Most helminth parasites of man are unable to replicate within the human host. Thus, the worm burden of an infected person (on which the pathology largely depends – see Box 1) is a function of the number of infective forms to which the person is exposed. But for some species of helminths, the ability to replicate in man has a marked effect on the course and duration of infection, and for the pathogenesis of disease. In this review, David Grove discusses the mechanisms by which such replication may occur, and considers how this ability affects our approach to therapy and control.

Worms with a capacity to replicate within humans may be divided into two categories (Table 1). Some, such as *Strongyloides stercoralis*, can replicate completely with repeated cycles of development. Others, such as *Echinococcus*, are not able to complete their life cycle within the human host, but a developmental, pre-adult stage which the person is exposed. But for some species of helminths, the ability to replicate in man has a marked effect on the course and duration of infection, and for the pathogenesis of disease. In this review, David Grove discusses the mechanisms by which such replication may occur, and considers how this ability affects our approach to therapy and control.

**Strongyloides**

*S. stercoralis* is by far the most important of the worms capable of replicating within humans. It has several unusual and poorly understood features which need to be considered in relation to this ability. All the parasitic adult worms are female, and the parasite reproduces by partenogenesis, but there is also a freeliving cycle in the soil involving both male and female worms. Neither of these factors is likely to be important, however, because the related worm, *S. ratti*, possesses both of these characteristics yet is unable to replicate in its hosts, even in immunosuppressed animals. What may be more relevant is that *S. stercoralis* is either larviparous or else the eggs hatch very rapidly within the bowel. This offers the potential for larvae to moult within the intestinal tract allowing L3 (infective stage) larvae to penetrate the mucosa of the lower gut. Alternatively, although first stage (L1) larvae cannot penetrate intact skin, they might be able to migrate into normal or ulcerated intestinal mucosa, but this possibility has not been fully investigated. Adults of *S. ratti* live between the enterocytes rather than in the lumen of the bowel. If *S. stercoralis* occupies a similar habitat, it is possible that some L1 could be deposited.

**Box 1. The Severity of Helminth Infections**

Three major factors determine the severity of disease in helminth infections – the worm burden, the location of worms, and reaction of the host to the parasite. The number of worms is the prime determinant of disease in most helminth infections. Thus, the severity of hepatosplenic schistosomiasis or the degree of iron deficiency anaemia in hookworm infection depend upon the worm burden. In some infections, the site of the worm is of importance; a single hydatid cyst in the liver may cause no significant illness, but the same parasite situated at the base of the brain may prove disastrous. Finally, the interaction between worm and host sometimes influences the development of disease. Thus, a patient with hookworm infection who is poorly nourished is likely to develop a microcytic anaemia, even with a low worm burden. For all infections, the integrity of the host immune system is of major importance in determining the severity of disease.
since then, there have been isolated cases in thailand and a further group of 32 cases reported from the philippines. other cases of capillariasis may have gone undetected as the eggs are virtually indistinguishable from those of trichuris trichiura.

<table>
<thead>
<tr>
<th>Table 1. Worms with some capacity to replicate within man</th>
</tr>
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<tbody>
<tr>
<td>Completely replicating</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
</tr>
<tr>
<td>Capillaria philippinensis</td>
</tr>
<tr>
<td>Hymenolepis nana</td>
</tr>
<tr>
<td>Incompletely replicating</td>
</tr>
<tr>
<td>Echinococcus granulosus</td>
</tr>
<tr>
<td>Echinococcus multilocularis</td>
</tr>
<tr>
<td>Toenia crassiceps</td>
</tr>
<tr>
<td>? Toenia solium</td>
</tr>
<tr>
<td>Worm(s) causing racemose cysticercosis</td>
</tr>
<tr>
<td>Sparganum proliferum</td>
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<tr>
<td>Unidentified flatworm larvae</td>
</tr>
</tbody>
</table>

directly into the mucosa whereupon they might enter the draining lymphatic or blood vessels and moult elsewhere in the body.

in the last 20 years or so, it has become increasingly recognized that massive infections may supervene in patients who become immunosuppressed, following administration of immunosuppressive drugs, irradiation, or the coexistence of an illness such as leprosy, lymphoma or malnutrition which suppresses immunity. this has led to renewed interest in the factors affecting the host–parasite relationship. in chronic infections, the patient can normally control parasite numbers and restrict the disease to affections of the skin and gut (urticaria, diarrhoea, abdominal pain and weight loss), even though the infection is not completely eliminated. if this balance is disturbed by impairment of the host’s immune system, the parasite is favoured with a disastrous, massive increase in numbers and the dissemination of larvae throughout the body.

in other infected persons however, it is quite probable that the scales are tipped in favour of the host, with a perhaps genetically determined capacity to eradicate the parasite. for example, in one study of veterans, who had been exposed to prolonged unsanitary conditions while prisoners-of-war in an endemic area and then returned to live in a non-endemic area (perth, w. australia), only one-third of these men were infected when investigated 35 years or more later. most of them had probably been exposed to strongyloides and indeed most of them were infected with hookworm, which follows a similar epidemiological pattern. support for a belief in the importance of genetic control of susceptibility to infection is also provided by the observation that a small proportion of mongrel dogs develop chronic infection whereas the majority eliminate the infection spontaneously and are resistant to reinfection. this capacity to eradicate infection can be abrogated, however, by immunosuppression of such dogs.

the mechanisms by which genes control the development of resistance (if they do), and by which the immune system maintains partial control of infection are unknown. recent development of models of disseminated strongyloidiasis in immunosuppressed dogs and in normal and immunosuppressed monkeys may allow elucidation of the mechanism of autoinfection and an analysis of how these parasites evade the host’s immune response.

intestinal capillariasis

recognition of infection with capillaria philippinensis is less than 20 years old and some details of its life cycle are still uncertain. male and female adult worms are parasites of the intestinal tract of humans and birds, while various species of freshwater fish act as intermediate hosts. early studies showed that monkeys were susceptible to infection and that often, more worms could be recovered from the gut than has been introduced originally, indicating that autoinfection had occurred. autoinfection also occurs in certain birds that may be the natural reservoir of infection. consistent with the idea that autoinfection occurs in humans was the finding that long-term treatment with thiabendazole was required and that relapses occurred frequently when the drug was stopped. the introduction of effective therapy with mebendazole, however, now makes it unlikely that the true natural history of this infection in humans will ever be observed.

the host–parasite relationship is complex; adult worms do not develop after ingestion of embryonated eggs by humans, but infection can be maintained by serial passage of adults and larvae in gerbils. it was noted in experimental monkeys that some adult females were larviparous whereas others were oviparous. thus, autoinfection presumably occurs when the adult worms become larviparous, but the stimulus required for females to follow such a course is unknown. similarly, the details of the rest of the autoinfective cycle and the host response to the worms remain a mystery.

hymenolepis nana

hymenolepis nana may develop in two ways in experimental animals, and presumably also in humans. if mice are fed with h. nana eggs, the hatched embryos (oncospheres) invade the intestinal mucosa where they become cysticercoid larvae (metacestodes), then migrate back into the intestinal lumen and become adult worms; autoinfection does not occur in these circumstances and mice are resistant to external reinfection. on the other hand, if mice...
are fed with cysticercoids obtained from beetroots or other intermediate hosts, no tissue phase develops initially. Instead, the larvae attach to the mucosal surface and develop into adult worms which produce eggs to initiate autoinfection. Oncospheres hatch, invade the mucosa to become cysticercoids, then return to the lumen to produce a second generation of adult worms; the mice are then generally resistant to reinfection. However, if hypothymic mice are infected with either eggs or cysticercoids vast numbers of adult worms result from repeated autoinfection. Furthermore, cysticercoids may invade the mesenteric lymph nodes, liver and lungs of T-cell-deprived mice. In this infection, it appears that the worms have an intrinsic capacity to multiply indefinitely and invade the tissues, but this tendency is prevented by an intact cell-mediated immune system. The extent to which similar phenomena occur in immunosuppressed humans is unknown; in any event *H. nana* rarely seems to cause significant disease in humans.

**Echinococcosis granulosus**

In most instances, the hydatid larvae (metacestodes) of *Echinococcus granulosus* do not replicate exogenously; the number of hydatid cysts present is usually a function of the number of eggs ingested by a patient. Echinococcal cysts become surrounded by an adventitious layer which usually walls off the parasite from the host. Cells of the germinal layer proliferate, giving rise to numerous scolecis and cause an increase in the size of the parasite. Asexual proliferation of the germinal layer normally takes place entirely endogenously. Some of these germinal cells initiate the production of new brood capsules and protoscolices, but a pool of uncommitted, undifferentiated cells remains which makes possible the perpetuation of larval echinococcal infection. As long ago as 1793, John Hunter suggested that pelvic hydatid cysts in humans were often secondary to rupture of a visceral cyst rather than the result of multiple infections. A corollary of this hypothesis was the likelihood that hydatid elements might be sown by surgical puncture of a cyst. Experimental verification of this concept was provided in 1889 when Lebedev and Andreev observed that young daughter cysts from human hydatid infections transplanted into the peritoneal cavity of rabbits developed into fully-fledged hydatid cysts; Deve then showed that secondary cysts could also develop from isolated scolecis. It is now well recognized that secondary echinococcosis with a marked increase in the number of cysts may ensue in humans following spontaneous rupture, trauma, or surgical interference with a primary hydatid cyst. Thus, the parasite has the intrinsic capacity to multiply, but this is usually hindered physically by the host-derived fibrous capsule surrounding the organism.

**Echinococcosis multilocularis**

In the first half of the nineteenth century, a number of pathologists described a peculiar affection of the liver which they took to be a neoplasm and called ‗alveolar colloid‘. In 1855, Virchow recognized the characteristic hooklets of *Echinococcus* in this lesion, thus proving that it was helminthic. Controversy ensued for the next century as to whether this worm was a variant of *E. granulosus* or a distinct species. *E. multilocularis* is now an accepted species, characterized pathologically by infiltration of the parasite into the surrounding parenchyma and sometimes by spread to distant organs, thus simulating a neoplasm. The proliferation arises in the undifferentiated cells of the germinal layer and occurs both endo-ously and exogenously. Unlike *E. granulosus*, *E. multilocularis* has no limiting adventitious layer of host origin to act as a barrier. Bud-like and tube-like extensions of the germinal layer that infiltrate the intercellular spaces and could break off and metastasize through the lymphatics and blood vessels to other organs have been described in experimentally infected animals and in parasites removed from humans. Thus, like *E. granulosus*, the metacestode of *E. multilocularis* clearly has an intrinsic capacity to multiply, but proliferation occurs exogenously as well as endogenously and the host is less adept at restricting spread of the parasite. Furthermore, there is some evidence to suggest that cell-mediated immunity may become depressed during the course of infection in experimentally infected animals. Proliferation of the parasite may be enhanced in immunosuppressed patients, but this has not yet been demonstrated.

**Cysticercosis cellulosae due to *Taenia solium***

Man is the definitive host of the adult...
tapeworm, *Taenia solium*, whose larval (metacestode) form gives rise to cysticercosis celluloseae. In this condition, cysticerci may be found throughout the body, but are most frequent in the subcutaneous and muscular tissues and in the central nervous system. Cysticercosis usually follows the ingestion of eggs in contaminated food or water and may also result from self-contamination by people with adult worms in their intestine (external autoinfection). Theoretically, a form of partial internal autoinfection could occur in *Taenia solium*. Leuckart suggested over a century ago that cysticercosis may follow release of eggs from ruptured proglottids in the intestinal lumen in persons infected with adult worms. This has led to recommendations that agents such as mepracrine, which expel adult worms unbroken, should be used in preference to niclosamide, which may digest the segments. Subsequent experience, however, has not confirmed this supposition. The demonstration that exposure to gastric rather than intestinal juice is necessary for the liberation of the oncosphere from each egg implies that internal auto-infection would be unlikely unless ova entered the stomach during reverse peristalsis, as in vomiting.

**Racemose Cysticercosis**

*Cysticercus racemosus* is the name given to a proliferating cestode larva that produces daughter cysticerci by exogenous budding from the bladder wall of the host. The parasite occurs only in the human central nervous system, usually at the base of the brain. The racemose cysticercus is generally regarded as an aberrant cystercus of *T. solium*, although some authors regard it as a sterile coenurus of *T. multiceps* or perhaps some other tapeworm species. If it is indeed an aberrant form of one of these worms, then the cause of such behaviour is obscure.

**Cysticercosis longicollis due to *Taenia crassiceps***

*Cysticercus longicollis*, the larval stage of *T. crassiceps* (a parasite of foxes and dogs) is found in small rodents and multiplies asexually in those hosts by exogenous budding. An infection with this parasite has been reported in a young Canadian woman in whom the parasite was limited to one eye. In this instance the parasite behaved as it would in its natural host; the unusual feature was the susceptibility of a human to infection.

**Sparganosis**

In 1905, Ijima reported the case of a Japanese woman who was infected with an accephalic, proliferating larval cestode that invaded the skin and subcutaneous tissue. Several years later, a similar infection was described in a man in Florida and the parasite was named *Sparganum proliferum*. Less than a dozen such cases have been reported since. The worm multiplies asexually by exogenous budding; the new proliferating buds separate from the parent body and migrate to new locations in the host where they repeat the process. The adult forms of these larvae are unknown, and it has been suggested that they are aberrant forms of cestodes that are yet to be discovered.

Reinforcing the view that the capacity to replicate is intrinsic to the worm rather than being dependent upon the host, is the finding in one patient that both specific and non-specific immunity was unimpaired.

Reports of several other patients infected with proliferating accephalic platyhelminth larvae have been reviewed recently; the precise taxonomic status of the worms remains uncertain and their biology is not understood at all.

**Mechanisms of Replication**

What should be clear from the foregoing discussion is that a review of the mechanisms of autoinfection with these worms is more properly a subject for parasitology tomorrow rather than parasitology today. Clearly, each of these helminths has an intrinsic capacity to replicate and is able to evade the host’s immune defences at least partially. The host may have a genetically determined susceptibility to infection, and this may be enhanced in immunosuppressed individuals. One feature that stands out from a perusal of Table 1 is that the majority of species involved are platyhelminths, and that most of these are cestodes. Asexual multiplication is a well-recognized feature of certain stages of the life cycles of many digenetic trematodes and some cestodes which use an indirect mode of transmission. Humans do not act as intermediate hosts for trematodes but may become infected as if they were by certain cestodes (albeit the worm usually comes to a dead end). Thus, those larval cestodes which have an intrinsic capacity to replicate do not necessarily lose this ability when a human is infected. Of all the nematodes which are hosts for trematodes but may become infected, only two replicate. Whether coincidentally or not, one undergos parthenogenesis, and both of them may be larviparous. These features may be relevant to autoinfection but other factors must also be operative.
Implications for Treatment

An ability to replicate imposes major impediments upon the effectiveness and philosophy of treatment. While it is desirable to eradicate worms with anthelmintics, it may be inappropriate, in view of drug toxicity, to be content with a major reduction in worm burden in many helminthiases. This is clearly unacceptable in infections where the worms can replicate, as persistent parasites are likely to build up worm numbers and eventually precipitate a relapse of symptoms. Unfortunately, completely effective drugs are not always available and recourse must sometimes be made to rescheduling the administration of drug, for example the chronic use of mebendazole in alveolar echinococcosis or repeated courses of thiabendazole therapy in immunosuppressed patients with persistent, disseminated strongyloidiasis. The development of highly active anthelmintics in these infections is urgently needed.

The same constraints are applicable to vaccines, should they ever be developed. The ideal vaccine must eradicate the infection rather than merely reduce the worm burden, otherwise residual parasites can multiply should the effects of the vaccine wane with the passage of time or if the patient subsequently becomes immunosuppressed.

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Progress in Warble Fly Eradication

D. W. Tarry

Warble flies (Fig. 1) are bee-like insects, belonging to the parasitic fly family Oestridae, which spend their entire 10-month larval period inside the body of the host animal, only emerging in the summer to complete their development to the free-flying adult stage (Fig. 2). In 1978, when almost 40% of cattle in Britain were infested, the Ministry of Agriculture, Fisheries and Food (MAFF) initiated a warble fly eradication scheme. We are now in the final stages of this plan, with infestation rates down to 0.01%. This represents a massive saving to the farming industry in terms of less damaged hides and improved production of milk and beef. It also represents an enormous improvement in animal welfare; cattle in the past often carried 20-30 of these large (2 cm long) grubs in pus-filled ‘warble’ lumps on their backs. Now they are never seen in most parts of the country.

In this review, David Tarry discusses the progress of warble fly control, warning that the problem could reappear unless stringent measures are taken to eradicate remaining foci and to control imported cattle.

Warble flies of the genus Hypoderma are principally found in the Northern Hemisphere between latitudes of 18°N and 60°N. Although warbles do not occur in Iceland and much of Scandinavia, they are found in at least 55 countries and represent a widespread problem over much of North America, Europe and large areas of the USSR and China (Fig. 3). A few countries in the neotropical region (Argentina, Brazil,