Biology, Systematics, Life Cycle, and Distribution of *Angiostrongylus cantonensis*, the Cause of Rat Lungworm Disease

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**Abstract**

*Angiostrongylus cantonensis* is a metastrongylid nematode in the family Angiostrongyliidae. It is the cause of angiostrongyliasis (rat lungworm disease), which manifests as eosinophilic meningitis. First described in 1935 from rats in China, A. cantonensis was placed in the genus Parastrongylus in 1986, but most workers have not adopted this treatment. The taxonomy of *A. cantonensis* and related worms is largely based on adult morphology, notably of the male bursa. However, identification of infective third stage larvae is more difficult. The natural life cycle involves rats as the definitive host and snails or slugs as the intermediate host. Human infection, as accidental hosts, results in worms maturing in the brain, but dying there instead of moving back into the bloodstream, as in rats, thereby leading to eosinophilic meningitis. The disease is an emerging infectious disease; *Angiostrongylus cantonensis* continues to be reported in new regions beyond its native range.

**Keywords**

Angiostrongyliasis, *Angiostrongylus cantonensis*, Emerging infectious disease, Eosinophilic meningitis, Parasitology, Rat lungworm disease, Slugs, Snails

**Introduction**

The parasitic nematode (roundworm) *Angiostrongylus cantonensis* (Chen, 1935) is responsible for the human disease known as angiostrongyliasis or rat lungworm disease, a major cause of eosinophilic meningitis (or meningoencephalitis), and with symptoms ranging from mild headache, through a range of inflammatory reactions, to coma and occasionally death. The severity probably being related to the number of worms present, their exact location, and the intensity of the host’s inflammatory reaction. It is an emerging infectious disease and it is important that understanding of all aspects of its biology, epidemiology, diagnosis, and treatment is increased and made more widely known. This short paper reviews key aspects of the basic biology, parasitology, and geographic spread of the causative agent, *Angiostrongylus cantonensis*, providing an avenue into the more detailed literature.

**Systematics**

**Classification and Diversity**

*Angiostrongylus cantonensis* is a nematode (phylum Nematoda) in the superfamily Metastrongylcoidea and family Angiostrongylidae. The systematics of the Angiostrongylidae is not well understood, with many species inadequately described and probably others not yet recognized, a situation that has advanced but little since Anderson expressed the hope over 30 years ago that this might improve. There are around 20 species in the genus *Angiostrongylus* globally. Two of these cause disease in humans: *Angiostrongylus costaricensis* Morera & Céspedes, 1971, which causes abdominal angiostrongyliasis, and which is a problem especially in South and Central America, and *Angiostrongylus cantonensis* (Chen, 1935), which causes eosinophilic meningitis, is spreading rapidly to many parts of the world, and is the subject of this paper.

*Angiostrongylus cantonensis* was first described from rats in China by Chen in 1935 and placed in the genus *Pulmonema*, as *Pulmonema cantonensis*. The same species was also described a short time later in 1937 as *Haemopotastrongylus ratti* by Yokogawa, who did not realize that it was the same species that had been described already by Chen. The genus *Pulmonema* was subsequently synonymized with *Angiostrongylus* and the species name *ratti* was synonymized with *cantonensis*. These nomenclatural changes were widely accepted so that the most common and widely used name for the species became *Angiostrongylus cantonensis*.

However, in 1986, Ubelaker split the genus *Angiostrongylus* into five genera, based largely on their anatomy, assigning species to each of the genera, based on morphology but also on the definitive host, as follows: *Angiostrongylus* (found in carnivores, eg, dogs, foxes, cats), *Parastrongylus* (murids, eg, mice and rats), *Angiocaulus* (mustelids, eg, martens), *Gallegostrongylus* (gerbils and one murid), *Stefanskostrongylus* (insectivores, eg, shrews, tenrecs, etc.). *Angiostrongylus cantonensis*, the definitive host of which is rats, was thus transferred to the genus *Parastrongylus*, becoming *Parastrongylus cantonensis*. However, although occasionally used, this classification has not been widely adopted and the species continues to be referred to most widely as *Angiostrongylus cantonensis*.

**Morphology and Identification**

*Angiostrongylus* larvae are roundworms (nematodes) with thin cylindrical bodies. Research has focused primarily on *Angiostrongylus cantonensis* and species closely related to it. *Angiostrongylus cantonensis* and *A. mackerrasae* (which was misidentified as *A. cantonensis* by Mackerras and Sandars in their detailed study) are extremely similar in size and anatomy, and the following data of Mackerras and Sandars for *A. mackerrasae* refer equally to *A. cantonensis*. First stage larvae are about 0.3 mm long and 0.015 mm in width; second stage larvae are about 0.45 by 0.03 mm; third stage larvae are similar in size, though a little thinner; fourth stage larvae reach about 1.0 by 0.4 mm. The newly molted sub-adults are about 2 mm by 0.06 mm; they grow to about 12 mm (females) and 11 mm (males) before leaving the rat’s brain and migrating to the pulmonary arteries (see the life cycle section, below), where they mature, reaching a size of up to about 35 by 0.6 mm (females) and 25 by 0.4 mm (males). A number of publications have provided good descriptions of *A. cantonensis*. 

**HAWAI'I JOURNAL OF MEDICINE & PUBLIC HEALTH, JUNE 2013, VOL 72, NO 6, SUPPLEMENT 2**
Genera and subgenera of Angiostrongylidae can be distinguished based on the appearance of the adult male caudal bursa, the apparatus used to clasp the female during mating. However, species of Angiostrongylus have rather few characters that serve to distinguish them and they are therefore difficult to identify. Nonetheless, adult males can be distinguished and identified based again on the appearance of the caudal bursa, although there is some intraspecific geographic variation in this structure. Third stage larvae can be distinguished from closely related species based on the appearance of the tip of the tail.

Life Cycle
The most detailed accounts of the life cycle of an Angiostrongylus species are those of Mackerras & Sandars for A. mackerrasae (which was not distinguished from A. cantonensis at the time). The life cycle of A. cantonensis is essentially the same and is summarized here (Figure 1). First stage larval worms are expelled in the feces of rats (the definitive host). Various species of rats can act as hosts. These infected feces are ingested by snails or slugs (intermediate hosts), but it may also be possible that the larvae enter the snail by penetrating the body wall or via the respiratory pore. Many species of snails and slugs can act as intermediate hosts. The larvae develop to the third larval stage in the snails, remaining at that stage until either the snail is eaten or dies. Once snails carrying third stage larvae are eaten by a rat, they move through the rat gut to the small intestine. They then penetrate the walls of the intestine and enter the blood stream. They then travel passively in the blood stream, a proportion of them eventually entering the central nervous system and reaching the brain. Once in the brain the larvae develop to the sub-adult stage. Light infections appear to cause little damage to the brain and no obvious behavioral or other reaction, but heavy infections may cause more serious damage as well as behavioral symptoms.

Having reached the sub-adult stage the worms leave the brain, passing into the venous circulatory system, and thence to the right ventricle of the heart and to the pulmonary arteries. Here the worms grow and mature, mate, and the females lay eggs. The eggs travel in the blood stream to the lungs (hence the name rat lungworm disease). The eggs hatch into first stage larvae in the tissue of the lungs. Depending on the level of infection, the rat may suffer significant damage to the arteries, caused by the bulk of the adult worms, and to the lungs, caused by inflammatory reactions to the larvae. These first stage larvae then break through the walls of the bronchioles and alveoli, move up the trachea in respiratory secretions, and are swallowed, to be released in the feces. The cycle then repeats when snails ingest these infected feces. Assuming the rat eats the infected snail as soon as the larvae in the snail reach the third stage, the cycle takes about 45 days.

Human Infection
Humans (accidental host) become infected primarily in the same way that rats do, by ingesting snails or slugs infected with third stage larvae either deliberately or accidentally. Larval development (Figure 2) follows the same course as in rats, up to the point at which the larvae reach the sub-adult stage in the person’s brain. Most of these worms are then unable to re-enter the circulatory system and after moving around within brain tissue they die. Neurological damage appears to be caused both by the physical damage caused by the movement of the worms in the brain and by the inflammation caused by the immune reaction to the worms, which seems to be a more intense reaction to
Figure 2. The truncated life-cycle of Angiostrongylus cantonensis, the rat lungworm, in an accidental (human) host.

the dead than to the live worms.\textsuperscript{22,30,31} Some worms apparently do find their way to the pulmonary artery and lungs, but do not reproduce.\textsuperscript{22,25,32} Worms have also appeared in the eyes.\textsuperscript{2,33,34} Other animals have also been shown to be susceptible to infection as accidental hosts.\textsuperscript{16,35-37} Humans can also be infected by ingesting paratenic hosts, which are hosts in which A. cantonensis larvae cannot develop but remain alive for some time.\textsuperscript{19,38,39} Paratenic hosts, which include a range of other animals (eg, freshwater shrimp, frogs, flatworms), become infected by eating infected intermediate hosts. If the intermediate hosts contain third stage larvae, these can then be passed to the person, in whom they develop and eventually die, as above.

Distribution of Angiostrongylus cantonensis

Angiostrongylus cantonensis was described from southern China in 1935.\textsuperscript{12} It was reported from Taiwan in 1937 and subsequently from other parts of Southeast Asia (Thailand, Malaysia).\textsuperscript{2} It probably originated somewhere in this region. Also by the 1960s, it had been reported from numerous Pacific islands,\textsuperscript{2,40} including New Caledonia, Vanuatu, Fiji, Guam, Saipan, Chuk, Pohnpei, Marshall Islands, Tahiti, Cook Islands, and Hawai‘i. Reports of cases of eosinophilic meningitis in many of these islands probably reflected the spread of A. cantonensis.\textsuperscript{1,2} It seemed to be confined to the tropics. Subsequently, it has been recorded widely,\textsuperscript{41} including in Okinawa\textsuperscript{42} and mainland Japan,\textsuperscript{43} Papua New Guinea,\textsuperscript{30} American Samoa,\textsuperscript{4} Indonesia,\textsuperscript{3} the Philippines,\textsuperscript{30} Australia,\textsuperscript{24} Sri Lanka,\textsuperscript{33,30} India,\textsuperscript{34,30} Réunion,\textsuperscript{26} Mauritius,\textsuperscript{30} Ivory Coast,\textsuperscript{26} Egypt,\textsuperscript{44} South Africa,\textsuperscript{45} Madagascar,\textsuperscript{30} Cuba,\textsuperscript{46} Jamaica,\textsuperscript{6} Puerto Rico,\textsuperscript{30} Haiti,\textsuperscript{47} Dominican Republic,\textsuperscript{48} Ecuador,\textsuperscript{49} Brazil,\textsuperscript{10,23} the Canary Islands,\textsuperscript{17} and the southeastern USA;\textsuperscript{16,50} the list may not be comprehensive. It has the potential to expand its range beyond the tropics, facilitated by climate change, as shown in China.\textsuperscript{28} There are increasing numbers of cases recorded in locations where A. cantonensis is not present (eg, various European countries and northern USA), mostly in people returning from regions where it is present.\textsuperscript{6,41-53} The rapid spread of the giant African land snail, Achatina fulica (sometimes referred to as Lissachatina fulica), has been suggested as a key factor in the spread of A. cantonensis, first across the Pacific and then to other regions of the world,\textsuperscript{54} but this hypothesis is not well supported.\textsuperscript{24,55} Achatina fulica is a good host of A. cantonensis,\textsuperscript{27,28} and in areas where it has invaded it has become abundant in urban and other anthropogenic habitats where people readily come into contact with it.\textsuperscript{36} But other invasive snail species are also good hosts,\textsuperscript{27,28} for instance, the semi-slug Parmarion martensi, which is abundant in some residential areas on the island of Hawai‘i.\textsuperscript{57} However, the spread of rats may be more important in spreading A. cantonensis, especially to areas to which A. fulica, P. martensi, and other good intermediate hosts are not present, such as Jamaica and the Canary Islands,\textsuperscript{24} and the diversity of possible intermediate snail and slug hosts facilitates this.\textsuperscript{58} The pathways for the spread of A. cantonensis are complex.

Conclusion

While the systematics of Angiostrongylidae is in need of detailed study, the complex life cycle of Angiostrongylus cantonensis is relatively well understood. The parasite is spreading widely around the world, resulting in cases of angiostrongyliasis in places where it had not previously been recorded, facilitated by ease of global travel, globalization of commerce, and climate change.

Conflict of Interest

The author identifies no conflict of interest.
Acknowledgements
This paper represents a contribution to the Rat Lungworm Disease Scientific Workshop held at the Ala Moana Hotel, Honolulu, Hawai‘i in August 2011. Funding for the workshop and for this publication was provided by the National Institute of Food and Agriculture, United States Department of Agriculture, through Award No. 2011-65213-29594. I thank Carlos Graeff-Teixeira and Ralph Robinson for valuable comments on a draft of this paper. The following provided photographs: David Preston, the snail in Figure 1; Ken Hayes, the semi-slug in Figure 2; Carlos Graeff-Teixeira, the adult female worm and the histological section in Figure 1; Alessandra Morassutti, the sub-adult worm in Figure 2.

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