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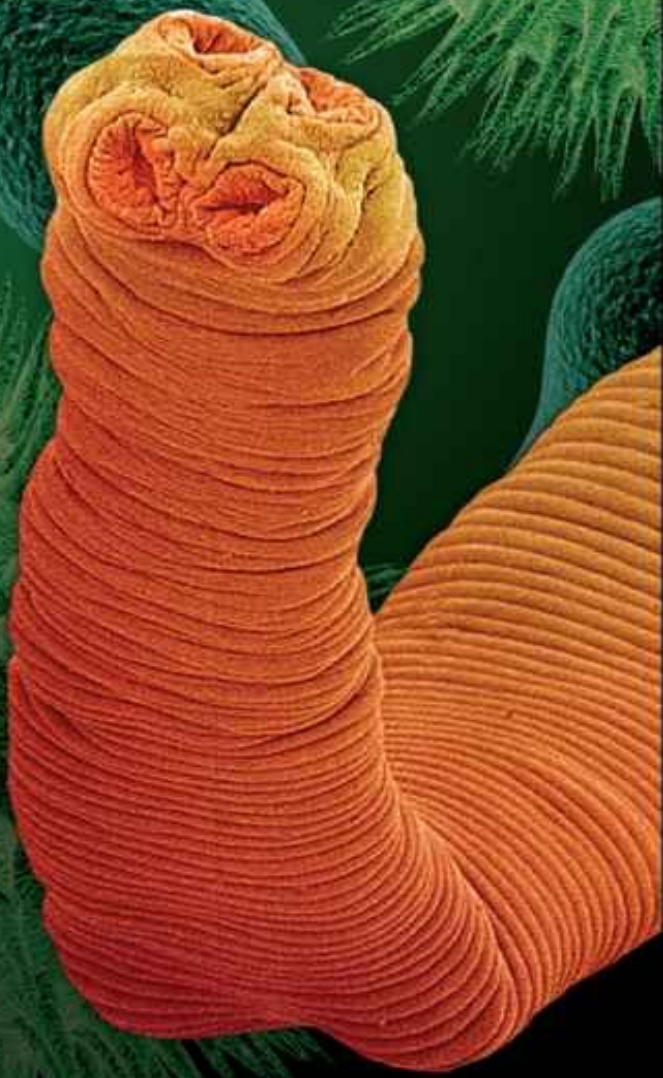
a compendium of unpleasant infections



DAVID I. GROVE

TAPEWORMS, LICE, AND PRIONS

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A compendium of unpleasant infections

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> We need reminding, now more than ever, that the capacity of medicine to deal with infectious diseases was not a lucky fluke, nor was it something that happened simply as the result of the passage of time. It was the direct outcome of many years of hard work, done by imaginative and skilled scientists, none of whom had the faintest idea that penicillin and streptomycin lay somewhere in the decades ahead. It was basic science of a very high order, storing up a great mass of interesting knowledge for its own sake, creating, so to speak, a bank of information, ready for drawing on when the time for intelligent use arrived.
>
> **LEWIS THOMAS**
> *The Medusa and the Snail:*
> *More notes of a biology watcher, 1979*

PART I
INFECTION

the search for its causes

Infectious diseases have been the major cause of sickness and death throughout recorded history, and no doubt in pre-history as well. We have all heard of the Black Death, tuberculosis, meningococcal disease, and swine flu. But what are infectious diseases? My trusty *Shorter Oxford English Dictionary* says they are diseases communicated by infections. But what is an infection? That same dictionary says in its third definition that an infection is ‘the agency, substance, germ or principle by which an infectious disease is communicated or transmitted’. This seems suitably vague and tautological. It reflects humanity’s understanding, or rather lack of understanding, of infectious diseases until recent times. The word itself is derived from the Latin word ‘infectus’, the past participle of ‘inficere’ meaning ‘to dip in’, ‘put into’, ‘taint’, or ‘stain’. Its use long antedated the knowledge of pathogenic micro-organisms and implied tainting with morbid matter, or contamination with noxious effluvia, vapours, and miasmata. In other words, nobody had a clue.

What about contagious diseases? Are they the same thing as infectious diseases? Some people use the two terms as synonyms but strictly speaking contagious diseases are a subset of infectious diseases acquired by touch. The word is derived from the Latin ‘tangere’ meaning ‘to touch’. Contagion has rather gone out of fashion these days so perhaps ‘contagious diseases’ is an expression best forgotten.

A rather better definition for an infectious disease is that it is an illness caused by a microbe, a word which was coined by the French surgeon Charles Sédillot (1804–1883) in 1878. This has the advantage of allowing us to include diseases caused by microbes which come from other people, from animals, from the environment, and from ourselves (for we all carry micro-organisms on our skin and in our mouth and bowel). But what is a microbe? Again the dictionary defines a microbe, which comes from Greek words *micros* and *bios* meaning ‘small’ and ‘life’, as ‘an extremely minute living creature whether plant or animal; chiefly applied to the bacteria causing diseases and fermentation’. So, a microbiologist is a person who studies the agents that cause infectious diseases whereas an infectious diseases doctor is someone who tries to cure a patient with an infection.

This is a rather more practical definition but it still has some problems. As you will soon see when we consider worms, these are not microscopic at all. Indeed some are huge; a tapeworm may reach 5 metres in length although its eggs are certainly microscopic. And are all infectious agents living? Until a couple of decades ago, everyone would have agreed that they are. Most infectious organisms carry the building blocks of life, DNA and RNA. Then it was found that viruses are made up of either DNA or RNA. Then, most confusingly of all, prions were discovered. We shall consider these in our penultimate chapter; they have neither DNA nor RNA and are

simply proteins. I don’t think anyone would consider these as living.

This book is concerned with the discovery of the most important infectious agents throughout history and in our own time, who discovered them, and how they were related to the diseases that they caused. In 1894, Robert Louis Stevenson died in Samoa at the age of 44 from tuberculosis. He once said that it is not a hard thing to know what to write; the hard thing is to know what to leave out. That has been my problem too. It is perforce a matter of my judgement.

You can read any individual chapter with profit if you are particularly interested in a certain disease or particular organism. However, you will gain more benefit if you read the book from beginning to end. This is because it is arranged in a manner which roughly reflects both the size of the organisms and the order in which they were discovered. It therefore somewhat matches the development and maturation of ideas in infectious diseases and the progressive introduction of novel, powerful technologies that have allowed new discoveries. Furthermore, technical terms or words tend to be defined the first time that they are used. If you are uncertain of the meaning of a word, flip over to the glossary near the end of the book and it may well be defined there. There is also a section there telling you how to pronounce unfamiliar words.

We begin with multicellular infectious agents—the worms, arthropods, and some fungi (the moulds). We then turn to single-celled creatures, first yeasts (also fungi) and protozoa. All of these organisms are like us in that they have a well-defined nucleus, so they are classified as eukaryotes. Next we examine the bacteria, a group of organisms now classified as prokaryotes, which although they have DNA and RNA, do not have a well-defined nucleus. Then we review viruses, which have no nucleus at all and must live inside another eukaryotic cell. Finally we reach the enigmatic proteinaceous prions.

Medical scientists have made enormous progress, especially over the last 150 years or so. But it has not been easy. It is a tale at one time or another of dogged determination, perseverance, flashes of insight, luck, serendipity, argument, dispute, and, on occasion, tremendous bravery. We owe an incalculable debt to those who have gone before us.

This book is meant to entertain and inform, not to be dreary and didactic. But like any historical inquiry, it is subject to error. It is dependent upon my assessments and judgements of the significance of events. There may even be one or two errors of fact, although I hope not. Limitations of space mean there are many stories that cannot be told. Perhaps there are important discoveries of which I am simply unaware. Enlightenment and correction from you, dear reader, are always welcome.

PART II
WORMS

Most people don't like worms very much. The Bible tells us that in Old Testament times, Job in his agony cried 'And though after my skin worms destroy this body, yet in my flesh shall I see God' (King James Version) while just after the time of Christ, King Herod 'was eaten of worms, and gave up the ghost'. Actually, they were probably not worms at all but fly maggots. It is not surprising then that worms are popularly thought of as any elongated, creeping, loathsome thing that is not immediately recognizable as something else. The ancient Romans had a word to describe these obnoxious creatures—'vermes'—from which we get our English word 'verminous' meaning 'wormy'. Another word you might come across is 'helminth', which means much the same thing. It is derived from the word *helmins* which was used by the ancient Greeks to denote worms found in the intestines of humans and animals. Nowadays the diseases caused by worms or helminths are called 'helminthiases' (singular: helminthiasis).

In contrast to those pathogens described in this book which are unicellular or subcellular and can only be seen with a microscope or electron microscope, worms are made up of many cells. This means they are usually big enough to be visible to the naked eye; in fact, intestinal tapeworms can reach an extraordinary several metres in length. So it was that cavemen knew and doubtless were terrified by the horrid, motile creatures that occasionally passed from the anus.

We now know that there are thousands of species of worms but it is only in the last two or three centuries that they have all been discovered and sorted out. Worms are soft-bodied invertebrates, that is, animals without backbones. Structurally, there are two forms—roundworms and flatworms. Functionally, they also fall into one of two groups. The first category contains the free-living worms that live happily and freely in favourable niches in the environment, feeding on any detritus they find tasty, and passing on from one generation to the next. They are not our concern. The second group, for at least part of their lives, must live in and feed on another animal, often in the process doing damage to their unfortunate host. A few of these worms will only live in humans, some live in humans and a variety of animals, but most will only live in particular species of fish, amphibians, reptiles, birds, or animals. These worms are parasites, a term which is derived from two Greek words, *para* meaning 'beside' and *sitos* indicating 'food'. You might like to think of a parasite as one who eats at the table of another.

Worms that live in the human intestine are called, naturally enough, 'intestinal worms'. Other worms live in the tissues of the body; you can think of these as 'tissue worms'. But parasitic worms, whether living in the intestines or tissues, have a problem—they have to get from one host to another host in order to allow the next generation of worms to appear. The way in which they do this is called a life cycle. For some intestinal worms, this is very simple; microscopic eggs are passed in the

faeces of one person, contaminate some food, and are ingested by another unsuspecting human in whom they develop once more into adult worms. Other worms find it much more difficult and have to be carried by a vector (such as a mosquito) from one person to another. Others again have to spend some time in a non-human animal, which is called an intermediate host. Here they look completely different from the worm found in humans. Indeed, in the case of tapeworms, they become cysts and do not look like worms at all.

We shall consider different sets of worms in the next five chapters. The first two are the giant intestinal roundworm, *Ascaris lumbricoides*, and tapeworms, especially the pork tapeworm. These are all parasites that dwell in the human bowel. They are large and obvious and the challenge has been to determine what illness, if any, they cause. Then we shall look at hookworms, which have a particularly cunning way of getting into you or me. After that we shall examine schistosomes (which cause a disease sometimes called bilharziasis) and which are particularly partial to snails and water. Finally, we shall review the filarial worms that cause elephantiasis but are only able to survive because mosquitoes like to suck our blood.

No matter which worm we are concerned with, the really exciting and sometimes controversial detective work has been to unravel the differing life cycles of these noxious beasts. Such understanding has often led to ways in which transmission can be interrupted and infection prevented.

1
Ascaris—the giant intestinal roundworm

SCIENTIFIC NAME:	*Ascaris lumbricoides*
COMMON NAME:	giant intestinal roundworm
DISEASE NAME:	ascariasis
DISTRIBUTION:	widespread especially in the tropics and subtropics
TRANSMISSION:	ingestion of eggs
LOCATION OF THE WORM IN A PERSON:	small intestine
CLINICAL FEATURES:	frequently without symptoms but may cause abdominal pain or discomfort and rarely intestinal obstruction
DIAGNOSIS:	passage of adult worms from the anus or finding eggs on microscopical examination of the stool
TREATMENT:	various anthelmintics such as mebendazole and pyrantel
PREVENTION:	avoid eating uncooked vegetables or ground-fruits that may have been grown in gardens contaminated with human faeces

Ancient man must have been well aware of, if not terrified by, the large motile creatures that he passed in his faeces from time to time. So impressive were these beasts that they were recorded in the writings of Egyptians, Greeks, Romans, and Chinese in the centuries before Christ. Furthermore, they recognized that there were two types of these worms, some round and some flattened. Thus Aulus Cornelius Celsus (*c*. 25 BC–AD *c*. 50), a Roman nobleman and writer of an encyclopaedia, wrote:

> Worms occasionally take possession of the bowel, and these are discharged at times from the lower bowels, or more nastily from the mouth; and we observe them sometimes to be flattened, which are the worse, at times to be rounded.[68]

The large rounded worms (Figure 1) were about 15–30 cm long and the Romans called them ‘lumbricus teres’ in view of their fancied resemblance to the common earthworm.

No-one paid much attention to the precise nature of these creatures. It was not until the late seventeenth century when an English doctor, Edward Tyson (p.16), described details of the anatomical structure of these worms and clearly distinguished them from

earthworms. What is more, he used a new-fangled magnifying instrument called a microscope and in 1683 described how he had found eggs in these worms. Tyson still called this worm ‘lumbricus teres’ and it was not until 1758 that the Swedish physician turned naturalist, Carolus Linnaeus (1707–1778), gave it the scientific name by which we still know it—*Ascaris lumbricoides*. The first (genus) name was a Greek word for a worm while the second (species) name means that it was like the ‘lumbricus’ of the Romans.

But the big question was: ‘Where do these worms come from?’ For many centuries it was generally believed that intestinal worms arose by a process of ‘spontaneous generation’. Belief in the spontaneous generation of animals and plants goes back to ancient times. How else could the sudden appearance of mushrooms after a heavy rain or the plagues of locusts or rodents in certain seasons be explained? Intestinal worms seemed excellent proof of this doctrine. It seemed impossible to account in any other way for the existence of such large organisms in the human intestine as they clearly had not been ingested as such.

These beliefs persisted from the ancients well into the Middle Ages. A famous Persian physician and philosopher named ibn Sina (known as Avicenna in the West, 980–1037) thought that with a proper mixing of the elements and under the influence of the stars, all animals and even man could be produced by spontaneous generation. In the sixteenth century, Paracelsus (1493–1541), a Swiss physician, botanist, alchemist, and astrologer, had similar fantastic ideas writing, ‘Many things will be changed in putrefaction so that they give birth to a noble fruit.’[239] Thus Paracelsus thought that worms were produced from putrefaction and a bird could be recreated from its own ashes in horse manure. Even the English doctor William Harvey (1578–1657), who discovered the circulation of the blood, was a prisoner of this idea and thought that worms arose spontaneously as a result of a special principle existing in putrid material.

Figure 1. Adult *Ascaris lumbricoides* about 20 cm long. Female on the bottom, male on the top.

Of course, all these notions were only theory and were utterly wrong. What was needed was a completely new approach. What was required was an *experiment* to prove or disprove the existence of spontaneous generation. The first to recognize this and do something about it was Francisco Redi (Figure 2), court physician to the Duke of Tuscany. Redi was born in Tuscany in Italy, was educated by the Jesuits, and graduated in medicine and philosophy from the University of Pisa. He was a great man of science and a brilliant investigator. For example, he was the first to experiment with snake venom, finding that it was innocuous by mouth but toxic when injected. He never married, was epileptic for the last nine years of his life, and died during a fit.

Redi thought it was possible that ‘worms’ were generated by insemination into putrefying matter, the latter merely serving as a suitable nest in which animals could deposit their eggs and in which the resultant offspring could find nourishment and grow.

First of all, Redi killed three snakes and put them in an open box to decay. Soon afterwards, he found that they were covered with maggots (which he called worms). Once all the meat had been consumed, however, the maggots all disappeared. In order to find out what had become of them, he repeated the experiment but this time, once the maggots had appeared, he covered all the exits from the box. He observed that some of the maggots became quiet, appeared to shrink and assumed a shape similar to an egg; we now call these structures pupae. There were pupae of different shapes so he separated them into their types and put them into glass containers covered with paper. After a week or so, he saw the pupae break open and flies came forth, the same kind of fly appearing from the same kind of pupa. So now he knew what happened to the maggoty worms. He repeated variations of this experiment many times and noticed that the meats became covered with eggs from which the maggots hatched. So he wrote in 1663:

Figure 2. Francisco Redi (1626–1697).

> Having considered these things, I began to believe that all the worms found in meat were derived from the droppings of flies, and not from the putrefaction of meat.[263]

This seemed especially likely because flies of the same kind as those that were bred had hovered over the meat before it became maggoty. But Redi made the crucial step, remarking that ‘Belief would be vain without the confirmation of experiment’.[263]

Thereupon Redi put a snake, some fish, some eels and a slice of veal from a milk-fed cow, each into separate, large, wide-mouthed flasks. Each flask was carefully sealed then a duplicate series was set up except that each flask was left open to the atmosphere. You can guess what happened. No maggots developed in the closed flasks whereas Redi saw flies go in and out of the open flasks and in them maggots appeared. So not only had Redi shown that maggots did not breed spontaneously in meat but he had traced the development of eggs through larval (the maggot) and pupal stages to adulthood. Even though he had designed and executed these wonderful series of innovative experiments, Redi had some mental blocks. He still thought that galls in plants and intestinal worms in humans probably arose by spontaneous generation through the agency of some vital force. How could he have been so muddled in his thinking on this important subject? Robert Bigelow, the translator into English of Redi’s books, surmised that ‘constant friendship with the Jesuits must have had a maleficent effect on (his) mind, as it exacted blind faith and put a limit to his logic’.[126]

Nevertheless, others gradually realized over the next century or two that Redi’s findings were generally applicable to all organisms although, as we shall see, the final death knell had to await the experiments of Louis Pasteur with bacteria in the middle of the nineteenth century. So, if worms such as *Ascaris* did not arise spontaneously in people, how did they get there?

Medical scientists began to pay more and more attention to eggs, especially what they looked like under the microscope. In 1849 in Moscow an investigator of natural history named George Gros obtained some eggs from an adult *Ascaris* worm,

moistened them and put them in an incubator at a temperature of about 15°C, then examined them periodically under a microscope. He noticed that things began to happen within each egg shell within 24 hours and there slowly assumed the shape of a coiled-up larva, although it took four months to reach a perfect state. These eggs were called embryonated eggs because they had an embryo or larva inside them.

Surely these embryonated eggs were infective? Ten years later in Paris, Casimir Davaine (p.197) took some of these eggs and put them in gastric (stomach) juice in a test tube to see whether the juice would destroy the egg shell and allow the larva to escape. Nothing happened! Not to be put off, Davaine then put some embryonated eggs into one fabric container and fresh, unembryonated eggs into another, then induced a dog to swallow them. Two days later, the fabric containers were recovered from the dog's faeces. On microscopic examination, he discovered that the unembryonated eggs were still there while in the other container, only a few free larvae could be found. He concluded that intestinal juices softened the egg shell so that if a larva was present within, it could pierce the wall and escape.

So it seemed easy; all you had to do was feed embryonated eggs to an animal and they would each hatch a larva in the intestine which would then develop into the big adult worms in the bowel. In 1861 Davaine gave 400 of these eggs to a cow. Four months later, there were absolutely no worms in the intestines. He then tried infecting a rat. This time he found that the eggs hatched larvae but they were expelled in the faeces within a day or two. What Davaine and his contemporaries did not know but which we now know is that this worm will only complete its development in humans. All other animals are resistant to infection with it, a phenomenon called 'natural immunity'. Why this should be, we still have little idea.

Thus everything was a big puzzle. Some investigators postulated that perhaps the eggs had to be taken up first by another animal, an intermediate host, in which they partly developed and then the animals harbouring these intermediate stage worms were eaten by people in whom they developed into the big adult worms. But all experiments were fruitless. This parasite did not seem to develop either partly or completely in the tissues or intestines of any other animal.

There seemed to be only one solution; give embryonated eggs to a human. In 1879, Battista Grassi (p.131), then a young medical practitioner who had been born in Lombardy, Italy, decided to undertake an experiment to settle the matter. On 30 August he ingested about 100 embryonated eggs. Twenty-two days later he triumphantly declared that he had found *Ascaris* eggs in his faeces, thus proving that direct infection had occurred. This perhaps seemed fair enough at the time, but in hindsight we know that something probably went wrong with the experiment because observations over the years were to show that it usually takes at least two to three months after ingestion of eggs for ova released by the newly developed adult worms to appear in the stool. Perhaps Grassi already had a low-level infection which he acquired naturally because it was common in his community. Or perhaps he mixed up his specimen with someone else's in the laboratory.

A few years later, Salvatore Calandruccio (1858–1908), a colleague of Grassi, repeated the experiment and swallowed a large number of embryonated eggs but failed to infect himself. However, he did have more success with a seven-year-old boy who

had been infected naturally and had been cured. Calandruccio gave the lad 150 eggs in a pill at the end of September 1886. He searched the stools assiduously for the next 20 days but found nothing and abandoned the search until the end of November, when he found the faeces to be packed with eggs. Following treatment with an anthelmintic (anti-worm drug) at the end of January, four months after infection, the boy expelled 143 worms, each about 20 cm in length. Grassi then published the results of this experiment without giving acknowledgement to Calandruccio. Calandruccio was furious. Scientists do not always behave properly towards each other!

But the point was made and it was becoming clear that *Ascaris* worms were not generated spontaneously but could be transmitted directly from person to person via eggs, provided the eggs had been left long enough in the external environment to become properly embryonated. The natural assumption was that a larva hatched from an egg in the intestine, stayed in the intestine and grew there into adult worms. This seemed to be supported by the earlier finding in 1872 by Arnold Heller (1840–1913) in Germany, during the autopsy of a madman, of 18 small worms between 2.75 and 13 mm in length in the small intestine. But assumptions can be wrong, and so was this one.

A clue was given in 1887 when Adolpho Lutz (1855–1950), a physician in São Paulo, Brazil, repeated Calandruccio's experiment. He gave 96 embryonated eggs to a 32-year-old woman over a period of one month. A few days later she developed severe bronchitis and a fever. When she was later given an anthelmintic, she passed 35 adult *Ascaris* worms. Did you spot the clue? Lutz didn't. It was the bronchitis the patient developed. Why that happened will become clear shortly.

You might also be wondering about the foolhardiness of parasitologists infecting themselves or others. You will find this is a recurrent theme in the study of infectious diseases. Even I have done it. But that is another story.

It was not until 1915 that the next stage in the saga unfolded. Francis Stewart (1879–1951) was a British doctor who had joined the Indian Medical Service. During World War I he was posted to Hong Kong. Perhaps to pass the time because there was no fighting in the region, he began to experiment with *Ascaris lumbricoides* and with *Ascaris suum*, a very similar worm which infects pigs. After a number of false starts he gave *A. lumbricoides* or *A. suum* embryonated eggs to some rats. One rat died and the rest seemed to have pneumonia so they too were killed and the lungs examined; they were teeming with larvae. The larvae had hatched from the eggs in the intestines and had apparently penetrated through the wall of the intestine, entered the blood vessels, and passed through the liver to the lungs, where they left the blood vessels and entered the airways and migrated upwards towards the mouth. Stewart found that these larvae were then swallowed and re-entered the intestinal tract. But instead of developing there into adult worms, the larvae passed right through the gut and were passed in the faeces. Neither *A. lumbricoides* nor *A. suum* was able to complete their development in rats so he could not follow and prove the whole cycle.

Clearly you could not perform similar experiments of feeding eggs to people then cutting them up to see what had happened. But what about *A. suum* and pigs? Stewart infected pigs with *A. suum* eggs but was only able to find intestinal worms on some occasions. With masterly understatement, he wrote in 1919 that these experiments

were very puzzling.

But help was at hand from two different Japanese parasitologists. In 1918, Sadao Yoshida (1878–1964) fed *A. lumbricoides* eggs to a guinea pig. He then recovered 50 larvae from the airways of the guinea pig then swallowed them himself; 75 days later he found eggs in his faeces. Thus, larvae recovered from the respiratory tract of another animal could develop into adult worms in the human bowel and there produce their own eggs. But did this mean that *Ascaris* eggs had to pass through an intermediate host before they could infect humans?

Final proof that this was not the case was provided in 1922 by the intrepid Shimesu Koino. On 28 August he ingested 2,000 *A. lumbricoides* eggs. A single larva was found in his sputum three days after infection, five on the next day, and 178 on the fifth day. He was unable to collect any sputum on the succeeding two days because he was seriously ill but larvae were then found on the following four days. Fifty days after ingestion of eggs, he took an anthelmintic and recovered 667 immature worms! Thus Koino had proven that *A. lumbricoides* larvae both migrate through the lungs and develop within the intestine of the same human host.

The life cycle was now clear and is illustrated in Figure 3. Infection occurs in areas where sanitation is poor and faeces are deposited on the ground. Transmission is particularly likely to happen when human faeces containing eggs are used as fertilizer in vegetable patches as happens in many poor rural areas. Finally, the warmer and moister the climate, the faster do eggs embryonate so that they are ready to infect the next person.

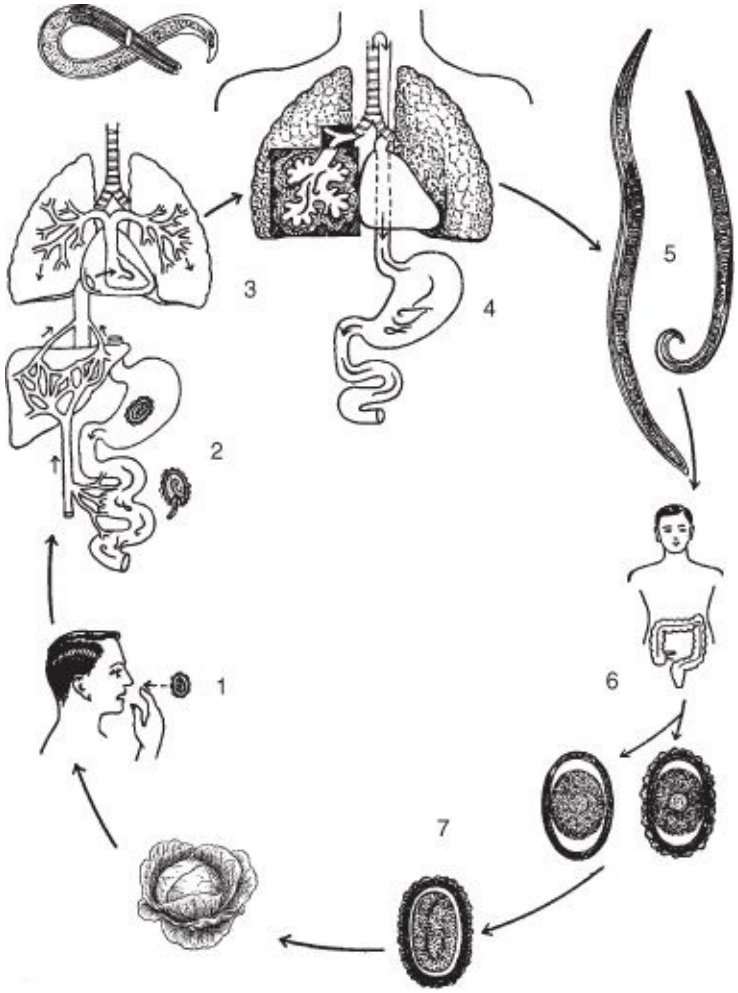

Figure 3. Life cycle of *Ascaris lumbricoides*. Infection begins when embryonated eggs are swallowed (1). The larvae hatch in the small intestine (2), penetrate the bowel wall, enter blood vessels, and are carried to the lungs (3). Here they leave the capillaries (small blood vessels) and enter the air spaces (alveoli), travel up the bronchi and trachea to the mouth where they are swallowed and return to the small intestine (4). There they grow over a couple of months and become adult worms (5) which eventually produce unembryonated eggs that are passed in the stools (6). Eggs deposited on the ground develop an infective larva within each one (7) over the next few weeks or months. Not to scale.

What do these worms actually do when they infect a person? All sorts of fanciful symptoms and signs were ascribed to this infection until late in the nineteenth century. Friedrich Küchenmeister, who we will meet in the next chapter, was closest to the truth when he wrote in his textbook in 1855 ‘as a general rule, the host and his guests agree very well together and give one another very little mutual trouble’.[172] Very heavy infections though can be quite serious. As we saw with Dr Koino, if very large numbers of eggs are ingested at much the same time, then there may be very severe inflammation of the lungs resembling pneumonia or bronchitis. We also know that