23. *Onchocerca volvulus* (Leuckart 1893)

Introduction

Onchocerca volvulus is a vector-borne, filarial nematode parasite. The adult worm lives in the subcutaneous tissues. Its offspring, microfilariae migrate and induce injury to a variety of anatomical sites contiguous with that tissue. There are no reservoir hosts for this parasite. The blackfly, *Simulium spp.*, is the vector of *O. volvulus*. This filarial parasite occurs mostly in West Africa, northern South America, and throughout Latin America. Onchocerciasis used to be the major cause of blindness[1] throughout sub-Saharan Africa, often affecting more than 50% of the inhabitants of towns and villages in endemic areas. The disease also causes a disfiguring dermatitis that at one time was second only to polio as a cause of long term disability in endemic areas. It was once so prevalent that people could not live in many places along riverbanks.

Vector control, together with a program of donation and administration of the Merck drug ivermectin (Mectizan) have resulted in dramatic reductions in the incidence and prevalence of this disease. For instance, between 1974 and 2002, the Onchocerciasis Control Program halted transmission in 11 west African countries (Benin, Burkina Faso, Cote d'Ivoire, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Senegal, Sierra, Leone and Togo), and prevented an estimated 600,000 cases of blindness. It has been further estimated that 18 million children born in the OCP area are now free from the risk of river blindness, and approximately 25 million hectares of land have now been rendered free of the disease.[2]

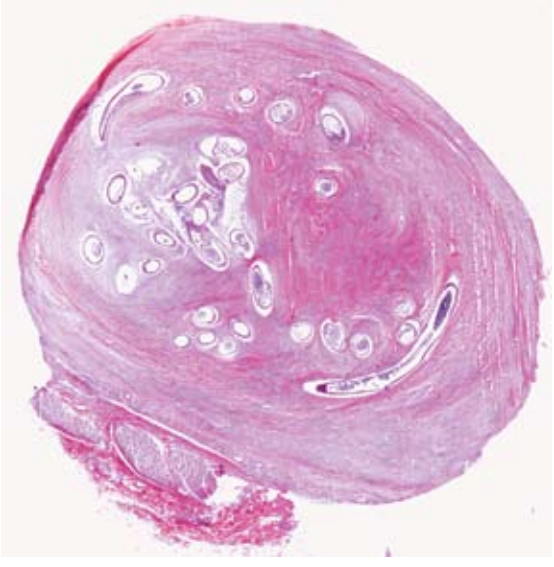


Figure 23.1. Cross section of nodule (onchocercoma) induced by *Onchocerca volvulus*. Numerous sections of adult worms are seen. 2.5 cm in diam.

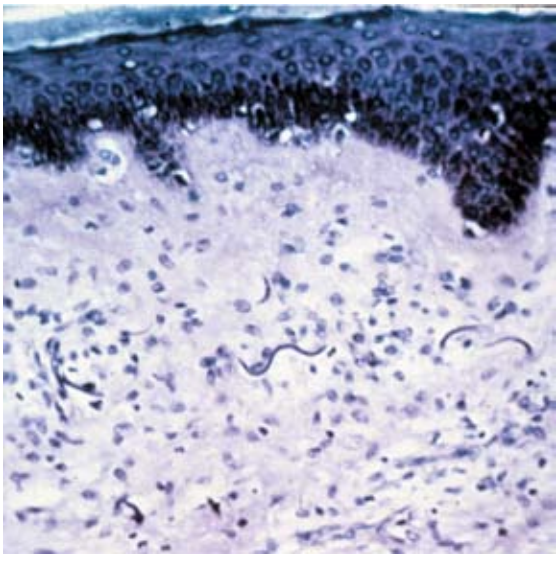


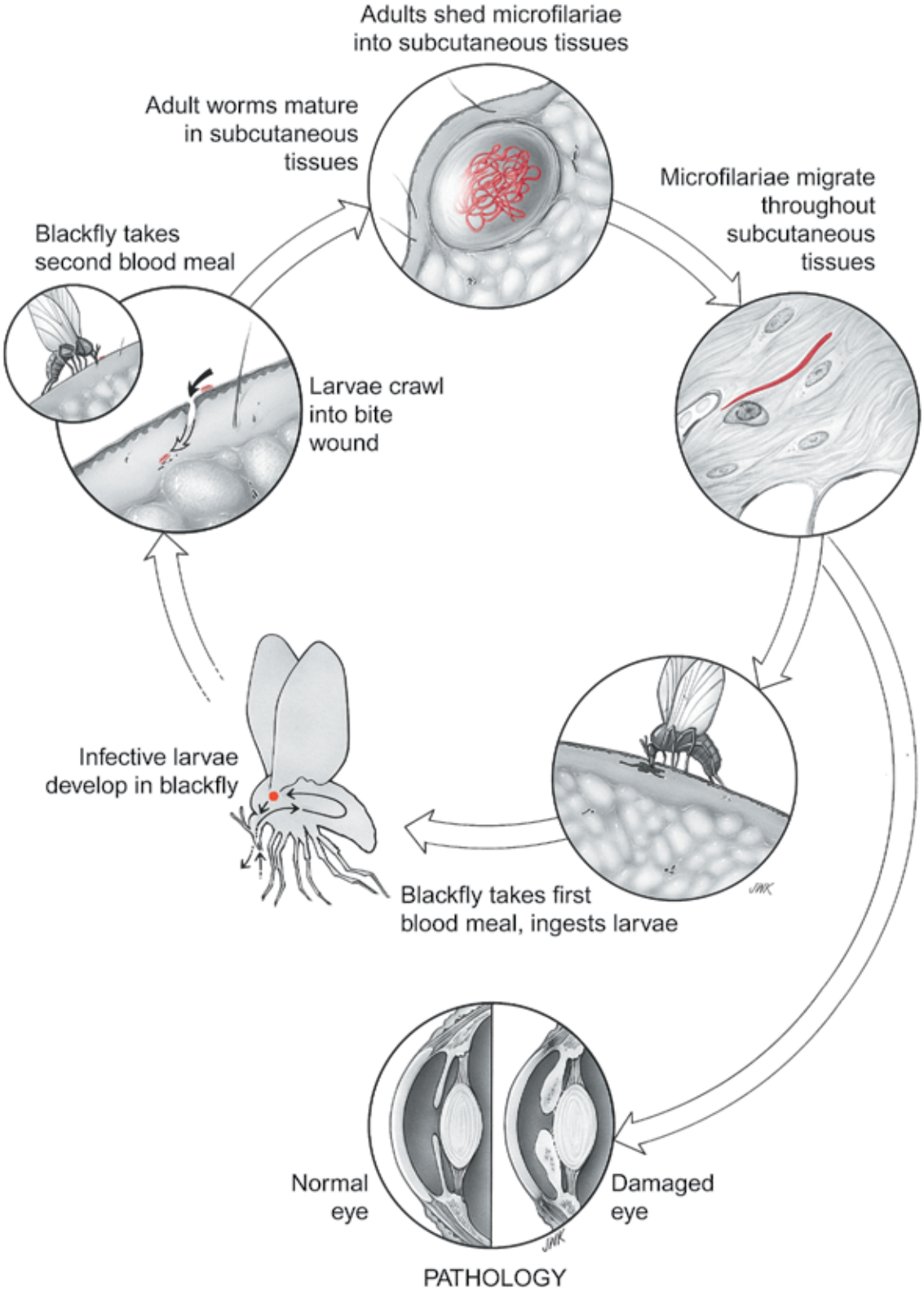
Figure 23.2. Section of skin with numerous microfilariae of *O. volvulus*.

Current estimates indicate that approximately 18 million people remain infected worldwide, with 99 percent or more living in Sub-Saharan Africa, Yemen, and small foci in Latin America (Mexico, Ecuador, Guatemala, Colombia, Venezuela and Brazil). Through a new African initiative, the African Programme for Onchocerciasis Control (APOC), a partnership under the leadership of the World Bank, WHO, UNDP, and FAO, which builds on the previous successes of the OCP, there is optimism that onchocerciasis might be completely eradicated in the coming decades. APOC aims to treat 75 million people with ivermectin per year by 2010, extending its reach to the remaining 19 endemic countries in Central and East Africa (Angola, Burundi, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Sudan, Tanzania and Uganda).[2] Similarly the Onchocerciasis Elimination Program for the Americas (OEPA) is working to eliminate river blindness in the seven Latin American countries by 2007.

Historical Information

Onchocerca volvulus was first described in Africa by Leuckart. He recounted his discovery of the parasite to Patrick Manson, who, in turn, published the full description in 1893, giving Leuckart full credit.[3] Earlier, O'Neill[4] observed the microfilariae of this filarial nematode in the skin of a patient from West Africa. Onchocerciasis in Latin America was not reported until 1917, when Robles[5] found ocular disease associated with the presence of nodules on the forehead of a small boy. He dissected the nodule and found that it contained

Onchocerca volvulus



the adult worms. Later Robles described the anatomy of the worm, the pathology of the disease, and epidemiology of the infection. Moreover, he suspected that the blackfly was the vector, which was later proved by Blacklock[6] in 1927.

Life Cycle

Adult females measure about 40 cm in length and 0.3 cm in width, while the male measures about 3 to 5 cm in length. Both sexes lie entwined about each other, locating to subcutaneous fibrous nodules, onchocercomas (Fig. 23.1), which vary in size depending on the number of adult worms in them. Some nodules are so small that they cannot be palpated.[7] Microfilariae are produced within the nodules, and leave these sites to migrate throughout the subcutaneous tissues (Figs. 23.2, 23.3). The blackfly (Fig. 38.5) acquires the larvae while taking a blood meal. The immature worms penetrate the insect's hemocele and the muscle fibers of the flight wing bundles in the thorax. After 6-8 days of development, during which the larvae molt twice, the now infective larvae leave the muscles, enter the cavity of the proboscis, and are deposited on the skin when the fly bites. Larvae enter the bite wound after the fly withdraws its biting mouthparts. The immature parasites invade the subcutaneous tissues with the aid of a protease[8] and take up residence there. After completing their development, they mate. Adults produce hundreds to thousands of microfilariae during their life span (about 700 microfilariae per day) of 8-10 years. Growth and molting of worms in the subcutaneous tissues induces formation of the fibrous nodules and also elicits an angiogenic response,[9, 10] resulting in the production of a network of vessels, the function of which is presumably to supply nutrients to the parasites and carry away metabolic wastes. A similar angiogenic response is induced by the Nurse cell-parasite complex of *Trichinella spiralis*.[11]

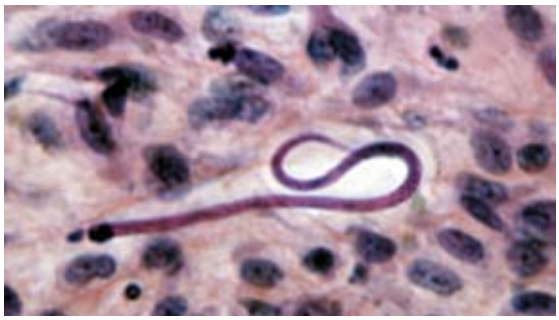


Figure 23.3. Higher magnification of a microfilaria of *O. volvulus* in skin. 310 μm x 7 μm.

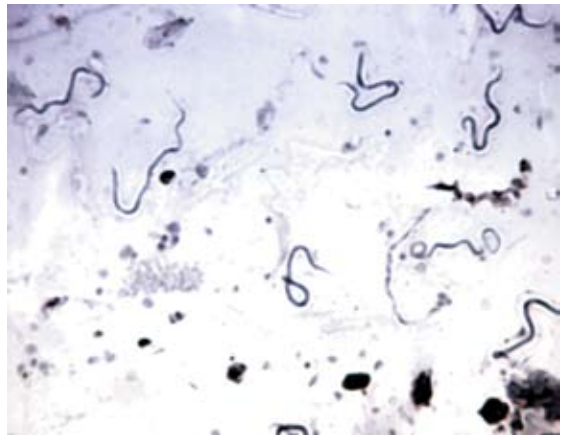


Figure 23.4. Impression smear of a skin snip from a patient heavily infected with *O. volvulus*. Microfilariae were visualized with Giemsa stain.

Cellular and Molecular Pathogenesis

Onchocerca larvae migrate through the tissues with the aid of macromolecules that promote tissue degradation, angiogenesis, and plasmin-mediated proteolysis.[8-10, 12] *O. volvulus* has impressive immunomodulatory properties, with the capacity to bias host responses to a Th2-type pattern. By this mechanism, host-cell-mediated Th1-type immunity is suppressed leading to impaired responses to PPD skin testing for tuberculosis,[13] tetanus, and other vaccinations,[14] and even increased susceptibility to intercurrent infections with lepromatous leprosy.[15]

The degree of pathogenesis varies directly with the intensity of infection and the degree of host responsiveness to dying adult worms and microfilariae and their secretions. Dead microfilariae induce inflammatory reactions that become more severe as the infection persists; this point is important when considering therapy. The lesions, primarily involving the skin and the eyes, occur as a consequence of cell-mediated immunity to parasite antigens. Individuals with the most vigorous cell-mediated immune responses develop the most severe manifestations.[1, 12, 17] The magnitude of the host immunopathologic response significantly influences the severity of clinical onchodermatitis.[17] Host mast cells play an important role in this phenomenon.[18]

The major ocular lesions occur in the cornea to produce a keratitis.[16] In this case, the keratitis results from an accumulation of punctate opacities in the cornea that arise from a unique immunopathologic damage to microfilariae in the eye. This is a Th2-dependent process with a heavy reliance on host interleukin 4.[16] In the skin, similar immune responses lead to pruritus and angioedema.

Subcutaneous nodules, the other hallmark of clinical onchocerciasis, vary in size from barely discernable to approximately 5 cm in diameter. Nodules develop over an 18-month period depending on the number of

adult worms in each. The number of nodules also varies, from an occasional one to several hundred, occupying large areas of subcutaneous tissue. In the latter instance, blackflies biting such individuals may actually expire due to the overwhelming nature of the infection in their flight wing muscles. Those areas in which peripheral lymphatics converge (e.g., occiput, suboccipital areas, intercostal spaces, axilla, and iliac crests) have the highest predilection for nodules. The body regions most affected differ according to geographic locales. In Africa, for example, the nodules predominate in the lower part of the body, whereas in Central America they tend to be found more often in the upper portions of the body. This difference is related to the biting habits of the vector insects, and the styles of clothing worn by the inhabitants of each endemic area.

O. volvulus, like *Wuchereria bancrofti*, contain bacterial symbionts of the genus Wolbachia. These are rickettsia-like organisms that are found in the body wall, in oocytes, and in all embryonic stages, including microfialriae.[19] The Wolbachia symbionts are believed to be essential for nematode fertility and are transmitted transovarially to the next worm generation, in a manner similar to mitochondria.[20] Wolbachia also contains endoxin-like products that are proinflammatory. This has led to the hypothesis that the bacterial symbionts contribute significantly to the skin and eye pathology of *O. volvulus*-infected patients.[19, 20]

Clinical Disease

Clinical onchocerciasis includes dermatitis, eye lesions, and onchocercomas.

Onchodermatitis

Mild infection (less than five nodules per infected individual) is usually asymtomatic. In contrast, moderate to severe infection (ten or more nodules, with many in the head and neck region) produce correspondingly more serious and more numerous symptoms. Involvement of skin is characterized by intense itching, which is associated with a rash consisting of numerous small, circular, elevated papules 1-3 mm in diameter. On white skin, the papules are reddish, but on black skin, they tend to be dark brown. The pruritus of onchodermatitis is intense and disabling. Occasional suicides result from the extreme discomfort associated with it.[1] The affected areas of skin become edematous and thickened, and lose their elasticity. The skin can take on an orange-peel quality. Over time, the skin will atrophy, especially over the buttocks, with appearance of wrinkles. Depigmentation can also occur, especially over the shins. Sometimes this is known as “leopard skin”. These sequelae are more common in Africa than in Central America, but Central American children who are infected may have facial lesions, reddish in color, described as *erysipelas de la costa*.

Lymphadenopathy

Lymph node involvement in Africa is usually found in the inguinal and femoral nodes, whereas in the American tropics it is in the head and neck. Advanced lymph node involvement can lead to adenocele formation.[1]

Ocular Lesions

All parts of the eye are affected in chronic, long-term infections. Initially, there may be conjunctivitis, with irritation, lacrimation, and photophobia, a reaction analogous to the dermatitis in response to dead microfilariae. The cornea at this time reveals the punctate lesions of keratitis. Slit-lamp examination reveals motile or dead microfilariae in the conjunctiva. A long-standing infection produces sclerosis and vascularization. Sclerosing keratitis is the leading cause of blindness due to onchocerciasis, and develops over a 20- to 30-year period. Onchocercal blindness peaks in those between 30 and 40 years of age; individuals most responsible for taking care of their families.[1] The anterior chamber is also invaded, and microfilariae can be seen there with a slit lamp. Finally, there may be iritis, iridocyclitis, and secondary glaucoma. Invasion of the posterior segment of the eye causes optic neuritis and papillitis; the choroid and the retina are also involved.

Diagnosis

Because of its highly focal distribution, a travel history is critical in order to entertain a clinical suspicion of onchocerciasis. A definitive diagnosis is usually made by examining a piece of skin (2-5 mm^2) dissected from the affected part of the body. In Africa, the specimen should be obtained from the lower part of the body, and in Central America from the upper part. The skin should be alcohol-cleansed, elevated with a needle, and cut with a scalpel blade. Next, a preferably bloodless piece should be placed in warm physiological saline and examined microscopically for motile microfilariae within 10 minutes. A representative sample of skin can be weighed and the number of microfilariae per milligram of tissue calculated as an index of the intensity of infection. In addition, the piece of skin can be pressed against a dry microscope slide, and the impression stained with Giemsa solution and examined microscopically for microfilariae (Fig. 23.4). Histologic sections of a subcutaneous nodule (Fig. 23.2, 23.3) may also reveal microfilariae. The sensitivity of skin snips has recently been improved by PCR amplification.[21, 22] The Mazzotti Test is a provocative challenge test using a 50 mg dose of diethylcarbamazine (DEC). Within 3 hours after treatment, patients with *O. volvulus* infection will develop pruritus. In heavily infected patients, the Mazzotti reaction can be severe and may exacerbate the ocular pathology in a patient. As an alterna-

tive, some physicians perform a type of patch test by applying DEC to a small region in order to elicit a local Mazzotti-like reaction.[23]

Serologic tests that measure IgG antibodies to O. volvulus are sensitive, but their specificity is poor, and not yet useful to the clinician. Efforts are underway to develop recombinant immunodiagnostic reagents.

Treatment

Ivermectin is the drug of choice for onchocerciasis. Ivermectin inhibits the release of microfilariae from the female.[24] Usually, a single oral dose of 150 mcg/kg administered every 6 months will slow or reverse the progression of both ocular and cutaneous diseases.[25] The drug is available through the Mectizan® Donation Program established in 1988 by Merck & Co. Ivermectin does not kill the adult worms encased in a nodule. Therefore, repeat dosing is necessary to suppress the release of microfilariae. In some patients more frequent interval dosing is required in order to suppress pruritus. Community-wide chemotherapy interrupts transmission of onchocerciasis.[26, 27] The major toxicity of ivermectin is generally not from the drug itself but rather from its ability to increase the antigen load from dead and dying parasites, leading to fever, angioedema and pruritus. These symptoms usually occur within 24 hours of treatment. In those patients with concurrent *Loa loa* infection, ivermectin can elicit severe reactions, including encephalopathy.[28] This point is especially critical in areas such as West and Central Africa, where there is epidemiologic overlap between the two helminth infections. In Latin America, the surgical removal of palpable subcutaneous nodules has led to successful resolution of the infection in some instances.

The possible role of Wolbachia endosymbionts in the inflammatory processes that lead to eye and skin changes in *O. volvulus* infection, as well as their role in embryogenesis and parasite fertility, has led to the suggestion that antibiotics could have a therapeutic activity for patients with onchocerciasis.[29] Prolonged administration of doxycycline (200 mg/day for 4-6 weeks) was shown to interrupt *O. volvulus* embryogenesis.[19] Further investigations on the role of antibiotics for the treatment of onchocerciasis are in progress.

Prevention and Control

Onchocerca volvulus distribution follows that of the dipteran vectors. Blackflies breed in fast-running water of mountainous streams in regions of Africa and South and Central America, and they have a fairly long flight range. Thus, onchocerciasis can be found several miles from the nearest endemic breeding site. Because much of the coffee of the world is grown on mountainous hillsides, the prevalence of onchocerciasis among workers on coffee plantations is high. The OCP was launched in 1974, with a primary emphasis on reducing simulium larval vector populations with DDT and other insecticides.[30] With the increasing availability of ivermectin In the later years of the program, the OCP increasingly focused on control using this drug as an agent of mass chemotherapy.[31]

In Africa, efforts to control onchocerciasis are currently being conducted by APOC.[2] Critical to the success of APOC is the Merck Mectizan Donation Program (MMDP), one of the first and largest public private partnerships devoted to a neglected disease. The MMDP was launched in 1987 when Roy Vagelos, then CEO of Merck made a historic announcement that his company would donate Mectizan® to anyone who needed it, for as long as it was needed.[2, 31] The MMDP works closely with the Task Force for Child Survival and Development, an affiliate of Emory University for this purpose. To date, the MMDP has donated an estimated 300 million treatments worth approximately $450 million.[2]

APOC works with the organizations previously involved with the OCP, as well as Merck, the governments of 19 developing countries, 27 donor countries, at least 30 NGOs, and more than 80,000 rural Africa communities.[2] This is done by coordinating with the ministries and NGOs to deliver Mectizan along with existing national health systems of the participating African countries. To accomplish its mission, APOC has implemented a novel system of community-directed treatment programs. By 2010 it is anticipated that the sight of nearly 500,000 people will be saved. In addition, the community-based health systems created by APOC are expected to provide a framework for additional pro-poor health interventions including those that target other neglected diseases such as soil-transmitted helminth infections, schistosomiasis, and trachoma.

In the seven onchocerciasis-endemic Latin American countries, OEPA has also made great strides through extensive use of Mectizan® treatments. Headquartered in Guatemala City, OEPA together with the Carter Center has reduced the number of people at risk for onchocerciasis from 4.7 million in 1995 to an estimated 500,000 persons in 2003 (www.cartercenter.org). In 2001, the Careter Center's International Task Force for Disease Eradication targeted onchocerciasis for eradication in the Americas.

As a complementary approach to onchocerciasis control, there have been some efforts to develop recombinant vaccines.[31, 32] This includes the Onchocerca homologue of a hookworm ASP and an aldolase, which have shown promise in laboratory animals.[33, 34]

References

1. Greene BM. Modern medicine versus an ancient scourge: progress toward control of onchocerciasis. J Infect Dis 166:15-21. 1992.
2. Levine R and the What Works Working Group. Millions Saved, Proven Successes in Global Health, Case 6, Controlling Onchocerciasis in Sub-Saharan Africa, Washington DC: Center for Global Development 2004; pp. 57-64
3. Manson P. *Filaria volvuloxus*. In: Hygiene and Diseases of Warm Climates (Davidson AH., ed). Y.J. Pentland, London. p. 1016. 1893.
4. O'Neill J. On the presence of a filaria in "crawcraw." Lancet 1:265-266. 1875.
5. Robles R. Enfermidad nueva en Guatemala. Juventud Med 17: 97-115. 1917.
6. Blacklock DB. The insect transmission of *Onchocerca volvulus* (Leuckart 1893). The cause of worm nodules in man in Africa. BMJ 1:129-133, 1927.
7. Duke BO. The population dynamics of *Onchocerca volvulus* in the human host. Trop Med Parasitol 44:61-8. 1993.
8. Lackey A. James ER. Et al. Extra-cellular proteases of *Onchocerca volvulus*. Exp Parasitol 68:176-185. 1993.
9. Tawe W. Pearlman E. Unnasch TR. Lustigman S. Angiogenic activity of *Onchocerca volvulus* recombinant proteins similar to vespid venom antigen 5. Mol Biochem Parasitol 109: 91-9. 2000.
10. Higazi TB. Pearlman E. et al. Angiogenic activity of an *Onchocerca volvulus* Ancylostoma secreted protein homologue. Mol Biochem Parasitol 129: 61-8. 2003.
11. Capo V. Despommier DD. Polvere RI. *Trichinella spiralis*: vascular endothelial growth factor is up-regulated within the Nurse cell during early phase of its formation. J Parasit 84:209-214. 1998.
12. Jolodar A. Fischer P. et al. Molecular cloning of an alpha-enolase from the human filarial parasite *Onchocerca volvulus* that binds human plasminogen. Biochim Biophys Acta 19: 1627: 111-20. 2003.
13. Rougemont A. Boisson Pontal ME. et al. Tuberculin skin tests and BCG vaccination in hyperendemic area of onchocerciasis (letter). Lancet 1:309. 1977.
14. Cooper PJ. Espinel I. et al. Human onchocerciasis and tetanus vaccination: impact on the postvaccination antitetanus antibody response. Infect Immun 67: 5951-7. 1999.
15. Prost A. Nebout M. Rougemont A. Lepromatous leprosy and onchocerciasis. BMJ 1:589-90. 1979.
16. Pearlman E. Lass JH. et al. Interleukin 4 and T helper type 2 cells are required for development of experimental onchocercal keratitis (river blindness). J Exp Med 182:931-40. 1995.
17. Ali MM. Baraka OZ. et al. Immune responses directed against microfilariae correlate with severity of clinical onchodermatitis and treatment history. J Infect Dis 187: 714-7. 2003.
18. Cooper PJ. Schwartz LB. et al. Association of transient dermal mastocytosis and elevated plasma tryptase levels with development of adverse reactions after treatment of onchocerciasis with ivermectin. J Infect Dis 186: 1307-13. 2002.
19. Hoerauf A. Buttner D. Adjei O. Pearlman E. Onchocerciasis. BMJ 326: 207-210. 2003.
20. Keiser PB. Reynolds SM. et al. Bacterial endosymbionts of *Onchocerca volvulus* in the pathogenesis of post-treatment reactions. J Infect Dis 185: 805-11. 2002.
21. Boatin BA. Toe L. et al. Detection of *Onchocerca volvulus* infection in low prevalence areas: a comparison of three diagnostic methods. Parasitology. 125:545-52. 2002.
22. Bradley JE. Unnasch TR. Molecular approaches to the diagnosis of onchocerciasis. Adv. Parasitol 37:57-106. 1996.
23. Kilian HD. The use of a topical Mazzotti test in the diagnosis of onchocerciasis. Trop Med Parasitol 39:235-238, 1988.
24. Greene BM. Taylor HR. et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. N Engl J Med 313:133-138. 1985.
25. Burnham G. Ivermectin treatment of onchocercal skin lesions: Observations from a placebo-controlled, double-blind trial in Malawi. Am J Trop Med Hyg 52:270-6. 1995.
26. Taylor HR. Pacque M. Munoz B. Greene BM. Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. Science 250:116-118. 1990.
27. Cupp EW. Ochoa JO. et al. The effects of repetitive community-wide ivermectin treatment on transmission of *Onchocerca volvulus* in Guatemala. Am J Trop Med Hyg 47:170-180. 1992.
28. Chippaux J-P. Ernould J-C. et al. Ivermectin treatment of loiasis. Trans R Soc Trop Med Hyg 86:289. 1992.
29. Hoerauf A. Mand S. et al. Doxycycline in the treatment of human onchocerciasis: Kinetics of Wolbachia endobacteria reduction and of inhibition of embryogenesis in female Onchocerca worms. Microbes Infect 5:261-73. 2003.
30. Omura S. Crump A. The life and times of ivermectin – a success story. Nature Rev Microbiol 2: 984-9. 2004.
31. Peters DH. Phillips T. Mectizan donation program: evaluation of a public-private partnership. Trop med Int Health 9: A4-15. 2004.
32. Lustigman S. James ER. Tawe W. Abraham D. Towards a recombinant antigen vaccine against *Onchocerca volvulus*. Trends Parasitol 18: 135-41. 2002.
33. Nutman TB. Future directions for vaccine-related onchocerciasis research. Trends Parasitol 18: 237-9. 2002.
34. MacDonald AJ. Tawe W. et al. Ov-ASP-2, the *Onchocerca volvulus* homologue of the activation associated secreted protein family is immunostimulatory and can induce protective anti-larval immunity. Parasite Immunol 26: 53-62. 2004.
35. McCarthy JS. Wieseman M. et al. *Onchocerca volvulus* glycolytic enzme fructose-1,6-bisphosphate aldolase as a target for a protective immune response in humans. Infect Immun 70: 851-8. 2002.