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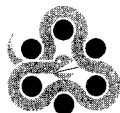
APPROACHES TO DESIGN AND SYNTHESIS OF ANTIPARASITIC DRUGS

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Volume 25

APPROACHES TO DESIGN AND SYNTHESIS OF ANTIPARASITIC DRUGS

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PREFACE

Since parasitism provides a survival advantage to organisms in nature, the prevalence of parasitic organisms in the world is widespread. Humans alone, for example, host around one hundred kinds of eukaryotic parasites. Many of these parasites cause disease in the host, some in normal course while others only when the 'normal' host-defence system is disturbed, for instance cryptosporidium is a major cause of wasting syndrome, and *Pneumocystis carinii* that of pneumonia in AIDS patients. The diseases caused by parasites in humans are many and varied. By taking appropriate public health measures parasitic diseases have been almost eliminated from developed countries, but continue to be a major health problem in developing tropical countries. Six major tropical parasitic diseases, viz. malaria, filariasis, schistosomiasis, African trypanosomiasis, Chagas' disease and leishmaniasis, together account for more than one million deaths annually and are the cause of morbidity in hundreds of millions more.

Antiprotozoal agents were the earliest chemotherapeutic agents to be discovered by design around the beginning of the 20th century - methylene blue as an antimalarial in 1891, iodinated 8-hydroxyquinolines for amoebiasis in 1904, trypan red for trypanosomiasis in 1907 and trypan blue for babesia in 1909. These discoveries provided useful chemical leads which in turn led to the development of important antiprotozoal drugs, particularly antimalarials, in the 1920s and 30s, and some of these drugs are in use even today. However, by the time the modern era of chemotherapeutic research got into its full stride in the wake of the discovery of sulfonamides and penicillin antibiotics in 1930s and 1940s respectively, parasitic diseases had been more or less controlled through public health measures in the developed countries where most of the research on new drugs was being carried out. Not much attention was, therefore, paid to the discovery of antiparasitic drugs. Of the new drugs discovered and introduced between 1988 and 1992 the Annual Reports on Medicinal Chemistry list 48 cardiovasculars and 44 antibacterials, but only 4 antiparasitic drugs, though parasitic diseases affect a much larger proportion of the human population than cardiovascular and bacterial diseases.

Another cause of concern is the increasing incidence of development of resistance by parasites to existing drugs, particularly antiprotozoals, which has resulted in the depletion of the already limited armamentarium of antiparasitic drugs. The major gaps in the chemotherapy of parasitic diseases are: non-availability of an

orally active, safe antileishmanial drug; low safety margin of primaquine, the only antirelapse antimalarial available; rising incidence of chloroquine/multidrug-resistant *P. falciparum* and emergence of pockets of chloroquine-resistant *P. vivax*; inadequacy of existing antitrypanosomal, antiamoebic/anti giardia drugs; non-availability of a really effective and safe macrofilaricide; and limited number of anthelmintic drugs. In view of the logistic difficulties faced by most developing countries in substantially improving public health measures in the foreseeable future, prophylactic and curative measures will have to be their mainstay for the prevention and control of parasitic diseases for many years to come. There is, therefore, urgent need to fill these therapeutic gaps. This will require much greater investment in research and development of antiparasitic drugs. It is worth mentioning here that as a result of the dramatic developments in molecular biology in recent years our understanding of the biology of parasites, of the pathophysiology of parasitic diseases, of host-parasite interactions and of the mechanisms evolved by parasites to evade attacks by the host defence system in order to survive and proliferate, has grown enormously. These advances have opened up a range of new possibilities for treatment of parasitic diseases. The big challenge is to convert this new knowledge to new chemotherapeutic agents.

In this book Dr. Satyavan Sharma has presented a comprehensive and up to date account of the chemotherapy of parasitic diseases, both human and veterinary. The book starts with an Overview of parasitic diseases in Chapter 1. The body of the book is divided into two parts, anthelmintic drugs (Chapter 2-12) and antiprotozoal drugs (Chapter 13-21). Both parts start with chapters highlighting the 'Biochemical Targets' available for chemotherapeutic interference. Individual chapters deal with one chemical class of compounds and describe their origin, structure-activity relationship, mode of action, and methods of synthesis and their status both in clinical and veterinary practice. The book will be useful to a wide spectrum of readers viz., students embarking on a research career in parasitic chemotherapy, clinicians (and veterinarians) and clinical pharmacologists desiring detailed information about the drugs currently in use, and pharmaceutical technologists wanting to update their knowledge of the methods of manufacture.

Sharma's involvement with parasitic chemotherapy started in 1969 when he joined me at the Central Drug Research Institute as a research fellow to work on the "*Chemotherapy of Filariasis*" for his Ph.D. degree. His special contribution in this field was the optimization of the activity of benzimidazoles, and one of the compounds synthesized by him, 82-437, has shown very significant oral macrofilaricidal activity.

cidal activity in experimental animals. After preclinical toxicity studies this candidate drug was under Phase 1 clinical studies at the time of his untimely death in a road accident on 19th March, 1993. His research career was wholly devoted to parasitic chemotherapy; indeed, he was one of the few fighters against this sadly neglected group of infections. This single-author book, which is becoming a rarity these days, reflects the dedication to and deep involvement of Satyavan Sharma in the subject. Satyavan had often discussed the scope and progress of the book with me, and had requested me to write the Foreword. Little did I realise at that time that he would be snatched away so soon. Editing the book has been very satisfying. I have thereby honoured the memory of a very valued student and colleague, whose promising career has been cut short.

I would like to record my special thanks to Mr. Ramesh Sharma, Satyavan's younger brother, who undertook the onerous task of getting the manuscript ready for the press; he was wholly responsible for the coordination between editor, artist and typist and also did much of the checking. Drs. Ram Pratap and Amita Dave did most of the proof reading and reference checking, and their help has been most valuable. The typing on the computer was done by Mr. V.K. Kanal and the computer-graphics was provided by *Multi Media Computer Point*, Lucknow. My most grateful thanks to them.

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CHAPTER 1

PARASITIC DISEASES : AN OVERVIEW

1. INTRODUCTION

Parasitic diseases continue to be the major public health problems in tropical developing countries. These are responsible for a high degree of morbidity, mortality and socio-economic under-development in these regions. According to WHO estimates the annual death toll due to parasitic diseases is nearly 2.5 million throughout the world [1,2]. The biggest killers of these are malaria, amoebiasis and hookworm infections responsible for killing 1,000,000-2,000,000; 40,000-110,000 and 50,000-60,000 patients, respectively, every year [2]. In view of the detrimental impact of parasitoses on human health and resulting economic losses, WHO has included five parasitic diseases, viz. filariasis, schistosomiasis, malaria, trypanosomiasis and leishmaniasis and one mycobacterial disease, viz. leprosy, amongst its priority research areas.

Parasitic infections are distributed world-wide but they are particularly endemic in the tropical zones of the globe. The main cause of the widespread prevalence of parasitic infections in the tropics is the climate; high temperature and humidity are ideal for parasite growth. This when combined with low standards of living, poor sanitation, lack of personal hygiene, inadequate prophylactic measures and abundance of disease carriers provide ideal situation for survival, dissemination and propagation of the parasites. Although most parasitic infections can be effectively prevented by proper prophylaxis, strict sanitary regulations and vector control, the implementation of these measures, pose practical problems in developing countries due to climatic factors and economic constraints. Immunotherapy and vaccination may emerge as useful tools to control and eradicate parasitic infections, but these are still in their early stages of development. Therefore, chemotherapy is the main tool available to combat parasitic diseases in humans and domestic animals.

Parasitic diseases are caused by the invasion of humans and animals by several species of protozoans and helminths. The pathogenic protozoans may invade the blood circulation, liver, spleen, or external organs such as mouth, gastrointestinal tract and vagina. A major population of the helminths, on the other hand, parasitize the gastrointestinal tract while some live in the blood circulation, lymphatics, connective and subcutaneous tissues, eyes, lungs, and liver. Most of the extra-intesti-

nal protozoal infections are acquired by the bites of an insect vector which injects infective larvae of the parasite while feeding on the blood of the victim. The intestinal protozoal diseases are contracted by ingesting protozoal cysts through food, drink and faecal contact. The helminth diseases in man may be acquired either by ingestion of helminth eggs through food, drinks or soiled hands or penetration of infective larvae through skin. The latter mode of infection may occur either by the bites of an arthropod vector or exposure of legs and arms to soil and water contaminated with infective larvae [3-6].

2. THE HELMINTH INFECTIONS

A variety of helminths belonging to the class nematoda (roundworms), trematoda (flatworms or flukes) and cestoda (tapeworms) are known to infect humans and domestic animals. The diseases caused by these worms are not only responsible for occasional deaths and wide range of health problems in man, but also exert detrimental effect on the nutritional and immune status of the host resulting in low resistance against other infections. The presence of helminth infections in livestock leads to decrease in output of animal products (milk, fat, butter, meat, eggs, wool and leather etc.) and has, therefore, strong socio-economic impact in countries with agro- and dairy-based industries [7].

The economic losses incurred by helminth infections have been assessed in several ways. In ascariasis the loss is due to the carbohydrate depletion by *Ascaris* worms in the patients. It has been estimated that a patient with 20 adult worms of *Ascaris lumbricoides* may lose 2.8 g of carbohydrate daily [8] which amounts to 2800 kg of carbohydrate per 1 million cases per day. Thus the world-wide loss of carbohydrate for 1100 million patients carrying ascariasis would be nearly 3080 tonnes per day. Stephenson and coworkers [9] have shown that ascariasis is not only associated with poor growth and protein-caloric malnutrition in pre-school children, but also reduces absorption of macronutrients and vitamin A. The authors also showed that economic loss due to ascariasis in Kenya in 1976 was about US\$ 5 million which could have been saved by the use of an anthelmintic costing about US\$ 1 million only.

The hookworms are other important human parasites which cause high degree of economic losses among the victims. An early estimate [10] showed that Japan suffered an economic loss of US\$ 60 million per year due to hookworm infections that could have been prevented by treating the patients with anthelmintics costing

only US\$ 7 million. Since hookworms survive on the direct blood feed from the hosts, their presence in human leads to heavy blood loss resulting in hypochromic anaemia. It has been estimated [11,12] that one *Ancylostoma duodenale* sucks 0.15-0.23 ml of blood per day. Thus, for 1 million patients carrying an average of 100 hookworms, the total blood loss would be 15,000-23,000 liter per day. In case of *Necator americanus* which consumes about 0.03 ml of blood daily from its host, the total blood loss for 1 million cases with an average of 400 hookworms would be nearly 12,000 liter daily.

The high degree of physical deformity (hydrocoele and elephantiasis of legs and arms) caused as a result of lymphatic filariasis and blindness due to onchocerciasis still pose major medical challenge in different countries of Asia, Africa and Latin America. Similarly, the grave clinical manifestations produced by tapeworm infections, schistosomiasis, trichinosis and hydatidosis continue to be major health problem for millions of people living both in the developing and developed nations of the world. Recent studies carried out by Stephenson and coworkers [13,14] in Kenyan subjects show that by deworming the infected population, it is possible to improve the growth and physical fitness in children and productivity in adults.

Worm infections are also known to exert detrimental effect on the health and productivity of cattle, equines, sheep, goats, pigs and fowls, thereby considerably hampering the yield of various animal products like milk, eggs and wool etc. Urquhart [15] has earlier estimated that the potential loss due to uncontrolled nematode parasites in ruminants was nearly US\$ 160 million. By treating the infected ruminants with anthelmintics costing US\$ 20,000, this loss was reduced to around US\$ 30 million. In Great Britain, about US\$ 100 million is lost annually due to liverfluke infections in sheep and cattle [16]. Similarly, in Florida, USA, the economic loss from liver condemnation was more than US\$ 500,000 per year which was due to liver fluke infections in cattle [17]. Stephenson *et al.* [18] have shown that pigs infected with *Ascaris* spp. and on low protein diet consumed 6.8 kg of food to gain 1 kg as compared to control pigs which needed only 3.3 kg of food to gain 1 kg of weight. It has been estimated that the total loss due to parasitic infections in livestock in USA is more than US \$ 3 billion per year [19]. Thus eradication of parasitoses from livestock is economical as it increases the productivity of the animals [20].

These are only a few examples which clearly demonstrate that treatment of helminth diseases in man and domestic animals is not only essential to have a healthier society but also to raise the living standards by boosting socio-economic

status of the people living in the tropics. A brief outline of the helminth diseases occurring in man and animals is given below.

2.1 Helminth diseases of human

Worm infections are amongst the earliest diseases known to mankind. Their impact on human health and its serious dimension was highlighted in the classical paper of Stoll "This Wormy World" published in 1947 [21]. Estimating the world population at that time as 2.1 billion, Stoll reported that nearly 650 million people were infected with the intestinal roundworm, *Ascaris lumbricoides*. The incidence (in million) of other intestinal nematode infections was as follows: hookworm disease (450), trichuriasis (350) and strongyloidiasis (35). With the increase in world population the prevalence of these worm infestations has proportionally increased. According to recent estimates [22,23] in a global population of 4.3 billion there are 1100-1300 million cases of ascariasis while the incidence of hookworm infection may touch the 1000 million mark. Similarly the number of cases suffering from trichuriasis, enterobiasis and strongyloidiasis may range from 500-1000, 300-500 and 50-100 million, respectively. In addition, nearly 400 million people around the world are known to suffer from the debilitating effects of filariasis, while there are 130 million cases of tapeworm infections and nearly 200 million people are infected with shistosomiasis in different parts of the world [24-26]. These figures indicate that helminthiasis is undoubtedly a wide-spread parasitic disease of the tropics. The following are the important helminths which are pathogenic to human.

2.1.1 Nematode (roundworm) infections

2.1.1.1 Ascariasis

It is caused by *Ascaris lumbricoides*, the adult worms of which live in the lumen of small intestine of man. The infection is acquired by consuming fruits, salad, vegetables and drinks contaminated with *Ascaris* eggs. Poor sanitation and lack of personal hygiene are the main reasons for the wide-spread prevalence of the disease. That is why ascariasis is primarily seen in people living in slums and rural areas where human excreta are disposed in the vicinity of residential localities. Children are the major victims of the disease.

Ascariasis has a worldwide distribution affecting nearly 1000-1300 million people with nearly 20,000 patients dying every year [1,2,26]. In addition to the protein-energy malnutrition caused in children, ascariasis is also associated with a series of pathogenic effects. The main clinical manifestations of the disease during migra-

tion of larvae from the gut to lungs are atypical pneumonia with inflammation of lung and liver cells, fever and eosinophilia. The adult worms may occasionally wander into liver, appendix and oesophagus or may obstruct the intestinal tract causing grave colic pains.

2.1.1.2 Hookworm infections

The hookworm disease is caused by the blood sucking nematodes, *Ancylostoma duodenale*, *A. ceylanicum* and *Necator americanus*, commonly known as hookworms, in the intestine of human. The infection normally takes place when farmers working in coffee, banana, sugarcane, sweet potato, rice and maize fields expose their bare feet to the soil fertilized with human excreta where the infective larvae penetrate the skin and enter the blood circulation. These larvae eventually grow into adult hookworms and live in the intestine where they engulf the intestinal villi into their buccal cavities and survive on direct blood feed from the host.

Hookworm infections are usually found amongst the field workers and poor masses of the tropics. The most common clinical symptom of the disease is hypochromic anaemia resulting from heavy blood loss. This leads to general weakness, fatigue, anorexia and poor health. Hookworm infection is also known to cause various gastrointestinal disturbances and epigastric pain. Children, with heavy worm burden, show poor mental and physical growth.

2.1.1.3 Trichuriasis

The disease is caused by *Trichuris (Trichocephalus) trichiura*, commonly known as whipworms, which live embedded in the intestine especially in the large bowel and caecum of man. The infection is cosmopolitan and is found more in children than adults. The usual mode of infection is the consumption of water and vegetables contaminated with the ova of *T. trichiura*. The disease is usually asymptomatic in the case of light infection; however, heavy infections may lead to anaemia, eosinophilia, abdominal pain, diarrhea, mucoid stool and occasional prolapse of the rectum.

2.1.1.4 Strongyloidiasis

Like hookworms, strongyloidiasis is also caused by penetration of the human skin by filariform larvae of *Strongyloides stercoralis*. The parasites possess slender and thread-like structures, hence called threadworms. They live burried in the intestinal mucosa of human.

The movement of larval and adult parasites produces several pathological changes like inflammation of the cells, allergic reactions and eosinophilia. The clinical manifestations of the disease include attacks of diarrhea, diffused abdominal pain, epigastric discomfort and hunger pains, which may lead to false diagnosis of peptic ulcer. Heavy infections may cause malabsorption, flatulence and abdominal distension.

2.1.1.5 Enterobiasis

It is a common helminth infection of man found mostly in children and is caused by *Enterobius (Oxyuris) vermicularis* called pinworms. The adult worms live attached to the mucosa of the lower ileum, caecum and terminal parts of the colon. Man acquires the infection by ingestion of eggs of *E. vermicularis*, which reach the mouth through soiled hands or while handling contaminated clothings and bathroom fixtures. Since the eggs are resistant to desiccation, the infection also occurs by consuming raw vegetables, food and drinks contaminated with pinworm eggs.

E. vermicularis does not produce significant pathological changes in the host except intense pruritis caused by the migrating gravid females and eggs laid by them on the perianal region. Scratching of the perianal skin may lead to dermatitis, eczema and secondary bacterial infections. The patient may also suffer from anorexia, restlessness, insomnia and mild to acute abdominal pain. Occasionally, vulvovaginitis may also occur in young girls.

2.1.1.6 Trichostrongyloidiasis

A number of species of *Trichostrongylus* (pseudohookworms) are known to parasitize the small intestine of sheep, goats, camels and occasionally humans in the tropics. *Trichostrongylus orientalis* is the main etiological agent in humans. The adult worms live embedded through their heads in the mucosa of the duodenum and jejunum. According to an early estimate [21] more than 5 million people suffered from trichostrongyloidiasis in Asia, Russia and CIS (former USSR) alone.

Human acquires the infection when the semi-filariform larvae of *Trichostrongylus* species enter the body through skin or mouth (while consuming contaminated drinks). The use of night-soil as fertilizer in some countries and resistant nature of the eggs provide a strong basis for propagation of this infection in farming communities.

Trichostrongyloidiasis is generally symptomless and little is known about its

pathology. However, severe infections may give rise to mild anaemia as the worms may suck blood with their capillary heads embedded in the mucosa.

2.1.1.7 Capillariasis (wasting disease)

This is a relatively new enteric helminth disease of human caused by a minute whipworm, *Capillaria philippinensis*, which was responsible for severe enteritis with high mortality in the Province of Ilocos Norte on the north west coast of Luzon of Philippines in 1967. Later the infection was reported from other adjacent provinces and from southern Thailand [27].

The adult worms of *C. philippinensis* are found embedded in the mucosa of the small intestine. Some worms may also be seen moving free in other parts of the alimentary canal such as larynx, oesophagus, stomach and colon. The infection occurs when infected fresh water fish and crustaceans are eaten raw by man. The infection causes a syndrome which resembles with that of autoinfected and disseminated strongyloidiasis giving rise to abdominal pain, vomiting, malaise, nausea and anorexia. In chronic cases, there is cachexia with muscle weakness, muscle wasting and depletion of minerals. In addition, there is protein losing enteropathy with extreme malabsorption of sugars and fat. There is continuous weight loss and often leads to death of the patient within 2-4 months [28].

2.1.1.8 Intestinal angiostrongyliasis

It is a newly discovered intestinal helminth infection of man found in Latin America. The causative agents of the disease, *Angiostrongylus costaricensis* and *A. cantonensis*, produce tumor-like lesions in the colon. Chemotherapy is usually not very satisfactory. Sometimes surgical intervention may be required.

2.1.1.9 Trichinosis

This is a disease caused by *Trichinella spiralis* which is essentially a nematode parasite of rats. The adult worms live in the small intestine of man. The infection also occurs in cats, dogs, pigs, polar bears, seals and whales. It is a widespread infection occurring throughout the temperate regions of the world and is found especially in people eating undercooked pork and pork products. The disease has been reported from several parts of United States, Hawaii, Alaska, South America, Africa, Europe, Russia, CIS (formerly known as USSR) and Asia.

Trichinosis is transmitted to humans, when they eat infected pork. The hogs and rats serve as the reservoirs of *T. spiralis*. However two hosts are required to

complete the life cycle of the worm. This may be a hog-to-man, rat-to-hog or hog-to-hog cycle for the *T. spiralis* development. Humans, hogs and rats are infected by eating infected pork containing the cysts of *T. spiralis*. On reaching the digestive tract, the larvae emerge from the cysts and mature into adult males and females within a few days. The fertilized females liberate 1000-1500 larvae in the intestinal mucosa. The larvae reach the different parts of the body through blood circulation and finally encyst in the muscles of diaphragm, chest wall, neck, limbs, larynx, tongue and eyes. These cysts survive for several years and develop into adults on getting favourable conditions.

The hogs become infected when they feed on the garbage containing infected pork scraps (hog-to-hog cycle). The hogs may also acquire the infection by eating rats infected with *T. spiralis* while rats get the disease by eating the infected pork (hog-to-rat cycle). The hog-to-man cycle arises when man eats the infected pork and pork products.

The presence of larvae and cysts of *T. spiralis* may cause localised inflammation, necrosis, damage of muscle fibres and increased eosinophil counts. Sometimes death may occur due to toxemia, trichinous encephalitis or myocardial damage caused by invasion of musculature by the larvae.

The clinical symptoms of the disease are variable and depend upon the intensity of the infection. The presence of adult and larval parasites may give rise to abdominal pain, nausea, vomiting, diarrhea and blood in stool. The migration of larvae leads to high fever, edema of face, eyelids, muscular pain in chest wall, cough, dyspnoea and stiffness of limbs. In severe cases, neurotoxic symptoms, myocardiasis, meningitis and encephalitis may also be observed in some patients.

2.1.1.10 Creeping eruption

Creeping eruption or larva migrans in man is caused by the presence of the larvae of dog and cat hookworms, *Ancylostoma caninum* and *A. braziliense* in the skin. Some other nematodes like *Uncinaria stenocephala* (European dog hookworm) and *Gnathostoma spinigerum* also produce somewhat similar cutaneous lesions. The creeping eruption is prevalent in different regions of the warm climates, especially in the Americas, Africa and Asia. It is estimated that nearly 10 million people around the world suffer from this disease [24].

Both wild and domestic cats and dogs are the natural reservoir hosts of *A. braziliense*. The female worms produce eggs which pass out with the stool and de-

velop into filariform infective larvae in the soil. Man gets infected when these larvae penetrate the skin. The larvae produce serpiginous tunnels under the skin and do not undergo further development.

The epidemiology and life cycle of *G. spinigerum* is different. The adult worms live in the alimentary canal of cats, dogs and tigers. The eggs produced by the adult females come out with the faeces and become embryonated in the soil. They hatch upon coming in contact with water and give rise to cylindrical, ensheathed and rhabditiform larvae. These larvae are ingested by copepods where further development of the parasite takes place. When fish, frogs, birds and snakes eat these infected copepods, they become infected and third stage larvae are generated. Human acquires the infection by eating the above infected intermediate hosts.

After infecting the humans, the larvae move under the skin at the rate of 2-3 cm per day producing linear, erythematous and serpiginous tunnels. This causes inflammation and pruritus and may also damage lungs, kidneys, eyes and other parts of the body. In the case of gnathostomiasis, the patient may show edema, eosinophilia and leukocytosis. Some fatal cases of eosinophilic myeloencephalitis caused by the migration of immature worms of *G. spinigerum* in brain [29] and urinary gnathostomiasis [30] have also been reported. The larvae of *G. spinigerum* can also cause abdominopleuropulmonary syndrome which may resemble like acute appendicitis or pleurisy.

2.1.1.11 Visceral larva migrans

This form of tissue helminthiasis is caused by the migration of the larvae of dog and cat ascarids, *Toxocara canis* and *Toxocara cati* in the visceral tissues of humans. The disease is more common in children than the adults who often come in contact with the eggs of *T. canis* or *T. catti* while playing on the ground polluted by cat and dog faeces. The infection by *Toxocara* in dogs is cosmopolitan; however, surveys indicate that it is prevalent in the U.S.A., Britain, Africa and some parts of Asia [31,32]. In humans the rate or incidence of visceral larva migrans is low; nevertheless nearly 10,000 people are estimated to carry this disease around the world [24].

After reaching the intestine of human, the eggs liberate larvae which penetrate the bowel wall and enter the portal blood system from where they are carried to the liver, lungs and different parts of the body. The larva seldom develops into the adult in the human intestine as man is not its natural host. In cats and dogs, the larvae develop into male and female adults.

The early phase of toxocariasis in man shows low to high eosinophilia which disappears as the infection grows chronic. Attacks of fever, malaise, nausea, vomiting, cough, abdominal pain, anorexia, weight loss and muscle and joint pain may be observed occasionally. In chronic cases, the patient may report of some eye problem like weak sight and impaired vision resulting due to migration of larvae in the eyes. Liver complications like hepatitis and lung problems like cough and asthmatic attacks may occur due to migration of larvae to liver and lungs, respectively. Similarly, involvement of brain in toxocariasis can give rise to an epilepsy like syndrome.

2.1.1.12 Filariasis

Filariasis is one of the most widespread parasitic diseases of the tropics affecting nearly 300-400 million people around the world [24,33]. According to recent estimates by the WHO, the world-wide prevalence of filariasis is about 280-290 million [1,2]. The main disease causing worms in humans are *Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, *Loa loa*, *Dipetalonema perstans*, *Dipetalonema streptocerca* and *Mansonella ozzardi*. The haematophagous arthropods, mosquitoes and flies, serve as the intermediate hosts in the life cycle of the parasite. The transmission of the infection to humans occurs when the mosquitoes feed on the blood of man. After reaching the blood circulation of man, the infective larvae undergo several moultings and develop into adult male and female worms living in lymph nodes, lymphatic vessels, connective tissues and other organs of the body. The female worms produce microfilariae which migrate to blood stream and are sucked by mosquitoes and flies where the life cycle of the parasite gets completed.

The early phase of the infestation by *W. bancrofti* and *B. malayi* is characterised by high fever, chills, enlargement of lymph nodes, pain and swelling in testes and thickening of the spermatic cord. Later the blockade of the lymphatic circulation occurs which leads to hydrocele and chyluria in the patients. In chronic cases, the obstruction of the lymphatic system may take place causing massive enlargement of legs (elephantiasis), arms, scrotum and breasts. The clinical characteristics of *L. loa* infection include appearance of painful Calabar swellings on face, limbs, head, wrist and forearms. Sometimes the adult worm may migrate in the eye ball giving rise to blindness and nervous disorders.

The *O. volvulus* infection, also called river blindness, is the most serious form of human filariasis responsible for blindness in a large population of the African con-

tinant. The early stage of ocular onchocerciasis, caused by the presence of microfilariae in the eyes, is marked by pain in the eyes, photophobia and lacrimation which gradually leads to conjunctivitis with eventual loss of vision. The infection also give rise to dermal problems and genital elephantiasis.

The filariases caused by *M. ozzardi* and *Dipetalonema* spp. are usually non-pathogenic. However, *M. ozzardi* may occasionally cause hydrocele and enlargement of lymph nodes while *D. perstans* may be associated with fever, abdominal pain, itching and edema of scrotum in the patients.

2.1.1.13 Guinea worm infections

The guinea worm infection is a very old parasitic disease caused by *Dracunculus medinensis* which are elongated thread-like filarial worms living in the deep connective and subcutaneous tissues of man. The infection has been reported from different parts of Africa, South America and Asia; however, it is endemic in Cameroon, Lake Chad, Sudan, Uganda and India.

Humans become infected with guinea worms by drinking water contaminated by infected *Cyclops*. On reaching the intestine, the *Cyclops* get digested by gastric juice liberating free larvae which pierce the intestinal mucosa and reach the connective tissues where they live and attain sexual maturity in about a year.

After fertilization the female worms migrate under the skin and produce a dermal blister which causes irritation. When the patient scratches the skin or the blisters come in contact with water, they burst liberating numerous motile rhabdiform larvae which are soon engulfed by the *Cyclops*; thus the life cycle of the parasite is completed.

The early stage of the infection produces no pathological sign. The worms require 8-12 months of incubation period before they are sexually mature. Symptoms appear only after the female is fertilized and is ready to discharge larvae. This stage is marked by appearance of reddish papular lesions on legs and arms which cause itching, fever, giddiness, urticaria and allergic reactions. Repeated scratching of skin or contact with water ruptures the blisters which release milky fluid with larvae which may lead to secondary infections. The migration of adult guinea worms to other parts of the body may result in neurological damage, joint swelling and arthritis.

2.1.1.14 Tropical pulmonary eosinophilia (TPE)

This is an allergic manifestation produced by the presence of various helminth

parasites such as *Ascaris lumbricoides*, *Trichinella spiralis*, *Strongyloides stercoralis*, *Toxocara* spp., *Brugia malayi* or *Dirofilaria* spp. in humans. The disease has been reported from different parts of Asia and Africa.

Since the disease is associated with the respiratory system, its histopathology is confusing. However, various lesions in the lungs may be seen with chest X-ray. The clinical symptoms of the disease may range from mild to severe attacks of cough, asthma and bronchitis. The eosinophil counts in blood may rise upto 20-90% and the leukocytes may increase upto 60,000/cu mm. The infection is usually taken to be confirmatory if the eosinophil counts exceeds 3000/cu mm and the total leukocyte count is more than 10,000 cells/cu mm in the blood. X-ray picture of lungs may show chronic bronchitis and other signs which are sometimes mistaken for Loeffler's syndrome or tuberculosis. In such cases, the antigen of *D. immitis* may be used to diagnose tropical eosinophilia [34,35].

2.1.2 Trematode (flatworm, fluke) infections

2.1.2.1 Schistosomiasis

Schistosomiasis is a major helminth disease of man caused by the invasion of the blood circulatory system by four species of blood flukes, viz. *Schistosoma haematobium*, *S. mansoni*, *S. japonicum* and *S. intercalatum*. The adult worms of human schistosomes have separate sexes but they are dioecious (existing together as males and females). The male worm has a groove (gynecophoral canal) along its ventral side in which it carries the female worm during most of its life span.

The adult worms of *S. haematobium* cause urinary schistosomiasis (bilharziasis) and live in the portal system, pelvic veins, particularly in the vesical and pelvic plexus and occasionally in the veins of the colon and rectum. The worms excrete their eggs in the urine of man but rarely in the faeces. The other three schistosomes (*S. mansoni*, *S. japonicum*, *S. intercalatum*) are responsible for intestinal bilharziasis and live in the portal blood system, mesenteric veins and haemorrhoidal plexus. Unlike the *S. haematobium* worms, these three blood flukes pass their eggs in the faeces and rarely in urine.

Schistosomiasis has a wide geographical distribution. It has been reported from various parts of Africa, Asia and South America affecting nearly 200 million people around the world [2] of which 20 million people are estimated to suffer from schistosomiasis in Egypt alone [36]. It has also been reported that *S. mansoni* infects nearly 70 million people throughout the world [37].