INTRODUCTION
The importance of diseases due to parasitic worms, and the immense contribution, which they make to human sufferings is frequently overlooked, especially in temperate climates where they are less common and their effects less marked than in the tropics and subtropics (Hruzik et al., 1977). During the last half century, however, there has been a deepening realization of the extent and gravity of human helminthiasis and of the fact that they are unremittingly corrosive, constituting a steady drain on the vitality of the host and lowering often fatally his resistance to other diseases, even though they themselves are rarely severe to cause death.

Among the various parasitic diseases, intestinal helminthiasis is a major health hazard (Choudhury, 1975a & b) and considered to be a plague of man and animals. Hookworms are important intestinal nematode parasites causing the disease "ancylostomiasis" - commonly known as 'Hookworm Disease'.

The infection with hookworms out ranks all other infection of man with the possible exception of Ascaris in the production of human misery, debility and inefficiency in tropics (Faust and Russell, 1964).

The parasites are of global distribution, being highly prevalent in tropics and subtropics. They occur more frequently in agricultural areas were the favourable soil temperature and high percentage of humidity provide ideal conditions for the growth and survival of infective larvae (Vanden Bossche, 1980).

**IMPORTANT PATHOGENIC SPECIES**

Hookworms which are pathogenic to man are *Ancylostoma duodenale* (old world hookworm) and *Necator americanus*
(American hookworm or new world hookworm). The third one is Ancylostoma ceylanicum, which also infects man, besides dog and cat and of which the distribution is limited (Areekul et al., 1970). The important hookworm species which parasitise live-stock and wild carnivores are:

- **A. braziliense** (dog and cat)
- **A. caninum** (dog and wild carnivores)
- **A. tubaeformis** (cat)
- **A. kusimaense** (badger and dog)
- **A. paraduodenale** (lion and related carnivores)
- **Bunostomum phlebotomum** (ox, zabu and sheep)
- **B. trigonocephalum** (sheep and goat)
- **Gaigeria pachyscelis** (sheep and goat in India and Africa)
- **Uncinaria** spp (dog, cat, fox, wolf, domestic pig and norther fur-seal)

**GEOGRAPHICAL DISTRIBUTION**

About 20-25% of the global population harbour hookworm parasites (Stoll, 1962; CCTA/WHO, 1963) and the number of infected persons throughout the world ranged between 726 and 907 millions (Davis, 1973; Janssen, 1974; Standen, 1975; McGinty, 1979). Of these about 359 million reside in Asia, 208 in USSR, 1.4 in Europe, 49 in Africa, 42 in tropical America and about 1.8 million in North America.

In the Asian continent, the most endemic countries are India, Malayisa, China and Japan. However, the disease is also quite prevalent in Pakistan, Burma, Sri Lanka, Bangladesh, Nepal, Turkey, Moracco, Algeria, Iran, the Arabian Peninsula, Hong Kong etc. (Chandler and Read, 1961; Fain, 1980).
In India the tropical climate, poor sanitation and poorer health education, favour the growth, multiplication and dissemination of all parasitic infection including hookworms. The incidence is particularly very high in the paddy cultivating areas (Raghavan, 1967), and tea and coffee estates where the prevalence may exceed 90% (Arora et al., 1976; Gaitonde and Renapurkar, 1979).

States with heavy infections are Assam, Andhra Pradesh, Bihar, Karnataka, Kerala, Maharashtra, Tamil Nadu and West Bengal whereas light infection occur in Uttar Pradesh (20.1%) (Yunus, 1977) and Pondicherry (26.8%) (Singh et al., 1978).

**SIGNS AND SYMPTOMS**

The hookworms are known to be notorious for their harmful effects. Being voracious blood suckers, they cause severe anaemia (Areekul, 1977; Lorenzi and Jamra, 1978; Akinkugbe, 1980; Loureiro et al., 1983) and the disorders associated with it. The other symptoms include syndrome of gastrointestinal ulceration (Tandon et al., 1966), physical and mental retardation (Watson, 1960), myocardial ailments, creeping eruptions, pneumonia, bronchospasm etc. In pregnancy, these infections may be associated with changes in renal function (Faust and Russell, 1964), resulting to toxaemia and albuminuria. The hookworms are also known to cause depletion in endocrine secretions delay in puberty and partial impotency in man (Watson, 1960; Faust and Russell, 1964).

**PATHOGENIC EFFECTS**

The pathology due to hookworm infection may conveniently be devided into primary and secondary phenomena. Primary phenomenon is associated
with the penetration and migration of infective larvae, while secondary phenomenon is related to the pathology caused by adult worms in the intestine.

a) Pathogenic effects due to larvae:

At the site of entry (skin penetration) there is relatively little mechanical damage to the skin layers, but as the larvae burrow down the blood capillary beds, considerable local tissue reaction occurs (Faust and Russell, 1964). If the pathogenic bacteria is also associated with the larvae, open lesions often develop ending into ground itch (dermatitis or water sore) (Watson, 1960). The filariform larvae of non-human species, when get entry to the human skin, they wonder in an aimless manners for long, producing reddish itchy papules along the path traversed by them (Chatterjee, 1967). The condition is called creeping eruption (Meyers and Neafie, 1976; Cypers, 1982).

During migration through the bronchoesophageal path, microscopic damage is produced at each site where the larvae breakout the blood capillaries into air sac, causing pneumonitis, bronchospams and cough.

b) Pathogenic effects due to adult worms:

The adult worms inhabit the small intestine (jejunum) of man, attaching themselves to the mucous membrane by means of their powerful buccal armature. A patient harbouring *A. duodenale*, looses about 0.15-0.23 ml of blood daily per parasite (Hoggland and Schad, 1978) and each patient, on an average harbouring about 100 worms, would loose about 15 ml of blood amounting to 15,000 liter/day/million cases and thus the world blood loss would be nearly 12 million litres a day.
Newly established young worms cause proportionately greater blood loss than older established worms, and it has been estimated that upto 0.67 ml per worm may be lost each day (Faust et al., 1970).

Van Brand (1948) suggested that the blood sucking tendency of hookworms are due to need for oxygen, supplied by the red blood corpuscles in a low oxygen environment in the intestine. Riva et al. (1981) noticed acute invasive intestinal bleeding caused by hookworms. Due to iron deficiency a hypochromic microcytic anaemia develops (Lee, 1975; Zuna et al., 1978; Areekul, 1979; 1980; Gupta et al., 1980; Foy and Kondi, 1981; Fleming, 1982; Varies and Banwell, 1982). The deficiency of folic acid and vitamin $B_{12}$ produces macrocytic hypochromic anaemia (Viera, 1980). The amount of iron loss through intestinal haemorrhage varied from 3.9 to 18.1 mg/day depending upon the intensity of infection (Maspes and Tamigaki, 1979, 1980).

In chronic hookworm infection haemoglobin level comes down to 4% (Foy and Kondi, 1957) and erythrocyte counts become $10^6/mm^3$ (Brumpt, 1958). Prolong chronic anaemia produces dullness, depression, confusion, poor memory and appearance of stupidity, dizziness, insomnia (Arora, 1951; Borrero et al., 1961) optical illusion, general nervousness and fidgety movements (Faust and Russell, 1964).

OBJECTIVE AND SCOPE OF THE PRESENT WORK

In view of the seriousness of the problem, deep and concerted efforts need to be made to combat the hookworm scourge. In the absence of any vaccine against hookworms, immediate and effective remedy lies in the successful treatment of suitable nontoxic drugs. A brief review
of literature (Chapter VII) would reveal that the currently available antihookworm drugs are either not very effective (bephenium hydroxy nepthoate, thiabendazole and tetramisole) or they have one or the other serious side effects (mebendazole). Further the restricted spectrum of activity limits their use in mixed helminthic infections - a common feature noticed in underdeveloped and developing countries. Thus, to have effective, nontoxic and broad spectrum drug(s), which besides having promise against hookworm, are also capable of controlling other commonly occurring helminth parasites, is the need of the day.

Therefore, in the present work a large number of rationally synthesized potential anthelmintic compounds were screened for their antihookworm activity. The compounds showing promise have also been tested against other helminthic parasite to ascertain the activity profile.

The other type of investigations relevant to chemotherapy are to understand the mechanism of anthelmintic action. Such studies may provide an insight as to how the drug reaches and affects their targets in the parasite. This will not only provide rationale to the synthesis of new molecules but also will add to the knowledge of the molecular biology of the invading organism.

For any biological investigation the basic requirement is to have a reliable test system. Earlier the chemotherapeutic assessments for antiascarid drugs were being made on earth worm which has no similarity with Ascaris except for its physical appearance. Earthworm is a free living creature and has absolutely different environmental and nutritional
requirements than *Ascaris* which is an obligatory parasite. As such the *in vitro* screening results obtained on earthworm obviously did not match with those obtained on ascarids in animals. Thus, the selection of experimental model should be based, as far as possible, on the similarities in life cycle pattern and pathological, biochemical and chemotherapeutic reactions to the target parasite.

Attempts to adapt true human hookworm (*N. americanus*) in hamsters have been successful, however, that was achieved by using hydrocortisone, an immunosuppressive drug. These agents are likely to bring about changes in the genetic make-up of the parasite resulting in altered chemotherapeutic response and as such should be avoided.

*Ancylostoma ceylanicum* a hookworm parasite of man, cat and dog and which has direct and short life cycle, is easy to maintain in small laboratory animal (hamster). Further the existence of positive correlation of chemotherapeutic responses between *A. ceylanicum* in hamsters and target parasite (in man) add to the selection of *A. ceylanicum* for experimental investigations. As such in the present study, *A. ceylanicum* was used as test parasite.

Since the knowledge on the life cycle and biological aspects of this parasite are meagre, it was thought worthwhile to explore the concealed biology of this nematode. Such a study is likely to provide a better understanding regarding the host parasite relationship especially the vulnerable points in its life cycle and the factors determining the therapeutic shift.