, Onchocerca volvulus* and *Loa loa*)
GDH Glutamate Dehydrogenase   EVs Extracellular Vesicle
HpARI immunomodulatory protein secreted by the rodent intestinal nematode *Heligmosomoides polygyrus*   p43 major ES of mouse whipworm *Trichuris muris*
MlF (Macrophage Migration Inhibitory Factor) is a pro-inflammatory cytokine in mammals. Homologs (similar) are found in almost all nematodes checked, and widely in plants, protozoa, mollusks, arthropods, fish, amphibians, birds
AIP-1 and AIP-2 are hookworm derived anti-inflammatory immunomodulators. DNase is enzyme that breaks down DNA, including DNA that is part of NETs, Neutrophil Extracellular Traps (created to catch pathogens in blood)

Preview of a few human nematode parasites (more next time)

Roundworms are mostly boring but are highly successful, including as human parasites. As noted before, nematodes are most prevalent human helminth parasites.

About 2 billion people have 1 of the big 3 soil borne nematodes in their gut today: *Ascaris* (sometimes called “roundworm infection”), *Trichurus* (whipworm) and *Ancylostoma* or *Necator* (hookworms). *Ascaris* juveniles make long journeys through the human body before getting to the intestine and growing to become the biggest of human intestinal nematodes. Whipworm eggs just pass from the mouth to the gut and molt in stages to become adults (another boring but efficient nematode lifecycle). *Ascaris* and whipworm adults eat your digested food, while hookworms bite into the intestinal wall to feed on your blood.

Adult *Ascaris*, the most common human nematode parasite, can grow up to 30 cm (1 foot) long, but female *Dracunculus* (Guinea worms) can be 1 meter (39 inches) long and *Dioctophyme* (the giant kidney worm) can be a little over 1 meter long. Luckily Guinea and giant kidney worms are very rare (just 14 cases of dracunculiasis in 2023, all in north Africa).

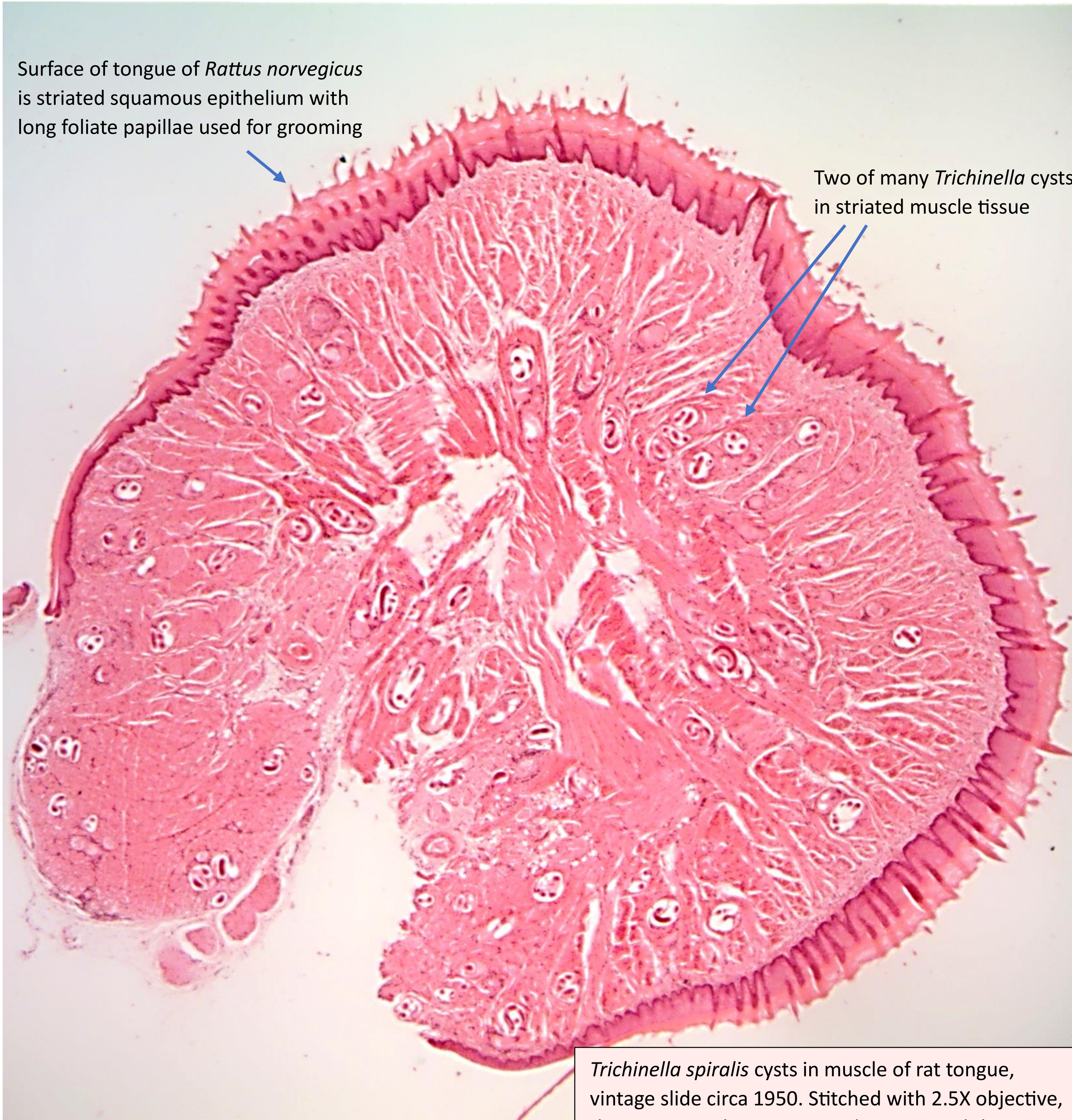
Trichinella is a tiny parasitic worm acquired by eating tainted meat. At 1.5 mm long (curled up into a 0.2 mm ball), the males are the smallest adult human nematode parasites.

Microfilaria of filiarial nematodes live in blood and are spread by biting insects. *Wuchereria* causes elephantiasis (disfiguring lymphatic swelling) and *Onchocerca* causes river blindness. *Dirofilaria* causes heartworm in our dogs and is rarely acquired by people. Microfilaria of *Mansonella streptocerca* are only about 0.2 mm (200 microns) long and 4 microns wide.

Strongyloides, the threadworm, is unique among human nematode parstes in being able to renfect the host directly without using another host. This can cause fatal hyperinfection in immunocompromised or unlucky people, including those with HIV or taking steroids fro COPD.

Angiostrongylus is a rat lungworm that may acquired by ingesting snails, causing eosinophilic meningitis in people.

Anisakis is a parasite of marine mammals that may be acquired from undercooked fish. It can cause a gut ache then other symptoms as it wanders around lost (we are an accidental host).

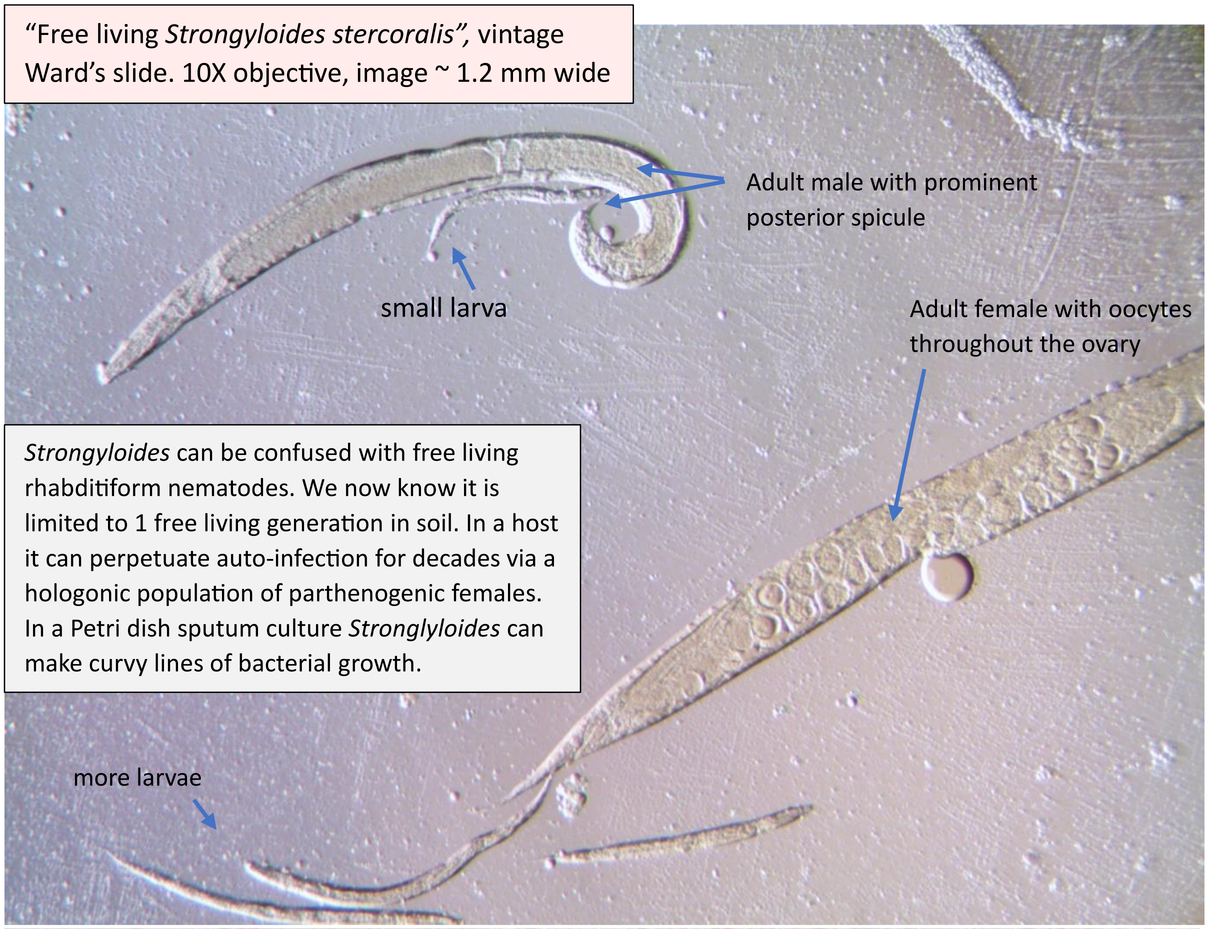


Trichinella spiralis cysts in muscle of rat tongue, vintage slide circa 1950. Stitched with 2.5X objective, the tongue is about 6 mm in diameter and the many *Trichinella* cysts are about 0.2 mm diameter

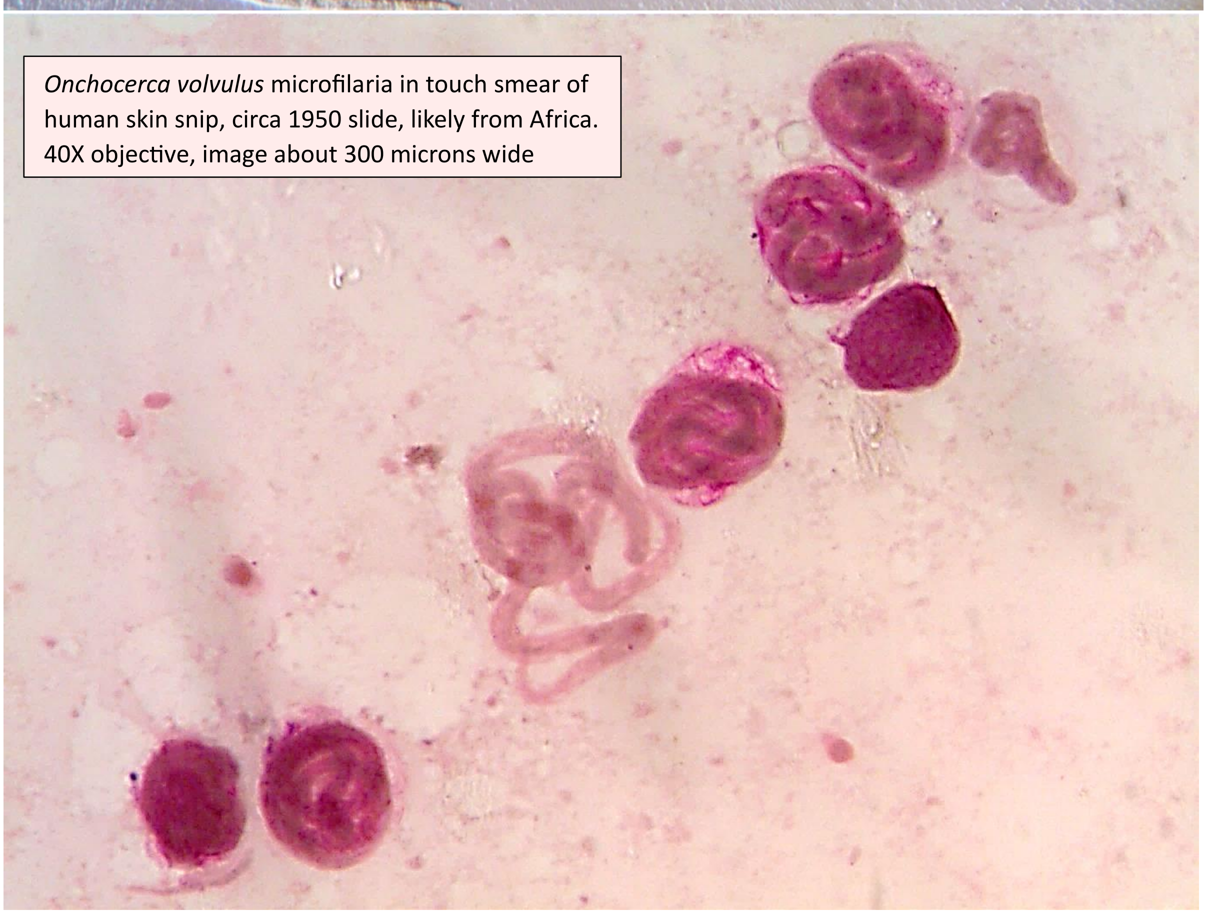
Trichinella spiralis is interesting. It sits low in the nematode family tree but evolved to be transmitted by meat eating land animals. 1.4 - 4 mm long (smaller coiled up), adult *Trichinella* are the smallest nematode parasites of humans. It can cause severe muscle pain in infected people, and may be one of the reasons Jews and Muslims eschew pork since antiquity. *Trichinella* was one of the first human parasites to be scientifically studied, leading to its elimination from domestic meat animals. Still, about 15 people a year get trichinellosis in the US, usually from undercooked game meat.

Trichinella spiralis in striated muscle. The coiled worm is sectioned 6 times in the cyst.
Modern slide by Leider in Germany, nicely stained
40X objective with slightly oblique lighting
image about 300 microns tall

"Free living *Strongyloides stercoralis*", vintage Ward's slide. 10X objective, image ~ 1.2 mm wide



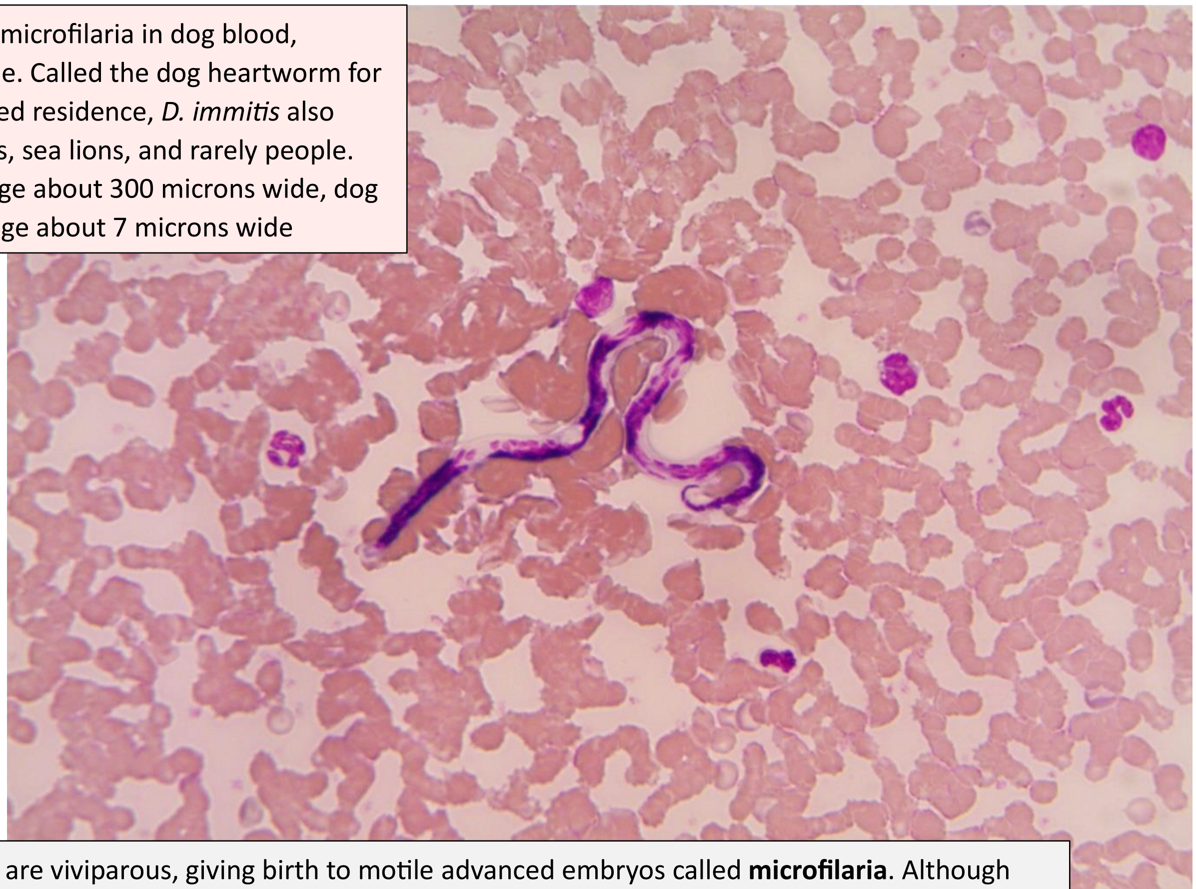
Strongyloides can be confused with free living rhabditiform nematodes. We now know it is limited to 1 free living generation in soil. In a host it can perpetuate auto-infection for decades via a hologonic population of parthenogenic females. In a Petri dish sputum culture *Stronglyloides* can make curvy lines of bacterial growth.



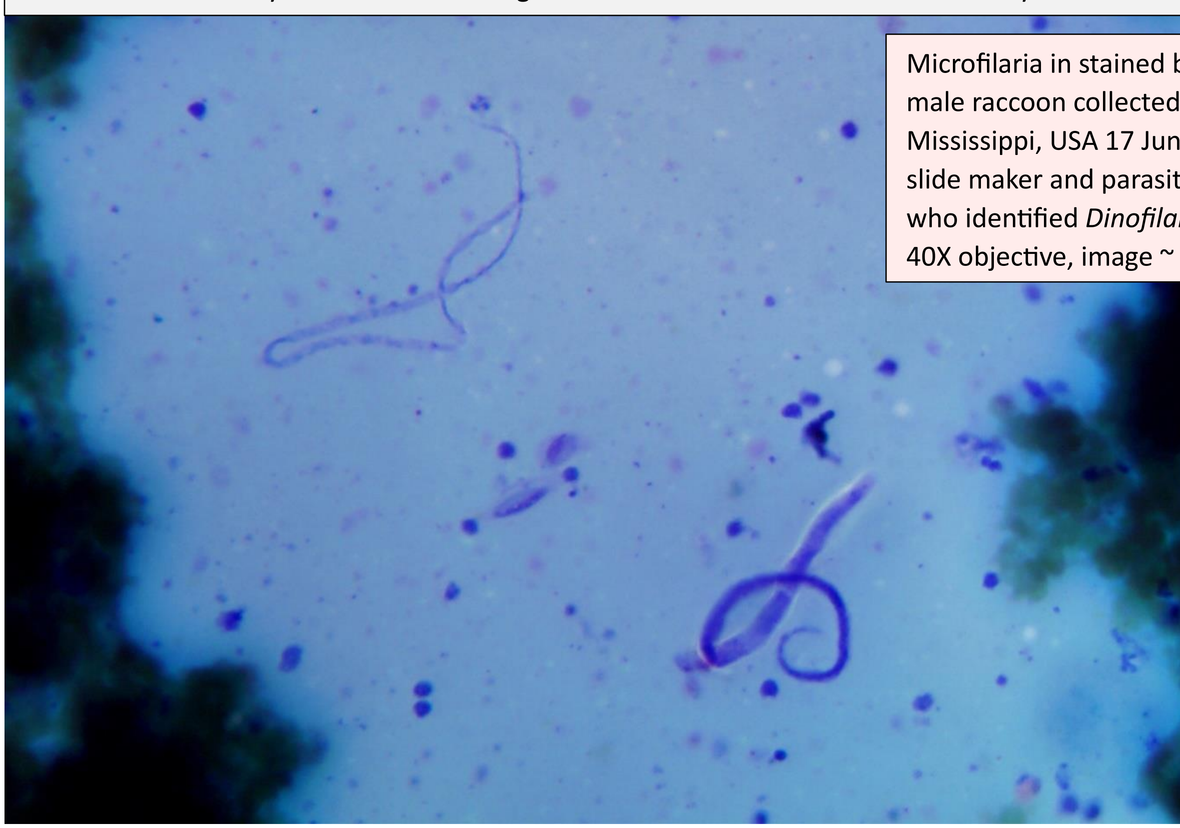
Onchocerca volvulus microfilaria in touch smear of human skin snip, circa 1950 slide, likely from Africa. 40X objective, image about 300 microns wide

Onchocerca volvulus microfilaria inside uteri, inside adult female worm, inside a nodule under the skin of an infected African patient. *Oncocerca* is a filaria causing skin and eye problems. It is carried by biting black flies whose larvae live in fast flowing rivers, hence the name "river blindness". Slide from Liberia by Dr. A Renz (see Filipe, Renz et al 2205).
Stitched using 40X objective, worm is about 300 microns in diameter.

Dirofilaria immitis microfilaria in dog blood, vintage Ward's slide. Called the dog heartworm for the adults' preferred residence, *D. immitis* also infects cats, wolves, sea lions, and rarely people. 40X objective, image about 300 microns wide, dog erythrocytes average about 7 microns wide



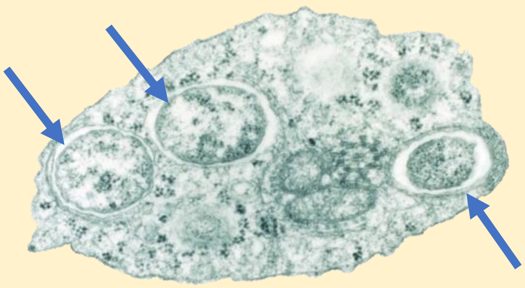
Filarial nematodes are viviparous, giving birth to motile advanced embryos called **microfilaria**. Although their organs are not fully developed, they travel throughout bodies, can be taken up by vector mosquitoes, and live from ½ to 5 years before maturing into L1 larva that molt 4 times on the way to adulthood.



Microfilaria in stained blood smear of dead male raccoon collected Leake County, Mississippi, USA 17 June 2018 by amateur slide maker and parasitologist LR Bircham who identified *Dinofilaria* and *Brugia spp*. 40X objective, image ~ 300 microns wide

Why is *Wolbachia* a hot biology subject?

In recent decades scientists found that many arthropods and nematodes, the most abundant and successful of all animals, have internal bacterial hitchhikers that variably harm or help them. Discovered in 1924, *Wolbachia* is a genus of gram-negative bacteria (related to the Rickettsiae that cause deadly spotted fevers) that live inside cells of arthropods and nematodes. Mostly ignored until DNA testing became widely used in the 21st century, *Wolbachia* turned out to be "the most abundant endosymbiont on earth", present in probably 50% of arthropods, including most insect species, many arachnids (spiders, mites), some crustaceans, and in filarial (blood-borne) nematodes. *Wolbachia* behaves differently in different hosts. It is a harmful parasite in insects, manipulating reproduction, but was later found be to be a beneficial symbiont in nematodes. (We arbitrarily call only eukaryotes parasites, but *Wolbachia* lives inside and takes nutrition from the host, so meets the definition despite not having a nucleus). Recently *Wolbachia* is being deployed in some mosquito control programs and may itself be targeted by antibiotics.



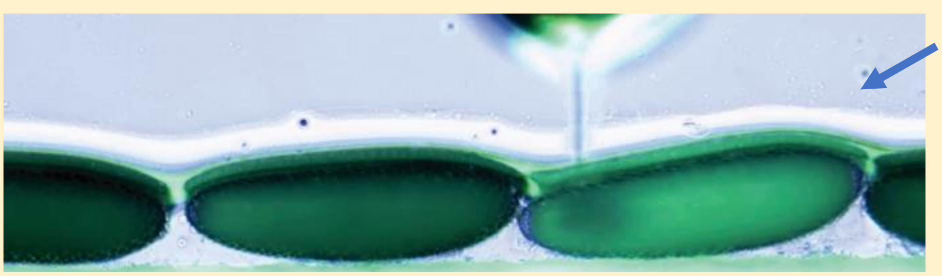
Blue arrows show 3 *Wolbachia pipiens* bacteria in vacuoles within a mosquito oocyte. Transmission electron micrograph; typical *Wolbachia* are about 0.2 to 0.4 microns in size, close to the limit of visibility of conventional light microscopes O'Neill PLoS 2004, image at Wikipedia

Parasitic master manipulator of insect reproduction

Wolbachia usually lives inside the gametes of the host, passing itself vertically to the next generation in eggs and sperm. Eggs are advantageous (having more cytoplasm living room) and *Wolbachia* manipulates insect reproduction to that end. Cytoplasmic incompatibility (by concurrently producing a poison that condenses chromatin and the antidote) allows infected female insects to live but kills males in a larval stage, or sometimes feminizes them. The bacteria may induce parthenogenesis, the production of female offspring from unfertilized eggs. A reduced host population becomes mostly infected females. Those infected mosquitoes are slightly less healthy, and resist carrying many viruses. *Wolbachia* is harmless to people, but false rumors the bacteria feminize men have cropped up.

Beneficial endosymbiont in some nematodes

In contrast to the case with insects, manipulative *Wolbachia* are beneficial to filarial nematodes (including the worms that cause elephantiasis and river blindness). *Wolbachia* synthesize needed amino acids and B vitamins and assist worm reproduction and development; filaria have become so dependent they will die without *Wolbachia*.

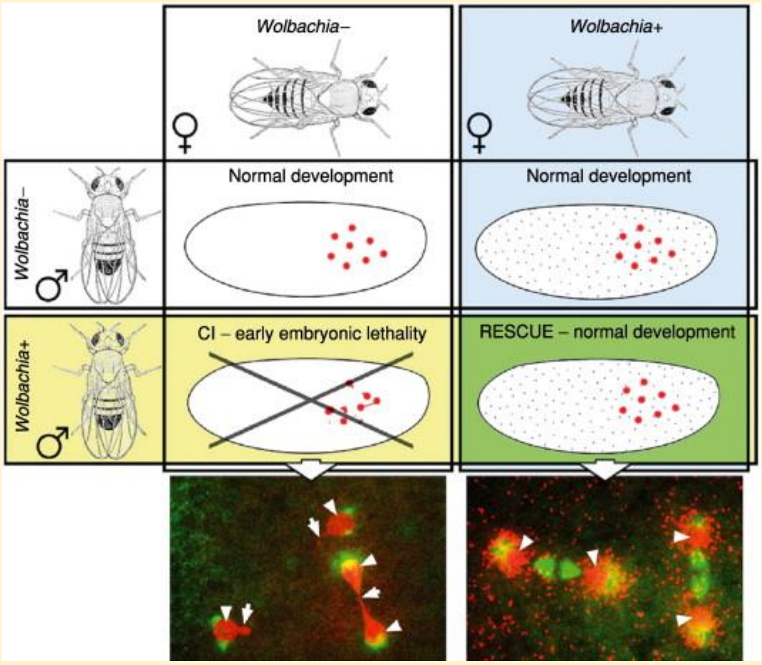


Aedes aegypti mosquito eggs being injected with *Wolbachia*. Infected mosquitoes have been released in the US, Asia, Europe, Africa, Brazil and Oceana, reducing dengue 60 to 90% in some areas. image- World Mosquito Program scienceline.org

Manipulating *Wolbachia* for human benefit

A. Spreading *Wolbachia*- Insect vectors including mosquitoes are harmed by *Wolbachia* and at the same time become less able to transmit human diseases including malaria and arboviruses. Therefore, disease control programs sometimes introduce *Wolbachia* infected mosquitos. The parasite spreads, vector populations become female and resistant to carrying human diseases including malaria, dengue, zika, chikungunya and yellow fever.

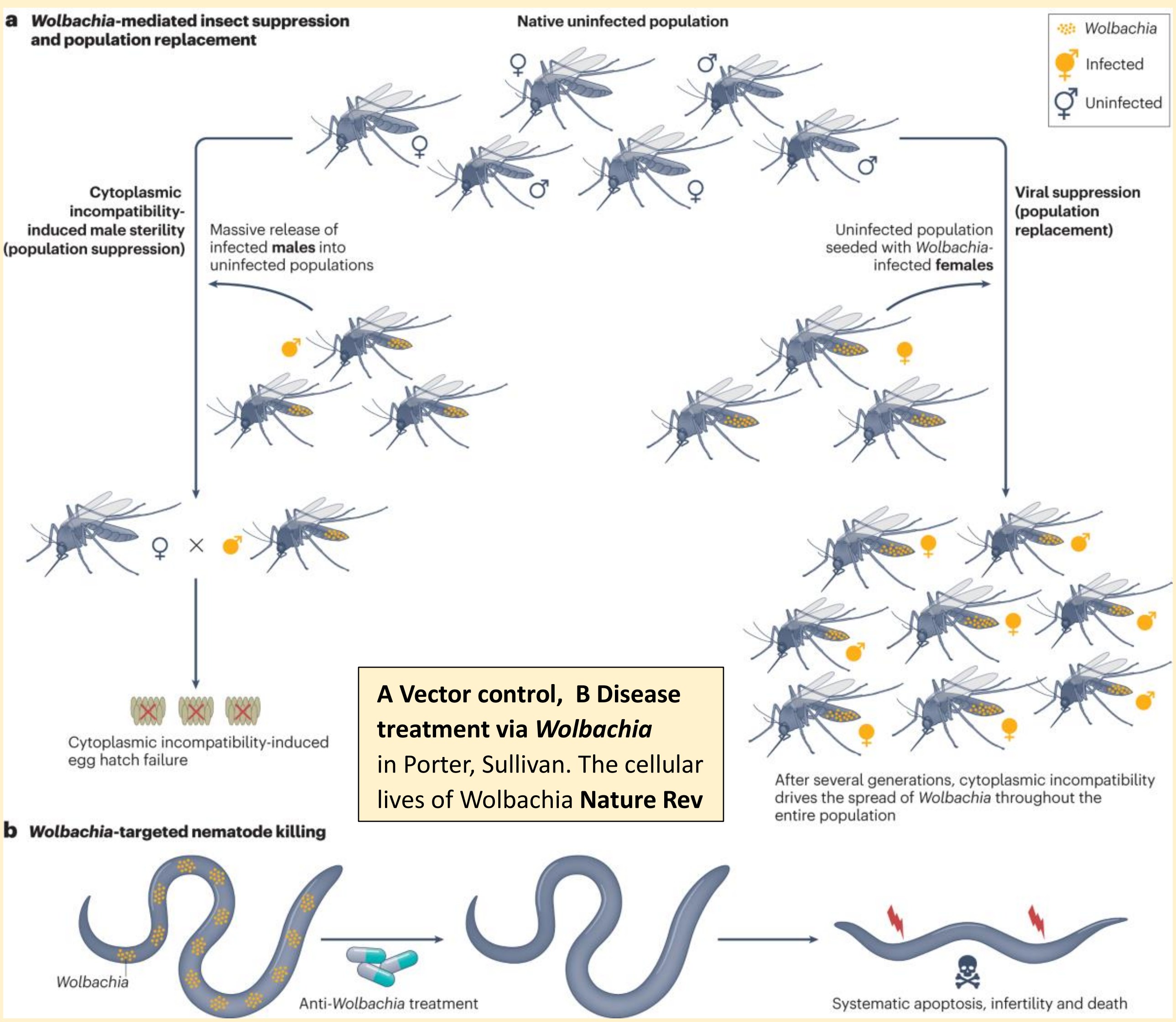
B. Killing *Wolbachia*- Filarial nematodes slowly die without their *Wolbachia* symbionts, so doxycycline (an antibiotic that kills *Wolbachia* and other intracellular bacteria) kills or sterilizes the *Onchocerca* and *Wucheria* nematodes that cause river blindness and elephantiasis, with less side effects than antiparasitic drugs (see figures following page).



Wolbachia manipulating hosts

***Wolbachia* Cytoplasmic Incompatibility**
When introduced, *Wolbachia* quickly spreads throughout host insect populations, due to its cytoplasmic incompatibility mechanism. Upper panels show outcomes of matings between infected and uninfected flies, and lower images show failed vs. successful separation of nuclei during mitosis (DNA is stained red).
image Clark et al. **Genetics** 2005
(see more detail of variable host population responses in subsequent panels)

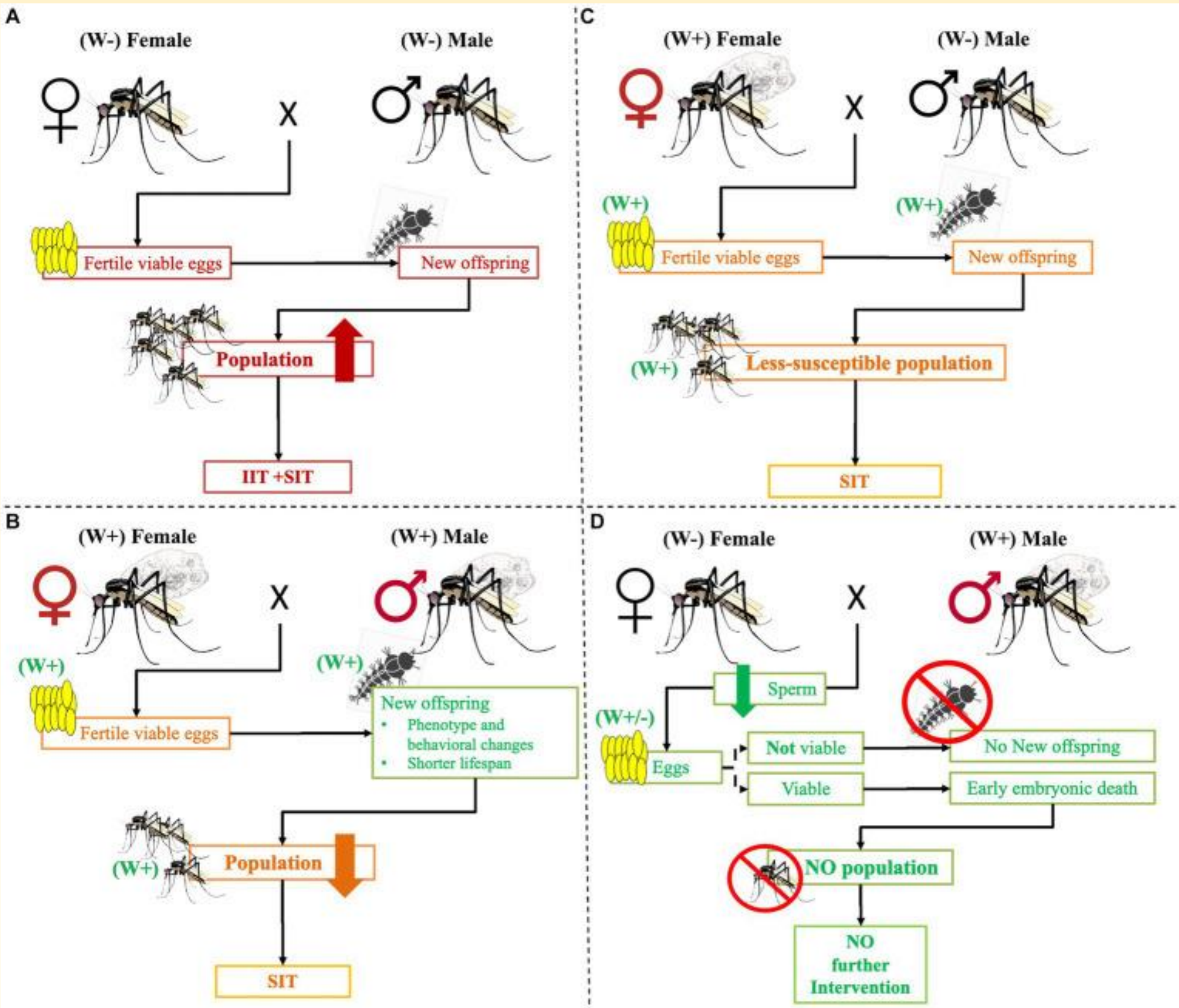
Wolbachia at work for us



A Vector control, B Disease treatment via *Wolbachia*
in Porter, Sullivan. The cellular lives of Wolbachia **Nature Rev**

Crosses between *Wolbachia*-infected or uninfected *Aedes* mosquitos, informing approaches to vector control

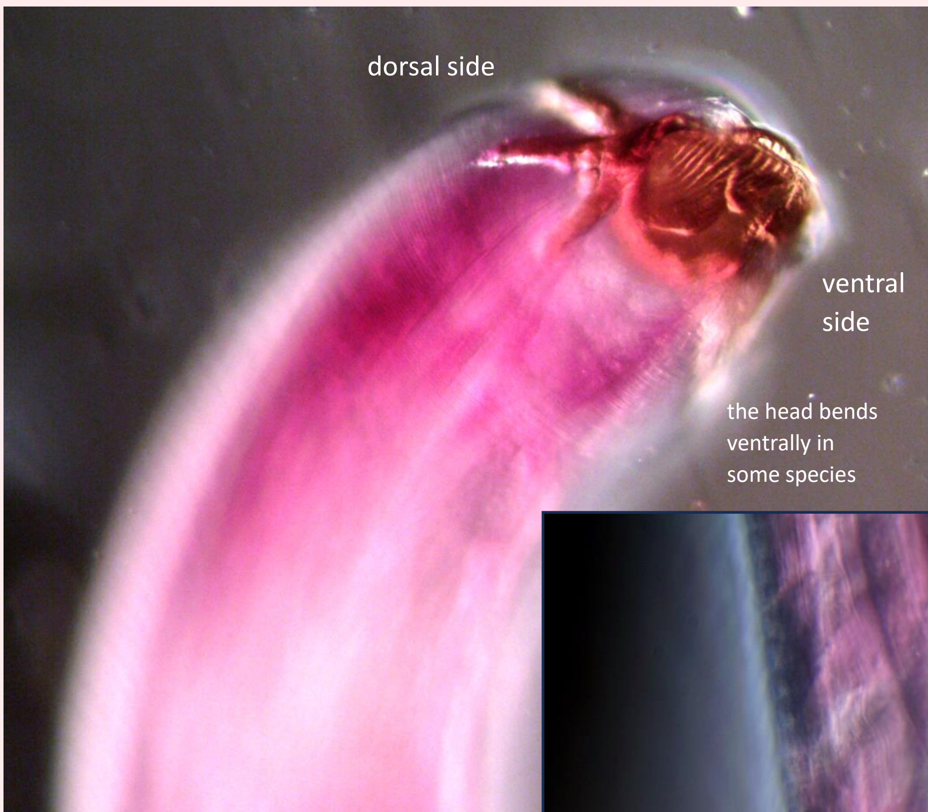
(A) Wolbachia uninfected mosquitoes mate, viable eggs grow the next generation. Intervention is needed.
(B) Infected females and males produce infected viable eggs. Development of the offspring continues sickly short-lived phenotype, adult behaviors change, and the population declines. SIT often needed.
(C) Infected females mate with uninfected males, produce infected eggs that can grow into short lived adults. The life span may be short and adults may not effectively bite humans. SIT often needed.
(D) Uninfected female mating with an infected male, nonviable egg or early embryonic death occurs. Success: IIT intervention worked.



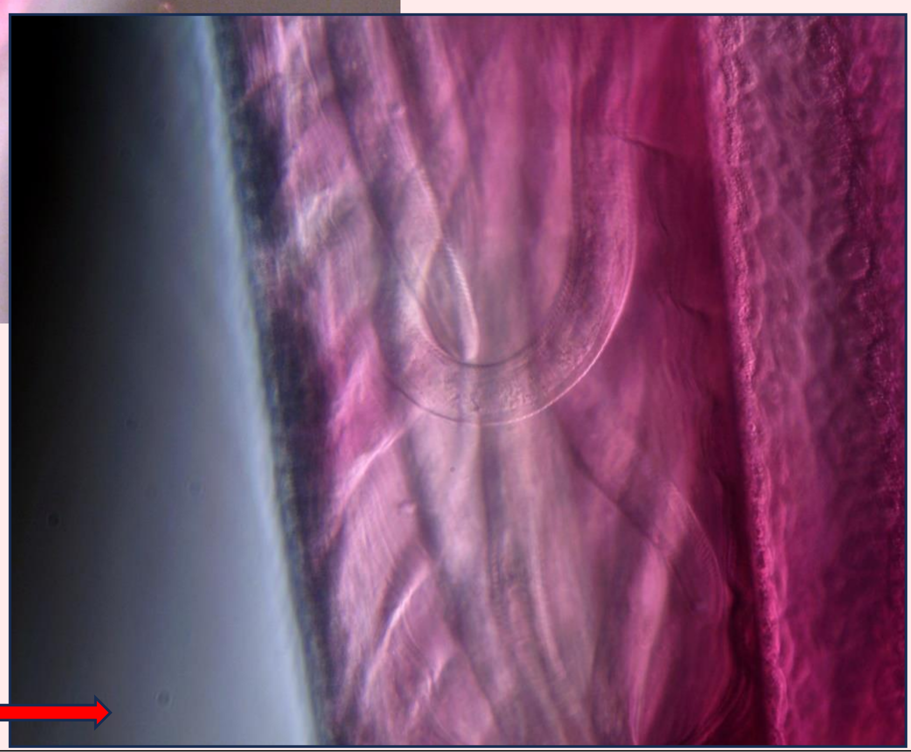
Key: W+ *Wolbachia* infected, W− *Wolbachia* uninfected, IIT Incompatible Insect Technology =release of W+ males (as in D) SIT Sterile Insect Technology =release of irradiated sterile male mosquitoes. Minwuyelet et al **Front Microbiol**

Live *Camallanus*: an amateur parasitology adventure in unexpected beauty

On 25 July 2021 my daughter caught a small (about 15 cm) bluegill (*Lepomis macrochirus* a very common fish) at a popular fishing pond in Red Wing, Minnesota, USA. She found dark red streamers hanging from the anus and I thought the fish must have eaten some red string or plastic trash. I had a magnifying loupe and was shocked to see the "string" was a cluster of thin worms, pulsating bright red. I pulled the worms out for microscopic observation, and they became even more wonderous the closer I looked. Red fluid sloshed back and forth every 4 seconds along the 4 cm long nematodes! The worms were gravid ovoviviparous females, full of about 10 thousand free wriggling 0.3 mm long L1 larvae, alongside ovaries making more eggs. A distinctive ridged buccal capsule pointed to *Camallanus,* a nematode genus that parasitizes many freshwater and marine fish, a few reptiles (mostly turtles) and rare amphibians. Adults attach to the gut of their host, causing hemorrhage, edema and perforations in some cases. *Camallanus* is in the same order as *Dracunculus* (Guinea worm), both using copepod secondary hosts and vertebrate definitive hosts. My surprising views of so much going on in the living, squirming, pulsating beautiful blood red nematodes are a special microscopy memory.

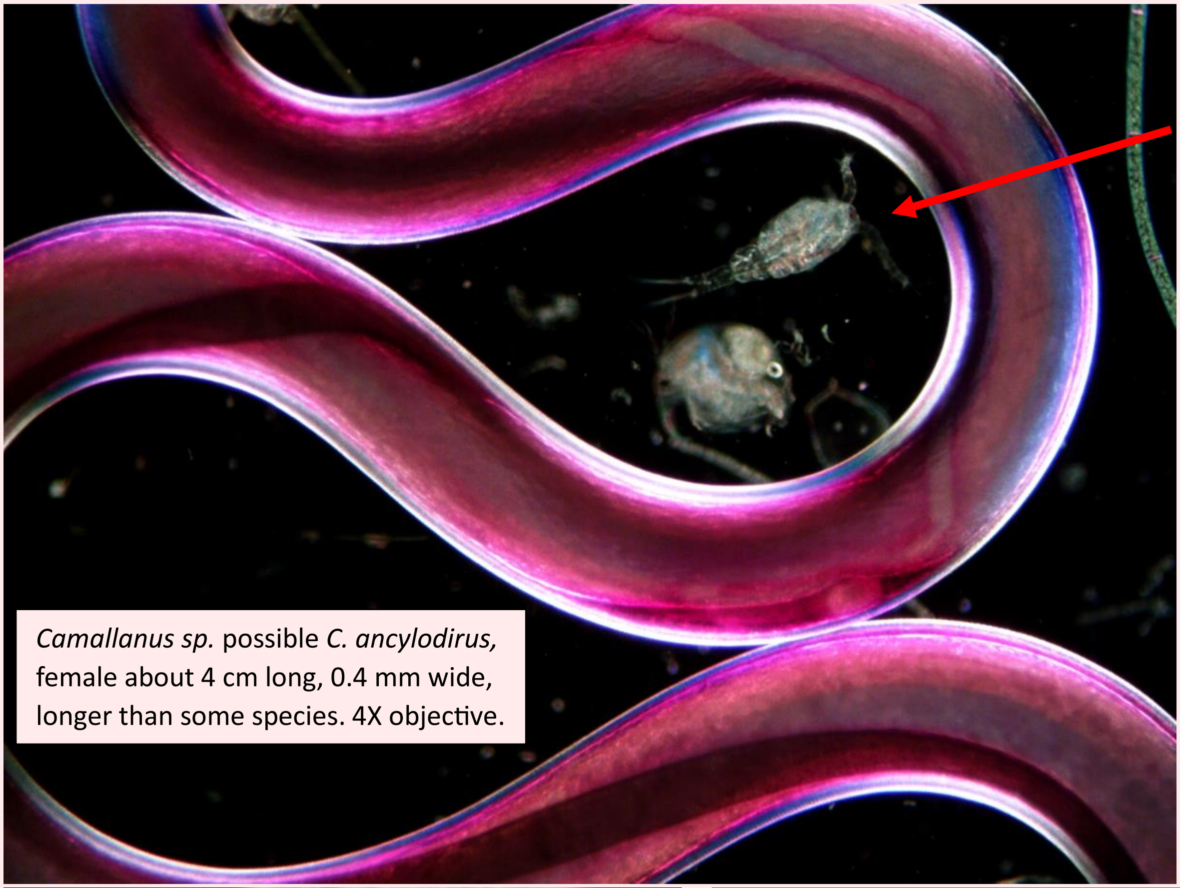


Live *Camallanus sp. ex Lepomis*, 2021-07-25 Red Wing, MN, USA female nematode anterior end showing buccal apparatus; the mouth slit is oriented vertically. 10X obj., cropped, strong oblique, the head is about 0.25 mm wide



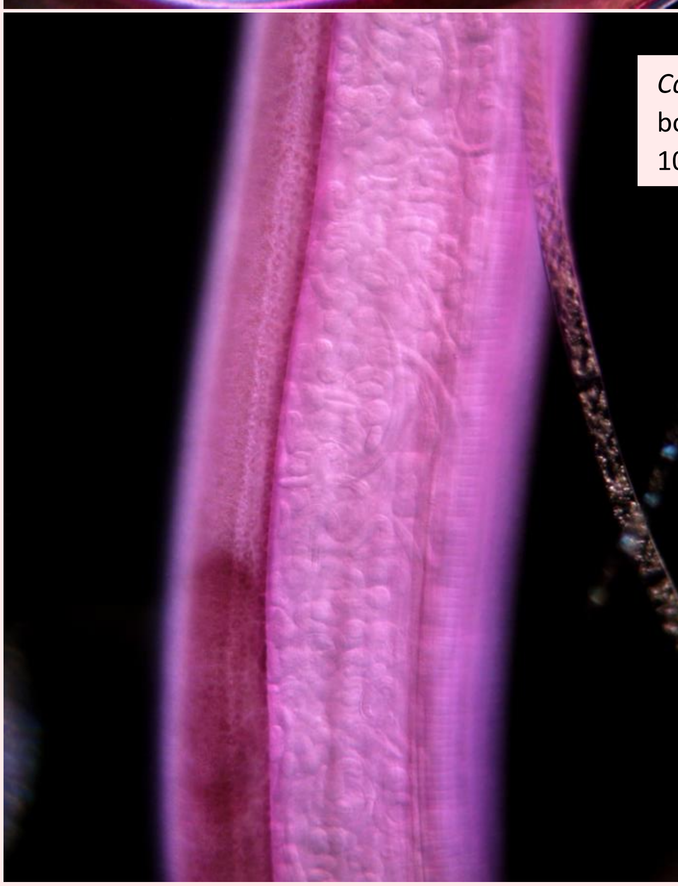
Camallanus sp. female, mid-body 2024-07-25 Red Wing, MN, USA showing squirming L1 larvae to left and ovary on right. Photographed alive, no stain, the red color is hemoglobin. Nematodes make globins, but can't make heme, taking it from the environment. 40X objective, strong oblique lighting image about 0.3 mm wide, larvae about 16 microns in diameter, 0.3 mm long

More live *Camallanus*



cyclopoid copepods are the worm's intermediate lost

Camallanus sp. possible *C. ancylodirus,* female about 4 cm long, 0.4 mm wide, longer than some species. 4X objective.



Camallanus sp. mid-body left, head on right below, body was packed with larvae, red is free hemoglobin 10X objective, dark field, each image ~ 1.2 mm tall

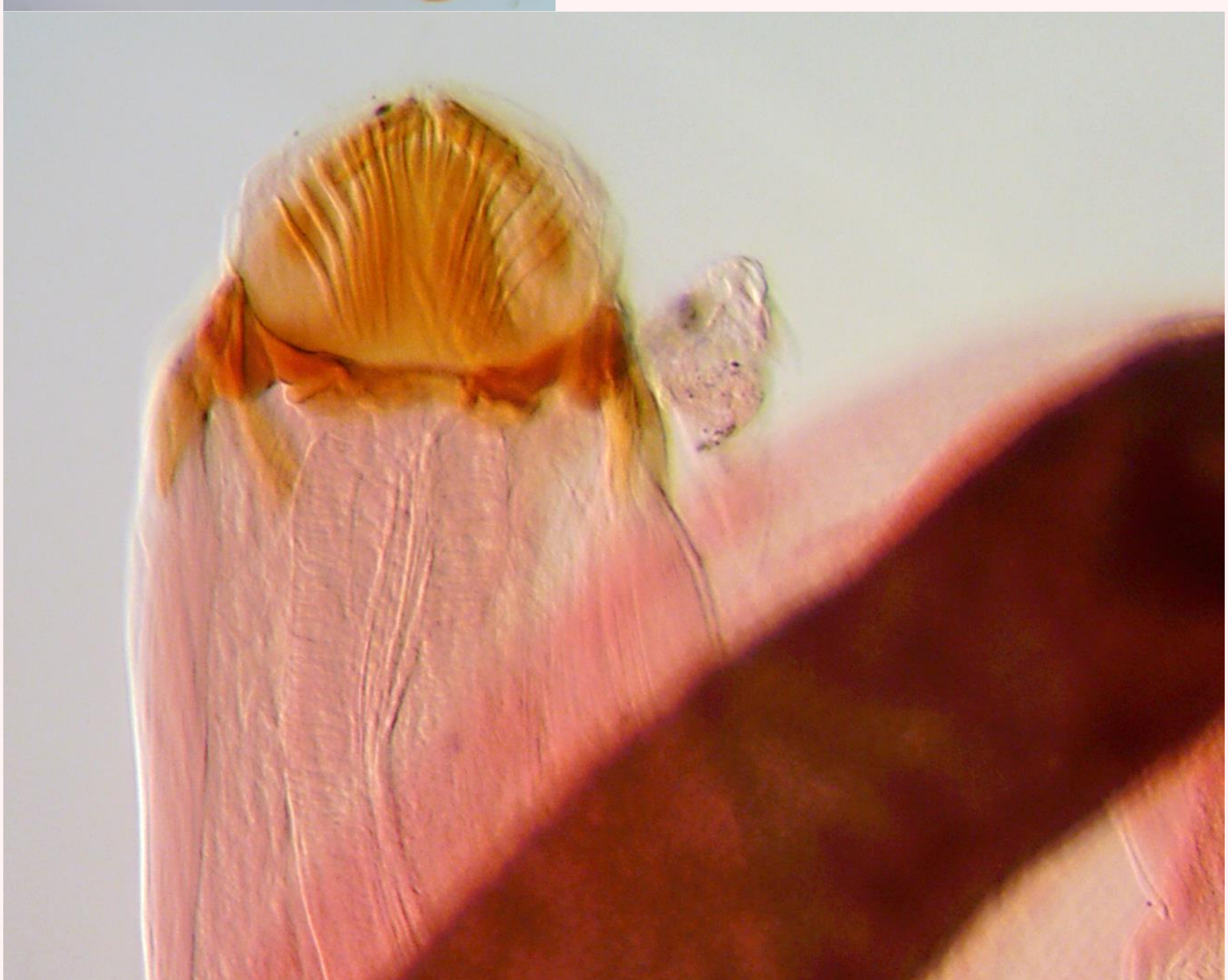
A different *Camallanus* species

I have a number of vintage microscope slide sets from biology teachers. Parasites are often teacher favorites to help illustrate interesting evolution and ecology. Two slides in a box of midcentury slides had nematodes about 2 cm long hand labelled "from duodenum of a turtle" and the year 1937. The stout, ridged buccal apparatus with supporting tridents is typical of *Camallanus*. Some species are found in amphibians or turtles, but it mostly parasitizes fish (using crustacean intermediate hosts). *Camallanus* can be deadly to pet fish.

Camallanus sp. nematode ex turtle

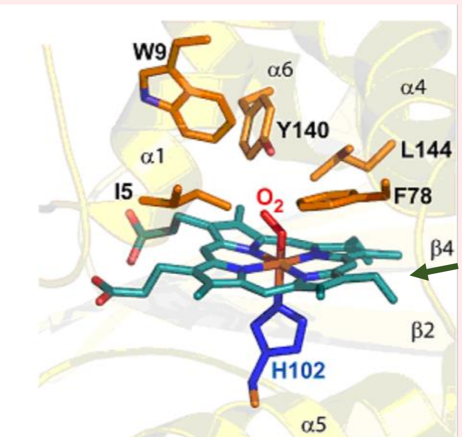
Left- whole nematode, 2.5X objective, slight crop, image about 4 mm wide, worm about 6 mm long

Below- head end, 20X obj. cropped, oblique lighting highlighting ridges on buccal plate, buccal ring with tridents, and muscular pharynx below the mouth. Buccal plate about 0.1 mm = 100 µ wide.



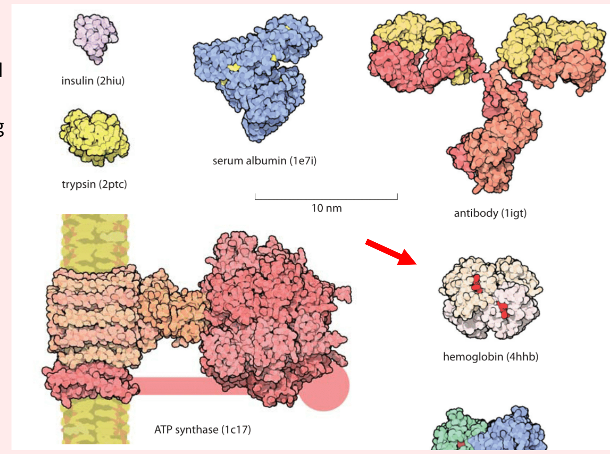
Why would a worm have hemoglobin?

Your red blood cells use hemoglobin to carry oxygen, but very few invertebrates have pigmented blood cells. It turns out hemoglobin is handy for many tasks. Thousands of variations of it exist and are found in some members of every kingdom of life: bacteria, protists, fungi, animals and plants. Hemoglobins are used to carry oxygen but also other gas molecules (carbon dioxide, nitrogen oxide), to catalyze redox chemical reactions, scavenge free radicals or detoxify poisons, send regulatory signals, and to work as chemical or light sensors. Many different worm-like creatures containing hemoglobin have been called "bloodworms": especially *Chironomus* midge (insect) larvae (sometimes sold frozen as pet fish food), but also *Tubifex* sludge worms (tiny aquatic annelids), some *Eisenia* and *Lumbriculus* species of earthworms (annelids), some marine bristle worms (annelids) including *Glycera*, and some parasitic nematodes including *Strongylus.* Large parasitic nematodes are more likely to make hemoglobin than free living nematodes. *Ascaris* is white but excretes some hemoglobin. Containing a hemoglobin that grabs oxygen tighter than that of a vertebrate host might help parasites get oxygen, and perhaps *Camallanus* uses it to deliver oxygen to unborn larvae.



Heme (green porphyrin ring with brown central iron) in hemoglobin of a bacterial O2 sensor. Nematodes can't synthesize heme, it is like a vitamin to them. Petrova et al. **Commun Chem** 2021

Hemoglobin (red arrow) size and shape compared to some other common proteins, bionumbers.org the red dashes in the molecule are 2 of the 4 heme domains



Human hemoglobin consists of 4 globulin subunits, each containing an iron ion bound in a porphyrin ring. The iron can reversibly bind oxygen by donating an electron (going from Fe 2^+ to Fe 3^+). Hemoglobin is closely related to myoglobin (an oxygen storage molecule in muscles, which has a single globulin chain and 1 iron atom) and to cytochromes (parts of the electron transport chains of mitochondria and chloroplasts). Human myoglobin and hemoglobin were the first 2 proteins to have their 3 D structures determined (by X-ray crystallography), around 1959. At about 17 kDa and 55 kDa (kDa = 1 kilo Dalton ≈ 1000X mass of hydrogen atom) they were thought to be gigantic proteins at the time but are now known to be sort of average sized. Your body makes 2 kinds, hemoglobin F and hemoglobin A, and others if you carry sickle or thalassemia genes (double Nobel laureate Linus Pauling invented hemoglobin electrophoresis in 1949 to make the diagnosis). If you don't have enough hemoglobin you are anemic, a problem with many different causes. Hemoglobins come in a variety of sizes and variations adapted for various tasks around the tree of life. Some of the most amazing are made by *Riftia pachyptila,* giant 2.4 m long tube worms living around deep sea volcanic vents in dark, hot, acidic, high pressure conditions. The annelid worms contain symbiotic bacteria (1/2 the worm's body mass) that make food from hydrogen sulfide (H_2S, their energy source, kills us at low concentrations by poisoning our wimpy hemoglobin), O_2 (electron acceptor), and CO_2 (carbon source). *Riftia* makes three different hemoglobins, 1 hyper-giant weighing 3285 kDa composed of 144 globin subunits each with an iron containing heme, plus linker peptides, and 2 other giant hemoglobins weighing 403 and 406 kDa containing 24 globin chains each. Life finds a way.

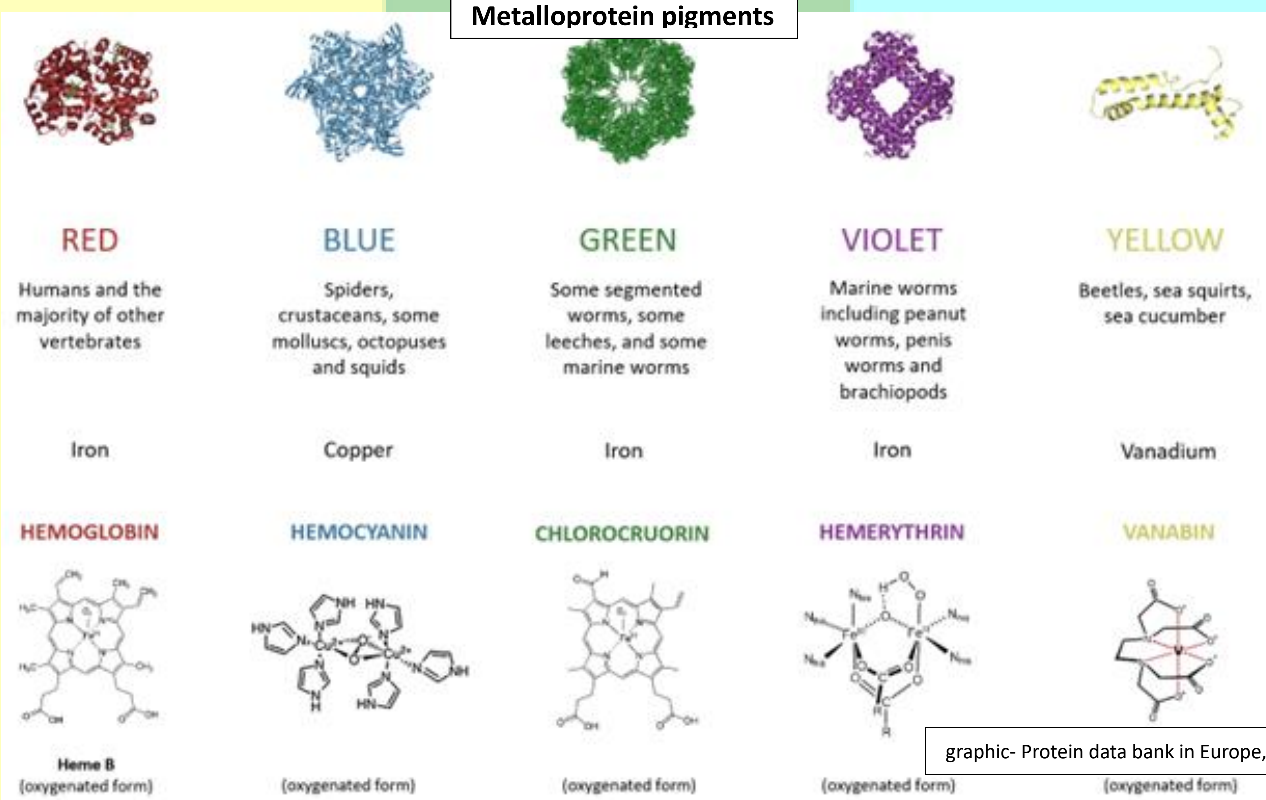
Riftia pachyptila giant tube worms on the Galapagos Rift in 2011; note the blood red color. image wikipedia

Plumbing and color diversity in the animal tree of life

Transporting oxygen is a problem all animals have to solve, especially the bigger ones. In microscopic forms the whole animal is close to the skin, so diffusion alone can work just fine, no circulatory organs needed. Flatworms and nematodes are also small enough not to need a heart, although as we have seen, *Camallanus* and some other nematodes do have hemoglobin, but they still don't have a true body cavity or blood. Most arthropods, annelids, mollusks and all vertebrates have a heart and circulatory system. Larger annelid worms, most mollusks and most arthropods, including insects, have an open circulatory system consisting of a heart (or a few hearts) and maybe a short aorta (vessel). They don't have small blood vessels or capillaries. Their heart is like a pump laying sideways in a bucket, making the water swirl around in a circle. A microscope reveals beating hearts in *Daphnia* water fleas, calanoid (but not cyclopoid) copepods and *Gammarus* amphipods for instance. If you look closely with oblique or other contrast methods you can watch colorless hemocytes tracing the circulation moving forward along the dorsum and backward along the belly. The circulating fluid, hemolymph, occasionally has an oxygen carrying pigment, but is usually clear. Cephalopod mollusks (octopi and squid) and vertebrates have a closed circulatory system with the heart pumping colorful blood that is always enclosed in arteries, capillaries and veins.

The circulating hemolymph of invertebrates is usually clear with a just a few clear hemocytes (forerunners of our white blood cells). But all vertebrates (save one Antarctic fish), along with a few mollusks, phoronids (horsehair worms), nemerteans (ribbon worms), annelids (segmented worms) and echinoderms (some sea cucumbers and brittle stars) have colored blood as their circulatory fluid: it contains blood cells with hemoglobin or other pigment. Reversible oxygen binding by the iron ion in hemoglobin allows blood to carry about 50X more oxygen than water alone, and many different animals independently evolved the capability. Fish, amphibians, reptiles and birds have nucleated red blood cells, and mammals alone have evolved tiny red blood cells with no nucleus. Their erythrocytes are bags of hemoglobin.

Metalloprotein pigments



graphic- Protein data bank in Europe, ebi.ac.uk/pdbe

Not all blood is red. There are four major kinds of respiratory pigments: hemoglobin, hemocyanin, erythrocruorin-chlorocruorin, and hemerythrin. Hemoglobin and chlorocruorin are globins containing a heme group with an iron ion. Hemocyanins have copper. Vanabins, containing vanadium, are found mostly in sea squirts (invertebrate chordates) and their purpose is uncertain. It is not oxygen transport, although vanabins turn yellow when exposed to oxygen.

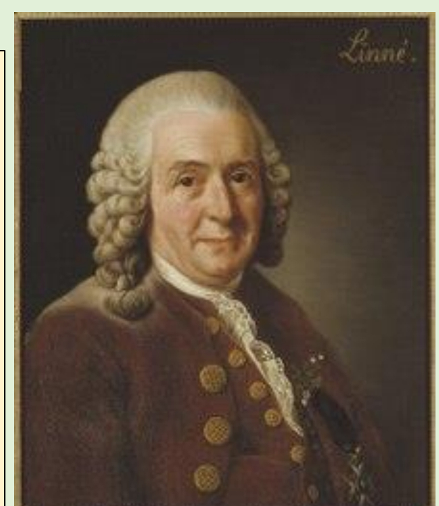
Linnean Taxonomy

Taxonomy, also called systematics, is the science of classifying organisms. Common names for animals and plants are inexact, and don't exist for microbes or new organisms, so scientists use their own rigidly structured naming system. Swedish genius Carl Linnaeus (b1707-d1778) set up the system scientists still use today (with modifications) in his *Systema Naturae,* first published in 1735. Linnaeus named over 12,000 species of plants animals during his career. Many Linnaean names, including *Homo sapiens,* are still used today (but altered by the recognition that Africans are the same species as Europeans). He named seven parasitic worms of humans: *Ascaris lumbricoides, Ascaris vermicularis* (now *Enterobius vermicularis*), *Gordius medinensis* (now *Dracunculus medinensis*), *Fasciola hepatica, Taenia solium, Taenia lata* (now *Diphyllobothrium latum*) and *Trichuris trichiura*. The Linnaean scheme is a hierarchy of different sized groups from Kingdom down to species. Individual species are usually referred to by a "binomial name" that includes genus and species, i.e. *Homo sapiens*. Linnaeus classified organisms according to obvious physical characters. Named and classified organisms gave Darwin a head start when he did his work one century later. Modern taxonomy usually classifies organisms into ranked groups based on their evolutionary ancestry (a literal family tree) also called phylogeny. Many but not all taxonomic groups are clades: groups containing all the descendants of a common ancestor. We break that rule sometimes because some subgroups seem distinct (birds are in a clade with dinosaurs, and insects are in a crustacean clade). We have also added more levels to taxonomy, particularly at the top levels after late 20th century biochemical and DNA methods allowed us to better see distinctions between microbes. There are just 2 domains: Prokarya (bacteria and archaea) and Eukarya (everything else). There are 4 or 5 eukaryotic kingdoms in most schemes nowadays: Protozoa (+/- Chromista), Plantae, Fungi, Animalia. Taxonomy continues to evolve as science gets more data.

An example of a modern classification, that of the human flea, an animal first named by Linnaeus:

bar 1 mm, K Walker Museum Victoria

Domain	Eukarya
Kingdom	Animalia
Phylum	Arthropoda
Class	Insecta
Order	Siphonaptera
Family	Pulicidae
Genus	Pulex
Species	irritans
Binomial	*Pulex irritans* Linnaeus 1758



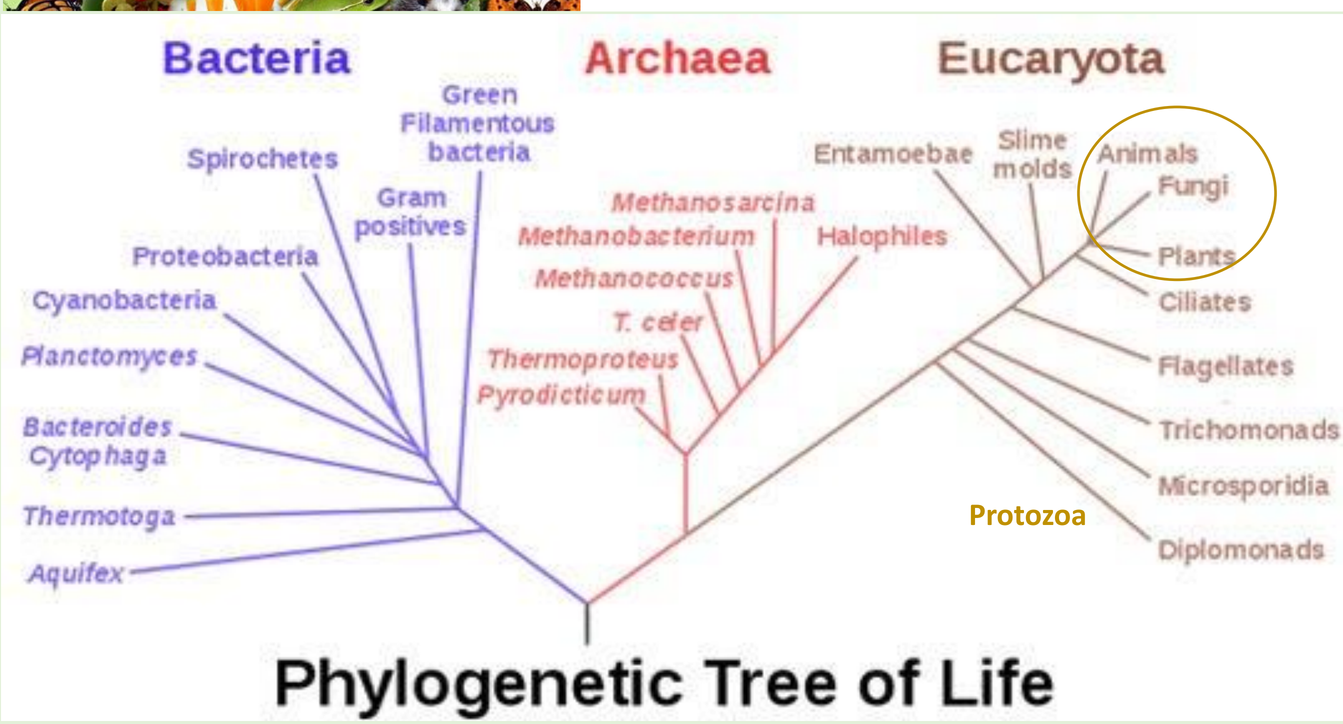
Linnaeus 1775 by Roslin, wikipedia

Evolution explains a lot

In 1859 evolution was a new theory, laid out in clear, logical and humble detail by Charles Darwin in his book *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. Darwin had gathered thousands of his own and others' observations about the varieties of life, but at that time known fossils were fewer and the mechanisms of inheritance were unknown (Czech monk Gregor Mendel discovered the laws of genetics in pea plants in the 1860's but no one knew of it for decades). Evolution is now a proven fact: millions of bits of evidence show life slowly changed into a myriad of different forms on planet earth. Evolution remains a powerful and changing (all science is subject to modification by additional data) central theory in biology that makes sense of puzzling new evidence from research, like 5 legged frogs and the COVID virus changing to be less deadly. I see rapid evolution in action in the hospital as bacteria continually evolve to be resistant to the most used antibiotics.

Upon careful reflection Darwin's theory seems inevitable. People created differing breeds of dogs and other animals through selective breeding. Nature does much the same thing. Darwin saw there is a struggle in nature for organisms to survive and produce offspring. It is observed that there are differences between individuals in a group (i.e. some are faster or slower), that all organisms come from the reproduction of parent organisms, and that parents make imperfect copies of themselves (we now know genes are shuffled and may mutate). In real circumstances (gazelles being chased by cheetahs for example) survival is not just random but favors certain bodily abilities (i.e. running faster) so the next generation comes from selected (faster) surviving parents and so each new generation becomes slightly adapted in particular ways. Over deep time (the earth is now known to be about 4.55 billion years old) a single cell became all the amazing life on the planet today, from bacteria to *Paramecium* to grass to mushrooms to worms to you. Every living thing becomes fined tuned for its way of life, making life look like it was designed. Yet there is no designer, just the results of how natural life processes work out based on chemistry, physics and maths.

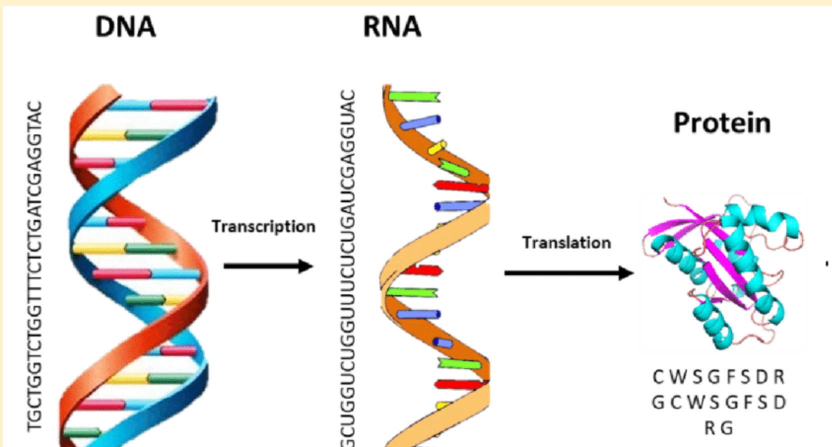
Most life is prokaryotic: Bacteria and Archaea, very tiny, no nucleus, on left. All multicellular organisms are in the small brown circle on the right. Between are Protists, bigger than bacteria, but mostly microscopic, nucleated single celled life. Carl Woese used ribosome RNA data for his 1990s tree.



The central dogma of molecular biology: DNA ➡ RNA ➡ protein

the dogma is now known to be addended by epigenetic tags and edits

Czech monk Gregor Mendel worked out laws of inheritance in pea plants in the 1860s. In the early 20th century chromosomes and their gene subunits were studied extensively in *Drosophila* (fruit flies). Chemists found the most important chemicals in cells seemed to be a myriad of different proteins (polymers of amino acid building blocks) that make up cell structures and carry out complex chemical reactions. In 1953 Watson and Crick (after seeing Rosalind Franklin's data) solved the puzzle of the double helix shape of the DNA molecule (deoxyribonucleic acid). Armies of scientists figured out the central mechanism of life: information builds complex molecules. Information in DNA is ***translated*** into mRNA, which leaves the nucleus and is ***transcribed*** into a unique protein by ribosomes (nanomachines of protein and special RNA). Because of the physics of water solutions, each protein self folds into a unique 3D shape that lets it do its job. The human genome was first sequenced in 2003. It is mind boggling. Each of your 200 very different types of cells (skin, muscle, etc.) contains the same complete blueprint for a human. But a complex system of **epigenetic** tags and edits turned genes off and on as needed so the single cell fertilized egg inside your mom could develop into the unique 35 trillion cell network that is you. Epigenetics also means genes are not destiny. Much more ill health is caused by hard lives of poverty, social discrimination and unhealthy habits causing epigenetic change and sick phenotypes than by being born with bad genes. Parasitic diseases are suffered mostly from lack of modern comforts such as indoor plumbing, not because of genetic susceptibility.



Abbasi, Minhas (2019)

DNA is passed "vertically" from parents to offspring by sex, but may also jump horizontally (some cells take in environmental DNA) and by rare endosymbiotic events (i.e. mitochondria, chloroplasts). Genomics has been a huge boon to biology research in the past 50 years. We can now explore evolutionary relationships through DNA trees, clone and genetically manipulate cells and animals, and can sequence the whole transcriptome (all the mRNA) of various cells to see what genes they are using (and which are silent).

Mirroring society, scientists have long been racist. Linnaeus did not include dark skinned peoples in *Homo sapiens*. A century ago most anthropologists were "**scientific racists**" and eugenicists who believed nonwhites corrupt human bloodlines (beliefs repeated by Hitler and a recent US president). James Watson thought DNA proved his 1950s racist ideas. Racism remains pervasive, but **scientifically, race does not exist**. **Race is a social construct.** Some 19th and 20th century US state laws made people with 1/8 or even "one drop of black blood" black. You might guess the ancestry of a person from skin color, but DNA tests show you are sometimes wrong. Rudolph Virchow tried to divide 19th century German school kids into racial groups (Aryan, Jew, Slav) using scientific body measurements but found he couldn't: variation within each group was far bigger than the difference between purported racial groups.

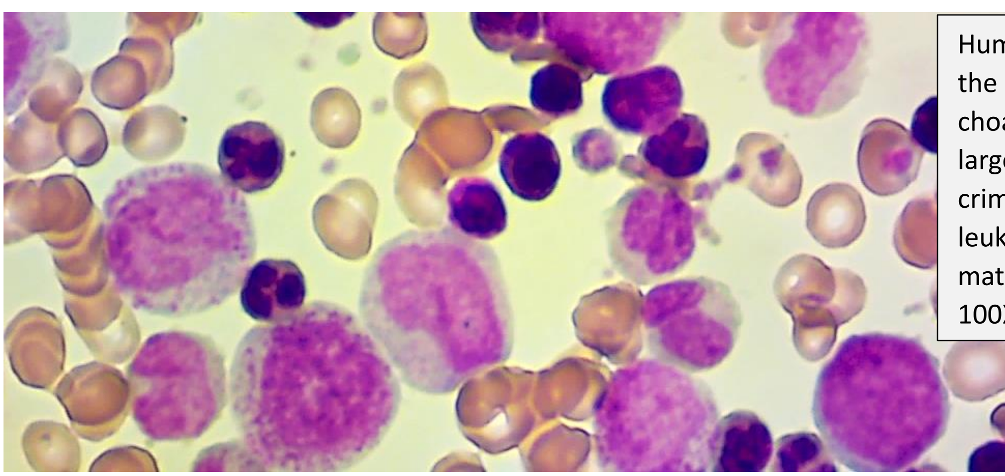
Cell Theory and the Theory of Evolution

These 2 great ideas are the foundation of modern biology and underlie scientific agriculture and healthcare. Both theories arose in mid19th century Europe and are reproven a million times daily in applications everywhere. (Soviet biologist Lysenko rejected Darwinism in 1930s-60s as “capitalist”, worsening famines in Russia and Mao’s China.)

As atoms make up matter, cells are the basic unit of all life. Robert Hooke saw tiny boxes in cork with his microscope in 1665, calling them “cells”. German scientists Theodor Schwann and Matthias Jakob Schleiden had better microscopes and in 1838 proposed all plants and animals are made up of cells. The multi-talented Rudolph Virchow completed the basic cell theory in 1855 by proclaiming all cells come from preexisting cells, *“omnis cellula e cellula”* in Latin.

Around the same time, a humble genius In England solved the mystery of why we have so many different kinds of animals and plants. In 1859 Charles Darwin published *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. Evolution is so logical it is inevitable. Living beings copy themselves, but often slightly imperfectly. In the struggle to live and breed some individuals can run faster or are otherwise favored. So the next generation comes from survivors that are a little different. Some populations become divided by barriers. Over deep time (life on earth is about 3.8 billion years old) a single cell divided zillions of times and became all the amazing life on the planet today, from bacteria to *Paramecium* to mushrooms to trees to you. Every living thing becomes fined tuned for its way of life, making life look like it was designed. Yet there was no designer, just the logical results of how natural life processes worked out, explainable by chemistry and physics.

Run the evolutionary clock backwards and eventually you get to the first living cell. Every cell in every being is a direct descendant of that single cell (if life arose more than once, the others got wiped out long ago). Everything alive today uses variations of the same DNA and protein biochemistry of our common ancestor cell. That first very tiny cell grew and split into 2 daughters. They also split into 2 and so on. Thanks to exponential math they filled the oceans. Some learned to make food from sunlight, producing oxygen as a toxic waste. After billions of generations there were many different kinds of cells and one day one gobbled up another as lunch, but the lunch didn’t die. The “lunch” became mitochondria, finding a nice new place to live and paying rent with high energy molecules. Naked DNA got organized into chromosomes inside a nucleus and life was off to do bigger things. With extra stored information, daughter cells could be different than each other yet still programmed to cooperate with each other. Multicellular life was born: bodies made of thousands or millions or eventually trillions of cells. Inside your body is a wonderland. It’s like a bustling city with skyscrapers and highways and factories populated by 35 trillion resident cells. All those cells came from 1 cell formed when your mom and dad had sex. And those sex cells came in turn from earlier and earlier cells. We have a massive convoluted family tree, all the way back to the first bacterial cell at a steaming hot, sulfurous deep sea vent 3.8 billion years ago. During all those years there were only a few great leaps; most of the changes were tiny and incremental (but added up over time). You, *Homo sapiens*, might be one of the great leaps, or not. You have the abstract reasoning required for complex language and math, leading to civilization and eventually to modern technologies powerful enough to destroy the planet or to create a paradise on earth. Please choose the latter.



Human blood cells, distant descendants of the last universal common ancestor and of choanoflagellate protozoa. In this case the large purple cells belong to a dangerous criminal gang (suspect chronic myelogenous leukemia with many large blasts and smaller maturing neutrophils, 1950’s hospital slide) 100X oil obj, cropped, RBCs about 7 μ wide

Parasite glossary part 1

Parasite an organism that lives in or on another, taking nutrients that would have benefited the host (viruses, some bacteria and fungi fit the definition, but we call only eukaryotes parasites)

Host a larger organism that harbors a parasite (a potentially harmful organism)

Symbiosis long term close relationship between different kinds of organisms; may be **mutualistic** (both benefit), **commensal** (one benefits, one unharmed) or **parasitic** (one helped, one harmed)

Endoparasite lives inside of host **Ectoparasite** lives on outside of host

Definitive host organism that harbors adult (sexually reproductive stage) parasites

Intermediate host organism that harbors immature stages (which often reproduce asexually)

Free living not a parasite; photosynthesizes or is a predator/scavenger, does not live inside creatures

Infestation harboring an animal (worm, arthropod) in or on body (**infection** is microbe/pathogen in body)

Parasite load number of parasites per host (affects potential harm of parasites)

Vector an organism (usually an intermediate host) that passes a parasite between hosts

Reservoir a population or community of organisms that can permanently harbor a parasite population

Zoonosis a disease transmitted from animals to people; many parasitic diseases are zoonotic

Parasite life cycle stages through which the parasite grows, reproduces and transmits itself in 1 or more hosts

Monoxenous also known as **monogenean** or **direct** parasitism; life cycle requires only a single host species

Heteroxenous aka **digenean, digenetic** or **indirect**; life cycle requires one or more extra intermediate hosts

Direct transmission hosts touch each other (sex counts), passing on a free-living life stage (including skin to skin passing lice) or by ingestion of free-living parasite or eggs (i.e. fecal-oral, by food with contaminated dirt)

Indirect transmission from one host to another through an intermediate host (i.e. a vector such as a tick)

Trophic transmission by eating an organism that contains a parasite (i.e. predation, or via uncooked meat)

Vertical transmission from mother to offspring (i.e. toxoplasmosis can by passed to fetus with severe results)

Iatrogenic transmission by medical care (i.e. from blood transfusion or organ transplant)

Parasitoid tiny wasps (some are “fairy flies”) whose larva eat a host from inside, eventually killing it

Hyperparasite a parasite of a parasite, i.e. some parasitoid wasps prey on other parasitoid wasps

Parasite glossary part 2

Brood parasitism raised by parents of another species, i.e. cuckoo birds lay eggs in other species' nests

Sexual parasitism i.e. male anglerfish attach to a female and shrink to just tiny sperm-making parasites

Reproductive parasitism a symbiont manipulating host reproduction for its own benefit, i.e. *Wolbachia*

Micropredator steals body fluids without consuming the whole victim (i.e. mosquitoes, leeches)

Kleptoparasite steals food from other species, i.e. frigatebirds and hyenas grab food from other animals

Social parasitism mimicry to gain care, i.e. some butterfly larvae mimic ants (in shape, smell) and are cared for by ant workers; not be confused with parasites thar live in their own social colonies; i.e. some trematodes

Parasitic castration some trematode and arthropod parasites gain added resources by neutering the host

Carcinogenic parasite increases cancer risk; some blood flukes can cause bladder, bile duct or liver cancer

Aberrant Host one that cannot support parasite development aka a dead end host

Accidental Host not the usual host, but can support parasite development (with or without dispersal)

Paratenic Host an accidental intermediate host that may sometimes be able to pass on the parasite

Autoinfection transfer of new parasite stage within one host, as occurs with some nematodes and flatworms

Hyperinfection repeated autoinfection leading to high parasite load and dissemination beyond usual infected organs (i.e. in the nematode *Strongyloides* runaway hyperinfection can be fatal)

Facultative or **Opportunistic Parasite** lives either free living or parasitic life cycle, depending on opportunity

Cloaca single opening of reproductive, GI and urinary tracts (in most vertebrates except mammals)

Coprozoic or Coprophagous living in or eating feces; typically harmless organism, passes through if ingested

Cyst fluid pocket bounded by membrane or wall; **encysted** organism can be parasite dispersal stage

Dispersive stage form of organism that travels by swimming or drifting in water, or carried by a motile host

Egg cell aka ovum, a female reproductive cell (gamete) **Egg** organic structure with zygote or embryo

Endemic means a disease is native to a particular place, typically cases occur much of the time

"ex" came from indicated host (i.e. *ex Homo sapiens* denotes specimen removed from a human)

Exotic a non-native species; if a nuisance or harmful then called an **invasive** species

Extant a kind surviving today **Extinct** no longer exists; some left fossils

Parasite and Biology glossary part 3

Prokaryote tiny cells without nuclei (bacteria, archaea) **Eukaryote** has nucleated cells (all other life)

Microorganisms all life too small to see with the naked eye, including bacteria, protists and tiny animals

Protozoa aka protists, single celled eukaryotes; free living (*Paramecium*) or parasitic (*Plasmodium*)

Helminth any parasitic worm (and rarely used more broadly, for any worm)

Platyhelminthes flatworms, the first worm phylum to evolve, and majority of species are parasitic

Cestodes tapeworms; parasitic flatworms with bodies like a segmented ribbon, no mouth

Hydatid Cyst cyst with multiple larval *Echinococcus* sp. tapeworms, causes hydatid disease

Trematodes flukes; parasitic flatworms with flat bodies usually shaped like a narrow leaf

Nematodes aka roundworms, mostly tiny free living very abundant worms, but many are parasitic

Filaria a superfamily of insect transmitted rhabditiform nematodes that live in host lymph and blood

Microfilaria infectious blood borne pre-larval stage of filarial nematodes

Hologonic having a single sex (female) colony; **or** gonads with germ cells throughout, i.e. *Strongyloides*

Arthropods animals with exoskeleton and jointed legs, includes mites, ticks, crustaceans, insects

Instar life stages in arthropods and nematodes, defined by molting

Genotype the genetic (DNA) code of an organism **Phenotype** is the observed appearance

Gene the unit of heredity, a section of DNA coding a specific protein **Genomics** studies DNA/RNA

Phylogeny hereditary and evolutionary relationships of different groups (**Taxonomy** mostly follows it)

Homologous same origin but modified (i.e. human arm and bat wing); or chromosomes that pair up

Gravid filled with eggs, as in a mature (female or hermaphrodite) nematode, or a tapeworm proglottid

Oviparous produces eggs **Viviparous** gives live birth to formed, often motile young

Ovoviviparous embryos develop in eggs that hatch inside the mother; includes some nematodes, snakes, fish

Senso lato in a broad sense, i.e. describing a taxonomic group **Senso stricto** in a strict sense

Ecology science of complex relationships between living organisms and their physical environment

Syncytium many cells fused into 1 multinucleate cell, i.e. helminth tegument, muscle fibers, in some infections

Botany, Zoology, Mycology, Microbiology, Developmental Biology, Evolutionary Biology, Cell Biology, Physiology, Anatomy, Systematics, Ecology, Biochemistry, Genetics, Paleobiology a few branches of Biology

Sex Glossary (sex is more complicated than I remembered)

Reproduction and sex are accomplished in many confusing ways. The birds, the bees and the trees inherited sex from protists: eggs and sperm fuse to become the next generation. Sex has big advantages over splitting in half: reducing what is passed on to a single cell gives most parasites the slip, and by combining genetic information from two parents, variation is boosted so evolution has more to select from.
Asexual Reproduction- genetic material is passed from only 1 parent to the next generation.

Binary fission- most cells pinch in 2 during mitosis, a few multicellular organisms also divide evenly
Budding- creating a growing blob that cleaves off, as in yeast and hydra
Fragmentation- metazoan (multicellular animal) dividing into many parts, as in some free living flatworms
Vegetative propagation- many plants and some animals (sea squirts) grow new individuals from runners
Sporogenesis- creation of small resistant forms as in ferns, moss, many fungi (by mitosis or meiosis)
Sporulation- in apicomplexan protists the oocyst nucleus divides by meiosis to form 8 haploid sporozoites
Merogeny- protist merozoites undergo additional rounds of asexual reproduction (i.e. erythrocytic cycle)
Sporocyst- trematode miracidia nucleus divides stepwise to form multiple germ balls which each become a redia, that may undergo another round of asexual reproduction before making multiple cercariae
Polyembryony- a single zygote becomes multiple identical clone embryos. Trematode sporocysts and redia are polyembryonic, as are social insect workers and armadillos (always identical quadruplets). Via differences in gene expression genetically identical clones may become different phenotype castes.
Parthenogenesis- development from an unfertilized egg, common in bdelloid rotifers, nematodes, social insects, rare vertebrates ("virgin births" are known in zebra sharks, boa constrictors Komodo dragons, turkeys). Parthenogenesis in flowering plants is called apomixis (clonal seed production).
Clones- multiple genetically identical copies, created asexually (phenotypes vary in some cases)

Sexual Reproduction- gametes derived from 2 parents join to become a single celled zygote which develops into an organism or organisms. Because of its advantages sex is common among bacteria (by conjugation and environmental gene acquisition) and eukaryotes (through gamete based sex).

Mitosis- standard eukaryotic cell division with 2 copies of each chromosome to both diploid daughter cells
Meiosis- Two sets of cell divisions create gametes with segregation of chromosomes into haploid sets
Diploid- full set of chromosomes from mom and dad (46 in most people, 23 pairs inc. 2 sex chromosomes)
Haploid- half set of chromosomes; found in gametes (4 in fruit flies, 23 in man, 39 in dog, 52 in carp)
Somatic cell- almost all cells in body, diploid, divide by mitosis
Germ cell/germ line- haploid gametes and those diploid cells that will produce gametes by meiosis
Gametes- sex cells: female egg/ovum and usually smaller motile (in higher animals) male sperm
Zygote- the single cell formed by fusion of gametes, i.e. the fertilized egg
Types fertilization- 1.conjugation 2. external fertilization (in water) 3. internal fertilization (by insertive sex)
Alternation of generations- diploid then haploid every other generation; obvious in corals and "lower" plants; in "higher" plants and animals only tiny gametes are haploid
Hermaphroditic- aka monoecious; both sex gonads in one individual (same time or sequential), common in plants and invertebrates; many mate with another hermaphrodite, some can self-fertilize (asexual)
Unisexual- aka dioecious or gonochoric ; separate sexes, individuals are male or female
Gender- a human social construct, not always congruent with biologic sex

(I am now an honorary biology professor, having succeeded in making sex boring.)

Privileged to be parasite-free

Most people reading this article don't need to worry very much about parasites personally, as they are probably living in a privileged place during a privileged time.

Since the origin of *Homo sapiens* in Africa about 300,000 years ago, most people harbored potentially harmful parasites in and on their bodies. Lice and intestinal worms were nearly universal. Then a combination of industrial and social revolutions starting about 300 years ago greatly improved health and comfort for most people today. If you are reading this then it is likely you have clean water and food supplies, shoes, indoor plumbing, window screens, floor boards and a solid roof, all diminishing the chances of worms burrowing into your feet or swallowed in contaminated water, and of bites by infected mosquitoes or reduviid bugs. In the past century **better living standards, scientific knowledge and public health measures eliminated the most significant human parasites from most developed nations.**

Great strides continue to made fighting parasites and poverty in the world. The WHO estimates intestinal worm infestations dropped from 60% to 25% of all humans so far in this century. Global median annual income more than doubled between 2000 and 2019 from $1325 to $2759 (with the mean about $12000 in 2019, and yours is likely higher). Global life expectancy increased 6.6 years between 2000 and 2019 from 66.8 to 73.4 years average (even as life expectancy in the US began to decline during the same timeframe).

But the global gains in well being are far from being evenly distributed. Severe inequalities make averages (means) deceptive when **almost half of the world's total wealth is held by the top 1%, and the bottom half divvies up just 0.74%**. Most people are poor and live in the "majority world" (a newer term for what we also call the third or developing world) and they are still lacking in money, health and fair governance. Without all the luxuries we take for granted, the parasites they suffer from are just a small part of the unfair miseries (wars, famines, imprisonment without trial if they criticize the dictator) borne by the powerless majority. **Most people today (4.3 billion) live in 95 countries with authoritarian regimes**.

Some people may feel sad about this sorry state of affairs. For some readers the best way to worry about parasites is by helping out people with parasites who have little way to help themselves. You might consider a charitable donation to Oxfam, Against Malaria Foundation or Deworm the World.

It's also perfectly fine to feel grateful for the cosmic lottery you've won. You weren't born in medieval times, living 30 miserable years with lice and worms. Many *Micscape* readers are males in rich European or North American countries. You likely know a European language and have computers and microscopes. You may be privileged by your race, gender, citizenship (in a former imperial power), and by your political and economic systems. **You likely enjoy the full modern wealthy liberal package: democracy, free speech, free press, good schools, private property, strong currency** and **universal health care** (last not available in US).

Left- a malnourished, parasite infested West African boy in *Medicines sans Frontiers* clinic, Liberia, 2004

Right- a *Micscape* contributor from Russia

(names withheld for privacy)

Parasites that US doctors should know about (but may not)

Because most harmful parasites have been eliminated from rich countries, doctors in the United States learn very little about parasites during their training. Most doctors know about just two nonfatal protist parasites, vaginal ***Trichomonas*** infections and diarrhea caused by ***Giardia***. They both are treated with a common antibiotic, and many US doctors have never prescribed an anti-parasitic drug, unless maybe ivermectin for a **scabies** mite skin rash. Perhaps 60 million people in the United States have latent toxoplasmosis, but that asymptomatic condition is not treated. **Cutaneous larva migrans** and **swimmer's itch** are harmless rashes after swimming or wading in contaminated water. They are caused when certain animal related roundworm larvae or schistosome cercariae penetrate your skin, but aren't very serious conditions as you are a dead end host for dog, cat, or duck micro-parasites that die under your skin.

Only one intestinal helminth is still widely endemic in the United States, nematode ***Enterobius vermicularis***, also called **pinworm**. It is most common in daycare age kids and although not harmful it can cause severe rectal itching and can recur after treatment. 20 to 40 million Americans may have pinworms, although many have no itching. There are shameful cases of doctors laughing at patients who thought they had intestinal worms when they really did have and see pinworms. Enterobiasis can be diagnosed by an old fashioned "scotch tape" microscopic exam (which most providers cannot order from a lab) and is treatable.

It is true that in developed nations symptomatic helminth infections are rarer than patients with a mistaken belief that worms are crawling in their body (about 2 to 27 per 100 thousand people per year in studies of **delusional parasitosis**). Because sometimes the patient is right, it might be prudent to do a CBC with differential (looking for **eosinophilia**, although it is more commonly from allergies). Stool specimen microscopic exams for parasite eggs and select serologies might be indicated if a patient has risk factors. No test is perfect, and if lab tests are done indiscriminately, most "positive" results will really be false positives.

Immigrants to the U.S. from developing countries, **travelers** returning from the tropics, and patients who are **immunosuppressed** by disease or medication are prone to parasitic infections. Very rarely Americans get parasites from food prepared by immigrant cooks, produce picked by immigrants, or by exposure to farm, pet or wild animals. Travelers can bring home various parasitic hitch hikers. Some parasitic infections (Chagas disease, schistosomiasis) require years of reinfections before severe illness, so a brief vacation is lower risk. A very serious acute infection in returned travelers is falciparum malaria. On average about 2000 people a year have malaria in the United States, and 7 of them died in 2018. Most of these victims came back from vacation in the tropics, or were immigrants returning from visiting family back home, and a very few cases were acquired in the southern U.S. or from blood transfusions. If you run a fever after returning from a trip to the tropics see a doctor and emphasize that you were in the tropics and could have malaria. Special blood smears and serology tests can diagnose malaria. People with weak immune systems caused by cancer treatments, HIV infection or some arthritis drugs are more susceptible to all infections, viral, bacterial and parasitic. Even with infection they may not run a fever or feel very sick. The nematode worm *Strongyloides* causes about 15 deaths a year in the US, mostly in patients immunocompromised by HIV virus or by steroids given for COPD. Unfortunately, many US doctors lack training about parasites. If you do not think the doctor has diagnosed you correctly, seek another opinion. If you slowly get ill with intestinal or other symptoms after foreign travel or immune compromise and have reason to think it is parasitic, see your primary doctor if you trust them. Or consider going to a travel or infectious disease doctor/provider, as they often know more about parasitic and rare infections.

US doctors should know some vector borne diseases

Some diseases spread by the bites of insects and other arthropods are caused by parasites (i.e. malaria, leishmaniasis) and were covered in these parasite articles. But many other vector borne diseases are caused by viruses or bacteria, not parasites. The definition of "parasite" is arbitrary, focusing on animals (protozoa used to be thought tiny animals) that exploit other animals. Viruses and rickettsial bacteria are obligate intracellular parasites, but are instead considered acute pathogens (indeed many can quickly kill a host). Some are rare and odd infections, spread by mosquitoes or creepy ticks that suck blood (ectoparasite vectors). Because these infections can be quickly fatal and may not respond to the most commonly used antibiotics, these diseases are vital to know. Although not parasites in the strict sense, vector borne diseases often end up in a seldom accessed old memory space next to parasites in doctor's heads.

Vector borne diseases in the United States and Europe may have wild animal reservoirs and are spread by biting arachnids (ticks, mites) or insects (mosquitoes, lice, fleas). The most common vector borne disease in the US is Lyme disease, caused by the tick carried spirochete bacteria *Borrelia burgdorferi*. After being first found in the US in 1999, West Nile virus infection quickly became the most common mosquito borne infection in the country. Occasionally the diagnosis of vector borne infections is straightforward, as when an avid gardener comes in with a fever and characteristic rash saying she sees deer every day, had multiple recent tick bites and wonders if she has Lyme disease. Her self diagnosis is likely right and she should be treated with doxycycline or another appropriate drug while awaiting blood test results. More often the patient is vaguely ill (or not at all) with body aches, headache, fever or rash, so a high index of suspicion is needed to recognize a vector borne illness rather than a nonspecific virus.

Doctors don't know everything and don't always make perfect diagnoses. Common viruses are much more common than rare infections. But doctors should consider vector borne and parasitic infections in patients in patients with unexplained fevers. Different areas of the US have different endemic vector borne and parasitic diseases, and doctors should learn the most common local diseases. Where I live in the northern US, the black legged tick *Ixodes scapularis* (locally called deer ticks) can carry bacteria causing Lyme disease, anaplasmosis, borreliosis and ehrlichiosis, and the Powassan virus (in addition to the protist parasite *Babesia*). Some of our common *Culex* mosquitoes (*C. tarsalis, C. pipiens, C. restuans*) carry West Nile virus and Western Equine Encephalitis and St. Louis Encephalitis viruses.

My med school mentor, Dr. John Bartlett, wanted every doctor to never miss Rocky Mountain Spotted Fever. Caused by the intracellular gram negative bacteria *Rickettsia rickettsii* it is the most serious tick borne disease in the US, killing about 30 annually. The disease and the ticks that carry it (the dog tick *Dermacentor variabilis* and others) are most common in the southeast US (it is rare in the Rocky Mountains). Death occurs in about 20% of untreated cases, so it is important to think of Rocky Mountain Spotted Fever in sick patients with a rash and fever (doxycycline is life saving, but cephalosporins are not).

Far left male, near left female *Dermacentor variabilis* from my dogs, in 2024 and 2015, about 3 mm and 6 mm long. Right: rash of Rocky Mountain Spotted Fever, Wikipedia

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Micscape is a high quality website hosted in the UK and made great by amateur contributors from around the globe. *Micscape* Magazine always has lots of good information for hobby microscopists wanting to learn more about how to do it yourself. (You should not be not be diagnosing or treating parasites yourself, but maybe information in my articles might help you enjoy an old microscope slide of a parasite).

For 2024 I offer *Micscape's* readers a series of articles about parasites, illustrated in part from my slide collection.

I am incurably curious about parasites and keep thinking I should know more. The internet makes it easy to learn more, so my articles are always longer than I intended at first.

Just look at the interesting pictures if you want. Don't be freaked out by parasites. They are everywhere in nature, but seldom cause harm to humans in the developed world, with a few exceptions.

Some people are real experts and know much more than I do on these subjects. I would be pleased to have any mistakes or misunderstandings corrected.

I am Ed Ward in the state of Minnesota, USA.
Your comments are always welcomed, my email is eward1897 AT gmail DOT com

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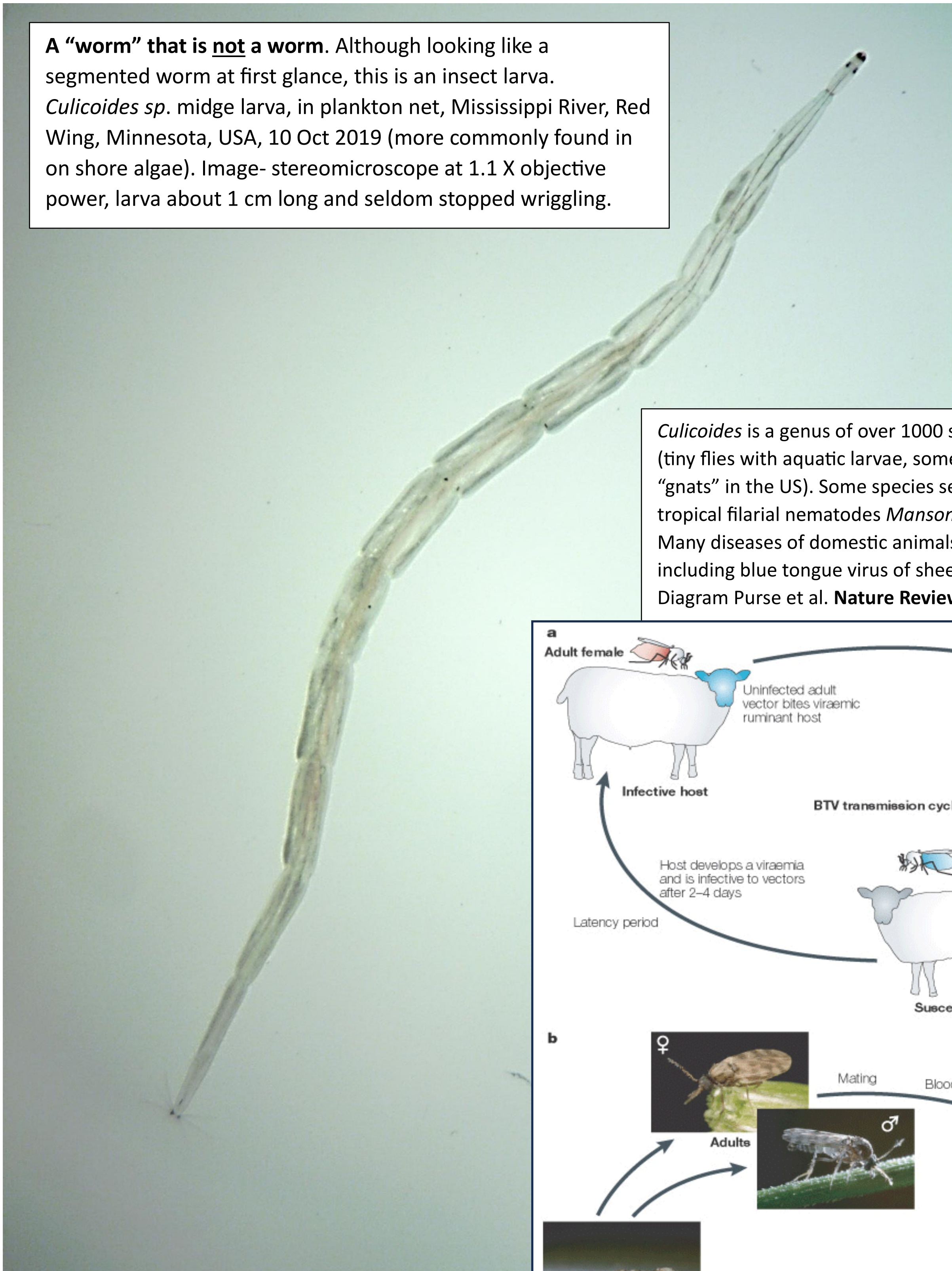
A "worm" that is <u>not</u> a worm. Although looking like a segmented worm at first glance, this is an insect larva. *Culicoides sp*. midge larva, in plankton net, Mississippi River, Red Wing, Minnesota, USA, 10 Oct 2019 (more commonly found in on shore algae). Image- stereomicroscope at 1.1 X objective power, larva about 1 cm long and seldom stopped wriggling.



Culicoides is a genus of over 1000 species of biting **midges** (tiny flies with aquatic larvae, sometimes colloquially called "gnats" in the US). Some species serve as vectors for the tropical filarial nematodes *Mansonella* and *Onchocerca*. Many diseases of domestic animals are spread by *Culicoides*, including blue tongue virus of sheep in Europe.
Diagram Purse et al. **Nature Reviews Microbiology** 2005