20.2.2 Filariasis

Filariasis is caused by parasites belonging to the order Filaroidea. *Wuchereria bancrofti* and *Brugia malayi* both cause lymphatic filariasis (elephantiasis), *Loa loa* causes fugitive swelling in particular around the eyes, and *Onchocerca volvulus* causes onchocerciasis (river blindness). All the diseases are caused by helminthic worms transmitted through bites of insects belonging to the order Diptera. Some of the symptoms of the diseases are caused by the presence of parasites restricting the flow of lymph fluid, others by the tiny microfilaria invading the skin and eyes. Approximately 120 million people are infected with the parasites and 40 million severely disabled. Onchocerciasis is estimated to have infected 17.7 million peoples, of which 500,000 have visual impairment and 270,000 are blinded. The disease is limited to the vicinity of rivers where the vector, blackflies of the genus Simulium, is endemic. Unfortunately, the burden of the disease often forces the population to leave these areas uninhabited. The infection can be treated with ivermectin or with a combination of ivermectin with albendazole (Figures 20.2 through 20.4). Ivermectin, a dihydro derivative of avermectin B_{1a} and B_{1b} obtained from *Streptomyces avermitilis*, acts by opening invertebrate-specific glutamate-gated chloride ion channels in the nerve end and muscles of the parasites. This leads to death of microfilariae, the first larval stage. The drug does not cause immediate death of the adult parasite but reduces the worm's life-span. Human glutamate-gated chloride channels are not affected by ivermectin (**20.8**).

The observation that filarial nematodes live in symbiosis with *Endobacteria wolbachia* has initiated experimental treatment with antibiotics like tetracycline, rifampicin, and doxycycline.

20.3 Infections Caused by Protozoan Parasites Belonging to Other Genera than Plasmodium

Protozoan parasites are single-celled organisms that have an animal-like nutrition (they cannot perform photosynthesis). The life cycle of protozoan parasites involves two hosts; the smaller of which typically is named the vector. Important genera are *Plasmodium*, *Trypanosoma*, and *Leishmania*. Protozoans in the guts like *Entamoeba histolytica* will not be described in this chapter.

20.3.1 Trypanosomiasis

Two major tropical diseases, American trypanosomiasis (Chagas disease) and African trypanosomiasis (sleeping sickness), are caused by *Trypanosoma cruzi* and subspecies of *Trypanosoma brucei*, respectively. Two subspecies of *T. brucei* exist. *T. b. gambiense* is found in Central and West Africa, whereas *T. b. rhodiense* is present in East and South Africa. African trypanosomiasis is spread with tsetse flies (*Glossina* species). If untreated, the disease may be lethal: for *T. b. rhodiense* in the acute blood stage, for *T. b. gambiense* when the parasites enter the CNS causing coma (explaining the name sleeping disease) and death. In 1990, 300,000 new cases were estimated each year, whereas intensive measurements have led to a decrease to 30,000 new cases in 2009. Treatment of infections with *T. b. gambiense* is based on therapy using a combination of nifurtimox (Figure 20.2, **20.6**) and eflornithine (**20.7**), whereas the only drugs available for the treatment of the disease caused by *T. b. rhodiense* are suramin (**20.10**) in the acute stage and in the late stage the arsenical drug melarsoprol (**20.5**), both developed almost 100 years ago. Suramin was developed based on a misconception of Paul Ehrlich that the ability of trypan red to stain *Trypanosoma* parasites could be used to combat these organisms. The same misconception was used to develop chloroquine (Section 20.5.1).

The mechanism of action of nifurtimox **(20.6)** is not understood in detail, but it is assumed to increase the level of reactive oxygen species inside the parasite. Eflornithine **(20.7)**, an analog of ornithine **(20.8)**, is a suicide substrate for ornithine decarboxylase. Inhibition of this enzyme prevents the parasite from generating polyamines which are important for the survival. Scheme 20.1 illustrates a normal decarboxylation of an α-amino acid in an enzyme using pyridoxal phosphate as a coenzyme.