SUMMARY
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*Oesophagostomum* spp. are common nematode parasites of sheep, goats, cattle, and also of monkeys. Infection with this parasite can cause serious gastro-intestinal symptoms, which may lead to death. Since the beginning of this century, the parasite has also been described in humans on several occasions. Human infection with *Oesophagostomum* has always been considered as a zoonosis, an accidental infection of man with an animal parasite. It was assumed that its life-cycle was not completed in this unsuitable host.

One of the first descriptions of human oesophagostomiasis was published in 1910, concerning a case originating in Brazil. In Indonesia and Malaysia also, the disease has been described, but most cases were seen in Africa. The first reports originated in Ethiopia (1905) and Nigeria (1911), followed by several reports from West-, Central and East-Africa. From 1980 on, Baeta and Gigase observed a large concentration of cases in the region of northern Togo and Ghana. Although human infection with *Oesophagostomum* had always been considered as a zoonosis, the large number of cases suggested that man could be more than an accidental host in these regions [Chapter 1].

The observations of Baeta and Gigase on human oesophagostomiasis finally led to the establishment of a broad research project in northern Togo and Ghana. In this thesis, several aspects of this research project are described.

The life cycle of *Oesophagostomum* has been studied in detail in several domestic animals, especially sheep and cattle. Adult worms, measuring about 1.5 cm, live in the intestinal lumen of the host. Here, they produce eggs that leave the host with the stools. Outside the host, in a warm and moist environment, these eggs develop into first-stage (L1) larvae that subsequently leave the egg-shell, and molt several times until the L3-stage is reached. The L3-larvae are infectious and are ingested by the host through grazing. Inside the host, the L3-larve penetrate the intestinal wall where they are encapsulated in the serosa of the intestines, or sometimes even in the omentum. In these tumour-like nodules, the larvae develop into L4-, L5- and finally the young adult stages that re-enter the intestinal lumen. There, they grow into adult worms and start producing eggs. The clinical symptoms are caused mainly by the nodules in the intestinal wall, which may be painful. They can also form a large conglomeration of nodules that may rupture into the peritoneal cavity, with sometimes fatal consequences. It is likely, though not proven, that the life cycle of *Oesophagostomum* species in man is similar.

The start of the research project was established with a number of questions in mind. The most important of these, mentioned in the introduction, are discussed below.
1. How can infection with Oesophagostomum be recognized?
Most nematode infections can be diagnosed by finding the eggs in the faeces. *Oesophagostomum* eggs, however, are morphologically identical to those of hookworm, an extremely common parasite of humans in Africa. In contrast, if the faeces is cultured under favourable conditions, the eggs develop into L3-larvae of *Oesophagostomum* or hookworm, that can be easily distinguished from each other (charcoal coproculture method). Using this method, a large number of stool samples was investigated. L3-larvae of *Oesophagostomum* could be cultured from human stool samples, indicating that in man too, *Oesophagostomum* parasites were able to complete the life cycle, and grow into adult, egg-producing worms [Chapter 2].

The sensitivity of the coproculture method for the diagnosis of infection with *Oesophagostomum* is fair (ca 80%). The sensitivity can be increased by performing the coproculture method in triplicate. There is a clear relation between the larval count and the worm burden, so that the number of *Oesophagostomum*-larvae cultured gives an impression of the intensity of infection (semi-quantitative interpretation). Coproculture is a simple, effective and cheap method of diagnosing *Oesophagostomum* infection, suitable for individual cases as well as on a large scale basis in research projects [Chapter 8].

An entirely different method is serological diagnosis. This method examines the presence of specific antibodies against *Oesophagostomum* in human serum samples. In 58 children and adults from Togo, and 89 controls, the presence of specific antibodies (IgG4) was investigated. The specificity of this method was very high (>95%), while the sensitivity was high in adults (86%) but less so in children. A clear advantage of this method is that serum samples can be collected and frozen, to be processed at a later stage, while stool cultures have to be performed immediately. For this reason, serological diagnosis is an effective method for screening a population for the presence of the infection. A disadvantage is the need for sophisticated equipment [Chapter 7].

2. What is the *Oesophagostomum* species involved?
The detection of *Oesophagostomum* L3-larvae in stool cultures showed that humans were infected with one of the *Oesophagostomum* species. A species identification, however, is possible exclusively by a detailed description of the adults worms. The adult specimens, obtained after anthelmintic treatment, showed most similarity with *O. bifurcum*, a common parasite of monkeys. The *Oesophagostomum* species infecting humans in the region of northern Togo and Ghana is therefore identified as *O. bifurcum* [Chapter 5]. The egg production is estimated at 5 000 eggs per day [Chapter 4].
3. What is the prevalence of Oesophagostomum infection in the research area?
To examine the occurrence of infection with Oesophagostomum in northern Togo and Ghana, numerous villages were visited. Of the 43 villages visited, the infection was found in 38. High prevalences (up to 60%) were noted especially in the smaller, isolated villages. A total of 3820 stool samples were collected and examined, and Oesophagostomum larvae could be cultured in 1057 cases (27.6%). Children under five were less often infected than older persons (Togo: 10% vs 31%; Ghana: 1% vs 15%). In persons of five years and older, women were more often infected than men (Togo: 35% vs 28%; Ghana: 18% vs 12%) [Chapter 3]. These differences cannot yet be explained satisfactorily. Do women have a higher risk of exposure, possibly because their daily duties in the household or on the field bring them into closer contact with the (unknown) source of infection? Or are there other factors, like immunological or genetic differences, that have an influence on the infection rates? A detailed study on the daily habits, social activities and duties of men, women and children would be necessary to answer these questions.

4. Does infection with O. bifurcum occur exclusively in northern Togo and Ghana? If so, what are the reasons for this? If not, why is the disease not recognized elsewhere?
Although the occurrence of Oesophagostomum infection in other parts of the world has not been investigated systematically, the case-reports from South-America, Asia and Africa suggest that the infection might be more widespread than currently thought. Clinical manifestations of human oesophagostomiasis can be confused with an acute appendicitis, colonic carcinoma or bowel obstruction, and it is quite well possible that the disease is just not recognized in other areas. On the other hand, among 30,000 biopsy specimens from Africa that have been investigated at the Tropical Institute of Antwerp, Oesophagostomum has been diagnosed exclusively in the specimens originating from the research area. To estimate the occurrence of Oesophagostomum outside the research area, a systematic study, focused on asymptomatic infections as well as the clinical manifestations of Oesophagostomum infection, is necessary.

5. How is the infection transmitted? What are the factors promoting an efficient transmission, and how can infection be avoided?
In animals, transmission of Oesophagostomum spp. occurs mostly through the oral route. Would transmission of O. bifurcum in humans be similar? Infectious L3-larvae of O. bifurcum were not able to penetrate the human skin, which makes percutaneous transmission improbable. Oral transmission, on the other hand, would seem possible since the L3-larvae are able to survive an acid environment (pH=2), a prerequisite for passing the stomach. Ingestion of the L3-larvae could occur through the ingestion of contaminated food or polluted water. The latter possibility is supported by the observation that L3-larvae are able to survive for months when they are submerged in water [Chapter 10]. We were not
able to demonstrate the presence of L3-larvae of *Oesophagostomum* in drinking water, but L3-larvae could be detected on some fruits that are eaten raw. This suggests that oral transmission is a possibility - not that it actually takes place. To find hard evidence for oral transmission, experimental infection of animal models would seem the most appropriate approach.

Transmission of *Oesophagostomum* infection occurs almost exclusively in the rainy season, when the L3-larvae are most vital. In the dry season the larvae become desiccated and lose their activity. However, they revive when water is added, even after several months of drought. This way, infectious larvae would be able to survive the hazardous dry season, and become active, and possibly infective again in the rainy season.

There is one other mechanism that could possibly increase the efficiency of transmission. During their development into adult worms in the host, some animal nematodes are capable of entering a dormant phase. This temporary interruption of the development usually takes place in the season when the chances of survival of the eggs and larvae are lowest. Completion of the life cycle occurs when the survival conditions become more favourable. This phenomenon, called 'Arrested Larval Development' increases the chances of transmission. There are indications that *O. bifurcum* is also capable of Arrested Larval Development [Chapter 9].

6. **Like in many other parasite infections, infection with O. bifurcum does not necessarily lead to disease. On the other hand, clinical oesophagostomiasis is sometimes difficult to confirm with parasitological tests. What is the relation between *Oesophagostomum* infection and disease?**

The series of Gigase et al. and of Haaf & van Soest showed that clinical manifestations of human oesophagostomiasis are very common in northern Togo and Ghana. However, the number of cases presented in these publications is quite small compared with the high prevalence of *O. bifurcum* infection in this region. To obtain an impression of an important manifestation of human oesophagostomiasis, the 'Tumeur de Dapaong', approximately 300 schoolchildren were followed for one year. In spite of a high prevalence of *Oesophagostomum* infection (58-66%), only a few had a 'Tumeur de Dapaong'. Of these, coproculture was not always positive for *Oesophagostomum*. Thus, infection and disease do not always go together [Chapter 10]. There are no reliable data on the prevalence of specific symptoms in other age groups. The number of patients presenting at the outpatient clinic with an acute abdomen or bowel obstruction can only give a superficial impression of the real prevalence. To estimate the incidence of specific symptoms, it is necessary to perform a cohort study in which a large, representative research population is followed clinically as well as parasitologically.
7. What are the possibilities for treating Oesophagostomum infection and disease?

Prior to this study, there were no data concerning the treatment of *O. bifurcum* infection. Therefore, several anthelmintics were tried among which albendazole proved to be most effective [Chapter 6]. When treated in the dry season, most subjects remain free of the infection until the rainy season, when reinfection quickly occurs. After treatment in the rainy season, many subjects become reinfected within several months [Chapter 9]. Treatment of symptomatic, clinically manifest cases could not be investigated systematically. Most patients with a 'Tumeur de Dapaong' are treated successfully with anti-inflammatory drugs, sometimes accompanied by antibiotics. Complications like intestinal perforation or bowel obstruction are always treated surgically.

**Conclusion**

Although human *Oesophagostomum* infection has always been considered as a zoonosis, *Oesophagostomum bifurcum* appears to be a highly common parasite of man in the region of northern Togo and Ghana. In this research project, several aspects of the epidemiology, taxonomy, treatment and life cycle have been studied. Since the infection can have serious, and sometimes fatal consequences, it is essential that the research on this 'new' parasite of man will be continued.