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INTESTINAL HELMINTHIASES AND HUMAN HEALTH
RECENT ADVANCES AND FUTURE NEEDS

by

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Introduction

A great deal of valuable work on intestinal helminthiasis has been done in recent years but there is a lamentable gap between the acquisition of knowledge and its practical application for the benefit of the community. While it is gratifying that there has been a resurgence of scientific interest in intestinal helminthiasis, it is necessary to alert health authorities to the fact that effective public health control can often be attained and should be a part of any national primary health care programme. By choosing appropriate measures and concentrating on the population groups at greatest risk, much may be achieved at reasonable cost.

This review, therefore, makes no attempt to be comprehensive but is written mainly from a public health view point and is selective, concentrating on work which either has an immediate practical application or is likely to lead to one in the near future.

Intestinal trematode infections

The introduction of praziquantel, an effective trematocidal drug (Wegner, 1984) has not only solved the problem of therapy but has also stimulated considerable interest in trematodiasis occurring in Southeast Asia.

Changing patterns of infection. In Taiwan, owing to ecological changes caused by industrialization and modern agricultural practices, paragonimiasis, schistosomiasis and fasciolopsiasis have almost disappeared but clonorchiasis has become more common. In Hong-Kong, where clonorchiasis was once highly prevalent, it is no longer so, as a result of control measures implemented in China, the main supplier of fish. However, clonorchiasis and metagonimiasis have become infections of the higher social classes in Hong Kong and Japan, owing to their frequent consumption of raw fish (Cross, 1984).

Raw fish is still a common dish throughout Asia (Seo, 1984) and is becoming increasingly popular in many other parts of the world, with yet unknown consequences for the consumer's health. Clinical pathological changes related to the migration of heterophyid flukes into the internal tissues and organs certainly deserve further study. The symptomatology and mucosal pathological changes of metagonimiasis have recently been well reviewed (Cho *et al.*, 1984).

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Fasciolopsiasis, which was probably introduced into Bangladesh in the 1940's, is now well established in the Dacca area, with a prevalence of up to 60% (Gilman *et al.*, 1982). In Uttar Pradesh, India, an endemic focus, with a prevalence of 22%, has recently been discovered (Chandra, 1984). The first indigenous case of fasciolopsiasis was reported from Indonesia (Hadidjaja *et al.*, 1982).

The introduction of Tilapia mossambica fish into the Lindu lake region of central Sulawesi, Indonesia, has caused the disappearance of Corbicular sp. clams, an intermediate host, and of Echinostoma lindoensis, once a common trematode in man in that area (Cross, 1984).

Diagnosis based on adult worms. The finding of heterophyid eggs in faecal sample hardly permits identification of the species (Lee *et al.*, 1984), while the differential diagnosis between Fasciola, Fasciolopsis and Echinostoma is difficult when only eggs are available.

In surveys throughout the Philippines, heterophyid eggs were found with prevalence rates ranging from zero to 13%, H. heterophyes being considered the most likely species involved. In Northern Luzon, Philippines, echinostomatid trematodiasis were diagnosed in 11% of over 7,400 faecal samples collected in 25 barangays, Echinostoma ilocanum being suspected as the most common species (Cross & Basaca-Sevilla, 1984). The eggs of Cathaemasia cabrerai sp.n. are difficult to distinguish from those of Echinostoma spp. (Jueco & Monzon, 1984). The results of faecal examination, therefore, cannot be interpreted to the species level unless the adult worms are also collected and examined.

The collection of adult trematodes after praziquantel therapy, however, can give spectacular results. At the Hospital for Tropical Diseases in Bangkok, 332 of 411 patients examined had one or more species of helminths, mostly trematodes; in total 101,993 trematode worms were collected, only three of which were not identified as to the species (Radomyos *et al.*, 1984).

Newly recognised trematode infections in man. Cathaemasia cabrerai was found in Manila in a thirty-four year old male patient suffering from epigastric pain and the passage of soft stools; symptoms disappeared after treatment with bithionol. Similar eggs were found in 14 of 39 stool samples collected in the patient's native village, Echague, Isabela. The infection was acquired from eating raw snails (Cabrera *et al.*, 1984).

The first human case of Fibricola seoulensis was described in Seoul in a twenty-five year old male patient hospitalized with fever and epigastric pain (Seo *et al.*, 1982). Subsequently, further asymptomatic human cases were reported among snake-eaters in South Korea. An experimental model of the infection has been established in rats and mice and, in experimental animals, changes in the structure of duodenal villi and inflammatory infiltration of the mucosa have been observed (Lee *et al.*, 1985).

Among the intestinal trematodes found recovered from patients by the Hospital for Tropical Diseases in Bangkok, two species Haplorchis pumillo and Echinostoma ilocanum have been reported as new species in Thailand (Radomyos *et al.*, 1984).

Taeniasis and cysticercosis

Much scientific interest but still few control programmes. Several scientific meetings have been organized on taeniasis and cysticercosis problems in the last few years: in San Miguel de Allende, Mexico in 1981 (Flisser *et al.*, 1982); in České Budějovice, Czechoslovakia in 1982 (Prokopic, 1983); in Liverpool, United Kingdom in 1983 (Craig *et al.*, 1984) and in Nairobi, Warsaw, Prague and Geneva (World Health Organization, 1983). These meetings reflect the growing awareness of the scientific community and the United Nations agencies of the public health importance of human cysticercosis and the economic importance of bovine cysticercosis.

Guidelines for the surveillance, prevention and control of taeniasis and cysticercosis have been elaborated (WHO, 1983). However, only a few countries have definite plans for controlling Taenia solium and T. saginata (Flisser et al., 1982, Pawlowski, 1980, Engelbrecht et al., 1985).

T. saginata taeniasis - a good model for gastroenterological research. T. saginata infection, either natural or induced, provides a good model for clinical research on human gut responses to an intestinal helminth. Taeniasis causes various clinical symptoms and signs which probably depend very much on the psychological and physical characteristics of the host: some patients lose their appetite and thus lose weight, others gain weight; some tolerate the infection for twenty years, others wish to be cleared of it overnight. Statistical cluster analysis has been found very useful in analysing symptoms (Pawlowski, 1983). Taeniasis is also known to cause patho-morphological changes in jejunal mucosa and functional disorders; reversible achlorhydria or lowered gastric secretion was found in 70% of patients (Pawlowski, 1983). Infective gastroenteritis with reduced gastric acidity is common, especially in those who are permanently exposed to various intestinal pathogens (Cook, 1985). The mechanisms by which the gastric and intestinal function and secretions are disturbed in intestinal parasitoses can easily be studied with modern gastroenterological techniques.

Research priorities. Research in cestodes, once very basic, now tends to concentrate on practical problems (Flisser et al., 1982) and there has been much progress regarding host-parasite relationships, in vitro culture, immunological studies in experimental and farm animals, the mechanisms regulating parasite populations, the diagnosis of human cysticercosis and the treatment of taeniasis. However, some urgent problems remain unsolved, such as the identification of T. solium carriers in human populations, the spread of taeniid eggs in the environment, better diagnosis of cysticercosis in animals and mass treatment for human taeniasis.

Hookworm infections

Hookworms do not belong to the neglected parasites any more. Considerable advances can be added to the monograph on hookworm infections in man (Miller, 1979) and the comparative studies on Necator americanus and Ancylostoma duodenale life cycles (Hoagland and Schad, 1978).

Realistic strategies for controlling hookworm disease through PHC. The lesson learned from the Rockefeller hookworm campaign in the 1920s, that anthelmintic treatment should be used for the control of hookworm disease only, is still valid.

The negative binomial distribution pattern is usually well marked; sometimes less than 10% of infected people harbour over 60% of the total hookworm population (Schad & Anderson, 1985). The identification of those who are heavily infected can be done on clinical grounds because most are anaemic.

Anthelmintics and iron treatment, targetted on anaemic individuals in the areas where hookworm and anaemia are prevalent, is an effective and cheap measure, which is a fortunate mixture of individual curative medicine and community control intervention and is eminently feasible through the primary health care system (WHO, 1985).

Hookworm disease has recently been well described by Gilles (1985). It is not a condition which should be ignored and, wherever hookworm infection and anaemia are prevalent, it should be part of primary health care to identify the main groups affected and to institute appropriate measures to reduce their hookworm loads and keep their haemoglobin at reasonable levels.

Studies of the Food, Nutrition and Poverty Programme of the United Nations University, organized in central Java and in the Cairo area, have shown not only that non-anaemic children tend to be faster and more accurate in response to the standard achievement test than anaemic children, but also that anaemic children when treated with iron become faster and more accurate in their response than those treated with placebo (Pollitt et al., 1985).

Advances in field epidemiology. Differences in the life cycles of N. americanus and A. duodenale (Hoagland & Schad, 1978) and the availability of simple techniques to distinguish between species (WHO, 1981) have facilitated many epidemiological studies, the results which suggest that both parasites are widely distributed throughout the tropics and that N. americanus is the dominant species in most of the areas investigated. Is this because Necator shows superior competitive abilities and/or is better adapted to the human host? Does A. duodenale not benefit much from the arrested development of larvae and higher egg resistance to environmental factors? The arrested development of A. duodenale larvae has been confirmed by some further observations in natural infections in man (Koshy et al., 1978 & Wang et al., 1984). Transmammary transmission of A. duodenale, suspected because of infections in four to five week old Nigerian infants, has not been confirmed by finding hookworm larvae in the milk (Nwosu, 1981) but one hookworm larva, probably N. americanus, was found in the milk of a Thai woman (Setasuban et al., 1980). There has been no information from field studies on the role of oral transmission, through infected vegetables or water, in ancylostomiasis.

A definite predisposition for hookworm infection has been confirmed in a West Bengal community (Schad & Anderson, 1985) but whether this predisposition is determined by genetic, ecological, behavioural or social factors still remains unclear.

There have been only a few studies on hookworm larvae survival in the environment; one showed that lipids are essential for survival of infective N. americanus larvae (Udonsi, 1984).

Renewed interest in basic research. Hookworms occurring in man can be kept in animal models: N. americanus in hamsters and A. duodenale in beagles. However, both strains adapted to laboratory animals are still not widely used in experiments. Most of the laboratory research has been performed using A. caninum, a more readily available hookworm.

The host response to the mucosal damage caused by A. ceylanicum is now better understood, following studies by transmission electron microscopy (Carroll et al., 1984).

A proteolytic enzyme secreted by Ancylostoma has been isolated and characterised (Hotez et al., 1985). It shows elastinolytic activities important for three major functions: liquefying and degrading the bolus of intestinal mucosa lodged in the hookworm buccal cavity, destruction of capillaries leading to extravasation of blood and, finally, the prevention of clotting, probably by the degradation of fibrinogen and fibrin, and conversion of plasminogen to miniplasminogen. As all these functions are essential for hookworm feeding and as some are known to be impaired in hookworms obtained from immunized dogs, specific antibodies to hookworm protease might be a basis for an eventual vaccine, although the role of such a vaccine in the control of human hookworm infections is problematic.

Studies on migratory behaviour and the survival pattern of A. caninum larvae in adoptively immunized mice show that the liver acts as an effective immunological barrier, and suggest that muscle fibres with lower oxygen potential and less direct inflammatory reaction may become a site favourable to hookworm larvae for their survival in an immune host (Vardhani & Johri, 1981). It is interesting to note that an Ancylostoma larva, probably A. caninum, has been found within a muscle fibre in man (Little et al., 1983) and that albendazole therapy was found to be effective against N. americanus migrating larvae in human volunteers (Cline et al., 1984).

Ascariasis

The proceedings of a special conference on ascariasis and its public health importance, organized in 1984 by the World Health Organization and Cornell University, New York, USA, give an up-to-date review of the subject (Crompton et al., 1985). A few recent achievements in basic laboratory research on Ascaris and some general comments may be added.

Epidemiology and control. During the last five years some classic epidemiological papers dealing with ascariasis have been published (Croll *et al.*, 1982, Hlaing *et al.*, 1984, Shuval *et al.*, 1984), the epidemiological situation of ascariasis in Burma, Kenya, Malaysia and Peru have been reviewed (Crompton *et al.*, 1985), and strategies for ascariasis control formulated (Pawlowski 1984a, Crompton *et al.*, 1985, WHO, 1985).

Anthelmintic treatment targetted to school-children has been shown to be as effective as mass-treatment of the entire community (Cabrera & Cruz, 1983). Calculation of the reproductive and reinfection rates may help to decide the frequency and choice of targetted treatment. Further well-monitored operational studies are needed in order to maximize the benefits of large-scale anthelmintic programmes. Although sanitation does not offer such spectacular results as anthelmintic therapy, it's role should not be underestimated. When one looks at the list of factors responsible for persistence of human ascariasis (Crompton & Pawlowski, 1985), it becomes obvious that environmental studies have been neglected (e.g the survival time of *Ascaris* eggs is unknown in most countries) and that techniques proposed for such studies (Kagei, 1983) need revision.

Anderson's (1985) studies have contributed much to our knowledge on the factors regulating the *Ascaris* population. The mathematical calculations are based on figures collected during field studies but the theoretical mathematical model cannot solve all the problems of field epidemiology because the generalization of the results valid for one village, e.g. Okpo village (Hlaing *et al.*, 1984) may not be relevant to the situation in the whole country or area and there are still factors in ascariasis epidemiology which can hardly be expressed in figures (Crompton *et al.*, 1985). Therefore, that part of the epidemiology which is based on observations, mainly related to the mode of transmission and spatial relations, must be regarded as equally important and also promoted.

Pathogenicity of ascariasis in man. The pathology of ascariasis in man and its related morbidity and mortality has recently been extensively reviewed (Crompton *et al.*, 1985). Reports are increasing in number that *Ascaris* related abdominal complications (intestinal obstruction, biliary ascariasis) are frequent in endemic areas and usually rate as one of the six major causes for hospitalization in paediatric surgery wards. However, in spite of several studies, the impact of *Ascaris* infection on nutrition and the role of *Ascaris* in allergic responses remain unclear.

Much scepticism about the effect of ascariasis in human nutrition was expressed at the Rockefeller Workshop in 1980 (Keusch, 1982) but, from Nesheim's (1985) review, it seems clear that both *A. suum* and *A. lumbricoides* can have demonstrable effects on gastrointestinal physiology and nutrient utilization, especially in heavily infected individuals. In *A. suum*, the negative effect of ascariasis on growth, food intake and fat absorption is visible and significant changes in the morphology of villi, hypertrophy of the tunica muscularis and lower lactase activity have been shown in pig small intestine. In human subjects, similar effects cannot always be demonstrated but impaired vitamin A absorption and lactase intolerance have been shown in some studies.

Community studies on the effect of ascariasis on growth and weight are extremely difficult to carry out satisfactorily and there have been no well controlled studies on food intake in children infected with *Ascaris*, although anorexia could be one of the major mechanisms affecting children's physical development (Crompton, 1984).

Allergy and the immunopathology of ascariasis is a fascinating subject for the *Ascaris* allergen is one of the most potent. Elevated serum IgE is common in ascariasis but it still remains unclear how this may affect the individuals' response to other allergens, for example with bronchospasm, skin eruptions or allergic gastrointestinal disorders (Coles, 1985, Lynch & Diprisco-Fuenmayor, 1984).

Ascaris - an attractive model for research. Although *Ascaris* allergy is a recognized occupational hazard for laboratory workers (Coles, 1985), the roundworms remain a convenient model for basic nematode research, but there are only a few studies which seem to have a direct application to human ascariasis.

Some factors which control embryonation of the Ascaris eggs and their invasiveness were reviewed by Crompton and Pawlowski (1985), but more research is needed.

In vitro culture techniques for nematode larvae are important for screening anthelmintic substances, as well as for biochemical and immunological research. Therefore, an important finding is that cultivation of A. suum third stage larvae in multi-well plates is improved by adding cholesterol (Urban & Douvres, 1984). It has also been shown in vitro that ecdysteroids control the moulting of A. suum and can play an important role in gametogenesis and embryogenesis (Fleming, 1985). Inhibition of human blood clotting which may facilitate the passage of nematode larvae through the blood stream has been demonstrated in soluble extracts of A. suum, in cuticle and secretory/excretory products (Crawford et al., 1982).

Both the anthelmintically active and the non-active benzimidazoles substantially inhibit fumarate reductase in A. suum in in vitro tests. Therefore, the most likely mechanism for the anthelmintic activity of the benzimidazole is through interference with the microtubule system of the parasite, which has been demonstrated in an A. suum model (Barrowman et al., 1984). Detailed characterization of the collagenous components of the adult A. lumbricoides cuticle (Winkfein et al., 1985) has not as yet found much practical application. However, this may come out of the studies on proteases and proteinase inhibitors in A. suum which may be essential for parasite survival and development (Martzen et al., 1985). Much work has been done on protective immunity against A. suum infection (Lloyd & Soulsby, 1985, Urban & Romanowski, 1985) but it may not be too relevant to human ascariasis. A radioimmunoassay search for a specific A. suum protein in a series of patients infected with different helminths has not confirmed its species specificity which might have been of diagnostic value (Tanaka et al., 1983).

Strongyloidiasis

Occurring in hot or warm regions, strongyloidiasis is usually a silent infection, well controlled by an immuno-competent host, which only becomes intensive and disseminated in immunocompromised patients. The risk factors for disseminated and frequently fatal strongyloidiasis are recent corticosteroid or other immunosuppressive treatment, haematological malignancy, prior gastric surgery, middle age and male sex, . Nowadays, it is a well accepted clinical principle to search for strongyloidiasis before inducing immunosuppression.

A high incidence of antibodies against the human T-cell leukaemia virus (HTLV-I) antibody in the serum of Strongyloides stercoralis carriers was reported from Okinawa (Nakada et al., 1984) but it is not clear whether this retrovirus infection permits proliferation of the parasite or whether chronic strongyloidiasis itself promotes HTLV infection. It is interesting to note, however, that strongyloidiasis has not yet been observed in AIDS patients infected with another retrovirus: human T-lymphotropic virus (HTLV-III).

Highly specific antilarval IgG antibodies and specific antilarval reaginic IgE antibodies can be demonstrated in most strongyloidiasis patients, respectively by using the ELISA technique and histamine release assay from peripheral basophils. Both of these antibodies can be usefully exploited for diagnostic purposes but it is doubtful whether they play a key role in protective functions. It has been suggested that, in chronic strongyloidiasis, patients develop serum modulating factors which inhibit lymphoblastic transformation and consequently depress T-cell immunity (Genta, 1984).

Is, then, impairment of the local intestinal immunity responsible for the development of invasive filariform larvae in the gut and the subsequent massive autoinfection which leads to disseminated strongyloidiasis? The answer is to be sought in experimental infections with S. ratti in rats (Genta et al., 1983) or with S. stercoralis in dogs (Grove et al., 1983, Schad et al., 1984) and in monkeys (Harper et al., 1984).

Primarily a parasite of primates in Africa and parts of Asia, Strongyloides fuelleborni, has not yet known been shown to be a frequent cause of severe pathology. However, in a limited area in the Gulf Province, Papua New Guinea, an S. fuelleborni-like parasite is responsible for 14% of all infant deaths, the infants dying with a "swollen belly syndrome", which can be partly caused by protein-losing enteropathy. The prevalence rate of this infection decreases with age and symptoms are less common in older children and adults. The transmission of this S. fuelleborni-like parasite to newborn babies is still a mystery and has not yet been clarified by the operational studies recently undertaken (Barnish & Barker, in press).

Trichuriasis

Trichuriasis is common all over the world and easily detectable by faecal examination but its clinical importance is less obvious, except in some areas where intensive infections are prevalent (e.g. Caribbean islands, Malaysia). However, the clinical expression of trichuriasis does not depend only on the parasite load but also on any concomitant or secondary infections (bacterial, protozoal), the patient's responsiveness (immune, allergic, neurotic) and general status (cachexia, prolapsus ani) (Pawlowski, 1984b).

Studies on Trichuris muris in mice have demonstrated that the anterior part of the worm burrows a tunnel through the enterocyte syncytium, which is further enlarged by the thicker posterior part of the worm pushing forward (Lee & Wright, 1978). How much mucosal damage is caused by Trichuris itself and the role that other factors play in secondary infections, haemorrhages, functional colonic disorders, etc., remain to be studied.

Some protective immunity seems to occur in trichuriasis especially in mice concurrently infected with other intestinal pathogens (Behnke *et al.*, 1984). Host local immune responses, especially those directed against the histotrophic phase of infection caused by juvenile worms, require further research.

Studies on the population distribution of T. trichiura confirm the overdispersion pattern but do not suggest any predisposition of certain individuals to heavy worm loads (Bundy *et al.*, 1985). Further work is needed on the dynamics of T. trichuris infections in human populations and on human trichuriasis of possible zoonotic origin (Pawlowski, 1984b).

Conclusion

An increasing amount of information is becoming available from parasitological, biochemical and immunological laboratories and much of it is on subjects directly related to human health (taeniasis/cysticercosis, strongyloidiasis, ascariasis). This is probably a reflection of the current policies of the various funding agencies. However, interest in some subjects (e.g. human trematodes, large-scale anthelmintic trials) is clearly a result of the new developments in anti-parasitic drugs. There are, nevertheless, some areas (strongyloidiasis and trichuriasis) where more laboratory and immunological research is needed. Better understanding of several clinical pathology problems requires stronger links between the clinics and parasitological laboratories.

The importance of field research (Garnham, 1979) is still underestimated, which explains considerable gaps between the knowledge needed and that which is available as well as between what is available and what is applicable.

A quantitative approach and studies on population dynamics have become important for the practical control of intestinal helminthiasis. However, ecological, environmental, behavioural and social studies, have not been able to explain the changing pattern of some infections (trematodiasis) or the persistence of others (taeniasis, ascariasis).

Changes in health priorities towards primary health care and greater emphasis on prevention and control are opening up new perspectives for cooperation between parasitologists and the human health services (Pawlowski, in press).

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