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Dysregulation of Strongyloidiasis: a New Hypothesis

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Pathogenicity is but an accident in the life of a parasite.
Theobold Smith, 1911

INTRODUCTION

No other human parasitic nematode has been associated with such a broad spectrum of manifestations and been implicated in so many different clinical syndromes as *Strongyloides stercoralis*. Like other enteric parasitoses, strongyloidiasis has been classically regarded as the cause of a wide variety of gastrointestinal ailments, ranging from the ill-defined "dyspepsia" and "postprandial bloating" (3, 14, 20, 81) to diarrhea and malabsorption (12, 82), although the occurrence of malabsorption has been disputed by a carefully controlled study (38). More severe gastrointestinal presentations have been reported for some patients, including upper and lower intestinal bleeding (9, 22), jejunal perforation (64), emphysematous gastritis (114), appendicitis (89), symptoms mimicking ulcerative colitis (8, 13), granulomatous hepatitis (75, 93), eosinophilic ascites (71), and profound electrolyte imbalance leading to cardiac arrest (63). A chronic, highly pruriginous dermatitis known as larva currens is well documented in patients infected with certain strains of *S. stercoralis* (5, 109), and chronic urticaria has also been described (16). Generalized purpura has been reported in association with overwhelming infections (62, 111). Intractable diarrhea, sepsis, pneumonia with alveolar hemorrhage, meningitis, and brain abscess are among the most common manifestations of the usually fatal disseminated hyperinfection (61, 74, 104). In addition to these well-documented syndromes, the literature on strongyloidiasis includes a number of legitimate speculations about the relationship of *S. stercoralis* to conditions such as parasitic vasculitis (112), arthritis (2, 33), and profound hypokalemia resulting in muscle paralysis (63, 108) as well as occasional fanciful claims that *S. stercoralis* is the cause of pancreatic carcinoma (106), depression (56), and sexual dysfunction (1, 96).

In contrast to this wealth of information about the clinical manifestations of *S. stercoralis*, our knowledge of the basic biology of this parasite and its relationship with its host remains grossly inadequate. The purpose of this article is to integrate the available biological and clinical information into a comprehensive theory of disseminated strongyloidiasis and indicate possible areas for future investigation.

THE LIFE HISTORY OF *S. STERCORALIS*: SIFTING FACT FROM MYTH

Schad, a particularly experienced investigator of the biology of *S. stercoralis*, has recently noted that although most contemporary review and textbook accounts of the life history of *S. stercoralis* are in general agreement, several uncertainties about the accepted pattern of this history remain unresolved (101). Because a number of these controversial aspects are crucial to the present discussion, I will explore them in some detail after outlining the life history of *S. stercoralis* as it is generally understood.

The Classic Life Cycle

As shown in Fig. 1, the life cycle begins when filariform larvae penetrate the intact skin of a susceptible host, enter a venous or lymphatic channel, and are passively transported to the lungs (40, 101). Here they break out of the capillaries into the alveoli, migrate upwards into the trachea as they

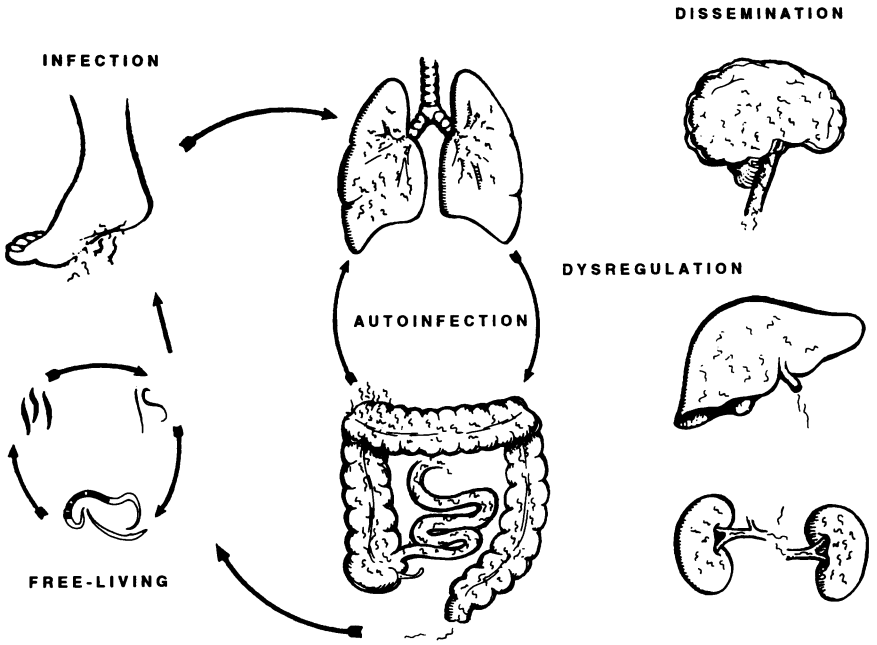

FIG. 1. Classic life cycle of *S. stercoralis*.

mature, and are eventually swallowed into the stomach. Males have been identified in the stools of infected patients and dogs only by Kreis in 1932 (68) and by Faust 1 year later (30). Since no other researchers have detected parasitic males, Kreis' and Faust's findings have been largely ignored (101). Parasitic females lodge in the lamina propria of the duodenum and the first portion of the jejunum, where they lay a small number of eggs per day. From the hatching eggs emerge rhabditiform larvae, which migrate into the intestinal lumen and eventually pass with the feces into the external environment. Here, depending on unspecified favorable or unfavorable circumstances of temperature and humidity, the rhabditiform larvae may either molt directly into infective (parasitic) filariform larvae, able to repenetrate the skin of a suitable host, or switch to a free-living cycle. In this latter indirect, or heterogonical, cycle, four ecdyses (molts) lead to the development of adult male and female worms. These mate and produce a generation of offspring whose filariform stage forms will have the ability to reenter parasitic life. A small portion of the rhabditiform larvae are believed to molt within the host's intestine into the filariform stage. These larvae penetrate the colonic wall or the perianal skin, complete the internal cycle, and establish themselves as mature adult females in the small intestine. This process, known as autoinfection, is believed to represent the mechanism by which *S. stercoralis* can persist virtually indefinitely in infected hosts.

Where Do All the Worms Go?

Serious questions about the validity of this model were not raised until studies in an experimental canine model of disseminated strongyloidiasis revealed that only a few larvae could be recovered from the lungs of dogs with massive hyperinfection (53, 54, 103). Later, in a series of experiments based on the compartmental analysis of radiolabeled larvae and interpreted by mathematical modeling, Schad and his colleagues at the University of Pennsylvania presented convincing evidence that, in these dogs, the tracheobronchial route was not used by the majority of the migrating larvae. According to their model, larvae starting their migration in the skin (as in a primary infection) or in the distal ileum (as in autoinfection) were not more likely to complete their cycle by passing through the lungs than through any other organ: in other words, the migratory pathway appeared to consist of a random spread throughout the body (102). The authors predicted that it would be difficult for clinicians to believe that the lungs may not be the principal migratory pathway of these parasites, given the large numbers of larvae often found in bronchoalveolar lavage fluid from hyperinfected patients. Their prediction is indirectly confirmed by the fact that no clinical report on human strongyloidiasis written since the publication of that article makes any reference to it.

Determining the autoinfectious migratory pathway is not only an issue of profound biologic importance but is also critical to our understanding of the host mechanisms that may participate in the regulation of internal infection. If we do not know where the larvae go, we cannot begin to ask germane questions about what happens to them.

REGULATION OF AUTOINFECTION

An Anthropocentric View

Although more complicated than that of any other human parasitic nematode, the life cycle outlined above is attractive because it fits the accepted concept of opportunistic infection and provides a simple framework on which to build an elegant explanation of the development of hyperinfection and dissemination. According to this paradigm, chronic, well-regulated infections are sustained by a relatively low and stable number of adult worms that reside in harmony within their host's intestine, where they lay eggs that promptly liberate rhabditiform larvae. Most of these larvae are passed with the stools, but an indeterminate percentage of them molt within the gut into filariform larvae and penetrate the intestinal wall or the perianal skin. After entering the venous circulation, they migrate to the lungs,

eventually complete the cycle, and establish themselves in the small intestine as adult females. By tacit consensus unsupported by solid evidence, the rate of autoinfection is believed to be regulated by the host's cell-mediated immunity (61, 74, 104). When this regulatory function fails, as happens in patients treated with corticosteroids, increasing numbers of autoinfective larvae complete the cycle, and the population of parasitic adult worms increases (hyperinfection). Eventually, the extraordinary numbers of migrating larvae deviate from the canonical route (intestine → venous bed → lungs → trachea → intestine) and disseminate to other organs normally not reached (meningeal spaces and brain, liver, kidneys, lymph nodes, and cutaneous and subcutaneous tissues), where they cause hemorrhage by breaking capillaries, elicit inflammatory responses, and implant gram-negative bacteria carried from the fecal material present in the colonic lumen. The result is disseminated strongyloidiasis, a fatal syndrome most frequently characterized by severe diarrhea, sepsis, pulmonary hemorrhage, and bronchopneumonia and less commonly by various combinations of meningitis, brain abscesses, hepatitis, splenitis, and purpura. This view of the pathophysiology of chronic autoinfection and dissemination, which most researchers with a specialized interest in this parasite, including myself, have espoused and propagated (40, 74, 101), is found on the postulate that the host is the only keeper of the balance. However, the assumption that *S. stercoralis*, if left unchecked by an external regulatory mechanism, would multiply inordinately and essentially commit suicide seems difficult to reconcile with the clever ways of *S. stercoralis*, a careful and versatile parasite whose destiny is so intimately connected to that of its host.

The Parasite's Viewpoint

The theory of host immune control fails to consider that the parasite may play a crucial role in its own regulation. That intestinal helminthic parasites could regulate the size of their own population was recognized by those who named the pork tapeworm *Taenia solium* and is clearly apparent to the speakers of languages such as Italian, in which the popular name for this parasite (*verme solitario*) clearly and even sympathetically conveys the message of the worm's loneliness. The adverse impact of increased population density on egg production and growth ("crowding effect") has been demonstrated for several intestinal nematodes (99). Although in such studies it is always difficult to separate the influence of host resistance from direct parasite-to-parasite effects, it seems clear that in a normal host-parasite relationship, the parasite may reach a particular population size or a critical biomass, and then unknown regulatory mechanisms intervene to limit the population (4, 99).

That hyperinfection and eventual dissemination may be the result of profound changes in the developmental biology of the parasite was first hypothesized by Galliard, a French experimental and clinical investigator whose work has been largely ignored (35–37). Among other astute observations, he noted that repeated passage in dogs seemed to alter the proportions of rhabditiform and filariform larvae in fecal cultures, speculated about the existence of different geographic strains of *S. stercoralis*, and investigated the relationship between glucocorticosteroids and adrenocorticotropic hormone (ACTH) in experimental canine hyperinfection. Not satisfied with host-centered explanations for hyperinfection, such as slowed intestinal transit or decreased resistance, Galliard suspected that changes occurring in the parasite itself disturbed its relationship with the host. Galliard did not, however, indicate what such changes might be.

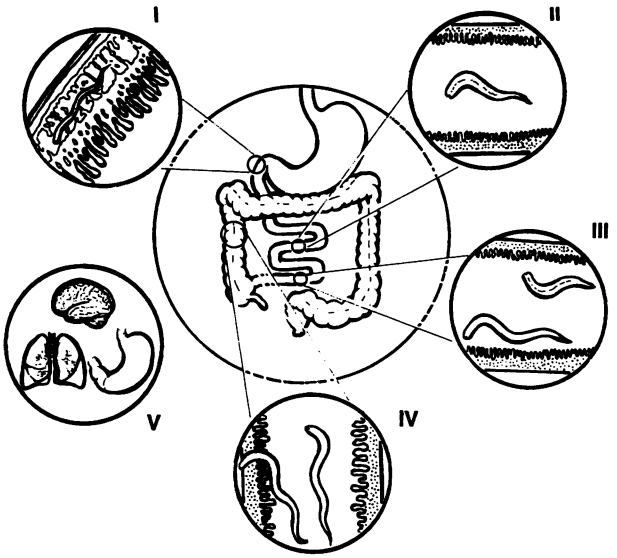

FIG. 2. Different compartments where regulatory mechanisms could be operative. (I) The adult female laying eggs in the lamina propria of the small intestine. (II) The intraluminal environment populated by rhabditiform larvae. (III) Representation of the unknown site where rhabditiform larvae molt into filariform larvae. (IV) The intestinal wall that filarifom larvae must cross to initiate a new autoinfectious cycle. (V) The unknown extraintestinal migratory spaces and tissues that may be reached by migrating larvae.

S. stercoralis is equipped with broad developmental plasticity, which allows it to shunt its reproductive resources in the direction most appropriate for the environmental conditions. In the external environment, unknown factors, probably related to the likelihood of transmitting the infection to new susceptible hosts, may pressure a larva to select parasitic or nonparasitic life. Although these mechanisms may be of great importance in the regulation of the universal population of this species, here I shall limit my discussion to the means by which a parasitic population in a single host not exposed to external reinfection ("closed population") may interact with its host to regulate its own size.

Possible Regulatory Sites of a Closed *S. stercoralis* Population

Figure 2 illustrates five scenes from the parasitic life of *S. stercoralis*. In each of the compartments, the parasite could be subjected to a number of different regulatory influences. The female adult work dwells in the lamina propria of the proximal small intestine (compartment I). In this location, a crowding effect might be operative in regulating the worm's longevity or reproductive activity. Longevity may depend on nutrient availability or on direct host influences (specific or nonspecific immune responses). Fertility and egg output might be affected by the parasites themselves (for example, through chemical mediators that would deliver a stimulatory or inhibitory message to the neighboring worms) or by the host, by means of specific immune responses (e.g., antibodies or sensitized T cells) or nonspecific inflammatory responses (e.g., lymphokines or eosinophils). In this compartment, similar mechanisms could affect egg viability and maturation. Once a feeding larva (stage L_1 or L_2) reaches the

small intestinal lumen (compartment II), its survival may be affected by the availability of appropriate nutrients and by other host-dependent environmental conditions, such as the acidity and composition of the intestinal fluid. At this level, secretory antibodies might also play a role in larval survival. Compartment III (arbitrarily symbolized as a more distal segment of the small intestine) represents the unknown site where the change (by molting) of rhabditiform larvae (L_2) into infective filariform larvae (L_3) takes place. This event, which is crucial to the maintenance of the autoinfectious cycle, may be predetermined at birth in each larva and may be either promoted or inhibited by intraluminal factors. Once the filariform larvae have developed, their progression to the successful completion of a new parasitic life cycle may be prevented by regulatory mechanisms in compartments IV (the colonic wall through which they migrate) and V (the extraintestinal spaces). These regulatory mechanisms may include inflammatory responses directed at the larvae when they cross the intestinal wall, during their residence in body cavities and fluids, and again when they cross into the intestine as a last step of their autochthonous cycle.

Having speculated about potential sites of regulatory activity, I would like to be able to present evidence that such events do or do not take place in these sites. Unfortunately, the existing information is minimal and fragmentary. In the few biopsy and resection specimens available from patients with chronic, well-regulated strongyloidiasis in which adult worms and eggs are visible, little or no inflammatory infiltrates were seen in the immediate proximity of the worms (43, 47). For some patients with severe but apparently not disseminated strongyloidiasis, conspicuous inflammatory changes in the small intestine have been described (113). These, however, were autopsy studies performed in Brazil, where many other enteric parasitoses are endemic, and the specificity of these findings has not been confirmed. In experimentally infected dogs sacrificed at various times during the course of uncomplicated, nondisseminated infections, no inflammatory cells are detected around the adult worms or their eggs (39, 54). The only conclusion that can be derived from these findings is that the adult worm is probably not a primary target of cellular responses. The possibility still exists, however, that antibodies or chemical mediators directly or indirectly affect the worms. Dead larvae of any type are found only rarely when fresh stool samples from infected hosts are examined. When they are found, they represent only a small percentage of the total larval output. Thus, it is unlikely that functionally significant intraluminal larval killing occurs. Neither the site nor the rate of larval molting is known; consequently, there is no information on how this phenomenon is regulated. Filariform larvae are frequently seen in histologic sections from the colon, lungs, lymph nodes, and other organs of patients who die of disseminated strongyloidiasis (43). The information obtained from the examination of these tissues contributes little to our understanding of the regulation of strongyloidiasis for the following reasons. First, it is virtually impossible to establish whether an organism seen in a tissue section was dead or alive when the tissue was obtained. Rarely, a larva can be seen within a granuloma, and this is clear proof that such a larva had been dead for some time. However, we still do not know whether it had been killed by the host or died accidentally during its migration and whether the release of antigens following its death elicited a more conspicuous inflammatory response than did the living larva. Because many more apparently intact larvae are usually seen in such specimens, I am inclined to believe that larval killing in host tissues is negligible. Second, the patients whose tissues contain visible larvae are those with overwhelming infections; therefore, the failure to find evidence of larvicidal activity in their tissues does not prove that this is not a mechanism of control in immunocompetent hosts. The small numbers of migrating larvae during controlled autoinfection essentially preclude the possibility of finding them in histologic sections from any organ, even in experimental animals. Thus, this question also remains unanswered.

HYPERINFECTION: THE ULTIMATE DYSREGULATION

Dissemination is a clinical concept that implies that large numbers of parasitic forms (mostly filariform larvae) reach extraintestinal organs and inflict clinically evident damage. In this discussion, I shall use the term in this sense, as it is generally understood. The reader should bear in mind, however, that the extraintestinal dissemination of larvae is likely to occur continuously during autoinfection, mostly through the lungs, according to the classic scheme, or through many other organs, if Schad's model of random migration is correct. During controlled autoinfection, the small numbers of wandering larvae remain undetected. The event that brings silent dissemination to the clinician's attention is hyperinfection, the amplification of the autoinfectious cycle that expands the previously stable parasitic population to a critical level beyond which the biomass of the parasites is incompatible with the host's health.

Let's Do the Numbers

Hyperinfection and dissemination remain abstract notions unless one analyzes the numbers involved in the progression from an asymptomatic parasitosis to an overwhelming, life-threatening infection. The numbers of adult worms residing in the intestines of immunocompetent patients with chronic asymptomatic infections are not known. Two sets of observations, however, suggest that such infections are sustained by very small numbers of intestinal parasites. First, it is rare to find more than a few rhabditiform larvae per gram of feces in the stools of infected patients. Although we do not know how many eggs are produced each day by the parasitic females, patients with clinically silent uncomplicated infection have been found to pass between 100 and 2,000 larvae per day in the feces (39). Dogs experimentally infected with an inoculum of 1,000 filariform larvae of a human strain of *S. stercoralis* pass between 0 and 30 larvae per g of feces per day (equivalent to a maximum of 3,000 to 5,000 total larvae per day). Usually, between 50 and 300 adult worms can be recovered from the intestines of these dogs, and certainly not all intestinal worms are recovered by the procedure used (39). The uteri of female worms recovered from infected animals rarely contain more than 10 or 12 eggs. One can estimate that each adult produces a maximum of 15 larvae per day. Therefore, if an extrapolation can be made from such imprecise data, the adult worm population of a host passing 1,000 larvae per day may be in the neighborhood of 70 to 100 individuals. Let us assume, for the sake of this discussion, that a patient harbors 100 worms in the small intestine and that each worm produces 10 larvae per day. In experimental studies with *Erythrocebus patas* monkeys (58) and beagle dogs (54, 103) infected with human strains of *S. stercoralis* and maintained on high doses of corticosteroids, we have recovered more than 300,000 adults from the intestine. Some of these dogs passed more than 20,000 larvae

per g of feces per day, and the total daily fecal volume was over 150 g. Thus, the daily larval production in these animals exceeded 3×10^6 units. Likewise, in reports of patients who die with disseminated strongyloidiasis, descriptions of the numbers of worms or larvae found in the gut lumen, body fluids, bronchoalveolar washings, and tissues are usually quite dramatic, with a liberal use of expressions such as "innumerable," "myriad," "enormous numbers," etc. (61, 74, 104). Thus, to understand the pathogenesis of disseminated strongyloidiasis, we must explain how the worm population can increase from 100 to 300,000, sometimes in the space of a few days or months.

To serve our purpose, a simple model of autoinfection must first explain how an intestinal parasitic population can be indefinitely maintained in a state of balance. Manipulation of some parameters of the model must then produce results similar to those observed in infected hosts. As in all modeling, we need to make some assumptions. Here I have assumed that (i) the duration of a complete autoinfectious cycle (from tissue penetration to production of eggs) is similar to that of the prepatent period (the time from the initial infection to the finding of larvae in the feces), or approximately 12 days; (ii) each adult worm produces 10 eggs per day, and each egg develops into a viable rhabditiform larva; (iii) the adult population sustaining chronic infection remains stable because dying adult worms are constantly replaced by the autoinfectious cycle; and (iv) the mortality rate of adult worms in an immunocompetent host is 10% per year. I have also assumed that the crowding effect—or the worms' ability to control their population—is completely debilitated during dysregulation and that the intestinal population can therefore grow indiscriminately until it reaches a critical size that kills the host. The "successful molting rate" (i.e., the percentage of L_2 larvae that transform intraluminally into L_3 forms and complete a cycle by growing to fecund adult females) that will sustain a balanced population is approximately 0.003%. This means that the molting of only 1 of every 33,000 L_2 produced is sufficient to replace the dying adults and maintain a stable population.

Table 1 depicts three possible scenarios resulting from substantial changes in the molting rate. In the first example, the successful molting rate was increased by a factor of 10^3, to 1 larva for every 33 L_2 produced. In this case, an initial population of 100 intestinal adult worms will grow to approximately 5,000 in the course of 15 cycles (6 months), and it will reach 340,000 worms in another 6 months. In the second example, assuming an increase in the molting rate to 30% (or a 10^6-fold increase from the baseline of 1 molt per 33,000 larvae), it will take only 2 months for the population to reach 360,000 worms. If all the larvae molt intraluminally and repenetrate successfully (as in the third example), more than 10^6 worms will be present in the gut in a little over 1 month. These figures are realistic, both in terms of worm numbers and time necessary to develop dissemination. The median duration of steroid therapy in a series of patients with lymphoma was 3 months (50). There are also many reports of patients who developed fatal dissemination after less than 10 days of high doses of intravenous methylprednisone or 20 days of oral prednisone (26, 59, 65, 78). Other patients were on low-dose steroids for years before developing disseminated strongyloidiasis, and epidemiological evidence in most of these cases indicates that the patients already harbored the parasite when steroid therapy was initiated (32, 60, 69). We do not known how many worms these patients had before steroid therapy had been started, or how many worms they had in the intestine when their dissemination became apparent. However, in one case I and my colleagues have reported (50), the patient had a small intestinal resection for lymphoma less than 3 months before dying of disseminated strongyloidiasis. In a retrospective detailed histopathologic examination of the resected segment of gut, we were unable to demonstrate even a single parasite. Yet, shortly before death, the patient was passing thousands of rhabditiform larvae per gram of stool, and several hundreds of filariform larvae per milliliter were present in his bronchoalveolar lavage fluid. As noted above, 300,000 worms were found in the intestine of experimentally infected steroid-treated monkeys and dogs.

TABLE 1. Three scenarios for different rates at which rhabditiform larvae become filariform in the intestinal lumen and complete an internal parasitic cycle

Molting rate and cycle	Days	No. of:			
		Adults in intestine	Larvae produced	Larvae completing cycle	Total adult worms
3%					
1		100	1,000	30	130
10	120	1,061	10,610	318	1,379
15	180	3,942	39,420	1,183	5,125
20	240	14,636	146,360	4,391	19,027
30	360	201,765	2,017,650	60,530	262,294
31	372	262,294	2,622,940	78,688	340,982
30%					
1		100	1,000	300	400
2	12	400	4,000	1,200	1,600
3	24	1,600	16,000	4,000	5,600
4	36	5,600	56,000	16,800	22,400
5	48	22,400	224,000	67,200	89,600
6	60	89,600	896,000	268,000	358,400
100%					
1		100	1,000	1,000	1,100
2	12	1,100	11,000	11,000	12,100
3	24	12,100	121,000	121,000	134,100
4	36	134,100	1,341,000	1,341,000	1,475,100

Manipulations of other parameters of the model do not yield results that so closely match the observed events. For example, a change in the adult worm death rate would be of little consequence for the size of the population. Thus, it appears that an increase in the successful rate of molting is the key element in the progression to clinically manifest dissemination. The next step, therefore, is to understand the mechanisms that regulate the larval molting rate. Because absolutely nothing is known on this topic, we must be open to two contrasting possibilities. The first is that the intraintestinal molting rate is naturally high (for example, 30%), that large numbers of penetrating filariform larvae are continuously stopped by the host's immune system, and that only an infinitesimal portion of them complete the cycle (1 in 33,000 in the previous example). A depression of host immunity would allow the larvae to molt freely and unchecked, resulting in a dramatic population increase. In the second scenario, the larval molting rate is naturally low, and changes in the host's intestinal ecosystem promote an accelerated molting rate.

Depressed Immunity: Where Is the Evidence?

Most authors reporting cases of disseminated strongyloidiasis seem to uncritically accept the postulate that a depression in cell-mediated immunity is responsible for the parasite's escape from host control. This view needs to be challenged. First, the phrase cell-mediated immunity, coined several years ago, has become rather ambiguous in light of recent advances in immunology. Second, and more important, there is substantial evidence that immunosuppression and immunodepression are neither necessary nor sufficient to precipitate the dissemination of a previously well-regulated infection. Before formulating a new hypothesis, it seems appropriate to summarize some of the findings that are difficult to reconcile with the theory of cell-mediated immunity.

(i) Protein-calorie malnutrition is the single most common cause of immunodeficiency worldwide (105). In developing countries, where strongyloidiasis is endemic and malnutrition is virtually universal, particularly among children, disseminated infections have been reported for only a few patients, mostly, but not exclusively, individuals receiving corticosteroids for autoimmune diseases. This has been true in Latin America (6, 17, 23, 95, 98), Asia (73), and Africa (19, 92, 115).

(ii) Lepromatous leprosy, a condition that profoundly depresses cellular immunity, is not associated with disseminated strongyloidiasis unless steroids are used to treat complications such as erythema nodosum leprosum (94). In a Thai leprosy resettlement village, where I and my coworkers performed a study of the immune responses against *S. stercoralis* antigens, none of 21 patients with leprosy and parasitologically demonstrated strongyloidiasis had evidence of hyperinfection or clinically severe disease (28).

(iii) Renal transplantation used to be one of the conditions most commonly associated with disseminated strongyloidiasis (19, 83). Surprisingly, since the introduction of cyclosporin A in the early 1980s, no new cases in such patients have been reported. In a recent review of the topic, all renal transplant recipients with hyperinfection had been treated with steroids (27). The possibility that cyclosporin A may have a direct adverse effect on *S. stercoralis*, as it does on schistosomes (11) and filariae (10), has been suggested but not proven (100).

(iv) When AIDS emerged as a clinical syndrome often heralded by opportunistic infections, the Centers for Disease Control guidelines included extraintestinal strongyloidiasis as one of the diagnostic criteria. Contrary to this prediction, AIDS has not resulted in large numbers of disseminated infections, even in areas where strongyloidiasis is highly endemic, such as Central Africa and Brazil (15, 31, 41, 97). In fact, it has been specifically mentioned as one of the "missing infections" in AIDS (76, 91) and has been removed from the list of the human immunodeficiency virus (HIV)-associated opportunistic infections (85). Occasionally, a clinical vignette about a patient with AIDS reported to have overwhelming or disseminated strongyloidiasis appears in the literature. In some of the reports, the patients did in fact have strongyloidiasis, but there was no evidence of extraintestinal dissemination (7). Other patients had concurrent conditions, for example, lymphomas, that had been treated with chemotherapeutic drug regimens that included corticosteroids (29, 77, 110). A recent brief report from southern Brazil (84) suggested that in an area of that country where *S. stercoralis* is endemic, HIV-infected patients have a higher prevalence of *S. stercoralis* infection than the HIV-negative population, but the authors readily admitted that the incidence of overwhelming strongyloidiasis does not seem to be higher in the HIV-positive patients. It is certainly problematic to continue to accept that *S. stercoralis* autoinfection is regulated by cell-mediated immunity if the profound derangements in this branch of the immune system caused by AIDS do not promote dysregulation.

(v) Human T-cell lymphotropic virus type I (HTLV-I) infection is associated with defects in cell-mediated immunity. In Okinawa (34, 86, 116) and Jamaica (87), patients infected with this virus have been shown to have an increased prevalence of chronic strongyloidiasis and lower total and parasite-specific immunoglobulin E (IgE) responses. Although no increased incidence of disseminated infection has been observed in these patients, Newton et al. recently reported a case of *S. stercoralis* hyperinfection in a West Indian man who was infected with HTLV-I and had decreased humoral responses against *S. stercoralis* antigens (88). The authors postulate that HTLV-I infection in certain individuals may selectively impair immune responses that are critical in controlling strongyloidiasis. This hypothesis is interesting, but the rarity of spontaneous hyperinfection among HTLV-I-infected persons in Jamaica and Okinawa suggests that other unknown factors must intervene to precipitate dissemination in these patients.

(vi) Attempts to induce hyperinfection in experimentally infected dogs by immunosuppressing them with azathioprine have been unsuccessful except when azathioprine was used in association with corticosteroids (103).

(vii) Over the past several years, I have been involved in clinical and experimental work aimed at finding a relationship between the degree of parasite-specific immune responses and the behavior of strongyloidiasis. Human studies were performed with patients evidencing a wide spectrum of clinical manifestations, ranging from asymptomatic chronic uncomplicated infection to disseminated strongyloidiasis with a fatal outcome. This work included the examination of in vitro lymphocyte responses to parasite antigens (51) and the analysis of various types of parasite-specific IgG, IgA, IgE, and IgG subclass antibody responses (6, 23, 44–46, 49, 52, 55, 79). Animal studies involving similar methods were performed with dogs (54) and monkeys (48) experimentally infected with a human strain of *S. stercoralis* and later immunosuppressed with corticosteroids to precipitate dissemination. The cumulative results of this work have been reviewed recently (42). Here, it may be sufficient to say that although these studies resulted in the development of a number of clinically and epidemiologically useful serologic tools, no relationship between the magnitude of any of the immune responses examined and the behavior of the infection could ever be demonstrated. In each population studied, a small percentage (between 2 and 5%) of subjects with chronic, apparently well-regulated strongyloidiasis had no detectable parasite-specific responses of any kind, yet these apparently nonresponsive subjects were not sicker than the other infected individuals, did not appear to have larger infections, and, in the short periods of observation while the studies were conducted, did not develop signs or symptoms suggestive of hyperinfection. In contrast, a number of severely ill patients who eventually died of disseminated strongyloidiasis had high levels of parasite-specific immune responses.

Two patients with acquired agammaglobulinemia and strongyloidiasis have been reported (24, 107). Both of them had large, difficult-to-treat infections with a detectable pul-

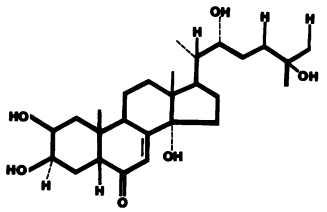

FIG. 3. 20-Hydroxyecdysone.

monary phase; neither, however, had the catastrophic clinical features of the dissemination syndrome.

One possible interpretation is, of course, that the tools at our disposal are not sensitive enough to detect subtler changes in the immune responses. However, the results of these studies further corroborate the circumstantial evidence discussed in this section that point at some other control mechanisms that may not necessarily depend on immune regulation.

Corticosteroids: the True Villains?

As a growing body of circumstantial evidence points away from the theory of immune regulation, a careful analysis of the published cases of disseminated strongyloidiasis suggests that corticosteroids may play a primary role in triggering the dissemination of strongyloidiasis.

(i) The vast majority of well-documented cases of hyperinfection and dissemination have occurred in patients receiving corticosteroids (26, 32, 50, 59–61, 65, 69, 74, 78, 98, 104, 105).

(ii) As mentioned above, in several well-documented cases, it took less than 10 days of high-dose corticosteroid treatment to transform a previously clinically silent undetected infection into overwhelming dissemination (32, 60, 69). I am not aware of any reports of patients who developed rapid dissemination after treatment with nonsteroidal immunosuppressive drugs.

(iii) Dexamethasone injected subconjunctivally in a patient who had undergone penetrating keratoplasty was sufficient to trigger severe disseminated strongyloidiasis complicated by sepsis, meningitis, and gastrointestinal hemorrhage (113).

(iv) The patients who develop rapid dissemination are most often those who receive parenteral corticosteroids. With rare exceptions (in patients with AIDS), disseminated strongyloidiasis is not accompanied by other opportunistic infections (for example, candidiasis, cytomegalovirus infection, or reactivation of toxoplasmosis). One possible interpretation is that it is not the degree of immunosuppression that is associated with dissemination but rather the agent used to suppress immunity.

(v) Disseminated strongyloidiasis has been reported in a man with a small cell carcinoma of the lung with ectopic production of ACTH (18) and in a diabetic woman receiving ACTH (21). Thus, elevated endogenous glucocorticosteroids may be sufficient to trigger dissemination.

FROM WORM TO BUTTERFLY

Ecdysteroids

Molting in insects (ecdysis) is controlled by the action of steroid molting hormones, known as ecdysteroids, that are primarily produced in the ovaries of adult females (57, 67). The formula of 20-hydroxyecdysone is depicted in Fig. 3.

Ecdysteroids in Parasitic Helminths

Ecdysteroids have now been identified in several parasitic helminths, although their function has not yet been elucidated (67, 80). Because ecdysteroidlike compounds were detected in the sera and urine of patients with filariasis and schistosomiasis, their potential use as markers of occult parasitic infections was explored (66). However, the initial enthusiasm for this line of investigation was dampened when similar substances were found in the serum of normal, nonparasitized individuals, although in lower concentrations (72). One possible interpretation of this latter finding is that certain metabolites of corticosteroids present in human serum and urine bear sufficient structural resemblance to ecdysone or 20-hydroxyecdysone that their epitopes can combine with the specific antigen-binding sites in the rabbit antisera used for the radioimmunoassays. It is attractive to speculate that if these compounds are able to compete for antibody-binding sites, they may also be able to compete for receptors and perhaps exert biologic activity in organisms equipped with such receptors. The relevance of these studies is substantial, as they provide the following background. (i) Ecdysteroids may be involved in transmitting molting signals in nematodes. (ii) The presence of ecdysteroidlike substances in humans with no parasitic infections indicates that some metabolites of human steroids may bear a structural resemblance to these molting steroids. (iii) In the presence of a great excess of such metabolites, as one would expect to find during glucocorticoid treatment, these metabolites might conceivably occupy ecdysteroid receptors in the parasites (receptors to which they do not bind under physiologic circumstances because of lesser specificity) and act as promoters of the molting process.

TOWARD A NEW THEORY OF DYSREGULATION

At this point, the stage is set to propose a new hypothesis to explain both the regulation and dysregulation of strongyloidiasis. The reader is cautioned that this is a highly speculative hypothesis based on very circumstantial evidence. It is presented to challenge an accepted yet equally speculative view of the regulation of this enigmatic parasite in the hope that a new theory will stimulate much-needed research on the basic biology of *S. stercoralis*.

Steroids, Not Immunosuppression, Precipitate Disseminated Strongyloidiasis

Over the course of the parallel evolution of humans and their parasites, *S. stercoralis* has developed the ability to reach an optimal population size in the duodenum of a human. If the initial infective dose (the number of larvae that penetrate the host's skin) is low, a higher rate of intraluminal molting is allowed until the size of the optimal adult population is reached. At this point, adult females decrease their production of ecdysteroids, and a very low molting rate, i.e., just enough to replace the dying adults, is maintained. During the initial adjustment period, the host has developed humoral and cellular immune responses directed at all tissue stages of the parasite (adults, eggs, and filariform larvae). These responses are not sufficiently strong to eradicate all the parasites, but they do exert an additional control over the size of the population. Their absence may allow the devel-

opment of larger parasitic populations, as in the case of the agammaglobulinemic patients described above, but does not cause total dysregulation because, to a large extent, the worms regulate themselves. Similarly, the presence of these host responses is not sufficient to prevent dissemination should the parasitic population's own regulatory mechanisms fail.

The amount of ecdysteroidlike substances generated by a normal healthy host is negligible. The administration of exogenous—and in some cases, even an excess of endogenous—corticosteroids results in increased amounts of ecdysteroidlike substances in the host's tissues, including the intestinal wall, where adult females reside. These substances send strong molting signals to many or even all the existing rhabditiform larvae, which transform intraluminally into filariform larvae in numbers unprecedented in the history of a regulated population. The available data are not sufficient to prove a dose-dependent effect, but it is indeed remarkable that the patients who developed fulminating hyperinfections after only a few days of steroid administration are those who received intravenous methylprednisone for acute transplant rejection (26, 59, 65, 78). Once a population has become very large (for example, 100,000 worms), it may continue to expand rapidly even at low molting rates, and the discontinuation of steroid therapy may not be sufficient to arrest the relentless growth process. The population has been irreparably dysregulated and forced to do what parasites have learned to avoid: kill their host.

Except When . . .

Like all theories, this one can be challenged from many sides, and it is just as vulnerable as any other theory. I shall address only the most obvious argument against it. How can we explain those rare patients who develop dissemination without receiving corticosteroids? A close scrutiny of the literature will reveal two broad categories of patients who developed disseminated strongyloidiasis in the absence of steroid therapy: (i) all cases reported before steroids were available, and (ii) severely malnourished children or youngsters from tropical countries. The former are exemplified by the patients reported by Ophulus in 1929 (90) and Kyle et al. in 1948 (70). Ophulus's patient was a 35-year-old man with chronic myocarditis. Even if the autopsy data are reinterpreted in light of modern knowledge, no apparent cause for immunosuppression can be identified. The patient studied by Kyle et al. was a man found at autopsy to have a huge mediastinal tumor of an unspecified nature. In this case, we may suspect a paraneoplastic syndrome with inappropriate ACTH production, similar to a more recent documented case (18). In Ophulus's case, and possibly in both, we may have to accept the concept that in some hosts, for reasons we do not understand, the adult worm population fails to achieve control of its density.

As for profoundly malnourished children in areas where *S. stercoralis* is endemic (25), I suspect that they acquired the initial infection when they were already immunodeficient and therefore incapable of mounting the initial response that may be crucial to the development of an ideal host-parasite relationship.

FUTURE DIRECTIONS

Strongyloidiasis is still an open field. Only a handful of researchers have dedicated their careers to this parasite, and our combined efforts have generated many more questions than answers. Among the basic biological questions, the regulation of intraluminal molting is, in my view, the most pressing issue and the one that, once unraveled, is most likely to explain how and perhaps why dissemination occurs. Clinically, the effects of *S. stercoralis* on the structure and function of the host's intestine remain unknown and await carefully controlled pre- and posttreatment studies. In the therapeutic arena, new drugs, both safer and more effective than thiabendazole, are urgently needed. Such drugs might be used not only to treat infected patients, but also to prevent dissemination in selected candidates for immunosuppressive and corticosteroid therapy.

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