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The Consequences of Parasitic Infection for the Behavior of the Mammalian Host

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As many as one billion people may be infected with animal parasites. The behavioral consequences of such infection, or of illness in general, is poorly understood. This issue is discussed using as an example infection of mice with *Toxocara canis*, the common roundworm of dogs. Current literature suggests that two-thirds of all dogs have been infected with this parasite, and 7% of all humans have antibodies to *T. canis*.

***T. canis* completes its life cycle in dogs, but when it infects aberrant mammalian hosts (e.g., humans or mice), larvae migrate through various organ systems including the brain, where they can remain viable and mobile for extended periods of time. Changes in motor activity, sensory reactivity, and learning of mice infected with *T. canis* have been observed. The pattern of behavioral changes is influenced by the infection regime and exposure to other toxicants such as lead.**

Scope of the Problem

The clinical manifestation of many diseases are dependent on factors such as the genetic constitution and environmental history of both the host and the infectious agent. The concept of zoonosis, the transmission of a disease from its animal host to humans, recognizes the complexity of the flow of disease or infectious agents among different hosts; some hosts may be better able to compensate for infection and thus are seen without symptoms, while others more clearly express the pathology. Variability in the reaction to parasitic infection is determined partly by genetic constitution of the parasite itself and the host (*1*), resulting in variable expressivity of the infection (*2*). "Parasites, with their bizarre pathology, often cause confusion in diagnosis, especially in countries where they are uncommon" (*3*). Part of the problem may lie in the fact that many of the pathological changes found associated with parasitic infection may be caused by inflammation or immunopathological reactions, with eosinophilia as a characteristic accompaniment (*3–5*).

Although perhaps more than 500 million humans are infected with animal parasites (*6*), little is known concerning the behavioral effects of parasitism in mammalian hosts. It is not commonly recognized, even in industrialized nations, that most people are exposed to, or infected with, one of a variety of parasites (e.g., Toxoplasma, an intracellular parasite, in the reticuloendothelial system, or trichomonads in the genital tract) (*3*). Commonly, people are unaware that they are infected, and accurate diagnosis of parasitic infection may not be made, even when symptoms are exhibited. The relationship between parasite and host is complex and may change over time. For instance, the parasite may stimulate the immune system, allowing the host both to respond minimally to subsequent re-exposures to the same parasite and to reject more pathogenic organisms. At the same time, the sick or infected organism may be particularly vulnerable to further environmental challenges. Furthermore, whereas some parasites were once relatively restricted to third world communities, increased international travel has increased the global spread of infection by such organisms.

T. canis: Brain and Behavior

We have examined the impact of *Toxocara canis*, the common roundworm of dogs, on the behavior of mice. In aberrant hosts such as humans or mice, as shown in Figure 1, the second stage larvae of this parasite migrate through various organs (liver, spleen, lung, brain, and eye) where they can remain viable for many years (*7*). In the dog, the natural host of *T. canis*, the adult stage of the parasite is normally found in the intestinal tract. However, in the aberrant host the parasite fails to reach maturity. Thus, there are no eggs passed in the feces, and only indirect diagnostic assays such as serological tests are available to suggest the presence of *T. canis* (*8*). The dimension of the problem is apparent when one takes into account: (a) a survey cited by Jacobs (*9*) that suggests that 38% of all American households in 1973 had dogs; (b) the high prevalence of infection of dogs by this parasite worldwide (*9–12*); (c) the high prevalence and long-term viability of *T. canis* eggs in

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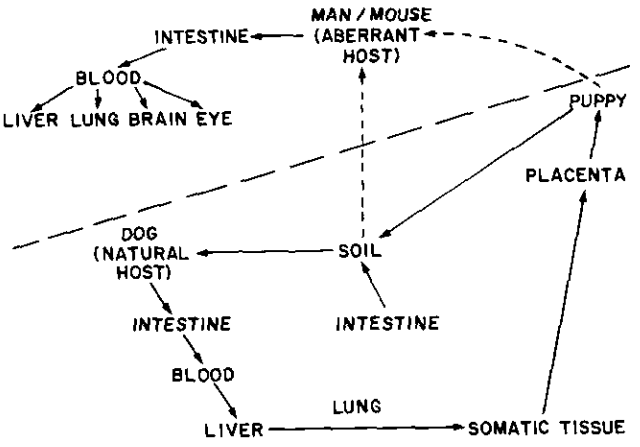

FIGURE 1. Life cycle of *Toxocara canis* in natural and aberrant hosts.

the environment (*13–17*); (d) the difficulty in detecting the presence of *T. canis*; (e) that anthelminthic treatment will kill only *T. canis* in the intestine and not during somatic migration; and (f) a growing body of literature suggesting a significant and detrimental impact of such infection on the behavior of mice. Any view that *T. canis* does not present a health hazard to humans seems premature and optimistic.

The current review discusses the impact of *T. canis* on the behavior of the aberrant mammalian host. We suggest that the immunopathological reaction to *T. canis* may be both a cause of changes in behavior and a symptom of infection and that the history of exposure to *T. canis* may alter reactions to subsequent exposure. Further, the host may gain protection through exposure to both other organisms (*3*) and other toxic substances (*18–20*).

T. canis may be the primary agent of visceral larval migrans (VLM) in the United States (*8,21*). In VLM, the ingestion of embryonated parasite eggs by abnormal hosts, including humans and mice, results in second stage larvae migrating through various organs. These *T. canis* larvae, which are less than 0.5 mm long (*9*) and 0.02 mm in width 1 week after infection (*22*), migrate through various organs of the aberrant host, including liver, lung, muscle, retina, and brain (*5,7,23–26*). The larvae may continue to circulate until they reach the brain, where, unlike other sites in which they may be sequestered, they are not encapsulated (*5,24*) and can remain viable for many years, allowing for continuing damage to the central nervous system (CNS). *T. canis* may be transmitted to humans and other unnatural hosts by direct contact with infected puppies as well as by ingestion of contaminated food, water, and soil. Children exhibiting pica are at increased risk for exposure to environmental contaminants, including the embryonated eggs of *T. canis* (*27*). Individuals probably are repeatedly exposed to *T. canis* in combination with other contaminants.

T. canis may alter a broad spectrum of behavior in the mouse, including reactivity to taste (*19*) and exploration of the environment (*18,28–30*). Altered patterns of learning performance in mice (*18*) and rats (*31*) also have been seen following infection with *T. canis*.

The changes in patterns of behavioral symptoms appear to be a complex interaction of the impact of *T. canis* on peripheral and central tissues (*32*). We observed marked effects of infection in mice on many behavioral measures when *T. canis* larvae are only beginning to actually enter the central nervous system (*32*). Furthermore, when CNS pathology had only begun to occur and when evidence of peripheral pathology was declining, behavior improved in a number of areas. In keeping with such considerations, rats and mice infected with *Schistosoma mansoni* performed poorly in learning of several tasks and were generally less active than their control counterparts (*33–38*). *S. mansoni* was chosen as an infective agent by those investigators since they believed that it did not invade the central nervous system. However, the evidence that *S. mansoni* reaches the brain has been reviewed recently (*39*).

Following infection with either *T. canis* (*28–30*) or *S. mansoni* (*34*), changes in motor activity have been observed. Nonetheless, we should be cautious in adopting a simplistic explanation of a causal relationship between general malaise, as reflected in motor behavior, and observed changes in behavior. For instance, we failed to find a difference between control and *T. canis*-infected mice in a motorically challenging and stressful swimming task when peripheral pathology was at its maximum (*32*). Stretch et al. (*37*) suggested that changes in motivation were critical to some aspects of the behavior displayed by the host following infection with *S. mansoni*. Furthermore, we reported recently that patterns of sensory reactivity, as reflected in changes in consumption when palatability of the available fluid was altered, changed following infection with *T. canis* (*19*). Such observations lend further support to the notion that the pattern of behavioral changes and task specificity observed following infection with *T. canis* cannot be attributed uniquely to either ability to perform complex motor tasks or general malaise.

Immunological Consideration

The immune system and the CNS must be viewed as intricately interrelated (*40*). Toxic substances affect the functioning of the immune system (*41*) in a complex fashion that depends on factors such as the age, sex, and mode of exposure of the subject (*42,43*). Thus, it is not surprising that immunopathological factors may account for some of the observed changes following infection with *T. canis*. Nelson (*3*) suggests that there may be cross-protection between infection with various related organisms. We found that exposure to lead also may diminish the behavioral impact of infection (*18–20*). That is, infected mice which were exposed either simultaneously (*18,19*) or previously (*20*) to lead showed less dramatic changes in behavior than infected animals without such exposure to a toxicant. Interestingly, the

neuropathology observed using light microscopic techniques was confined primarily to large myelinated fiber tracts, but was not different between animals exposed to parasite alone or in combination with lead (*5*). These data suggest that evidence for both the pattern of specific behavioral deficits and instances of resistance may occur depending on the regime of infection and exposure to other environmental toxins.

Humans and other aberrant hosts most likely experience repeated exposures to parasites. Recently we examined the impact of single versus multiple exposures to *T. canis* (*4*). In this situation, we anticipated a more heightened and sustained host immune reaction to secondary and subsequent infections of the parasite (*44–50*). Prior work had noted that the pattern of larval distribution in various organ systems is different in rodents given single versus multiple doses of *T. canis* (*51–53*). Our data supported the notion that prior exposure could indeed protect the organisms against subsequent exposures to *T. canis*. Both the pathological changes observed and the pattern of behaviors exhibited by the mice were influenced by the infection regime. However, the results also indicated the complexity of the interaction(s) between the parasite and its host. Thus, factors such as the specific "dose" (*28*), the time of measurement since infection (*32*), exposure to other toxins (*18–20*), or the pattern of repeated infections (*4*) all may alter the nature and extent of changes in the observed behavior of the organism.

Conclusions

It is surprising that this area of research has generated so little interest given the obvious impact of parasitic infection on several critical aspects of the behavior of the host ranging from sensory/motor processing (*19,29,54–56*) and agression (*57*) to learning (*18,31,34,58*). Indeed, investigations of the role of physical health or disease (*59–61*) on psychological processes in general are relatively rare. Thus, although several aspects of behavioral toxicology have become popular areas of research (e.g., the consequences of exposure to lead), many domains of research remain virtually unexplored. It is our belief that such lines of research will be critical before we can understand the etiology of a number of behaviorally significant disorders. Indeed, disease is an orphan in most psychobiological research, and the dualistic view that behavior is either organic or psychological remains common. However, to truly understand behavior, attention will have to be paid to the exquisitely complex interactive networks of adaptive processes which define any individual living organism.

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