CHAPTER 1

General Introduction
Multinodular disease

Juvenile L4/L5 develop in colonic wall nodules

Ingested?

Characteristic L3, 830μm in length, develop on ground in 7 days given moist environment

Life cycle of Oesophagostomum bifurcum

Egg laying adult worms 12 mm in length inhabit colonic lumen

Eggs, 65μm in length and morphologically identical to hookworm, are passed in stool
INTRODUCTION

*Oesophagostomum species* are nematodes in the Strongyloides family, deriving their genus name from the characteristic shape of the adult stage head: there is a secretory pore (stomum) clearly visible in the cephalic groove near the proximal gut \(^1\) (Figure 1).

*Oesophagostomum spp.* have as their definitive hosts a wide array of animals, including domestic animals and primates, and are found extensively throughout the world. They have a simple, direct life cycle \(^5\)\(^-\)\(^32\). Adult worms inhabiting the intestinal lumen produce eggs which are passed with the stool. On the ground, given a warm and moist environment \(^33\), the eggs develop through 1\(^st\) and 2\(^nd\) stage larvae to 3\(^rd\) stage (L3) in the space of a few days. L3 can migrate away from the faeces \(^34\), and are ingested by the definitive host. L4 develop within intestinal wall nodules, re-entering the lumen to become egg producing adults.

This cycle is usually completed in less than 2 months, but in some species, the histotropic stages of the helminth may enter an ‘arrested phase’, allowing the parasite to release its eggs during a season favouring transmission \(^35\)\(^-\)\(^38\). Some species have biphasic tissue dwelling stages, firstly in the small intestine and then in the colon \(^39\).

HUMAN *O. BIFURCUM* INFECTION

Human involvement with Oesophagostomum was suspected to be zoonotic in nature from primates infected with various species of Oesophagostomum \(^40\)\(^-\)\(^42\), resulting in the assumption that humans could not be a definitive host. Responding to the observation that many human case reports of Oesophagostomum induced disease emanated from northern Ghana and Togo, Polderman and Gigase discovered, in 1986, that *Oesophagostomum spp.* can complete its life cycle in the human intestinal tract resulting in egg release \(^43\). Blotkamp *et al* identified the species to be *O. bifurcum* \(^44\), but within northern Ghana and Togo despite primate infection with this species, the monkey
population is too small to provide a reservoir for a human infection of such prevalence. Combined, these observations suggested human to human transmission. The actual mode of transmission remains unknown, although pigs are able to act as transport hosts and L3 are able to withstand desiccation for long periods of time. It is not known whether *O. bifurcum* has an arrested larval development stage.

![Map illustrating O. bifurcum endemic area in northern Ghana and Togo](image)

**Figure 2**: Map illustrating *O. bifurcum* endemic area in northern Ghana and Togo and villages referred to in subsequent chapters.

*Oesophagostomum bifurcum* infection is highly endemic within northern Ghana and Togo (Figure 2), with an estimated 250,000 people infected and more than 1 million at risk. The distribution of the parasite within this area is highly focal, as is the distribution of the parasite load within a community, children and women being most frequently and heavily infected. Transmission predominantly occurs during the rainy
season, but eggs continue to be excreted throughout the dry season, although with reduced intensity \(^5\). The mean daily egg production per adult female worm has been estimated at 5000, which is in keeping with other strongyle helminths \(^2\).

Diagnosis of *O. bifurcum* infection can be established using stool cultures \(^4\), a fastidious test with a 7 day delay to allow for development of eggs into the L3 stage (Appendix 1). Stool cultures rather than simple smear techniques are necessary due to the morphological similarity of hookworm and *O. bifurcum* eggs, both strongyle in appearance \(^4\). A positive stool culture result for *O. bifurcum* presumably indicates that tissue-dwelling juveniles have smoothly developed into lumen dwelling egg-laying adults. An ELISA diagnostic test based on the detection of specific IgG\(_4\) has also been described for *O. bifurcum* diagnosis \(^5\), although its use has been hampered by technical difficulties.

**HUMAN OESOPHAGOSTOMIASIS**

Various species of *Oesophagostomum* have been reported from clinical cases of human oesophagostomiasis, including *O. bifurcum*, *O. aculeatum*, *O. stephanostomum*, *O. apiostomum*, and *O. brumpti*, but confusion has been rife as to the exact classification of these worms. Changes in taxonomy \(^5\) now dictate that in West Africa, *O. bifurcum* is most common, whereas *O. stephanostomum* and *O. aculeatum* are the prevalent species in East Africa and Asia respectively.

Before the late 1980s, there were 61 cases of oesophagostomiasis reported from northern Ghana and Togo, 22 of them confirmed by worm identification and classified as *O. bifurcum* \(^15\), (Appendix 2). The importance of oesophagostomiasis within this area is suggested by the fact that several of the affected ethnic groups have names for the disease in their languages, and instantly recognise the condition when it is described to them: 'Turtle in the belly'.

53 reports of the disease have been published from many other areas of the world, including Ivory Coast \(^5\), Guinea \(^6\), Kenya \(^6\), Uganda \(^20\), Sudan \(^6\), Ethiopia \(^6\).
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Zimbabwe, Brazil, Indonesia, Brunei and Malaysia (Appendix 2). Nothing is known of the endemic situation in these places, although there have been two reliable reports of adult Oesophagostomum worms being found in the stool of Nigerians. On eleven occasions, the patients were Europeans or North Americans with a travel history.

![Figure 4: Pathology specimens of the multi-nodular presentation and Dapaong tumour. Approx real life size.](image)

Examination of these reports highlights two apparently distinct clinical disease entities. The presentations are not related to the species of oesophagostomum involved.

A multi-nodular presentation comprises hundreds of pea-sized, pus-filled, worm-containing nodules in the thickened, oedematous submucosa and subserosa of the colonic wall, but seems to have no distinctive clinical findings. Physiological dysfunction leading to persistent diarrhoea and severe weight loss can develop. The mucosa generally remains intact but rectal bleeding has been reported. Surgical emergency can result from luminal narrowing of the colon, or bowel obstruction secondary to inflammatory adhesions.

A uni-nodular presentation, entitled ‘Tumeur de Dapaong’ by the Togolese surgeon Baeta in 1986, presents as a pus-filled, worm-containing, granulomatous mass in the abdominal wall or within the abdominal cavity. Cutaneous abscesses and fistulas, peritonitis secondary to nodule rupture, bowel obstruction secondary to inflammatory adhesions, incarcerated inguinal hernia, and volvulus can occur. One case describes a cutaneous nodule in the midline of the back.
at the level of the 6<sup>th</sup> thoracic vertebrae containing *Oesophagostomum species*.

**DIAGNOSIS AND TREATMENT**

Diagnosis of oesophagostomiasis has been problematic in the majority of case reports, rarely being made before exploratory laparotomy or a pathology report (Figure 4): the clinical symptoms and signs are also commonly induced by other pathology, making diagnosis by history and clinical examination alone infeasible. Oesophagostomiasis often presented with findings indistinguishable from appendicitis. Appendicular abscess, desmoid tumours, actinomycosis, amoebiasis, schistosomiasis, abdominal ileocaecal tuberculosis, diverticular disease, inflammatory bowel disease or cancer, along with the many causes of acute abdomen, may also be mimicked. When the disease presented as acute abdomen with guarding, physical examination was rendered even less conclusive, necessitating blind emergency exploratory laparotomy. Even during surgery, without prior awareness of the appearance, oesophagostomiasis could easily be mistaken for cancer, non-specific inflammatory abscess or abdominal tuberculosis. Stool cultures, whilst useful for identification of *O. bifurcum* infection, detect the presence of lumen-dwelling egg-laying adult worms, and hence are conceptually inappropriate and unreliable for detection of the tissue-living juvenile stages of the parasite.

The treatment of oesophagostomiasis described in the literature was always surgical, although it has been stated that some cases of Dapaong Tumour will spontaneously regress if left untreated. Albendazole has been shown to be the most effective anthelmintic for removal of the lumen dwelling adult worms, giving cure rates of 100% after 1 month following treatment at the start of the dry season. Albendazole is a benzimidazole derivative related to mebendazole, but has the advantage of greater
absorption after oral administration\textsuperscript{95} and a wider spectrum of activity\textsuperscript{96-100}. It acts principally by interfering with the polymerisation of tubulin, needed for the production of helminthic microtubules\textsuperscript{101-103}. As well as causing worm death, it has an ovicidal action preventing egg production\textsuperscript{99}. Side effects are only seen with long term treatment, but may include nausea, rash, reversible alopecia, neutropenia and altered liver function tests\textsuperscript{104}.

For the last 10 years, doctors at the Baptist Medical Centre in Nalerigu (see following section) have periodically diagnosed cases of oesophagostomiasis on clinical grounds, and were particularly comfortable with cases where a Dapaong tumour presented adhered to the abdominal wall. Incision and drainage through the skin or albendazole (200/400mg stat dose) with amoxycillin (5 days of 250mg twice daily) were used for non acute cases of abdominal wall tumour. In order to elucidate the differential diagnosis, exploratory laparotomy was needed for both multi-nodular cases and uni-nodular cases not adhered to the abdominal wall, treatment being surgical removal of the affected bowel section (colectomy) or unroofing of the nodule. Appendix 3 gives the detailed clinical working description and management of oesophagostomiasis used at BMC.

Indigenous healers and medicine men have devised a technique for removing the ‘evil’ from a Dapaong tumour. Several superficial skin incisions are made over the area of the mass (Figure 5), after which a small earthenware pot full of black paste containing various herbs is placed over the wounds and vigorously shaken for several minutes. The ‘poison’ thus drawn out, resolution can occur. Numerous radiating skin incisions surrounding the umbilicus are sometimes administered for peri-umbilical pain caused by a Dapaong tumour (Figure 6).
NALERIGU HOSPITAL IN NORTHERN GHANA

Northern Ghana is situated at approximately 10 degrees north of the equator and 0 degrees longitude, and consists of rolling Savannah grassland. A rainy season from May until October delivers most of the 800 to 1000 mm of rain, and the eerie, dry, sand-laden Harmattan winds blow in from the Sahara Desert in January and February. The temperature varies between 20 degrees centigrade in August-September to 40 in February, and the humidity, close to 100% during the rains, falls to around 30% during the Harmattan.

The Baptist Medical Centre (BMC), a Christian Mission hospital, is located in the Nalerigu-Sakogu Subdistrict of the East Mamprusi District, in the Northern Region of Ghana, 103 miles (165 km) northeast of Tamale, 68 miles (109 km) southeast of Bolgatanga, and 36 miles (58 km) from the Togo border. Approximately 30,000 patients present to the BMC out patient department (OPD) each year, and some 2000 major surgeries are performed. 40% of OPD presentations are given a diagnosis of malaria, and other common conditions include diarrhoeal diseases, upper and lower respiratory tract infections, gynaecological disorders and skin conditions. Since 1998, whilst remaining a Mission hospital, BMC has been incorporated into the Health Care System of the Ministry of Health, working together with the government health posts in Langbinsi, Gambaga, Sakogu, Nakpanduri, Nasuan, Garu, Bimbugu, Binde, and Bunkpurugu. BMC is the only hospital in East Mamprusi District, which has an estimated population of 250,000, but patients from other parts of the Northern Region, the Upper East and Upper West Regions, and southern Ghana, as well as patients from Togo attend for treatment. There are also hospitals in Tamale, Bolgatanga, Bawku and Dapaong. The official BMC catchment area for its Public Health role includes 45 communities with an estimated population of 35,000 people.

The majority of the population in this area inhabit villages comprising 50 or so compounds each surrounded by part of the owner's farmland. The compounds, incorporating between 5 and 10 clay huts, are positioned in a circle and joined by a connecting wall, forming a central courtyard which is used for drying foodstuffs. The main compound entrance passes between a further 2 - 4 huts used for housing animals (sheep, goats, pigs, cows, Guinea fowls, doves and chickens), and an adjacent area in front of the compound is employed for socializing and playing. Domestic animals, tied throughout the rainy season but free to roam during the dry season, form an important status symbol, and are used for food on special occasions. They are highly parasitized.
but veterinary care is haphazard and poorly accepted. Most people are subsistence farmers with little formal education: the illiteracy rate is about 90%. There are schools in 10 of the BMC catchment area communities, many of the schools having only one teacher. BMC is the largest employer in the area.

Most of the communities obtain water from streams and hand-dug wells, and in the dry season, they dig holes in the dry river beds. In 1994, the Ghana Baptist Mission completed a well-drilling program in which 38 boreholes were installed within the District, but only a third of these remain operational, due to the lack of spare parts and a loss of interest from the communities. The staple diet, based on maize and millet, is remarkably uniform within northern Ghana, although rice is occasionally consumed. Sauces are made from tomatoes, onions, dried fresh-water fish and hot peppers, together with ground nut paste, alayfu (spinach) and okru. The land has been over-farmed, necessitating the use of chemical fertilizers.

In Nalerigu, with a population of approximately 11,000 people, 40 individual landlords have installed pit latrines in their homes, and there are 3 public toilets, one of which is well maintained. In the remaining 44 communities under BMC, there are 15 pit latrines. The majority of people therefore resort to ‘free-ranging’ in the fields between the compounds.

Nalerigu was finally hooked to the national electricity grid in November 1998. Previous to this, BMC generated its own power supply from diesel generators located on the hospital compound. Telephone calls are sometimes possible from the District Capital of Gambaga, 5 miles from the hospital. The East Mamprusi roads, when existent, are in extremely poor condition, often being destroyed during the rainy season. Further details about Ghana are contained in Appendix 4.

THE PROJECT

The oesophagostomum research project in West Africa commenced in 1986, with the discovery by Ton Polderman, Paul Gigase and Coby Blotkamp that humans were definitive hosts for *O. bifurcum*. Since then, Harmen Krepel and Djemila Pit have studied aspects of the epidemiology, treatment and transmission of *O. bifurcum* infection, and Robin Gasser and Jaco Verweij have described a PCR diagnostic test, which is highly sensitive for stool egg diagnosis. By genetic studies, they are attempting to detect differences between the *O. bifurcum* present in humans and the *O. bifurcum* found
in monkeys within Ghana. This current research aims to complete some of the gaps between parasitological and clinical knowledge of oesophagostomiasis. The Ghanaian Ministry of Health in Tamale and Bolgatanga gave their support to the project, and were involved in the planning of the studies. The base was Nalerigu, with the laboratory split between the hospital and a purpose built house in town. From January 1996 until October 1998, weekly oesophagostomiasis clinics were held at BMC. The majority of the village work was performed in Mangol, near the Togo border, 1 hour drive from Nalerigu.

THE THESIS

Despite the multitude of reports of oesophagostomiasis from many areas of the world, they have been in the main sporadic and were lacking in solid clinical details. There has never been a set of cases described by the same clinician with time to compile the presenting clinical symptoms and signs together with the demographic trends. As a result, a classification of the disease has never been formulated, and its epidemiology has not been described.

The ideal diagnostic test is reliable, simple, cheap, available, and non-invasive, and any such test is a compromise between these parameters. Previously, due to the vague, poorly localising signs and symptoms of oesophagostomiasis, many of the reported cases were suspected but not confirmed until exploratory laparotomy. Clearly, this degree of effort and risk is unacceptable for a diagnostic procedure. Ultrasound, a revolutionary technology invented for obstetric use in the 1960’s, allows non-invasive visualisation of internal organs. Oesophagostomum nodules are pus filled and would therefore appear as echo free ovoid abdominal lesions.

There was some economy of effort by clinicians in always performing exploratory laparotomy, as management was invariably by colectomy. But with ultrasound to monitor the efficacy of treatment, more conservative management methods could be attempted, with the aim of killing the nodule dwelling worms thus allowing resolution of the inflammatory process.

Infection with Schistosoma mansoni is diagnosed by stool examination, but egg counts are not a reliable marker for morbidity. We became aware that the same situation was true for O. bifurcum: whilst there are an estimated 250,000 infected people,
as diagnosed by stool cultures, there are only 50 cases of the disease diagnosed at Nalerigu hospital each year (Chapter 2). In schistosomiasis, ultrasound is now the most important method for detection and quantification of hepatosplenic pathology, a more reliable morbidity marker than egg output, and it was predicted that if we were able to see the histotrophic development stages of *O. bifurcum*, the same could be true for oesophagostomiasis. From clinical, surgical and pathological observations, oesophagostomum nodules are pus-filled, 1 - 11 cm diameter, usually solitary, and most commonly present in the wall of the proximal colon. They would not be found in individuals outside the endemic area. We would therefore expect abdominal lesions seen by ultrasound in asymptomatic individuals to have an appearance and distribution compatible with these observations, if they have been induced by *O. bifurcum*. In order to prove that an ultrasound lesion of this description was caused by *O. bifurcum*, it would be necessary to image such a lesion in a patient requiring surgery for an unrelated cause, and then during the operation to demonstrate that the lesion contained an *O. bifurcum* worm.

In contrast to other imaging techniques, ultrasound of the abdomen can be considerably handicapped by observer bias. Subjectivity is an inherent characteristic of the method, both in the realtime appraisal of the findings, and in the decision as to which view to represent photographically. If it is to be used by other working groups for the diagnosis and assessment of *O. bifurcum* induced pathology, an estimation of the extent that inter- and intra-observer variation affects its reliability is of paramount importance.

It was postulated that all *O. bifurcum* stool positive individuals have previously possessed colonic nodules as part of the normal life cycle of *O. bifurcum*, as is the case with primates where *O. bifurcum* necessarily passes through a developmental stage in the colon wall surrounded by a nodule, but it could be that human nodules seen by ultrasound are pre-clinical pathology. Following the natural progression and regression of the nodules was therefore necessary, to determine the frequency of these 2 scenarios.

In order to rid the world of parasites, the ultimate goal of most research work in this field is intervention. Albendazole has been used for the treatment of hospital cases of oesophagostomiasis, presumably acting by killing the histotrophic juvenile worms. It was anticipated that treating pre-clinical colonic pathology would reduce nodule longevity and their progression into clinical disease.
Once I had a house in Africa....