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(Self-) infections with parasites: re-interpretations for the present

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Previously, scientists sometimes resorted to infecting themselves or colleagues with parasites, usually to assess the pathogenicity and obtain insight into the life cycles of the parasites, host specificity, and epidemiology. However, with recent research addressing the possible beneficial impact of intestinal helminths on a range of immune-mediated diseases in humans, these studies offer valuable information, although many are now considered unethical owing to a lack of experimental oversight and informed consent. Here, we critically review cases in which humans were deliberately infected with parasites. Moreover, we summarize the contribution of (self-) infections and propose protist and helminth candidates, chosen on the basis of several criteria, to test as possible therapy for selected human diseases.

Changing attitudes towards (self-) infections with parasites

In this review, we want to convince readers that experimental (self-) infections with parasites can be re-interpreted from a perspective that was usually not on the minds of scientists, who, mainly in the past, subjected themselves and other individuals to these experiments. In most cases, (self-) infections were used to elucidate life cycles of parasites, their transmission, host specificity, and/or pathogenicity; such data were difficult or even impossible to obtain by other means. Interestingly, many of these experiments are relatively unknown or forgotten, and most do not comply with ethical rules. In fact, ethical rules have changed dramatically over the past decades, and many of the experiments briefly surveyed here would be unacceptable under the International Code of Medical Ethics and the World Medical Association Declaration of Helsinki (Box 1). These codes of ethics, which put forward the necessity of informed consent and appropriate experimental oversight, were established to protect patients and research subjects from the deplorable exploitation that occurred in the past, including experimentation on institutionalized subjects, prisoners, those from less developed countries, and others who refused or were unable to consent.

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Keywords: self-infection; volunteers; protists; helminths; autoimmune diseases; helminth therapy.

1471-4922/
 http://dx.doi.org/10.1016/j.pt.2014.06.005

Positive aspects of parasitic infections

Recent research provides a rapidly growing body of evidence that some intestinal helminths may have unexpected beneficial functions for our bodies. Indeed, the steep increase in allergies in industrialized countries, chronic inflammatory diseases, and various immune-mediated disorders correlates with the efficient elimination of helminth infections over the past decade [1,2]. Not only has this correlation been further corroborated, but recent circumstantial evidence suggests that humans infected with helminths tend to have a lower incidence of immunological disorders, cardiovascular diseases, and even lower cholesterol [3,4].

Some parasites seem to be tuned finely to a given host, causing minimal, if any, pathogenicity [5]. In fact, their inherent immunogenicity may have a positive effect, owing to manipulation of the immune response of the host (reviewed in [6–8]). A solid causal link came from epidemiological studies, which demonstrated an inverse association between the presence of hookworm infections and numerous immunological disorders [9–12] (Figure 1). Generally speaking, the so-called 'Old Friends Hypothesis' postulates that contact with any kind of antigen stimulates the proper development of the immune system, whereas low exposure to antigens predisposes an individual towards hyperactive and otherwise inappropriate immune responses [13]. Hence, helminth parasites may have important protective effects against immunological disorders during early immune maturation [13].

Such an effect has been documented in clinical studies with humans with Crohn's disease (CD), ulcerative colitis (UC), and some other immune-mediated disorders (Figure 1), in which infection with a given helminth species resulted in a marked, and sometimes even dramatic, health improvement with no noted adverse effects [14–17]. Clinical studies have so far been performed with the pig whipworm, *Trichuris suis*, which occasionally parasitizes humans, and the hookworm *Necator americanus*, for which humans are a natural host [18]. Although some additional use of controlled infections with *T. suis* eggs have received much attention, for instance, positive effects on multiple sclerosis and autism [19,20] or pecan and other food allergies [21], the results are based on a small number of patients and can be considered only preliminary. Moreover, the effect of helminth therapy on rheumatoid arthritis or type I diabetes has also been studied in the murine model [7,22]. These important results inevitably point out

Box 1. Ethical rules according to the international conventions

International Code of Medical Ethics (57th World Medical Association General Assembly, Pilanesberg, South Africa, October 2006; http://www.wma.net/en/30publications/10policies/c8/index.html) defines the duties of: (i) physicians in general; (ii) physicians to patients; and (iii) physician to colleagues. We focus primarily on the duties with regard to patients:

- to always bear in mind the obligation to respect human life.
- to act in the patient's best interest when providing medical care.
- to owe his/her patients complete loyalty and all the scientific resources available to him/her. Whenever an examination or treatment is beyond the physician's capacity, he/she should consult with or refer to another physician who has the necessary ability.
- to respect a patient's right to confidentiality.
- to give emergency care as a humanitarian duty unless he/she is assured that others are willing and able to give such care.
- in situations when he/she is acting for a third party, ensure that the patient has full knowledge of that situation.
- not to enter into a sexual relationship with his/her current patient or into any other abusive or exploitative relationship.

World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013; http://www.wma.net/en/30publications/10policies/b3/index.html) states that medical progress is based on research that ultimately includes studies involving human subjects and defines the main ethical principles for this kind of research. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration. Moreover, this declaration defines that some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

Students, who are in an unequal power relationship and may feel obligated to participate in such research, are an example of a vulnerable group.

the renewed interest in controlled infections of humans with parasites. Therefore, in light of this argument, the time has come to reinterpret (self-) infections from the past carefully, along with briefly surveying reasons why they were originally conceived and executed. Although the first well-documented reports appeared at the end of the 18th century, most studies emerged during the early 20th century. The number dramatically declined during the second half of the last century, which is probably attributable to the development of ethical principles in research involving humans (Box 1).

One of the main contributions of (self-) infections is the observation of clinical effects and pathogenicity of the parasites studied. Whereas patients with any clinical symptoms seeking medical care inevitably attribute those to the pathogenic effect of parasites, even when the causal relation between the parasite and the symptom remains unproven, (self-) infections of typically healthy individuals are more likely to provide reliable data on the actual pathogenic effect and clinical signs. Unfortunately, there is an obvious tendency to select and keep citing studies reporting mainly pathogenic symptoms, whereas those noting negligible and/or mild clinical effects seem to be ignored frequently. A typical example is that of the broad tapeworm *Diphyllobothrium latum*, which is invariably associated with deficiency in vitamin B_{12} in the majority of medical and parasitology textbooks [26]; however, this was only documented in tiny fractions of infected humans, and was not observed in several recent self-infections.

(Self-) infections have also provided invaluable data on host specificity of several important human parasites, particularly protists. Indeed, without experimental human infections, the life cycles of parasites that solely mature in humans perhaps would not have been elucidated. From an epidemiological point of view, (self-) infections provided crucial data on the prepatent period and spontaneous clearing of infection, parasite fecundity, and longevity [24,25]. However, many studies would not comply with present ethical standards (Box 1), and the experimentation on uninformed 'volunteers' during the 20th century should never happen again. Below, we provide an overview of

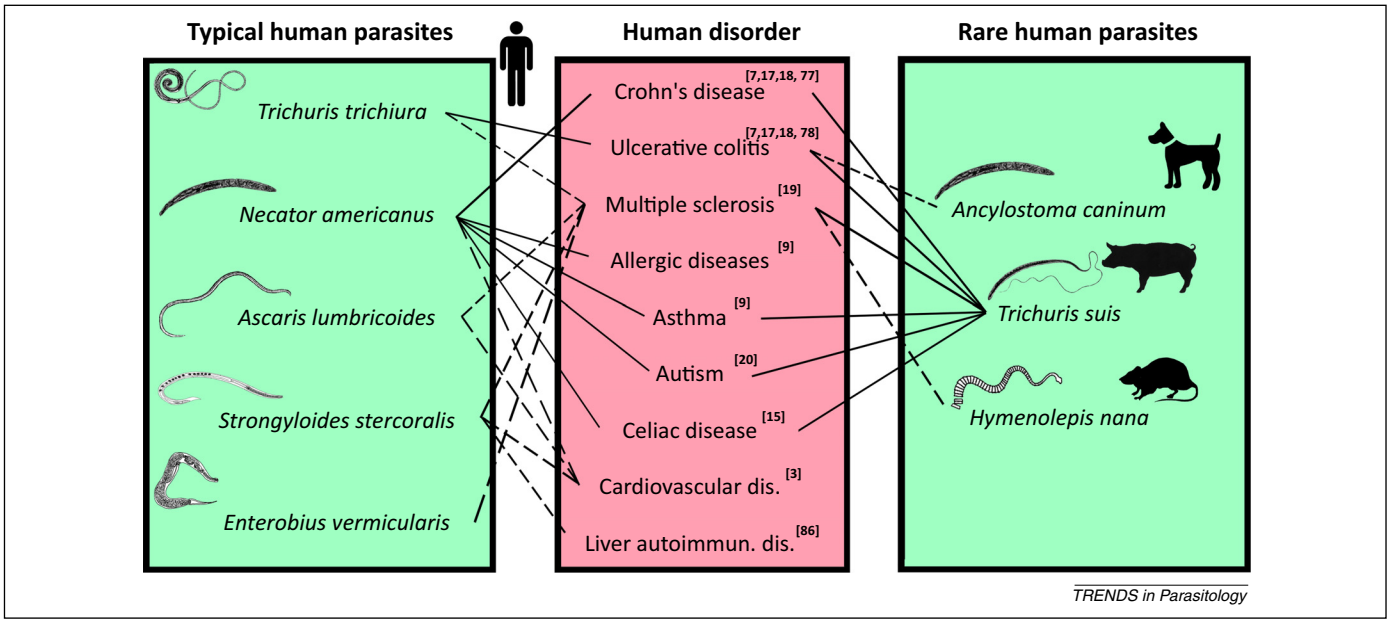

Figure 1. Overview of helminth species connected with immune-mediated disorders. Helminths used in therapy and those negatively associated with the occurrence of the immune-mediated disorders; solid lines connect parasites used in therapy of a given disease; broken lines connect parasites negatively associated with a given disease [3,7,9,15,17–20,77,78,86].

available information on (self-) infections and identify candidates with potentially beneficial effects on human health.

(Self-) infections with pathogenic protists

Relatively robust data inferred from self-infections or infections of individuals exist on the transmission and host specificity of trypanosomes causing African sleeping sickness of humans and nagana of livestock. In 1903, Ascenco inoculated himself and two Africans with trypanosomes from cows (i.e., nagana) [26], and Taute and Huber repeatedly infected themselves and 131 Africans with trypanosomes derived from the blood of dogs, horses, and mules [27]. Moreover, Corson injected himself and several volunteers with flagellates from vertebrate hosts and let himself and a colleague be bitten by infected tsetse flies, whereas Lester transferred 10 million trypanosomes from animals into three Europeans and 40 native Africans, probably without their informed consent [28,29]. Fortunately, none of these experiments resulted in a human infection but did provide strong evidence for the existence of morphologically indistinguishable subspecies of *Trypanosoma brucei* with different host specificity.

The life cycle and transmission by mosquitoes of *Plasmodium*, the causative agent of malaria, were deduced approximately 100 years ago in courageous experiments performed by Manson and others, who infected themselves with the tertian malaria; however, this is not to say that these discoveries would not have occurred eventually in experiments with proper oversight. *Anopheles* mosquitoes fed on a malarial patient in Rome were sent to London, where Manson allowed them to engorge on him, developing a microscopically documented disease [30]. To test the hypothesis that the spring bouts of malaria were due to infections acquired during the previous autumn, Schüffner and two colleagues successfully infected themselves with *Plasmodium vivax* through mosquito bites [31]. Moreover, two unnamed researchers infected themselves with *Plasmodium cynomolgi* to test the transmission of malaria from macaques to humans and showed typical clinical signs of malaria [32].

Clarification of other epidemiological aspects of malaria was achieved because of volunteers experimentally infected with *Plasmodium* spp from various primates and vice versa via *Anopheles* bites or blood inoculation. Most of these human infections were unsuccessful except for experiments with four *Plasmodium* spp. from Old and New World monkeys (*P. brasiliensis*, *P. eylesi*, *P. inui*, and *P. knowlesi*) and two from chimpanzees (*P. rodhaini* and *P. schwetzi*); these experiments led to new avenues for chemotherapy and vaccines [33–35] (reviewed in [36]).

Entamoeba histolytica is the causative agent of infamous amebiasis. Sadly, this knowledge was gained at the expense of Fritz Schaudinn's life, who died at the age of 35 from overwhelming amebiasis, a result of self-infection with the intention to distinguish between the harmless *Entamoeba dispar* and the pernicious *E. histolytica* [37]. Even so, this tragedy did not prevent Westphal and his friend from carrying out several experimental infections with *E. histolytica* cysts derived from the stool of a heavily infected patient, which resulted in severe dysentery. These life-threatening experiments with amebae demonstrated the dependence of clinical signs on infection dose and detected conspicuous differences in virulence of the same strain to different humans [38].

Maggiore inoculated humans with *Leishmania donovani* obtained directly from the bone marrow of a patient. Fortunately, this flagellate, responsible for the frequently lethal visceral leishmaniasis, did not establish an infection. The same author recorded another negative case of self-infection with *Leishmania tropica* [39]. Later, Thomson reported his unsuccessful self-infection with *Leishmania* spp., whereas Adler was able to experimentally induce and treat a *L. donovani* sore on his arm [40]. A type of intentional infection was 'leishmanization', that is, vaccinations with cultured virulent parasites, which was performed on a large scale in Iran, Israel, and the former Soviet Union. However, these campaigns were eventually abandoned owing to problems with the viability and infectivity of the injected organisms, the development of large uncontrolled lesions, and the enhancement of other skin diseases, as well as immunosuppression [41].

Several species of *Cryptosporidium* cause diarrhea in humans, which was determined by experiments with healthy volunteers infected with *Cryptosporidium hominis*, and who subsequently suffered from cryptosporidiosis associated with diarrhea, nausea, and vomiting [42]. In other experiments, volunteers developed less severe disease after swallowing *Cryptosporidium meleagridis* oocysts [43]. Outcomes of other experiments on volunteers infected with *Cryptosporidium* led to research on the development of vaccines (reviewed in [44]). Lastly, in 1953, five male volunteers were inoculated with cultured *Trichomonas vaginalis*. Three of them developed urethritis and had to be treated [45]. It is obvious that none of the abovementioned protists can be considered as a potential candidate for treatment of autoimmune diseases.

(Self-) infections with pathogenic helminths

Schistosomes were used in self-experimentations by Barlow, who infected himself with hundreds of cercariae of *Schistosoma haematobium*. His account of a more than 4-year-long infection provided unique data on clinical symptoms of urinary schistosomiasis [46]. Haas showed that cercariae of *Schistosoma* penetrated his skin extremely fast [47]. Kobayashi self-infected with another pathogenic helminth, a tapeworm of the genus *Spirometra* known to cause sparganosis, demonstrating penetration of the plerocercoid larvae through his intact skin [48]. Mueller and Coulston implanted larvae of *Spirometra* under their skin and observed development of the infection for half a year, but eventually resorted to surgery to remove growing larvae that migrated within their bodies [49]. Several researchers even decided to bring parasites from endemic areas in their own bodies for experimentations in their home countries [46,50–53].

The threadworm *Strongyloides stercoralis* is the most studied parasite in self-infections, and detailed descriptions of clinical signs and the course of infection in volunteers who exposed themselves to different doses of its larvae are available (reviewed in [54]). For example, Sandground infected himself several times; the initial infection

involved application of as many as 2500 larvae of *S. stercoralis* from another man to his forearm. He interpreted his illness following a later accidental exposure, characterized by malaise and eosinophilia, as the lack of immune protection following the initial infection [55]. As part of an extensive study on the transmission of *S. stercoralis* in different animal hosts, Faust experimentally infected himself and a volunteer with hundreds of larvae obtained from chimpanzee feces, which led to local erythema, bronchitis, and eventual shedding of larvae in the stool. After being inoculated with 500 threadworm larvae derived from feces of a rhesus monkey, another volunteer developed local erythema and shed larvae, but lacked pulmonary symptoms and the infection later resolved spontaneously [56]. Desportes infected himself by applying 2500 *Strongyloides* larvae from the stool of a pre-mortem gibbon to his forearm. In an eloquent report, he described erythema, cough, epigastric burning, constipation, and diarrhea [57]. Finally, Tanaka successfully infected himself with human-derived *S. stercoralis* larvae, allowing exact estimation of the prepatent period and a subjective description of acute strongyloidiasis in a previously uninfected individual [58]. An inexcusable case of self-infection, which was not at all in accordance with the ethical standards for research, was conducted by Wang, who intentionally infected himself and two other family members with lymphatic filaria, namely *Brugia malayi*; he had been documenting their infections for 10 years [59]. A vast historical account of helminth infections, including self-infection, is presented in a book by Grove [60].

Non- or mildly pathogenic human protists

Dobell occupies a unique position among scientists who used themselves to test the course of parasitic infections. He carried out successful experiments with *Endolimax nana*, *Entamoeba coli*, and *Trichomonas* spp. isolated from macaques, whereas his self-infections with *Dientamoeba fragilis* and *Enteromonas* spp. from the same hosts failed [61–65]. Furthermore, he provided evidence that *Entamoeba coli* is transmissible to humans, but remained physically normal during the infection, which persisted for approximately 6 weeks. In other self-infections, Dobell demonstrated that direct transmission of *D. fragilis* via trophozoites was unlikely because he remained asymptomatic and in 10 years never observed this protist in his stool, even after swallowing millions of trophozoites [65].

Experimental infections of 19 prisoners with defined numbers of cysts (up to one million) of the diplomonad *Giardia intestinalis* showed that individuals who were given doses higher than 10^4 cysts became infected, yet all but two almost symptom-less infections disappeared spontaneously after initial detection of parasites in the stool [25]. Failed transfers of *Neobalantidium* (*Balantidium*) *coli* administered as cysts and trophozoites from a naturally infected human to two volunteers exemplify the limits of experimental infections even with directly transmissible protists [66].

Non- or mildly pathogenic human helminths

One of the most detailed self-infection studies is that of Barlow, who on five occasions swallowed as many as 36 giant intestinal flukes (*Fasciolopsis buski*) obtained from a Chinese patient. He provided the first experimental evidence of a successful passage of a human-infective trematode from one definitive host to another, with the subsequent release of eggs [51]. A few years later, the same author swallowed 185 metacercariae of *F. buski* after their release from experimentally infected snails, eventually recovered 124 adult flukes from his stool, and observed surprisingly few clinical symptoms [50].

Early elucidation of life cycles of parasites would not have been possible without ostensibly 'ruthless' experimental infections. In 1855, Küchenmeister administered larvae of the pig tapeworm *Taenia solium* obtained from fresh meat to a murderer 48 h before his execution, and postmortem found juvenile cestodes in his intestine, thus linking *Cysticercus cellulosae* to the larval stage of *T. solium*, and later confirmed his conclusions by similar follow-up studies [67]. After life cycles were established, self-infections were instrumental in long-term descriptions of clinical signs, such as in the case of another human intestinal taeniosis caused by the beef tapeworm *Taenia saginata*, carefully followed for 2 years by Štěrba and by a volunteer in Taiwan for more than 5 months; in the latter case, *Taenia asiatica* was identified as *T. saginata* [68,69].

Another well-known human parasite, the broad tapeworm *D. latum*, was subject to several voluntary infections. Leiper together with two colleagues swallowed its plerocercoid stages brought from Switzerland to England and provided a detailed account on his infection for more than 6 years [70]. In Russia, Tarasov infected himself repeatedly and expelled a total of 26 m of these tapeworms after several years of an unapparent infection. However, a massive infection with seven plerocercoids caused him abdominal pain and weight loss, leading to the expulsion of 38 m of tapeworms following treatment [71]. More recently, two parasitologists deliberately swallowed *D. latum* plerocercoids and kept the infection without any clinical signs for more than 4.5 years [72].

Finally, one of us (J. Lukeš, unpublished) also became intentionally infected in February 2013 with three specimens of this large tapeworm and, despite massive production of eggs (up to 50 000 eggs per gram), has observed no symptoms so far. As mentioned above, clinical signs of *D. latum* infection, such as pernicious anemia, megaloblastic

Box 2. Websites discussing helminth therapy and present-day self-experimentators

- Discussion forums on helminth therapy in regard to several disorders:
  http://forum.bodybuilding.com/showthread.php?t=143189453&-page=1
  http://autismtso.com/about/background/
  http://www.crohnsforum.com/showthread.php?t=13294
  http://groups.yahoo.com/neo/groups/helminthictherapy/info?nolmage=true
  http://bodyecology.com/articles/helminth-therapy.php#.Uk1gpdJcWS8
- Video with Dr. James Logan (London School of Hygiene and Tropical Medicine), who infected himself with hookworms and provides detailed documentation of the course of the infection (http://www.channel4embarrassingillnesses.com/video/in-detail/dr-james-logan-s-hookworm-experiment/).

bone marrow hyperplasia, and low vitamin B_{12} levels [23], are copied from one textbook to another despite the fact that they were probably caused by poor diets or malnutrition and have not been reported subsequently [73,74].

The giant roundworm *Ascaris lumbricoides* infects approximately one billion humans worldwide and represents a serious health problem, mainly in tropical countries [75]. A unique long-term study by Brudastov and his colleagues provided direct evidence of the longevity and survival of its infective eggs, given that 40% of infected humans developed ascariasis upon digestion of eggs that had been stored in soil for up to 10 years [76]. Shockingly, a university student was accused of infecting his uninformed roommates with eggs of *A. lumbricoides*. Two of them almost died of strong allergic reactions to the larvae [53]. Administration of eggs of the pinworm *Enterobius vermicularis* from a young boy co-infected with *Dientamoeba fragilis* resulted in a massive infection for both Ockert and another volunteer with the latter protist, proving for the first time the unanticipated role of pinworm eggs as vectors of *D. fragilis* [77]. Interestingly, other reports on (self-) infection with this widespread and likely rather benign worm are not available.

Even though the pig whipworm is not a human parasite, it has a key role in current attempts to use therapeutic helminth infections in treating humans with autoimmune diseases (Figure 1). Weinstock, one of the first individuals to note the connection between the decrease of parasitic infections and the rise of autoimmunity, infected a volunteer with CD who was unresponsive to traditional treatment

Table 1. Parasites mentioned in this review and others used in human therapy[a]

Typical human parasites	Host other than humans	Infectious stage	Transmission	Mig	Aut	LC	Cycle in laboratory
Entamoebidae							
Entamoeba histolytica	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Apicomplexa							
Cryptosporidium hominis	No	Oocysts in environment	Oral	No	Yes	1	Yes (lab rodents)
Cryptosporidium parvum	Many mammals	Oocysts in environment	Oral	No	Yes	1	Yes (lab rodents)
Plasmodium vivax	No, possibly primates	Sporozoites inoculated by vector	Vector (*Anopheles*)	No	No	2	Yes (primates)
Kinetoplastida							
Leishmania donovani	Canines	Sporozoites inoculated by vector	Vector (*Phlebotomus*)	No	No	2	Yes (lab rodents)
Leishmania tropica	Hyraxes	Sporozoites inoculated by vector	Vector (*Phlebotomus*)	No	No	2	Yes (lab rodents)
Trypanosoma brucei	African animals[b]	Sporozoites inoculated by vector	Vector (*Glossina*)	No	No	2	Yes
Trypanosoma b. rhodesiense	Wild animals	Sporozoites inoculated by vector	Vector (*Glossina*)	No	No	2	Yes
Trypanosoma b. gambiense	Livestock	Sporozoites inoculated by vector	Vector (*Glossina*)	No	No	2	Yes
Digenea							
Schistosoma haematobium	Rarely in primates	Larvae in water	Cutaneous	Yes	No	2	No
Cestoda							
Hymenolepis nana	Rodents	Larvae in insects	Oral	No	Yes	1–2	Yes (beetles, mice)
Taenia saginata	No	Larvae in intermediate host	Oral	No	No	2	No
Taenia solium	No[c]	Larvae in intermediate host	Oral	Yes	No	2	No
Spirometra erinaceieuropaei	Carnivores	Larvae in intermediate host	Oral and/or cutaneous	Yes	No	3	Yes (copepods, mice, cats)
Nematoda							
Ancylostoma duodenale	No	Larvae in soil	Oral and/or cutaneous	Yes	No	1	Yes (coproculture)
Ascaris lumbricoides	No	Eggs in soil	Oral	Yes	No	1	No
Brugia malayi	Primates, cats, pangolin	Larvae injected by vector	Vector (mosquitos)	Yes	No	2	Yes
Enterobius vermicularis	No	Eggs in environment	Oral	No	No	1	No
Necator americanus	No	Larvae in soil	Cutaneous	Yes	No	1	Yes (coproculture; hamsters)
Trichuris trichiura	Primates	Eggs in soil	Oral	No	No	1	Yes (pigs)
Rare or accidental human parasites							
Apicomplexa							
Cryptosporidium meleagridis	Birds	Oocysts in environment	Oral	No	Yes	1	Yes
Cryptosporidium tyzzeri	Mice	Oocysts in environment	Oral	No	Yes	1	Yes
Plasmodium cynomolgi	Primates	Sporozoites inoculated by vector	Vector (*Anopheles*)	No	Yes	2	Yes

[a]Abbreviations: Aut, autoinfection; LC, number of hosts in life cycle; Mig, migration through human body.

[b]Livestock, antelopes, zebras, carnivores, and so on.

[c]Experimentally in lar gibbon (*Hylobates lar*).

Table 2. Parasites as possible candidates for therapy of human immune-mediated disorders[a]

Typical human parasites	Host other than humans	Infective stage	Transmission	Mig	Aut	LC	Cycle in laboratory
Entamoebidae							
Endolimax nana	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Entamoeba coli	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Entamoeba hartmanni	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Iodamoeba buetschlii	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Stramenopiles							
Blastocystis hominis[b]	Pigs, dogs, primates	Cysts in environment	Oral	No	Yes	1	Yes
Ciliophora							
Neobalantidium coli [*Balantidium*]	Pigs and great apes	Cysts in environment	Oral	No[c]	Yes	1	Yes (short survival)
Fornicata							
Chilomastix mesnili	Primates	Cysts in environment	Oral	No	Yes	1	Yes
Giardia intestinalis[d]	Other mammals[d]	Cysts in environment	Oral	No	Yes	1	Yes
Parabasala							
Enteromonas hominis	No	Cysts in environment	Oral	No	Yes	1	Yes
Dientamoeba fragilis	Great apes	Trophozoites[e]	Oral[d]	No	Yes	1	Yes
Pentatrichomonas hominis	Various mammals	Trophozoites in environment	Oral	No	Yes	1	Yes
Cestoda							
Diphyllobothrium latum[f]	Carnivores	Larvae in fish	Oral	No	No	3	Yes[f]
Digenea							
Fasciolopsis buski[g]	Pigs	Larvae on plants	Oral	No	No	2	Yes (snails, dogs)
Nematoda							
Strongyloides fuelleborni	Primates	Larvae in soil	Unknown[h]	Yes	No	1	Yes (primates)
Strongyloides stercoralis	No	Larvae in soil	Cutaneous	Yes	Yes	1	Yes (coproculture)[i]
Trichostrongylus colubriformis	Various mammals[j]	Larvae in soil	Oral	No	No	1	Yes (mammals)
Rare or accidental human parasites							
Cestoda							
Hymenolepis diminuta	Rodents, dogs	Larvae in insects	Oral	No	No	2	Yes (beetles, rats)
Nematoda							
Ancylostoma caninum	Dogs	Larvae in soil	Cutaneous and/or oral[k]	Yes[j]	No	1	Yes (coproculture, dogs)
Ancylostoma ceylanicum	Felids, canids	Larvae in soil	Oral[k]	No	No	1	Yes (coproculture, hamsters)
Cyclodontostomum purvisi	Rodents	Larvae in soil	Oral[l]	No	No	1	Yes (rats)
Necator spp.[m]	Great apes	Larvae in soil	Cutaneous and/or oral	Yes	No	1	Yes (coproculture)[l]
Strongyloides ransomi[n]	Pigs	Larvae in soil	Cutaneous and/or oral	Yes	No	1	Yes (pigs)
Syphacia obvelata	Rodents	Eggs in environment	Oral	No	No	1	Yes (rats)
Trichostrongylus affinis[o]	Rodents	Larvae in soil	Oral	No	No	1	Yes (mammals)
Trichuris suis	Pigs	Eggs in soil	Oral	No	No	1	Yes (pig)
Trichuris vulpis	Canines	Eggs in soil	Oral	No	No	1	Yes (dogs)

[a]Abbreviations: Aut, autoinfection; LC, number of hosts in life cycle; Mig, migration through human body.

[b]Subtypes 1–8; subtypes 1 and 4 were most common in patients with irritable bowel disease (IBD), whereas subtype 3 was most common in nonIBD individuals.

[c]Migration in immunosuppressed humans.

[d]Assemblage A (primates, dogs, cats, livestock, rodents, and other wild mammals) and B (primates, dogs, and other wild mammals).

[e]Transmission via nematodes (*Enterobius vermicularis, Ascaris lumbricoides* and *Trichuris trichiura*).

[f]Also *Diphyllobothrium dendriticum* and *Diphyllobothrium nihonkaiense*; laboratory cycle includes copepods, fish, and hamsters.

[g]Potentially pathogenic.

[h]Lactogenic transmission; up to 100% of children in some localities of Papua New Guinea infected.

[i]Free-living generations; transplacental transmission; reports from cats and dogs may include other species.

[j]Includes ruminants, primates, rabbits, and squirrels.

[k]No migration if larvae swallowed; transplacental and lactogenic transmission possible.

[l]Life cycle unknown; only one human case.

[m]*Necator gorillae, Necator exilidens* and *Necator suillus*; laboratory cycle also in hamsters.

[n]One human case.

[o]Other species and/or genera of Trichostrongylidae found in humans may also be considered (e.g., *Haemonchus contortus, Marshallagia marshalli, Ostertagia ostertagi, Teladorsagia circumcincta*, and others).

with a dose of 2500 *T. suis* eggs [17]. Use of the pig whipworm was based on a previous study that fully complied with regulatory agencies and had informed consent of the volunteers [78]; this study proved that *T. suis* can colonize human intestines without adverse effects. Within several weeks, during which adult worms developed, the patient showed major improvement in the CD symptoms. In another trial, three patients with UC were infected with the same parasite, and all reported substantial improvements with no adverse effects [17]. In two additional trials involving 29 and 54 patients with CD or UC, respectively, significant alleviation and remission was recorded in 72% cases, with no adverse effects reported. In the colitis trial, 43% of treated patients improved after several weeks [79].

Broadhurst and colleagues [80] reported a case of a man with severe UC, refractory to drugs and high-dose steroids. Whereas cyclosporine or colectomy were advised owing to extensive ulceration and crypt abscesses, the patient instead chose to infect himself with eggs of the human whipworm, *Trichuris trichiura*. Ingestion of hundreds of *in vitro* germinated eggs led to complete elimination of his symptoms [80].

The second most intensively studied parasite in connection with autoimmune disorders is the hookworm, *N. americanus*, initially used by a scientist 40 years ago to infect himself with 250 larvae to cure a long-lasting and heavy hay fever, achieving total elimination of all symptoms [81]. Perhaps the most recent self-infection with *N. americanus* was superbly documented from the invasion of larvae through the skin until the establishment of the adults in the intestine. The self-experimenting scientist reported not only clinical symptoms during the migration, but also the alleviation of his food allergy (Box 2).

Concluding remarks and future perspectives

Up to 400 species of human-infectious, parasitic protists and helminths have been described [82]. An exhaustive search of the literature allowed us to identify among them several species with the potential for controlled therapeutic infections of humans with primarily autoimmune diseases (Figure 1; Table 1). In general, these are either genuine human parasites with negligible or very limited pathogenicity or animal model species with close relatives, which are infectious for humans [17]. The additional advantage of the latter parasites is their inability to complete their life cycles in humans; yet, they are able to stimulate an immune response, as seen with *T. suis*. The potential of certain helminths was recognized many years ago (Table 2), and we found further support for their therapeutic applications; although, in other cases, such as those of *Hymenolepis nana*, *Ancylostoma duodenale*, *Ascaris lumbricoides*, and *Enterobius vermicularis*, we feel obliged to exclude them from the list owing to identified shortcomings, for example, the risk of autoinfection or migration through the human body (Table 1). Interestingly, some helminths have remained overlooked (Tables 1 and 2).

Indeed, evaluation of criteria (Box 3) relevant for helminths already tested on humans (Figure 1) allowed us to identify additional protist and helminth species that may also qualify, but data from experimental infections are lacking (Box 2). At present, the drug with *T. suis*, called Trichuris Suis Ova (TSO), is undergoing Phase III clinical trials as part of a drug approval process by the company Ovamed GmbH (http://www.ovamed.de/tso/clinical-studies), and one can only hope that it will successfully pass the requested criteria and become part of standard medical practice, although Ovamed already markets TSO (http://www.ovamed.de). Numerous experimental infections with hookworms were promising [9,83,84] and provided motivation for further research. However, the progress is slow for patients, who tend to resort to spontaneous and uncontrolled treatments, such as the acquisition of infectious stages from the environment or from unreliable sources (Box 2; http://autoimmunetherapies.com).

Box 3. Eligibility criteria of parasites suitable for therapy

- Life cycle without somatic or visceral migration, or possible migration should be minimal
- None or low pathogenicity for humans, with mild clinical symptoms that last for a short period
- Localization of the adult stage in the gastrointestinal tract
- Minimal chance of spreading of the infectious stages from the experimentally infected humans to the environment: parasites with low and/or depressed fecundity, and/or indirect life cycles, and/or unable to multiply in human body to cause autoinfection
- Availability of pure and/or sterile infectious stages, for example, from cultures or gnotobiotic animals
- Sufficient knowledge of the biology, epidemiology, host spectrum, and pathogenicity of the parasite

Interestingly, so far, no human-dwelling protists, which are often part of the intestinal microbiome, have been tested for their potential to stimulate an immune response in a manner beneficial for humans with allergies, UC, CD, and other diseases. Hence, there are no supporting data on their possible therapeutic applications. Owing to the lack of clinical symptoms in humans, protists such as *E. dispar*, *E. coli*, *Entamoeba moshkovskii*, *E. nana*, *Blastocystis* spp., and others seem to behave more like commensals than parasites and, hence, are potentially suitable for experimental infections with benefit for human health; the same applies for a handful of intestinal helminths (Table 2). Yet, the prevailing view postulates that all human parasites necessarily cause a disease and have to be eliminated. This is even reflected in selective usage of the literature, because reports that do not provide evidence of pathogenicity tend to be undercited or remain overlooked. Such skewed evaluation of the data is unfortunate, and it is one of the main aims of this review to rectify this situation.

Based on the data available, we hope that the major promise of patients successfully treated with controlled infections by *T. suis* can be extended to other diseases as well as additional parasites and/or commensals. Experimental infections may be performed with prospective species identified by our analysis (Figure 1; Tables 1 and 2), but there is a clear imperative to comply with the current ethical and safety rules (Box 1). We share the opinion that 'perhaps the most important factor governing the success of these therapies is showing that the drug concept is effective in the human situation and not only in mice' [85].

Acknowledgments

We are grateful to Jiří Vávra and Josef Chalupský for providing valuable opinions on the literature. Comments of three reviewers are also much appreciated. This research was supported by the Czech Grant Agency

P506/12/1632 and by Praemium Academiae award to J.L., who is a Fellow of the Canadian Institute for Advanced Research. Finally, we acknowledge the use of research infrastructure that has received funding from the EU 7th Framework Programme, grant agreement no. 316304.

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