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Heterologous antagonistic and synergistic interactions between helminths and between helminths and protozoans in concurrent experimental infection of mammalian hosts

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Abstract. Experimental concurrent infection with two or more parasite species in mammalian host models may result in heterologous antagonistic and synergistic interactions ranging in magnitude from reduced/enhanced growth and fecundity to blockage/enhancement of establishment/expulsion. With some exceptions only, there is a reasonable correlation between the levels of interaction monitored by parasitological and by clinico-pathological parameters. Heterologous antagonistic interactions mediated by functional and specific immunological cross-reactivity occur between closely related parasite species exhibiting a marked immunobiological similarity. In contrast, antagonistic interactions between antigenetically more remote species of helminths, protozoan-induced resistance to helminth infection and helminth-induced suppression of concurrent protozoan infection generally appear mediated by immunologically non-specific factors like macrophage activation and inflammatory reactions. Synergistic heterologous interactions between helminths, helminth-induced enhancement of concurrent protozoan infection and interference with the development and maintenance of resistance to helminth infection in response to concurrent protozoan infection are generally thought to be mediated by non-specific parasite-induced immunosuppression. Concurrent experimental infection is very complex. There are problems and limitations in extrapolating from experimental studies on concurrent infection in laboratory animals to natural polyparasitism. This fact, coupled with the complex influence of ecological factors on the pattern and frequency of concurrent natural infection means that major consequences of natural concurrent parasite infection have not been definitively demonstrated. Appropriately planned and controlled field studies and further laboratory experiments on primate and domestic animal models are imperative for elucidation of the importance of heterologous interactions in concurrent parasite infection for the disease pattern in man and domestic stock. Experimental studies hitherto conducted on concurrent parasite infection pointing to natural heterologous interactions may be a valuable starting point for further studies.

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Concurrent infection with two or more parasite species in man and domestic stock is the basis for the enduring interest in experimental studies on multiple parasitism. This paper presents a review of the available information accumulated from studies on synergistic and antagonistic heterologous interactions between helminths and between helminths and protozoans. The effects of these interactions on the disease picture are also discussed. Other recent publications contain valuable reviews of resistance against *Schistosoma* spp. in mice (Dean 1983), of cross resistance in concurrent metacestode infections (Gemmell and Johnstone 1977) and of resistance to trematode infection using heterologous antigens (Hillyer 1984). In addition, Hsu et al. (1980) briefly listed a number of

examples of heterologous antagonistic interactions between various schistosomes in the mammalian host. Reviews of site selection and site segregation by parasitic helminths in heterologous interactions and their importance for the development of helminth communities have been provided by, for example, Schad (1966), Holmes (1973) and Halvörsen (1976). In addition, Dobson (1985) recently introduced mathematical modelling for population dynamics of "competition" between parasites.

A complex set of interacting and interrelated factors govern the types and characteristics of heterologous interactions which develop in concurrent experimental infections. A given combination of two parasite species may thus result in a range of types of either antagonistic or synergistic interactions, depending on factors like relative timing and size of infections. The complexity of experimental concurrent infection must be recognized, but in spite of this, and for the sake of clarity, each type of interaction is dealt with separately in the present review. Aspects and consequences of this complexity are dealt with in the discussion. Also discussed is the importance of experimental studies for elucidating the importance of natural multiple parasitism in man and domestic stock. For clarity, references are mainly in the tables and only to a limited extent in the text.

Heterologous antagonistic interactions in schistosome infections in mice and hamsters

Resistance to heterologous schistosome infection can be reflected in reduced establishment of worms after challenge infection ("reduced challenge worm establishment"), in reduced total tissue egg counts and often also in reduced tissue egg counts per worm pair. It is frequently induced by species of schistosomes capable of producing significant numbers of eggs in the experimental rodent host (Table 1). Reductions in *Schistosoma mansoni* challenge worm establishment appear to require patent mixed-sex primary infections of a certain size and a significant deposit of eggs in the tissue at the time of challenge (Malek 1981; Nelson et al. 1968). However, reductions in *S. haematobium*

Table 1. Heterologous antagonistic interactions in schistosome infections in mice and hamsters. *att*, attenuated by passage in the hamster; *zooph*, zoophilic strain; *human*, human strain

Resistance induced by	Resistance directed against	Experimental host	
		Mouse	Hamster
Resistance induced by schistosomes producing significant numbers of eggs			
Schistosoma bovis	*S. mansoni*	[a]	
S. mattheei	*S. mansoni*	[a]	
S. rodhaini	*S. mansoni*	[a]	
S. haematobium	*S. mansoni*		[b]
S. mansoni	*S. haematobium*		[b c]
S. mansoni	*Schistosomatium douthitti*	[d]	
Heterobilharzia americana	*S. mansoni*	[e]	
S. mattheei (att)	*S. mattheei*	[f]	
S. japonicum (zooph)	*S. japonicum* (human)	[g]	
S. japonicum (human)	*S. japonicum* (zooph)	[g]	
S. spindale	*S. incognitum*	[h i]	
Resistance induced by schistosomes producing no or insignificant numbers of eggs			
Ornithobilharzia turkestanicum	*S. bovis*	[j]	
O. turkestanicum	*S. haematobium*	[j]	
O. turkestanicum	*S. mansoni*	[j]	
S. mattheei (single-sex)	*S. mansoni*	[k]	
S. indicum (single-sex)	*S. incognitum*	[l]	
S. spindale (single-sex)	*S. incognitum*	[h i]	
Resistance induced by schistosomes undergoing early attrition			
Trichobilharzia szidati	*S. mansoni*	[m]	
S. spindale	*S. incognitum*	[n]	

[a] Nelson et al. 1968; [b] Smith et al. 1976; [c] Mansour et al. 1984; [d] Hunter et al. 1961; [e] Malek 1981; [f] Taylor et al. 1977; [g] Sadun et al. 1961; [h] Agrawal et al. 1983; [i] Agrawal and Sahasrabudhe 1984; [j] Massoud and Nelson 1972; [k] Amin and Nelson 1969; [l] Agrawal et al. 1979; [m] Pedersen et al. 1982; [n] Varma et al. 1983

challenge worm establishment may be induced in hamsters by prepatent *S. mansoni* infections (Mansour et al. 1984). Single-sex male infections with *S. indicum* or *S. spindale* and exposures to cercariae of *S. spindale* resulting in no adult worm establishment induce marked resistance to *S. incognitum* challenge in mice judging by worm establishment. The level of worm establishment suggests that resistance does not develop either to *S. mansoni* challenge in *S. haematobium* and *Schistosomatium douthitti*-infected mice or to *S. mattheei* challenge in *S. bovis*-infected mice (Hunter et al. 1961; Nelson et al. 1968; Halawani et al. 1977). However, this may reflect the low susceptibility of mice to *S. haematobium*, *S. bovis* and *S. douthitti*. Resistance to *S. mansoni*, *S. bovis* and *S. haematobium* challenge, judged by tissue egg counts, may be induced in mice by primary mixed-sex infections with *Ornithobilharzia turkestanicum*. This is in spite of *O. turkestanicum* producing insignificant numbers of eggs in the mouse. A reduction in the egg production capacity of *S. mansoni* challenge infections may also be induced in mice by primary single-sex *S. mattheei* infections producing no eggs. Primary exposures of mice to cercariae of *Trichobilharzia szidati*, the schistosomulum of which in the mouse is killed during early migration, may result in reduced tissue egg counts, but unaltered worm establishment, from a *S. mansoni* challenge infection, and reductions in tissue egg counts per worm pair of *S. mattheei* and *S. rodhaini* have been recorded in mice following *S. mansoni* challenge (Nelson et al. 1968). Reductions in tissue egg counts could be due to a decreased egg production capacity, a prolongation of the prepatent period or even to an increase in the rate of destruction of the eggs in the tissue. Finally, initial infection of mice with *S. japonicum* reduced the histological tissue reaction following a challenge exposure to cercariae of the bird schistosome *Gigantobilharzia sturniae* (Hunter et al. 1956) and Michael et al. (1979) demonstrated a suppression of the granulomatous reaction to eggs of *S. mansoni* in the liver of mice concurrently infected with *S. haematobium*.

The mechanism responsible for heterologous resistance between schistosomes in mice and hamsters has not yet been found. However, the importance of presence of eggs produced by worms of the primary infection at the time of challenge for reduction in challenge *S. mansoni* worm establishment in mice agrees well with observations made on the homologous *S. mansoni*/mouse resistance model (Dean 1983). This is also the case for the early attrition of the *S. haematobium* challenge in *S. mansoni*-infected hamsters (Smith et al. 1976).

Heterologous antagonistic interactions in schistosome infections in sheep, cattle and non-human primates

Exposure of sheep and cattle to cercariae of *S. haematobium* and *S. mansoni* results either in no adult schistosome establishment, or in only a few worm pairs which produce insignificant numbers of eggs. This also applies to baboons and rhesus monkeys exposed to cercariae of non-human strains and species of schistosomes. However, heavy and repeated exposure to cercariae of heterologous schistosome species and strains, as well as exposures to heterologous radiation-attenuated cercariae, may induce significant resistance to challenge with homologous schistosome species and strains. Resistance in this case is measured using parasitological parameters such as worm establishment, tissue egg counts (total and per worm pair) and faecal egg excretion (Table 2). This resistance is generally accompanied by alleviation of disease in sheep and calves, but not in rhesus monkeys and baboons. Significant alleviation was thus not found following *S. japonicum* (human strain) challenge of rhesus monkeys heavily exposed to cercariae of a non-human strain of *S. japonicum* (Murrell et al. 1973) or following *S. mansoni* challenge of baboons heavily and repeatedly exposed to cercariae of *S. bovis* and *S. rodhaini* (Taylor et al. 1973). This seems to be explained by the fact that egg counts in essential organs remain unaffected and by an apparently increased granulomatous reaction to *S. mansoni* eggs in *S. bovis*- and *S. rodhaini*-exposed baboons. In contrast, resistance to *S. japonicum* challenge is apparently not induced in rhesus monkeys following even heavy exposures to *S. bovis* cercariae (Eveland et al. 1969) and exposure of baboons to only moderate numbers of *S. rodhaini* cercariae has not induced resistance to *S. mansoni* challenge (Taylor et al. 1976). The mechanism responsible for this type of heterologous resistance remains unknown, but a parallel might be drawn with resistance to homologous schistosome challenge induced by exposure to radiation-attenuated cercariae.

Heterologous antagonistic interactions may also develop between homologous schistosome species of sheep, cattle and non-human primates. Thus, there may be reciprocal resistance in cattle, and possibly also in sheep, between *S. bovis* and *O. turkestanicum*. A marked resistance may develop to *S. mansoni* challenge in *S. japonicum*-infected rhesus monkeys and in baboons harbouring primary patent infections with *S. haematobium*. The resistance to *S. mansoni* challenge in *S. haemato-*

Table 2. Heterologous antagonistic interactions in schistosome infections in sheep, cattle and non-human primates. ( ), evidence only; *zooph*, zoophilic strain; *human*, human strain; *irr*, attenuated by irradiation; *att*, attenuated by passage in the hamster

Resistance induced by	Resistance directed against	Experimental host			
		Sheep	Cattle	Rhesus monkey	Baboon
Resistance induced by schistosomes producing no or insignificant numbers of eggs					
Schistosoma haematobium	*S. bovis*		[a]		
S. haematobium	*Ornithobilharzia turkestanicum*		[a]		
S. mansoni	*S. mattheei*	[b]	[c]		
S. bovis	*S. mansoni*			[d e]	[f]
S. bovis	*S. haematobium*			[g]	
S. mattheei	*S. mansoni*			[d]	
S. rodhaini	*S. mansoni*				[f]
Schistosomatium douthitti	*S. japonicum*			[h]	
S. japonicum (irr)	*S. mansoni*			[e]	
S. mansoni (irr)	*S. japonicum*			[e]	
S. japonicum (zooph)	*S. japonicum* (human)			[i j k]	
Resistance induced by schistosomes producing significant numbers of eggs					
S. mattheei (att)	*S. mattheei*	[l]			
O. turkestanicum	*S. bovis*	([a])	[a]		
S. bovis	*O. turkestanicum*	([a])	[a]		
S. haematobium	*S. mansoni*				[m]

[a] Massoud and Nelson 1972; [b] Preston et al. 1972; [c] Hussein et al. 1970; [d] Amin et al. 1968; [e] Eveland et al. 1969; [f] Taylor et al. 1973; [g] Hsü et al. 1966; [h] Hsü et al. 1964; [i] Hsü and Hsü 1961; [j] Hsü and Hsü 1963; [k] Murrell et al. 1973; [l] Dargie et al. 1977; [m] Webbe et al. 1979

bium-infected baboons was reflected in reduced worm establishment and reduced faecal egg excretion, but an increased retention of eggs resulted in unaltered *S. mansoni* tissue egg counts. However, a suppression of the granulomatous reaction to the *S. mansoni* eggs in the *S. haematobium*-infected baboons allows the resistance to be paralleled by alleviation of the disease. The demonstration by Webbe et al. (1979) that sera from *S. haematobium*-infected baboons show a cytotoxic reaction to *S. mansoni* schistosomula in vitro may point to the involvement of specific immunological factors in the resistance, and this may be seen in view of the suggested occurrence of common functional antigens. Finally, preliminary observations indicate that a primary *S. mansoni* infection in the chimpanzee may induce resistance to *S. japonicum* challenge (Hsü and Hsü 1968) and that a reciprocal cross resistance may exist between *S. mansoni* and *S. haematobium* in vervet monkeys (Obuyu 1969, cited by Webbe et al. 1979).

The distribution of lechwe schistosomes (*S. margrebowiei* and *S. leiperi*) does not overlap those of human (*S. mansoni* and *S. haematobium*) or bovine schistosomes (*S. mattheei*) (Pitchford 1976, 1977). Results from immunological tests on children in areas free from human schistosomiasis but endemic to schistosomiasis in lechwe (Pitchford and Wolstenholme 1977) combined with the distribution data have been put forward as evidence that exposure to lechwe schistosomes induces heterologous resistance to infection with *S. mansoni* and *S. haematobium* in man and to *S. mattheei* in cattle. Epidemiological evidence also suggests an interaction in the primary definitive hosts between the two lechwe schistosomes *S. margrebowiei* and *S. leiperi* (Wright et al. 1979). These suggestions based on epidemiological evidence require experimental confirmation.

Heterologous antagonistic interactions between schistosomes and other trematodes, and between trematodes and other helminths

Using worm establishment as the resistance criterion, patent solid infection of mice with a range of *Schistosoma* species may induce a marked resistance to heterologous challenge with *Fasciola hepatica* and *Echinostoma revolutum* (Table 3). A patent, primary *S. mansoni* infection in mice may also induce a marked resistance to challenge with *Trichinella spiralis* (reduced establishment, reduced tissue larvae counts, enhanced expulsion), with *Ascaris suum* (reduced lung larvae counts), and presumably also with *Nippostrongylus brasiliensis*. However, resistance to *A. suum* challenge, measured by liver larvae recovery rates on day 2 fol-

Table 3. Heterologous antagonistic interactions between schistosomes and other trematodes, and between trematodes and other helminths. ( ) evidence only. Note that resistance induced by *F. hepatica* against *S. douthitti* is reflected only in decreased survival of eggs deposited in the liver

Resistance induced by	Resistance directed against	Experimental host			
		Mouse	Rat	Sheep	Cattle
Schistosoma mansoni	*Fasciola hepatica*	[a] [b]	([c])		
S. bovis	*F. hepatica*	[d]		[e]	[f]
S. bovis	*F. gigantica*				[g]
S. intercalatum	*F. hepatica*	[d]			
S. mansoni	*Echinostoma revolutum*	[d] [h]			
S. bovis	*E. revolutum*	[d]			
S. mansoni	*Ascaris suum*	[i]			
S. mansoni	*Nippostrongylus brasiliensis*	[j]			
S. mansoni	*Trichinella spiralis*	[k]			
A. suum	*Schistosomatium douthitti*	[i]			
N. brasiliensis	*S. mansoni*	([j])			
F. hepatica	*S. mansoni*	[a] [l] [m]			
F. hepatica	*S. douthitti*	[n]			
F. hepatica	*N. brasiliensis*		[o]		
N. brasiliensis	*F. hepatica*		[p]		
F. hepatica	*Hymenolepis microstoma*	[q]			
F. hepatica	*Taenia taeniaeformis*		[r]		
F. gigantica	*S. bovis*				[g]
T. hydatigena	*F. hepatica*			[s] [t]	

[a] Christensen et al. 1978; [b] Hillyer 1981; [c] El-Azazy and van veen Schillhorn 1985; [d] Christensen et al. 1981b; [e] Monrad et al. 1981; [f] Sirag et al. 1981; [g] Yagi et al. 1986; [h] Sirag et al. 1980; [i] Crandall et al. 1966; [j] Hunter et al. 1967; [k] Aboul Atta and El-Sheikh 1981; [l] Hillyer 1976; [m] Christensen et al. 1980; [n] Maldonado-Moll 1977; [o] Goose 1977; [p] Doy et al. 1981; [q] Lang 1967; [r] Campbell et al. 1979b; [s] Campbell et al. 1977; [t] Dineen et al. 1978

lowing challenge, was not induced in mice harbouring prepatent *S. mansoni* infections (Bindseil 1970). It has been suggested that immunological non-specific factors like the schistosome-egg-induced inflammation in the liver and intestines, and even liver fibrosis/necrosis, might contribute to or be responsible for the schistosome-induced resistance to heterologous helminth challenge. However, the recent demonstration by Hillyer (1985) of induction of resistance in mice to *F. hepatica* with a *Fasciola/Schistosoma* cross-reactive defined immunity antigen might point to the involvement of an immunologically specific mechanism. In contrast, *S. mansoni* infection in mice failed to induce resistance to infection with *Onchocerca lienalis* microfilariae. Resistance was judged by microfilariae recovery rates following injection of *O. lienalis* microfilariae into mice harbouring patent infections with *S. mansoni* (Townson et al. 1985).

Examples of heterologous helminth-induced resistance to schistosome challenge in mice using worm establishment as the criterion include *A. suum*-induced resistance to *S. douthitti*, and *N. brasiliensis*- and *F. hepatica*-(patent infection) induced resistance to *S. mansoni* challenge infection. *N. brasiliensis* infection enhances IgE antibody-dependent eosinophil adherence and cytotoxicity to DNP-coupled schistosomulae of *S. japonicum* (Kojima et al. 1985a, b), and there have been repeated demonstrations of induction of significant resistance to *S. mansoni* infection in mice and hamsters, using different immunizing regimes with various types of purified *F. hepatica* antigen (see review by Hillyer 1984). Both provide strong evidence for the involvement of immunological factors of a possible specific nature. Hillyer and Serrano's (1983) induction of resistance in mice to infection with *S. mansoni* by immunization with *Paragonimus westermani* whole worm extract antigen is a related finding. Significant "negative" findings include failure of *A. suum* to induce resistance to *S. mansoni* and of *T. spiralis* to induce resistance to *S. mansoni* and *S. douthitti* in mice, as judged from challenge worm recovery (Weinman 1960; Jachowski and Bingham 1961; Hunter et al. 1963; Crandall et al. 1966). However, the egg production capacity per worm pair of *S. mansoni* seems suppressed in mice concurrently infected with *T. spiralis* (Aboul Atta and El-Sheikh 1981). Finally, intravenous injection of *T. spiralis* larvae, resulting in marked eosinophilia, in naive baboons and those already harbouring primary *S. mansoni* infections

has failed to increase the level of resistance to *S. mansoni* (re)infection (Sturrock et al. 1985).

Patent *F. hepatica* infections in rats may induce significant resistance to *N. brasiliensis* challenge, and a marked resistance to *F. hepatica* oral metacercarial infection, but not to intraperitoneally implanted newly-excysted juveniles, was demonstrated in rats harbouring 4- but not 2-week-old infections with *N. brasiliensis*. The resistance mechanism remains unknown, but the level of resistance to *F. hepatica* challenge was correlated with the level of *N. brasiliensis*-induced intestinal eosinophilia. *F. hepatica* challenge of mice harbouring 25-day-old infections with the bile duct cestode *Hymenolepis microstoma* may result in a change in site of attachment and an expulsion of part of the cestode population. This may possibly be a result of the *F. hepatica*-induced bile duct damage. In line with this, the decreased survival of eggs of *S. douthitti* in the liver of concurrently *F. hepatica*-infected mice may be induced by the *F. hepatica*-induced damage of the liver parenchyma rather than by an immune reaction. Besides, *F. hepatica* challenge of rats harbouring 6-week-old metacestode infections with *Taenia taeniaeformis* may significantly reduce the number of metacestodes developing from the primary infection and infection of rats with *F. hepatica* may stimulate a substantial level of resistance to a *T. taeniaeformis* egg challenge. In contrast, no resistance to *F. hepatica* challenge appears to develop in rats harbouring 4-, 6- and 12-week-old primary *T. taeniaeformis* infections (Campbell et al. 1979b). This finding is paralleled by failure of different immunization regimens using *T. hydatigena* cysticerci antigens to induce resistance to *F. hepatica* challenge in rats and mice (Rajasekariah et al. 1979).

Infection of sheep for 3 and 9 months, but not for 3 weeks, with *Cysticercus tenuicollis*, the metacestode stage of *T. hydatigena*, may induce a marked reduction in the *F. hepatica* challenge worm establishment and egg excretion and in the *F. hepatica*-induced liver pathology. A similar marked resistance has been observed in sheep to *F. hepatica* at challenge 3 weeks after anthelmintic termination of a 3-month-old *C. tenuicollis* infection. However, resistance was not observed at *F. hepatica* challenge 3 weeks and 6 months after termination by anthelmintics of *C. tenuicollis* infections of 3 weeks and 3 months duration, respectively. Nor was it found with simultaneous infection. No resistance developed to a *T. hydatigena* egg challenge in sheep harbouring primary patent *F. hepatica* infections (Campbell et al. 1977, 1979a; Dineen et al. 1978).

Attempts to repeat the demonstration of *C. tenuicollis*-induced resistance to *F. hepatica* challenge have failed in experiments on goats, sheep and calves (Mitchell and Armour 1981; Hughes et al. 1978). Hughes et al. (1978) suggested that the *C. tenuicollis*-induced resistance to *F. hepatica* challenge could be a result of non-specific immunopotentiation due to extensive use of the immunostimulatory drug levamisole. This stimulated Mitchell and Armour (1981) to examine resistance to *F. hepatica* in sheep combining levamisole treatment and prior intestinal helminth and metacestode infection. The results led the authors to suggest that this heterologous helminth-induced resistance actually requires the simultaneous use of an immunostimulatory agent, e.g. levamisole. However, the final clarification of the *C. tenuicollis*-induced resistance to *F. hepatica* in sheep requires further studies. Differences in breeds of sheep and parasite strains used might also be responsible for the diverging results.

Resistance to heterologous challenge with *F. hepatica* may develop in sheep and cattle harbouring newly patent infections with *S. bovis*, as reflected in reduced *F. hepatica* challenge worm establishment and reduced *F. hepatica*-induced liver pathology. A marked reduction in *F. gigantica* challenge worm establishment has been demonstrated in cattle harbouring primary patent *S. bovis* infections. The mechanism responsible for this resistance to *Fasciola* spp. in sheep and cattle remains unknown, but may be immunological. In contrast, a primary, old patent *S. bovis* infection in sheep (Monrad et al. 1981) and repeated, heavy exposure of calves to cercariae of *S. mansoni* resulting in no adult worm establishment (Knight 1985) have failed to induce resistance to heterologous *F. hepatica* challenge. Resistance to *F. gigantica* challenge was also not induced in cattle exposed to primary infection with irradiated *S. bovis* cercariae (Yagi et al. 1986). However, some evidence was obtained by Hammond (1973) for resistance to experimental *F. gigantica* challenge in sheep harbouring naturally acquired infections with the bile duct cestode *Stileria hepatica*. A marked reduction in *S. bovis* challenge worm establishment has been demonstrated in cattle harbouring primary patent infections with *F. gigantica*. A significant "negative" finding comprises lack of resistance to *F. hepatica* challenge in sheep 13 weeks after the second of 2 exposures, given 2 weeks apart, to a mixture of 5000 third stage larvae of *Ostertagia circumcincta* and *Trichostrongylus vitrinus* and 15 weeks after inoculation of 5000 *A. suum* eggs (Mitchell and Armour 1981). Besides, daily infections of

calves over a prolonged time with *O. ostertagi* larvae and *F. hepatica* metacercariae gave rise neither to antagonistic nor synergistic interactions (Burden et al. 1978). This indicates that the fascioliasis/ostertagiasis disease complex (see e.g. Reid et al. 1967) represents a simple accumulation of the disease induced by each of the parasites separately.

Heterologous antagonistic interactions between intestinal nematodes, cestodes and acanthocephalans

The expulsion of both primary and homologous challenge (secondary and superimposed) helminth infections is, in some cases, mediated by immunologically specific factors. However, in many cases it is mediated through intestinal inflammatory reactions with non-specific effects, although mediated through specific immunological reactions (see Larsh and Race 1975). These inflammatory reactions are associated with changes in mucosal architecture, mucus production, intestinal motility, levels of vasoactive amines, enzymes and prostaglandins, and alterations in net-fluid flux across the epithelial cells. This may lead to antagonistic heterologous interactions by rendering the intestinal environment physically and/or physiologically unsuitable for the establishment and/or survival of even phylogenetically remote helminths. Such antagonistic interactions may be reflected in change of location, reductions in growth and fecundity, reduced establishment of primary infections and enhanced expulsion of both primary and challenge infections. Two or more of these effects occur commonly simultaneously. The level of interaction is generally most marked when "critical" periods in the development of the "target" infection coincide with the period of maximum inflammation induced by the concurrent infection. Such antagonistic interactions, which are often reciprocal, have been demonstrated in mice and rats infected with different worm combinations of species of the cestode genus *Hymenolepis*, the acanthocephalan *Moniliformis dubius* and species of the nematode genera *Ancylostoma*, *Angiostrongylus*, *Ascaris*, *Aspiculuris*, *Nematospiroides*, *Nippostrongylus*, *Strongyloides*, *Syphacia*, *Trichinella* and *Trichuris* (Table 4). Besides, infection with *A. lumbricoides* in mice appears to increase the resistance to a challenge infection with *Toxocara canis*, as reflected in delayed migration through the liver and in decreased survival of larvae (Olson 1962; see also Sharp and Olson 1962). Embryonated eggs and second stage larvae of *T. canis* and third stage larvae of *A. caninum*, but not third stage larvae of *Haemonchus contortus*, administered via the mesenteric vein into guinea pigs, may induce a significant level of protection to *A. suum* challenge infection given by mesenteric vein injection of second stage larvae, assessed on the basis of larval recovery rates from the lungs (Stromberg and Soulsby 1977). Stromberg and Soulsby (1977) give other examples of failures of different "heterologous" immunization regimes to induce resistance to *A. suum* in rodent models. It has been suggested that some of the antagonistic interactions between intestinal helminths are brought about by competion for nutrient and/or by direct mechanical interference (see Holmes 1973). However, as discussed above, most seem to be induced by immunologically non-specific factors. However, immunologically specific factors, based on functional immunological cross-reactivity, are responsible for the reciprocal cross resistance between *T. spiralis* and *T. muris* in mice (Lee et al. 1982), between *T. spiralis* and *T. pseudospiralis* in mice (Palmas et al. 1985) and between *T. spiralis* and *S. ratti* in rats (Moqbel and Wakelin 1979). Specific immunological factors also appear responsible for *S. ratti*-induced resistance to *N. brasiliensis* in rats (Nawa et al. 1982) and for *N. brasiliensis*-induced resistance to *N. dubius* challenge in mice (Brindley and Dobson 1983). Specific immunologically mediated cross resistance between intestinal helminths may appear to be more common than hitherto anticipated.

The outcome of concurrent experimental infection with digestive tract nematodes in sheep depends on the size and relative timing of infection. However, heterologous antagonistic interactions have commonly been demonstrated with reduced establishment/survival following simultaneous infection and following challenge of animals harbouring primary infections, and with enhanced expulsion as a result of lack of specificity of the self-cure reaction. Available examples include (among others) *T. colubriformis*-induced resistance to *Nematodirus spathiger*, *T. vitrinus* and *H. contortus* (Muller 1968; Shumard et al. 1957; Dineen et al. 1977); non-reciprocal *Oesophagostomum columbianum*-induced resistance to *O. venulosum* (Dash 1981); *H. contortus*-induced resistance to *N. battus*, *O. circumcincta*, *T. axei* and *T. colubriformis* (Stewart 1953, 1955; Reinecke 1966; Mapes and Coop 1970, 1971; Turner et al. 1962); *O. circumcincta*-induced resistance to *H. contortus* and *T. colubriformis* (Stewart 1953, 1955; Reinecke 1966; Muller 1968; Turner et al. 1962); *T. axei*-induced resistance to *T. colubriformis*, *H. contortus* and *O. circumcincta* (Stewart 1953, 1955; Durie 1962; Muller

Table 4. Heterologous antagonistic interactions between intestinal nematodes, cestodes and acanthocephalans in mice and rats. Examples of heterologous antagonistic interactions between intestinal nematodes in sheep and cattle are listed in the text. *N. dubius*-induced resistance to *N. brasiliensis* does not seem to occur in the hamster (Hölmes 1962b)

Resistance induced by	Experimental host and resistance directed against	
	Mouse	Rat
Moniliformis dubius		*Nippostrongylus brasiliensis* [a] *Hymenolepis diminuta* [b c]
Trichinella spiralis	*H. diminuta* [d] *Trichuris muris* [f g] *H. nana* [j k l] *H. microstoma* [n] *Ascaris suum* [q] *N. brasiliensis* [s] *Aspiculuris tetraptera* [t u] *T. pseudospiralis* [v w] *T. nelsoni* [w] *T. nativa* [w] *Syphacia obvelata* [x]	*Angiostrongylus cantonensis* [e] *H. diminuta* [h i] *N. brasiliensis* [m] *Strongyloides ratti* [o p] *T. pseudospiralis* [r]
A. suum	*H. diminuta* [y] *N. brasiliensis* [z]	
N. brasiliensis	*A. suum* [z a'] *T. spiralis* [s] *H. nana* [e'] *Nematospiroides dubius* [h' i]	*S. ratti* [b' c'] *A. cantonensis* [d'] *T. spiralis* [f' g'] *H. diminuta* [j' k']
Ancylostoma caninum	*T. spiralis* [l' m'] *N. dubius* [n'] *H. nana* [o']	
H. nana	*H. diminuta* [p'] *T. spiralis* [j] *A. caninum* [q']	*H. diminuta* [p']
H. citelli	*H. nana* [l r'] *H. microstoma* [s'] *H. diminuta* [s']	
H. microstoma	*H. diminuta* [t'] *N. dubius* [u'] *H. nana* [l] *H. citelli* [s']	
H. diminuta	*H. nana* [r'] *H. citelli* [s' t']	
S. ratti		*N. brasiliensis* [b' c']
S. obvelata	*A. tetraptera* [t u]	
A. tetraptera	*T. muris* [w']	
T. muris	*A. tetraptera* [w'] *T. spiralis* [g]	
N. dubius	*N. brasiliensis* [i' x']	*N. brasiliensis* [h']
T. pseudospiralis	*T. spiralis* [u] *T. nativa* [w] *T. nelsoni* [w] *S. obvelata* [x]	*T. spiralis* [r]
T. nativa	*T. nelsoni* [w]	

[a] Holland 1984; [b] Holmes 1961; [c] Holmes 1962a; [d] Behnke et al. 1977; [e] Au and Ko 1979; [f] Bruce and Wakelin 1977; [g] Lee et al. 1982; [h] Christie et al. 1979; [i] Silver et al. 1980; [j] Ferretti et al. 1984; [k] Larsh and Campbell 1952; [l] Weinmann 1964; [m] Kazacos 1975; [n] Howard et al. 1978; [o] Kazacos 1976; [p] Moqbel and Wakelin 1979; [q] Matov and Kamburov 1968 (cited by Kazacos 1975); [r] Britov 1975 (cited by Palmas et al. 1985); [s] Kennedy 1980; [t] Stahl 1966; [u] Behnke et al. 1976; [v] Palmas et al. 1985; [w] Martínez-Fernández et al. 1981b; [x] Martínez-Fernández et al. 1981a; [y] Bindseil and Andreassen 1981; [z] Eriksen 1981; [a'] Crandall et al. 1967; [b'] Kazacos and Thorson 1975; [c'] Nawa et al. 1982; [d'] Kocan 1974; [e'] Larsh and Donaldson 1944; [f'] Sinski 1972; [g'] Louch 1962; [h'] Hitcho and Thorson 1974; [i'] Brindley and Dobson 1983; [j'] Hendrix et al. 1975; [k'] Morcock and Roberts 1976; [l'] Cox 1952; [m'] Goulson 1958; [n'] Liu and Ivey 1961; [o'] Vyas et al. 1980 (cited by Vyas et al. 1981); [p'] Heyneman 1962; [q'] Vyas et al. 1981; [r'] Weinmann 1966; [s'] Alghali and Grencis 1986; [t'] Hopkins et al. 1977; [u'] Courtney and Forrester 1973; [v'] Hopkins 1980; [w'] Keeling 1961; [x'] Bruna and Xenia 1976

Table 5. Heterologous antagonistic interactions between larval cestodes, between adult and larval cestodes, between non-intestinal nematodes and between filarial nematodes and other helminths. +, primary infection/exposure; ++, "immunization" (somatic and excretory/secretory larval antigens, intramuscular injection of eggs/activated embryos, passive transfer of immune serum); *mff*, microfilariae. *D. filaria* induced resistance to *D. viviparus* challenge was demonstrated by Sinclair (1967) in the guinea pig

Resistance induced by	Resistance directed against	Experimental host				
		Mouse	Rat	Rabbit	Sheep	Cattle
Mesocestoides corti	*Taenia crassiceps* +	a b				
T. crassiceps	*M corti* +	a b				
T. hydatigena	*T. ovis* +, ++				c d e f g h	
T. hydatigena	*T. pisiformis* +, ++			c i j k l		
T. hydatigena	*T. saginata* ++					m n
T. hydatigena	*Echinococcus granulosus* ++				o p	
T. ovis	*T. pisiformis* ++			c k l		
T. ovis	*E. granulosus* ++				e o p	
T. ovis	*T. hydatigena* ++				c d q r s	
T. ovis	*T. saginata* ++					n
T. pisiformis	*T. taeniaeformis* ++		t			
T. pisiformis	*T. hydatigena* ++				r	
T. pisiformis	*T. ovis* ++				l	
T. saginata	*T. taeniaeformis* ++	u				
T. taeniaeformis	*T. saginata* ++					u
T. taeniaeformis (rat strain)	*T. taeniaeformis* (mouse strain) +	v				
T. taeniaeformis (mouse strain)	*T. taeniaeformis* (rat strain) +		v			
T. crassiceps	*T. taeniaeformis* +, ++	u				
T. taeniaeformis	*Hymenolepis nana* +	w				
T. crassiceps	*H. nana* +	w				
Dictyocaulus filaria	*D. viviparus* +					x y z
D. viviparus	*D. filaria* +				a′	
Dipetalonema vitae	*Onchocerca lienalis* mff +	b′				
O. gutturosa	*O. lienalis* mff +	b′				
Trichinella spiralis	*O. lienalis* mff +	b′				
O. cervicalis mff	*O. lienalis* mff +	b′				

[a] Novak 1984; [b] Joysey 1986; [c] Gemmell 1964a; [d] Gemmell 1969a; [e] Heath et al. 1979; [f] Rickard and Bell 1971; [g] Gemmell 1965a; [h] Gemmell 1970; [i] Rickard and Coman 1977; [j] Ermalova et al. 1968 (cited by Rickard and Coman 1977); [k] Gemmell 1965b; [l] Gemmell 1969b; [m] Wikerhauser et al. 1971; [n] Rickard and Adolph 1976; [o] Gemmell 1967; [p] Gemmell 1966; [q] Varela-Diaz et al. 1972; [r] Gemmell 1964b; [s] Blundell et al. 1968; [t] Miller 1932; [u] Lloyd 1979; [v] Conchedda and Ferretti 1983; [w] Weinmann 1964; [x] Parfitt and Sinclair 1967; [y] Lucker et al. 1964; [z] Vegors et al. 1963; [a′] Wilson 1970; [b′] Townson et al. 1985

1968; Reinecke 1974; Turner et al. 1962; Reinecke et al. 1979) and reciprocal resistance between *Cooperia oncophora* and *C. pectinata* (Herlich 1965). A similar reciprocal resistance between *C. oncophora* and *C. pectinata* has been demonstrated in calves (Herlich 1965). It has been suggested that specific immunological factors are responsible for *T. colubriformis*-induced resistance to *T. vitrinus* (Dineen et al. 1977), but most suggestions point to the involvement of immunologically non-specific factors in the cross resistance between digestive tract nematodes in sheep.

Heterologous antagonistic interactions between larval cestodes, between adult and larval cestodes, between non-intestinal nematodes and between filarial nematodes and other helminths

Primary *Taenia* spp. and *Mesocestoides corti* metacestode infections, immunization with somatic and excretory/secretory larval *Taenia* antigens, intramuscular injection of *Taenia* eggs or activated embryos, and passive transfer of immune serum may induce a marked resistance to heterologous challenge infection in mice, rats, rabbits, sheep and cattle with related or unrelated larval cestodes. The challenge infection is normally peroral inoculation of eggs or activated embryos (Table 5). Resistance may be induced by antigens and eggs/embryos of *Taenia* species to which the experimental host is non-susceptible or has only low susceptibility. The heterologous resistance is most commonly reflected in reduced metacestode establishment, although reduced metacestode survival has also been reported. Thus, in most cases, the early developmental stages appear both to induce and to be the target of the resistance mechanism, which in turn appears to be immunologically specific based on cross-reacting functional antigens. In addition,

reciprocal cross resistance may develop in mice between *M. corti* and *T. crassiceps* following intraperitoneal implantation of metacestodes. Resistance has also been reported to *H. nana* challenge infection in mice harbouring metacestode infections with *T. taeniaeformis* and *T. crassiceps*. A significant finding is the failure of exogeneous antigens released by *T. hydatigena* larvae developing in filtration membrane diffusion chambers implanted intraperitoneally into dogs to stimulate any measurable resistance to challenge infection with *E. granulosus* protoscolices (Rickard et al. 1975).

Resistance to infection with *Dictyocaulus viviparus* in cattle and with *D. filaria* in sheep may develop as a result of previous exposure of cattle to *D. filaria* and of sheep to *D. viviparus*. This is in spite of the low compatibility between *D. filaria* and cattle and between *D. viviparus* and sheep. A guinea pig model also shows *D. filaria*-induced resistance to *D. viviparus* (Sinclair 1967). High doses of crude larval antigen preparations of *H. contortus* and *T. colubriformis* administered intraperitoneally induce partial protection to infection with *D. viviparus* in guinea pigs (Silverman et al. 1962). However, the crude nature of the antigens prevents any conclusions on involvement of specific immunological factors.

Cross resistance has been demonstrated in mice between microfilariae of *Onchocerca cervicalis* and *O. lienalis*. Resistance to *O. lienalis* microfilarial infection has been induced in mice implanted intraperitoneally with adult *O. gutturosa* and *Dipetalonema vitae* and in mice harbouring primary *T. spiralis* infections. Repeated exposures of cats to 10 krad attenuated *Brugia pahangi* larvae establishes low level infections with sexually sterile worms. Such infections may induce substantial resistance to development of the macrofilarial stages of a subsequent *B. patei* challenge (Oothuman et al. 1979). Vaccination of jirds with 40 krad attenuated third-stage larvae of *Litomosoides carinii* may induce a marked reduction in the size of a *B. pahangi* challenge infection (Storey and Al-Mukhtar 1982). The antigenic familiarity between many filarial nematodes (see Maizels et al. 1983, 1985) may suggest that heterologous antagonistic interactions between closely related filarial nematodes could be mediated by specific immunological factors. This suggestion is supported by the fact that the IgE-dependent platelet-mediated in vitro killing of larval filariae occurs in both homologous and heterologous systems (Hague et al. 1985). In contrast, the resistance to *O. lienalis* microfilarial infection induced in mice harbouring *T. spiralis* infections may be mediated by immunologically non-specific mechanisms, mediated by the non-specific *T. spiralis*-induced potentiation of macrophage mediated immunity.

Heterologous antagonistic effects of protozoans on helminths

Infections with *Toxoplasma gondii* and *Trypanosoma cruzi* may induce significant resistance to *S. mansoni* establishment in mice (Mahmoud et al. 1976; Kloetzel et al. 1971, 1973). Resistance to *T. spiralis* infection, reflected in reduced establishment, enhanced expulsion or reduced tissue larvae counts, may develop in mice and rats concurrently infected with *T. gondii* and *Eimeria nieschulzi*, respectively (Copeland and Grove 1979; Stewart et al. 1980; Yusuf et al. 1980). Such protozoan-induced resistance to helminth infection is generally thought to be due to enhanced macrophage-mediated non-specific resistance. Besides, *T. gondii* challenge of mice harbouring primary patent *S. mansoni* infections may result in fewer eggs in tissue per established schistosome worm pair (Kloetzel et al. 1977). *H. diminuta* worms may experience reduced growth in rats concurrently infected with *T. lewesi* or *Plasmodium berghei* (Fenwick 1980; Rigby and Chobotar 1966). The immunosuppression associated with a range of protozoan infections (see Terry and Hudson 1982) is furthermore reflected in a *P. yoelii*-, *T. brucei*- and *T. gondii*-induced suppression in mice of the granulomatous reaction to *S. mansoni* eggs in concurrent infections and/or to *S. mansoni* eggs "implanted" into the lungs of protozoan-infected mice (Abdel-Wahab et al. 1974; Mahmoud et al. 1977; Fagbemi et al. in preparation). This may, as in the *T. gondii*/*S. mansoni* model (Mahmoud et al. 1977), alleviate the level of hepatosplenic murine schistosomiasis.

Heterologous antagonistic effects of helminths on protozoans

Examples of helminth-induced resistance to blood protozoan challenge infection in rodent models, as reflected in reductions in the parasitaemia level (Table 6) include suppression of different species of *Plasmodium* by *S. mansoni*, *S. ratti* and *T. spiralis*, suppression of *Babesia microti* by *S. mansoni*, *N. dubius* and *F. hepatica* and suppression of *Leishmania tropica*, *Babesia rodhaini*, *Trypanosoma equiperdum*, *T. lewesi* and *Entamoeba histolytica* by *T. spiralis*. Patency of infection at challenge appears necessary for *S. mansoni*-induced resistance to protozoan challenge (see Lewinsohn 1975; Lwin et al.

Table 6. Heterologous antagonistic effects of helminths on protozoans

Resistance induced by	Resistance directed against	Experimental host			
		Mouse	Rat	Hamster	Field vole
Fasciola hepatica	*Babesia microti*	[a]			
Schistosoma mansoni	*B. microti*	[b]			
Nematospiroides dubius	*B. microti*	[c]			
S. mansoni	*Plasmodium chabaudi*	[d e f]			
S. mansoni	*P. yoelii*	[d f g]			
S. mansoni	*P. berghei*				[h]
Strongyloides ratti	*P. berghei*		[i]		
Trichinella spiralis	*P. berghei*	[j k]			
T. spiralis	*Trypanosoma equiperdum*		[l]		
T. spiralis	*T. lewesi*		[l]		
T. spiralis	*Leishmania tropica*	[k]			
T. spiralis	*Entamoeba histolytica*			[m]	
T. spiralis	*B. rodhaini*	[k]			
T. spiralis	*Giardia muris*	[n]			
T. spiralis	*Eimeria nieschulzi*		[o]		

[a] Fagbemi et al. 1985a; [b] Fagbemi et al. 1985b; [c] Mzembe et al. 1984; [d] Lwin et al. 1982; [e] Long et al. 1981; [f] Kusel and Phillips 1978; [g] Christensen et al. unpublished; [h] Yoeli 1956; [i] Bailenger and Guy 1982; [j] Ngwenya 1982; [k] Meerovitch and Pocock 1981; [l] Meerovitch and Ackerman 1974; [m] Meerovitch and Ghadirian 1980; [n] Roberts-Thomson et al. 1976; [o] Stewart et al. 1980

1982; Fagbemi et al. 1985b). The different levels of suppression of *B. microti* in different strains of *T. brucei*-infected mice experiencing comparable degrees of anaemia, and the normal course of infection with *P. yoelii* and *P. chabaudi* in severely anaemic *T. brucei*-infected mice (Millott and Cox 1985) appear to disprove the suggestion often put forward that *S. mansoni*- and *F. hepatica*-induced suppression of concurrent blood protozoan infections could be due to the helminth-induced change in the erythrocyte kinetics combined with a protozoan preference for erythrocytes of specific age classes. It has been suggested that *N. dubius*-, *S. ratti*-, and *T. spiralis*-induced suppression of blood protozoan infections may be mediated immunologically by non-specific factors involving macrophage activation. This mechanism might also be involved in *S. mansoni*- and *F. hepatica*-induced suppression of blood protozoan infections. Besides, some evidence has been obtained for suppression of experimental *P. falciparum* infection in owl monkeys harbouring naturally acquired *Tetrapetalonema barbascalensis* microfilarial infections (Schmidt and Esslinger 1981). Acquirement of *P. falciparum* infection following anthelmintic treatment of heavily *A. lumbricoides*-infected children has been suggested to support the concept of helminth-induced suppression of protozoan infection (Murray et al. 1977, 1978). In contrast, primary patent relatively heavy *F. hepatica* infections in intact and splenectomised calves affect neither the course nor the pathogenicity of subsequent experimental *B. divergens* infection (Hughes et al. 1977). Antagonistic interactions could not be demonstrated in rats concurrently infected with *T. brucei* and *L. carinii* (Hendow et al. 1976).

The suppression of the intestinal protozoan species *Giardia muris* and *E. nieschulzi* by *T. spiralis* infection in mice and rats, respectively is reflected in reduced cyst excretion. This may be due to the *T. spiralis*-induced intestinal inflammation making the intestinal environment unfavourable for the establishment/multiplication of the protozoans. Finally, prolongation of excretion of cysts of *Eimeria ninakohlyakimovae* following anthelmintic treatment of sheep concurrently infected with *T. colubriformis* may support helminth-induced suppression of intestinal protozoan infections (Yvore et al. 1980; see also Gretillat 1981).

Heterologous synergistic interactions between helminths

Concurrent helminth infection may result in heterologous synergistic interactions (Table 7). This is reflected by increased initial establishment and delayed expulsion of primary infections, by interference with innate resistance to infection and with development of resistance to homologous challenge infection and, less marked by enhanced growth and fecundity. The delay in the expulsion of *N. brasiliensis*, *T. muris*, *T. spiralis* and *Hymeno-*

Table 7. Heterologous synergistic interactions between helminths. ( ), evidence only.

Effect induced by	Effect directed against	Experimental host		
		Mouse	Rat	Sheep
Schistosoma mansoni	*Dipetalonema vitae*		[a]	
S. mansoni	*Echinostoma revolutum*	[b]		
Nematospiroides dubius	*Nippostrongylus brasiliensis*	[c d e f]		
N. dubius	*Trichinella spiralis*	[g h]		
N. dubius	*Trichuris muris*	[i j]		
N. dubius	*Hymenolepis diminuta*	[k]		
N. dubius	*H. microstoma*	[l]		
N. dubius	*H. citelli*	[m]		
T. spiralis	*Strongyloides ratti*		([n])	
T. spiralis	*H. nana*	[o p]		
S. ratti	*N. brasiliensis*		[q]	
N. brasiliensis	*S. ratti*		[q]	
S. ratti	*H. nana*	([r])		
Ascaris suum	*H. nana*	[s]		
E. revolutum	*S. mansoni*	[t]		
Taenia hydatigena	*T. ovis*			[u v]
Fasciola hepatica	*Haemonchus contortus*			[w]

[a] Hague et al. 1981; [b] Christensen et al. 1985; [c] Jenkins 1975; [d] Bruna and Xenia 1976; [e] Colwell and Wescott 1973; [f] Wescott and Colwell 1980; [g] Behnke et al. 1978; [h] Hagan and Wakelin 1982; [i] Jenkins and Behnke 1977; [j] Behnke et al. 1984; [k] Hopkins 1980; [l] Courtney and Forrester 1973; [m] Alghali et al. 1985; [n] Moqbel and Wakelin 1979; [o] Larsh and Campbell 1952; [p] Ferretti et al. 1984; [q] Nawa and Korenaga 1983; [r] Brumpt 1933; [s] Weinmann 1964; [t] Christensen et al. 1981a; [u] Varela-Diaz et al. 1972; [v] Gemmell 1969b; [w] Presidente et al. 1973

lepis spp. in concurrently *N. dubius*-infected mice and of primary *S. ratti* and *H. nana* infections in *T. spiralis*-infected rats and mice is generally believed to be a result of the immunosuppression associated with *N. dubius* and *T. spiralis* infection (see Terry and Hudson 1982; Ali and Behnke 1984). This suggestion is supported by the experiments by Hagan and Wakelin (1982) which demonstrated that MLN cells of mice concurrently infected with *N. dubius* and *T. spiralis* failed to transfer an accelerated expulsion of the latter from naive recipients. Conversely, MLN cells capable of accelerating expulsion in mice infected only with *T. spiralis* failed to do so when *N. dubius* was present. In addition, *N. dubius* was shown to delay the onset of the changes which allow for increased blast cell localization in the intestines of *T. spiralis*-infected mice.

There is other evidence for heterologous synergistic interactions between helminths being mediated by immunosuppression. The delay in expulsion of both *N. brasiliensis* and *S. ratti* in concurrently infected rats is paralleled by a delay in the onset of the intestinal mast cell response (Nawa and Korenaga 1983). Besides, *S. mansoni* interferes only with the innate resistance of rats to infection with *Dipetalonema vitae* if the infection is timed to ensure that the moult of the stage 4 larvae into adult worms, the developmental process blocked in normal rats, takes place during maximum *S. mansoni*-induced immunosuppression (Hague et al. 1981). Mechanisms responsible for the increase in the *S. mansoni* worm establishment in heavily *E. revolutum*-infected mice and in the establishment of *H. nana* in *A. suum*-exposed mice remain to be demonstrated. Immunosuppression/immunotolerance, as judged by blockage of expulsion, has been demonstrated in heavily *E. revolutum*-infected mice (Christensen et al. 1981a). Besides, an active suppression of the immune response or a depression of the efficiency of an unaltered immune response due to extensive intestinal pathology have been suggested responsible for the *S. mansoni*-induced delay in the expulsion of subsequent *E. revolutum* infections when challenge infection takes place during late prepatent *S. mansoni* infection. Another significant finding is the enhanced survival rate of cysticerci of *T. ovis* in sheep in response to prior feeding with eggs of *T. hydatigena*. An increased faecal egg count and a delayed expulsion of *H. contortus* in concurrently *F. hepatica*-infected sheep have also been found. Evidence for other synergistic heterologous interactions between helminths includes

1. "Enhancement" of *T. pisiformis* in rabbits following oral dosing with *T. ovis* eggs (Rickard and Coman 1977).

2. Increase in the egg production capacity of *O. turkestanicum* in mice concurrently infected with *S. mansoni*, *S. bovis* or *S. haematobium* (Massoud and Nelson 1972)

3. Enhancement of the granulomatous reaction to *S. mansoni* eggs deposited in the liver of mice concurrently infected with *T. spiralis* (Aboul Atta et al. 1982)

4. Increase in the susceptibility of rhesus monkeys to infection with *S. bovis* and *S. mattheei* in response to concurrent infection with *S. mansoni* (Amin et al. 1968)

5. "Enhancement" of *T. axei* infection in *H. contortus*- and *O. circumcincta*-infected sheep (Turner et al. 1962)

6. Synergistic association in pigs between the lung worm metastrongyles *Metastrongylus apri* and *M. pudendotectus* (Ewing and Todd 1961a, b)

7. An increased *A. suum* establishment, based on liver larvae recovery, following challenge of mice harbouring primary, late prepatent *S. mansoni* infections (Bindseil 1970).

In addition, data have been presented suggesting that clinical infections with *H. contortus* in lambs may alter the normal self-limited course of infection with *N. spathiger* (Turner and Colglazier 1954; Kates and Turner 1960).

Heterologous synergistic effects of protozoans on helminths

Protozoan-induced immunosuppression (see Terry and Hudson 1982) is taken as responsible for synergistic effects of protozoans on helminths in concurrent infections. Examples of such synergistic effects include increased initial establishment and delayed expulsion of primary infections and interference with the development and maintenance of resistance to homologous challenge infection (Table 8). The increased establishment of *S. mansoni* in mice infected with *T. cruzi* and *Plasmodium* spp.

Table 8. Heterologous synergistic effects of protozoans on helminths. ( ), evidence only

Effect induced by	Effect directed against	Experimental host		
		Mouse	Rat	Goat
Increased establishment of primary infection				
Trypanosoma cruzi	*Schistosoma mansoni*	[a]		
Plasmodium yoelii	*S. mansoni*	[b]		
P. chabaudi	*S. mansoni*	[c]		
P. yoelii	*Echinostoma revolutum*	[d]		
T. congolense	*Haemonchus contortus*			[e]
T. brucei	*Nippostrongylus brasiliensis*		[f]	
Delay/blockage of expulsion of primary infection				
T. brucei	*E. revolutum*	[g]		
T. brucei	*N. brasiliensis*		[h i]	
T. brucei	*Hymenolepis diminuta*	[j]		
T. brucei	*Trichuris muris*	[k]		
T. cruzi	*H. diminuta*	[l]		
P. berghei	*Strongyloides ratti*		[m]	
P. berghei	*T. muris*	[k]		
Babesia microti	*T. muris*	[n]		
B. hylomysci	*T. muris*	[n]		
Eimeria nieschulzi	*N. brasiliensis*		[o]	
Toxoplasma gondii	*T. spiralis*	[p]		
Interference with development of resistance to homologous challenge infection				
T. brucei	*E. revolutum*	[g]		
T. brucei	*T. muris*	[k]		
P. yoelii	*E. revolutum*	[d]		
P. berghei	*T. muris*	[k]		
E. nieschulzi	*T. spiralis*		[q]	

[a] Kloetzel et al. 1973; [b] Kusel and Phillips 1978; [c] Long et al. 1981; [d] Christensen et al. unpublished; [e] Griffin et al. 1981a, b; [f] Wedrychowicz et al. 1983; [g] Christensen et al. 1984; [h] MacLean 1982; [i] Urquhart et al. 1973; [j] Fagbemi and Christensen 1984; [k] Phillips et al. 1974; [l] Machnicka and Choromanski 1979; [m] Bailenger and Guy 1982; [n] Phillips and Wakelin 1976; [o] Bristol et al. 1983; [p] Copeland and Grove 1979; [q] Duszynski et al. 1978

needs to be confirmed in more comprehensive studies. However, the increased establishment of initial infection of *E. revolutum* in *P. yoelii*-infected mice, of *N. brasiliensis* in *T. brucei*-infected rats and of *H. contortus* in *T. congolense*-infected goats appear well documented. Delay in expulsion of a number of helminth species has been demonstrated in mice and rats concurrently infected with different species of the protozoan genera *Plasmodium*, *Trypanosoma*, *Babesia*, *Toxoplasma* and *Eimeria*. There are also examples of interference with the development of resistance to homologous challenge infection with *E. revolutum*, *T. muris* and *T. spiralis* in response to concurrent protozoan infection. Besides, there is also evidence for an increased rate of "maturation" of *C. punctata* in calves in response to concurrent *Eimeria* spp. infection (Davis et al. 1959a). A significant finding is the failure of *P. chabaudi* and *B. microti* to affect acquisition of resistance to homologous reinfection with *S. mansoni* in mice (Long et al. 1981; Christensen et al. (unpublished)). Also, *T. lewesi* does not affect the development and maintenance of acquired resistance to *N. brasiliensis* in rats (Ashley 1962). Experimental immunological evidence that these synergistic interactions are mediated by immunosuppression consists of (1) suppression of the eosinophilic response to *T. spiralis* in concurrently *T. gondii*-infected mice (Copeland and Grove 1979); (2) decreased humoral and cellular response to *H. diminuta* antigens in mice concurrently infected with *T. cruzi* (Machnicka and Choromanski 1979); (3) gross impairment of production of serum protective antibodies to *N. brasiliensis* and decreased *N. brasiliensis*-induced mast cell proliferation in the intestinal wall in rats concurrently infected with *T. brucei* (Urquhart et al. 1973); (4) a reduction of local and systemic antibody responses to *N. brasiliensis* antigens in rats concurrently infected with *T. brucei* and *N. brasiliensis* (Wedrychowicz et al. 1983, 1984); and (5) a blockage of antibody production to *E. revolutum* juvenile worm tegumental antigens in mice concurrently infected with *E. revolutum* and *T. brucei* (Simonsen and Andersen 1986).

Heterologous synergistic effects of helminths on protozoans

Mice harbouring primary infections with *S. obvelata*, *T. muris* and *S. mansoni* may experience an increased susceptibility to *E. histolytica*. This is evident from increased damage to the caecal wall and from an increase in the rate of amoebic tissue invasion (Knight and Warren 1973; Knight and Chew 1974; Vinayak and Chopra 1978). It is believed that this is due to intramucosal tissue damage, possibly combined with a reduced immunological responsiveness. The magnitude of the effect generally appears to be correlated with the size of the helminth infection. Clinico-pathological observations have, furthermore, provided strong evidence for increased susceptibility of calves to infection with *Eimeria* spp. in response to concurrent infection with *C. punctata*, *T. colubriformis* and *S. papillosus* all of which inhabit the same general region of the small intestine as *Eimeria* spp. (Davis et al. 1959a, 1960a, b). No similar effects were, however, associated with infection in calves with the stomach nematode *O. ostertagi* (Davis et al. 1959b). However, concurrent infection with *T. spiralis* and *T. gondii* and with *B. microti* and metacestodes of either *T. crassiceps* or *T. taeniaeformis* in mice may increase the number of *T. gondii* cysts in the brain and the *B. microti* blood cell parasitaemia (Nichol and Sewell 1984; Yusuf et al. 1980). These effects may be caused by immunosuppression. Besides, measurements of morbidity indicate that primary *S. mansoni* infections in mice may potentiate the pathogenetic effect of subsequent *T. gondii* infection, although its intensity, measured parasitologically, seems unaffected (Kloetzel et al. 1977). Concurrent *S. mansoni* and *T. cruzi* infection in mice normally results in increased, and commonly prolonged, *T. cruzi* parasitaemia (Kloetzel et al. 1971, 1973). *S. mansoni* infection in the field vole, despite causing an initial suppression of *P. berghei*, may decrease the ability to finally eliminate a heterologous challenge infection with this parasite (Yoeli 1956). Concurrent *N. brasiliensis* and *P. berghei* infections in the rat may increase protozoan blood cell parasitaemia (Golenser et al. 1976). Besides, observations on nutritional status and metabolism of infected rats provide some indirect evidence for a *N. brasiliensis*-induced increase in the intensity of concurrent *E. nieschulzi* infection (Frandsen 1983, 1985). Finally, in several experiments *S. mansoni* infection suppressed a subsequent *P. yoelii* infection, but there is one instance of increased *P. yoelii* parasitaemia in mice harbouring primary *S. mansoni* infections (Lwin et al. 1982).

Discussion

Concurrent infection with two or more parasite species occurs commonly in domestic stock and man, especially in subtropical and tropical parts of the world (see Ogunrinade and Adegoke 1982; Buck et al. 1978a, b). It has often been suggested

that such concurrent infections, mediated by antagonistic or synergistic heterologous interactions, may influence the parasite transmission pattern and disease picture. Augmentation or alleviation of the amount of disease experienced might be a consequence of concurrent infection. Besides, concurrent infection might make clinical and laboratory diagnosis less accurate, decrease the bioavailability and toxicity of drugs used for treatment and decrease the efficiency of disease control campaigns based on immunization (see Buck et al. 1978a).

Unexpected frequencies of some multiple infections, i.e. positive correlation coefficients, have occasionally been demonstrated, for example between *D. vitae*, *D. streptocerca* and *Loa loa* in man in part of the African rainforest (Buck et al. 1978b), between *T. trichuris* and *E. histolytica* in man (Jung and Beaver 1951), between *S. bovis* and *Paramphistomum microbotrium* in cattle (Ogunrinade and Adegoke 1982), between *T. brucei* and other cattle trypanosomes in cattle (Willett 1972), and between frequency of schistosomal colonic polyposis and infection with *E. histolytica* in man (El Raziky et al. 1983). Negative correlation coefficients, on the other hand, have also been demonstrated, for example between *S. bovis* and *F. gigantica* in cattle (authors' calculation from data in Magzoub and Adam 1977), between *F. hepatica* and *E. granulosus* (hydatid cysts) in cattle (Froyd 1960), and between visceral leishmaniasis and *S. mansoni* infections in man (Chunge et al. 1985). Positive correlations, however, may reflect a parallel transmission ecology rather than a synergistic heterologous interaction. A positive correlation may thus be expected, for example, between *S. bovis* and *P. microbotrium* as both are transmitted in the same aquatic environment by a common snail host. Furthermore, the transmission of a range of intestinal protozoan and helminth infections is linked to low levels of hygiene and poor sanitary conditions. Ecologically determined, unexpected frequencies of some multiple infections are therefore to be expected. Besides, heterologous antagonistic and synergistic interactions between parasites are normally reflected quantitatively rather than qualitatively, i.e. by a modulation of the course of infection rather than by the presence of one parasite species being determined by that of another. This fact, combined with a complex influence of ecological factors on the pattern and frequency of concurrent infection mean that major consequences of concurrent parasite infection for the disease picture in man and domestic stock have not been definitively demonstrated. It also seems obvious that appropriately planned and controlled experimentation is imperative for any understanding of concurrent parasite infection in man and domestic stock.

Concurrent infection with two or more parasite species in experimental mammalian host models may commonly, as outlined above, result in heterologous interactions of either antagonistic or synergistic nature. These range from reduced/enhanced growth and fecundity to inhibition/enhancement of establishment/expulsion. It should be stressed, however, that concurrent experimental infection involving "inappropriate" timing of infection and/or only light infections commonly does not give rise to antagonistic or synergistic interactions. The two parasite populations may in this case develop independently of each other and the disease picture is of a simple additive nature.

Definitive information on mechanisms responsible for heterologous antagonistic and synergistic interactions in concurrent infection seems relatively limited. Cross-reactive antigens have been found for a number of species of helminths (see references in Aronstein et al. 1986), but most of these may be unimportant from the point of view of heterologous interactions. However, well-founded evidence suggests that immunologically specific factors, based on functional immunological cross-reactivity, are responsible for at least some cross-resistance between intestinal helminths. They may also be responsible for most, if not all, of the heterologous antagonistic interactions demonstrated between larval cestodes in the intermediate mammalian host. Furthermore, it appears reasonable to suggest that they are involved in heterologous antagonistic interactions between species of schistosomes and between different microfilarial infections. However, most other examples of antagonistic interactions are generally thought to be induced by immunologically non-specific factors. Resistance to non-intestinal helminths induced by other helminths and by protozoans, and helminth-induced suppression of blood protozoans, are thus generally believed due to enhanced macrophage-mediated non-specific resistance. This would parallel the BCG-induced resistance to helminth and protozoan infections as well as the suppression of *Plasmodium* and *Babesia* infections by rickettsia, viruses, other protozoans and a variety of other agents (see Cox 1975; Klesius 1982; Millott and Cox 1985). Although immunologically specific cross-resistance may occur between intestinal nematodes, cross-resistance between intestinal helminths may often be induced by non-specific effects of intestinal inflammation. However, such in-

testinal inflammation may originally be initiated by immunologically specific mechanisms. Similar non-specific effects seem responsible for helminth-induced resistance to intestinal protozoans. Most synergistic heterologous interactions seem to be based on non-specific parasite-induced immunosuppression although enhancement of and tissue invasion by intestinal protozoans may at least partly be the result of helminth-induced damage of the intestinal epithelial lining. However, further studies are obviously required for a final and detailed elucidation of the mechanisms responsible for heterologous interactions in concurrent parasite infection in experimental mammalian host models.

Experimental studies have demonstrated that a complex set of factors govern the types and characteristics of heterologous interactions in concurrent infection. A given combination of two parasite species may thus result in a range of interactions and the antagonistic ones are commonly reciprocal. Such reciprocal antagonistic interactions may be found between schistosomes, microfilarial infections, intestinal helminths, larval metacestodes in the mammalian intermediate host and even in combinations of more distinctly related helminths, such as *F. hepatica*, *N. brasiliensis* and *S. mansoni*. This reflects the reciprocal nature of both the specific immunological cross-reactivity and the non-specific immunological factors (macrophage activation, inflammatory reactions) responsible for the antagonistic interactions. Reciprocal cross-resistance has even been demonstrated in rats between *T. spiralis* and *E. nieschulzi* with the suppression of *E. nieschulzi* resulting from intestinal inflammation and with the effect on *T. spiralis* suggested induced by macrophage-mediated non-specific resistance (Stewart et al. 1980). The complexity of concurrent infection may furthermore be illustrated by a given combination of two parasite species giving rise to either synergistic or antagonistic interactions depending for example on the relative timing of infection. Both increased and decreased establishment of *S. mansoni* has thus been reported in *T. cruzi*-infected mice (Kloetzel et al. 1973), and *T. hydatigena* infection in sheep may in some cases decrease and in others increase the survival of concurrent *T. ovis* infection (see Tables 5, 7). Moreover, mice harbouring primary patent *S. mansoni* infections are highly resistant to *E. revolutum* challenge whereas expulsion of *E. revolutum* in mice is delayed/blocked when the challenge infection is given during the late prepatent period of the *S. mansoni* infection. Besides, *S. mansoni* challenge of heavily *E. revolutum*-infected mice may result in increased *S. mansoni* worm establishment (see Tables 3, 7). Another interesting example is the suppression of *P. yoelii* in mice harbouring primary patent *S. mansoni* infections and the increase in the establishment of *S. mansoni* in mice harbouring a primary chronic *P. yoelii* infection (see Tables 6, 8). Besides, synergistic and antagonistic interactions may both develop even in a given concurrent infection. Thus, a reduced initial establishment followed by a delay in the expulsion of *N. brasiliensis* has been demonstrated in *N. dubius*-infected mice (Bruna and Xenia 1976), and an initial suppression followed by prolonged persistence of *P. berghei* has been reported in *S. mansoni*-infected field voles (Yoeli 1956). In addition, obviously contrasting findings possibly arising from differences in parasite and host genetics have been reported. For example, Lwin et al. (1982) demonstrated an enhancement of the infection with a virulent strain of *P. yoelii* in *S. mansoni*-infected mice whereas Kusel and Phillips (1978) and Christensen et al. (unpublished) using similar experimental setups but different parasite and mouse material demonstrated a marked suppression of *P. yoelii* in *S. mansoni*-infected mice. Both the immunologically specific and non-specific responsiveness of the host is influenced by genetical, nutritional and physiological factors and this certainly adds to the complexity of the phenomenon of heterologous interactions.

The criteria for heterologous antagonistic and synergistic interactions have primarily been parasitological, and to a much lesser extent clinicopathological. However, there is often a reasonable correlation between levels of interaction judged by both types of parameters. Such a correlation has thus been demonstrated in (1) resistance between schistosomes in sheep, cattle and baboons (see Table 2); (2) resistance to *F. hepatica* challenge infection in sheep and calves harbouring primary *S. bovis* infections (Monrad et al. 1981; Sirag et al. 1981); (3) resistance in mice to *S. mansoni* induced by prior infection with *T. gondii* (Mahmoud et al. 1977) and by prior exposure to cercariae of *T. szidati* (Pedersen et al. 1982); (4) suppression of *B. microti* infection in *S. mansoni* and *F. hepatica* infected mice (Fagbemi et al. 1985a, b); (5) enhancement of *H. contortus* infection in concurrently *T. congolense*-infected goats (Griffin et al. 1981a, b). However, unaltered egg counts in essential organs, possibly combined with an increase in the granulomatous reaction to the eggs, are held responsible for the lack of significant alleviation of disease, in spite of a very marked resistance defined by parasitological parameters, following *S. japonicum*

(human strain) challenge of rhesus monkeys heavily exposed to cercariae of a non-human strain of *S. japonicum* (Murrell et al. 1973) and following *S. mansoni* challenge of baboons heavily and repeatedly exposed to cercariae of *S. bovis* and *S. rodhaini* (Taylor et al. 1973). On the other hand, the possible potentiation of the pathogenicity of *T. gondii* in *S. mansoni*-infected mice is not reflected in a parallel increase in the intensity of infection as measured by parasitological parameters (Kloetzel et al. 1977). These findings highlight the problems of using only parasitological criteria for determining possible disease-related consequences of concurrent infection.

Heterologous antagonistic and synergistic interactions are common phenomena in experimental concurrent helminth infection. However, their great complexity and the limitations of experimental rodent models make extrapolation from experimental studies to naturally occurring polyparasitism questionable. For example, mice are very susceptible to both bovine and human schistosomes, and rhesus monkeys elicit an extremely effective immunological response to infection with schistosomes. This should, in fact, preclude the use of mice and rhesus monkeys in studies of aspects of schistosome zooprophylaxis in man. Experimental setups comprising a single, massive heterologous challenge infection following maturation of a primary infection can reflect the complexity of natural parasite transmission to only a limited extent. Furthermore, the intensity of experimental infection is generally very high, inducing high levels of non-specific immunological responsiveness or non-specific immunosuppression. Experimental concurrent infection may therefore give rise to heterologous antagonistic and synergistic interactions which are normally not expected in natural polyparasitism. For example, resistance to *S. mansoni* challenge infection in baboons induced by prior exposure to cercariae of non-human schistosomes is based on very heavy and repeated cercarial exposures, and baboons exposed to low, and biologically more reasonable, numbers of *S. rodhaini* cercariae actually failed to develop resistance to a heterologous challenge infection with *S. mansoni* (Taylor et al. 1976). These findings, combined with the limited value of the mouse and rhesus monkey models indicate that experimental work supporting schistosome zooprophylaxis in man (see Nelson 1974) may be rather limited.

Experimental studies have, in spite of their basic limitations, provided much valuable information on aspects of the nature and characteristics of heterologous interactions between parasites in the mammalian host. One of their most important virtues is their indication of potential heterologous interactions between parasites in both man and domestic stock under field conditions. Studies comprising selective, curative and preventive drug treatment of domestic stock populations in the natural transmission environment would make one of several starting points for further work on the disease-related consequences of potential heterologous interactions between parasites arising as a consequence of natural polyparasitism. The information from hitherto conducted experimental studies on concurrent parasite infection may serve as a valuable guideline for further field studies.

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