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OF INFECTION AND PATHOLOGIC CHARACTERISTICS

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RODENT SCHISTOSOMIASIS: PREVALENCE OF INFECTION AND PATHOLOGIC CHARACTERISTICS

By

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ABSTRACT

RODENT SCHISTOSOMIASIS: PREVALENCE OF INFECTION AND PATHOLOGIC CHARACTERISTICS

By

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Studies were undertaken to determine the extent of natural infection with *Schistosomatium douthitti* (Fam. Schistosomatidae) in a local rodent population and to examine pathologic characteristics of both natural and experimental infections with the parasite. Wild meadow voles, *Microtus pennsylvanicus*, were trapped and examined for the presence of the blood fluke. Seventy percent of the 47 voles captured were found to be infected, in some cases with over 200 worms. *S. douthitti* infections were also found in 2 other small rodents in the area: *Peromyscus leucopus*, the white footed mouse and *Zapus hudsonius*, the jumping mouse.

Comparison of experimentally infected laboratory mice and meadow voles showed that levels of infection which produced fatal schistosomiasis in mice did not produce signs of clinical disease in voles. Examination of histologic changes in the tissues of infected animals revealed that both species produced a granulomatous response to schistosome ova, but that differences occurred between mice and voles in the cellular composition of the host reaction. Naturally infected voles also appeared unaffected by infection with

S. douthitti. The tissue response of these wild voles resembled that of experimentally infected voles.

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Introduction

Infection with schistosomes is currently estimated to occur in some 200 million people throughout the world (Dorozynski, 1976). The range of these blood flukes, digenetic trematodes of the Family Schistosomatidae, is presently expanding as the extension of irrigation systems in underdeveloped nations provides new areas suitable for the snail intermediate host of the parasite (Dorozynski, 1976). The widespread morbidity resulting from the infection and its potentially fatal consequences have resulted in the past two decades in the recognition of schistosomiasis as a leading public health problem in portions of Africa, Asia and South America. The World Health Organization of the United Nations has listed schistosomiasis as one of six parasitic diseases to be attacked in a special program of Research and Training in Tropical Disease (WHO, 1978). Efforts to date to control and eliminate the parasite have revolved around chemotherapy and snail eradication. Both methods are not only costly, but labor intensive and emphasis has currently been placed on the development of vaccines and more effective drugs for mass treatment (WHO, 1978).

Although the importance of human schistosomes has overshadowed other aspects of infection with this group of trematodes, blood flukes are not uncommon parasites of other non-human mammals

and birds (Yamaguti, 1958). Infection rates amongst wild and domestic animals may be high and Lawrence and Condy (1970) for example, have reported infection rates of *Schistosoma mattheei* of up to 92% in Rhodesian cattle. Outbreaks of severe disease may result in substantial economic loss to the farmer (Strydom, 1963). Hussein et al (1975) have referred to a report of an outbreak of *Schistosoma bovis* in the Sudan in which 8,000 head of livestock died. While schistosomes in animals are therefore important in their own right, their relevance to human disease should not be overlooked. Cases of human infection with schistosomes of other mammals have been reported. Pitchford and Visser (1962), in a survey of a South African community, found 80% of the cattle and 40% of the women and children infected with *S. mattheei*. Infections of both wild and domestic animals with *S. mansoni* and *S. japonicum* in some areas may act as important reservoirs of infection for the human population (Martins, 1958). Finally, although the species of host and parasite may vary, the pathogenesis of the disease appears to be largely similar, and these animal systems may thus provide useful model systems for the study of the mechanism of disease in human schistosomiasis.

This last consideration may prove to be especially significant in the light of increasing interest in the immunological response of the host to the parasite and the potential for vaccine development. Much of the current understanding of schistosomiasis has grown from experimental studies conducted primarily with infections of laboratory mice with the human parasite *S. mansoni*. Warren (1964) has maintained that the mouse provides an experimental system in

which the parasite behaves as it does in the human, but whether this correspondence is exact in all aspects is questionable. Cheever (1965b), in a study performed with several different species of rodents, found that the cellular reaction to the parasite varied and suggested that caution be used in interpretation of results in laboratory animals. Von Lichtenberg (1968) points not only to the difference in cellular reaction between mice and humans, but also to differences in the hepatic vascular anatomy of the two species.

The situation is further complicated by apparent strain differences within the species of fluke. Infections of *S. mansoni* in wild rodents in Africa appear to be incidental and unlikely to be maintained independently of the human cycle of infection (Pitchford and Visser, 1962). In South America, however, infection rates in wild rodents may be high and the parasite seems to be successfully established in and transmitted by these animals (Antunes et al, 1973).

This type of qualitative difference in reaction to natural infection with the human parasite in rodents can also be seen, although less strikingly, in laboratory infections (Warren, 1967; Hsü and Hsü, 1960), and may be especially misleading in attempts to establish the degree of immunological resistance developing in infected individuals. The presence of immunity to reinfection in man has never been satisfactorily established (Warren, 1973a) and it is probably dangerous to attempt to generalize from the reactions elicited by the parasite in a host for which it is not primarily adapted. It may therefore be more valuable to develop

an understanding of the development of disease and the formation of immunological resistance in the natural host-schistosome systems.

Knowledge of the epidemiology of schistosome infections, like that of the pathogenesis of the disease, has been derived exclusively from studies with the human schistosome species. Workers in the field, frequently medical personnel, have produced many surveys of rates of infection in endemic areas. These reports, while useful in directing eradication and treatment efforts to areas of high endemicity, have done little to answer questions about the frequency and intensity of exposure encountered by individuals in these areas, and the actual extent of debility due to disease in a community. MacDonald (1965) and Hairston (1965), amongst others (see Cohen, 1977), have proposed mathematical models for human schistosome populations but these have proven largely impractical as predictive tools in field situations.

Prohibitions against human experimentation contribute to the difficulty in understanding the mechanisms of transmission of the parasites. Cultural factors which influence water contact and perceptions of infection and disease, further obstruct accurate interpretation of data. Warren (1973a) has suggested that evidence of decreasing egg production with increasing age, which has been commonly accepted as indirect evidence of resistance to infection in humans, may be as convincingly explained by reduced contact with water as individuals grow older. The enumeration and elimination of these various social and cultural factors in a field situation present an almost insurmountable difficulty. Here too,

the study of the non-human mammalian schistosomes may prove to be an exceptionally valuable means of developing an appreciation of the basic parameters of schistosome infection.

The following pages contain the report of preliminary work on attempts to utilize one of these mammalian schistosomes---*Schistosomatium douthitti*. Both basic epidemiological and pathological studies are presented. The Literature Review provides a brief comparative picture of schistosomiasis in man and animals and a short review of the current knowledge of the non-human mammalian schistosomes.

LITERATURE REVIEW

Schistosome Life Cycle and Clinical Schistosomiasis

Life Cycle

Adults of the species belonging to the Family Schistosomatidae parasitize the blood vessels of various organs. Unlike other Trematodes which are hermaphroditic, adult schistosomes are dioecious. Eggs passed in the feces or urine (and, in the case of *Schistosoma nasale*, in the nasal secretions) of the definitive host hatch when they contact water to release a swimming, non-feeding larval stage---the miracidium. During its short life span of a few hours, this larval form must locate a suitable snail intermediate host. Metabolic products of the snail in the water act as attractants and stimulants to the miracidium which penetrates through the skin of the snail (Chernin, 1974). In the sporocyst form within the snail, the parasite undergoes a phase of repeated asexual division to produce the next phase of the life cycle, the cercaria. Under the appropriate environmental stimuli, which vary with the species of schistosome, cercariae are released into the water (Wright, 1971). Although other digenetic trematodes must pass through a further stage of larval development (the metacercaria), within the schistosomes it is the cercaria which is infective for the definitive host. The cercaria, responding to chemical stimuli like the miracidium, penetrates through the skin of the host with the aid of enzymatic

secretions (Smithers, 1976). After a period of migration and maturation the schistosome finally comes to rest in its appropriate location within the circulatory system. This simple life cycle, combined with the primitive sanitary facilities prevalent in many developing nations, make infection in endemic areas difficult, if not impossible to avoid.

Mammalian Schistosomes

Three species of schistosome are important in the generation of disease in humans. *S. mansoni*, found in the mesenteric venous system, is distributed over a wide area, including parts of Africa, the Middle East, the West Indies and South America. *S. japonicum*, which, like *S. mansoni*, lives in the mesenteric veins of the host, occurs throughout much of the Far East. The range of the third species of human schistosome, *S. haematobium*, extends through large areas of Africa and the Middle East. Unlike the adults of the other two species, those of *S. haematobium* are found in the vesical and pelvic venous plexuses. Although human infections with other species of schistosome do occur (for example, *S. mattheei* and *S. intercalatum*), they are not considered of widespread importance as causes of disease and will not be further discussed here as human parasites (Hunter et al, 1976).

A variety of species of schistosomes occur in non-human mammals ranging from rodents (Price, 1931) to hippopotami (McCully et al, 1967) and elephants (Rao and Hiregandar, 1953). The difficulty involved in examining dead animals for the presence of schistosomes, and the failure of schistosome eggs to float in

standard flotation solutions, have probably led to an underestimation of the number and range of species. These mammalian schistosomes, as a group, appear to be highly successful and are distributed over a large part of the world. With only a few exceptions, adult parasites are found in the mesenteric veins of the host. The following discussion will concentrate on those schistosomes, of both man and animals which occur in the intestinal venous system.

Clinical Schistosomiasis

Schistosome Dermatitis

Several distinct clinical syndromes are associated in both man and animals with the different stages of the parasite life cycle and with variation in duration of infection. The first form of the parasite to be encountered is the cercaria, and response by the host will depend on the species of parasite and the immunological experience of the host. That non-human parasites will readily penetrate human skin was first appreciated by Cort in Michigan in 1928. Further work in Michigan has shown that the cercariae of *Trichobilharzia* and *Gigantobilharzia*, parasites of birds, and of *Schistosomatium douthitti*, a schistosome of rodents, will produce the familiar condition known as "swimmer's itch" (Cort, 1950). This dermatitis has been shown by Olivier (1949) to be a sensitization phenomenon. Initial exposure to the cercaria results in mild itching directly associated with penetration. Macules may develop, but are not long-lived, rarely lasting twenty-four hours. These primary exposures commonly go unnoticed or are attributed to other causes. Subsequent penetration

by cercariae, however, will result in a characteristic allergic reaction with intense and long lasting itching, erythema and production of papules which may last as long as a week (Olivier, 1949). Histologically, in both man and experimental animals, secondary exposure is marked by congestion and infiltration at the site of penetration by polymorphonuclear cells, lymphocytes and macrophages. Primary exposure produces this same infiltrate but at a much reduced intensity and with a smaller component of monocytes (MacFarlane, 1949, Olivier, 1949; Kagan and Meranze, 1955; Batten, 1956). In massive infections of *S. douthitti* in rhesus monkeys, Kagan (1953) was able to demonstrate that a few abnormal adults developed in the liver, but the normal fate of incompatible cercaria is entrapment and death in the dermal and basal layers of the skin. Sensitized individuals show enhanced clearance of the dead cercariae by neutrophils and phagocytes (MacFarlane, 1949).

Whether or not the human schistosomes produce this same syndrome of sensitization and dermatitis in their natural host is not clear. In early work in an area in Egypt endemic for *S. haematobium*, Barlow (1936) reexposed local peasants, known to be infected, to cercariae of *S. haematobium* and was able to show the development of an apparently typical schistosome dermatitis. The local population seemed familiar with the condition and associated it with schistosomiasis. Barlow also infected himself with *S. haematobium* and reported characteristic signs of schistosome dermatitis (Barlow and Meleney 1949). Later authors (Elwi, 1967; Jordan and Webbe, 1969) however, have suggested that dermatitis

due to human schistosomes is uncommon in endemic areas, although Europeans seem to develop the condition following exposure to cercariae. The widely documented dermatitis known as "Kabure" which occurs in Japan and other areas of the Far East endemic for *S. japonicum*, appears to be caused largely by penetration of cercariae of an avian schistosome (Miyake, 1967).

In animals also, penetration by cercariae of schistosomes specific for the host does not seem to provoke a significant dermatitis. Redness at the site of penetration has been observed by Lawrence (1977a) with *S. mattheei* and by Hussein (1971) and Massoud (1973) in experimental infections of calves with *S. bovis*. A mild maculopapular reaction to experimental infections of *S. douthitti* in laboratory mice was described by Batten (1956).

Acute Schistosomiasis

The path followed by the immature worm, or schistosomulum, once the skin is penetrated has not been thoroughly documented. It is most commonly believed that after a short period in the skin, the young worm enters a capillary and is carried to the heart and lungs and thence to the systemic circulation. An alternative hypothesis suggests that upon reaching the lungs the schistosomulum leaves the circulatory system and migrates through the diaphragm. Kagan (1958) found large numbers of *S. douthitti* in the thoracic cavities of experimentally infected mice. In massive infections, respiratory symptoms may be associated with this phase although lower levels of infection are rarely associated with clinical disease. Olivier (1952) found rapidly resolving focal hemorrhages

in the lungs of mice infected with *S. douthitti*, *S. japonicum* and *S. haematobium*. Interestingly, far fewer hemorrhages were produced by the *S. mansoni* infections, the schistosomula were found in the lung over a much longer period of time and a smaller proportion of cercariae administered eventually established as adults than with the other two species. Olivier suggested that these observations may reflect the behaviour of a parasite in an abnormal host as compared to that of *S. douthitti* and *S. japonicum*, both schistosomes normally occurring in rodents.

Following this migratory phase adult worms are found in the mesenteric veins (or the veins of the vesical plexus in the case of *S. haematobium*) where copulation occurs and egg deposition begins. Female worms lie within the depression formed by the body of the male known as the gynecophoric canal, leaving it only to migrate as far as possible into the capillaries where the ova are deposited. Estimates of the number of eggs produced per day are as high as 150-300 for female *S. mansoni*, while *S. japonicum* females may produce some ten times that number (Warren, 1973b). To reach the external environment and continue the transmission cycle, the egg must penetrate the capillary wall and pass through the tissue of the intestine, finally breaking through into the lumen of the gut where it is incorporated into the fecal material. Ova of *S. haematobium* correspondingly penetrate through the wall of the bladder and are passed out of the body in the urine. This passage through the tissue occurs over a period of several days and may be aided by the production of proteolytic enzymes as well as by the peristaltic movements of the gut, in the case of parasites

of the mesenteric veins (Jordan and Webbe, 1969). Miracidia within the ova are immature when the eggs are deposited and develop to maturity during this phase of tissue migration. The period required for the infection to become patent (determined by the presence of eggs in the feces or urine) varies from as little as 28 days for *S. douthitti* (Price, 1931) to 109 days described in a voluntary infection with *S. haematobium* (Barlow and Meleney, 1949).

Clinically, the period of final migration of worms and increasing production of metabolic products coupled with the initiation of ovoposition is associated with an acute or toxemic disease syndrome. In steers heavily infected with *S. mattheei*, Lawrence (1977a) observed severe diarrhea, with blood in the feces, abdominal pain and straining coincident with the beginning of egg production by the parasites. Similar observations were made by Massoud (1973) in calves, sheep and goats infected with *S. bovis*. Chimpanzees heavily infected with *S. mansoni* showed an elevation in temperature and bloody diarrhea six weeks after infection (Sadun et al, 1966). Acute signs of *S. mansoni* infection in humans, like the cercarial dermatitis, are reported primarily from Europeans (Jordan and Webbe, 1967). Beginning 3-8 weeks after exposure, the toxemic stage of infection generally takes the form of a mild febrile illness. Acute schistosomiasis is a much more frequent manifestation of infection with *S. japonicum*. This characteristic acute syndrome, known as Katayama Fever, occurs 2-12 weeks following exposure and varies in severity in relation to the intensity of infection. Fever, diarrhea and generalized or abdominal pain and nausea are the most common

presenting symptoms (Hunter et al, 1961; Edington and Gilles, 1976).

With the possible exception of Katayama Fever and isolated cases of infection of Europeans with the African schistosomes, the acute form of schistosomiasis accompanies only heavy exposure to the parasite. Mild experimental infection in general produces either no acute disease or disease of such a mild nature that its identification in field situations would be difficult (Jordan and Webbe, 1969).

Chronic Schistosomiasis

The estimated average life span of the human schistosomes is 5-10 years with some convincing evidence that indiviual worms may live as long as twenty years (Warren et al, 1974). The presence of resistance to reinfection in humans has not yet been proven (Warren, 1973a), and in areas endemic for the disease individuals can probably expect to be infected throughout much of their lives. Consequently, schistosomiasis is most commonly presented as a chronic disease.

For a complete discussion of the clinical signs and symptoms associated with chronic schistosomiases the following references may be consulted: Edington and Gilles, 1976; Hunter et al, 1976; Jordan and Webbe, 1969 and Mostofi, 1967. Briefly, signs and symptoms associated with chronic schistosomiasis *mansoni* and *japonicum* include varying degrees of abdominal pain, nausea, and diarrhea containing blood and mucus. Grossly, the intestinal tract appears reddened with occasional petechial hemorrhages and

tortuous mesenteric veins. In some cases, particularly in infections of *S. japonicum*, ulcers may develop. Inflammation of the submucosa leads to epithelial hyperplasia resulting in the formation of polyploid lesions. Liver, spleen and mesenteric lymph nodes are often enlarged and discolored by the accumulation of schistosome pigment. The liver is frequently spotted with small white foci. In severe cases Symmer's clay pipe-stem fibrosis with its characteristic lesions along the portal tracts may be observed. Portal hypertension develops and leads to ascites and may be accompanied by the development of esophageal varices. Rupture of these varices may result in rapidly fatal hemorrhage. In occasional cases dyspnea or pneumonia may develop as a consequence of infection. If symptoms are severe enough death may result, but a fatal outcome of infection is rare.

S. haematobium, because of its location in the urinary tract, produces disease of a different nature. The most characteristic symptom of infection is hematuria. In areas of Egypt where the prevalence of disease is high, the appearance of blood in the urine was, until recently, considered an important sign of virility (Makar, 1967). Further symptoms reported are fever, headache, pain at micturition and muscular pain. Gross organ lesions are not as apparent as in the hepatosplenic schistosomiases. Macroscopic lesions of the bladder most commonly take the form of so-called "sandy patches", in which the mucosa is roughened and raised and the overlying epithelium is thickened. Ureters, the reproductive system, liver and lungs may be involved in the infection. Lesions of the ureters may be severe enough to result in obstruction with

consequent hydronephrosis. Involvement of the gastrointestinal tract is rare, although some lesions may be found in the rectum. An association between infection with *S. haematobium* and carcinoma of the bladder has been frequently recognized in endemic areas.

The naturally occurring schistosomes of other mammals produce lesions of the same nature as the human parasites. The hepatosplenic form of the disease results in fibrotic changes in large areas of the liver (Basson et al, 1970; Hussein et al, 1973; Bartsch and Ward, 1976; Lawrence, 1978a) Hemorrhagic lesions of the intestine have been reported (Hussein et al, 1973). However, the importance of the disease in natural infections is difficult to assess. Fatal infections in experimental animals exposed to large numbers of cercariae occur at the same time as, or shortly after, egg deposition begins (McCully and Kruger, 1969; Malherbe, 1970). Descriptions of field outbreaks of schistosomiasis in domestic animals also appear to be more closely related to acute rather than chronic disease (Strydom, 1963; Hurter and Potgieter, 1967; Lawrence and Condy, 1970; Reinecke, 1970; VanWyck et al, 1974).

Immunopathology of Chronic Disease

For many years the etiology of the lesions of chronic schistosomiasis was poorly understood. The prevalence of the disease in areas where malnutrition and other parasitic diseases are widespread made it difficult to establish which pathological changes could be specifically attributed to schistosome infections. Malnutrition was frequently invoked by early workers as the cause of the hepatomegaly and cirrhotic liver lesions seen in patients

(Warren, 1972).

As awareness grew of the potential severity of schistosomiasis attention was directed to the adult fluke as the cause of disease. However, while the toxemic stage of schistosomiasis seems to be related, at least in part, to the migration and metabolic products of the worms themselves, the flukes normally do not appear to play a major part in the production of the chronic lesions. McCully et al (1967) have suggested that the generalized endophlebitis seen in infected hippopotami may be due entirely to the presence of adult *S. hippopotami*. At the same time, they point out that the hippopotamus may be an abnormal host of the parasite. However, the cause of the endophlebitis seen in cattle infected with *S. mattheei* (McCully and Kruger, 1969; Hussein, 1971; Lawrence, 1978b)and *S. bovis* (Massoud, 1973) may be associated with the presence of adult worms. Photomicrographs of the human schistosome species show adult worms eliciting no response in the walls of the veins surrounding them (Smith and von Lichtenberg, 1974). Similarly, the existence of a toxin elaborated by adult worms and producing chronic hepatic lesions has not been demonstrated. The absence of disease in laboratory animals with massive unisexual infections (Warren, 1961) and the finding by Raslavicius (1965) that hepatic lesions did not develop in the uninfected parabiotic partner of an infected animal also point to the relatively nonpathogenic nature of the living worms. It has also been suggested that it is instead the dead flukes and the reaction that they elicit in the liver that produces the chronic fibrosis and portal hypertension. However, treatment of infection and death of large numbers

of worms in mice before the initiation of ovoposition does not result in the production of disease (Warren, 1961).

The importance of the schistosome egg in the generation of schistosomiasis has come to be appreciated only within the last two decades, largely, as will be discussed below, through studies by Kenneth Warren and his coworkers. Following the deposition of ova in the capillaries by the female worms, many eggs are able to migrate successfully through the intestine and reach the external environment. Others are surrounded by the tissue reaction of the host, and die within it. A significant number are swept up by the circulation and carried to other organs where they are trapped and killed by the host response. In *S. japonicum* and *S. mansoni* infections the presinusoidal capillaries of the liver capture the majority of these eggs, which are transported in the portal circulation. Only in long-lasting infections are ova seen in significant numbers in the lungs and other organs (Edington and Gilles, 1969).

As the ova become lodged in small vessels they form a mechanical barrier to blood flow. In mice with severe hepatosplenic disease, however, Bloch et al (1972) demonstrated that even large numbers of eggs alone would not significantly affect portal flow or parenchymal perfusion. It is rather the granulomatous host reaction surrounding the ova which interrupts portal circulation and leads eventually to portal hypertension and arterial compensation (Andrade and Cheever, 1971). Cheever (1965a) found a direct relationship between the size of the granuloma surrounding the eggs and the development of portal hypertension. The damage

caused by the ova in the vessels they block and the resulting host reaction leads also to the massive fibrotic changes seen in chronically infected livers (Warren, 1972).

Further observations of the granulomatous response to the eggs of *S. mansoni* in mice indicated that immunological sensitization of the host to the eggs occurs shortly after the onset of egg production. Eggs appearing in the tissue soon after ovoposition begins do not elicit as intense a granulomatous reaction as those appearing several weeks later in the course of infection (Warren, 1972). In an experimental procedure devised by von Lichtenberg (1962) schistosome ova are injected via the tail vein of mice and become trapped in the lungs where granuloma formation can be observed. Under these conditions, more uniform and easily controlled than those occurring during infections with adult flukes, it has been shown (Warren and Domingo, 1970) that secondary exposure to ova results in more rapid cellular infiltration and granuloma formation. Bentonite particles injected by the same method elicit a constant foreign body reaction despite previous exposure. If bentonite particles are coated first with a soluble egg antigen preparation (SEA) and then injected into mice previously sensitized with an intraperitoneal injection of *S. mansoni* eggs, the reaction elicited by the bentonite and SEA will be identical to the granuloma forming around ova in the lungs (Boros and Warren, 1970).

Additional evidence of immunological sensitization has been provided by the ability to significantly reduce the formation of granulomas in the lung model with the use of immunosuppressive

drugs (Domingo et al, 1967), thymectomy (Domingo and Warren, 1967), and antilymphocyte serum (Domingo and Warren, 1968b). This sensitization can be transferred with the spleen or lymph node cells of infected animals (Warren et al, 1967). On the basis of these observations, Warren has proposed that granuloma, or pseudotubercle formation in response to schistosome ova is consistent with an immunological reaction of the delayed type hypersensitivity category, and that schistosomiasis is consequently an immunopathological disease (Warren et al, 1967).

The substances which act as antigens in the delayed type hypersensitivity response (DTH) have not yet been completely identified. Eggs when laid are immature, development of the miracidia occurring throughout the period of tissue migration, and proteins released by the ova to facilitate passage through the tissue may play an important part in the stimulation of granuloma formation (Warren, 1976). Hang et al (1974) have shown that immature eggs possess little ability to induce a host reaction. Miracidia alone, however, are incapable of producing the pseudotubercle, as are purified egg shells, indicating the importance of the whole egg as an antigenic stimulus (von Lichtenberg and Raslavicius, 1967). Some work has been done that indicates that products of the schistosome eggs may stimulate other host reaction pathways. Using the lung granuloma system of von Lichtenberg, Smith et al (1971) have shown that SEA coupled to bentonite particles is unable to sensitize mice to further injections of SEA unless lysophosphatides of the type released by the egg are also present. These workers suggest that the lysophosphatides released by the

ovum may have an adjuvant effect and facilitate uptake of egg antigens by phagocytic cells through activation of inflammatory pathways. Kellemeyer and Warren (1970) were able to cause partial suppression of granuloma formation around eggs of *S. mansoni* in mice by previous administration of ellagic acid, which consumes kininogen, the parent molecule of bradykinin. They propose that the inflammatory pathways may play a greater role in the overall DTH reaction than is currently appreciated.

The sequence of events which produces the egg granuloma has been followed histologically in an almost bewildering variety of host-schistosome systems. The most extensively studied of these have involved the human parasites in a number of laboratory rodent hosts. However, histopathological studies have been performed with *S. bovis* infections in cattle (Hussein, 1971, 1975) and sheep (Hussein et al, 1976), with *S. mattheei* in cattle and sheep (McCully and Kruger, 1969; Lawrence, 1978a, b); with *S. incognitum* in sheep (Srivastava and Dutt, 1962); with *S. douthitti* in mice (Kagan and Meranze, 1957, 1958) and with *Heterobilharzia americana* in raccoons (Bartsch and Ward, 1976) amongst others.

Several classificatory schemes have been proposed (Hsü et al, 1972; von Lichtenberg et al, 1973) to characterize discrete stages of host reaction to the ova. While such descriptive schemes are perhaps useful in determining predominant cell types at different periods during granuloma formation and resolution, they also tend to obscure the nature of the granuloma as an actively evolving pathological process. The establishment of these categories also emphasizes differences between host-parasite systems which may be

irrelevant to a wider appreciation of the mechanism of host response to the parasite.

Despite the variety of schistosome species and hosts employed a generally uniform picture of host response can be drawn. The arrival in the tissue of the newly deposited immature egg elicits only a mild inflammatory reaction. As the miracidium within the egg matures, polymorphonuclear cells, particularly eosinophils, and monocytic cells accumulate. Macrophages become increasingly prominent and an epithelioid granuloma, often containing giant cells, surrounds the egg. Usually there is an accompanying peripheral halo of lymphocytes, plasma cells and eosinophils. With the death and destruction of the egg, fibroblasts and collagen deposition predominate. Most commonly, all traces of the egg disappear, but in some cases, particularly with ova of *S. japonicum*, calcification may occur.

The development of the granulomatous response to the egg is rapid. In naive mice, *S. mansoni* ova injected into the tail vein produced granulomas in the lung which reached peak diameter in 16 days and thereafter declined in size, although some reaction was still visible after 96 days (Warren and Domingo, 1970). In sensitized animals the same peak intensity was reached in only 8 days. In the same study the rate of clearance of the ova from the lungs of mice was examined. After 96 days only 15% of the original inoculum of *S. mansoni* eggs remained. In sensitized animals this rate of clearance was increased. Modulation of granuloma formation occurs as the infection progresses. In mice infected with *S. mansoni* for 16 weeks or more, granulomas forming

around newly arrived eggs are smaller than those which developed earlier in the infection (Andrade and Warren, 1964; Domingo and Warren,1968a). The activity of blocking antibody or suppressor T cells has been suggested as the possible means by which such modulation might be achieved (Ramalho-Pinto et al, 1976; Warren, 1976).

As in many other helminth infections, the eosinophil appears to be a consistently important cell in the host response to the schistosome eggs. It is frequently the dominant cell in early granuloma formation (Cheever, 1965b; Hsü et al, 1973) and may be found in the generalized inflammatory infiltration which develops in the portal tracts of the liver and in the intestine (Hussein, 1972; Lawrence, 1978). Peripheral eosinophilia is encountered in animals infected with schistosomes, usually reaching a peak during the period of initial egg production (Hussein and Tartour, 1973; Mahmoud et al, 1975; Lawrence, 1977b). Despite its apparent significance, the role of the eosinophil in the host reaction is poorly understood. Several recent studies, however, have indicated possible functions of the cell. Mahmoud et al (1975b) have reported that the partial immunity of mice to secondary infection with *S. mansoni* can be eliminated by treatment of animals with anti-eosinophil serum. James and Colley (1976), have proposed, based on *in vitro* studies, that the eosinophil is an important agent of egg destruction. The involvement of the eosinophil in the modulation of inflammation (Leid and Williams, 1978) may also prove to be of importance in the understanding of its significance in schistosome and other helminth infections.

Despite the frequency with which the general pattern of pseudotubercle formation occurs, variation exists not only between host species, but within a species and even within individual animals. In a comparative study of *S. mansoni* infections in several laboratory rodents, Cheever (1965b) found that while eosinophils and fibroblasts were the most frequent cell types encountered in the hepatic granulomas of mice, macrophages were more prominent in multimammate rats and mast cells were present in unusually high numbers in the granulomas of gerbils. Von Lichtenberg (1973) observed variation in the responses of individual hamsters to eggs of all three human schistosome species, and Bartsch and Ward (1976) in a study of *H. americana* found that occasional ova in the liver of raccoons were surrounded by eosinophilic microabscesses rather than the usual granuloma.

The importance of such differences in the reaction to the ova is difficult to evaluate, but probably, in general, it is not indicative of major differences in the response to the fluke and its ova. However, Warren and his colleagues (Warren et al, 1975) have suggested within the past several years that the response of laboratory animals to the eggs of *S. japonicum* may reflect a qualitatively different reaction than is observed with the other, thoroughly studied human schistosomes. Studies of normal infections of *S. japonicum* in mice have shown that ova do not elicit a granulomatous reaction as soon after their arrival in the tissue as do eggs of *S. mansoni* and *S. haematobium*. When a response does occur it frequently results in the production of large eosinophilic necrotic granulomas. Normal infections with adult *S. japonicum*

or injection of eggs intraperitoneally do not sensitize mice to subsequent intravenous injection of eggs. Although both these methods are effective in sensitizing animals to *S. mansoni* or *S. haematobium*, the authors point out that the observed difference may only represent a requirement for higher concentrations of antigen to successfully sensitize animals to *S. japonicum* (Warren et al, 1975).

S. mansoni has been found naturally only in a few species of rodents and primates besides man. *S. haematobium* appears to be a successful parasite only of humans. However, *S. japonicum* is capable of utilizing a number of species of wild and domestic animals, as well as humans, as final hosts (Jordan and Webbe, 1969). This relative nonspecificity may reflect a less highly evolved host-parasite relationship than exists for the other two species. The host response to the parasite and its ova may be correspondingly less efficient. Infection with *S. japonicum* has always been considered the most severe of the human schistosomiases (Warren et al, 1975) because of the heavier egg output by the female. Alternatively, this difference in severity of infection may support the suggestion of Fine et al (1973) that a highly evolved and specific DTH response is a largely advantageous mechanism for destroying a pathogen of the nature of the schistosome ovum. The granuloma provides a rapid and local means of destroying eggs and egg antigens. Furthermore, under conditions in which granuloma formation is inhibited by means of thymectomy, irradiation and antilymphocyte serum eggs become surrounded by large areas of coagulative necrosis with destruction of hepatic parenchyma.

Invasion by bacteria is common and the survival of animals is significantly reduced (Buchanan et al, 1973). Further investigations may reveal that those individuals suffering most severely from schistosome infections are those least capable of mounting an efficient DTH response to the ova. If this should be the case, the current understanding of schistosomiasis as an immunological disease may require modification.

The role of DTH reactions in other helminth infections has received little attention. Studies utilizing *Capallaria hepatica* have been performed by Solomon and Soulsby (1973)and by Raybourne et al (1974). This nematode parasite resides in the liver of rats or man and migrates through the liver parenchyma depositing ova which are retained in the liver and liberated only when the liver is ingested by another animal. A granulomatous, anamnestic DTH response develops to these eggs which appears strikingly similar to the schistosome granuloma. Work with other helminths may reveal a more important role for DTH in the immunological response to parasitic infections than that presently attributed to it.

Biology and Epidemiology of Non-Human Mammalian Schistosomes

Many aspects of the biology and life cycles of the schistosome parasites of both wild and domestic animals have been adequately described in the literature. However, while there are some reports of the prevalence of infection in endemic areas, little attention has been paid to the development and severity of the disease in infected animals or to the possible role played by schistosomes

in the regulation of wild animal populations. There are several factors which have contributed to the scarcity of information. As in the human schistosomiases, the predominantly chronic nature of the disease in animals makes it difficult to diagnose clinically. Even the more clearly demarcated clinical syndrome associated with acute schistosomiasis may be hard to differentiate from other conditions. VanWyck et al (1974) have cautioned that rinderpest, ngana, coccidiosis, arsenical poisoning and Johne's Disease all share some clinical signs with schistosomiasis *mattheei* in South Africa. Additionally, these mammalian flukes are primarily parasites of tropical regions where interest and money available for research are directed to the human schistosomes. In these areas, standards of animal husbandry may be low and veterinary care inadequate. Consequently, the picture which can be assembled of the biology and epidemiology and animal schistosomiasis is at best fragmentary.

Schistosomes of domestic animals

A variety of schistosome parasites of domestic animals is found in domestic animals in the Far and Middle East, India, Africa and Southern Europe. *S. japonicum* is shared by approximately thirty other species of mammal in the Far East (Cheng, 1971). However, its importance as a pathogen in its non-human hosts has been entirely overshadowed by the human disease. Interest in these animal infections has revolved around their roles as reservoirs of human infection. The prevalence of infection may be quite high, as indicated by a survey conducted by Pesigan et al

(1958) in the Philippines. They found that 38% of the cattle and 22.7% of the rats sampled were infected with *S. japonicum*. Unfortunately, further research into the nature of the disease or its economic importance does not appear to have been performed, although Cheng (1971) states that heavy losses of draft animals have been reported from several Chinese provinces.

Two schistosomes of ruminants are common in livestock in much of Africa. *Schistosoma bovis*, a parasite of the mesenteric veins of cattle, sheep and goats, is found in an area covering most of north and central Africa, extending as far south as Zambia and Tanzania. *Schistosoma mattheei* is a parasite of mammals in South Africa, its range extending northward into Tanzania and Zambia (Hussein, 1973). Natural infections have been reported from domestic ruminants, antelope, primates (including man) and several species of rodents (Dinnik and Dinnik, 1965). *S. mattheei* also parasitizes the mesenteric veins, although reports of flukes in the venous drainage from the urogenital tract of cattle are not infrequent (Hussein, 1973).

Surveys for the presence of these parasites in domestic animals have revealed strikingly high rates of infection in some areas. Pitchford (1961) found 70-90% of the cattle surveyed in the Transvaal infected with *S. mattheei*. In certain regions of Kenya 100% of the cattle from European farms were infected with schistosomes (Dinnik and Dinnik, 1965). In the Sudan, Makek (1969) found *S. bovis* in 37% of the cattle and 45% of the sheep examined. It has been estimated by other authors that as many as 90% of the cattle in the Sudan may be infected with

S. bovis (Hussein, 1973).

Despite the high rates of infection and descriptions of typical schistosome lesions found in infected animals (McCully and Kruger, 1969; Hussein et al, 1973), reports of accompanying clinical disease are rare. That several of these surveys were conducted at abbatoirs on animals considered healthy at the time of slaughter is an indication of the absence of overt disease. McKenzie (1970) found that 40% of slaughtered cattle were infected with *S. mattheei*. A survey of 2900 Rhodesian slaughter cattle for *S. mattheei* revealed an infection rate of 69% and led the authors to conclude that infection was of little economic significance (Lawrence and Condy, 1970). Malek (1969) described several cattle in the Sudan which were parasitized by numerous *S. bovis*, but showed few gross lesions and were apparently healthy.

Other schistosomes of domestic animals

The most common schistosome of domestic animals in the Middle East is *S. bovis*. Its presence has been reported in sheep, goats and cattle in Iraq, Iran and Israel. *S. bovis* has also been described from several locations in southern Europe (Hussein, 1973). Infections in these areas have not yet been thoroughly investigated, but the high rates of infection in some regions again point to the relatively low pathogenicity of the parasite (Montgomery, 1906; Lengy, 1962; Arfaa et al, 1965; Ramajo and Martin, 1972).

Although the Indian subcontinent probably contains more species of schistosomes of importance to the livestock industry

than any other area of the world (Srivastava and Dutt, 1962), information on these infections is singularly lacking. Morphological descriptions of the parasites and histological examinations of the lesions they induce are available (Datta, 1932; Rao, 1938; Kalapesi and Purohit, 1954; Tewari et al, 1966) but research on disease processes has not been performed. Datta (1932) described a syndrome of persistent debility accompanied by hepatic lesions in horses, which he attributed to infection with *S. indicum*, but no conclusive experimental studies have been carried out.

The importance of the host species in the pathogenesis of schistosomiasis has been emphasized by observations on *S. nasale* in Indian bovids. Adults of this unusual schistosome are found in the nasal veins and eggs are released into the environment in the nasal secretions. The granulomatous response which develops in cattle frequently blocks the nasal cavities producing a marked dyspnea commonly known as "snoring disease" (Dutt, 1967). In buffalo, however, the infection appears to be almost entirely asymptomatic. Dutt and Srivastava (1968), in a survey of a herd of 200 cattle and 60 buffalo, found that all animals were infected with *S. nasale*. Seventy percent of the cattle showed definite clinical signs of infection, while none of the buffalo appeared to be clinically affected by the parasite. Dutt (1967) showed that this difference is due entirely to the host response. Cattle experimentally exposed to cercariae derived from buffalo flukes developed clinical disease, while buffalo infected with cercariae produced from the eggs of cattle schistosomes did not.

Clearly, these fluke infections of domestic animals in many

ways resemble the human schistosome infections as they are currently understood. Distribution of the parasites is wide; in endemic areas rates of infections are high, although many infections may as asymptomatic. While the acute syndrome is more recognizable it occurs only infrequently. The social and economic impact of chronic schistosomiasis, the form of the disease most commonly encountered, is difficult to accurately evaluate. However, as a consequence of these similarities it is encouraging to believe that the tools developed to control and eliminate infection will be of value to both groups of schistosomiases.

Schistosomes of wild mammals

The importance of schistosome infections in wild mammals lies not only in their effects on individual animals, but also in their ability to influence host population levels. The latter effect may be accomplished subtly through such mechanisms as a reduction in the fertility of infected animals or, more obviously, by the production of clinical schistosomiasis. From an epidemiologic perspective these host-parasite systems offer an opportunity to examine the parameters influencing transmission of the parasites uncomplicated by the restrictions imposed by man on domestic animals.

Systematic investigation of a wild mammal schistosome has been undertaken only in South Africa with *S. mattheei* (Basson et al, 1970; Pitchford et al, 1973; Pitchford et al, 1974). Although the parasite is found in a number of wild animal species, the African buffalo (*Symmers caffer*) appears to be the most important host. In a survey of 100 culled buffalo the incidence of infection

was 62%. The prevalence and intensity of infection increased with increasing age of the buffalo and were especially high in older, solitary animals. These "reitbuffels," as they are commonly known, are no longer herd members and are generally restricted in their movements to riverbanks. They can frequently be observed wallowing in the mud and water (Basson et al, 1970). This observation of higher worm burdens in older animals may be natural evidence of the absence of resistance to reinfection seen in laboratory infections of cattle with *S. mattheei* (Lawrence, 1973). There was no indication of ill health in the infected buffalo, although in some cases the schistosomal lesions were striking.

In two studies by Pitchford et al (1973, 1974) the extent of infection with *S. mattheei* in the Kruger National Park was thoroughly established. Fecal samples of a number of animal species were collected and examined for schistosome ova. On the basis of rate of infection, fecal characteristics, gregariousness, range and water-entering behaviour, host species were assigned to categories in relation to their ability to support the adult parasite and successfully introduce the schistosome ova to water. The distribution of *S. mattheei* in the area studied could be seen as consisting of a number of foci of infection, each centered around a water source. In each of these foci the parasite was either independently maintained, or was the product of repeated introduction. The buffalo, with its large range, waterloving habits and high rate of infection was seen as the primary source of infection.

The nature of the water supply in a given area could be

correlated with the prevalence of the infection. Where animals relied on fast-flowing rivers with thick vegetation along their banks, *S. mattheei* infections were infrequent. In other locations where water was provided by man-made lakes or ponds, infection rates were higher. The value of these studies lies in their delineation of the relative importance of each factor which influences transmission of the schistosome. Current work in South Africa on the behaviour of *S. mattheei* in wild mammals and its eventual comparison with infections of domestic animals may lead to an increased understanding of the delicate relationship between host and parasite.

Other schistosomes of wild mammals

Several other schistosome parasites have been briefly described from wild mammals (Price, 1931 Rao et al, 1932; LeRoux, 1933, 1955; Schwetz, 1953); one of these, *Schistosomatium douthitti*, will be discussed in a later section. Another schistosome of wild mammals which has received some attention experimentally is *Heterobilharzia americana*, one of two schistosomes of mammals found in North America. Adult flukes have been reported from the portal and mesenteric venous systems of the raccoon, nutria (*Myocaster coypus*), dog, opossum, bobcat, swamp rabbit, and white-tailed deer in Florida, Louisiana, North and South Carolina and Texas (Malek, 1961; Bartsch and Ward, 1976). Experimental infections have also been produced in the mouse, hamster, rabbit, guinea pig and cat, although all but the first two of these laboratory hosts do not contain large numbers of eggs in the feces

(Lee, 1962). The raccoon has been suggested by Lee (1962) to be the most important natural host in the areas studied. In two locations surveyed by Malek (1961) in Louisiana, 21 of 39 and 25 of 52 raccoons were found to be infected with *H. americana*. Two naturally infected dogs in poor condition with diarrhea have been described (Malek, 1961; Pierce, 1963), but in the absence of firm experimental evidence of the pathologic effects of *H. americana*, it is not possible to determine the role of the fluke in affecting the condition of these animals.

An interesting but apparently anomalous schistosome has been described by McCully et al (1967) from the vascular system of the hippopotamus. Identified as *S. hippopotami*, these flukes were distributed throughout the venous and arterial systems of a large proportion of 97 culled hippopotami. Egg production by the parasite was limited to worms in the veins of the adrenals. These unusual characteristics of infection have led the authors to suggest that the hippopotamus may be an abnormal host of this fluke. Remarkably, although the schistosomes excited a profound reaction in the vessel walls, all animals appeared clinically healthy.

Infections of African rodents with *S. mansoni* have been observed in a number of species since 1952 (Kuntz, 1952). These infections are infrequent and it is now agreed that they are probably unimportant as reservoirs for human infection, in contrast to infections of several primate species (Martins, 1958; Pitchford and Visser, 1962). In South America, however, since the introduction of *S. mansoni* as a consequence of the slave trade, the parasite

has successfully adapted to a number of native rodent species (Martins, 1958; Barbosa, 1972). Although viable ova have not been found in the feces of all infected animals, Antunes et al (1973) have demonstrated experimentally the successful completion of the parasite life cycle using infections of *Nectomys squamipes squamipes*. The prevalence of *S. mansoni* in wild populations of these aquatic rodents is as high as 57% in some rural areas. While it is not yet clear that *S. mansoni* infections in *Nectomys* are maintained independently of the human cycle, the impact of the rodent infections on human schistosomiasis may be extensive. Incidental findings of *S. mansoni* have been made in a variety of other animals ranging from cattle (Barbosa et al, 1962) to the giant anteater (Rijpstra and Swellengrebel, 1962), but these infections are not known to be of significance in the distribution of the parasite.

Schistosomatium douthitti

Natural Infection

Only two of the schistosome species of mammals found throughout the world are native to North America. *Heterobilharzia americana*, a parasite of the raccoon, bobcat, nutria, and occasionally the dog, is restricted to the southeastern U.S. (Malek et al, 1961). The rodent parasite, *Schistosomatium douthitti*, has been reported from a more extensive area covering the north-eastern and central United States, Alaska and Canada (Price, 1931; Penner, 1942; Swartz, 1966; Choquette et al, 1973). Like most schistosomes, adult *S. douthitti* which reach a length of about 1 cm, are found

in the mesenteric veins of the host. Since the first detailed description of the fluke by Price (1931), *S. douthitti* has been identified in the meadow vole, *Microtus pennsylvanicus* (Price, 1931); the muskrat, *Ondatra zibethica* (Penner, 1938); the redbacked vole, *Clethrionomys rutilus* (Swartz, 1966); and the porcupine, *Erithizon dorsatum* (Choquette et al, 1973).

Several species of Lymneid snails are known to be capable of acting as intermediate hosts for *S. douthitti*. Naturally infected *Lymnea palustris* and *L. stagnalis* and *Physa gyrina* (Price, 1931) have been reported. *L. catascopium* (Kagan, 1954) and *Pseudosuccinea columnella* have been successfully infected in the laboratory (Malek, 1970).

Examination of snail populations for the presence of *S. douthitti* has yielded uniformly low rates of infection. Bourns (1961) examined 2474 *L. stagnalis* and *L. palustris* between 1957 and 1960 and found only 3.7% infected. Surveys by workers in other areas revealed rates of infection ranging between .5% and 8.6% (Brackett, 1940a; Farley, 1962a). Bourns (1961) also observed that a seasonal variation in the prevalence of infection occurs when measured by the ability of snails to shed cercariae. Monitoring of *L. palustris* and *L. stagnalis* between May and November showed that the percentage of infected snails increased through the early summer and reached a peak of about 6% in late summer and fall. A similar observation has been made by Blankenspoor (personal communication). This peak in infected snails coincides with the period when the greatest numbers of mature snails are found (Brackett, 1940a)

Penner (1942) stated that the muskrat (*Ondatra zibethica*) was the most important natural definitive host of *S. douthitti* and available information on prevalence of natural infections stems almost exclusively from muskrat surveys. Like the snail intermediate hosts, the muskrats examined have shown only low rates of infection. Penner (1938) surveyed 330 muskrats in Wisconsin and found only 32 infected animals. Between 1938 and 1942 he examined a further 374 muskrats and found 11.2% infected (Penner, 1942). A survey by Gilford (1954) of 250 muskrats in Illinois detected only 1 infected animal. Beckett and Gallachio (1967) found 2 of 130 animals infected in Ohio, and of 12 muskrats inspected in central and southern Michigan, 2 were infected (Ameel, 1942). Two authors have reported briefly on infection of *Microtus pennsylvanicus* with *S. douthitti*. Price (1931) found that one of three animals trapped in southeastern Michigan was infected, and Farley (1962a) discovered one fluke in one of 13 voles captured.

Much of the interest in field infections of *S. douthitti* results from the ability of the parasite to produce "swimmers' itch", the dermatitis associated with host sensitization to the penetration of cercariae of non-human schistosome species (Cort, 1950). Although dermatitis can be produced experimentally with *S. douthitti* (Herber, 1938; Olivier, 1949), instances in which this species has been implicated in the production of clinical cases of swimmers itch are rare (Cort, 1950). The preference of the intermediate hosts for still, weedy water, and the release of cercariae only in the evening hours are probably major factors which limit the occurrence of *S. douthitti*-related dermatitis.

Laboratory Infections

Although field work with *S. douthitti* has not been extensive, laboratory investigations have produced information about a number of aspects of the development and behavior of the parasite. Tanabe (1923) first described the fluke, calling it *S. pathlopticum*, following observations of laboratory mice infected with cercariae from naturally infected snails. (Price (1931) later published a more detailed description of all stages of the life cycle of a parasite which she named *S. douthitti*. Penner (1942) subsequently established that only a single species was involved and assigned the name used by Price.

Several species of mammalian hosts have been shown to be susceptible to laboratory infections with *S. douthitti*. These include the deer mouse, *Peromyscus maniculatus* (Price, 1931); the laboratory mouse (Tanabe, 1923), the snow shoe hare, guinea pig (Penner, 1939) and nutria (Malek, 1970). While the rat is capable of maintaining adult worms, Price (1931) reported that all eggs released by the worms were trapped by the host tissue reaction. Experimental exposure of other animals, including the cat (Price, 1931) and bat (Dery, 1957) did not result in the development of mature parasites.

Several authors have explored the possibility that the parasite may develop to maturity in primates. Brackett (1940b) was unable to recover either mature or immature flukes from the liver of rhesus monkeys infected with cercariae. Penner (1941), however, recovered schistosomula from the lungs 5 1/2 days following infection of a rhesus monkey, and Kagan (1953) found sexually mature

worms in the portal system of rhesus monkeys 12-15 days after infection. Worms in these animals were not as well developed as mouse worms of a similar age, and infections were spontaneously terminated after 2-3 weeks.

Life Cycle

The miracidia of *S. douthitti* are mature when the egg is released in the feces, and the larvae emerge when the egg contacts water. Farley (1962b) found that the half-life of the miracidium at room temperature is about 10 hours. Miracidia are positively phototaxic (Wright and Lavigne, 1972) and capable of responding to chemical stimuli (Wright and Ronald, 1972). Formation of the mother sporocyst in the snail is followed by the development of several daughter sporocysts (Price, 1931). Cercariae are usually first produced by the snail about six weeks following exposure to infection, although lowered temperatures increase the incubation period (Kagan et al, 1954). Darkness is the only stimulus required for release of the cercariae (Olivier, 1951); Kagan et al (1954) found that up to 5000 cercariae could be released by a single naturally infected snail in one evening. Shortly after emerging, the cercariae move to the surface of the water where they hang suspended until a suitable host is encountered (Kagan et al, 1954). Cercariae probably rarely live longer than 24 hours (Cort, 1950).

Penetration of the skin of the definitive host is followed by a migratory phase, with the schistosomula reaching the liver of mice approximately 6 days after exposure to the cercariae

(Olivier, 1952). Worms spend a short time in the veins of the liver and migrate into the mesenteric veins on about the tenth day of infection (Short, 1952). Sexual development and mating of adult worms have been followed by El-Gindy (1951), Short (1952), and Armstrong (1965). Eggs can first be detected in the mesenteric veins 22 days after infection, but ova are not recovered from the feces for approximately another week (Price, 1931).

The interesting observation that female *S. douthitti* are capable of parthenogenetic reproduction in the absence of males (Short, 1947) has led to further studies detailing the genetic constitution of the parasite (Short, 1955; Short and Menzel, 1955). Parthenogenetically produced ova are fully infective for snails (Short and Menzel, 1960) and ultimately produce normal adult worms (Short, 1948).

Histological Studies

The histopathology of the host reaction to *S. douthitti* has been followed in both the skin and internal organs of experimentally infected mice. Batten (1956) examined the skin of mice exposed to cercariae of *S. douthitti* and observed a histiocytic and neutrophilic response to the parasite. Kagan and Meranze (1955) also infected both naive and sensitized mice. The response in both groups was composed primarily of polymorphonuclear cells, but following sensitization the host reaction occurred more quickly and was more highly localized around invading cercariae with a higher proportion of monocytes and fibroblasts participating.

Kagan and Meranze (1957, 1958) also followed the response

to ova in the liver and other organs. Eggs in the liver were seen to excite the formation of pseudotubercles with some areas of inflammation and necrosis. Lesions ultimately became replaced with connective tissue and eggs were destroyed entirely. The reaction to ova in immune mice was identical to that in naive mice after a similar period of time. Livers of mice whose infections had been chemotherapeutically treated 57 days after infection were essentially normal in appearance 270 days following removal of worms (Kagan and Meranze, 1957).

In the intestine focal inflammatory reactions and pseudotubercle formation were observed around the ova. Eggs in the spleen were also associated with granuloma formation. In heavily infected animals ova were found in the lungs, where they were surrounded by inflammatory nodules. Mesenteric lymph nodes and Peyer's Patches were enlarged and infiltrated with ova. Other organs, including the bone marrow and kidneys, were unaffected.

Immunological Studies

The potential value of *S. douthitti* infection as a model for the investigation of host reaction to schistosomes, with particular reference to the immunological response, was recognized by Kagan (1952). In a series of experiments, Kagan (Kagan, 1952; Kagan and Lee, 1953; Levine and Kagan, 196) demonstrated that a partial immunity to reinfection develops following primary infection. Worm burdens may be reduced by as much as 50% in challenge infections, and those worms which do develop are stunted. This partial immunity developed about 35 days following primary exposure and

continued throughout the period of experimentation (123 days). The 35 day period coincides approximately with the period elapsing before large numbers of eggs are deposited by the female worm.

Additional evidence for the role of the ova in the generation of the observed resistance has been provided by several experiments. A primary infection of male worms alone was unable to induce resistance, while single-sex infections of female worms, which will produce eggs parthenogenetically, are as effective an immunizing agent as normal infections (Kagan, 1952). Chemotherapeutic removal of mature worms, followed by reinfection 8 to 52 days later resulted in reduced establishment of flukes for about three weeks after treatment. This three week period corresponds to the length of time that tissue bound eggs would survive (Kagan and Lee, 1953). Finally, Hunter and Crandall (1962) demonstrated a partial immunity following a series of injections of ova or supernatants of egg suspensions. The mechanism of this partial resistance is obscure. Attempts by Levine and Kagan (1960) to immunize mice possibly with injections of serum from infected hamsters were unsuccessful, but no further investigations into the nature of the immunity have been performed.

The possible value of *S. douthitti* in the production of vaccines against human schistosomes has been explored in several studies. Hunter, Weinmann and Hoffman (1961) found that while primary infections of *S. mansoni* in mice were effective in reducing the number of worms establishing from subsequent exposure to *S. douthitti*, the reverse did not occur. Hsü et al (1964) found that infections of *S. douthitti* in rhesus monkeys led to reduced

susceptibility to challenge infections with *S. japonicum*. Non-specific interactions between *S. douthitti* and other parasites which reduce the numbers of adult flukes or the longevity of tissue bound eggs have been observed with *Ascaris suum* (Crandall et al, 1966) and *Fasciola hepatica* (Maldonado-Moll, 1977).

During the past decade interest in *S. douthitti* has diminished and currently little experimental work is being conducted. This natural rodent parasite system, however, provides a practical and valuable opportunity for the study of the relationship between host and schistosomes and the full extent of its usefullness has yet to be determined.

Microtus pennsylvanicus

Approximately 55 species of vole are found in North America and northern Eurasia (Orr, 1971). In the Western Hemisphere these rodents of the Family Cricetidae are found in almost every region from the Arctic Circle to Guatemala (Cahalane, 1947). Although none is a true desert dweller, voles have adapted to a variety of habitats including woodland, fields and marshes. The most common and widespread vole in North America is *Microtus pennsylvanicus*, commonly known as the field mouse, meadow vole or meadow mouse. The length of the mature meadow vole ranges from 8.8 to 12 cm, and adult weights vary from 20 to 68 grams. The pelage of the meadow vole is dark brown above with grey underparts. Unlike mice, with which they are most commonly confused, voles have short, hairy tails and the pinnae of the ears are barely visible above the fur (Burt, 1975).

M. pennsylvanicus does not hibernate and is active throughout the 24 hour day, with periods of least activity at noon and midnight. The meadow vole is territorial, with a home range rarely exceeding 1/15 of an acre (Burt, 1975). Voles forage actively throughout their territories, constructing elaborate systems of tunnels in the undergrowth which lead to buried stores, nests and occasionally to open water. Nests may be found either above or below the ground (Hatt, 1930). While the preferred habitat is close to water, meadow voles can be found in fields and grassland (Orr, 1971). Although research on the tendency of *M. pennsylvanicus* to enter water does not appear to have been performed, anecdotal evidence of the vole's swimming ability and of the readiness with which it enters the water is available from observers extending as far back as Audubon (Hatt, 1930; Cahalane, 1947; Orr, 1971).

M. pennsylvanicus, like many other rodents, eats a remarkable variety of foods. The diet is composed primarily of seeds, leaves, flowers, stems and roots, but grains, alfalfa and clover, tubers and bulbs will also be utilized. In winter voles may girdle vines, trees and shrubs in order to feed on the cambium. They also eat carrion of any kind, as well as insects, crayfish and snails (Cahalane, 1947).

Meadow voles, in turn, are eaten by virtually all major predators. They are preyed upon by hawks and owls, raccoons, foxes and snakes, and this high rate of attrition is countered only by their prolificacy. Breeding can occur throughout the year, although it is rare in winter. A single female will produce several litters annually, each containing one to nine young.

Gestation lasts about 21 days. Females are sexually mature at approximately 4 weeks of age and males at about 6 weeks (Burt, 1975).

Field experimentation with *M. pennsylvanicus* has been most concerned with the striking cyclical nature of population increases and declines. As with the more familiar lemming, meadow vole populations fluctuate between several hundred and 1 or 2 animals per acre over a 3 to 4 year period. Several explanations for these dramatic reductions have been proposed including outbreaks of disease or increased predator activity. More recent hypotheses stress the importance of dispersal during periods of high population density and genetic variation leading to reduced fitness of remaining animals. For a more complete discussion of population changes, see Krebs and Meyer, 1974.

Despite the extensive use of natural populations of *M. pennsylvanicus* by animal behaviour and population biologists, few workers have utilized the meadow vole in laboratory studies. Consequently, only limited information is available related to maintenance of the vole in the laboratory. Poiley, 1949; Lee and Horvath, 1969; Shenk, 1976; and Dietrich and Preston, 1977, have described basic laboratory management and maintenance of breeding populations, and observations of litter size and frequency of breeding have been reported by Colvin and Colvin, 1970; and Morrison et al, 1976. Basic organ weights and hematologic values for *M. pennsylvanicus* have also been published (Dietrich, 1973; Dietrich et al, 1973).

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ARTICLE

PREVALENCE AND INTENSITY OF INFECTION OF THE MEADOW VOLE (MICROTUS PENNSYLVANICUS) WITH SCHISTOSOMATIUM DOUTHITTI (FAM. SCHISTOSOMATIDAE) IN MICHIGAN

Prevalence and intensity of infection of the meadow vole (*Microtus pennsylvanicus*) with *Schistosomatium douthitti* (Fam. Schistosomatidae) in Michigan

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Abstract

A survey was conducted for the presence of *Schistosomatium douthitti* in a local population of meadow voles, *Microtus pennsylvanicus*, in southern lower Michigan. Thirty-three of the 47 voles examined were infected and worm burdens ranged from 1 to 236. *S. douthitti* was also identified from the jumping mouse, *Zapus hudsonius* and the white-footed mouse, *Peromyscus leucopus*.

INTRODUCTION

Schistosomatium douthitti (Fam. Schistosomatidae) is one of two mammalian schistosomes indigenous to North America (Malek et al, 1961). Infections have been reported from the northeastern and north midwestern United States, Canada and Alaska (Penner, 1942; Swartz, 1966; Choquette et al, 1973). Several species of Lymneid snails are capable of acting as intermediate hosts of the parasite, including *L. stagnalis* and *L. palustris* (Kagan et al, 1954). Adult flukes have been described from the mesenteric veins of the muskrat, *Ondatra zibethica* (Penner, 1938), the meadow vole, *Microtus pennsylvanicus* (Price, 1931), the redbacked vole, *Clethrionomys rutilus* (Swartz, 1966), and the porcupine, *Erethizon dorsatum* (Choquette et al, 1973).

Penner (1942) suggested that the muskrat, *O. zibethica*, is the most important natural host and surveys for infection have dealth entirely with this species. Although the mesenteric veins of several hundred muskrats from various regions of the country have been inspected in a series of surveys, rates of infection with *S. douthitti* have not been found to exceed 11% (Ameel, 1942; Penner, 1942; Gilford, 1954; Beckett and Gallicchio, 1967). To determine whether these data from the muskrat are representative of *S. douthitti* infection in other rodents, a survey of a local population of the meadow vole, *M. pennsylvanicus* in Michigan, was undertaken. The results indicate that a high prevalence of infection occurs in this host, and that other small rodents may also become infected.

MATERIALS AND METHODS

Live trapping of meadow voles was conducted at two permanent ponds at the Rose Lake Wildlife Research Area in southern lower Michigan. The ponds were shallow, but fairly extensive in area, the smaller about one half acre in size, while the larger covered an area of approximately two acres. In locations where voles were captured, the vegetation was composed primarily of cattails, *Typha latifolia*.

The presence of *S. douthitti* in the area was initially established by the collection of Lymneid snails, later identified as *L. palustris*. Snails were taken to the laboratory where they were exposed to a minimum of 12 hours of light followed by an hour of darkness which stimulated the release of cercariae. After cercariae of *S. douthitti* were identified, 60 Sherman live traps baited with oatmeal or peanut butter and oatmeal were placed around the perimeters of the ponds. Between July 21 and October 2, 1976, 47 *M. pennsylvanicus* were trapped.

Captured animals were returned to the laboratory where they were given intraperitoneal inoculations of a solution containing a lethal dose of sodium pentobarbital and approximately 100 units of ammonium heparin. Voles were sexed, weighed, and the portal and mesenteric venous systems perfused with phosphate buffered saline. The perfusate was filtered through 5 micron pore size Nuclepore^{R} filters (25 mm diameter) (Nuclepore Corporation, Pleasanton, CA 94566) which retained any worms present. The filter was then transferred to a microscope slide and parasites could be readily sexed and counted under the light microscope.

RESULTS

Thirty three (70%) of the 47 voles examined were found to be infected with *S. douthitti*. The proportion of male and female voles infected was approximately equal: 76% of 29 males and 67% of 18 females. The worm burdens in the infected animals were found to range from 1 to 236 parasites with an average of 40 worms per infected vole. All male infections were found in three animals, but the remaining 44 infected voles contained mature, egg-bearing female flukes. All animals captured appeared healthy and in every case but one there were no gross lesions directly attributable to schistosome infection. The single exception was a heavily infected (228 worms) female whose intestine contained numerous plaques along its length resembling the schistosome ova aggregates observed in mice experimentally infected with *S. douthitti*.

In addition to captured voles, 13 jumping mice, *Zapus hudsonius*, and 8 white-footed mice, *Peromyscus leucopus* were also examined. Three (23%) of the *Z. hudsonius* and 2 (25%) of the *P. leucopus* were also found to be infected with small numbers of *S. douthitti*, ranging from 1 to 17 parasites.

DISCUSSION

Results obtained in this survey indicate that *S. douthitti* occurs more frequently in some rodent populations than would be expected from previous studies of muskrats. In fact, the high prevalence of infection in *M. pennsylvanicus* suggests that the meadow vole rather than the muskrat, *O. zibethica*, may serve as

Table 1. Relationship between age of meadow vole and worm burden

Weight Class	Juvenile	Subadult	Adult
	<22g	22-33g	>33g
Worm burden-range	1-11	6-72	2-236
Worm burden-average	4.75	23.81	76.58

the most important host in the maintenance and transmission of this fluke. However, the difficulty of examining the mesenteric veins of dead animals may have prevented the identification of all muskrats infected with low numbers of parasites, and the prevalence of infection may actually be greater in muskrats than is currently appreciated.

It is of interest to examine the relationship between the rate and intensity of infection and the age of infected voles. While it was not possible to determine exactly the ages of trapped animals, guidelines for estimating relative ages of voles based on weight have been proposed by Krebs et al (1969). If the rates of infection and ranges of worm burdens for each of these age groups are determined (Table 1), it can be seen that the animals in the subadult and adult classes not only have higher rates of infection, but also carry heavier worm burdens than the juvenile animals. The presence of large worm burdens only in older animals suggests that reinfection might occur throughout the course of the animal's life. Kagan (1952) demonstrated with experimental infections of *S. douthitti* in laboratory mice that, although a partial resistance to reinfection occurs, a proportion of challenge cercariae establish as adult worms in the mesenteric veins. Continuous exposure to cercariae in the natural situation might then result in increasing worm burdens as the host ages.

However, these survey results may also represent the outcome of seasonal variation in cercarial output by snails, and consequently variation in the degree to which animals may be exposed to the parasite. Observations of Bourns (1961) and Blankenspoor

(1977, personal communication), that shedding of cercariae reaches a peak in late summer, when these voles were collected, militate against this hypothesis. Further observations of the distribution of infection over the course of the year will be necessary to appreciate more fully the pattern of infection.

The role of other infected rodents in the transmission of the parasite is unknown. Natural infections of *S. douthitti* in both *Z. hudsonius* and *P. leucopus* have not been described previously in the literature. The number of animals examined, however, was insufficient to determine accurately the prevalence of infection.

It is hoped that further examination of natural infections of *S. douthitti* in its rodent hosts will provide some insights into the dynamics of the host-schistosome relationship, which may ultimately be valuable in the interpretation of epidemiologic characteristics of infections of man and domestic animals.

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ARTICLE

PATHOLOGIC CHARACTERISTICS OF INFECTION WITH SCHISTOSOMATIUM DOUTHITTI (FAM: SCHISTOSOMATIDAE) IN THE LABORATORY MOUSE AND THE MEADOW VOLE, MICROTUS PENNSYLVANICUS

Pathologic Characteristics of Infection with *Schistosomatium douthitti* (Fam: Schistosomatidae) in the Laboratory Mouse and the Meadow Vole, *Microtus pennsylvanicus*

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ABSTRACT

Laboratory mice and meadow voles (*Microtus pennsylvanicus*) were infected with *Schistosomatium douthitti*, a natural rodent schistosome. Mice developed marked and often fatal clinical schistosomiasis at levels of infection which produced no signs of disease in voles. Examination of tissues of infected animals showed that despite wide individual variation, each host species developed a characteristic granulomatous response to the schistosome ova. Naturally infected meadow voles also showed no sign of clinical schistosomiasis even when maintaining a worm burden of several hundred adult *S. douthitti*. Histologic response of these wild voles to the parasite ova resembled that of the experimentally infected *M. pennsylvanicus*.

INTRODUCTION

The proposal that chronic schistosomiasis is an immunopathological phenomenon (Warren et al, 1967) has led many investigators to examine the histological course of events in the development of the schistosome egg granuloma. Results derived from experimental infection of laboratory rodents with *S. mansoni* have provided the greater part of the current knowledge of the cellular reaction to the parasite ova. However, rodent host species differ markedly in their responses to *S. mansoni* ova (Cheever, 1965b) and unqualified extrapolation of conclusions drawn from studies in rodents to the human may be misleading.

Consequently, experimentation with natural host-schistosome systems may prove to be extremely valuable in the understanding of disease processes and the pathogenesis of schistosomiasis. *Schistosomatium douthitti* is one of a small number of these natural schistosome systems which lends itself to laboratory investigation. A North American fluke, *S. douthitti* is found primarily in the meadow vole, *M. pennsylvanicus* and the muskrat, *Ondatra zibethica* (Kagan et al, 1954). The value of this parasite as a model for the study of schistosomiasis was recognized by Kagan and Meranze some two decades ago (1957, 1958). They followed the course of infection in experimentally infected mice and observed some similarities in the histopathologic reactions in mice infected with *S. mansoni*. Also like *S. mansoni* (Warren, 1972), *S. douthitti* in large numbers is highly pathogenic in mice.

The syndrome of clinical schistosomiasis in mice infected with *S. douthitti* is in sharp contrast to that seen in the vole.

Naturally infected meadow voles have been found carrying worm burdens many times greater than those which would prove fatal to mice (Zajac and Williams, 1978). This striking difference in the pathogenicity of the parasite in two rodent hosts is comparable to a situation seen with several mammalian schistosomes of domesticated ruminants. *S. mattheei*, for example, a common parasite of sheep and cattle in southern Africa, has been noted by several authors (Strydom, 1963; McCully and Kruger, 1969; Lawrence, 1974) to produce clinical schistosomiasis more frequently in sheep than cattle. The clinically important nasal granulomas formed in response to the presence of *S. nasale* in Indian cattle do not develop in similar infections of buffalo (Dutt and Srivastava, 1968).

S. douthitti infections in mice and voles provide a convenient and easily manipulated schistosome system in which to explore the comparative pathogenesis of schistosomiasis in two closely related host species. Furthermore, the identification of those factors determining the development of disease may be highly relevant to a clearer understanding of disease processes in human infections. In view of these consideratons, a study was undertaken to compare the cellular reaction to infections of *S. douthitti* in mice and voles. Both similarities and differences were observed and their possible significance is discussed.

MATERIALS AND METHODS

Histopathological examinations were carried out on tissues from mice and voles experimentally infected with *S. douthitti* and from wild voles naturally infected with the parasite. Six week old female mice (Spartan Research, Haslett, Michigan)and both male and female juvenile and adult meadow voles from a locally derived laboratory strain were infected with cercariae of *S. douthitti*. The parasite was maintained in the laboratory in infected *Lymnea catascopium* and was derived from the University of Michigan (Ann Arbor) strain originally established from locally infected snails.

Cercariae were administered via an intraperitoneal inoculation and adult worm burdens were determined by perfusion of the mesenteric and portal venous systems. The perfusate was filtered through a 5 micron pore size Nuclepore^{R} filter (Nuclepore Corporation, Pleasanton, California) which retained any schistosomes present. Worms were then counted on the filter under the light microscope. Animals whose tissues were examined contained on postmortem examination, worm burdens ranging from 2 to 29 *S. douthitti*.

A minimum of 3 animals of each species was sacrificed on Days 15, 30, 45, 60 and 90 after infection (DAI). The clinical condition of infected animals was observed and a gross pathologic examination made of the internal organs after death. The liver, spleen, small intestine, cecum, lungs, mesenteric lumph node and kidneys were removed and placed in 10% buffered formalin. Control tissues were similarly removed from uninfected animals. Tissues were routinely sectioned and stained with hematoxylin and eosin and

with Giemsa stain. Determination of maturity of the schistosome embryo within the egg in tissue sections was based on the classification of von Lichtenberg et al (1973).

In addition, tissues of wild *M. pennsylvanicus* naturally infected with *S. douthitti* were examined. Voles were live trapped as described previously (Zajac and Williams, 1978) and returned to the laboratory where they were sacrificed and the portal and mesenteric systems perfused. Tissues were preserved, sectioned and stained in the same manner as for experimentally infected animals.

RESULTS

Clinical Schistosomiasis and Gross Pathologic Changes

Voles experimentally infected with *S. douthitti* did not show clinical signs at any stage of infection. No weight loss or behavioural changes were observed. Hair coat and consistency of feces remained normal. All internal organs appeared normal on postmortem examination. Occasionally, pinpoint white spots were seen on the surface of the liver, but no alteration was seen in its color or consistency. Wild voles naturally infected with *S. douthitti* were all apparently healthy at the time of capture. Hair coat, behaviour and fecal pellets appeared normal. There were no internal changes directly attributable to schistosome infection with the exception of one animal which had raised areas, about 1 mm in diameter, along the mesenteric border of the serosal surface of the cecum and small intestine.

Mice with adult worm burdens exceeding approximately 15 *S. douthitti* first developed signs of clinical schistosomiasis

about 6 weeks following infection. Progressive unthriftiness with staring and unkempt hair coat, weakness and emaciation were observed, accompanied by mild hemorrhagic diarrhea. Examination of the internal organs revealed greatly enlarged mesenteric lymph nodes and spleens. The liver usually contained pinpoint white spots on its surface and blood was observed in the lumen of the cecum.

Mice maintaining a mild chronic infection only infrequently showed pronounced unthriftiness. In some cases, fecal pellets were hard and dry and contained visible traces of blood. The spleen and mesenteric lymph nodes were enlarged. The liver also appeared enlarged and was darker in color than normal with numerous white spots on its surface. The cecum occasionally contained some blood. Along the length of the intestine were small raised areas, about 1 mm in diameter, which, when examined with a dissecting microscope, proved to be aggregates of schistosome eggs surrounded by connective tissue.

Histopathologic Observations

Voles

Although the changes associated with infection with *S. douthitti* and *M. pennsylvanicus* were uniform enough to permit some descriptive generalizations, great variation in the appearance of lesions was detected throughout the period of observation both within and amongst individuals. However, the relative frequency of each type of reaction in the overall response of the vole varied at different periods during infection.

Fifteen DAI changes associated with infection were visible only in the liver. A periportal infiltrate consisting primarily of mononuclear cells and eosinophils was observed in some portal areas (Fig. 1). The most striking change was the presence of schistosome derived pigment in hepatic phagocytic cells. In some cases these cells were multinucleated and contained up to 25 nuclei.

Thirty DAI schistosome ova measuring 65-75 μ in length were visible in the liver and intestinal tissue. In both organs ova were primarily surrounded by an unstructured mixture of eosinophils, and mononuclear cells with some macrophages and lymphocytes (Fig. 2). The degree to which each cell type occurred in these reactions varied remarkably from egg to egg, although the eosinophil appeared to play a consistently important role and in some cases was the only cell type observed around an ovum. These eosinophilic reactions at times covered an area up to 20 times greater than that of the egg (Fig. 3). Giant cells also participated in these reactions and could frequently be seen directly apposed to the egg. In the intestine another type of granulomatous response was observed in which the giant cell was the primary component. Ova, either singly or in clumps ranging from 2 to 20 eggs were circumscribed by giant cells. In egg clumps, the giant cells around the eggs formed a continuous matrix (Fig. 4). On the periphery of the giant cell reaction highly variable numbers of eosinophils and lymphocytes were present. The intestinal mucosa appeared normal and there was no indication of hemorrhage into the intestinal lumen.

Schistosome ova were present in all stages of development from those containing an undifferentiated mass of cells to those

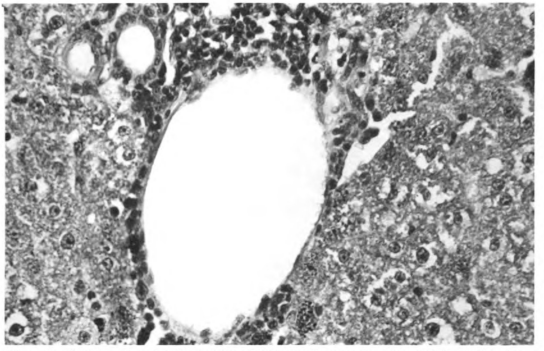

Fig. 1 Vole. Typical mononuclear cell periportal infiltrate in the liver. x 433.

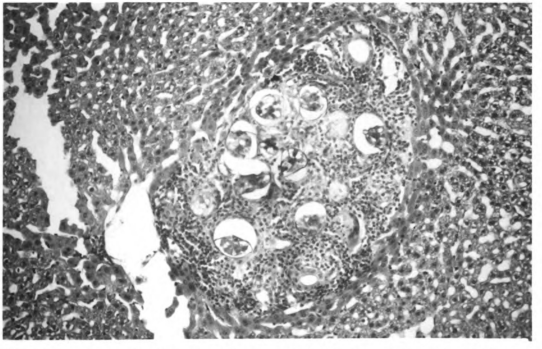

Fig. 2. Vole. Diffuse inflammatory reaction surrounding ova in the liver. x 200.

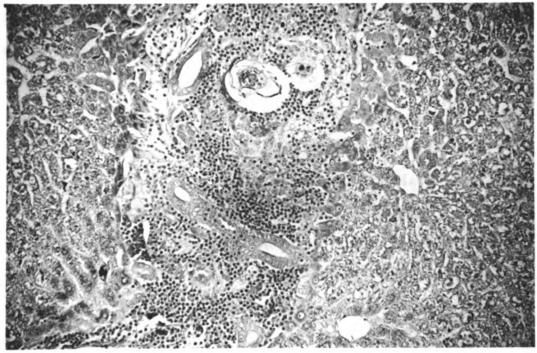

Fig. 3. Vole. Intense eosinophil response surrounding ova in the liver. x 176.

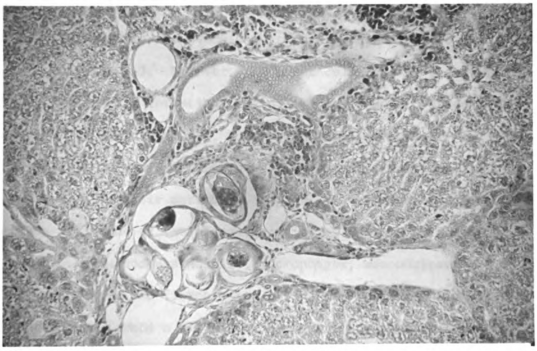

Fig. 4. Vole. Hepatic giant cell granuloma. x 186.

with well developed embryos. The type and composition of the reaction associated with the egg could not be correlated with the reaction to the parasite ova and was generally highly localized around eggs. In the intestine all eggs and accompanying reactions were limited to the lamina propria. No generalized cellular infiltration was apparent in the intestine. In the liver, distribution of the ova did not seem to follow a consistent pattern. Periportal cellular infiltrates were of the same magnitude and composition as those observed at 15 DAI but with the added appearance of occasional plasma cells. Small areas, containing about several dozen eosinophils apparently unrelated to ova were seen in the liver parenchyma in some cases. Mast cells were seen both within and on the periphery of some granulomas and the number of mast cells in the portal areas had increased.

Little change in the overall pattern of response at 30 DAI was detectable 45 DAI. However, the giant cell type of granuloma was more frequent in intestinal tissue and had begun to appear in the liver. In many instances, these granulomas were highly organized with only small numbers of plasma cells, eosinophils or lymphocytes on their periphery (Fig. 5). Other, more diffuse reactions with some of the characteristics of classic epithelioid granulomas, contained eosinophils, macrophages, mononuclear cells, lymphocytes and fibroblasts. Frequently, eosinophils and lymphocytes formed a halo around a central cellular mass of macrophages and giant cells surrounding the egg. Plasma cells seemed to have increased in both liver and intestine. The periportal infiltrates contained more plasma cells and as previously

noted, plasma cells were often encountered on the periphery of the giant cell granulomas. Pigment continued to be present in hepatic phagocytic cells. In most reactions to ova an accumulation of pigment was visible.

The frequency of the giant cell granuloma increased at 60 and 90 DAI. By the end of this period of observation this type of reaction was the most typical encountered in the intestine and was also present in the liver along with the eosinophilic reactions and more diffuse epithelioid granulomas. Some of these hepatic reactions were highly complex, including within a single response confluent areas of macrophages, giant cell, eosinophils and plasma cells (Fig. 7, Fig. 8). In the intestine eggs continued to be seen only in the lamina propria. Mature ova could be found in both liver and intestine, where they were sometimes encountered close to the epithelium (Fig. 6).

Although some fibroblasts were observed in the egg granulomas, collagen deposition was not marked. Periportal fibrosis was not a feature of the response in the vole. Nor did extensive connective tissue replace dead eggs. While the eosinophil continued to participate in many reactions, plasma cells had become increasingly more numerous. In one animal, by 90 DAI plasma cells outnumbered all other cells in the periportal infiltrate. Plasma cells were found closely associated with giant cell granulomas. Calcification of ova and central necrosis with granulomas were seen extremely rarely. Sixty DAI schistosome pigment was readily recognizable in the spleen, but neither ova or pigment were seen in other organs examined, nor were changes resulting from infection seen

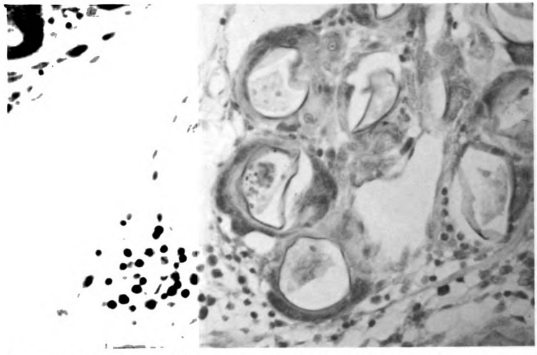

Fig. 5. Vole. Typical intestinal giant cell granuloma. Darkly staining plasma cells are present on the periphery. x 440.

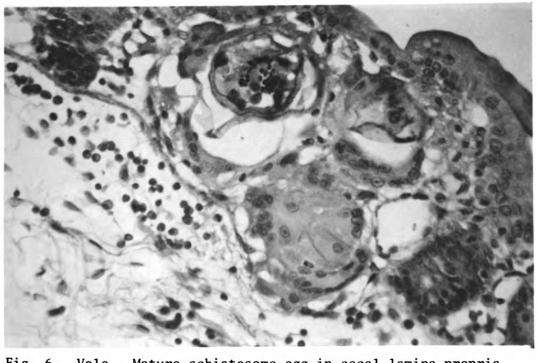

Fig. 6. Vole. Mature schistosome egg in cecal lamina propria partially associated with giant cell reaction. x 338.

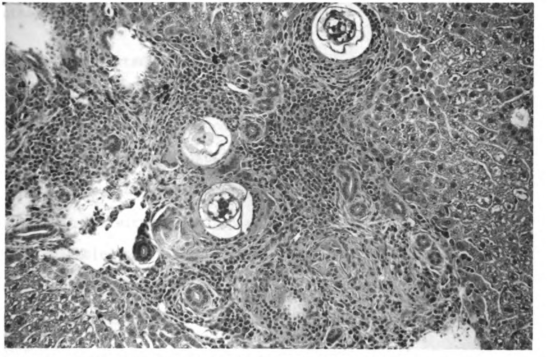

Fig. 7. Vole. Complex hepatic reaction to schistosome ova. x 160.

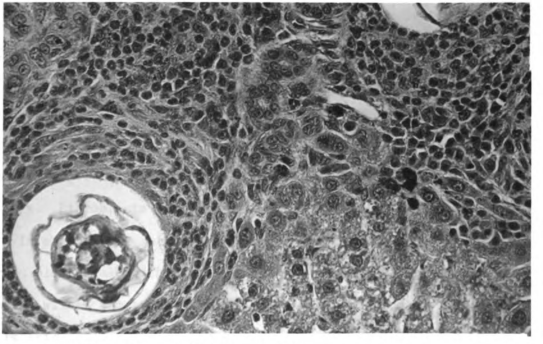

Fig. 8. Vole. Fig. 9 detail. x 433.

in other organs.

Naturally Infected Voles

The tissues of 14 wild *M. pennsylvanicus* naturally infected with *S. douthitti* were examined. These animals carried worm burdens ranging between 8 and 236 parasites. Although it was not possible to determine how long fluke infections had been established, the microscopic appearance of their tissues most closely resembled that of laboratory voles infected for 60 and 90 days. Reaction to the ova of the parasite was generally not very marked. Often ova in both the liver and intestine were surrounded only by a giant cell with a few eosinophils or plasma cells at the periphery (Fig. 11). Plasma cells were prominent both in periportal areas and surrounding the giant cell granulomas.

The overall response of some animals was more extensive than those containing only giant cell granulomas. Ova in these voles were surrounded by epithelioid granulomas or by an unstructured accumulation of eosinophils or eosinophils and mononuclear cells. However, the giant cell granuloma was the most common response seen. Extensive fibrosis was not visible in naturally infected animals. Fibroblasts were not evident in giant cell granulomas.

In one heavily infected vole (228 parasites) clumps of eggs formed plaques along the length of the intestine. The ova were usually within a matrix of giant cells often bordered by plasma cells (Fig. 9). Ova were present at all stages of development. In the small intestine mature eggs were observed in the lamina propria of the villi unassociated with any reaction (Fig. 10).

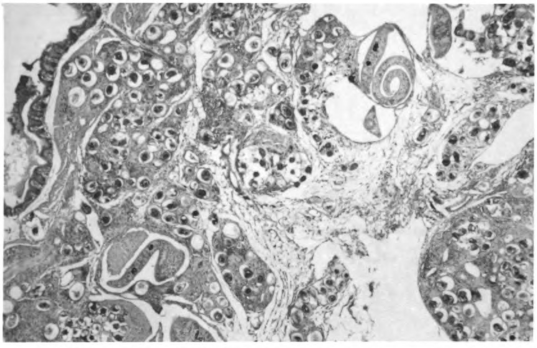

Fig. 9. Wild vole. Adult schistosomes and ova in cecum of a heavily infected animal. x 40.

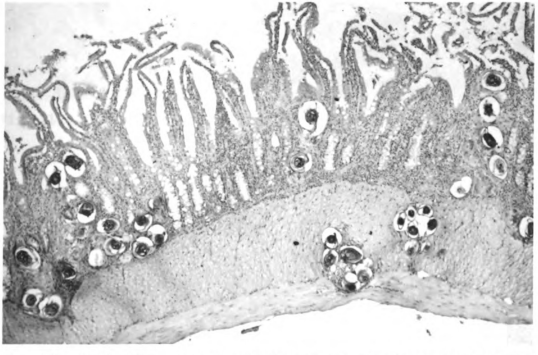

Fig. 10. Wild vole. Mature schistosome ova in the small intestine unaccompanied by host response. x 64.

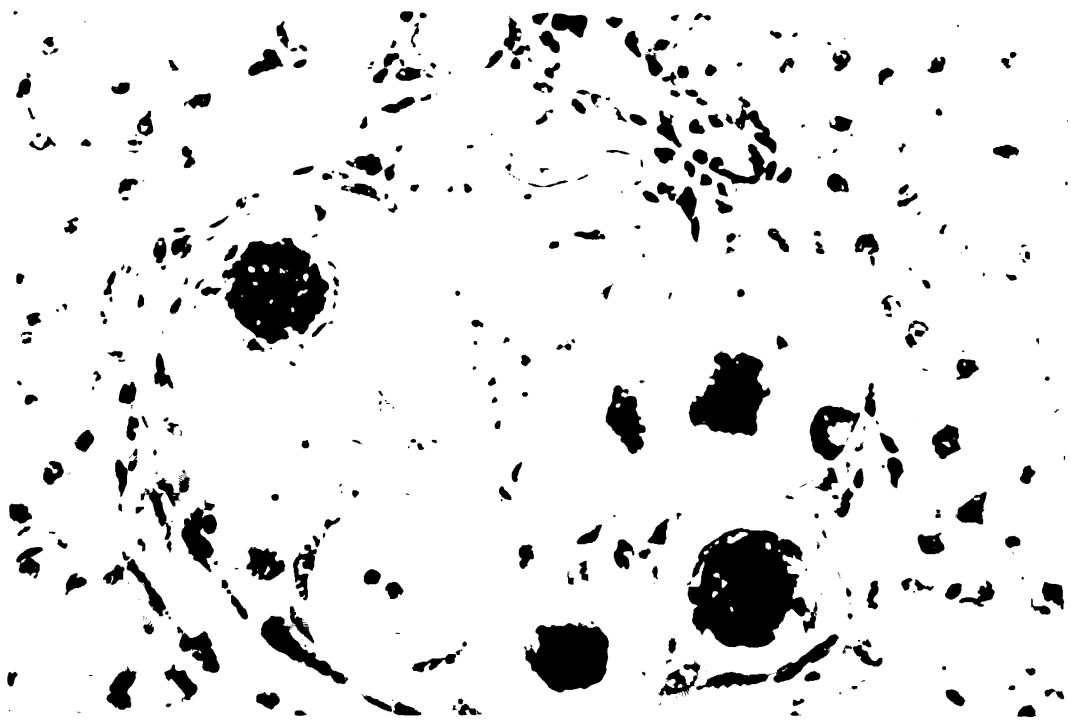

Fig. 11. Wild vole. Typical giant cell granuloma in the liver. x 360.

Few ova were visible in the liver, but there the reaction was very highly circumscribed and of the giant cell type and plasma cells were prominent. Adult schistosomes were also present in the blood vessels of the intestine, where they appeared to elicit no reaction in the wall of the parasitized vein.

Mice

In mice, as in voles, the cellular composition of the reaction to schistosome ova was variable and could not be correlated with the stage of maturity of the ova. Also, as has been observed with *M. pennsylvanicus* eggs at all stages of development could be found unassociated with significant tissue reaction (Fig. 13, Fig. 18).

Mice infected for 15 days had no schistosome lesions in their tissues. No adult schistosome pigment was present in the liver, however, a cellular infiltrate was observed in some portal areas composed of mononuclear cells, eosinophils and some lymphocytes and neutrophils (Fig. 12).

Thirty DAI schistosome pigment was visible in hepatic phagocytic cells. Ova in both the liver and intestine were generally surrounded by an unstructured collection of eosinophils, macrophages, mononuclear cells and lymphocytes similar to those seen in voles (Fig. 15). In some instances, an extensive eosinophilic response was observed. In the intestinal tissue ova were observed not only in the lamina propria, but also in the submucosal muscle and connective tissue. Submucosal muscle showed an increased number of mast cells in areas near ova and their accompanying reactions.

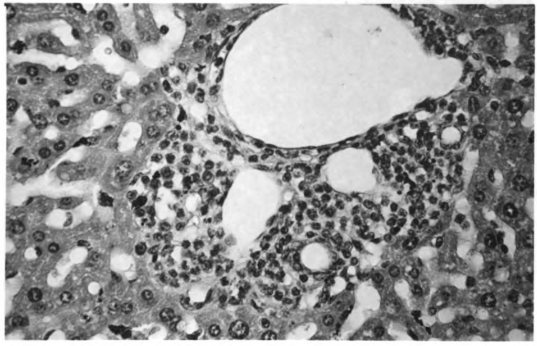

Fig. 12. Mouse. Mononuclear cell periportal infiltrate in the liver. x 421.

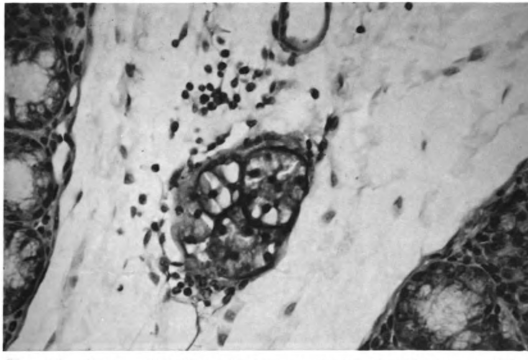

Fig. 13. Mouse. Undifferentiated ova in the intestine. x 400.

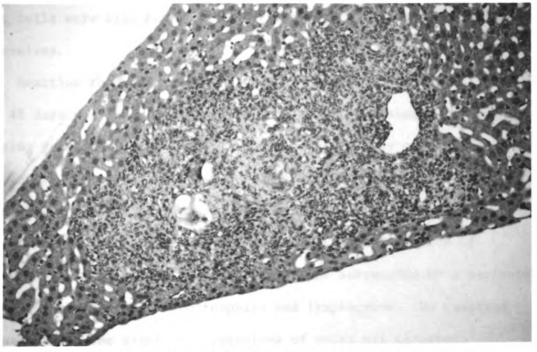

Fig. 14. Mouse. Extensive inflammatory reaction in the liver. Eosinophils are prominent. x 200.

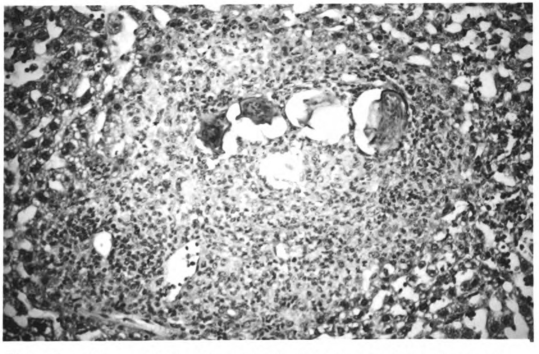

Fig. 15. Mouse. Unstructured host response to ova. Numerous cell types are present. x 205.

Mast cells were also seen with some frequency within the granulomas themselves.

Reaction to parasite ova in tissue from animals infected for 45 days was largely similar to that of 30 day animals. Developing granulomatous responses to eggs were in many cases diffuse and covered an extensive area in relation to the size of the ovum (Fig. 14), while other ova were enclosed in more organized epitheliod granulomas (Fig. 16). Typically, a central area of macrophages, fibroblasts and giant cells was surrounded by a periperal border of eosinophils or eosinophils and lymphocytes. No reaction comparable to the giant cell granuloma of voles was observed.

In the intestine ova were seen in all layers, where they frequently elicited an active reaction (Fig. 19). Only infrequently, however, were calcification of eggs and central necrosis of the granulomas observed. The intestinal muscoa appeared intact and there was little evidence of hemorrhage into the intestinal lumen.

By 60 and 90 days post infection massive involvement of the intestinal tract was present in some individuals (Fig. 20, Fig. 21). Extensive inflammatory reactions similar in character to those described at earlier stages involved all parts of the intestinal tissue. In the liver, fibrosis was observed in the periportal areas and within established granulomas (Fig. 17). Plasma cells appeared more frequently in the hepatic portal infiltrates, as they did in the intestine, but were not a prominent part of the reaction in either location. As in the voles, schistosome pigment was visible in the spleen at 60 DAI, but further involvement of other

organs was not visible.

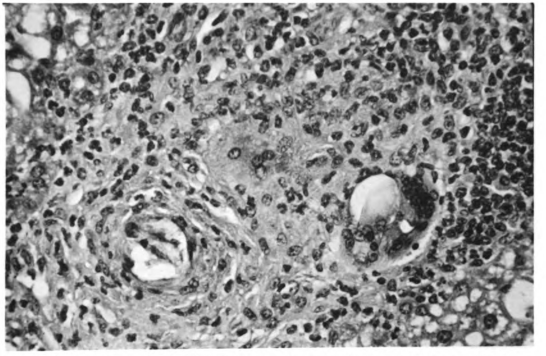

Fig. 16. Mouse. Epithelioid granuloma with lymphocytes and eosinophils present on the periphery. x 400.

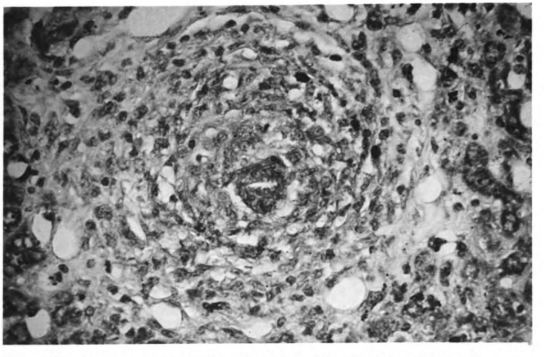

Fig. 17. Mouse. Granuloma showing prominent deposition of connective tissue. x 400.

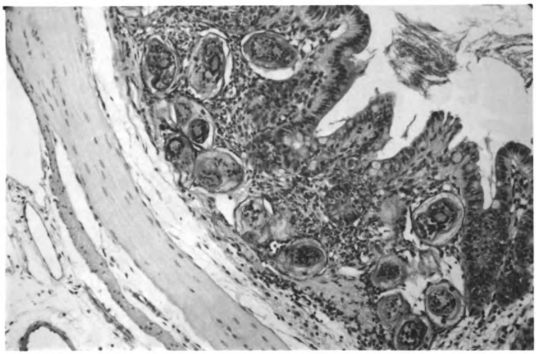

Fig. 18. Mouse. Mature ova in the lamina propria of the small intestine. x 200.

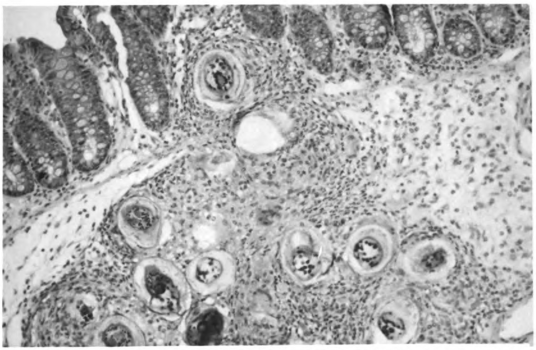

Fig. 19. Mouse. Intestinal granuloma containing mature ova. x 150.

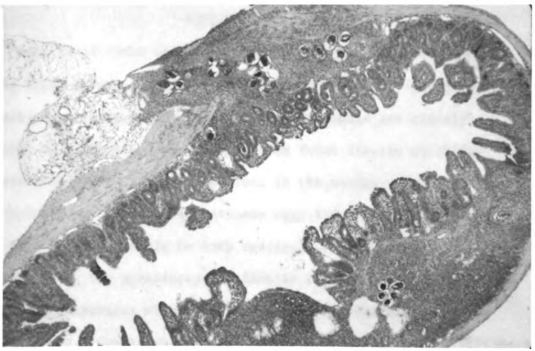

Fig. 20. Mouse. Schistosome ova and extensive host reaction in the small intestine. x 45.

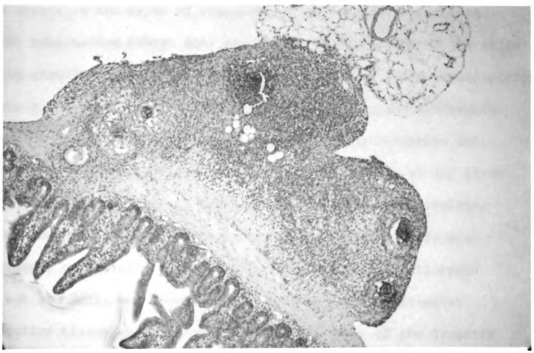

Fig. 21. Diffuse host reaction in the submucosal tissue of the small intestine. x 64.

DISCUSSION

Results of these studies permit several general conclusions to be drawn about the clinicopathologic course of *S. douthitti* infections. Experimental infections in the mouse are clearly capable of producing a severe and often fatal disease which has no parallel in equivalent infections in the meadow vole, *M. pennsylvanicus*, although schistosome eggs and associated lesions are readily demonstrable in both species. Wild voles naturally infected with the parasite are evidently capable of maintaining massive worm burdens with no appearance of ill health or loss of condition. Comparison of the histologic reaction to schistosome ova shows that marked variation occurs between individuals of each host species. Within the tissue of individual animals variation also occurs in the types of reactions which develop, but maturity of the schistosome embryo does not appear to be related to the stage of the granuloma associated with it. The types of cells participating in mouse and vole reactions are generally similar, and differences between the two hosts are manifested primarily as variation in the degree to which particular cell types are present at any given time. In the vole fibrosis does not seem to be a characteristic of the reaction, whereas both giant cells and plasma cells are prominent; on the other hand, in the mouse these two cell types are not abundant, but fibroblastic activity and deposition of connective tissue is extensive. However, in view of the dramatic difference in the degree of clinical disease seen in the two hosts, the nature of the responses to ova were not as dissimilar as might be expected. Mice and voles both showed an absence of response

to adult worms, so that like *S. mansoni* (Smith and von Lichtenberg, 1974), *S. douthitti* adults appear to stimulate little host reaction. A generalized vasculitis comparable to that seen in the vessels of cattle infected with *S. bovis* (Hussein, 1971) and *S. mattheei* (Lawrence, 1978b) is certainly not a feature of this infection.

The sequence of events observed in mice confirms the results described by Kagan and Meranze (1957, 1958) who demonstrated that the development of schistosome lesions in laboratory mice experimentally infected with *S. douthitti* shares a number of characteristics with the response described by other authors for murine *S. mansoni* infection. However, it is clear that while basic similarities occur in the host response in mice and voles, differences between the two species are present and future research will attempt to identify the underlying reasons for these differences. Nonimmunological factors probably contribute to the observed variation, but it also seems likely that species variation in the manifestation of delayed type hypersensitivity to schistosome ova could play a large part in influencing the pathogenicity of the infection in the two rodent species.

Several factors increase the difficulty of quantifying the differences between the response of the two hosts. For example, accurate description and detailed sequencing of events leading to the development of the mature granuloma is hampered by the wide variation existing between and even within individuals at any given time after infection. Likewise, the continuous arrival of ova in the tissue makes it impossible for the observer to relate the type of reaction with the length of time an egg has been

present in a particular organ. Von Lichtenberg et al (1973) and Hsü et al (1972) attempted to correlate the stage of development of the schistosome embryo with the maturity of the granuloma, but the former workers concluded that both inflammatory and granulomatous reactions could be seen surrounding eggs at all stages of development.

In both species the eosinophil was one of the most striking constituents of the response to the parasite throughout infection. Its prominence, both in the peripheral blood and in granuloma formation has been recorded by several authors (Cheever, 1965b; Hussein and Tartour, 1973; Mahmoud et al, 1975; Bartsch and Ward, 1976; Lawrence 1978a). In view of these observations it is surprising that Kagan and Meranze (1957, 1958) did not identify the eosinophil to be an important component of response to *S. douthitti*. The function of this cell in the host response to schistosome ova has not yet been elucidated. James and Colley (1976) have postulated that the eosinophil plays an important part in the destruction of the egg, but their observations have been based on experiments performed in an *in vitro* system. Currently, there is no evidence to suggest that similar events occur *in vivo*. The participation of the eosinophil in the modulation of inflammation has recently been described (Leid and Williams, 1978) and its function in this capacity should be investigated particularly in light of the presence of mast cells in the schistosome granulomas.

The prominent giant cells and plasma cells and the absence of fibrosis in the response of the vole to ova of *S. douthitti*

may all be factors in influencing the clinical course of infection. The compact giant cell granuloma seen in voles may more effectively contain the metabolic antigens of the schistosome embryo which could otherwise stimulate a more extensive inflammatory reaction. Giant cell granulomas intrude less on normal tissue than the more diffuse epithelioid granuloma seen in mice. This consideration is likely to be particularly important in view of the finding of Cheever (1965a) who demonstrated a direct relationship between granuloma size and the development of increased portal pressure. The extensive fibrotic response seen in chronically infected mice prolongs the period of tissue damage and extends its area, and this too probably contributes to an increase in portal pressure. Plasma cell activity has been suggested as another means of modulating the intensity of the reaction to ova (Warren, 1976), by the production of blocking antibodies which may enhance the capture and sequestration of egg antigens, thereby preventing the stimulation of a more elaborate and destructive inflammatory reaction. The prominence of plasma cells in the reaction of the vole may therefore also form a part of the mechanism whereby extensive tissue damage is avoided in this species.

Some indication of the importance of these differences between mice and voles is provided by the observations on wild vole tissue. Wild *M. pennsylvanicus*, at times carrying massive worm burdens, were found to be apparently healthy. The tissue reaction to schistosome ova in these infected animals was dominated by the giant cell granulomas. In the light of the intensity with which voles are preyed upon by most predators in the area (Burt, 1975), any

reduction in the fitness of infected animals would be expected to result in their almost immediate elimination from the population. It seems reasonable to suppose therefore that infection and the associated tissue reaction did not affect the performance of the voles adversely.

It is important to recognize, however, that while the form of the granuloma and plasma cell activity may contribute to the inhibition of chronic disease in voles, these factors do not necessarily account for the remarkable absence of clinical disease early in infection when mice suffer a high rate of mortality. At this stage, about six weeks following exposure to cercariae, there was little difference in the appearance of the tissue reaction to ova in the two host species. It seems likely that additional factors, as yet unidentified, also contribute to the differential mortality seen in the two hosts. One possible mechanism has been suggested by Lawrence (1973) in work with *S. mattheei*. He found that cattle are able to inhibit egg production of *S. mattheei* adults shortly after patency is reached, thereby directly eliminating the stimulus leading to clinical schistosomiasis. Sheep, which are far more susceptible to the disease, do not show a similar decrease in egg production (Lawrence, 1974). Whether comparable differences occur in mice and voles infected with *S. douthitti* is not known, but the importance of the quantity of eggs produced by the parasite should be pursued in future studies.

The most thoroughly studied mechanism of affecting the severity of disease in schistosomiasis is the modulation of granuloma formation developing over the course of infection, first described

by Andrade and Warren (1964). The mechanism of this modulation has not been conclusively established, but both suppressor T cells and the activity of blocking antibodies have been implicated so far (Lewis and Colley, 1976; Warren, 1976). No evidence of modulation of response in mice was visible in this study, but more extensive experimentation may demonstrate its presence in *S. douthitti* infections of mice.

It is currently impossible to select one factor which is responsible for the absence of disease in voles infected with *S. douthitti*. A more realistic assessment may be that several factors, each of which would be ineffective alone, contribute to the reduction in pathogenicity of the parasite. Some of these factors may be characteristic of the vole's response to a wide range of pathogens. Although little information is available on histopathologic responses of the vole, Robb-Smith (1946) has reported that fibrosis is limited in the reaction of the European meadow vole, *Microtus agrestis*, to *Mycobacterium* infection. While giant cells and plasma cells were present in the response to the bacteria, they were not abundant, and the prominence of these cells in *S. douthitti* infections of the vole may reflect more specific immunologically mediated adaptations to the parasite. In any event, the pecularities of the nature of the vole reactivity justify further interest in this system. Understanding the components of the response of the vole may, in the future, provide important and useful insights into potential means of attenuation of immunologic disease in man.

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