8.9.3 Guinea worm disease (dracunculiasis) 1495

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8.9.3 Guinea worm disease (dracunculiasis) 1495 of adult worms, both within and between individuals. For tropical pulmonary eosinophilia a full 21 days of treatment is indicated, and may need to be repeated. Doxycycline is given at a dose of 200 mg/kg daily for 4 weeks. Unless the patient is coinfected with L. loa a single dose of iver- mectin 200 μg/kg is then given to clear microfilariae. For patients with hydrocele, and perhaps those with other morbidities, the doxy- cycline is given for 6 weeks. For Brugia infections, doxycycline 100 mg/kg for 6 weeks has been recommended. Surgical and supportive management The acute manifestations of filariasis can mimic strangulated hernia and testicular torsion. The surgical treatment of filarial hydrocele is the same as that for nonfilarial disease. Scrotal lymphoedema can be treated surgically, usually with preservation of the testes. Lymphosaphenous anastomosis is being used for leg elephant- iasis; many other procedures have been used in the past, often with disappointing results (Fig. 8.9.2.2). Bacterial infection is common in those with lymphoedema, espe- cially when skin integrity is breached. Early use of antibiotics, anti- bacterial soaks, together with resting the affected limb, lessens the risk of increasing lymphoedema; supportive bandaging re-applied each morning reduces chronic oedema. FURTHER READING Alexander NDE (2015). Are we nearly there yet? Coverage and com- pliance of mass drug administration for lymphatic filariasis elimin- ation. Trans R Soc Trop Med Hyg. 109, 173–4. Babu BV, Babu GR (2014). Coverage of, and compliance with, mass drug administration under the programme to eliminate lymphatic filariasis in India: a systematic review. Trans R Soc Trop Med Hyg, 108, 538–49. Beaver PC (1970). Filariasis without microfilaremia. Am J Trop Med Hyg, 19, 181–9. Dreyer G, et al. (1999). 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Adult worms enter subcutaneous tissue and can reach a metre in length. Clinical presenta- tion is usually with a skin blister, most often on the leg, sometimes pre- ceded by allergic prodromal symptoms. Bacterial infection and local scarring with disability are common complications. Most patients in endemic areas recognize their condition, but irrigation of ulcers can re- veal larvae. Treatment is by physical removal of the worm; anthelmin- tics have no role in management. Provision of safe water for drinking is the key to prevention. The disease is now nearing eradication.

 Introduction The clinical manifestations of Guinea worm and its surgical removal were known in antiquity. Attention was drawn to the seasonal occur- rence of painful limb blisters that broke down to reveal a ‘worm’ in the floor of an ulcer. Dracunculus medinensis is the longest nematode infecting humans; in the Bible it is described as the ‘fiery serpent’. It was the first human parasite to be shown to have an arthropod inter- mediate host: in 1870 the Russian naturalist Fedtschenko described the worm’s early development in Cyclops, a ‘water flea’. Eradication programmes based on public health measures alone have been very

successful. In 1986 3.2 million cases were reported from a total of 20 countries, but by 2016 this had been reduced to 25 in 4 African countries: Mali, Chad, South Sudan, and Ethiopia.
Aetiology: The biology of the parasite The life cycle of the Guinea worm is shown in Fig. 8.9.3.1. Mature female worms, 70–120 cm in length, migrate along fascial planes and subcutaneous tissue to reach the skin, usually below the knee. Tissue damage caused by worm products produces a blister that soon ulcerates (Fig. 8.9.3.2). Immersion of the affected part in water causes the worm to contract and expel numerous rhabditiform first-stage larvae from the uterus at the ruptured anterior end of the worm (Fig. 8.9.3.3). The larvae swim vigorously in water for up to 7 days, and some are ingested by predatory copepod crustaceans of the genus Cyclops. They penetrate the gut of the intermediate host, and develop with two moults in the haematocele over a period of 14 days to become infective third-stage larvae. When water containing infected Cyclops is swallowed, the re- leased infective larvae burrow though the wall of the duodenum to reach retroperitoneal tissue. After about 60 to 90 days the worms mate, and the females begin their migration towards the limbs; the male worms die and may later calcify. Ten months after infection most female worms, containing fully formed larvae, have reached their destination; within the next month they will rupture through the skin to begin the cycle anew. Epidemiology Guinea worm transmission is predominantly rural, with an annual cycle that often coincides with the planting or harvesting season. Usually, young adults and farmers are most at risk, and there is no immunity. The seasonal morbidity causes great economic hard- ship. Water sources containing Cyclops are easily contaminated by infected persons, including those seeking relief by immersing their painful lesion. In semiarid areas transmission occurs in temporary ponds during the rainy season; in wetter areas flooding and water turbidity limits transmission during the rains, and infection oc- curs in shallow wells during the dry season. There is normally no (a) (b) (c) (d) Copepod Released larva Third-stage larva First-stage larva Emerging worm Fig. 8.9.3.1 Life cycle of Guinea worm in humans: (a) copepods infected with third-stage larvae are ingested in drinking water; larvae are released in the intestine, migrate to the body cavity, mature, and mate; (b) gravid female worms migrate to the limbs, cause a blister to form, and release first-stage larvae into water; (c) first-stage larvae are ingested by copepods; and (d) larvae undergo two moults in the copepod and are infective after 2 weeks. Fig. 8.9.3.2 Blister at site of imminent emergence of the female worm. Courtesy of the late P. E. C. Manson-Bahr. Fig. 8.9.3.3 Emergent female worm being wound out on a stick. Copyright D. A. Warrell.

8.9.3 Guinea worm disease (dracunculiasis) 1497 (a) Fig. 8.9.3.4 (a) Localities/villages reporting dracunculiasis cases, 2014. (b) Annual number of new dracunculiasis cases reported worldwide, 1989–2014. Reproduced with permission from WHO Weekly Epidemiological Record No. 19, 2015, 90, 201–216, © WHO 2015.

section 8 Infectious diseases 1498 (b) Fig. 8.9.3.4 Continued

8.9.3 Guinea worm disease (dracunculiasis) 1499 zoonotic reservoir, although infected dogs have recently been found in a few endemic areas, and primates can be experimentally infected. Related Dracunculus spp. are found in mink, raccoons, and otters in North America. Geographical distribution This infection was previously endemic over wide areas of the Middle East and the Indian subcontinent. Largely as a result of improved and protected water sources the infection disappeared from the central Asian republics between 1926 and 1933, from Iran in the 1970s, and from Saudi Arabia in the 1980s. It was eradicated from Pakistan in 1996 and India in 2000. It is now limited to sub-Saharan Africa within the Sahel and Guinea savannah, between latitudes 2° north and 18° north (Fig. 8.9.3.4). Previously it occurred in the Americas, having been introduced with the slave trade, but by the 1880s it had disappeared. Clinical features The blister (Fig. 8.9.3.2) is the first sign of infection in most patients. In others, pre-emergent worms may be seen or felt under the dermis; some are actively motile (Fig. 8.9.3.5). Allergic prodromal symp- toms, with urticaria, facial oedema, dyspnoea, and gastrointestinal manifestations, may precede the blister by a few days and disappear when the blister ruptures. Most patients have one or two worms each season, but up to 50 have been recorded. Most gravid worms emerge from the lower limb, but other sites include the buttocks, trunk, arms, scrotum, and vulva. Uncomplicated cases resolve within 4 weeks. Local complications derive from sensitization to worm products, inappropriate self-treatment, and bacterial infection; these can cause severe pain and prolonged disability. Gravid worms failing to reach the skin release larvae within the host’s body, inducing vigorous tissue reactions and abscesses, sometimes presenting as buboes, epididymo-orchitis, or acute arthritis. Joint involvement, often with secondary bacterial in- fection, is also common near the site of emergence; this leads to an- kylosis and tendon contractures, with deformities and permanent disability. Immature female worms may die before reaching the skin and become encapsulated by host tissue; some calcify. They may also enter ectopic sites, including the orbit, pericardium, and central ner- vous system. Mortality is usually less than 1% and results from sys- temic or local bacterial infection. Tetanus is a significant risk when spores contaminate open lesions. Diagnosis Most patients in endemic areas recognize their condition. Worms release larvae on contact with water, and these can be seen as a milky cloud. When the worm is not visible, ulcers may be irrigated with sa- line and the centrifuged deposit examined for larvae. Onchocerciasis may also be endemic in Guinea worm infected countries and a worm found in the floor of an ulcer could be O. volvulus; another source of confusion is spargana tapeworm larvae. Patient management Local treatment can be very painful and must often be repeated. Warm moist packs should be applied for several hours, followed by gentle massage along the tract of the worm towards the ulcer. Light traction is then applied to the worm; breakage must be avoided as this greatly aggravates the situation. Analgesics and antibacterial soaks are useful, and oral antibiotics are often necessary. Between local treatments the lesion must be bandaged to reduce the risk of bacterial infection and contamination of water sources. Pre-emergent worms can be surgically removed, a practice originating in India. A small incision is made adjacent to the worm near its midpoint, and a loop of worm is lifted out with a blunt curved probe. Massage is applied along the length of the worm to-wards the incision, and by gentle traction the whole worm can usu- ally be removed. In the event of breakage, the worm ends should be ligated to minimize contact between host tissue and worm antigens. Deep abscesses require surgical treatment. Anthelmintics have no role in the treatment of Guinea worm. Control and eradication Several factors facilitate control: Guinea worm is recognized by local communities as a major health problem, there are no carriers beyond the annual cycle, and there is usually no animal reservoir. The provision of safe water for drinking is the key to control; it is unrealistic to expect piped water supplies in most endemic areas, but covered tube wells or hand-dug wells provided with parapets are appropriate. Additional measures are filtration of household water with finely woven cloth, and the application of temephos to ponds to kill copepods. National programmes have played a major role in many endemic areas. Case-detection surveys and health education can be inte- grated into existing primary healthcare systems. Rumours of cases are common especially when cash rewards are offered. Unhygienic local treatments such as mud or leaf poultices and crude methods of worm extraction must be discouraged. Several international health agencies took up the challenge of Guinea worm eradication in the mid-1980s, with an initial target eradication date of 1995. Much has been achieved, but the target was Fig. 8.9.3.5 Guinea worm in the scrotum. Copyright D. A. Warrell.

section 8 Infectious diseases 1500 missed. The initial expensive hydrological programmes were later replaced by the training of local cadres who could recruit patients within 24 hours of worm emergence to ‘containment centres’ for treatment and education to prevent water source contamination. In some areas, private-sector initiatives have been able to gain commer- cially from the publicity achieved by adopting control in a defined area. Transmission from a patient is reported as ‘contained’ when it is detected less than 24 h after emergence, the patient has not entered a water source since emergence, and has been properly managed by the volunteer worker and seen by the supervisor with 7 days of worm emergence. Countries reach the precertification stage of eradication 1 year after reporting their last indigenous case. Ghana was certified free of Guinea worm in 2014 and there were no cases in Sudan. Cases were reported from 54 villages in 2014 compared with 103 in 2013 and 92 of the 126 cases reported were indigenous to the re- porting village, the others were infected elsewhere. The infection remains endemic in Mali, Chad, South Sudan and Ethiopia. There were 22 cases in 2015, 25 in 2016 and 30 in 2017. Dogs infected with Dracunculus are present in Chad and a few in Ethiopia, the worms are genetically identical to the human parasite and the epidemio- logic role of dogs is uncertain, but the cycle may include river fish guts or perhaps frogs; infected dogs must be kept away from water sources. Chad had reported no cases for a decade until 2010, there are now many infected dogs along the Chari river. The last stages of eradication will be the most difficult, as vertical programmes then become inefficient. 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Weekly Epidemiological Record, 90, 201–16. 8.9.4 Strongyloidiasis, hookworm, and other gut strongyloid nematodes Michael Brown ESSENTIALS Strongyloides stercoralis and hookworms are common soil-transmitted nematodes in tropical and subtropical regions. After the organisms penetrate exposed skin, most infections are asymptomatic, but heavy infections can result in significant morbidity. Strongyloidiasis The roundworm S. stercoralis infects an estimated 30 million to 100 million people. Clinical manifestations include: (1) skin—often the only clinical manifestation, commonly in the form of larva currens, a serpiginous, pruritic, erythematous eruption at the site of migrating larvae; (2) lungs— cough and tracheal irritation; less commonly wheeze; patchy infiltrates on chest radiography with eosinophilia; (3) intestinal—epigastric pain and diarrhoea; (4) Strongyloides hyperinfection—occurs in patients who are immunosuppressed; severe diarrhoea is a common feature; mor- tality is high. Infection is persistent and may present decades after ex- posure. Diagnosis is usually by microscopy or culture of stool; serology is useful as a screening test. Treatment is typically with ivermectin or albendazole. Improved sanitation and appropriate footwear can reduce the acquisition of infection. Hookworms Hookworm infections, mainly caused by Ancylostoma duodenale and Necator americanus, affect more than 500 million people, predomin- antly in sub-Saharan Africa and Asia. Clinical manifestations include: (1) migratory/larval—ground itch (a pruritic, papular, and erythematous rash on the feet or hands); occasionally pneumonitis with eosinophilia; (2) intestinal—occasionally profuse watery diarrhoea, but most people are asymptomatic excepting for iron-deficiency anaemia (sometimes with haemoglobin <2 g/dl) in those with heavy infections, which are a particular problem in infants and pregnant women, in whom it affects pregnancy adversely. Diagnosis of acute infection is clinical and of chronic infection by discovering eggs in the stool by microscopy. A single dose of albendazole will reduce the worm load to levels below those likely to cause disease; complete eradication can be achieved with repeated doses. Population-based control programmes, using single-dose antihelmintic therapies, aim to reduce anaemia, and improve child- hood growth and cognitive development in countries with high prevalence of soil-transmitted helminths. Integration with other hel- minth control programmes is most effective. Increasing attention is being paid to the effect of coinfection with hookworm on other dis- eases such as malaria, tuberculosis, HIV, and asthma. Nonhuman hookworms These cannot complete their life cycle in humans but are cap- able of causing significant morbidity, including: (1) cutaneous larva migrans—usually due to dog hookworms; presents as in- tensely pruritic lesions on exposed areas of the skin; diagnosis is clinical, although the worm may be visualized in skin biopsies; albendazole is effective; (2) Ancylostoma caninum-associated enter- itis; (3) oesophagostomiasis; (4) trichostrongyliasis.

8.9.4 Strongyloidiasis, hookworm, and other gut strongyloid nematodes 1501 Strongyloides stercoralis Aetiology Human strongyloidiasis is due to infection with Strongyloides ster coralis, a roundworm (nematode). The organism is one of the few helminths that can complete its life cycle in humans. Infection is by percutaneous penetration of exposed skin, with subsequent migra- tion and maturation of the worms in the human host. Epidemiology S. stercoralis infects an estimated 30–100 million people, with a dis- tribution throughout tropical and subtropical areas. Prevalence in rural areas of sub-Saharan Africa, Southeast Asia, and Central and South America is between 10 and 40%, with Brazil and Thailand having particularly high prevalence; a lower level of active trans- mission persists in temperate regions such as southern Europe and the southern United States of America. In highly endemic areas, in- fection intensities peak in childhood and then plateau or decline. Because of the chronicity of infection, prevalence remains high in immigrants from endemic areas, reaching 30–80% in Southeast Asian immigrants screened in North America. A prevalence greater than 30% has been observed among former British servicemen who were prisoners of war in the Far East in 1941–1945, screened 30 years or more after exposure. Case–control studies have identified HIV, HTLV-1, alcoholism, and some malignancies as risk factors for infection, some of these also being risk factors for hyperinfection (see next). Pathogenesis and life cycle Filariform larvae in moist soil penetrate exposed skin and pass, via the bloodstream, to the lungs, and into the alveolar spaces. From there, the larvae ascend the trachea and are swallowed, reaching their final habitat in the crypts of Lieberkühn in the duodenum and upper jejunum, where they mature. Once the worms have reached maturity in the small intestine, the adult males are rapidly elimin- ated, leaving parthenogenetic adult parasitic females, 2.5 mm in length, attached to the mucosa, where they deposit eggs. One month after infection, the resulting rhabditiform larvae bore through the epithelium into the gut lumen. At this stage, most larvae follow an indirect developmental route—they are excreted in the faeces and develop into free-living adults, which produce eggs from which in- fectious filariform larvae develop, with potential to penetrate ex- posed skin and re-infect humans percutaneously, thus completing the life cycle. Some larvae by contrast develop directly via three moults into filariform larvae. These are usually passed in the faeces and can survive in the soil for many weeks. However, some can re- invade the host in the lower gastrointestinal tract or perianal skin before evacuation. It is this process of autoinfection that explains the persistence of S. stercoralis infections for decades after exposure, and allows for the multiplication of worms that might lead to the phe- nomenon of hyperinfection seen in immunosuppressed patients. Strongyloidiasis, like most helminth infections, is associated with a type 2 immune response, with raised IgE levels and increased cir- culating eosinophil numbers. In immunosuppressed patients, some elements of this immune response are lacking. The pathogenesis of hyperinfection is not well understood. A possible explanation is that immunosuppression facilitates the direct route of strongyloides development, leading to multiplicative autoinfection, increasing larval intensities, and ultimately, dissemination of larvae beyond the gut mucosa into other organs. Pathogenic Gram-negative bacteria, carried from the intestine into the bloodstream and other organs, contribute to the severe morbidity and mortality associated with dis- seminated strongyloidasis. Clinical features Most infected individuals are asymptomatic. In such patients, diag- nosis might only be considered as part of investigation for peripheral eosinophilia. Cutaneous Skin symptoms are often the only manifestation of infection, com- monly in the form of larva currens, a serpiginous pruritic erythema- tous eruption on the legs, buttocks, and back, at the site of migrating larvae, that can advance as quickly as 15 cm/h (Fig. 8.9.4.1). The rash is more diffuse and migrates more rapidly than the cutaneous larva migrans associated with hookworm infections. It can occur with the initial infection, but is also sometimes seen in people with chronic strongyloidiasis. Pulmonary The migratory phase might be associated with cough and tracheal ir- ritation and, less commonly, with wheeze, which may be persistent. Patchy infiltrates might be seen on chest radiographs. When larvae become trapped in the lung during migration, eosinophilic pneu- monia occasionally occurs. Pulmonary manifestations, including Fig. 8.9.4.1 Characteristic serpiginous rash of larva currens on the shoulder of a traveller with Strongyloides stercoralis infection acquired in India. The rash was transient, but recurrent and widespread. Courtesy of R. H. Behrens, Hospital for Tropical Diseases, London.

 pneumonia, bacterial lung abscesses, and acute respiratory distress syndrome are more prominent in hyperinfected patients (see next). Intestinal Intestinal symptoms are generally mild in people with light infec- tion. Epigastric pain mimicking peptic ulcer disease may occur within 3 weeks of infection and persist. Diarrhoea is usually chronic and mild, but can occur early and be associated with bloody stools. In more severe cases, usually associated with hyperinfection, intes- tinal oedema with malabsorption, mesenteric lymphadenopathy, and ascites may occur. An eosinophilic granulomatous enterocolitis resembling Crohn’s disease is well described in older patients on cor- ticosteroids. Subacute intestinal obstruction, biliary stenosis, and necrotizing enteritis are occasionally seen. Special circumstances/Complications Strongyloides hyperinfection Patients on long-term corticosteroids, and those undergoing chemotherapy or organ transplantation, are at risk from severe manifestations of strongyloidiasis. This also occurs in patients with lymphoma or leukaemia without chemotherapy, most commonly in those with T-cell leukaemia caused by human T-cell leukaemia virus (HTLV)-1 infection. It is also well described in HTLV-1-infected patients without overt malignancy, and very rarely in patients with AIDS. Disseminated disease has a mortality rate of 60–70%. Severe diarrhoea is a common feature. Gram-negative pneumonia, bacter- aemia, or meningitis caused by enteric pathogens that have breached the mucosal barrier along with the strongyloides larvae are frequent manifestations. Petechial haemorrhages in the skin, especially around the umbilicus, and hepatitis may occur. Peripheral eosino- philia is usually absent in disseminated disease. Clinical investigations Microscopy of stool might reveal rhabditiform larvae, but the sen- sitivity of direct smears is low. Formol-ether concentration tech- niques are more useful, but multiple stool samples may be required to detect light infections. Culture techniques have been developed to enhance the diagnostic yield. Agar plate cultures have the highest yield; tracks made by larvae migrating across the plate can be seen. Charcoal culture and filter-paper methods make use of the indirect life cycle: stool is incubated for several days to allow the develop- ment of adults and second-generation filariform larvae. Larvae might also be isolated by duodenal aspiration, or by the string test, although these are of limited sensitivity. Molecular techniques, such as real-time and nested polymerase chain reaction (PCR) on stool, perform well. In disseminated infection, larvae are found in the sputum and in biopsies from tissues such as the gastrointestinal tract and lung. Enzyme-linked immunosorbent assays (ELISA) for strongyloides- specific IgG have high sensitivity for strongyloides infection. It is useful as a screening test, particularly before embarking on im- munosuppressive therapy. There is cross-reaction with filarial anti- bodies, and levels may take over a year to become negative after treatment, so specificity may be limited. Treatment and prevention Albendazole 400 mg once or twice daily for 3 days is moderately effective in chronic infections, and is better tolerated than thiaben- dazole 25 mg/kg twice daily for 3 days, which is now rarely used. The treatment of choice is ivermectin 200 μg/kg as a single dose or for two doses 1–14 days apart. Cure rates are more than 90% with a single dose, compared with less than 75% with albendazole. Prolonged courses of treatment are necessary in patients with severe or disseminated disease. Subcutaneous veterinary pre- parations have been used when parenteral treatment is required, although encephalopathy can develop, in association with high serum levels. Improved sanitation and appropriate footwear can reduce the acquisition of infection. Once established, strongyloides should be eradicated in any patient being considered for immunosup-pressive therapy, because of the potentially lethal consequences of hyperinfection. Areas of uncertainty, controversy, and future developments Global prevalence and disease burden are not well understood, due to the limited number of high quality community-based preva- lence studies, or indeed hospital-based prevalence studies among patients at risk of hyperinfection. The limited diagnostic sensitivity of stool microscopy, and limited specificity of serology, are also factors. There has been much interest in use of PCR techniques to provide better diagnostic precision and thus better analyses of risk factors for infection; and in newer serological methods to assess cure. Several specialist guidelines have advocated screening for strongyloides before immunosuppression (e.g. for haematological malignancies, inflammatory bowel disease, transplantation). It is likely that, given the high prevalence of chronic infection in these populations, most patients do not progress to severe disease; further evidence on the pathogenesis of immunosuppression-associated hyperinfection, and on the cost-benefits of screening, are needed to improve practice in these settings. The same is true for screening of immunocompetent immigrants, in whom the health burden of chronic infection is not well established. Another area of interest is the impact of strongyloides coinfection on other infections, for example, tuberculosis. Studies suggest a sup- pressive effect of coinfection on anti-TB immune responses, which suggests there could be an impact of strongyloides infection and of antihelminthic treatment on risk of progression to and of severity of, active tuberculosis. Strongyloides fuelleborni Strongyloides fuelleborni fuelleborni is a parasite of primates in tropical Africa and Asia, which can also infect human populations sharing similar habitats. Prevalence rates up to 20% have been re- ported among forest-dwelling communities. Infections are gen- erally asymptomatic. Unlike S. stercoralis, eggs are passed in the stool, and might be confused with hookworm ova. Benzimidazole therapy is effective. A phylogenetically distinct nematode, Strongyloides fuelleborni kellyei, has been found in rural communities in Papua New Guinea. Infection intensities are highest among young children. It is associ- ated with ‘swollen belly sickness’ in 2-month-old infants, which is characterized by abdominal distension, respiratory distress, gener- alized oedema, and gastrointestinal disturbance.

8.9.4 Strongyloidiasis, hookworm, and other gut strongyloid nematodes 1503 Hookworm Aetiology Human hookworm disease is principally caused by the two species that can complete their life cycles in humans: Ancylostoma duode nale and Necator americanus. Infection is by percutaneous penetra- tion of exposed skin, with subsequent migration and maturation of the worms in the human host. Epidemiology Estimates suggest that more than 1 billion people are infected with hookworm, predominantly sub-Saharan Africa and Asia. Although significant overlap occurs, the distribution of A. duo denale is more restricted geographically than that of N. ameri canus. Necator is more widespread in sub-Saharan Africa, the Americas, Southeast Asia, and India; Ancylostoma is also widely distributed in Southeast Asia, but is more common in temperate regions, North Africa, and the Middle East. As with other intes- tinal helminths, most infected people harbour a few adult worms, but a minority are heavily infected. Social, behavioural, and gen- etic factors determine which individuals within a community are most heavily infected. Unlike most other intestinal helminth infections, the prevalence and intensity of hookworm infection increases with age. Pathogenesis and life cycle The life cycles of the two hookworm species are similar. Larvae in moist soil penetrate exposed skin, usually on the feet or buttocks. They enter the circulation after 10 days, are carried to the lungs, and cross into the alveolae, from where they are transported to the pharynx and swallowed. The adults, approximately 10 mm in length, attach themselves to the small intestinal mucosa with their buccal cavities, which contain hooked teeth (ancylostoma) or cut- ting plates (necator). After 3 to 6 weeks the females produce up to 30 000 eggs per day, which are passed in the faeces. The eggs hatch within 48 h, but the larvae can remain viable for up to 6 weeks in appropriate soil conditions. Adult hookworms live for 1 to 9 years. Infection can also be acquired by the ingestion of contaminated soil, and the transmission of infective larvae via breast milk is well recognized. Infection is associated with tissue and peripheral eosinophilia, and specific IgG and nonspecific IgE responses. Regulatory cyto- kine responses are probably crucial in limiting immunopathology in established infection. Equally important are a range of worm- derived immunomodulatory molecules that interfere with neutro- phil migration and adhesion, inhibit complement, induce T-cell apoptosis, and prevent blood coagulation. Secreted anticoagulants, including serine protease inhibitors of factor Xa, are responsible for anaemia, the main consequence of infection. Radioisotope studies have demonstrated that hookworm infections produce a daily blood loss of up to 0.3 ml per worm per day. This translates into a loss of up to 100 ml per day in heavily infected people. The degree of anaemia is partly a function of worm burden, but also of iron stores. Variations in dietary iron intake, as well as coinfection with other parasites such as schistosomes and malaria, account for some of the geographical differences in the incidence of hook- worm anaemia. Clinical features Migratory/larval Repeated exposure to penetrating hookworm larvae results in ground itch, a pruritic papular erythematous rash on the feet or hands. Larval pulmonary migration is generally asymptomatic, but can cause a pneumonitis characterized by fever, cough, wheeze, haemoptysis, and peripheral eosinophilia. Symptoms can last sev- eral weeks, but are rarely severe. Oral ingestion of A. duodenale larvae can result in Wakana disease, which presents with nausea, vomiting, cough, pharyngeal irritation, and dyspnoea. Intestinal Recently acquired human hookworm infection occasionally causes profuse watery diarrhoea. Most people with established infection are asymptomatic. The major morbidity associated with hookworm infection is iron-deficiency anaemia in those with heavy infections. Haemoglobin concentrations of less than 2 g/dl are not uncommon. Hookworms were first identified in the investigation of anaemic miners in 19th century Europe, notably in Cornish tin mines, where an extreme form of anaemia (chlorosis or 'green disease') was preva- lent. Now eradicated in developed countries, hookworm remains a major cause of anaemia in the developing world. It is particularly common among women of reproductive age, and a major con- tributor towards adverse outcomes in pregnancy, being responsible for over 20% of pregnancy-associated anaemia. Studies have also highlighted an even higher burden of anaemia due to hookworm among elderly residents in high prevalence settings. Fatigue and list- lessness are the principal symptoms, and probably have a significant economic impact in areas of high prevalence. High-output cardiac failure is a major cause of death in patients with severe anaemia. Malabsorption is not a frequent consequence of hookworm infec- tion, but protein loss does occur and might contribute to the oedema seen in severe infections. Dyspepsia, nausea, and a range of nonspecific symptoms are common in those with heavy worm burdens. Pica, a craving for eating soil, is well described in patients with hookworm anaemia. Growth and cognitive development There has been debate about the effect of chronic hookworm infec- tion on growth and cognitive development in childhood. Seminal work in an impoverished community in the southern United States of America in the 1920s demonstrated an inverse association be- tween IQ and hookworm intensity. The results of subsequent studies have been inconclusive. Intervention trials in East Africa have sug- gested a modest effect of heavy hookworm infection on growth, and the balance of evidence suggests that heavily infected subjects do have impairments of memory and other specific cognitive functions. It is not known to what extent these effects are mediated by, or are independent of, anaemia. Treatment results in improved cognitive performance and school attendance among those with the heaviest infections. Clinical investigations The diagnosis of acute hookworm infection is clinical. Characteristic symptoms are usually associated with peripheral eosinophilia. The diagnosis of chronic infection is made by discovering eggs in the stool by microscopy. Symptomatic infection is readily diagnosed by

section 8 Infectious diseases 1504 direct microscopy of a single stool sample, as the worm burden is high in these patients. Where diagnosis of lighter infections is required (e.g. in the investigation of eosinophilia), the diagnostic yield is in- creased by examining multiple stool samples, using concentration methods, or by culture techniques. The latter allow for the develop- ment of third-stage larvae, which can be used to identify the infecting hookworm species and differentiate from related nematode species. Semiquantitative techniques, such as the modified Kato smear, or more sensitive faecal flotation methods, can be used to estimate in- fection intensity. Hookworm eggs degenerate rapidly after excretion, and laboratory processing should be performed as soon as possible. Treatment, prevention, and control A single dose of albendazole 400 mg, will kill more than 80% of adult hookworms and thus reduce the worm load to a level below that likely to cause disease. Complete eradication can be achieved with repeated doses. Treatment is well tolerated, and can safely be given to children and in pregnancy (although not recommended in the first trimester). Single-dose mebendazole is much less effective. For patients with anaemia, anthelmintic treatment should be combined with iron replacement. Patients with heart failure or severe anaemia during pregnancy frequently require transfusion of packed red cells. In developing countries where the prevalence of hookworm and other intestinal helminths is high, the increasing availability of safe, affordable, single-dose anthelmintics makes mass deworming pro- grammes feasible (Fig. 8.9.4.2). The impact of empirical population- based treatment (e.g. in schools), can be sustained in the face of ongoing transmission by repeated treatment at 3- to 12-month inter- vals. These strategies can be integrated with control programmes for other helminthiases. The World Health Organization set a target date of 2020 for routine anthelmintic treatment to be provided to 75% of school-age children at risk of infection. Current global coverage is close to this target, which has already been achieved by many African and southeast Asian countries. The outcomes of national control programmes on anaemia have been mixed. School-based programmes miss the most vulnerable populations (preschool chil- dren and pregnant women), and new targets for expanded coverage to include these groups have been introduced. Furthermore, pro- grammes combining albendazole with antischistosomal treatment have had more impressive outcomes, suggesting that in coinfected populations both helminths contribute to anaemia. The age–intensity distribution of hookworm infection is likely to limit any benefit of mass treatment programmes on hookworm transmission. The provision of better footwear (although clearly protective against infection) and improved sanitation for infected communities probably has only a marginal role, at least in the me- dium term, in reducing transmission. Vaccines offer potential for better hookworm control, but development has been hampered by challenges in generating relevant animal models and in eliciting safe immune responses in early clinical studies. Nonhuman hookworms Nonhuman hookworms cannot complete their life cycle in the human host, but are capable of causing significant morbidity in the skin and gastrointestinal tract. Cutaneous larva migrans Cutaneous larva migrans presents as intensely pruritic lesions on exposed areas of the skin. The rash is commonly seen on the feet or buttocks, but can occur elsewhere (Fig. 8.9.4.3). Dog hookworms, Fig. 8.9.4.2 School-based treatment as part of a mass anthelmintic treatment programme in Burkina Faso. Courtesy of A. Gabrielli, Schistosomiasis Control Initiative. (a) (b) Fig. 8.9.4.3 Cutaneous larva migrans: (a) caused by probable Ancylostoma braziliense infection acquired on a beach in the Caribbean, and (b) heavy infection with Ancylostoma braziliense acquired in Brazil. (a) Courtesy of D. Webster; (b) copyright D. A. Warrell.

 such as Ancylostoma braziliense, are usually implicated. Like human hookworms, these species thrive in sandy soil and frequently in- fect travellers visiting beaches in the Caribbean, Southeast Asia, and Africa. Untreated, the rash can persist for months, with gradual spread through the epidermis leaving serpiginous tracks. Secondary bacterial infection can sometimes occur. Diagnosis is clinical, al- though the worm can be visualized in biopsies taken from the leading edge of the lesion. Topical albendazole or thiabendazole are usually effective, although short courses of oral albendazole or iver- mectin are more effective. Ancylostoma caninum-associated gastroenteritis First described in Australia in the 1980s, a distinctive eosinophilic enteritis has been linked to infection with A. caninum, a dog hook- worm. The global distribution of this disease is unknown. Oral in- gestion might be the predominant route of infection. Manifestations range from a limited aphthous ileitis with tissue and peripheral eosinophilia, which may be asymptomatic, to a severe painful eo- sinophilic gastroenteritis with gut oedema, ascites, and regional lymphadenopathy. Immature hookworm larvae can be identified in the lesions, although the diagnosis might only be made at lapar- otomy. Benzimidazoles are effective. Oesophagostomum spp. Human oesophagostomiasis, usually caused by Oesophagostomum bifurcum, is common in forested areas of West Africa, but rare else- where. Prevalence in some areas of Togo and northern Ghana has reached 75%. The nematode can complete its life cycle in humans, and is distinct from related species in primates. Humans probably ac- quire the disease by ingesting infective third-stage larvae, although a percutaneous route of infection has not been excluded. The larvae migrate to, and develop within, the colonic wall before returning to the intestinal lumen where they reach adulthood and excrete eggs. Intense tissue reactions occur around the larvae, forming nodules along the wall of the (usually ascending) colon. Although these in- fections are generally asymptomatic, heavy infections can result in the development of multiple pea-sized nodules, with gross mucosal and serosal oedema, and microabscess formation (Fig. 8.9.4.4). Children are most commonly affected and present with abdominal pain, diarrhoea, and weight loss. Solitary palpable painful inflam- matory masses, known as Dapaong tumours, also occur within the bowel wall and in extraintestinal sites, such as the mesentery or ab- dominal wall. Nodules can be detected ultrasonographically. Ova are morphologically indistinguishable from those of hookworm, but can be differentiated by culturing third-stage larvae. Treatment with short courses of albendazole is effective and may obviate the need for surgery. Mass treatment campaigns have reduced the burden of disease. Trichostrongylus spp. Trichostrongylus spp. are ubiquitous nematode parasites of herbi- vores, particularly domesticated animals such as sheep, goats, cattle, and donkeys. Human infection occurs most commonly among herders, with a prevalence of more than 80% reported among Iranian nomads. Sporadic human infections occur in urban en- vironments through contact with the faeces of domestic animals. Infective larvae hatch in the soil, and are ingested with contaminated vegetables. There is no migratory phase; the adults develop in the duodenal mucosa, and produce eggs after a long prepatent period. Most infected people are asymptomatic, although eosinophilia is common. Epigastric pain, diarrhoea, and rectal bleeding may occur. Diagnosis is made by finding eggs (which might be mistaken for hookworm ova) by stool microscopy. The adults are occasionally seen at endoscopy. Benzimidazole anthelmintics may be effective, although resistance is increasing; a single dose of ivermectin 200 μg/ kg is usually sufficient. Areas of uncertainty, controversy, and future developments Recent molecular studies have demonstrated that a proportion of patent hookworm infections is, in fact, due to infection with Ancylostoma ceylanicum, a hookworm species whose natural hosts are cats and dogs. Surveys in Asia have demonstrated that this is the second most common hookworm infection among humans, comprising nearly 25% total patent infections in some surveys. Experimental infections demonstrate significant morbidity, with ‘ground itch’, abdominal pain, eosinophilia, and establishment of chronic infection with anaemia. There are limited data, however, on the health burden associated with naturally occurring infection. One particular area of interest is the effect of hookworm infection on the immunes system. Helminth infections have a similar global distribution to other pathogens. Our understanding of the immune response to helminth infection has stimulated interest in the effect of helminths on subjects coinfected with other microorganisms, particularly malaria, tuberculosis, and HIV. Hookworm infection in pregnancy or early childhood is associated with a slight increase in incidence and severity of malaria. There are demonstrable effects of hookworm infection on immune responses to mycobacterial antigens, although hookworm does not appear to increase the inci- dence of tuberculosis or accelerate the progression of HIV infection. There is evidence that childhood or maternal infection with some helminths, especially hookworm, may protect against the develop- ment of infantile eczema and/or atopy. These findings lend support to the ‘hygiene hypothesis’ that the increasing prevalence of allergy Fig. 8.9.4.4 Excised colon from a young

Ghanaian adult with Oesophagostomum bifurcum-associated disease. Multiple nodules and serosal oedema are present. The diagnosis was made at laparotomy after the patient presented with abdominal pain and peritonism. Courtesy of A. M. Polderman, Leiden University Medical Center, Netherlands.

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