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HOST GENDER IN PARASITIC INFECTIONS OF MAMMALS: AN EVALUATION OF THE FEMALE HOST SUPREMACY PARADIGM

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ABSTRACT: A review of current literature on mammalian hosts' sexual dimorphism (SD) in parasitic infections revealed that (1) it is a scarcely and superficially studied biological phenomenon of considerable significance for individual health, behavior, and lifestyles and for the evolution of species; (2) there are many notable exceptions to the rule of a favorable female bias in susceptibility to infection; (3) a complex network of molecular and cellular reactions connecting the host's immuno-neuro-endocrine systems with those of the parasite is responsible for the host–parasite relationship rather than just an adaptive immune response and sex hormones; (4) a lack of gender-specific immune profiles in response to different infections; (5) the direct effects of the host hormones on parasite physiology may significantly contribute to SD in parasitism; and (6) the need to enrich the reductionist approach to complex biological issues, like SD, with more penetrating approaches to the study of cause–effect relationships, i.e., network theory. The review concludes by advising against generalization regarding SD and parasitism and by pointing to some of the most promising lines of research.

THE FEMALE HOST SUPREMACY PARADIGM IN PARASITIC INFECTIONS

It is widely held that female mammals are more resistant to parasitic infections than males because of gender-associated differences in exposure and of testosterone's immunosuppressive properties. The paradigm implies that sexual dimorphism (SD) to parasitism is mediated only, or principally, by the host's immune system and usually disregards the parasites' direct response to the distinct sex-steroid profiles of their female and male hosts.

The female supremacy paradigm in parasitic infections has existed for a long time (Addis, 1946), and despite thoughtful recommendations against simplification (Zuk and McKean, 1996), it is rarely questioned. In several prestigious journals, however, it has recently been a matter of debate, particularly in association with mortality trends in humans (Moore and Wilson, 2002; Owens, 2002) and several infectious diseases (Zuk and McKean, 1996; Doprado et al., 1998; Watanabe et al., 1999; Klein, 2000; Ganley and Rajan, 2001; Hughes and Randolph, 2001; Roberts et al., 2001; Verthelyi, 2001). It has also been associated with a number of broader subjects, i.e., evolution of sexual reproduction (Zuk, 1994), decision making of the host, social hierarchy (Barnard et al., 1998; Gourbal et al., 2002), mating behavior (Kavaliers and Colwell, 1993; Morales et al., 1996; Willis and Poulin, 2000), and energy costs of infection and the immune response (Hansen et al., 2003). We decided to reexamine the paradigm in the light of the current understanding of the immune and endocrine systems of potential hosts because we found that it conflicted with our observations regarding experimental murine cysticercosis caused by *Taenia crassiceps*.

EXPERIMENTAL MURINE *TAENIA CRASSICEPS* CYSTICERCOSIS CONFLICTS WITH THE PARADIGM

Taenia crassiceps is an intestinal cestode of canines (definitive host) and of various extraintestinal tissues of rodents (intermediate host) in its larval (cysticercus) stage (Freeman, 1962). Experimental cysticercosis caused by *T. crassiceps* in mice simply requires the intraperitoneal injection of live cysticerci (Culbreth et al., 1972). Intraperitoneal cysticerci reproduce asexually by exogenous budding, developing massive parasite loads in a few months (Smith, Esch et al., 1972; Smith, Parrish et al., 1972) that may even approximate the host's body weight, without causing it apparent discomfort (Larralde et al., 1995). The cysticerci also survive and reproduce in vitro under usual culture conditions in media free of fetal calf serum. These features of experimental murine cysticercosis have made it a convenient model in studying the immunological, genetic, and sexual factors involved in susceptibility to infection and parasite proliferation (Sciutto et al., 2002). Sexual differences to infection in mice are still a matter of research. Thus, experimental findings have shown that in different congenic and syngenic strains of mice, females become infected more often than males and carry more cysticerci than males, with significant between-strain variations (Sciutto et al., 1991; Huerta et al., 1992; Larralde et al., 1995; Terrazas et al., 1998; Morales-Montor, Baig et al., 2001; Morales-Montor, Baig, Hallal-Calleros et al., 2002; Morales-Montor, Baig, Kabbani et al., 2002; Morales-Montor, Hallal-Calleros et al., 2002). Estrogens favor parasite reproduction, whereas androgens appear to inhibit it (Bojalil et al., 1993; Terrazas et al., 1994; Morales-Montor, Baig, Hallal-Calleros et al., 2002). Gonadectomy and thymectomy equalize parasite loads between sexes by greatly increasing those in males and slightly decreasing those in females (Huerta et al., 1992; Terrazas et al., 1994; Morales-Montor, Baig, Hallel-Calleros et al., 2002). Male mice are better protected by vaccination than females (Cruz-Revilla et al., 2000). Externally administered 17β-estradiol and dihydrotestosterone (DHT) are able to restore parasite loads to their normal levels in castrated animals. T cells, but not antibodies, also restore the effects of thymectomy (Bojalil et al., 1993). The TH1 response hinders parasite growth early in infection (Terrazas et al., 1999; Toenjes et al., 1999; Spolski et al., 2000; Rodriguez-Sosa et al., 2002), whereas the TH2 response prevails at later times of infection but is incapable of slowing parasite growth (Terrazas et al., 1998; Toenjes et al., 1999). In chronic infections, the male mouse is feminized (estrogenized and deandrogenized) to a degree that

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inhibits male sexual behavior (Morales et al., 1996). Feminization is apparently caused by overexpression of P-450 aromatase (Morales-Montor, Hallal-Calleros et al., 2002), triggered by the high levels of interleukin-6 (IL-6) in late infections (Morales-Montor, Baig et al., 2001; Morales-Montor, Mohamed et al., 2001). Cytokine profiles of infected male and female mice do not show major differences, except for the levels of IL-4, which are higher in males during early infection only (Terrazas et al., 1998).

These findings led to the initial proposal of a sex steroid, immunoendocrine interaction that controls the reproduction of cysticerci, one in which androgens were postulated to favor a TH1 response that limits parasite growth and in which estrogen favors a TH2 response that permits parasite reproduction (Huerta et al., 1992; Bojalil et al., 1993; Terrazas et al., 1994; Morales-Montor, Baig et al., 2001; Morales-Montor, Baig, Hallal-Calleros et al., 2002; Morales-Montor, Baig, Kabbani et al., 2002). Other studies also support the purported correlation between androgens and TH1 response and between estrogen and TH2 response (Morales-Montor, Baig et al., 2001; Morales-Montor, Baig, Hallal-Calleros et al., 2002; Morales-Montor, Baig, Kabbani et al., 2002; Morales-Montor, Hallal-Calleros et al., 2002).

Signs of SD in cysticercosis were recently reported for other host and taeniid species. For example, sex steroids have been implicated in porcine cysticercosis caused by *Taenia solium* because both castration and pregnancy nearly double the prevalence of naturally acquired cysticercosis in rural pigs (Morales et al., 2002). In humans, women are more frequently afflicted than men by severe neurocysticercosis (Del Brutto et al., 1988) and show higher inflammatory profiles (Fleury et al., 2003). Because sex steroids affect experimental *T. crassiceps* infections in laboratory mice and extend to natural infections of *T. solium* in humans and pigs, as well as *Trichinella spiralis* in rats (Klein et al., 1999), our initial suspicions regarding the general validity of the female supremacy paradigm were strengthened.

Other ongoing research has shown that in *T. crassiceps* murine cysticercosis several physiological systems of the host respond to the host's sex hormones, and so does the parasite either by limiting or by prompting its reproduction. For example, the central nervous system of infected and feminized male mice responds to intraperitoneal infections by overexpresssion of the *c-fos* gene in the hypothalamus, hippocampus, and preoptic area (Morales-Montor, Arrieta et al., 2003). It would appear that hormonal changes induced in the host act to promote the overexpression of the *c-fos* gene involved in cellular differentiation and proliferation of both parasite and host cells (Escobedo et al., 2004), as they do in other stress and immune challenges (Pacheco-Lopez et al., 2002). Thus, in murine cysticercosis, parasite proliferation is responsive not only to the host immune system and testosterone but also to a complex network that integrates the nervous, immune, and endocrine systems of the host and the parasite's physiological systems. The conflict between male biases in *T. crassiceps* cysticercosis with the host female supremacy paradigm expectations is undeniable and requires explanation.

TESTING THE FEMALE HOST SUPREMACY PARADIGM IN A WIDER REPERTOIRE OF PARASITIC INFECTIONS

The paradigm of female host supremacy in parasitic infections of mammals, as well as the robustness of the corresponding endocrinological and immunological factors postulated as its mechanisms, was evaluated using current literature (Medline, n = 110: 1995–2002), as well as several frequently cited classic articles and a few recent ones published in 2003. After examining this literature, however, the general validity of the female supremacy paradigm was seriously weakened by too many exceptions. What emerged was a complex host immuno-neuro-endocrine network that was related to the parasite physiologically and that seems more likely to control the complexities involved in certain host–parasite interactions than testosterone alone.

When infections that documented sex bias in infection parameters (Infection-SD) or immune profiles (Immune-SD) were found, the possibility of a cause–effect relationship was examined further. Each infection was classified as either sexually dimorphic, noting the sex favored by the bias (females $>$ males or females $<$ males), or undefined (females = males). Infection-SD was evaluated in terms of prevalence, intensity, severity, morbidity, mortality, hormonal profiles, or behavioral changes in infected animals. The biological meaning of these parameters differs substantially. Thus, some relate to the probability of infection, i.e., prevalence, and others to the outcome of infection, i.e., mortality, but they were assumed to be equivalent indications of sex bias. Immune-SD parameters include antibody production, lymphoid cell responses to mitogens or antigens, cytokine production, hypersensitivity reactions, and protective effects of vaccination. Immune-SD parameters also have important functional differences in their nature and context of expression, i.e., populations, individuals, cells, and molecules, in their role as effectors or mediators of immune responses, in their operation under in vitro or in vivo conditions, and in their ability to protect from infection. These immune parameters were scored as ''greater than'' or ''smaller than'' with respect to the opposite gender. The Immune-SD and Infection-SD data collected were used to examine how the 2 are connected.

FIRST GENERAL SIGNS OF PARADIGM WEAKNESS

The total number of references examined is relatively small, i.e., only 110. The search identified just 46 different parasite species occurring in 10 species of mammalian hosts, a minute sample considering the many thousands of parasite (Hoberg, 1997) and mammalian species (Anderson et al., 1984). Forty-three references reported SD (Table I), and the rest (67) were concerned with molecular interactions between the endocrine and immune systems or with hormonal, behavioral, and immune effects on the host (Fig. 1).

The human medicine bias in SD research is obvious because 56% of all the articles were oriented to the study of infections affecting humans or experimental animal infections (usually in rodents) having a human counterpart, i.e., malaria, schistosomiasis, trypanosomiasis, toxoplasmosis, and cysticercosis. Most references in the list do not directly explore SD but rather describe the in vitro effects of sexual hormones or cytokines on the immediate response of some immunological or endocrinological component derived from hosts of either sex in rather

TABLE I. Infection-SD or Immune-SD in different host–parasite relationships documented to date (some parasites infect more than 1 host species).

Parasite	Host	Dimorphism	Prevalence	Intensity	Severity	Mortality	Mechanisms	Other observations	Reference
Brachylaima cribbi	Mice	Yes	♀ < ♂	♀ < ♂				Expulsion of worms in C57 BL/6J mice is mediated by an immune response	Butcher et al. (2002)
Brugia malayi	Human	Yes	♀ < ♂	♀ < ♂					Ganley and Rajan (2001)
Brugia pahangi	Rat	Yes	♀ < ♂	♀ < ♂					Bell et al. (1999)
Dipetalonema vitae	Hamster	Yes	♀ < ♂	♀ < ♂			17β-estradiol and progesterone are associated with protection in females		Reynouard et al. (1984)
Eimeria vermiformis	Mice							Females distinguish between infected and noninfected males	Kavaliers and Colwell (1993), Kavaliers (1995)
Heligmosomoides polygrus	Mice						Peripheral immune response is reduced in infected males and it is associated to higher levels of corticosterone	High-ranking infected males are less aggressive	Barnard (1998)
Heterakis spumosa	Mice	Yes	♀ < ♂	♀ < ♂			Testosterone favors the development of the parasite and its survival		Harder et al. (1992)
Hymenolepis diminuta	Rat	Yes in response to treatment					Infected males have decreased levels of testosterone in plasma	A deficient diet in vitamin G complex inhibits growth of the parasite in females only. Females distinguish between infected and noninfected males	Addis (1946), Wills and Poulin (2000)
Ixodes ricinus	Voles						Testosterone reduces innate and acquired resistance to tick feeding	Tick feeding favors transmission of other parasites	Hughes and Randolph (2001)
Leishmania donovani	Mice	Yes	♀ < ♂	♀ < ♂				Macrophages treated in vitro with testosterone have an increased number of promastigotes	Zhang et al. (2001)
Leishmania major	Mice	Yes	♀ < ♂	♀ < ♂				Testosterone treatment in females increases parasite number and orchidectomy in males decreases it	Mock and Nacy (1988)

TABLE I. Continued.

Parasite	Host	Dimorphism	Prevalence	Intensity	Severity	Mortality	Mechanisms	Other observations	Reference
Leishmania mexicana	Mice	Yes	♀ < ♂	♀ < ♂	♀ < ♂		Infected females produce more IFN-γ and infected males more TNF-α	Lesion growth as a result of treatment with IFN-γ–neutralizing antibody in females equaled that in males	Satoskar and Alexander (1995)
Leishmania spp. (*Leishmania viannia guyanensis* and *Leishmania viannia panamensis*)	Hamster	Yes	♀ < ♂	♀ < ♂	♀ < ♂		The increased severity in males was associated to a greater intralesional expression of IL-4, IL-10, and TGF-β, which are disease promoters	Testosterone treated females have larger lesions than untreated females	Travi, Osorio et al. (2002)
Nippostrongylus brasiliensis	Rat	Yes	♀ < ♂	♀ < ♂			Testosterone affects goblet cell function and proliferation, delaying parasite expulsion		Tiuria et al. (1995)
Plasmodium chabaudi	Mice	Yes	♀ < ♂	♀ < ♂	♀ < ♂	♀ < ♂	Testosterone decreases the levels of total IgG, IgG1, and IgG2b, increases CD8+, and decreases Ig+ cells in infected females	Oral treatment with testosterone increases mortality in females	Benten et al. (1997), Mossmann et al. (1984)
Plasmodium chabaudi	IFN-γ $R^{-/-}$KO mice	Yes	♀ < ♂	♀ < ♂		♀ < ♂	Male sex hormones modulate the TH1–TH2 cell function		Zhang et al. (2000)
Plasmodium chabaudi	IL-$4^{-/-}$ KO mice	Yes	♀ < ♂	♀ < ♂		♀ < ♂	Male sex hormones modulate the TH1–TH2 cell function		Zhang et al. (2000)
Plasmodium chabaudi	IL-$10^{-/-}$ KO mice	Yes	♀ > ♂			♀ > ♂	The pathology may be due to direct stimulation of TNF-α by the parasite		Li (1999)
Schistosoma haematobia	Human	Yes		♀ = ♂			Females have higher levels of specific IgA, TGF-β, and IL-10 with a low specific proliferation compared with males		Remoue et al. (2001)
Schistosoma mansoni	Human	Yes	♀ < ♂	♀ < ♂	♀ < ♂				Mohamed-Ali et al. (1999)
Schistosoma mansoni	Mice	Yes	♀ > ♂	♀ > ♂	♀ > ♂	♀ > ♂		Testosterone treatment in females or castrated males reduces mortality. DHEA treatment reduces parasite number in females	Nakazawa et al. (1997), Fallon et al. (1998)

TABLE I. Continued.

Parasite	Host	Dimorphism	Prevalence	Intensity	Severity	Mortality	Mechanisms	Other observations	Reference
Schistosoma mansoni	Hamster	Yes	♀ < ♂	♀ < ♂					Barrabes et al. (1980)
Strongyloides ratti	Rat	Yes	♀ < ♂	♀ < ♂				Testosterone treatment or macrophage blocking increases worm recovery in females	Watanabe et al. (1999)
Strongyloides venezuelensis	Rat	Yes	♀ < ♂	♀ < ♂			Testosterone restitution increases susceptibility and estradiol restitution decreases it	Gonadectomy in male rats decreases parasite loads, whereas it increases the loads in females	Rivero et al. (2002a, 2002b)
Taenia crassiceps	Mice	Yes	♀ > ♂	♀ > ♂			During infection there is a TH1–TH2 shift; in the acute infection IL-12 promotes CD4+-specific proliferation; in the chronic infection, IL-6 predominates and stimulates the aromatase activity, which increases serum estradiol in males	Chronically infected males lose their sexual behavior. Infection changes the response to the predator, facilitating the parasite cycle. Vaccination is more effective in males than in females	Sciutto et al. (1990, 1991), Larralde et al. (1995), Morales et al. (1996), Terrazas et al. (1998, 2002), Gourbal et al. (2001), Morales-Montor, Baig et al. (2001)
Taenia solium	Pigs		♀Nonpregnant > ♀pregnant; ♂noncastrated > ♂castrated				Low levels of androgens or high levels of estrogens probably influence susceptibility to infection		Morales et al. (2002)
Taenia solium	Human	Yes			♀ > ♂			Women develop a greater degree of inflammation when cysticerci are found in brain parenchyma and have more CSF* inflammation and increased cellularity in the CSF than men	Del Brutto et al. (1988), Fleury et al. (2003)
Toxoplasma gondii	Mice	Yes	♀ > ♂	♀ > ♂	♀ > ♂	♀ > ♂	Male SCID* more rapidly produce IL-12 and higher levels of IFN-γ. Males produce higher levels of TNF-α and IFN-γ at the onset of the infection, controlling parasite multiplication	Testosterone treatment reduces parasite numbers and mortality in females. Infection produces infertility in females	Stahl (1994), Roberts et al. (1995), Walker et al. (1997), Liesenfeld et al. (2001)

TABLE I. Continued.

Parasite	Host	Dimorphism	Prevalence	Intensity	Severity	Mortality	Mechanisms	Other observations	Reference
Trichinella spiralis	Voles	Yes	♀ < ♂	♀ < ♂				Polygamous males have higher testosterone levels than monogamous males concomitant to infection	Klein et al. (1999)
Trypanosoma cruzi	Mice	Yes	♀ < ♂	♀ < ♂			Intact males have higher levels of lytic antibodies	Dominant males have higher levels of testosterone and are less parasitized. Ovariectomy increases infection; estrogen replacement reduces the parasitemia. Orchiectomized males have fewer parasites than controls; testosterone replacement increases parasitemia	Doprado et al. (1998, 1999), Schuster and Schaub (2001)

* CSF, cerebrospinal fluid; SCID, severe combined immunodeficiency disease.

unrealistic in vitro conditions, i.e., cell culture media containing (contaminated with) fetal calf serum rich in growth factors and antibiotics. The biochemical results were then mistakenly assumed to operate in a similar manner in the more complicated context of an in vivo infection.

The analysis developed by the literature search casts doubt on the validity of the general female supremacy paradigm. The most notable shortcomings relate to (1) the poor representation of host–parasite systems among cited references, (2) the heavy human medical bias of the more thoroughly explored infections, (3) the unequal meanings of infection and immune parameters measuring SD in host susceptibility to infection, (4) the questionable protective function for many of the immune parameters, and (5) the excessive use of the reductionist approach in explaining events occurring at higher levels of complexity by way of the direct extrapolation of events occurring in vitro.

THE PREVALENCE AND MECHANISMS OF SD IN SPECIFIC PARASITE INFECTIONS

Table I summarizes the 43 references describing 32 infections in 8 host–parasite systems (some parasite species infect more than 1 host species, and 1 host species is infected by more than 1 parasite species) that provided information on the subject of Infection-SD or Immune-SD. In this data set, in 22 of 32 instances (68%) of the 8 systems, females fared better than males in prevalence, intensity, or consequence of infection (severity), varying from insignificant to pronounced. In 5 of 32 instances (16%), males scored better than females, and in 5 of 32 cases (16%), results could not be defined one way or another. In effect, 32% were exceptions to the paradigm. Furthermore, it is of interest to note (Table I) that severity of infection and mortality indicators were not studied as extensively as prevalence and intensity of infection. Severity of infection was reported in only 28% of the cases cited, and in 60% of these situations, female hosts fared better than males. Only in human schistosomiasis, by *Schistosoma haematobium*, was severity the same for both sexes. Mortality, in contrast, was only reported in 19% of the infections, half of which favored female hosts and the other half males. It is clear, therefore, that SD in severity and mortality have been insufficiently explored to make general and categoric statements.

Sex-associated immunological differences (Immune-SD) were reported in only 10 of 32 infections, and multifeatured immune profiles are described in only 5. Table II focuses on the 5 host–parasite systems in which several infection and immune parameters were evaluated at the time of infection. No uniform pattern or sex bias is discernable. In malaria, toxoplasmosis, and cysticercosis, infections are more prevalent and intense in female than in male mice. However, in leishmaniasis and schistosomiasis, it is the male host that is more frequently and intensely parasitized. The immune parameters studied also vary in each infection, without clear association to infection parameters. Comparison of immune profiles in all 5 infections is possible only for interferon-γ (IFN-γ), which was found to be more elevated in males than in females in all but 1 infection (murine leishmaniasis). Levels of tumor necrosis factor-α (TNF-α) were greater in females than in males with malaria; however, in leishmaniasis, schistosomiasis, and toxoplasmosis, males exhibited higher levels of TNF-α than females. In leishmaniasis

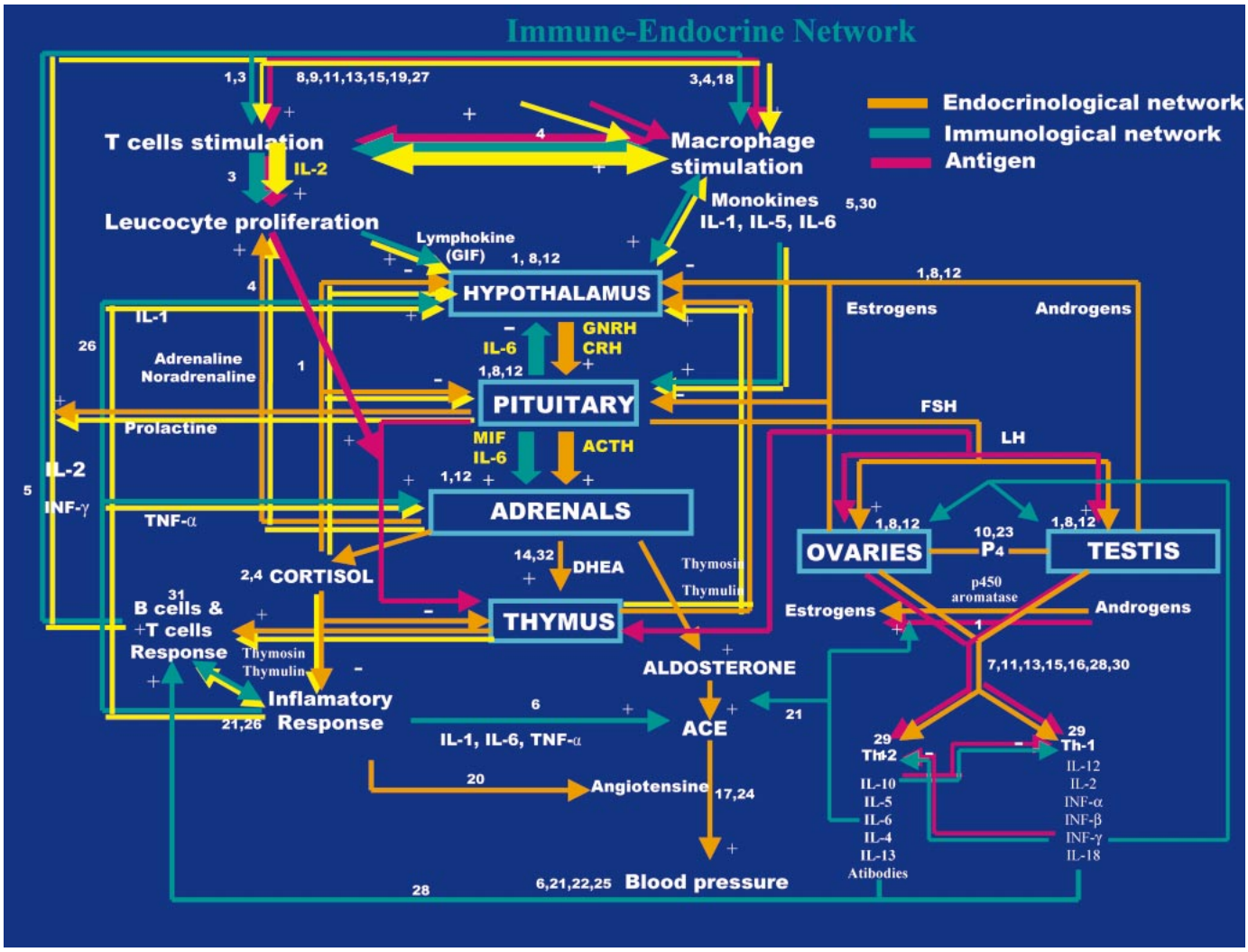

FIGURE 1. The HINEP network circuitry. The magnitude and complexity of the network includes practically all the host's sexual hormones and many of the immunological components described connecting among themselves and with the parasites systems. Arrows (←, ↑, →, ↓) denote connections between nodes; each points to the direction of the signal. ± Signs refer to stimulatory or inhibiting effects. The numbers near each connection code denote the references cited in the figure: (1) Spinedi et al. (2002), (2) Esch (2002), (3) Medzhitov and Janeway (2002), (4) Murtaugh and Foss (2002), (5) Henri et al. (2002), (6) Pramparo (2002), (7) Hughes and Randolph (2001), (8) Verthelyi (2001), (9) Roberts et al. (2001), (10) Thaker et al. (2001), (11) Liesenfeld et al. (2001), (12) Morales-Montor, Baig et al. (2001), (13) Taylor-Robinson (2001), (14) Kurtis et al. (2001), (15) Remoue et al. (2001), (16) Ganley et al. (2001), (17) Salzet and Verger-Bocquet (2001), (18) Zhang et al. (2000), (19) Soliman et al. (2001), (20) Feterowski et al. (2001), (21) Peeters et al. (2001), (22) Chae et al. (2001), (23) Barnea (2001), (24) Franco et al. (2001), (25) Gavras (2001), (26) Weinstock and Elliott (2000), (27) Grossman (1989), (28) Zhang et al. (2000), (29) Balemba et al. (1998), (30) Benedetto et al. (2000), (31) Hunter and Reiner (2000), and (32) Freilich et al. (2000).

and schistosomiasis of mice and humans, respectively, Immune-SD is observed in IFN-γ and TNF-α. In contrast, infection by *Leishmania mexicana* shows no dimorphism in IL-4, IL-10, and IL-12, whereas in infections with other species of *Leishmania*, there is a clear increase in IL-4 and IL-10 in males measured at the site of the lesions. In schistosomiasis, IL-10 production is clearly dimorphic (higher levels favoring females). Murine leishmaniasis exhibited the least dimorphic TH2 cytokine profile of the 5 infections, which contrasts with its very significant favorable female bias toward infection. In male-biased murine cysticercosis, INF-γ was higher in males; IL-2, IL-6, and proliferative responses were equal in both sexes, and IL-10 was higher in females. In addition, in murine cysticercosis, there was a reversal in the sexual bias toward IL-4 with time of infection. Males have higher amounts of IL-4 than females in early infection, but this is reversed in chronic infection. No change in profiles with time of infection was reported for the other 4 parasitic infections. These observations support the suspicion that the relationship between SD to infection, and the immune system's mediating effects are not simple and clearly involve many of the immune effectors. The host's immune response does not seem to be gender specific because no clear sex-related strategy can be detected. One would expect that hosts would have evolved immunological responses that are complementary to parasite strategies at different times of infection, number of parasites, location in the host's tissues, and offensive and defensive mechanisms. For example, extracellular stages of the parasite would be vulnerable to antibodies and

TABLE II. Host–parasite relationships in which several infection and some immune parameters were measured at some point during infection. The immune parameters collected varied in each infection.

Parasite	Host	Dimorphism	Prevalence	Intensity	INF-γ	TNF	IL-2	IL-4	IL-6	IL-10	IL-12	IgA	Specific proliferation	Reference
Leishmania mexicana	Mice	Yes	♀ < ♂	♀ < ♂	♀ > ♂	♀ < ♂		♀ = ♂		♀ = ♂	♀ = ♂			Satoskar and Alexander (1995)
Leishmania spp.	Hamster	Yes	♀ < ♂	♀ < ♂				♀ < ♂		♀ < ♂				Travi, Arteaga et al. (2002)
Schistomsoma haematobia	Human	Yes	♀ < ♂	♀ < ♂	♀ < ♂	♀ < ♂				♀ > ♂		♀ > ♂	♀ < ♂	Remoue et al. (2001)
Taenia crassiceps	Mice	Yes	♀ > ♂	♀ > ♂	♀ < ♂*		♀ = ♂	♀ < ♂*	♀ = ♂	♀ > ♂*			♀ = ♂	Terrazas et al. (1998)
Plasmodium chabaudi	Mice IL-$10^{-/-}$	Yes	♀ > ♂	♀ > ♂	♀ < ♂	♀ > ♂		♀ > ♂† ♀ = ♂			♀ = ♂			Li (1999)
Toxoplasma gondii	Mice	Yes	♀ > ♂	♀ > ♂	♀ < ♂	♀ < ♂					♀ < ♂		♀ < ♂	Roberts et al. (1995), Walker et al. (1997)

* In acute infection.
† In chronic infection.

complement because of their direct effect on the parasite's external surface (Philipp et al., 1980). Such antibody-mediated damage has been documented to affect some parasite life cycle stages but certainly not all, i.e., tachyzoites in toxoplasmosis (Johnson and Sayles, 2002), early larvae in cysticercosis (Restrepo et al., 2001), merozoites in malaria (Daly and Long, 1995), trophozoites in amoebiasis (Ghosh et al., 1998), and promastigotes in leishmaniasis (Rafati et al., 2001). However, some of the extracellular stages of parasites manage to escape from the circulation and become sequestered inside their target cells, apparently unscathed by antibodies or other harmful immune effectors. An immune response against intracellular parasites would largely depend on the expression of parasite antigens on the infected cell's membrane (Kyes et al., 2001) and the triggering of innate immune effectors. Attraction of effector leukocytes (polymorphonuclear leukocytes, eosinophils, and basophils), cytotoxic T lymphocytes, and natural killer (NK) cells to the site of parasite infection should aid in parasite destruction or at least in containment of their growth or dispersal. Thus, an inclination toward TH2 profiles, with high levels of antibody production, would be most appropriate against extracellular stages of parasites. A TH1 response, which kills infected cells, would be most effective against intracellular parasites (Sher et al., 1992). If female hosts truly favor TH2 responses, they should be more resistant to extracellular parasites and to intracellular infections in their initial stages when the parasites are migrating toward their protected intracellular locations. In contrast, if androgens favor TH1 responses, then males should handle intracellular parasites more effectively, especially during late stages of infection. Despite the attractive congruence of these speculations on immunity and SD to infections, Table II shows no clear sign of such patterns in the strategies of hosts or parasites. Lack of congruity between expected and observed results most likely come from unsound expectations regarding the role of the immune system in sexually dimorphic parasitic infections.

A detailed understanding of the mechanisms leading to the destruction of host or parasite or to a mutually tolerable stalemate requires further research and the application of a more potent and discerning technology. It might also be useful to use other conceptual approaches in exploring host–parasite systems, i.e., SD and host–parasite specificity, among others. Most research on these topics uses a reductionist approach, attempting to link microscopic events and effectors. However, the network or systems approach, where some functions are distributive to the entire network and not localized in some of its parts, is rarely considered (Oltvai and Barabasi, 2002; Strohman, 2003).

THE HOST–IMMUNO-NEURO-ENDOCRINE–PARASITE NETWORK IN CHARGE OF INFECTION AND SD

The usual experimental strategy for examining the mechanisms of immunoendocrine interactions is to add a sexual hormone or a cytokine to an isolated component of the immune, neurological, or endocrine system and then to measure its response. With results obtained by this approach and also with some of the in vivo data in Tables I and II, we constructed a flowchart of the immune and neuroendocrine systems that included all interactions across species, sexes, cells, and types of responses. The result was an all-encompassing host–immuno-

neuro-endocrine–parasite (HINEP) network connecting components within and between the systems of the host and the parasite (Fig. 1). The magnitude and complexity of the HINEP network includes practically all sexual hormones and many of the known immunological components. Simple inspection suggests the networks possible relevance to many other biological scenarios other than infection. Some of the events in the immunoendocrine network involve cellular differentiation, reproduction or death and de novo synthesis of receptors. The prominent and varied connections of the HINEP network with other hormones, well known to be related to stress and the inflammatory process (Besedovsky and del Rey, 2002; Dantzer et al., 2002), suggest that the network can also influence innate immune mechanisms (Yokoyama and Scalzo, 2002). The HINEP network of the host is related directly with the parasite (Morales-Montor, Baig et al., 2001; Morales-Montor, Mohamed et al., 2001), affecting its reproductive capacity through sexual and adrenal steroids that favor the expression of genes related to cellular differentiation and proliferation (Escobedo et al., 2004). The HINEP network contains circuits with forward and backward regulation, producing a great range of effects on the parasite or the host using several venues. Because some of the events in the HINEP network involve cellular reproduction and de novo synthesis of receptors, the network would seem capable of adapting and evolving.

There are other immunoendocrine networks described in the literature, which focus on the connections of the immune system with adrenals and nervous system, but secondarily or not at all with the gonads (Besedovsky and del Rey, 2002). The HINEP network presented in this study adds to the existing networks by incorporating the gonads and sex steroids as intrahost connections and the parasites' physiological systems as interhost connections.

Sex steroids act on a variety of immunocompetent cells affecting clonal expansion, phagocytosis, apoptosis, antigen presentation, and physiological responses to cytokines and chemokines. Thus, there is no question regarding the capacity of sex hormones to modulate the immune response. The significant question is, rather, what is their end effect on the host–parasite relationship and at which point does it act in each gender of host? A node in the network likely to be present under a strong sex-steroid modulation of acquired immunity includes the TH1–TH2 immune responses (Rook et al., 1994; Martin, 2000). Conflicting effects of androgens and estrogens on TH1–TH2 may possibly adjust the relationship of each host sex with the parasite and achieve either ''pacifist'' coexistence or ''belligerent'' confrontation. Antigen presentation, clonal expansion, cell activation, or apoptosis and effector macrophage functions, inflammation, and chemotactic responses are also likely candidates for significant hormonal control. The exploration of direct sex-steroid effects is as yet incomplete, and their end effects on the whole immune system, especially when acting in unison, are seldom studied. As can be gathered from the summary of a single hormone's actions on some of the immune parameters cited in Table III, estradiol seems to stimulate TH2, but there is no proof that it shuts down TH1 other than in experiments using mitogens instead of antigens. Similarly, testosterone decreases some B-cell–associated effector functions by reducing the levels of some TH2 cytokines (IL-1, IL-6, TNF-α) but has not been shown to interfere with TH1 functions. Dehydroepiandrostenedione (DHEA) stimulates TH1 immune parameters without apparent effect on TH2. DHT has effects similar to testosterone. Progesterone downregulates effector mechanisms (NK cytotoxic activity and macrophage cytokine and nitric oxide production), and prolactin also acts on the TH1–TH2 modulation node. Based on these observations and considering they probably are not independent effectors, however, it would be adventurous to predict a single hormone's end effect on a host's immunological protection or vulnerability to infection. This is even more likely when many of the sex hormone levels are not independent effectors and some hormones are probably operating simultaneously on the host's immune system when confronted with a parasite. Furthermore, more complexity and less predictability are to be expected from the likelihood of immune cytokines acting directly on the parasite, as do the sex steroids.

Notwithstanding the problem in understanding how real physiological networks actually work, their nodes might differ in terms of the number of connections. Herein lies the only hope for understanding relatively simple cause–effect relationships in parasitism. Firing of the most connected nodes may extend widely and rapidly throughout the network, inducing a significant change of phase in its equilibrium state and prompting the emergence of new properties (Oltvai and Barabasi, 2002; Strohman, 2003). Identification of the most connected nodes would be a way to begin their study as principal participants in SD to infection. To clarify the relationship existing between a host's SD and immunity with susceptibility to infection, we must look for these hierarchic nodes in the HINEP network. Some of them may be apparent at sexual maturity, but others might be more difficult to identify, having operated in the early ontology of the female or male immune and endocrine systems and then disappearing by the time of sexual maturation. One could hypothesize that important neuroendocrine system connections with the immune system are established during embryonic development, when gonadal differentiation occurs (Klein et al., 2002; Sinisi et al., 2003) and principal criteria for immunological self- and danger signal recognition also appear to be set (Matzinger, 2002; Medzhitov and Janeway, 2002).

To illustrate the HINEP network's explanatory and predictive properties of parasite infections, circuits that are turned on in experimental cysticercosis and schistosomiasis are illustrated with different colors in Figure 1. The circuits are not identical, but in both, IL-6 is a prominent feature, and the consequences of its overexpression, i.e., feminization, a TH2-leaning immune response, would be expected in other infections with all the rest being equal. In the network, there are also circuits capable of masculinizing the infected female if P-450 aromatase is directly inhibited, or by inhibition of GNRH in the hypothalamus, mediated or not by IL-6, or by enhancing the expression of 5α-reductase type II by means of an IL yet to be identified. In the opposite direction, the DHEA upregulation of TH1, for instance, endows the endocrine system with an ability to participate in immunological defense, a prediction that has yet to be verified in TH1-sensitive infections (Baszler et al., 1999; Suzuki, 1999; Rogers et al., 2002). In the network's schistosomiasis example, the parasite actively induces an immune response, which progressively leans toward TH2. Then, the increase in IL-β expression in the hypothalamus stimulates CRH production, which, in turn, stimulates pituitary adrenocorticotropin hormone (ACTH) (Morales-Montor, Newhouse et al.,

TABLE III. Effects and mechanisms of action by hormones on immunocompetent cells.*

Hormone	Effect on immune system cells	References
Estradiol	Polyclonal B cell activator; promotes B cells into plasma cells; ↓ bone marrow and thymus mass; ↑ IL-10 and IL-6 secreting cells; ↓ IFN-γ and IL-2 production; downregulates NK activity; upregulates phagocytocis by macrophages; ↑ serotonin and histamine release	Mandrup-Poulsen et al. (1995), Gaillard and Spinedi (1998), Chen et al. (2001), Roberts et al. (2001), Verthelyi (2001), Spinedi et al. (2002), Kitaya et
DHT	↓ T-cell response to mitogen; ↓ mast cell secretion; ↓ IL-1, IL-6, and TNF-α production; ↑ IL-2, TNF-α, and IFN-γ mRNA	Bijlsma et al. (2002), Morales-Montor, Baig, Hallal-Calleros (2002), Tanriverdi et al. (2003) al. (2003), Maret et al. (2003), Ou et al. (2003)
Testosterone	↓ B-cell response to mitogen; ↓ mast cell secretion of histamine and serotonin; ↓ IL-1, IL-6, and TNF-α production	Zhang et al. (2000), Bijlsma et al. (2002), Morales-Montor, Baig, Hallal-Calleros (2002), Tanriverdi et al. (2003)
Progesterone	↓ NK cytotoxic activity; ↑ TNF-α secretion; ↓ macrophage cytokine secretion; ↓ NO production	Mandrup-Poulsen et al. (1995), Gaillard and Spinedi (1998), Verthelyi (2001), Spinedi et al. (2002)
Cortisol	↓ Prostaglandins and leukotrienes production; modulates T- and B-cell maturation; affects trafficking and activation of proinflammatory cells; ↓ the production of IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, and TNF-α	Derijk and Berkenbosch (1991), Mandrup-Poulsen et al. (1995), Loria et al. (1996), Nussdorfer and Mazzocchi (1998), Feterowski et al. (2001), Besedovsky and del Rey (2002), Esch (2002), Morales-Montor, Mohamed et al. (2003)
DHEA	↑ IL-2 production; ↑ IFN-γ production; ↓ IL-6 secretion; ↓ TNF-α production; protects against neurooxidative damage; ↑ T-cell immunity; ↑ DTH reaction	Derijk and Berkenbosch (1991), Mandrup-Poulsen et al. (1995), Loria et al. (1996), Nussdorfer and Mazzocchi (1998), Feterowski et al. (2001), Besedovsky and del Rey (2002)
CRH	↑ IL-1 and IL-6 production; ↑ chemotaxis and superoxide production; ↑ B-cell proliferation; ↑ expression of T cells IL-2 receptors	Derijk and Berkenbosch (1991), Mandrup-Poulsen et al. (1995), Nussdorfer and Mazzocchi (1998), Besedovsky and del Rey (2002), Esch (2002)
ACTH	↑ Antibody production; cytokine secretion and proliferation	Panerai and Ottaviani (1995), Nussdorfer and Mazzocchi (1998), Ottaviani et al. (1999)
Prolactin	↑ Lymphocyte proliferation in response to antigen and mitogens; ↑ IFN-γ and IL-2 secretion; ↓ cell death mechanisms in immune cells; induces NK cells to their differentiation to prolactin-activated killer cells	Derijk and Berkenbosch (1991), Matera et al. (2001), McMurray (2001), Yu-Lee (2002)
VIP	↓ Production of proinflammatory agents; ↑ production of anti-inflammatory cytokines; both functions in activated macrophages; ↑ Th2 cell differentiation	Delgado et al. (2001), Voice et al. (2002), Ganea and Delgado (2003)
GH	↑ Adhesion of thymocytes to thymic epithelial cells; ↑ release of thymocytes from thymic nurse cells; ↑ intrathymic T-cell traffic	Sternberg (1997), Weinstock and Elliott (2000)
Thyroid hormones	Affects primary B-cell development because of reduced proliferation of immature B-cell precursors	Dorshkind and Horseman (2001)
Vasopresin and oxitonin	↑ Cell proliferation	Dorshkind and Horseman (2001)
Encephalins	Low doses: ↑ activates B and T cells; high doses: immunosuppression	Dorshkind and Horseman (2001)
Endorphins	↓ Antibody production and proliferation	Machelska and Stein (2002)
hCG	↓ Proliferation of T and NK and induction of T suppressors	Pope (1990)
Melatonin	Affects thymocyte maturation and differentiation	Hotchkiss and Nelson (2002)

* Abbreviations and symbols: DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; CRH, corticotrophin; ACTH, adrenocorticotrophic hormone; VIP, vasointestinal peptide; GH, growth hormone; hCG, human chorionic gonadotrophin; DTH, delayed-type hypersensitivity; ↓, decrease activity; ↑, increase activity.

2001). Concomitantly, IL-6 and migration inhibitory factor could be regulating ACTH production directly in the pituitary gland. The ACTH production, in turn, stimulates adrenal glands to produce cortisol and DHEA, together with TNF-α, which can directly inhibit parasite growth. Infection triggers the immune response of the host by mediating the neuroendocrine system at HPA axis level (Morales-Montor, Mohamed et al., 2003). The consequent microenvironment could be more permissive for the establishment and growth of the schistosome. The network also exhibits the possibility of HPA axis hormones to act directly on the parasite, affecting its reproductive capacity through adrenal steroids that favor the expression of genes related to cellular differentiation and proliferation (Morales-Montor, Mohamed et al., 2001). On the other hand, in cysticercosis, the nodes of interaction are by way of the hypothalamus–pituitary–gonadal axis. Infection with the metacestode results in a feminization process and in a TH1–TH2 shift of the host's immune response. The cysticerci actively induce a TH2 immune re-

sponse. Then, the increase in IL-6 production in turn stimulates estradiol production by directly activating the enzyme P-450 aromatase and at the same time increasing pituitary follicle-stimulating hormone levels. Estradiol would then cycle back to favor the TH2 response further. In turn, the decreased testosterone production inhibits the TH1-dependent cellular response. The consequence is the change of the host's hormonal microenviroment from restrictive (male) to permissive (female) for cysticerci growth. The network also illustrates the possibility that the host's sex hormones may act directly on the parasite, affecting its reproductive capacity through sex steroids that favor the expression of genes related to cellular differentiation and proliferation in many animal species (Fig. 1).

The HINEP network's prowess, with its manifold forward and backward regulations in operation, is congruent with the variegated profiles of Infection-SD and Immune-SD in the various host–parasite systems. It does not, however, necessarily imply or deny that there will be differences between sexes in the final results of a given confrontation with a parasite, reached perhaps by different mechanisms in different host sexes. A functional feature of complicated, random, or scale-free networks is its stability before random perturbations, whereas strategic perturbations ''break'' them to pieces (Oltvai and Barabasi, 2002; Strohman, 2002). This could explain why there are some sex-unbiased parasitic diseases. Perhaps only a few parasites are capable of triggering a profound general change in the state of the network that results in Infection-SD, a property limited to those parasites connecting with the complex hierarchical immunological nodes of the network and the sex steroids.

IS THE HINEP NETWORK INVOLVED IN OTHER MEDICAL AND BIOLOGICAL PUZZLES?

The literature search revealed an extremely complex HINEP network, involving hormones and cytokines that predict potent interactions in events generally attributed to the exclusive operation of single systems in response to simple precepts (reproduction and defense). Therefore, much plasticity and multifunctionality in a network are not without risk. Absence of control could lead to the loss of tolerance and autoimmune problems (Derijk and Berkenbosch, 1991; Lechner et al., 1996) or be involved in the immune compromise of aging (Panerai and Ottaviani, 1995), in the pathophysiology of some infections in which inflammation is a prominent effector of pathology (Mandrup-Poulsen et al., 1995; Henri et al., 2002), or even in some combination of all the above. Moreover, the HINEP network could connect parasite infections with other diseases that seem alien to the immunological and endocrinological domains, such as arterial hypertension (Peeters et al., 2001), atherosclerosis (Chae et al., 2001), and cancer (Herrera and Ostrosky-Wegman, 2001; Polat et al., 2002).

Many other biological questions emerged from the review of the literature on SD, each pointing to avenues for future research. We shall focus on 2 of the more prominent ones, which, in turn, involve many subsidiary possibilities. First, why is there SD in the immune response? Second, is there evidence to suggest that parasites have influenced the evolution of their hosts' Immune-SD?

The very complexity of the HINEP network hints at reasons for Immune-SD other than the self or foreign concept. Perhaps it has evolved as the best mechanism for individuals of either sex to confront infection successfully, even if by different mechanisms, and also to solve with precision gender-specific challenges, like pregnancy (Grossman, 1989), or perhaps the consequences of their territorial, mating, and social behaviors (Zuk, 1994; Kavaliers et al., 2001).

The selective pressure driving evolution toward Immune-SD, matching in importance the defense of the host against infection, is to permit reproduction in a dioecious species without much immunological compromise (Grossman, 1989; Gaillard and Spinedi, 1998; Agrawal and Lively, 2001; Charles et al., 2002; Moore and Wilson, 2002; Owens, 2002; Potti et al., 2002; Tella et al., 2002). This compromise could be achieved by a transient, immunologically specific allowance of female pregnancy with an offspring that is half-foreign, designed in terms of immunoendocrine signaling that does no damage to an effective response to a pathogen (Martal et al., 1995; Matzinger, 2002; Medzhitov and Janeway, 2002). Pregnancy demands for immunological allowance would originate from the advantage of species diversification gained through gender dichotomy. Its satisfaction would call for occasionally fastidious but transient immunoendocrine regulation by hormones and cytokines so that the fetus is not damaged (Barnea, 2001). Immune-SD may provide males with the specialized ability to better cope with their more stressful and dangerous lives when displaying their sex-specific behaviors (Kavaliers et al., 2001; Spinedi et al., 2002). Thus, the hosts that get the best trade-off between the need to diversify and the need to survive would appear to have the better chances to evolve. Even the parasite could benefit from the host's Immune-SD. For example, the parasite-restrictive males in the case of murine cysticercosis may be regarded as behaviorally enhanced vehicles toward the parasite's final destiny in the gut of carnivores (Willis and Poulin, 2000; Gourbal et al., 2001). In turn, the cysticercus-permissive females, when infected with the eggs of *T. crassiceps*, would act as the optimal hosts for their massive reproduction (Poulin and Thurn, 1996; Zuk and McKean, 1996; Panhuis et al., 2001).

The level of complexity introduced in the decision-making process of immune events by the powerful HINEP network regulatory capacity promises to enlighten persistent immunological puzzles such as tolerance and autoimmunity, the connection with infection of seemingly unrelated physiopathological events such as hypertension and cancer, and the role of Immune-SD in species diversification and individual behavior. The roles of sex steroids in the ontological development of the immune system and in acquired and innate immune responses promise invaluable insights and beg for more research.

CONCLUSIONS

There are many exceptions to the female host supremacy paradigm in parasitic infections of mammals, too many to leave unquestioned. Indeed, testosterone is involved in the immunoendocrine interactions triggered by infection, but so are many other hormones and cytokines that act as a network in which the contributions of its single effectors are unclear. Instead, important properties, like infection and immune sex-associated differences, may emerge from the network as a whole. The role of the host's immune system as the only effector of SD in parasitism is not clear; it is insufficiently explored, and it is not

uniformly implemented, even in the most studied host–parasite systems. Finally, the parasite's direct response to the hormonal environment of each host sex has been overlooked as a significant contributor to host SD in parasitic infections. In fact, it would appear that the conflicting findings in murine *T. crassiceps* cysticercosis with the female supremacy paradigm in parasite infections provoke even greater sensitivity to the host's sex steroids, i.e., parasite driven estrogenization and deandrogenization of infected male mice and permissiveness of the female mice TH2 inclined immune profile toward cysticercus proliferation.

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