Section of Comparative Medicine

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Some Aspects of Resistance to Animal and Human Helminths [*Abridged*]

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Acquired Resistance and its Effect on Populations of *Ostertagia ostertagi*

Even in those nematode infections in which a resistance to the establishment of new worms develops only after very prolonged experience of infection, the size and activity of worm burdens is regulated by a number of mechanisms. In many infections fæcal egg counts have been shown to decrease logarithmically. If this means that burdens of adult worms also decrease in this way, and in some instances this has been demonstrated, it would follow that the rate at which adult worms are lost is proportional to the number present. Such a density-related loss could represent a potent regulatory mechanism for, at any rate of infection, the worm burden would rise to and remain at that level at which the consequent rate of loss balanced the new infection. The worm burden of a grazing animal might be expected, therefore, to vary directly as the concentration of larvæ per unit weight of pasture herbage.

In infections in calves of the trichostrongylid nematode *Ostertagia ostertagi* a resistance to the establishment of new infection is very slow to appear and, typically, fæcal egg counts decrease logarithmically. A series of experiments has shown that worm burdens are regulated by a balance between new infection and a density-related loss, but it appears that the loss varies as the square of the number of adult worms present. In animals receiving new infection daily the worm burden is proportional to the square root of the effective rate of new infection; in animals infected on one occasion only the decrease in worm numbers appears to be hyperbolic and not logarithmic. Such a form of loss implies that there is a random element in the process of loss, that whether a particular worm is, or is not, lost on any given day depends on chance and not on its individual susceptibility to some harmful factor to which the entire population is equally exposed. It means also that the chance of loss, or the intensity of the factor which occasions the loss, is proportional to the number of worms present and does not persist after the worms are lost. One might visualize worm loss as being caused by a transient and localized change in the environment of the worms.

In a calf infected by a single dose of larvæ, the worm burden does not begin to decrease for some forty or fifty days. If, in an animal receiving larvæ daily each day's input of worms behaved in this way, the worm burden would increase for eighty to a hundred days. In fact, it reaches a steady level in half this time, a finding which suggests that the initiation of worm loss depends on some host response. Experiments involving the replacement of one population by another have suggested that another determinant is the age of the worms which may affect their susceptibility to changes associated with the host response.

As the host's experience of infection increases, it provides less favourable conditions for the development of the worms which consequently grow to a smaller size and are less prolific. There is also an increase in the proportion of females in which the vulval flap is vestigial or absent. It is a consequence of the regulation of worm burdens by a balance between the gain and loss of worms that there is a constant replacement of worms and that the worms present at any point in time will have developed during a relatively short preceding period. Their state of development will, therefore, give an indication of the host's present state of resistance.

There is not, in infections of *O. ostertagi*, a constant relationship between fæcal egg count and the number of adult worms. In animals infected on one occasion only the egg count begins to decline logarithmically from an early peak before the worm burden decreases. In animals infec-

ted daily and in which the number of worms remains constant, the egg count follows the same course as in animals infected once only. In animals receiving infection daily at different rates and in which different levels of worm burden are therefore maintained, the fæcal egg counts are identical. This must mean that the egg output of the entire population is limited directly. The environment of the worms will sustain a certain rate of egg production irrespective of the number of females present. The egg output is likely to be limited to a point well below that of which the worms are potentially capable. That this limitation on egg output breaks down in animals treated with cortisone, in immunologically incompetent animals and in some clinically affected animals suggests that the phenomenon is associated with an immune response. The logarithmic form of the decrease in egg count means that the egg output at any moment bears a constant relation to the preceding output. The limitation of egg output depends on previous egg laying activity which probably acts by inducing a transient change in the host – a mechanism similar to, but distinct from, that which occasions worm loss.

A proportion of the worm larvæ ingested fail to develop beyond the early fourth stage. The precise nature of this phenomenon is obscure but both the condition of the infective larvæ and the resistance of the host appear to play a part. Very large numbers of these inhibited forms can accumulate; the average bovine at the end of its first grazing season carries enough to kill it were they to develop simultaneously. This they may occasionally do, to give rise to outbreaks of ostertagiasis in animals which may not have been exposed to infection for some months. More commonly, however, resumption of development is at a more modest rate and the usual replacement of worms may be from this source.

This brief account may serve to show that even where protective immunity is not involved, worm burdens are effectively regulated.

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Resistance of the Host to *Fasciola hepatica*

Among helminths most nematodes can be shown to be host specific or to have a very narrow range of hosts but very little is known about the origin and mechanisms of barriers to infection. In the preferred host, the possibly related phenomenon of resistance to reinfection may be manifested in a variety of ways. There may be barriers to invasion, to the migration or to development. Worms may be stunted in growth, their sexual maturity delayed, egg-laying may be reduced or suppressed and the mature worms themselves may be eliminated gradually or dramatically.

Unlike a typical nematode, the trematode *Fasciola hepatica* has an extremely wide range of definitive hosts – probably almost any mammal – and in several of these the parasite can live an apparently well-adjusted existence, producing large numbers of eggs and living for a long time. Possibly as a corollary to its lack of selectivity, *Fasciola* does not seem to be active in eliciting resistance to reinfection. Most evidence for this comes from field observation: there is, for example, little to suggest that sheep in an area where fascioliasis is endemic acquire an immunity. At Weybridge, long-term experiments in which animals were exposed to repeated reinfection with metacercariæ showed that with sheep the output of fluke eggs increased with time and at death large numbers of parasites were recovered. With cattle, however, comparatively few fluke eggs were passed in the fæces; the numbers decreased with time to a very low level. At slaughter relatively few parasites were recovered. This comparative resistance of cattle possibly results from the marked pathological changes in the bovine liver making it unsuitable as an environment for the fluke. Recent work by Ross (1965) supports this hypothesis.

Interest in the problems of resistance to fascioliasis has revived recently with the realization that existing methods of control of fascioliasis are not very satisfactory and with the knowledge that with another helminth parasite – *Dictyocaulus viviparus* – protection can be given by administration of larvæ which have been attenuated by irradiation. Some of the few recorded experiments which have been designed to determine whether an active immunity to *F. hepatica* can be elicited have, in fact, involved the use of irradiated metacercariæ. Thorpe & Broome (1962) found evidence of a protective effect in rats; animals which had been given suitably attenuated metacercariæ became infected with fewer flukes when later challenged with normal metacercariæ. This result, which is contrary to most other evidence (e.g. Hughes 1962, 1963) could be explained on the premise that irradiated cercariæ which die in the liver may be more antigenic than are those which proceed through a normal course of development. Because of the paucity of experimental evidence of the existence of resistance to *Fasciola* it seemed important to establish whether an active resistance could be elicited in a laboratory animal by the use of normal metacercariæ. The rabbit was chosen because it is a well-adjusted host both under field conditions and in the laboratory.