Hookworm infection

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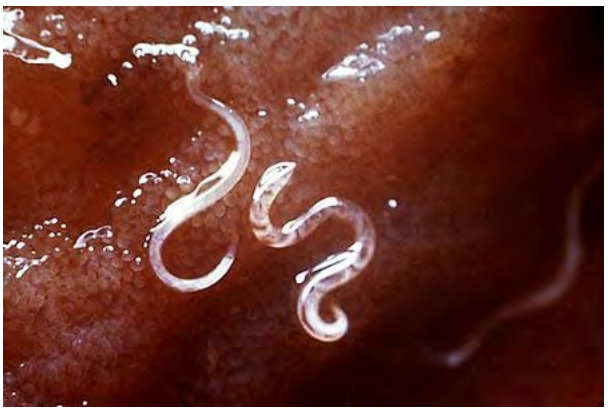
Hookworm infection, also known as **hookworm disease**, is an infection by a parasitic bloodsucking roundworm. Hookworm infections include ancylostomiasis and necatoriasis. These worms live in the small intestine which may be that of a bird or mammal such as a dog, cat, or human. Hookworm infection in pregnancy can cause poor growth, premature birth and a low birth weight of the baby. Hookworms in children can cause intellectual and growth problems.

Hookworm infection



Hookworms

Classification and external resources

Specialty	Infectious disease
ICD-10	B76.8 (http://apps.who.int/classifications/icd10/browse/2016/en#/B76.8)
ICD-9-CM	126.9 (http://www.icd9data.com/getICD9Code.ashx?icd9=126.9)

Two species of hookworms commonly infect humans: *Ancylostoma duodenale* and *Necator americanus*. *A. duodenale* is the more common type in the Middle East, North Africa, India and (formerly) in southern Europe, while *N. americanus* is the more common type in the Americas, Sub-Saharan Africa, Southeast Asia, China, and Indonesia. *A. tubaeforme* infects cats, *A. caninum* infects dogs and *A. braziliense* and *Uncinaria stenocephala* infect both cats and dogs. Hookworms are much smaller than the giant roundworms *Ascaris lumbricoides*. The most significant risk of hookworm infection is anemia, secondary to loss of iron (and protein) in the gut. The worms suck blood and damage the mucosa. However, the blood loss in the stools is not visibly apparent.

Hookworm infection affects over half a billion people globally.[1] It is a leading cause of health problems in mothers and children in developing countries of the tropics and subtropics. In developed countries, hookworm infection is rarely fatal, but anemia can be significant in a heavily infected individual. Hookworm infection is a soil-transmitted helminthiasis and therefore classified as a neglected tropical disease.[2] Ancylostomiasis is the disease caused when *Ancylostoma duodenale* hookworms, present in large numbers, produce an iron deficiency anemia by sucking blood from the host's intestinal walls.

Contents

Terminology

The term *hookworm* is sometimes used to refer to hookworm infection.[3] A hookworm is a type of parasitic worm (helminth).

Signs and symptoms

There are no specific symptoms or signs of hookworm infection, but they give rise to a combination of intestinal inflammation and progressive iron-deficiency anemia and protein deficiency. Coughing, chest pain, wheezing, and fever will sometimes result from severe infection. Epigastric pains, indigestion, nausea, vomiting, constipation, and diarrhea can occur early or in later stages as well, although gastrointestinal symptoms tend to improve with time. Signs of advanced severe infection are those of anemia and protein deficiency, including emaciation, cardiac failure and abdominal distension with ascites.

Larval invasion of the skin (mostly in the Americas) can produce a skin disease called cutaneous larva migrans also known as *creeping eruption*. The hosts of these worms are not human and the larvae can only penetrate the upper five layers of the skin, where they give rise to intense, local itching, usually on the foot or lower leg, known as *ground itch*. This infection is due to larvae from the *A. Braziliense* hookworm. The larvae migrate in tortuous tunnels between the *stratum basale* and *stratum corneum* of the skin, causing serpiginous vesicular lesions. With advancing movement of the larvae, the rear portions of the lesions become dry and crusty. The lesions are typically intensely itchy.[4]

Pathophysiology

Morphology

A. duodenale worms are grayish white or pinkish with the head slightly bent in relation to the rest of the body. This bend forms a definitive hook shape at the anterior end for which hookworms are named. They possess well-developed mouths with two pairs of teeth. While males measure approximately one centimeter by 0.5 millimeters, the females are often longer and stouter. Additionally, males can be distinguished from females based on the presence of a prominent posterior copulatory bursa.[5]

N. americanus is very similar in morphology to *A. duodenale*. *N. americanus* is generally smaller than *A. duodenale* with males usually 5 to 9 mm long and females about 1 cm long. Whereas *A. duodenale* possesses two pairs of teeth, *N. americanus* possesses a pair of cutting plates in the buccal capsule. Additionally, the hook shape is much more defined in *Necator* than in *Ancylostoma*.[5]

Pathology

Hookworm infection is generally considered to be asymptomatic, but as Norman Stoll described in 1962, hookworm infection is an extremely dangerous infection because its damage is "silent and insidious."[6] There are general symptoms that an individual may experience soon after infection. Ground-itch, which is an allergic reaction at the site of parasitic penetration and entry, is common in patients infected with *N. americanus*.[5] Additionally, cough and pneumonitis may result as the larvae begin to break into the alveoli and travel up the trachea. Then once the larvae reach the small intestine of the host and begin to mature, the infected individual will suffer from diarrhea and other gastrointestinal discomfort.[5] However, the "silent and insidious" symptoms referred to by Stoll are related to chronic, heavy-intensity hookworm infections. Major morbidity associated with hookworm infection is caused by intestinal blood loss, iron deficiency anemia, and protein malnutrition.[7] They result mainly from adult hookworms in the small intestine ingesting blood, rupturing erythrocytes, and degrading hemoglobin in the host.[3] This long-term blood loss can manifest itself physically through facial and peripheral edema; eosinophilia and pica caused by iron deficiency anemia are also experienced by some hookworm-infected patients.[5] Recently, more attention has been given to other important outcomes of hookworm infection that play a large role in public health. It is now widely accepted that children who suffer from chronic hookworm infection can suffer from growth retardation as well as intellectual and cognitive impairments.[3][8] Additionally, recent research has focused on the potential of adverse maternal-fetal outcomes when the mother is infected with hookworm during pregnancy.

The disease was linked to nematode worms (*Ankylostoma duodenalis*) from one-third to half an inch long in the intestine chiefly through the labours of Theodor Bilharz and Griesinger in Egypt (1854).

The symptoms can be linked to inflammation in the gut stimulated by feeding hookworms, such as nausea, abdominal pain and intermittent diarrhea, and to progressive anemia in prolonged disease: capricious appetite, pica (or dirt-eating), obstinate constipation followed by diarrhea, palpitations, thready pulse, coldness of the skin, pallor of the mucous membranes, fatigue and weakness, shortness of breath and in cases running a fatal course, dysentery, hemorrhages and edema.

Blood tests in early infection often show a rise in numbers of eosinophils, a type of white blood cell that is preferentially stimulated by worm infections in tissues (large numbers of eosinophils are also present in the local inflammatory response). Falling blood hemoglobin levels will be seen in cases of prolonged infection with anemia.

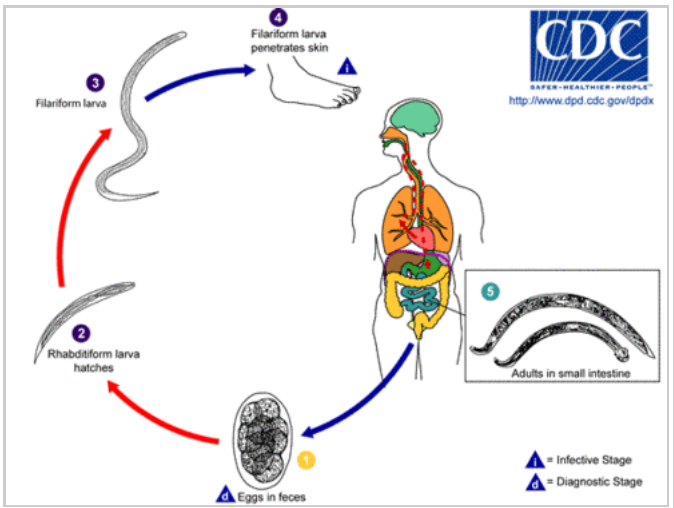
In contrast to most intestinal helminthiases, where the heaviest parasitic loads tend to occur in children, hookworm prevalence and intensity can be higher among adult males. The explanation for this is that hookworm infection tends to be occupational, so that coworkers and other close groups maintain a high prevalence of infection among themselves by contaminating their work environment. However, in most endemic areas, adult women are the most severely affected by anemia, mainly because they have much higher physiological needs for iron (menstruation, repeated pregnancy).

An interesting consequence of this in the case of *Ancylostoma duodenale* infection is translactational transmission of infection: the skin-invasive larvae of this species do not all immediately pass through the lungs and on into the gut, but spread around the body via the circulation, to become dormant inside muscle fibers. In a pregnant woman, after childbirth some or all of these larvae are stimulated to re-enter the circulation (presumably by sudden hormonal changes), then to pass into the mammary glands, so that the newborn baby can receive a large dose of infective larvae through its mother's milk. This accounts for otherwise inexplicable cases of very heavy, even fatal, hookworm infections in children a month or so of age, in places such as China, India and northern Australia.

An identical phenomenon is much more commonly seen with *Ancylostoma caninum* infections in dogs, where the newborn pups can even die of hemorrhaging from their intestines caused by massive numbers of feeding hookworms. This also reflects the close evolutionary link between the human and canine parasites, which probably have a common ancestor dating back to when humans and dogs first started living closely together. Filariform larvae is the infective stage of the parasite, infection occurs when larvae in soil penetrate the skin, or when they are ingested through contaminated food and water following skin penetration, larvae

Life cycle

See the image for the biological life cycle of the hookworm where it thrives in warm earth where temperatures are over 18 °C. They exist primarily in sandy or loamy soil and cannot live in clay or muck. Rainfall averages must be more than 1000 mm (40 inches) a year for them to survive. Only if these conditions exist can the eggs hatch. Infective larvae of *Necator americanus* can survive at higher temperatures, whereas those of *Ancylostoma duodenale* are better adapted to cooler climates. Generally, they live for only a few weeks at most under natural conditions, and die almost immediately on exposure to direct sunlight or desiccation.



Hookworm life cycle

Infection of the host is by the larvae, not the eggs. While *A. duodenale* can be ingested, the usual method of infection is through the skin; this is commonly caused by walking barefoot through areas contaminated with fecal matter. The larvae are able to penetrate the skin of the foot, and once inside the body, they migrate through the vascular system to the lungs, and from there up the trachea, and are swallowed. They then pass down the esophagus and enter the digestive system, finishing their journey in the intestine, where the larvae mature into adult worms.[3][9]

Once in the host gut, *Necator* tends to cause a prolonged infection, generally 1–5 years (many die within a year or two of infecting), though some adult worms have been recorded to live for 15 years or more. On the other hand, *Ancylostoma* adults are short-lived, surviving on average for only about 6 months. However, the

infection can be prolonged because dormant larvae can be "recruited" sequentially from tissue "stores" (see Pathology, above) over many years, to replace expired adult worms. This can give rise to seasonal fluctuations in infection prevalence and intensity (apart from normal seasonal variations in transmission).

They mate inside the host, females laying up to 30,000 eggs per day and some 18 to 54 million eggs during their lifetime, which pass out in feces. Because it takes 5–7 weeks for adult worms to mature, mate and produce eggs, in the early stages of very heavy infection, acute symptoms might occur without any eggs being detected in the patient's feces. This can make diagnosis very difficult.

Civilian Public Service workers built and installed 2065 outhouses for hookworm eradication in Mississippi and Florida from 1943 to 1947.

Biological life cycle

N. americanus and *A. duodenale* eggs can be found in warm, moist soil where they will eventually hatch into first stage larvae, or L1. L1, the feeding non-infective rhabditoform stage, will feed on soil microbes and eventually molt into second stage larvae, L2. L2, which is also in the rhabditoform stage, will feed for approximately 7 days and then molt into the third stage larvae, or L3. L3 is the filariform stage of the parasite, that is, the non-feeding infective form of the larvae. The L3 larvae are extremely motile and will seek higher ground to increase their chances of penetrating the skin of a human host. The L3 larvae can survive up to 2 weeks without finding a host. While *N. americanus* larvae only infect through penetration of skin, *A. duodenale* can infect both through penetration as well as orally. After the L3 larvae have successfully entered the host, the larvae then travel through the subcutaneous venules and lymphatic vessels of the human host. Eventually, the L3 larvae enter the lungs through the pulmonary capillaries and break out into the alveoli. They will then travel up the trachea to be coughed and swallowed by the host. After being swallowed, the L3 larvae are then found in the small intestine where they molt into the L4, or adult worm stage. The entire process from skin penetration to adult development takes about 5–9 weeks. The female adult worms will release eggs (*N. americanus* about 9,000–10,000 eggs/day and *A. duodenale* 25,000–30,000 eggs/day) which are passed in the feces of the human host. These eggs will hatch in the environment within several days and the cycle will start anew.[3][7][10]

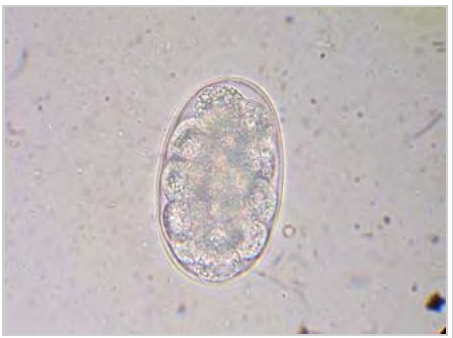
Incubation period

The incubation period can vary between a few weeks to many months and is largely dependent on the number of Hookworm parasites an individual is infected with.[11]

Diagnosis

Diagnosis depends on finding characteristic worm eggs on microscopic examination of the stools, although this is not possible in early infection. Early signs of infection in most dogs include limbular limping and anal itching. The eggs are oval or elliptical, measuring 60 µm by 40 µm, colorless, not bile stained and with a thin transparent hyaline shell membrane. When released by the worm in the intestine, the egg contains an unsegmented ovum. During its passage down the intestine, the ovum develops and thus the eggs passed in feces have a segmented ovum, usually with 4 to 8 blastomeres. As the eggs of both *Ancylostoma* and *Necator* (and most other hookworm species) are indistinguishable, to identify the genus, they must be cultured in the

lab to allow larvae to hatch out. If the fecal sample is left for a day or more under tropical conditions, the larvae will have hatched out, so eggs might no longer be evident. In such a case, it is essential to distinguish hookworms from *Strongyloides* larvae, as infection with the latter has more serious implications and requires different management. The larvae of the two hookworm species can also be distinguished microscopically, although this would not be done routinely, but usually for research purposes. Adult worms are rarely seen (except via endoscopy, surgery or autopsy), but if found, would allow definitive identification of the species. Classification can be performed based on the length of the buccal cavity, the space between the oral opening and the esophagus: hookworm rhabditoform larvae have long buccal cavities whereas *Strongyloides* rhabditoform larvae have short buccal cavities.[5]


Hookworm egg

Recent research has focused on the development of DNA-based tools for diagnosis of infection, specific identification of hookworm, and analysis of genetic variability within hookworm populations.[12] Because hookworm eggs are often indistinguishable from other parasitic eggs, PCR assays could serve as a molecular approach for accurate diagnosis of hookworm in the feces.[12][13]

Prevention

The infective larvae develop and survive in an environment of damp dirt, particularly sandy and loamy soil. They cannot survive in clay or muck. The main lines of precaution are those dictated by good hygiene behaviors:

- Do not defecate in the open, but rather in toilets.
- Do not use untreated human excreta or raw sewage as fertilizer in agriculture
- Do not walk barefoot in known infected areas.
- Deworm pet dogs and cats. Canine and feline hookworms rarely develop to adulthood in humans. *Ancylostoma caninum*, the common dog hookworm, occasionally develops into an adult to cause eosinophilic enteritis in people, but their invasive larvae can cause an itchy rash called cutaneous larva migrans.

Moxidectin has been released in the United States as part of Advantage Multi (imidacloprid + moxidectin) topical solution for dogs and cats. It utilizes moxidectin for control and prevention of roundworms, hookworms, heartworms, and whipworms.

Children

Most of these public health concerns have focused on children who are infected with hookworm. This focus on children is largely due to the large body of evidence that has demonstrated strong associations between hookworm infection and impaired learning, increased absences from school, and decreased future economic productivity.[3] In 2001, the 54th World Health Assembly passed a resolution demanding member states to attain a minimum target of regular deworming of at least 75% of all at-risk school children by the year 2010.[14] A 2008 World Health Organization publication reported on these efforts to treat


Ethiopian children treated for schistosoma and hookworms.

at-risk school children. Some of the interesting statistics were as follows: 1) only 9 out of 130 endemic countries were able to reach the 75% target goal; and 2) less than 77 million school-aged children (of the total 878 million at risk) were reached, which means that only 8.78% of at-risk children are being treated for hookworm infection.[15]

School-based mass deworming

School-based mass deworming programs have been the most popular strategy to address the issue of hookworm infection in children. School-based programs are extremely cost-effective as schools already have an available, extensive, and sustained infrastructure with a skilled workforce that has a close relationship with the community.[14] With little training from a local health system, teachers can easily administer the drugs which often cost less than US$0.50 per child per year.[16]

Recently, many people have begun to question if the school-based programs are necessarily the most effective approach. An important concern with school-based programs is that they often do not reach children who do not attend school, thus ignoring a large amount of at-risk children. A 2008 study by Massa *et al.* continued the debate regarding school-based programs. They examined the effects of community-directed treatments versus school-based treatments in the Tanga Region of Tanzania. A major conclusion was that the mean infection intensity of hookworm was significantly lower in the villages employing the community-directed treatment approach than the school-based approach. The community-directed treatment model used in this specific study allowed villagers to take control of the child's treatment by having villagers select their own community drug distributors to administer the antihelminthic drugs. Additionally, villagers organized and implemented their own methods for distributing the drugs to all children.[17] The positive results associated with this new model highlight the need for large-scale community involvement in deworming campaigns.

Public health education

Many mass deworming programs also combine their efforts with a public health education. These health education programs often stress important preventative techniques such as: washing your hands before eating, and staying away from water/areas contaminated by human feces. These programs may also stress that shoes must be worn, however, these come with their own health risks and may not be effective.[18] Shoe wearing patterns in towns and villages across the globe are determined by cultural beliefs, and the levels of education within that society. The wearing of shoes will prevent the entry of hookworm infections from the surrounding soils into tender skin regions; such as areas between the toes.[19]

Sanitation

Historical examples, such as the hookworm campaigns in Mississippi and Florida from 1943 to 1947 have shown that the primary cause of hookworm infection is poor sanitation, which can be solved by building and maintaining toilets. But while these may seem like simple tasks, they raise important public health challenges. Most infected populations are from poverty-stricken areas with very poor sanitation. Thus, it is most likely that at-risk children do not have access to clean water to wash their hands and live in environments with no proper sanitation infrastructure. Health education, therefore, must address preventive measures in ways that are both feasible and sustainable in the context of resource-limited settings.

Integrated approaches

Evaluation of numerous public health interventions has generally shown that improvement in each individual

component ordinarily attributed to poverty (for example, sanitation, health education and underlying nutrition status) often have minimal impact on transmission. For example, one study found that the introduction of latrines into a resource-limited community only reduced the prevalence of hookworm infection by four percent.[20] However, another study in Salvador, Brazil found that improved drainage and sewerage had a significant impact ($p<0.0001$) on the prevalence of hookworm infection but no impact at all on the intensity of hookworm infection.[21] This seems to suggest that environmental control alone has a limited but incomplete effect on the transmission of hookworms. It is imperative, therefore, that more research is performed to understand the efficacy and sustainability of integrated programs that combine numerous preventive methods including education, sanitation, and treatment.

Treatment

Anthelmintic drugs

The most common treatment for hookworm are benzimidazoles, specifically albendazole and mebendazole. BZAs kill adult worms by binding to the nematode's β-tubulin and subsequently inhibiting microtubule polymerization within the parasite.[7] In certain circumstances, levamisole and pyrantel pamoate may be used.[3] A 2008 review found that the efficacy of single-dose treatments for hookworm infections were as follows: 72% for albendazole, 15% for mebendazole, and 31% for pyrantel pamoate.[22] This substantiates prior claims that albendazole is much more effective than mebendazole for hookworm infections. Also of note is that the World Health Organization does recommend anthelmintic treatment in pregnant women after the first trimester.[7] It is also recommended that if the patient also suffers from anemia that ferrous sulfate (200 mg) be administered three times daily at the same time as anthelmintic treatment; this should be continued until hemoglobin values return to normal which could take up to 3 months.[5]

Hookworm infection can be treated with local cryotherapy when the hookworm is still in the skin.[23]

Albendazole is effective both in the intestinal stage and during the stage the parasite is still migrating under the skin.[23]

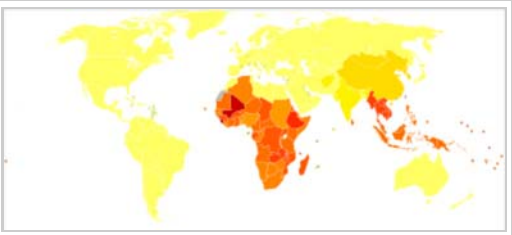
In case of anemia, iron supplementation can cause relief symptoms of iron deficiency anemia. However, as red blood cell levels are restored, shortage of other essentials such as folic acid or vitamin B12 may develop, so these might also be supplemented.

Reinfection and drug resistance

Other important issues related to the treatment of hookworm are reinfection and drug resistance. It has been shown that reinfection after treatment can be extremely high. Some studies even show that 80% of pretreatment hookworm infection rates can be seen in treated communities within 30–36 months.[7] While reinfection may occur, it is still recommended that regular treatments be conducted as it will minimize the occurrence of chronic outcomes. There are also increasing concerns about the issue of drug resistance. Drug resistance has appeared in front-line anthelmintics used for livestock nematodes. Generally human nematodes are less likely to develop resistance due to longer reproducing times, less frequent treatment, and more targeted treatment. Nonetheless, the global community must be careful to maintain the effectiveness of current anthelmintic as no new anthelmintic drugs are in the late-stage development.[7]

Epidemiology

It is estimated that between 576–740 million individuals are infected with hookworm.[1][7] Of these infected individuals, about 80 million are severely affected.[12] The major etiology of hookworm infection is *N. americanus* which is found the Americas, sub-Saharan Africa, and Asia.[3] *A. duodenale* is found in more scattered focal environments, namely Europe and the Mediterranean. Most infected individuals are concentrated in sub-Saharan Africa and East Asia/the Pacific Islands with each region having estimates of 198 million and 149 million infected individuals, respectively. Other affected regions include: South Asia (50 million), Latin America and the Caribbean (50 million), South Asia (59 million), Middle East/North Africa (10 million).[7] A majority of these infected individuals live in poverty-stricken areas with poor sanitation. Hookworm infection is most concentrated among the world's poorest who live on less than $2 a day.[3]



Disability-adjusted life year for hookworm disease per 100,000 inhabitants in 2002.

no data	35–40
less than 10	40–45
10–15	45–50
15–20	50–55
20–25	55–60
25–30	more than 60
30–35	

While hookworm infection may not directly lead to mortality, its effects on morbidity demand immediate attention. When considering disability-adjusted life years (DALYs), neglected tropical diseases, including hookworm infection, rank among diarrheal diseases, ischemic heart disease, malaria, and tuberculosis as one of the most important health problems of the developing world.

It has been estimated that as many as 22.1 million DALYs have been lost due to hookworm infection. Recently, there has been increasing interest to address the public health concerns associated with hookworm infection. For example, the Bill & Melinda Gates Foundation recently donated US$34 million to fight Neglected Tropical Diseases including hookworm infection.[24] Former US President Clinton also announced a mega-commitment at the Clinton Global Initiative (CGI) 2008 Annual Meeting to de-worm 10 million children.[25]

Many of the numbers regarding the prevalence of hookworm infection are estimates as there is no international surveillance mechanism currently in place to determine prevalence and global distribution.[3] Some prevalence rates have been measured through survey data in endemic regions around the world. The following are some of the most recent findings on prevalence rates in regions endemic with hookworm.

Darjeeling, Hooghly District, West Bengal, India (Pal *et al.* 2007)[26]

- 42.8% infection rate of predominantly *N. americanus* although with some *A. duodenale* infection
- Both hookworm infection load and degree of anemia in the mild range

Xiulongkan Village, Hainan Province, China (Gandhi *et al.* 2001)[27]

- 60% infection rate of predominantly *N. americanus*
- Important trends noted were that prevalence increased with age (plateau of about 41 years) and women had higher prevalence rates than men

Hoa Binh, Northwest Vietnam (Verle *et al.* 2003)[28]

- 52% of a total of 526 tested households infected
- Could not identify species, but previous studies in North Vietnam reported *N. americanus* in more than 95% of hookworm larvae

Minas Gerais, Brazil (Fleming *et al.* 2006)[29]

- 62.8% infection rate of predominantly *N. americanus*

KwaZulu-Natal, South Africa (Mabaso *et al.* 2004)[30]

- Inland areas had a prevalence rate of 9.3% of *N. americanus*
- Coastal plain areas had a prevalence rate of 62.5% of *N. americanus*

There have also been recent technological developments that will hopefully facilitate more accurate mapping of hookworm prevalence. Some researchers have begun to use geographical information systems (GIS) and remote sensing (RS) to examine helminth ecology and epidemiology. Brooker *et al.* utilized this technology to create helminth distribution maps of sub-Saharan Africa. By relating satellite derived environmental data with prevalence data from school-based surveys, they were able to create detailed prevalence maps. The study focused on a wide range of helminths, but interesting conclusions about hookworm specifically were found. As compared to other helminths, hookworm is able to survive in much hotter conditions and was highly prevalent throughout the upper end of the thermal range. Hopefully this information along with more detailed prevalence maps can lead to more effective public health measures.[31]

Improved molecular diagnostic tools are another technological advancement that could help improve existing prevalence statistics. Recent research has focused on the development of a DNA-based tool that can be used for diagnosis of infection, specific identification of hookworm, and analysis of genetic variability in hookworm populations. Again this can serve as a major tool for different public health measures against hookworm infection. Most research regarding diagnostic tools is now focused on the creation of a rapid and cost-effective assay for the specific diagnosis of hookworm infection. Many are hopeful that its development can be achieved within the next 5 years.[12]

History

Discovery

The symptoms now attributed to hookworm appear in papyrus papers of ancient Egypt (c. 1500 BC), described as a derangement characterized by anemia. Avicenna, a Persian physician of the eleventh century, discovered the worm in several of his patients and related it to their disease. In later times, the condition was noticeably prevalent in the mining industry in England, France, Germany, Belgium, North Queensland, and elsewhere.

Italian physician Angelo Dubini was the modern-day discoverer of the worm in 1838 after an autopsy of a peasant woman. Dubini published details in 1843 and identified the species as *A. duodenale*. Working in the Egyptian medical system in 1852 German physician Theodor Bilharz, drawing upon the work of colleague Wilhelm Griesinger, found these worms during autopsies and went a step further in linking them to local endemic occurrences of chlorosis, which would probably be called iron deficiency anemia today.

A breakthrough came 25 years later following a diarrhea and anemia epidemic that took place among Italian workmen employed on the Gotthard Rail Tunnel. In an 1880 paper, physicians Camillo Bozzolo, Edoardo Perroncito, and Luigi Pagliani correctly hypothesized that hookworm was linked to the fact that workers had to defecate inside the 15 km tunnel, and that many wore worn-out shoes.[32] In 1897, it was established that the skin was the principal avenue of infection and the biological life cycle of the hookworm was clarified.

Eradication programmes

In 1899, American zoologist Charles Wardell Stiles identified progressive pernicious anemia seen in the southern United States as being caused by the hookworm *A. duodenale*. Testing in the 1900s revealed very heavy infestations in school-age children. In Puerto Rico, Dr. Bailey K. Ashford, a US Army physician, organized and conducted a parasite treatment campaign, which cured approximately 300,000 people (one-third of the Puerto Rican population) and reduced the death rate from this anemia by 90 percent during the years 1903–1904.

On October 26, 1909 the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease was organized as a result of a gift of US$1 million from John D. Rockefeller, Sr. The five-year program was a remarkable success and a great contribution to the United States' public health, instilling public education, medication, field work and modern government health departments in eleven southern states.[33] The hookworm exhibit was a prominent part of the 1910 Mississippi state fair.

A doctor examines a boy for signs of hookworm in Coffee County, Alabama, 1939.

The Commission found that an average of 40% of school-aged children was infected with hookworm. Areas with higher levels of hookworm infection prior to the eradication program experienced greater increases in school enrollment, attendance, and literacy after the intervention. Econometric studies have shown that this effect cannot be explained by a variety of alternative factors, including differential trends across areas, changing crop prices, shifts in certain educational and health policies and the effect of malaria eradication.[34] No significant contemporaneous results were found for adults who should have benefited less from the intervention owing to their substantially lower (prior) infection rates. The program nearly eradicated hookworm and would flourish afterward with new funding as the Rockefeller Foundation International Health Division. The RF's hookworm campaign in Mexico showed how science and politics play a role in developing health policies. It brought together government officials, health officials, public health workers, Rockefeller officials and the community. This campaign was launched to eradicate hookworms in Mexico. Although the campaign did not focus on long-term treatments, it did set the terms of the relationship between Mexico and the Rockefeller Foundation. The scientific knowledge behind this campaign helped shaped public health policies, improved public health and built a strong relationship between USA and Mexico.[35]

In the 1920s, hookworm eradication reached the Caribbean and Latin America, where great mortality was reported among people in the West Indies towards the end of the 18th century, as well as through descriptions sent from Brazil and various other tropical and sub-tropical regions.

Treatments

Early treatment relied on the use of Epsom salt to reduce protective mucus, followed by thymol to kill the worms.[36] Later tetrachloroethylene was the leading method. It was not until later in the mid-20th century when new organic drug compounds were developed.[37]

Research

Anemia in pregnancy

It is estimated that a third of all pregnant women in developing countries are infected with hookworm, 56% of

all pregnant women in developing countries suffer from anemia, 20% of all maternal deaths are either directly or indirectly related to anemia. Numbers like this have led to an increased interest in the topic of hookworm-related anemia during pregnancy.[38] With the understanding that chronic hookworm infection can often lead to anemia, many people are now questioning if the treatment of hookworm could effect change in severe anemia rates and thus also on maternal and child health as well. Most evidence suggests that the contribution of hookworm to maternal anemia merits that all women of child-bearing age living in endemic areas be subject to periodic anthelmintic treatment. The World Health Organization even recommends that infected pregnant women be treated after their first trimester.[7] Regardless of these suggestions, only Madagascar, Nepal and Sri Lanka have added deworming to their antenatal care programs.[39]

This lack of deworming of pregnant women is explained by the fact that most individuals still fear that anthelmintic treatment will result in adverse birth outcomes. But a 2006 study by Gyorkos et al. found that when comparing a group of pregnant women treated with mebendazole with a control placebo group, both illustrated rather similar rates in adverse birth outcomes. The treated group demonstrated 5.6% adverse birth outcomes, while the control group had 6.25% adverse birth outcomes.[38] Furthermore, Larocque et al. illustrated that treatment for hookworm infection actually led to positive health results in the infant. This study concluded that treatment with mebendazole plus iron supplements during antenatal care significantly reduced the proportion of very low birth weight infants when compared to a placebo control group.[40] Studies so far have validated recommendations to treat infected pregnant women for hookworm infection during pregnancy.

A review of effects of antihelminthics (anti-worm drugs) given in pregnancy found that there was not enough evidence to support treating pregnant women in their second or third trimesters.[41] The women who were treated in the second trimester and the women who had no treatment showed no difference in numbers of maternal anemia, low birth weight, preterm birth or deaths of babies.[41]

The intensity of hookworm infection as well as the species of hookworm have yet to be studied as they relate to hookworm-related anemia during pregnancy. Additionally, more research must be done in different regions of the world to see if trends noted in completed studies persist.

Malaria co-infection

Co-infection with hookworm and *Plasmodium falciparum* is common in Africa.[42] Although exact numbers are unknown, preliminary analyses estimate that as many as a quarter of African schoolchildren (17.8–32.1 million children aged 5–14 years) may be coincidentally at-risk of both *P. falciparum* and hookworm.[43] While original hypotheses stated that co-infection with multiple parasites would impair the host's immune response to a single parasite and increase susceptibility to clinical disease, studies have yielded contrasting results. For example, one study in Senegal showed that the risk of clinical malaria infection was increased in helminth-infected children in comparison to helminth-free children while other studies have failed to reproduce such results,[44] and even among laboratory mouse experiments the effect of helminths on malaria is variable.[45] Some hypotheses and studies suggest that helminth infections may protect against cerebral malaria due to the possible modulation of pro-inflammatory and anti-inflammatory cytokines responses.[46] Furthermore, the mechanisms underlying this supposed increased susceptibility to disease are unknown. For example, helminth infections cause potent and highly polarized immune response characterized by increased T-helper cell type 2 (T_h2) cytokine and Immunoglobulin E(IgE) production.[47] However, the effect of such responses on the human immune response is unknown. Additionally, both malaria and helminth infection can cause anemia, but the effect of co-infection and possible enhancement of anemia is poorly understood.[37]

Hygiene hypothesis

The hygiene hypothesis states that infants and children who lack exposure to infectious agents are more susceptible to allergic diseases via modulation of immune system development. As Mary Ruebush writes in her book *Why Dirt is Good*, "what a child is doing when he puts things in his mouth is allowing his immune response to explore his environment. Not only does this allow for 'practice' of immune responses, which will be necessary for protection, but it also plays a critical role in teaching the immature immune response what is best ignored.[48]" The theory was first proposed by David P. Strachan who noted that hay fever and eczema were less common in children who belonged to large families.[49] Since then, studies have noted the effect of gastrointestinal worms on the development of allergies in the developing world. For example, a study in Gambia found that eradication of worms in some villages led to increased skin reactions to allergies among children.[50]

Although the exact mechanism is unknown, scientists hypothesize that the helper T cells are key players. Allergic diseases, which are immunological responses to normally harmless antigens, are driven by a TH2-mediated immune response. Bacteria, viruses, and parasites, on the other hand, elicit a TH1-mediated immune response which inhibits or down-regulates the TH2 response.[51] TH1 also inhibits the activity of TH17 which is heightened in numerous inflammatory diseases including multiple sclerosis and asthma.[52] More research is currently being performed to better understand the possible mechanism for the hygiene hypothesis.

Vaccines

While annual or semi-annual mass antihelminthic administration is a critical aspect of any public health intervention, many have begun to realize how unsustainable it is due to aspects such as poverty, high rates of re-infection, and diminished efficacy of drugs with repeated use. Current research, therefore, has focused on the development of a vaccine that could be integrated into existing control programs. The goal of vaccine development is not necessarily to create a vaccine with sterilizing immunity or complete protection against immunity. A vaccine that reduces the likelihood of vaccinated individuals developing severe infections and thus reduced blood and nutrient levels could still have a significant impact on the high burden of disease throughout the world.

Current research focuses on targeting two stages in the development of the worm: the larval stage and the adult stage. Research on larval antigens has focused on proteins that are members of the pathogenesis-related protein superfamily, *Ancylostoma* Secreted Proteins.[53] Although they were first described in *Anyclostoma*, these proteins have also been successfully isolated from the secreted product of *N. americanus*. *N. americanus* ASP-2 (Na-ASP-2) is currently the leading larval-stage hookworm vaccine candidate. A randomized, double-blind, placebo-controlled study has already been performed; 36 healthy adults without a history of hookworm infection were given three intramuscular injections of three different concentrations of Na-ASP-2 and observed for six months after the final vaccination.[54] The vaccine induced significant anti-Na-ASP-2 IgG and cellular immune responses. In addition, it was safe and produced no debilitating side effects. The vaccine is now in a phase one trial; healthy adult volunteers with documented evidence of previous infection in Brazil are being given the same dose concentration on the same schedule used in the initial study.[53] If this study is successful, the next step would be to conduct a phase two trial to assess the rate and intensity of hookworm infection among vaccinated persons. Because the Na-ASP-2 vaccine only targets the larval stage, it is critical that all subjects enrolled in the study be treated with antihelminthic drugs to eliminate adult worms prior to vaccination.

Adult hookworm antigens have also been identified as potential candidates for vaccines. When adult worms attach to the intestinal mucosa of the human host, erythrocytes are ruptured in the worm's digestive tract which causes the release of free hemoglobin which is subsequently degraded by a proteolytic cascade. Several of these proteins that are responsible for this proteolytic cascade are also essential for the worm's nutrition and survival.[55] Therefore, a vaccine that could induce antibodies for these antigens could interfere with the hookworm's digestive pathway and impair the worm's survival. Three proteins have been identified: the aspartic protease-hemoglobinase APR-1, the cysteine protease-hemoglobinase CP-2, and a glutathione S-transferase.[56][57] [58] Vaccination with APR-1 and CP-2 led to reduced host blood loss and fecal egg counts in dogs.[56][57] With APR-1, vaccination even led to reduced worm burden.[56] Research is currently stymied at the development of at least one of these antigens as a recombinant protein for testing in clinical trials.

Hookworm in therapy

Moderate hookworm infections have been demonstrated to have beneficial effects on hosts suffering from diseases linked to overactive immune systems. This is possibly explained by the hygiene hypothesis.[49] Research at the University of Nottingham conducted in Ethiopia observed a small subset of people with hookworm infections were half as likely to experience asthma[59] or hay fever.[60] Potential benefits have also been hypothesized in cases of multiple sclerosis,[61] Crohn's Disease[62] and diabetes.

Some research conducted has shown favourable results using hookworms to treat coeliac disease.[63][64] Though research points to anti-allergenic properties associated with hook worm infections, the FDA does not currently recognize hookworms as a treatment.

See also

- List of parasites (human)
- Helminthiasis

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Notes

- This article incorporates text from a publication now in the public domain: Chisholm, Hugh, ed. (1911). "article name needed". *Encyclopædia Britannica* (11th ed.). Cambridge University Press.

External links

- CDC Department of Parasitic Diseases images of the hookworm life cycle (http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Hookworm_il.htm)
- Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dpd/parasites/hookworm/factsht_hookworm.htm)
- Dog hookworm (*Ancylostoma caninum*) at MetaPathogen: facts, life cycle, references (http://www.metapathogen.com/hookworm/acaninum/)
- Human hookworms (*Ancylostoma duodenale* and *Necator americanus*) at MetaPathogen: facts, life cycle, references (http://www.metapathogen.com/hookworm/humanhookworms/)

Categories: Strongylida | Parasitic nematodes | Neglected diseases | Conditions diagnosed by stool test | Parasites of cats | Cat diseases | Parasites of dogs | Dog diseases

Infectious diseases with eradication efforts
