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REVIEW

Murine schistosomiasis as a model for human schistosomiasis mansoni: similarities and discrepancies

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Abstract Human schistosomiasis has been studied extensively since its discovery by Theodore Bilharz in 1851. Because of its medical importance as a chronic debilitating disease in the tropics and subtropics, continuing research efforts are still going on. The use of animal models still represents a major cornerstone in this field, with murine hosts, especially mice, as the most preferable experimental units. Murine schistosomiasis has been employed as a model for studying various aspects of human schistosomiasis, including biology, pathogenesis, immunology, chemotherapy screening, and vaccine development. However, there may be differences between murine and human schistosomiasis. The present article tries to explore some of these aspects that may help researchers in the field of schistosomiasis.

Justification for murine modeling

Despite the calls of those engaged in animal rights against the use of laboratory animals in experimentation, there are many justifications raised by others as to alleviate human suffering. Experimental animals, particularly murine, have been used extensively in many aspects of schistosomiasis research. Is that an acceptable philosophy or not is still a matter of debate. In case of schistosomiasis, the complex nature of schistosomes and their complicated interaction with the mammalian host necessitates the use of live animal models in various aspects of schistosomiasis research (Farah et al. 2001). Schistosome infections in experimental animals, including murine hosts, are less complex, or at least more readily studied, than infections in humans (Cheever et al. 1994a). Experimental schistosomiasis of laboratory animals has frequently been used to model the anatomopathologic and pathophysiologic features of the infection in humans as well as for the study of immunity and chemotherapeutic efficacy (Cheever et al. 2002). However, there are also differences in many aspects between schistosomiasis in murine hosts and humans. Generally, human males develop more severe parasitic infections with larger parasite burdens than female do (Goble and Konopka 1973), whereas the opposite phenomenon occurs in experimental schistosomiasis mansoni (Eloi-Santos et al. 1992). The latter authors reported that fewer adult worms develop in male than in female mice initially infected with the same number of cercariae (Eloi-Santos et al. 1992). One important justification for the use of experimental modeling of schistosomiasis for many aspects, particularly for vaccine development, is the ethical issue. It is unethical and impractical to expose humans to infection after immunizing them with a vaccine still under experimentation.

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Biological aspects

Murine infections differ from the human, monkey, and baboon infections in many ways, especially in the number of adult worms per unit of body weight and the distribution

of ova between the liver and mesenteric circulation (Stavitsky 2004). However, all of these species develop hepatic granulomatous inflammations that have similar dynamics and cellular compositions and are spontaneously down-modulated (Stavitsky 2004). It is noteworthy that there is no evidence that schistosomes evolved in primate hosts. However, a phylogeny based on DNA sequences showed that they have evolved in host phyla, rodents, and ungulates (Mehlhorn 2008). These studies led to the conclusion that the human parasite *Schistosoma mansoni*, the agent of intestinal schistosomiasis, is close to a rodent parasite, whereas the human parasite *Schistosoma haematobium*, the agent of urinary schistosomiasis, is related to ungulate parasites (Mehlhorn 2008).

Permissive versus nonpermissive hosts

Numerous animals have been used as models for studying various aspects of schistosomiasis covering a wide range of disciplines from biology to chemotherapy. Differences in the biological preferences and final habitat in the definitive host may account for differences in the suitability of the experimental animal models for different schistosomes. Permissive hosts are those animal hosts in which schistosome parasites can reach maturity (Cioli et al. 1977; Farah et al. 2001). Differences in susceptibility to infection with *S. mansoni* vary between different species and even between strains within the species, with the physiologic and reproductive status of the worm strongly influenced by the host (Cioli et al 1977). Cioli et al. (1977) studied the survival, growth, and egg laying capacity of *S. mansoni* worms surgically transplanted from mice into rats or from rats into hamsters. They found that in the rat, worms were stunted, localized in the liver, and laying nonfertile eggs in small numbers. When transferred to the hamster, they increased in size approaching normal hamster-grown worms within 3 weeks following transplantation, were localized in the mesenteric veins, and produced large numbers of eggs (Cioli et al. 1977). Conversely, when adult mouse worms were injected into rats, they regressed in size, remained in the liver, and produced small numbers of incompletely developed eggs. Furthermore, in the nonpermissive host (the rat), the suppression of growth and egg laying was not permanent, since on transfer into a permissive environment (the hamster), stunted worms can resume growth and oviposition (Cioli et al. 1977). Generally speaking, mice and hamsters are among the most susceptible host species while rats are known to be rather resistant hosts for schistosomes (Warren and Peters 1967). The laboratory rat (*Rattus norvegicus*) is considered a semipermissive host in that the majority of worms are removed before reaching maturity in the portal tract in a self-cure around day 28. Although the schistosome larvae are faster in this host than in the mouse, only 25% to 30% reach the liver, and IgE has been directly implicated in this phenomenon (Dunne and Mountford 2001; Capron and Capron 1994). On the other hand, the black rat (*Rattus rattus*), which is a natural host for *S. mansoni*, is considered a fully permissive host (Dunne and Mountford 2001).

Maturation and fecundity of *S. mansoni* in mice

S. mansoni matures over a 5-week period in mice (Cheever et al. 2002). One of the constraints that preclude long-term studies in mice is that the average lifespan of schistosomes is substantially longer than that of a mouse (Farah et al. 2005). Fewer worms develop in male rodent hosts than in females when exposed to the same number of cercariae (Nakazawa et al. 1997). Fulford et al. (1998) attributed the resistance of male mice to schistosomiasis to the increased dehydroepiandrosterone (DHEA) levels. Male mice deprived of their major source of testosterone by castration exhibit infection level and survival characteristics of female mice. In addition, female mice treated with exogenous testosterone display the worm burden, organomegaly, and survival attributes of intact male mice. When mice were challenged with 60 cercariae each, the number of worms acquired was found to be significantly inversely correlated with the serum DHEA concentration (Fulford et al. 1998). Generally, it was found that only about 20% to 50% of invading cercariae reach maturity in the hepatic portal system of mice, and oviposition begins from day 42 onwards, whereas the majority of nonmaturing larvae are trapped and die in the lungs (Smithers and Doenhoff 1982). Quantitatively, in humans and mice, roughly comparable numbers of eggs per worm pair are deposited in the tissues; however, the density of eggs per gram of tissue is much higher in mice infected with a single worm pair than it is in the most heavily infected human subjects (Cheever 1969). In fact, this finding reflects it in the outcomes of experimental murine schistosomiasis when it is used to model human schistosomiasis in many aspects including the study of immunopathology, evaluation of drug efficacy, etc... Therefore, the results obtained in murine hosts may not translate accurately to the case of human. Cheever (1969) reported that the intensity of infection in experimental animals is frequently greater than 50 worm pairs per kilogram body weight, and in mice, it can never be substantially lower than this. However, in man, worm burdens greater than five worm pairs per kilogram body weight have seldom been reported.

Whether the maturity and fecundity of female schistosomes are immune dependent could be explored by reviewing the following studies: Harrison and Doenhoff (1983) reported the reduced fecundity of *S. mansoni* in mice treated with cyclophosphamide and betamethasone immune-depressant drugs at the time of infection as well as

in T-cell-deprived mice by adult thymectomy and injection of antithymocyte serum a month before infection. Worm counts were not affected by chemotherapeutic immunosuppression, but injection of mice with antithymocyte serum at the time of infection marginally increased the size of the mature worms (Harrison and Doenhoff 1983). On the other hand, treatment of mice with hydrocortisone acetate around the time of infection reduced the mature worm burden and the fecundity of the surviving worms (Harrison and Doenhoff 1983). The effect of radiation on the maturation and fecundity of *S. mansoni* was also studied. Aitken and Wilson (1989) studied the maturation of *S. mansoni* in mice exposed to various sublethal doses of radiation. They found that treatment of mice with 500 rad of radiation prior to infection did not alter parasite maturation; however, a reduction in worm burden was induced by doses in excess of that magnitude (Aitken and Wilson 1989). The authors reported that worms developing in mice treated with 800 rad commenced egg laying about 1 week later than worms in intact mice, and the rate of egg deposition appeared to be lower in irradiated hosts. They stated that their findings opposed the hypothesis that the immune response of mice controls the primary immune response (Aitken and Wilson 1989). In fact, this finding was also confirmed in immunodeficient humans that reflects a similarity in this pattern between murine and human schistosomiasis. In immunodeficient humans, Karanja et al. (1997) reported decreased fecal egg excretion in patients with both *S. mansoni* and human immunodeficiency virus infections.

Davies et al. (2001) first reported that *S. mansoni* uses an alternate developmental pathway in immunodeficient mice in which it fails to receive and exploit the appropriate immune signals but is influenced by hepatic $CD4^+$ T lymphocytes populations. This alters the trematode development at an early infection stage, leading to the appearance of attenuated forms that prolong the survival of host and parasite (Davies et al. 2001). It could be understood from the latter finding that liver might play an important role in host–parasite interaction in infected individuals and with immunodeficiency. More recently, it has been reported that the development of female schistosomes from infectious cercariae to mature egg-producing adults requires not only male schistosomes but also an intact adaptive immune system (Hernandez et al. 2004). Moreover, they found that only male development is directly influenced by the adaptive immune system, and subsequently mature males stimulate the development of mature females (Hernandez et al. 2004). This important finding also points out to the importance of adaptive immune responses in the development and maturation of schistosomes.

It was found that the number of eggs per worm pair in the tissues increases with time in a nearly linear fashion, while the number of eggs per worm pair in the feces decreases by half between the 8th and 20th weeks of infection in mice (Cheever et al. 1994b). Moreover, the relationship between the intensity of infection and fecal egg excretion was complex (Cheever et al. 1994b). Therefore, it is clear that passage of eggs in feces is not always a good indication for the deposition of eggs in tissues (Cheever et al. 1994a). It was demonstrated that, in *S. mansoni*-infected mice, the mean total egg count of the small intestine and the mean number of eggs per gram in the small and the large intestine were higher than the corresponding egg counts in the liver (Tiboldi 1979). In addition, the increase in weight of the small intestines of infected compared with uninfected mice was greater than the increase in weight of the corresponding livers (Tiboldi 1979). It was found that there is an immune dependence of fecal egg excretion of *S. mansoni* in mice (Doenhoff et al. 1978). The authors found that T-cell-deprived CBA mice subsequently infected with *S. mansoni* had substantially fewer parasite eggs in their feces than similarly infected immunologically intact control animals. However, the number of parasite eggs deposited in the tissues of T-cell-deprived mice was by comparison only marginally lower than in control mice. Subsequent administration of serum obtained from normal mice with chronic *S. mansoni* infections partially restored the egg excretion rate in infected deprived mice and also resulted in an increased number of eggs being deposited in the liver and intestine of these animals (Doenhoff et al. 1978). Cheever et al (1993) compared the infections by *S. mansoni* and *S. japonicum* in nude mice (nu/nu) with those in nu/+ heterozygotes or intact mice. They detected no substantial difference among the nude strains of Swiss NCR, C3H, BALB/c, and C57B1/6 after their exposure to *S. mansoni* infections, which were frequently lethal to nude but not to intact mice between the seventh and ninth weeks of infection, and nude mice that survived the ninth week of infection generally lived until the 12th week (Cheever et al. 1993). They found a similarity between the number of eggs per mature worm pair in the tissues of *S. mansoni*-infected nude and intact mice, but nude mice passed fewer eggs in the feces. Moreover, transfer of serum from infected intact to nude mice resulted in excretion of eggs in their feces equivalent in number to intact mice (Cheever et al. 1993).

Immunopathologic aspects

In fact, many phenomena associated with the immunopathology of *S. mansoni* have been identified and studied in the murine models.

Granuloma formation and fibrosis

Granulomas in schistosomiasis depend predominantly on $CD4^+$ T cells and represent a form of delayed-type

hypersensitivity (Stadecker et al. 2004). T-cell-depleted mice show only diminished granulomas (Mathew and Boros 1986). Mice infected with *S. mansoni* develop granulomas in the liver and intestines that elicit the clinical syndrome of hepatosplenomegaly, tissue fibrosis, portal hypertension, ascites formation, and bleeding, resembling those in human schistosomiasis (Weinstock and Boros 1983a). Many eggs are swept back by the blood flow into the liver, where they become trapped in the sinusoids and induce a highly polarized Th2 response (Grzych et al. 1991; Pearce et al. 1991). This highly polarized Th2 response regulates granuloma formation around tissue-trapped eggs and activates macrophages contributing to the host survival (Herbert et al. 2004). Such reduction in immune responsiveness during schistosomiasis helps to minimize the immunopathology in a setting where the immune system is incapable of eliminating the pathogen; however, it does not serve the survival of the pathogen (Wilson et al. 2007). Schistosome-infected mice have been found to exhibit maximal granulomatous reaction to the eggs by the eighth week of infection.

Granulomas are composed principally of macrophages, eosinophils, and lymphocytes (Weinstock and Boros 1983a), while mast cells are infrequent in 8-week granulomas in most mouse strains and become more frequent in chronic infections (Weinstock and Boros 1983b). Then, granulomas around recently deposited eggs become smaller after the eighth week of infection due to the T-lymphocyte down-modulation of the immunity (Chensue and Boros 1979). Granulomas in the colon and small intestine of mice are smaller than those in the liver and are not always subject to the same down-regulation (Santos et al. 1992). In addition to their smaller size, intestinal granulomas in murine schistosomiasis are only mildly fibrogenic compared to hepatic granulomas (Santos et al. 1992). Cheever et al. (1993) reported that nude mice of various strains showed minute granulomas around eggs in the liver and minimal hepatic fibrosis. Reconstitution with fetal thymus or with splenocytes from normal or *S. mansoni*-infected mice partially or completely restored hepatic granuloma size, granuloma eosinophils, hepatic fibrosis, and excretion of eggs in the feces (Cheever et al. 1993). The classic histologic appearance of schistosomal liver disease, i.e., intense fibrotic bands interspersed with hepatic parenchyma with normal architecture, is known as Symmers' clay pipestem fibrosis (Andrade et al. 2006). The morphological features of hepatic fibrosis in mice were described as being greatly similar to those of human schistosomiasis (Henderson et al. 1993). The immunoregulatory antiegg idiotypes were absent from mice and humans displaying Symmers' fibrosis; however, these were detected in those without Symmers' fibrosis (Montesano et al. 1989; Montesano et al. 1997). The Th2 cytokine IL-13 plays a major role in the development of hepatic fibrosis (Chiaramonte et al. 1999; Fallon et al. 2000; Wynn et al. 2004). Thus, IL-13 is a major contributor to the morbidity of the disease. Chiaramonte et al. (1999) showed that recombinant IL-13 stimulated collagen synthesis in fibroblasts, and its harmful effects may be mediated directly through its profibrogenic activity.

Murine schistosomiasis also plays an important role in the study of collagenesis and collagenolysis processes in the inflammatory fibrotic liver disease (Takahashi et al. 1980; Takahashi and Simpser 1981). Unlike mice in which most hepatic fibrosis is related to the granulomas (Dunn et al. 1977; Olds et al. 1985), such relation is less clear in humans where most fibrosis is periportal (Cheever and Yap 1997).

Use of murine hosts to study immunopathology

In fact, murine hosts contributed greatly in understanding many phenomena related to the immunopathology of human schistosomiasis. However, the relevance of immune responses of inbred mouse strains to humans is questionable and, hence, necessitates carrying out further studies in primate models (Farah et al. 2005). Generally, in murine hosts, it was shown that Th1 responses are associated with protection, whereas Th2 are associated with immunopathology (Sher et al. 1990). However, human studies of resistance to reinfection indicated a role of eosinophilia and specific IgE production (Hagan 1993). On the other hand, another difference is that humans can be born to schistosome-infected mothers, and in utero exposure to parasite antigens will be a factor in the subsequent development of immune responses to the parasite, whereas murine hosts are usually bred from uninfected mothers (Fallon 2000).

Among the various animal models, the rat appears as an excellent experimental system for investigation of antibody-mediated immunity to *S. mansoni* in spite of being a semipermissive host (Capron and Capron 1986). Rat monoclonal antibodies have allowed the identification of effector and regulatory mechanisms operating in human schistosomiasis, together with the characterization of protective antigens, leading to promising approaches to vaccine development (Capron and Capron 1986). Murine studies have focused primarily on $CD4^+$ cells as the source of cytokines that determine the type 2 outcome of infection and regulate the granulomatous response to parasite eggs (Fallon 2000).

Amiri et al. (1992) identified TNF-α as the specific immune signal molecules necessary to reconstitute granuloma formation in severe combined immunodeficient (SCID) mice, having normal macrophages but lacking functional B or T lymphocytes in schistosome-infected

mice. In addition, it was found that the worms require TNF-α for egg laying and for excretion of eggs from the host, showing successful exploitation of the host-derived immunoregulatory protein as a signal for replication and transmission (Amiri et al. 1992).

Mouse modeling has also been used for describing the implications of Th1 versus Th2, since both molecular and cellular immunology studies were facilitated by the availability of immunologic tools as well as the production of transgenic and knockout mice (Farah et al. 2005). In murine models of schistosomiasis, schistosome eggs and egg-derived antigens are potent and independent inducers of type 2 T-cell responses (Grzych et al. 1991; Pearce et al. 1991). Although the parasite-stimulated Th response peaks during the early stages of infection, it declines with the progression of infection to the chronic stages in a process referred to as immunomodulation (Maizels et al. 2004). It was found that such immunomodulation is due to the Fas-mediated apoptosis of lymphocytes, but not eosinophils, in murine schistosomiasis (Rumbley et al. 2001). In humans, IL-10 was suggested to be an important cytokine in regulating the immune response and possibly controlling morbidity of human schistosomiasis mansoni, and that the production of interferon gamma (IFN-γ) might be associated with resistance to infection (reviewed in Corrêa-Oliveira et al. 1998). It was found that IFN-γ is an antifibrogenic agent in vivo (Czaja et al. 1989), and treatment with IFN-γ decreased granuloma size and inhibited the progression to hepatic fibrosis in murine schistosomiasis (Czaja et al. 1989). In chronic human schistosomiasis, an elevation in IL-4 and decrease in IFN-γ levels in the serum (Zwingenberger et al. 1991) were found.

Mouse models suggested that Th1 responses predominate in the early acute phase followed by SEA-stimulated Th2 response and down-modulation of Th1 responses through mechanism dependent on IL-10 (Hesse et al. 2004). It was reported that innate effectors and regulatory T cells producing IL-10 cooperate to reduce morbidity and prolong survival in schistosomiasis (Hesse et al. 2004). Watanabe et al. (2009) reported that the proportions of natural T regulatory cells (Treg) and activated $CD4^+$ T cells (Tact) for both splenic and granulomatous cell populations are greater in mice with hypersplenomegaly syndrome (HSS) than those with moderate splenomegaly syndrome (MSS). However, the ratios of Treg to Tact in MSS mice are significantly higher than those of HSS mice. It should be noted that the majority of mice develop MSS resembling the intestinal form of chronic human schistosomiasis, whereas only 20% of mice develop HSS that is more consistent with the severe hepatosplenic form of chronic human schistosomiasis mansoni (Watanabe et al. 2009). In a study of *S. mansoni*-infected mice coinfected with murine AIDS (MAIDS), it was found that MAIDS did not influence the hepatic granulomatous reaction to *S. mansoni* in coinfected mice (Lacroix et al. 1998). In contrast to a previously raised controversy, they concluded that infection with *S. mansoni* neither enhanced Th2 cytokine production nor accelerated MAIDS progression in animals subsequently challenged with the retroviral complex (Lacroix et al. 1998).

Role in testing the efficacy of chemotherapy

The first step in screening drug leads in the chemotherapy of human schistosomiasis is the use of animal models, mainly rodents. Only compounds that show antischistosomal activity with acceptable safety in rodents are then to be tried in primates (Cles 1999). These animals are challenged with the infection and then treated with the chemical or naturaceutical compound under investigation. The treatment outcomes in the treated groups are then compared with those of the infected untreated controls. The most common parasitological criteria for the evaluation of chemotherapeutic efficacy include adult worm recovery after perfusing animals, tissue egg count, fecal egg count, and the alteration in oogram pattern (Smithers and Terry 1965; Pellegrino et al. 1962; Cheever 1968). Tiboldi (1979) argued that the small intestine is a valuable organ for pathophysiologic studies in acute murine schistosomiasis mansoni. He recommended the use of simple parameters such as total egg count of small intestine, the number of eggs per gram of tissue in small and large intestine, and the weight and length of the small intestine (Tiboldi 1979).

The chemotherapeutic agent may also be evaluated on the basis of histopathologic findings by studying the histopathologic appearance of the hepatic parenchyma, granuloma characteristics, or fibrosis. Scanning electron microscopy has also been employed to study the ultrastructural alterations induced by chemotherapeutic agents on adult schistosomes. Among these ultrastructural alterations, swelling, lysis, and vacuolization of the tegumental matrix and the disappearance of the basal membrane are the typically studied (Ramirez et al. 2007). Mice were also employed in studying the pharmacokinetics of antischistosomal drugs. For instance, Botros et al. (2006) studied drug-metabolizing enzymes and praziquantel bioavailability in mice harboring strains of *S. mansoni* with different drug susceptibilities. They suggested that *S. mansoni* strains with less susceptibility to praziquantel induce a lower inhibition of hepatic drug-metabolizing enzymes, i.e., cytochrome P450 (CYP450) and cytochrome b5 (cyt b5), with a subsequent higher metabolic transformation of the drug (Botros et al. 2006). It is, however, worth mentioning that due to the difference in metabolism between mice and humans, the schistosomicidal drugs that show effectiveness

in humans may show little activity in rodent models (Farah et al. 2005). In fact, literature is rich in studies that used murine models for testing the efficacy of chemicals and plant extracts against schistosomiasis, their mode of actions, and the possibility of resistance emergence. However, the results of efficacy may or may not translate into clinical settings. Another shortcoming in the use of mice as models for chemotherapy and reinfection experiments is the development of severe pathology and anatomical changes, leading to portacaval shunting in some strains of mice that become resistant to schistosome infection because they have a predisposition to form anastomoses in the absence of infection (Wilson 1990).

Role in vaccine experimentation

Murine hosts have also been extensively used for testing the efficacy of vaccines against schistosomes. However, non-primate models may not adequately reproduce human infection, and that nonhuman primate models, like baboons, may be more accurate (Nyindo and Farah 1999). World Health Organization selected six of the most promising vaccine candidate antigens for investigation in laboratory mice, including glutathione S-transferase (*Sm*28), paramyosin (*Sm*97), triose phosphate isomerase, fatty acid-binding protein (*Sm*14), internal membrane protein (*Sm*23), and myosin heavy chain (rIrV5) (Dunne and Mountford 2001). We are going to present the role of murine hosts in only two vaccine candidates. First, *Sm*28, both naïve and recombinant, has given some degree of protection reaching up to 70% in murine hosts (Balloul et al. 1987b). Immunization of Fischer rats and BALB/c mice with the purified 28,000-Da protein caused a marked decrease (up to 70%) in the parasite burden in both experimental infection models (Balloul et al. 1987a). Second, *Sm*97 has been recognized by the use of sera of mice vaccinated with various extracts of adult schistosomes and larval schistosomula (Lanar et al. 1986; Pearce et al. 1988). They found that mice immunized intradermally with extracts of *S. mansoni* in combination with the adjuvant BCG produced antibodies predominantly against a single parasite protein with a molecular weight of 97 (*Sm*97). Paramyosin was isolated from *S. mansoni* adult worms, and antibodies to *Sm*97 were shown to react with this molecule as well as with a known paramyosin from molluscan muscle (Lanar et al. 1986). Pearce et al. (1988) reported that paramyosin stimulates T lymphocytes from vaccinated mice to produce lymphokines that activate macrophages to kill schistosomula. In fact, the experimental vaccines in animal models for schistosomiasis were largely reviewed by Siddiqui et al. (2008) and need not to be rereviewed.

Of great interest are the recent findings of Tallima et al. (2009) who suggested that schistosome infection elicits production cytokines antagonizing each other, resulting in impaired Th17 and Th1/Th2 immunity, and subsequent decline in resistance to primary infection. They reported that such an immune evasion mechanism may have profound implications for vaccination against schistosomes. More recently, based upon murine studies, Farias et al. (2010) showed that *S. mansoni* stomatin-like protein 2 (SmStoLP-2) had protective potential against schistosomiasis and could be useful in a combination vaccine.

Concluding remarks

Murine hosts are still indispensable for studying various aspects of human schistosomiasis. Despite the presence of some extent of dissimilarities between murine hosts and humans regarding some aspects of the disease, the use of such hosts, particularly mice, makes it easy to comprehend many phenomena of the disease. They continue to constitute a major tool for the control of the disease through the developments of novel chemotherapeutic agents and vaccines. It is believed that the forthcoming era in development and testing of vaccine candidates is really in need for the use of murine models as the primary models for such investigations before the use of nonhuman primates or carrying out human trials. However, due to many differences between the murine and human infections, the extrapolation of the data obtained from mice to the human condition is not an easy mission. Murine schistosomiasis has been the most studied experimental model in many aspects of the disease. However, there are some differences between the murine model of schistosomiasis and human disease in endemic areas that were reviewed and summarized by Abath et al. (2006) as follows:

- Experimental infections involve a single exposure while most schistosome infections in humans are acquired gradually.
- Intensity of infection is generally high in murine models while the intensity of human infection varies, but is generally low.
- Experimental murine hosts are infected with defined isolates of *S. mansoni* while human infection occurs with natural isolates of the parasite.
- Time and dose of infection in murine schistosomiasis are defined; however, it is difficult to define how long individuals have been infected.
- Some pathologic features of chronic infection are difficult to reproduce in mice while chronic liver disease is characterized by Symmers' fibrosis in humans.
- Genetic background can be homogeneous in murine hosts while it is heterogeneous in humans.

– Coinfection with other parasites can be avoided in murine hosts while coinfection with other parasites is common in humans.

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