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Research Article

CLINICAL

Overcoming Evolutionary Mismatch by Self-Treatment with Helminths: Current Practices and Experience

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Abstract *Background.* Biome depletion, or loss of biodiversity from the ecosystem of the human body, is a major "evolutionary mismatch" underlying a variety of inflammatory diseases in Western populations. Enhancing biodiversity via exposure to helminths has effectively treated immune diseases in a variety of experimental animal models and in a few published studies involving human subjects. *Purpose.* This study probes another untapped resource for helminthic therapy: the methods and outcomes reported by individuals currently self-treating with helminths. *Procedures.* Helminth providers were interviewed, surveys were collected from self-treaters, and publically available information was compiled. *Results.* More than 250 anecdotal experiences of self-treatment were assessed, and the total number of individuals worldwide currently self-treating was estimated at between 6,000 and 7,000. A wide range of inflammation-related diseases, including inflammatory bowel disease, allergies, and autoimmunity, were effectively treated. *Conclusions.* This study finds that the therapy is being refined through experience and is now expanding to treat widespread neuropsychiatric problems such as depression, anxiety, migraine headaches, bipolar disorder, and perhaps Parkinson's disease.

Keywords anxiety; evolutionary mismatch; helminth, helminthic therapy; migraine; self treatment

1. Introduction

Pandemics of allergic and autoimmune disease are a part of the Western culture [1]. A variety of other inflammation-related diseases that affect neuropsychiatric function, including anxiety disorders and migraine headaches, have also reached pandemic levels. Furthermore, it seems likely that increasingly common developmental disorders such as autism may be associated with the inflammation that plagues Western society [2,3,4,5]. In addition, the incidence of common cancers, including breast and prostate cancer, is associated with inflammation [6,7,8] and thus, perhaps, the Western lifestyle.

A number of factors induce inflammation in Western populations [9,10,11]. These factors, known as "evolutionary mismatches," refer to the presence of environmental or cultural factors for which the human organism is not adapted. Inflammatory diets as well as a lack of exercise certainly play a role in this fish-out-of-water model of disease. Modern living and work environments tend to produce chronic psychological stress as well as vitamin D deficiency, both immune destabilizing factors. However, the one evolutionary mismatch with probably the most dramatic impact on the immune system is a loss of biodiversity associated with the human body [9,10,11]. Although originally attributed to hygiene [12], it is now apparent that a wide range of factors in Western society, mostly technological in nature, lead to depletion of the biome, or the life associated with the ecosystem of the human body [9, 10,11]. Biome depleting factors include food preservation technology such as refrigerators, plastic containers, and canning machines. In addition, water handling technology such as toilets, water treatment facilities, and hot water heaters effectively deplete the human biome. Furthermore, a variety of other factors, ranging from the widespread use of shoes to the industrialization of farming practice, profoundly alter the biome by creating a barrier between humans and the soil. Species severely depleted or even lost from the biome of the human body in Western populations include almost all indwelling eukaryotic organisms (e.g., intestinal helminths and protozoans) and potentially a variety of soil-associated bacteria [13].

It is predicted, based on a variety of animal studies as well as epidemiologic and evolutionary considerations, that reintroduction of helminths into the population will have a profound effect on inflammatory-related diseases [9,10, 11]. Published studies have already demonstrated the effects of helminths on multiple sclerosis [14] and inflammatory bowel disease [15,16,17,18] in humans. Furthermore, it is predicted that exposure to helminths will positively affect neuropsychiatric function [19,20] as well as the incidence of cancer [6,7].

The general approach to enriching the biome with helminths is one of domestication. Many naturally occurring helminths might make undesirable additions to modern society due to a lack of effectiveness, association with adverse side effects, problems with communicability, or potentially some combination of these and other factors. Thus, the animals that are the most advantageous with the least drawbacks must be selected and cultivated for human benefit. This process of domestication with helminths has already begun, with pioneering individuals from diverse backgrounds isolating specific helminths or combinations of helminths and evaluating their effects on disease [15, 21,22]. For a variety of reasons, much of this work has been conducted outside of mainstream medicine [21]. These "self-treaters" have a rich and varied experience with helminth therapy, but this experience is not readily accessible in a systematically compiled format.

It is the purpose of this article to describe current practices and outcomes in self-treatment with helminths. Multiple approaches to this goal were utilized, including interviews with helminth providers, collection of surveys from individuals self-treating with helminths, and compilation of publically available information regarding self-treatment with helminths. It is hoped that this study will provide a basis for future clinical studies and for education of physicians who may need to discuss the ever-increasing amount of information regarding helminthic therapy with their patients.

During this assessment of self-treatment practices with helminths, it is important to clearly distinguish two very different issues. The first is the potential for biome enrichment in general and helminthic therapy in particular to resolve a wide range of inflammatory diseases. For reasons described above, we and others hold an extremely favorable opinion of this approach, and have, in the strongest of terms, argued for immediate and thorough clinical investigation of the topic. The second issue, very distinct from the first, is the utility and effectiveness of current self-treatment practices in helminthic therapy. Although the theoretical basis behind the self-treatment practice is sound, we recognize that conclusions which can be drawn from self-treatment practices have limitations. Indeed, those limitations are, to a large degree, brought to light in this study. That being said, experience involving self-treatment with helminths has become extensive, and ignoring that experience would be detrimental to the medical community.

2. Methods

2.1. Overall approach

Studies were approved by the Duke Institutional Review Board. Consent was waived for evaluation of publically available information, and the requirement to obtain a signed consent for individuals completing survey forms or participating in interviews was waived. At no time during the study was any protected health information gathered, ensuring anonymity of the participants.

The overall approach used to evaluate current practice and outcomes in self-treatment with helminths was threefold. First, individuals producing, selling, and/or distributing helminths ("providers") for self-treatment with helminthic therapy were interviewed. Second, surveys were distributed through social media websites and via helminth providers for individuals self-treating with helminths. Finally, publically available information regarding self-treatment with helminths from a wide range of sources, including books, articles, films, and social media websites, was compiled and evaluated. The multiple methodologies facilitated acquisition of more diverse information than would have been obtainable with a single method alone, and allowed triangulation between methods to strengthen conclusions regarding some aspects of the practice of self-treatment with helminths. The three approaches are described in detail below.

2.2. Interviews with helminth providers

Individuals producing and/or distributing helminths either commercially ($n = 8$ individuals from five companies) or noncommercially ($n = 2$) were contacted regarding their experience with helminth therapy. During each interview, if appropriate, the following topics were addressed: number of patients treated, type of diseases treated, outcomes, any cases of particular interest (both in terms of positive effects and adverse side effects), considerations during production of helminths, and any other issues the provider wished to discuss. In some cases, a provider might have experience with, for example, distribution but not production, so questions were adjusted accordingly. Providers were encouraged to contact one of the authors (WP) at any time if new information became available, so the interviews were essentially open ended.

No personal identifying information was recorded during interviews with providers, ensuring that the interviewees remained anonymous. Interviews were conducted by phone or by e-mail, depending on provider preference. In either case, the responses from the interviewees were recorded by one of the authors (WP) by hand, and voice recordings or copies of e-mails were not kept, again to ensure anonymity of the interviewees.

2.3. Survey for individuals self-treating with helminths (self-treaters)

As a second approach to evaluating the practice and effects of self-treatment with helminths, surveys were made available to individuals self-treating with helminths. The surveys were designed to evaluate the demographics of "self-treaters," the types of diseases being treated, the effectiveness of treatment, and the method(s) of treatment

with helminths. The survey is provided in the supplemental information (see Supplementary Material). The survey was designed to be mailed back to one of the authors (WP) with no participant identifying information, ensuring confidentiality in the process. Upon receipt, surveys were screened for any protected health information, and that information, if present, was redacted. Surveys were distributed via social networks of self-treaters, with the assistance of providers of helminthic therapy, and with the assistance of one organizer of social media sites for self-treaters. All providers contacted ($n = 8$) expressed a willingness to help distribute the survey to their customers.

A Wilcoxon signed-rank test was used to evaluate paired data from the survey, and the Mantel-Haenszel chi-square test (a.k.a. General Association CMH) was used to perform unpaired comparisons.

2.4. Collection of publically available information

As a final approach to evaluating the practice and effects of self-treatment with helminths, publically available information was collected and assessed. The acquisition of publically available information for scientific purposes is becoming more popular [23,24], especially for accessing low-prevalence and hard-to-reach populations [25], and has been identified as a valuable source of information for helminthic therapy in particular [21]. However, special considerations must be made to protect the identity of research subjects when conducting this type of research [26]. With this in mind, no protected health information was collected, and no information that could be pinpointed with an automated search of the internet was collected, minimizing the risk to study subjects. The only exception to this was the inclusion of reports of self-treatment with helminths that were published by Turton in the peer-reviewed literature [27,28,29]. In this arm of the study, information was obtained from more than 180 sources, including social media sites, websites describing helminthic therapy (including websites maintained or organized by helminth providers), magazine articles, two videos, one book, and one movie. Peer-reviewed scientific literature was also used, but only articles describing "self-treatment" (3 published articles) were compiled with the rest of the data regarding self-treating. (Peer-reviewed work describing clinical trials was considered separately.) Efforts were made to avoid collection of duplicate experiences that were published in more than one place. In many cases, deleting duplicates was straightforward, although it is possible that a small number of experiences were duplicated.

3. Results

3.1. Overview of helminth use

The helminths currently in use for self-treatment of disease are the porcine whipworm (*Trichuris suis* ova; TSO), the human hookworm (*Necator americanus*; NA), the human whipworm (*Trichuris trichiura* ova; TTO), and the rat tapeworm (*Hymenolepis diminuta* cysticercoids; HDCs). At the present time, five companies provide helminths for sale. One provides TSO; one provides NA and TTO; one provides NA only; one provides NA, TTO, and HDCs; and one provides HDCs only. In addition, an unknown number of private individuals produce their own helminths for noncommercial private or community use. One of these noncommercial providers, a producer and distributer of HDCs to approximately 70 individuals, was recruited to participate in the study along with the commercial providers.

The strains of TSO currently available (one company) is the strain used by Weinstock in clinical trials reported in 2005 [16,18], originally obtained in collaboration with the United States Department of Agriculture. The strains of NA (three companies) and TTO (two companies) currently in use were acquired by individuals when traveling in areas where the organisms are endemic. However, the organisms in use today were not derived from a single source, and thus the strain may vary depending on the company. (The organisms were acquired at different locations and at different times, depending on the company.) All of the HDCs currently in use (two companies and one noncommercial provider) were derived from stocks originally obtained from Carolina Biological Supply (Greensboro, NC, USA).

Based on interviews with helminth providers, the total number of individuals self-treating with helminths as of January 2015 was approximately 4,000, 900, 600, and 500 for TSO, NA, TTO, and HDCs, respectively (Table 1). The total number of individuals using helminths is somewhat less than the sum of individuals using each helminth, since an unknown number of individuals use multiple helminths simultaneously. Furthermore, the number of individuals utilizing private sources of helminths is unknown and difficult to estimate. Given these limitations, we roughly estimate that between 6,000 and 7,000 people in the world today are currently self-treating with helminths as of early 2015.

3.2. Provider interviews

One commercial provider (out of eight total) and one noncommercial provider (out of two total) were contacted who did not have sufficient experience to help with the study. That is, they had only recently begun providing helminths and did not have any outcomes to report. These providers were not included in the study. Commercial helminth providers ($n = 7$) with appreciable experience were interviewed. All providers were, at the time of the interviews, associated with one of four commercial companies providing helminths. Of the six providers who provided information regarding their personal history of providing helminths, the average number of years of experience as a provider was about five, and ranged from two to eight. In

addition, one of the authors (WP) was made aware of a private (noncommercial) helminth provider, who was invited to participate in the study along with the commercial providers. This noncommercial provider of HDCs, mentioned above, had three years of experience providing helminths. All providers ($n = 8$) agreed to interviews and readily provided the information requested regarding their experience providing helminths. In addition, all providers had personal experience self-treating with helminths, and provided information regarding their personal experience. Several providers had professional experience with more than one helminth, and information was gleaned from providers regarding all currently available helminths used for therapy: porcine whipworm (TSO; two providers), human hookworm (NA; three providers), human whipworm (TTO; two providers), and rat tapeworm (HDCs; five providers).

All providers had detailed knowledge regarding the effects of helminths based on the feedback of their customers. Interviews with providers yielded a wealth of information regarding the use and outcomes of helminthic therapy, although no personal identifying information of the provider's clients was ever discussed. This information was compiled with survey data and publically available information, and is described in Section 3.5.

3.3. Survey results

A total of 58 surveys were received (Table 1). Participants had an average age of 45.0 ± 16.8 years (mean $\pm$ SD) with a range of 9–78 years. Most participants had chronic conditions, with an average duration of 28.4 years. Twelve percent (7/58) of the participants were < 18 years of age. Survey participants had a male/female ratio of 0.87 (27/31) and were 93.1% Caucasian, with the rest of the participants either Hispanic ($n = 1$), mixed Hispanic/Caucasian ($n = 2$), mixed Asian/Caucasian ($n = 1$) or Eastern European ($n = 1$).

Of the 58 participants, 57 were currently using helminths, and one stated that they were not currently using helminths, but had used helminths in the past. The surveys received reflected a disproportionate number of HDC users, with almost 80% of the surveys (46/58) being from individuals using HDCs. This bias was traced to the efforts of the noncommercial supplier, who said that his "clients" were quite grateful for their cost-free therapy and were happy to submit the surveys as a favor to him, albeit with an occasional reminder in some cases. In contrast, one of the commercial suppliers described a history of extreme difficulties in obtaining survey results for his product, despite repeated efforts and a survey about 20-fold shorter than the survey employed in this study. His experience apparently reflected the current situation, with almost 70% (40/58) of the surveys coming from the noncommercial supplier despite the fact that his clients accounted for only about 1.1% (70/6,500) of the estimated total number of helminth users.

Table 1: Source of information and helminths used. The middle column describes the number of independent sources of information, for example, a single blog, a single book or a single provider. The column on the right describes the number of individual self-treaters attributed to the sources in the middle column. [a]Only stories involving specific individuals that were not apparently duplicated in other sources were used. [b]Data were compiled in January of 2015. The estimated number of individuals using helminths at the present time does not generally change substantially in a period of months. However, the number of individuals using HDCs has risen from about 500 in January of 2015 to between 700 and 750 by April of 2015. [c]Publically available summary statistics from providers were not utilized, since updated numbers were obtained by interview.

Source of information	Number of sources	Organisms used; number of individuals[a]
Providers interviews	7	TSO; 4,000 NA; 900 TTO; 600 HDCs; 500[b]
Surveys	58	TSO; 0 NA; 8 TTO; 1 HDCs; 44 NA + TTO; 2 NA + HDCs; 2 None at present; 1
Publically available information		
Peer-reviewed literature	3	TSO; 0 NA; 1 TTO; 1 HDCs; 1
Books and magazine articles	7	TSO; 1 NA; 10 TTO; 0 HDC; 1
Web-based social networking sites	166	TSO; 11 NA; 114 TTO; 11 HDCs; 6 NA + TSO; 1 TSO + NA + TTO; 2 TSO + TTO; 3 NA + TTO; 27 NA + HDCs; 2
Videos and movies	3	TSO; 2 NA; 2 TTO; 1 HDC; 1
Provider-derived information[c]	5	TSO; 2 NA; 2 TTO; 1 NA + TSO; 4

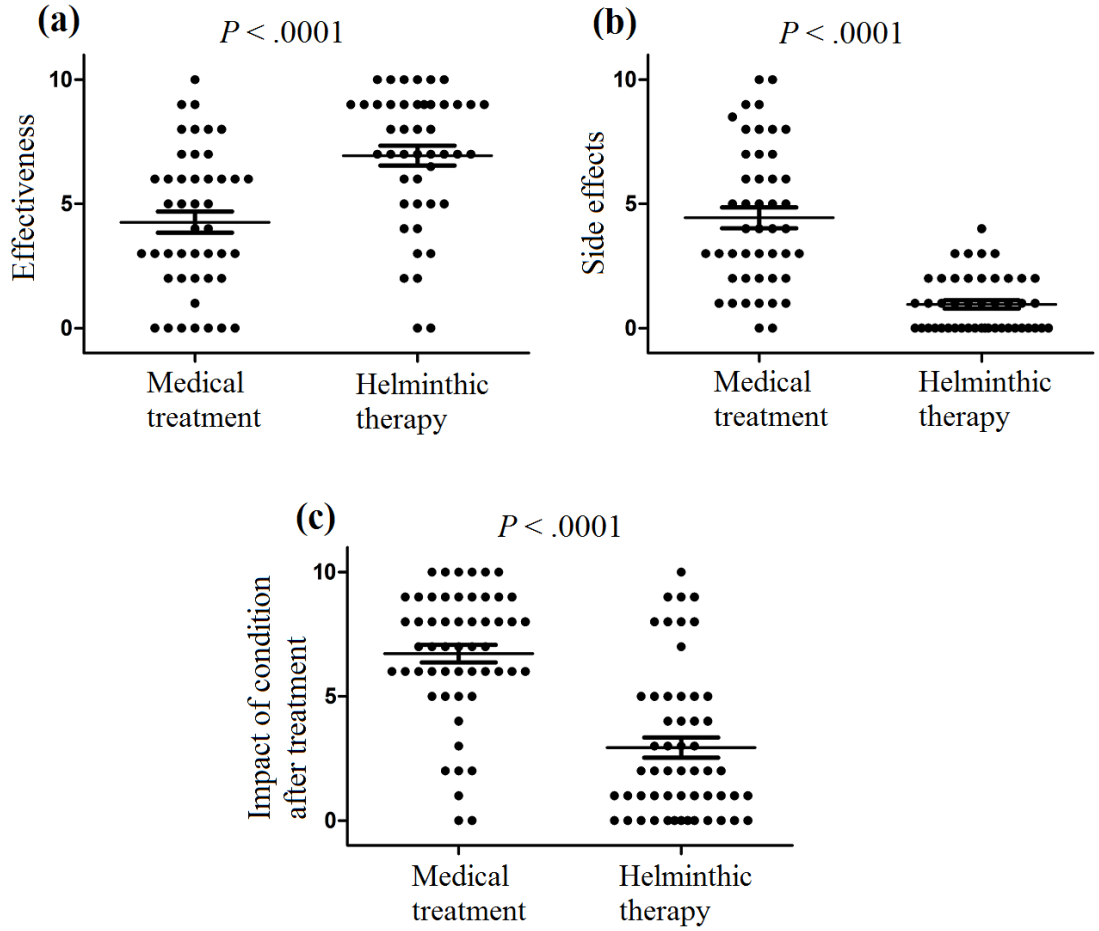

Figure 1: Self-reported effectiveness of disease treatment and side effects of modern medical practice compared to helminthic therapy by the survey participants. Participants used an 11-point scale from 0 to 10. The only participant to rate the side effects of helminth treatment as high as a 4 on that scale attributed the side effects to depletion of vitamins and nutrients by the helminths and stated that the side effects were "remedied by taking (dietary) supplements."

The preponderance of survey participants receiving free helminths precluded some analyses of the data that were intended during the design of the original study. For example, the assessment of changes in availability of helminths over time, the relative ease with which different helminths can be obtained, and the participant's experiences, either favorable or unfavorable, with helminth providers were all factors that were of interest during the original study design, but were confounded by the bias toward individuals receiving helminths free of charge.

If the surveys involving the use of HDCs were not considered, another bias was noted. All 12 of the remaining respondents using helminths were using either NA (8/12), TTO (1/12), or both NA and TTO (2/12), but none were currently using TSO. Since the use of TSO accounts for as much as two-thirds of the total population self-treating with helminths, the survey is also, apparently, biased against TSO users. One potential reason for this bias is evident in the publically available information (described below); TSO users, which comprise the majority of self-treaters, are apparently much less involved with social media sites than NA users, and distribution of the survey was dependent to a considerable extent on social media groups.

The survey data indicated that a wide variety of inflammatory-related diseases were being treated using helminths (Table 2). The participants in the survey indicated that their self-treatment with helminths more effectively treated their disease and had fewer side effects than did medical treatments they obtained by traditional means (Figure 1). The survey results were compiled with information from provider interviews and from publically available information, and are described in Section 3.5.

3.4. Publically available information

An effort was made to eliminate duplicate stories from the study. This was particularly important when considering news items, in which case the same individual's experience might be encountered dozens or even hundreds of times.

Table 2: *Survey results.* The participant's overall ratings of effectiveness in alleviation of disease symptoms/adverse side effects are given, unless the participant clearly stated that some conditions were treated (effective) while others were not (not effective). Thus, the ratings from a single participant may appear more than once, depending on the number of conditions reported. Scores are on an 11-point scale, from 0 to 10, with 0 being either no effectiveness or no side effects, and 10 being either very effective or horrible side effects (e.g., a rating of 10/0 would be the most effective therapy with the least side effects, whereas a rating of 0/10 would describe a completely ineffective therapy with horrible side effects). The number using each helminth or combination of helminths is listed in parentheses beside the helimth. The scores obtained from participants that were apparently "underdosed" with HDCs (as judged by incomplete effects and low number of helminths) are in bold font. The descriptions of conditions used are those provided by the participants, so there may be some overlap between conditions that are listed separately (e.g., seasonal allergies, hay fever or allergies), and some terms may not correspond exactly with accepted medical terms. *The participant with depression who rated helminthic therapy as 5/0 was the one who stopped taking medications at the time he began helminthic therapy (participant no. 45, see Section 3 and Table 4).

Organism	Disease treated (number of observations)	Effectiveness/side effects
NA (8)	Acid reflux (1)	0/2
	ADHD (1)	5/2
	Allergy (3)	6/1, 0/2, 9/3
	Anxiety (2)	5/2, not effective
	Asthma (3)	6/1, 0/2, 9/3
	Autism (1)	5/1
	Brain fog (1)	effective
	Chemical allergies or sensitivity (3)	6/1, 5/2, 2/3
	Chronic fatigue (1)	0/2
	Churg-Strauss syndrome (1)	0/2
	Colitis (1)	5/1
	Common immune deficiency (1)	5/1
	Depression (1)	5/2
	Eczema (1)	9/3
	Epilepsy (1)	5/2
	Facial pain (1)	0/2
	Food allergies (1)	5/2
	Hay fever (1)	effective
	Irritable bowel syndrome (1)	not effective
	Migraine (1)	6/1
	Mood swings (1)	6/1
	OCD (1)	5/2
	Palatal myoclorus (1)	0/2
	Rhinitis (2)	6/1, 0/2
	Samter's syndrome (1)	9/0
	Tourette's (1)	5/2
TTO (1)	Barrett's esophagus (1)	6/1
	Stomach erosion (1)	6/1
	Ulcerative proctitis (1)	6/1
HDC (44)	ADHD (2)	**7/1**, 9/2
	Acne (1)	7/2
	Agoraphobia (1)	**6.5/0**
	Allergies (14)	9/0, 10/0, 9/0, 10/0, 9/0, **7/0**, **7/0**, 9/0, 10/2, **0/0**, 7/2, **8/0**, 7/2, 9/4
	Anger management (1)	**6.5/0**
	Angioedema (1)	**8/1**
	Anxiety (4)	9/0, 10/0, **6.5/0**, **7/1**
	Anxiety and panic disorder (1)	**8/0**
	Arthritis (1)	**7/0**
	Asthma (3)	9/0, **7/1**, 7/2
	Autism (2)	3/1, 3/1
	Bipolar disorder (5)	9/0, 10/0, 9/0, 9/2, 10/2
	Brain fog (1)	7/2
	Bronchitis (1)	9/0
	Chronic fatigue (1)	9/0
	Contact dermatitis (1)	9/0
	Cracked skin (1)	10/0
	Dandruff (3)	9/0, 9/0, 10/0
HDC (44)	Depression (6)	9/0, 9/0, **6.5/0**, 10/0, 5/0,* 9/2
	Diabetes II (1)	**6.5/0**
	Diverticulitis (1)	**5/2**
	Eczema (2)	9/0, **5/0**
	Food allergies (5)	**7/0**, 7/2, 9/0, 9/4, 7/2
	Foot odor (1)	9/0
	Gastric reflux (1)	**7/1**
	Gastrointestinal inflammation (1)	9/4
	Guttate psoriasis (1)	9/4
	Headaches (nonmigraine) (1)	9/4
	Heart disease (1)	10/0
	Hemorrhoids (2)	9/0. 10/0
	High blood pressure (1)	10/0
	Hives (1)	10/2
	Inflammatory bowel disease (1)	**5/2**
	Irritable bowel (4)	**6/0**, **7/0**, 5/0, 7/2
	Itchy, dry scalp (1)	10/0
	Lactose sensitivity (3)	10/0, **6/0**, **7/0**
	Lyme disease (2)	3/1, 3/1
	Migraine (4)	10/0, **4/0**, **6/0**, 8/0
	Multiple sclerosis (1)	**4/0**
	Pet allergies (4)	10/0, 10/0, 9/0, **8/0**
	PTSD (1)	**6.5/0**
	Raynaud's disease (1)	1/1
	Reaction to insect bites (1)	10/0
	Recovery from burns (3)	9/0, 9/0, 6.5/0
	Respiratory syncytial virus (RSV) disease (1)	**7/1**
	Response to bee stings (1)	9/0
	Response to cold virus (2)	10/0, 10/0
	Response to surgical procedures (1)	10/0
	Scoliosis (pain from) (1)	7/2
	Seasonal affective disorder (1)	9/2
	Seasonal allergies (5)	**8/0**, **6/0**, 10/0, **5/0**, 7/2
	Sensory processing/integration disorder (1)	**5/0**
	Skin rashes (1)	**6.5/0**
	Urticaria (1)	**8/1**
	Varicose veins (1)	10/0
NA + TTO (2)	Acid reflux (1)	2/1
	Allergies (1)	7/1
	Allergic rhinitis (1)	2/1
	Autism (1)	7/1
	Crohn's (2)	2/1, 7/1
	Entercolitis (1)	7/1
	Food intolerance (1)	2/1
	Heavy metal toxicity (1)	7/1
	Internal hemorrhoids (1)	2/1
	Leaky gut syndrome (1)	7/1
	Lymphoid nodular hyperplasia (1)	7/1

Table 2: Continued.

Organism	Disease treated (number of observations)	Effectiveness/side effects	Organism	Disease treated (number of observations)	Effectiveness/side effects
NA + TTO (2)	Mitochondrial dysfunction (1)	7/1	NA + HDC (2)	Anosmia (1)	9/1
	Peripheral neuropathy (1)	2/1		Bronchospasy (1)	9/3
	Raynaud's syndrome (1)	2/1		Celiac disease (1)	9/3
	Reactive gastritis (1)	2/1		Chronic sinusitis (1)	9/1
	Respiratory system damage (1)	2/1		Eczema (1)	9/3
	Tinnitis (1)	7/1		Food allergies (1)	9/3
	Tourette's (1)	7/1		Nasal polyps (1)	9/1
	Vasculitis (1)	2/1		Pet allergies (1)	9/3
				Psoriasis (1)	9/3
				Seasonal allergies (1)	9/3

With this principle in mind, a total of 268 experiences of self-treatment with helminths were acquired from 234 sources. However, approximately 23% of these experiences encountered did not describe an outcome, did not state which helminth was used or did not state what disease or disorder was treated, so these were eliminated from the study. This screening process yielded 207 individual experiences of self-treatment with helminths from a total of 184 sources. A considerable amount of general information regarding the use of helminths was also obtained. The nature of sources (e.g., social media site versus a book or a movie) and the helminths used are described in Table 1. Interestingly, 76.4% of the total experiences with helminthic therapy involved NA. Since the use of NA accounts for approximately 15% of the total population self-treating with helminths, the publically available information is apparently biased strongly toward NA and against TSO. The potential reasons that TSO users discuss their experience with helminths in a public forum less often than do NA users is unknown.

The publically available information indicates that a wide variety of inflammatory-related diseases were being treated using helminths (Table 3). This publically available information was compiled with information from provider interviews and from surveys, and is described in the next section.

3.5. Helminths: description, dosage, and side effects

3.5.1. The porcine whipworm (TSO)

General

TSO is a noncommunicable organism in humans. It is isolated from pig feces in a highly controlled manner. Whipworms burrow into the intestinal wall and live in the lower small bowel and upper large bowel, but TSO must be ingested every 1.5 to 2 weeks for effective use since it does not survive to maturity in the human body. The pH and/or other nutrients in the media in which the organisms are stored are apparently important for the effectiveness of the organism in humans. Inexplicably, clinical trials are in progress [30] using TSO preparations widely thought by self-treaters to be less effective than the formulation originally used in clinical trials [16, 18] and currently used by self-treaters (source: provider interviews, $n = 2$, and publically available information). Individuals self-treating with TSO do so with the approval or at least the acceptance of a physician. (Note added in proof: all clinical trials with the potentially less effective formulation of TSO were terminated because of a lack of effectiveness.)

Dosage

The dosage of TSO is well established, with most individuals using 2,500 ova every two weeks. However, many individuals who do not respond to this dose do respond when the dosage is doubled (either 2,500 TSO/week or 5,000/two weeks) (source: provider interview and publically available information).

Use

TSO is used to treat Crohn's disease, ulcerative colitis, irritable bowel syndrome, autism, rheumatoid arthritis, lichenoid lesions, and multiple sclerosis. It is extremely effective at treating food allergies, but less effective than NA at treating seasonal allergies (source: provider interview).

Effectiveness

According to a provider, "80% of all patients who took TSO have either achieved remission or at least a condition close to remission." This is consistent with the original information published by Weinstock [16, 18], although, as described above, the use of TSO has expanded beyond Weinstock's studies, which involved only treatment of inflammatory bowel disease. It is noteworthy that suppliers of helminths other than TSO (i.e., competitors of TSO providers) support the effectiveness of TSO as reported by a TSO supplier.

Side effects

The side effects of TSO are well described in the literature, and involve usually minor gastrointestinal problems [31] or no problems at all [16, 18, 32]. One report using 2,500 TSO every 21 days in 96 patients (49 on TSO, 47 on placebo) indicated that TSO caused some stomach upset in some patients and generally occurred during the first

Table 3: *Publically available information regarding the use and effectiveness of self-administered helminthic therapy.* The descriptions of conditions used are those provided by the participants, so there may be a lack of clear distinction or overlap between conditions that are listed separately (e.g., food allergies vs. allergies), and some terms may not correspond exactly with accepted medical terms. The number of anecdotes involving each helminth or combination of helminths is listed in parentheses beside the helminth. *A positive or desirable outcome was defined as a success, and no effect or a negative effect was defined as failure. As described in Section 2, duplicate individual experiences were eliminated from the study when possible. In addition, approximately 24% of the publically available reports of self-treatment on social media websites did not indicate either a particular helminth, a disease treated or an outcome, and were excluded from the study.

Organism	Disease treated (number of observations)	Success rate*
TSO (16)	Autism (1) (undisclosed number)	100%; "most" respond well
	Crohn's disease (3)	66.7%
	Food allergies (1)	100%
	Food intolerances (1)	100%
	Lymphocytic colitis (1)	100%
	PANDAS (1)	100%
	Parkinson's disease (1)	100%
	Ulcerative colitis (7)	85.7%
NA (129)	Acne (2)	100%
	Anxiety (1)	100%
	Allergies (22)	77.3%
	Asthma (8)	87.5%
	Autism (undisclosed number)	Less than TSO and HDCs
	Autoimmune hepatitis (1)	100%
	Celiac disease (1)	100%
	Chronic fatigue syndrome (4)	50%
	Chronic hives (1)	100%
	Chronic Lyme's disease (1)	100%
	Congestion (1)	100%
	Crohn's disease (19)	94.7%
	Depression (1)	100%
	Eczema (13)	84.6%
	Eosinophilic esophagitis (5)	60%
	Fibromyalgia (2)	50%
	FODMAP intolerance (1)	100%
	Food allergies (5)	100%
	Food intolerances (7)	100%
	Food sensitivities (2)	100%
	Fuch's heterochromic iridocyclitis (1)	100%
	Gluten sensitivity/intolerance (4)	100%
	Hashimoto's disease (2)	0%
	Hay fever (2)	100%
	Hereditary angioedema (HAE) type III (1)	100%
	Histamine sensitivity (2)	50%
	Hives (1)	0%
	Irritable bowel syndrome (11)	81.8%
	IgA nephropathy (1)	100%
	Lactose intolerance (1)	100%
	Lupus (4)	75%
	Lyme's disease (1)	0%
	Migraines (1)	100%
	Mixed connective-tissue disease (3)	100%
	Multiple chemical sensitivity (4)	100%
	Multiple sclerosis (7)	100%
	Nasal congestion (2)	100%
	Neuropathy (1)	0%
	PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) (1)	100%
	Perennial nonallergic chronic sinusitis (2)	100%
	Psoriasis (2)	50%
	Raynaud's disease (1)	100%
	Reactive arthritis (1)	100%
	Recurring nasal polyps (1)	100%
	Relapsing-remitting multiple sclerosis (1)	100%
	Rheumatoid arthritis (1)	100%
NA (129)	Rhinitis (1)	0%
	Salicylate sensitivity (2)	50%
	Sinusitis (4)	75%
	Sjögren's syndrome (4)	100%
	Type I diabetes (1)	100%
	Ulcerative colitis (1)	100%
TTO (14)	Ankylosing spondylitis (1)	100%
	Allergies (2)	100%
	Asthma (1)	100%
	Autism (undisclosed number)	not effective
	Barrett's esophagus (1)	100%
	Crohn's disease (2)	100%
	Inflammatory bowel disease (2)	100%
	Lymphocytic colitis (1)	100%
	Ulcerative colitis (10)	70%
	Ulcerative proctitis (1)	100%
HDC (9)	Allergies (2)	100%
	Allergic rhinitis (1)	100%
	Asthma (undisclosed number)	Generally successful
	Autism (1; undisclosed number)	100%; generally successful, but "not everybody" is helped
	Bloating, constipation, diarrhea (undisclosed number)	Generally successful
	Bowel irregularities (1)	100%
	Crohn's disease (1)	100%
	Eczema (2)	100%
	Food intolerances (1)	100%
	Irritable bowel syndrome (1)	100%
	Migraine headache (1)	100%
	PANDAS (1)	100%
	Ulcerative colitis (1)	100%
TSO + NA (5)	Asthma (1)	100%
	Crohn's Disease (3)	33.3%
	Inflammatory Bowel Disease (1)	100%
	Multiple sclerosis (1)	100%
	PANDAS (1)	100%
	Sjögren's syndrome (1)	100%
TSO + TTO (3)	Crohn's disease (1)	100%
	Ulcerative colitis (2)	100%
TSO+TTO+NA (2)	Allergies (1)	100%
	Asthma (1)	100%
	Autism (1)	100%
NA + TTO (27)	Acne (1)	100%
	Allergies (2)	100%
	Anxiety (1)	100%
	Autism (1)	100%
	Car sickness (1)	100%
	Chronic bronchitis (1)	100%
	Crohn's disease (10)	100%
	Dandruff (1)	100%
	Eczema (1)	100%
	Eosinophilic esophagitis (1)	100%
	Food allergies (2)	100%
	Inflammatory bowel disease (2)	50%
	Mania (1)	100%
	Multiple sclerosis (1)	0%

Table 3: Continued.

Organism	Disease treated (number of observations)	Success rate*	Organism	Disease treated (number of observations)	Success rate*
NA + TTO (27)	Myalgic encephalomyelitis (1)	100%	NA + HDC (2)	Multiple sclerosis (1)	100%
	Papules (1)	100%		Poor sense of well being (1)	100%
	Ulcerative colitis (2)	100%			

two months of treatment [31]. Almost 50% of the placebo group experienced adverse gastrointestinal side effects in that study, suggesting that it was conducted in a relatively sensitive manner that could detect very mild side effects. However, this study utilized a formulation of TSO that is apparently different than either the formulation currently in use in clinical trials or the formulation currently used by self-treaters (i.e., at least three distinct formulations have been used), and it remains unknown what impact the formulation has on the side-effect profile. That being said, the only studies conducted with the formulation currently in use by self-treaters did not observe any adverse side effects [16, 18]. Consistent with this latter observation, we found in participant surveys, publically available information, and in interviews with providers ($n = 3$) that the primary "problem" with TSO for most individuals was not perceived to be a lack of effectiveness or the presence of adverse side effects, but rather the financial cost of the product.

3.5.2. The human hookworm (NA)

General

The human hookworm [33] burrows through the skin, leaving behind a rash in most cases. After tunneling through the skin, the organism makes its way through the lungs and eventually into the GI tract. NA is transmissible between humans, although cold weather, the use of a toilet, and a lack of human contact with soil prevent transmission. The organisms are cultured from human feces, and methods have been developed to extensively purify the organism. However, one provider has noted that highly purified NA (free of bacterial counts by culture methods) have a greatly reduced shelf life compared to less pure NA, although the effectiveness of the purified organisms appears to be the same as long as they remain alive. Providers were initially surprised that NA does not survive more than a year or two in many people. Individuals self-treating with NA generally do so in a manner independent of a physician's advice.

Dosage

As with all helminths, the dosage of NA depends strongly on the individual. However, helminth providers disagree to some degree on the appropriate dosage of the organism, with one provider in particular recommending less reliance on doses of NA that approach the threshold for adverse reactions and relatively more reliance on a healthy lifestyle in general. Despite this disagreement, a first exposure of 25 to 50 organisms is generally used, followed by additional treatments of 25 to 50 organisms within a few (three to nine) months to achieve a steady state of 50 to 110 organisms. An example of this treatment and the effects of the treatment are shown in Figure 2 (case number 8 in the survey). A maintenance dose of 25 to 50 organisms every six months to two years is generally taken to maintain the colony.

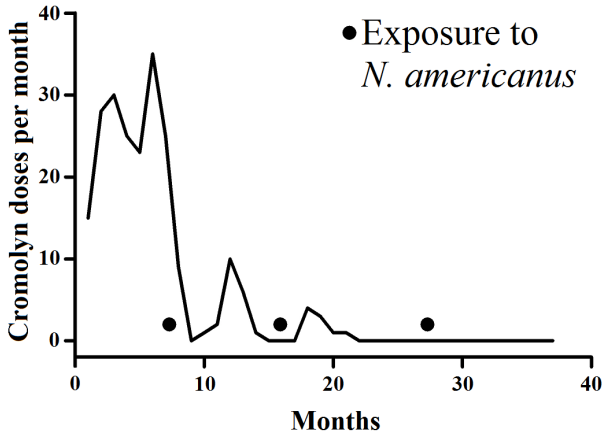

Figure 2: The effect of exposure to *N. americanus* on airway hypersensitivity to exhaust from internal combustion engines. Participant number 8 in the survey, a 61-year-old male, reported sensitivity to fumes from any internal combustion engine. After becoming progressively worse over a period of 6 to 12 months, medical attention was sought. At the time the participant sought medical attention, he was unable to walk on the street due to the risk of being exposed to car exhaust, and attacks could be triggered in parking lots or by being exposed to lawn mowers 50 yards upwind. Driving became extremely risky, despite precautions (a cartridge face mask and the air-conditioning set to recirculation mode to block the outside air from entering the car). After having adverse reactions to several drugs (e.g., Asmanex, Proventil, Singulair, and Alvesco) over a course of 6 months, inhaled Cromolyn was used. The number of doses of Cromolyn taken each month afterward is shown in the graph. One dose was taken during each attack to avert suffocation. The dots represent the three doses of hookworm (the first dose of 35 and two subsequent doses of 50). The first benefit of the helminth exposure was noticed 45 days after exposure. The participant reports that "I no longer experience stress in conducting my activities of daily living and, although helminths have not made my lungs 100% nonreactive, I consider myself 85% back to normal, which has given me my life back."

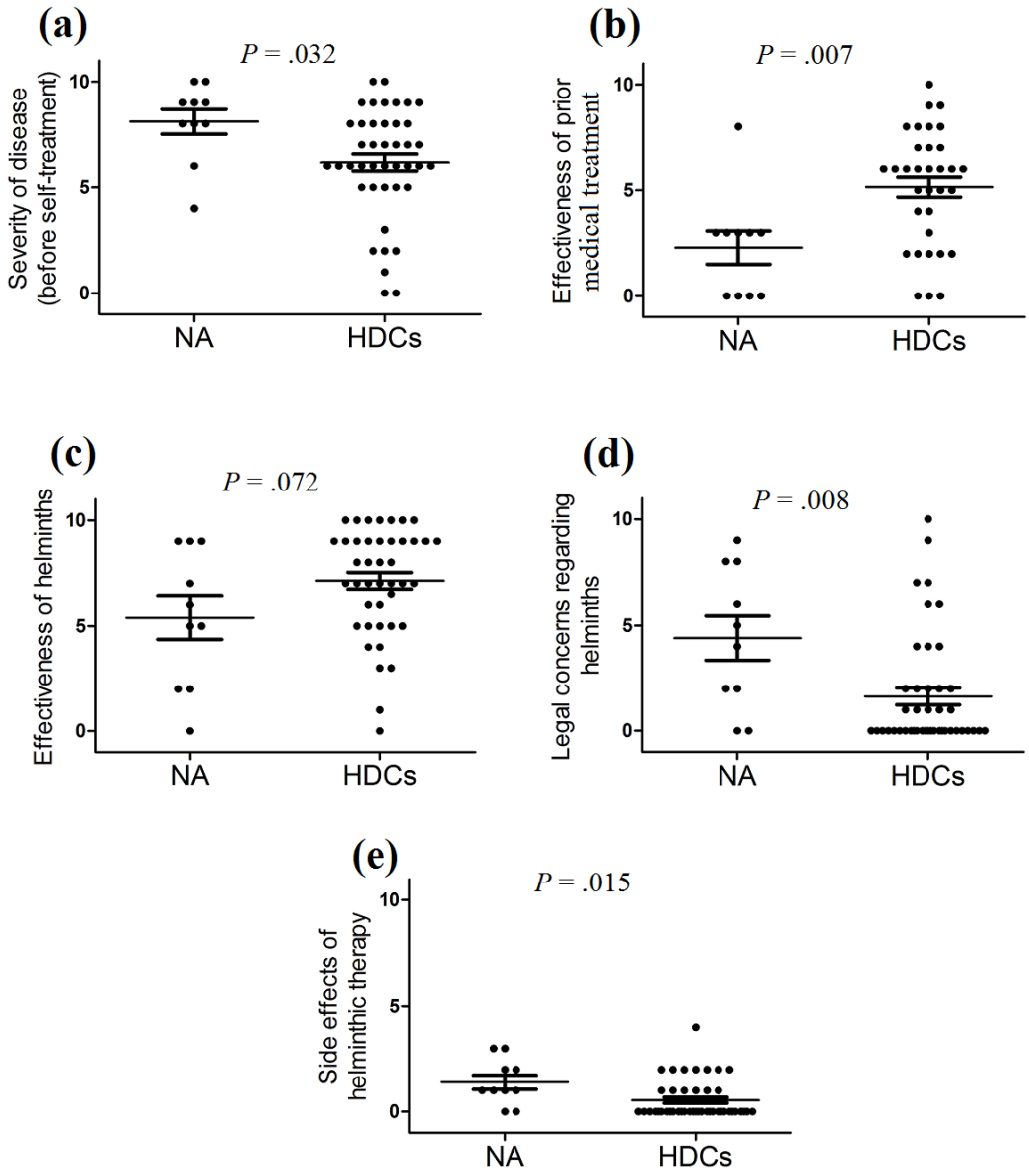

Figure 3: Comparison of answers from survey participants using NA ($n = 10$) versus those using HDCs ($n = 44$). The group using NA includes 2 participants using both NA and TTO. Participants used an 11-point scale from 0 to 10 to rank (a) severity of disease before helminthic therapy (but after standard medical therapy), (b) effectiveness of prior medical treatment, (c) effectiveness of helminths at treating disease symptoms, (d) their legal concerns regarding helminthic therapy, (e) and the side effects of helminthic therapy. The data reveal a number of differences between survey participants using NA versus those using HDCs; comparisons were all statistically significant except comparison of the effectiveness of the helminths at treating disease.

Use

Most people using NA are "very ill," according to helminth providers ($n = 2$). This assessment agrees well with the survey data (Figure 3). The majority of individuals using NA have inflammatory bowel disease, although a number of patients with multiple sclerosis are also self-treating with NA (Table 3). Some people are using NA to treat a variety of allergic conditions, including seasonal allergies and psoriasis, but this is usually secondary to more debilitating diseases. (i.e., individuals are not using NA to treat for allergic conditions, but these conditions are treated secondarily as a result of treating their primary condition, usually inflammatory bowel disease or multiple sclerosis.)

Effectiveness

There is general agreement among suppliers that healthier individuals respond better to helminthic therapy than

do very sick individuals. In general, only about 50% of the "most difficult cases" of allergic disease, often accompanied by "immune syndromes," or syndromes associated with inflammation, may respond to helminthic therapy with NA. Furthermore, for individuals that are "very sick" with ulcerative colitis and Crohn's disease, helminthic therapy with NA proves successful in only about 40% and 65% of cases, respectively (source: provider interview). On the other hand, NA is apparently very effective at alleviating seasonal allergies (sources: publically available information and provider interviews, $n = 2$), consistent with the original report by Turton [29], with rates of remission reaching 80%. NA is extremely effective at treating relapsing-remitting multiple sclerosis, with a success rate exceeding 90%. The success rate for treating progressive multiple sclerosis is less, at about 50% (source: provider interview).

Side effects

NA is a well-known communicable organism of substantial historical significance, with uncontrolled colonization of the population causing substantial morbidity in the Southern United States prior to 1950. In sufficient numbers, the organism can cause lethargy, anemia, and severe stomach pain. A single large dose (generally considered to be more than a therapeutic dose of 50 organisms) can lead to a life-threatening pneumonia. However, the side effect profile is much different for controlled exposure; we have not noted any reports of death from therapeutic exposure to NA (or to any other helminth). Therapeutic doses of NA (25 to 50 organisms), especially on the first dose, can cause fatigue in more than half of individuals, with about 10% describing the fatigue as "severe." In addition, use of NA is associated with skin rashes at the site of entry in about 80% of individuals, and GI symptoms in almost 90% of all individuals, including diarrhea in about two-thirds of individuals. The GI symptoms are most often "mild" and not generally viewed as outweighing the benefits of the therapy. However, GI symptoms may last for several weeks in some individuals. One helminth provider noted that patients with fibromyalgia in particular responded very adversely to NA. Two other providers noted issues with the skin reaction associated with NA administration. One noted that some individuals with autism cannot tolerate the skin rash, which can become severe over time. The second noted that the skin reaction may depend on the number of bacteria associated with the preparation, and pointed out that new procedures for isolation of NA reduce bacteria substantially and may reduce the skin reaction.

3.5.3. The human whipworm (TTO)

General

TTO [34] has a life cycle similar to that of TSO (see above), although it effectively colonizes humans rather than pigs. It is cultivated from human feces as is NA. Providers were surprised to find that TTO can live in humans for up to 4 years, longer even than NA. Individuals self-treating with TTO generally do so in a manner independent of a physician's advice.

Dosage

As with all helminths, the dosage of TTO depends strongly on the individual, but generally falls within 1,000 to 2,000 ova per patient. The colony is generally maintained in the gut, requiring additional exposures every one to two years to maintain the colony.

Use

Like NA, TTO is primarily used by patients that are "very ill." As such, it is expected that the success rate will be reduced compared to therapies targeted as less desperately ill patients. TTO has less of a systemic effect (i.e., less impact on conditions such as allergy that affect areas outside the colon) than does NA, but is thought by some providers to possibly be more effective than NA for some conditions of the large bowel. Perhaps surprisingly, TTO apparently does not have the "emotional effects" (i.e., the effects on neuropsychiatric function, particularly with autism) that are seen with TSO. For this reason, and perhaps because TTO is more difficult to cultivate than NA, this organism is not used as commonly as NA. Although two suppliers provide TTO, only one provides it to customers on a regular basis.

Effectiveness

TTO is effective in "up to 50%" of Crohn's cases in the large bowel, but it is not as effective as NA. Based on interviews with providers, TTO is probably most effective for ulcerative colitis.

Side effects

Uncontrolled colonization with TTO, especially when occurring in the presence of uncontrolled colonizations with other helminths, may have adverse effects, including bloody diarrhea and anemia, which are generally not seen with therapeutic doses. However, therapeutic use of TTO is known to cause some allergic-like reactions in some individuals, and some individuals may actually get worse on the therapy, according to one provider.

3.5.4. The rat tapeworm (HDCs)

General

The rat tapeworm [35] is the only worm in current use belonging to the flatworm class. (The other organisms in use are all roundworms.) As such, it has a substantially different life cycle than the other helminths. Adult organisms are maintained in rats, the "primary hosts," which experience no apparent adverse symptoms as a result of the colonization.

Like colonization with some other tapeworms, colonization with the rat tapeworm is generally self-limiting. In other words, the number of organisms that survive in a single host is limited, thus protecting the host and ensuring survival of the worm. The organisms require an intermediate insect host to complete their life cycle. For therapeutic purposes, the organisms are farmed in grain beetles, which obtain the HDCs by ingesting rat feces containing the eggs. Except in rare cases, HDCs, like TSO, do not grow to maturity in humans, so repeated exposure is required. Over half of individuals currently self-treating with HDCs began the practice based on (as a result of) the advice of a physician.

Based on provider interviews, the effectiveness of HDCs in humans is dependent on the manner in which the organisms are cultured, with the age of the HDCs as well as the nutritional support and housing temperature of their insect hosts being important. Furthermore, one provider noted that the organisms are not resistant to cold weather, although other providers have not noted any sensitivity to the cold. The storage conditions of the organisms for shipping are not uniform between providers and may be important in this regard.

Dosage

The dosage of HDCs is relatively standard, with most (about 80%) of individuals using 30 HDCs every 3 to 4 weeks or 20 HDCs every 2 to 3 weeks. However, some variation does exist, with most of the remaining 20% of individuals using up to 50 DHCs every 2 weeks and a few others (less than 5% of the total users) using as few as 1 per week or 5 every 4 weeks. In general, self-treaters using higher doses started with an initial lower dose and increased the dose until complete effectiveness, particularly with neuropsychiatric issues (see below), was achieved. Furthermore, freshly isolated HDCs are apparently somewhat more effective than at least some preparations of purified and shipped HDCs. Thus, as might be expected, the dosage of purified and shipped HDCs is generally higher than the dosage of fresh product. However, some individuals do not notice the difference between purified and shipped HDCs versus fresh HDCs (see paragraph on "Effectiveness" below).

Use

The use of HDCs is growing rapidly, and its popularity has surpassed that of TTO since these data were initially complied in January of 2015. (By April of 2015, the number of users of HDCs had surpassed 700, whereas the number of users of TTO has remained relatively steady at about 600.) Because of the relatively low cost of HDCs and potentially other factors (see Section 4), individuals are trying HDCs even without being extremely sick (Figure 3). A wide variety of illnesses are being treated (Table 2), including a number of allergic and autoimmune conditions. In addition, individual users and helminth providers report positive effects on a broad spectrum of conditions, including autism, heart arrhythmias, gum disease, hemorrhoids, reactions to bug bites, reactions to burns, and wound healing. Perhaps most striking was the reported effect on neuropsychiatric function described by the survey participants (Table 2). Based on reports from both survey participants and from providers, the organisms apparently have a profound effect on ADHD, bipolar disorder, migraine headaches and nonmigraine headaches, depression, and a variety of anxiety disorders, including PTSD. The apparently wide range of effects on inflammatory-related conditions affected by HDCs is potentially explained by a systemic decrease in inflammatory potential, and sheds new light on the effects of biome depletion on public health.

Effectiveness

Treatment with HDCs is apparently effective in more than 90% or even 95% of cases, which is slightly better than treatment with other helminths. This increased effectiveness is likely due, at least in part, to the relatively less ill population using the organisms. Whether the helminth itself makes a difference is unknown. It is possible, based on very limited information from survey participants and from provider interviews, that HDCs have more of an impact on neuropsychiatric function than does NA (see Section 4). However, comparisons between the effectiveness of HDCs and other helminths, especially TSO, are very difficult if not impossible to make based on the information available.

The production of HDCs among suppliers is not standardized, and the effectiveness of various preparations may vary. The majority of our data from user surveys comes from a single, noncommercial supplier. That noncommercial supplier uses the same production protocol as one of the commercial suppliers up to the point of extracting the helminths from their intermediate hosts (grain beetles). However, commercial suppliers use a washing/cleaning process to reduce microbial contamination of the HDCs, thus avoiding overgrowth of microbes and spoilage of the sample during shipping. In contrast, the noncommercial supplier harvests the HDCs within a few hours of administration (see discussion above about differences regarding the effectiveness of fresh and stored HDCs).

Side effects

Uncontrolled colonization with roundworms (e.g., NA and TTO) often leads to adverse reactions. Although HDCs do not generally colonize (grow to adulthood) in humans, uncontrolled colonization with the rat tapeworm has been previously reported in the peer-reviewed literature. Such colonizations are generally asymptomatic and discovered by accident while screening for other conditions [28,36,37]. Although much rarer than adverse reactions to roundworms, adverse reactions associated with uncontrolled HDC colonization have been reported [38,39,40,41]. The rarity

of case reports associated with HDC colonization, despite the fact that the organisms are very common in nature [42], probably reflects the fact that HDCs fail to colonize (live to adulthood) in the vast majority of individuals who encounter the organism. Fortunately, the rare adverse events associated with uncontrolled colonization with HDCs have been effectively treated with antihelminthic drugs.

As the newest organism on the market, the side effects of controlled exposure to HDCs in humans are less well established than with other organisms. HDCs are considered "helminths light" by some ($n = 3$) providers, with considerably less adverse side effects than NA. This agrees with the survey data (Figure 3). Unlike roundworms, they do not breach the epithelial barrier of the gut, remaining strictly in the lumen of the bowel. About 20% of self-treaters report mild and temporary (< 12 hours) gastric upset immediately following exposure, which does not generally outweigh the positive effects of the helminths for the self-treaters. However, this side effect can apparently be avoided without loss of effectiveness by decreasing the dose and increasing the frequency of administration. Less than half of 1% of HDC users did not tolerate 10 HDCs per month, but did tolerate 5 HDCs per month. In addition, less than one-half of 1% of individuals have reported severe GI symptoms (cramping and vomiting) following exposure to HDCs, but these symptoms have not been associated with every dose (i.e., one dose might be associated with an adverse reaction, but other doses are not). One individual (roughly 0.2% of the current self-treaters using HDCs) was actually colonized (tapeworm eggs were identified in the stool), although no symptoms of infection (no ill effects) were noted.

3.5.5. Parkinson's disease

Of particular note were two reports, one from provider interviews describing the effects of HDCs, and the other from publically available information describing the use of TSO, indicating that self-treatment with helminths might be an effective treatment for Parkinson's disease. Based on the available information, the authors believe that the reports are authentic. In the case of treatment with TSO, a female with Parkinson's reported "They (TSO) actually have a brilliant effect on dyskinesia and the need for drugs. It reduces the need for levodopa considerably." In the case of the patient using HDCs to treat Parkinson's, the noncommercial supplier had the male user's doctor contact one of the authors (WP) and confirm that the patient (a) had Parkinson's, (b) was wheelchair-bound before helminthic therapy, and (c) was now mobile and able to travel without the aid of a wheelchair. Although the information we obtained is scant, the well-established connection between Parkinson's disease and the gut [43] suggests the idea that helminthic treatment for patients with Parkinson's or at least a subset of patients with Parkinson's is a reasonable idea.

One provider thought that helminths might slow but not halt the progression of Alzheimer's disease, and that prevention rather than treatment is important for this disease. However, this was a "guess" based on the experience of only one individual using HDCs. The observation that Alzheimer's disease, perhaps like Parkinson's disease, may be associated with the gut [44,45] potentially provides an incentive for clinical trials using helminthic therapy in Alzheimer's patients.

3.5.6. Considerations regarding side effects of helminthic therapy

A consistent observation (from providers and from publically available information) was that the risks of helminth therapy probably increase with the degree of sickness being treated. Relatively healthy individuals, for example, treating anxiety disorders with HDCs, appear to be at very low risk. On the other hand, individuals with nondescript inflammatory syndromes were more likely to respond adversely to helminths. Fortunately, a "bailout" option is always available with helminthic therapy, since effective antihelminthic drugs are affordable and readily available. Furthermore, TSO and HDCs are short lived in the human body, and are eliminated within days and weeks, respectively, upon cessation of therapy.

Two providers expressed the view that adverse GI side effects, in some cases, may simply be the result of the immune system "waking up" and attacking pathogens which had previously escaped immune surveillance. One provider in particular noted two cases in which one-time adverse reactions (reactions that were present only once during self-treatment, usually toward the beginning) were associated with decreases in infection-related chronic inflammatory issues, and that the self-treaters felt that this was due to their immune system clearing out chronic infections following helminthic therapy. This view, if confirmed, may have implications for a variety of inflammation-associated diseases, including cancer and autoimmunity, which can be triggered by chronic infection [46,47].

Hypothetical concerns about problems with contamination of helminth preparations with infectious agents have thus far proven to be unfounded. Hundreds of thousands of doses have been administered to date, without reports of transmission of infectious disease. All except one of the companies currently supplying helminths (see Section 4) have delivered thousands of doses without any reported incidence, suggesting that the process of domesticating helminths may not be fraught with technical difficulty. Indeed, transfer of the entire fecal material from donors screened for infectious disease has proven safe when used for treating a type of colitis in a number of published reports [48], so there is no apparent reason to fear infection from TTO or TSO (orally administered helminths of fecal

origin) as long as the health status of the donor can be confirmed. In addition, effective methods for obtaining NA and TSO with low levels of bacterial contamination have been developed and are expected to reduce the risk of contamination with pathogens. Furthermore, HDCs are isolated from nontoxic grain beetles, suggesting that food-grade safety practices during preparation may be sufficient to ensure quality for that organism.

It is hoped that, eventually, all helminths will be regulated (i.e., systematically certified or otherwise guaranteed) in a manner that enhances customer confidence and improves safety without incurring excessive expense. Such practices should decrease the hypothetical risk of transmitting infectious disease. However, it might be argued that even completely sterile helminths could potentially lead to infection because the organisms are immunosuppressive, and immunosuppression increases the risk of infection. Our laboratory has probed this issue using an experimental enrichment of the biome in laboratory rats, and found enhanced rather than suppressed immune function in the biome enriched animals [49]. Enhanced immune function would, hypothetically, reduce the risk of infection and is consistent with the view expressed above that helminthic therapy could aid the immune system in clearing chronic infections. Thus, while considering the risk of infection as a result of helminth therapy, the hypothetical possibility that the absence of helminths (i.e., biome depletion) enhances the prospect of succumbing to infectious disease should be considered. Furthermore, given the tendency for the modern immune system to aberrantly react to a variety of stimuli, it is possible that chronic conditions such as shingles and Lyme disease are associated with adverse immune reactions to infectious organisms such as the varicella zoster virus and species of Borrelia, respectively. Although speculative, it is possible that these inflammation-related conditions or at least the severity of these conditions are associated with biome depletion. Thus, strictly hypothetical concerns regarding the risk of infection as a result of helminthic therapy run both ways; it may increase or it may decrease the risk of a serious infection. Perhaps more importantly, many autoimmune diseases and potentially some cancers are known to be triggered by infection in a manner that depends on the presence of biome depletion and other immune destabilizing factors [12]. Thus, the known risks of infection favor having an enriched rather than a depleted biome.

Self-treatment with helminths apparently has some of the same drawbacks as the use of modern pharmaceuticals, including a lack of compliance with effective treatments and usage of inappropriate doses. For example, some individuals have been underdosed and others overdosed, particularly early on during the use of a "new" helminth. Underdosing in particular was very common, as 16 out of 44 (36%) of the participants taking HDCs were apparently underdosed (see Table 2). As an example of one individual who was apparently underdosed, case number 35 in our survey involved a 49-year-old male with partial resolution of war trauma-associated PTSD using 20 HDCs per month (Table 4). Yet, several suppliers with experience using HDCs indicated that higher doses of HDCs (40 to 50 HDCs every two to three weeks) can be helpful for individuals with partial resolution of symptoms using lower doses of HDCs. Confirming this view, the individual associated with case number 35 eventually ended up with 40 HDCs every two weeks, and is "as normal as he can ever remember" (i.e., the same neurological function as prior to his wartime experiences) based on information obtained from a provider. In addition, some "compliance issues" were noted by providers. The noncommercial supplier, for example, reported difficulty getting many of his nonpaying "clients" to pick up their helminths on a regular basis. Perhaps as concerning was the observation that some individuals do not take helminths on a consistent basis to remain disease free, but rather take them only when they relapse and experience disease. For example, a substantial number of the individuals responding to the survey (37%, or 21 out of 57 responses to the question) inadvertently lost their helminths at some point. In addition, some problems with inaccessibility of suppliers are evident, although this does not affect most people. However, the situation is hopefully improving, with the addition of two new commercial suppliers within the past year.

Case number 45 from the survey is probably important to consider in terms of the potential side effects of helminthic therapy. In this case (Table 4), the participant abruptly halted his antidepression medications and began taking HDCs. Although confident in his actions because of the effects of HDCs on his adult daughter and a friend, the outcome was severe depression. The participant resumed his medication and, fortunately, recovered rapidly. Nonetheless, this case highlights potentially disastrous consequences that a lack of education regarding the effects of helminths might have, and emphasizes the need for physicians to be well informed regarding helminthic therapy so that they may discuss pertinent issues with their patients.

4. Discussion

4.1. Piecing together the history of self-treatment with helminths: the past to the present

The recent history of helminthic therapy can readily be ascertained through provider interviews and publically available information. Although Turton's cure of hayfever by self-treatment with helminths was reported in 1976 [29], the modern era of helminth therapy began about 10 years ago with the publication of Weinstock's work with TSO [16, 18]. This event coincided with the first availability of helminths for interested individuals; private citizens could

Table 4: *Self-reported effects of self-treatment with helminths on neuropsychiatric function.* *Text was selected involving neuropsychiatric function; text involving treatment of other conditions (e.g., allergy) was omitted. Text in parentheses was added for explanation or clarity, and some spelling and grammatical errors were corrected.

Number of participants	Organism used	Participant's description of effect on neuropsychiatric function*
1	NA	"(My) behavioral and mood changes (are) less severe" after treatment.
6	NA	"(After self-treatment with helminths, my) anxiety continues, (although my) brain fog is much improved."
12	HDC	"(After self-treatment with helminths, my) depression is reduced by 99% and my anxiety attacks are almost gone. The intensity (of the anxiety attacks was) reduced significantly (by self-treatment with helminths) from high to low."
22	HDC	"(After self-treatment with helminths), my generalized anxiety is still difficult to manage but is better regulated to the point I am able to focus and maintain quality of life. I no longer experience panic attacks."
24	HDC	"Before my self-treatment with helminth therapy, my ADHD was unbearable. I could not concentrate on anything. My mood was unstable to say the least. One moment I would be fine and the next I would be depressed. (After treatment), my ADHD is more manageable, my memory has improved, and my mood is 100% more even."
25	HDC	"(Before self-treatment with helminths, I had) debilitating depression and anxiety, and complete apathy and inability to participate in daily life. (After treatment), I have not had a single depressive episode. My anxiety persists, but it is not as bad. I have recently taken steps to confront and manage my weight through intensive holistic lifestyle changes. I do not believe I would be capable of this change without the helminth treatment."
27	NA HDC	"I also (in addition to effects on sinus problems) unexpectedly experienced brightening of mood and improvement in cognitive function with helminth treatment."
35	HDC	"(Before treatment), I had PTSD, agoraphobia, uncontrollable anger, and a mad-at-the-world attitude. Since helminth therapy, I no longer think of ways to eliminate (kill) people that frustrate me. I have started reading books again after 5 years of not being able to concentrate. I can control my anger mostly now and think of possible alternative ways of dealing with problems. I still do not like crowds but I can deal with being in one. Loud sudden noises still startle me, but I control my breathing and get back to "normal" pretty quick."
36	HDC	"(Before treatment), in my 30's, I was diagnosed with depression and anxiety. In my 50's, I was diagnosed as bipolar. Since the beginning of self-treatment, my symptoms have subsided. My wellbeing has improved 100%."
37	HDC	(After treatment, I have) less anxiety and am able to think clearer. The helminths seemed to help in areas that were positive but unexpected.
38	HDC	"(The participant was self-described as having bipolar disorder.) When I get angry I used to (before helminth therapy) have thoughts of killing the person that made me angry or maybe just hurting them severely, but now (after therapy) I am not angry often or depressed."
45	HDC	(The participant suffered a depression/anxiety episode following self-treatment with helminths), "probably because of stopping antidepressant (medications) abruptly after 15 years of usage." (The participant stopped the medication after observing the effects of HDCs on the depression of a family member, and recovered rapidly after resuming the medication.)
47	HDC	(The participant was self-described as having bipolar disorder without mentioning other conditions, and rated the effectiveness of self-treatment with helminths as 9 on a 10-point scale, versus 7 for standard medical treatments. The side effects of helminths and standard medical care were rated at 0 and 3 on the 10-point scale, resp.)
50	HDC	"Professional diagnosis with clinical depression and seasonal affective disorder." (No other conditions were described by this participant, who rated the effectiveness of self-treatment with helminths as 9 on a 10-point scale, versus 4 for standard medical treatments. The side effects of helminths and standard medical care were rated at 2 and 3 on the 10-point scale, respectively. The adverse effect of the helminths, a stomach ache lasting less than 12 hours, was alleviated without losing effectiveness by cutting the dose of helminths in half and doubling the frequency of administration.)

purchase TSO directly from the company Ovamed if they were able to provide a doctor's statement of support. The production of TSO was well regulated, with excellent quality assurance standards, but the therapy was very expensive, costing more than $12,000 per year for the typical regimen (source: publically available information and provider interviews). Because of this high cost and the lack of insurance coverage for its use, only the wealthy could afford treatment without substantial sacrifice, and the use of TSO remained a difficult decision for most. Shortly thereafter, in 2007, the first supplier of NA and TTO began operations, with the formation of Autoimmune Therapies. The cost of therapy with these organisms was about half the cost of therapy with TSO, but still in the range of $6,000 or more for the first year, when considering travel expenses. Furthermore, no regulatory control of NA and TTO production was available, making the decision to self-treat potentially more difficult due to uncertainty about product quality. The next year, an additional company, WormTherapy, emerged providing NA and TTO, and the price of that therapy soon decreased to the range of about $1,000–$1,200 per year (including travel expenses for treatment from WormTherapy). However, payment for 3 years of therapy was required prior to the initiation of therapy, and regulation of NA and TTO production was still not available. At the same time, procedures for cultivating NA became widely accessible, and an unknown number of individuals began to cultivate their own NA for private use. The year 2011 saw a setback in helminth therapy, as the original formulation of TSO, shown to work by Weinstock, was taken off the market. However, the setback was temporary, with the original formulation becoming available again in 2012 (sold by Tanawisa). In that same year, the relative ease with which HDCs are cultivated using grain beetles as intermediate hosts encouraged some individuals to begin production of HDCs for private use. The year 2014 saw substantial changes in the availability of helminthic therapy in terms of both cost and the species available. First, HDCs became commercially available for therapy. WormTherapy began to offer the organisms, and one new company, Biome Restoration, opened its business with HDCs being the only product (sold as a dietary supplement). The cost per typical monthly dose of HDCs from Biome Restoration, $45 including shipping, is currently the lowest cost of any helminth per dose, with a total cost per year of therapy at approximately $600.

A second advance in 2014 was the emergence of a new company, Wormswell, offering NA at $200 per dose of 25 organisms, reducing the cost of treatment with that organism for individuals using less than about 125 organisms per year. However, some individuals cannot benefit from this potential reduction in cost, since Wormswell is currently unable to ship to the United States for regulatory reasons. Finally in 2014, the price of TSO was reduced by about 40% following the implementation of new technology by Tanawisa for isolating the organisms. However, therapy with TSO remains the most expensive helminth therapy available, and the regulatory environment for NA and TTO has not improved. On the other hand, individual companies are establishing their reputations, and customer confidence is becoming relatively well grounded. At the same time, HDCs have been viewed as a dietary supplement (akin to yogurt) rather than a drug by the UK regulatory agency (MHRA), and TSO has been classified and regulated as a herbal rather than a pharmaceutical medicine by Thailand's regulatory agency. In summary, helminth therapy is in transition. What was a costly and sometimes risky venture into the unknown, undertaken by only a few 10 years ago, is rapidly becoming a readily available and well-established resource currently used by thousands of individuals.

4.2. Changing expectations for helminthic therapy

Some of the information gathered in this study was more or less expected given previously published information. All sources of information (surveys, publically available information, and provider interviews) indicate that self-treatment with helminths effectively treats many individuals with autoimmune conditions and diseases associated with inflammation of the bowel. This finding is consistent with published studies using human subjects and is supported by numerous studies in laboratory animals [6,14,15,17, 50,51]. Self-exposure to helminths was also effective in treating allergies in many cases. The observation that human hookworm could treat hayfever was first noticed by Turton [29] almost 40 years ago, but still came as a surprise (source: provider interview) to many self-treaters using hookworm to treat inflammatory bowel disease during the early days of the practice (2007–2010). However, it is now expected by most self-treaters that helminths will positively affect allergies as well as other allergy-related conditions such as psoriasis and contact hypersensitivity (source: provider interviews and participant surveys).

The information we collected in this study suggested that treatment of allergies with helminths may be much more effective if the participants are given a respite from exposure to antigen. For example, treatment for allergies against domestic animals or against certain foods may work better for people who are not regularly exposed to those stimuli. By the same token, self-treatment of seasonal allergies, a condition which naturally involves only transient exposure to antigen, is apparently very effective. Thus, it is possible that exposure to helminths may effectively attenuate or even prevent a future reaction against an allergen, but less effectively downregulate an ongoing reaction.

Some of the information we obtained, particularly regarding the effects of helminths on neuropsychiatric function, was rather unexpected by self-treaters and helminth providers alike. The effects of helminth exposure on neuropsychiatric function covered a broad area, and included treatment and even resolution of depression, migraine headaches, chronic fatigue, anxiety disorders, and bipolar disorder. Furthermore, two anecdotes involving a positive effect on Parkinson's disease were reported. Although several scientists, including ourselves, have predicted that biome enrichment should have a positive benefit on neuropsychiatric function [4,11,19,52], this issue has not received widespread attention. The reason that the potentially broad effect of helminths on neuropsychiatric function we observed in this study is not already a matter of public knowledge is probably multifactorial. First, the profound effects of inflammation on neuropsychiatric function are only now being widely recognized by the medical community. Indeed, until recently, any suggestion that systemic factors might exert an important influence on neuropsychiatric function has been virtually taboo in mainstream psychology and psychiatry [53,54]. Furthermore, most studies involving biome depletion and neuropsychiatric function have focused on bacteria rather than helminths [52], despite the fact that the microbial composition of the biome is much less affected by Western culture than is the eukaryotic (nonmicroscopic) portion of the biome [3]. Perhaps for these reasons, studies in animal models regarding the effect of eukaryotic symbionts on neuropsychiatric function are entirely lacking, and no studies in humans have been initiated except for a study on the effects of TSO (with a formula thought to be less effective than that used by self-treaters) on patients with autism. What is more intriguing is the fact that, despite 10 years of practice in self-treatment with helminths, few reports of changes in neuropsychiatric function as a result of exposure to helminths had surfaced until 2014. The changing face of helminth therapy, described above, may account for this paucity of reports. Until recently, practitioners of helminth therapy were generally very sick with inflammatory disease, and any alleviation of anxiety may have been attributed to the decrease in inflammatory disease. Some individuals with autism had experienced decreases in anxiety or anxiety-related symptoms as a result of intentional exposure to helminths, and by 2010 this was widely known within certain communities of individuals searching for new therapies for autism (source: provider interviews; $n = 3$ and publically available information).

However, the beneficial effects on patients with autism were assumed to be specific for autism, and it was not recognized that neurotypical individuals with neuropsychiatric impairment might also benefit. Finally, the recent appearance of HDCs on the market may have been pivotal in the recognition that exposure to helminths has a beneficial effect on neuropsychiatric function. That species of helminth may have a more potent effect on neuropsychiatric function than other helminths in widespread use, particularly NA and TTO (source: provider interviews; $n = 3$). As stated by one provider, "The emotional impact of the HDC was something that I did not really expect. We never saw that with hookworm." In addition, perhaps because HDCs are easy to obtain and relatively less expensive than other helminths, some individuals with relatively minor allergies tried helminth therapy, serendipitously observing an effect on neuropsychiatric function (source: publicly available information and provider interviews; $n = 2$). The initial observations that HDCs affect neuropsychiatric function in neurotypical individuals were made by self-treaters in mid-2012, and a group of individuals aware of this potential effect on neuropsychiatric function subsequently began to use HDCs specifically to treat anxiety (source: interview with noncommercial provider). Regardless of the reason that this effect of helminths on neuropsychiatric function has remained heretofore undescribed, this observation holds a great promise for the future and should encourage rigorous scientific study of this effect in humans and in laboratory models.

4.3. The placebo effect

The use of prospective, double-blinded, placebo controlled studies is considered the gold standard in modern medicine. Such studies are generally considered necessary to alleviate the placebo effect, an extremely potent mediator of sickness and health via the patient's expectations regarding drug effects. The placebo effect is so potent that it can subvert even blinded studies via the "active placebo effect," whereby the patients deduce whether or not they are on drugs or placebo due to the presence or absence, respectively, of side effects from the drugs [55]. However, for several reasons, some if not most of the effects of helminths observed in this study are apparently not due to a placebo effect:

(a) Some of the effects of helminthic therapy were unexpected and encountered while treating for another condition. This situation occurred in the early days of helminthic therapy when practitioners treating their inflammatory bowel disease were surprised to see their allergic conditions improve, and more recently when practitioners treating their allergic conditions were surprised by positive effects on neuropsychiatric function. Such surprises are not likely due to placebo effects.

(b) Participants know when their "coverage" runs out (see, e.g., the case report by P'ng Loke's group [56]). The coverage time varies from individual to individual and depends very strongly on the helminth used, indicating that the power of suggestion is not dictating the outcome.

(c) Participants have been able to determine specific production conditions that make the organisms effective or ineffective (for both HDCs and TSO), again suggesting that the reported effect is due to the organisms themselves and not the thought that the organisms are present. In other words, self-treaters have determined that particular methods of production of both HDCs and TSO are preferable to other methods of production of these organisms, indicating that helminths produced in a specific manner, not the idea of exposure to helminths in general, is responsible for the effects reported.

(d) Many participants were treating chronic conditions which had persisted for decades and/or had proven resistant to treatment with modern medicine, suggesting that neither real drug effects nor placebo effects have proven helpful in the past. This observation suggests that "regression to the mean" does not likely account for all of the effects observed.

(e) The noncommercial provider, when describing the effects of HDCs on neuropsychiatric function, observed a reproducible ($n = 5$) tendency for the person self-treating to downplay the results compared to people with close, longstanding relationships with the self-treater. Specific examples were given; spouses of self-treaters described the effects of helminths on their self-treating spouse as "life changing" (the husband of a self-treater), having a "dramatic impact" (the wife of a self-treater), or "a miracle, a completely different person" (the wife of another self-treater), whereas in each of those particular cases, the self-treater indicated the presence of "possibly some effect." This might be attributed to a disbelief in the idea that an organism in the gut can have a profound impact on neuropsychiatric function, or perhaps a lack of self-awareness regarding changing neuropsychiatric function. Regardless of the cause, this observation potentially reflects the presence of an "antiplacebo effect."

(f) Because of the lag between exposure to helminths and the appearance of noticeable effects, often weeks or even months, the memory of exposure to helminths has often been put aside, making it a "pleasant surprise" when the effects are noticed. This "surprise" factor is particularly evident with seasonal allergies, which typically occur only once or twice per year.

4.4. Selection bias, survivor bias, and conflict of interest issues

Of the three branches of the study, the interviews with helminth providers were essentially unaffected by selection

bias. At least one individual associated with each existing company was interviewed, eliminating selection bias. Although the respondents can be said to have a conflict of interest due to their commercial attachments, this is mitigated by the following:

(a) One provider was noncommercial (producing and distributing helminths with no financial gain). His views, free of financial conflict of interest, were consistent with those obtained from the other providers.
(b) Three providers had substantial knowledge of helminths which they had sold in the past but no longer sold. Thus, it would be in their best financial interest to downplay the role of helminths that they no longer sell. However, the information provided by these individuals was consistent with information obtained by providers currently selling the helminths in question.
(c) Providers willingly explained under what conditions the helminths they sell are not entirely effective. For examples, several providers indicated that the very sickest patients are the hardest to treat, one provider of NA explained that NA works much better for relapsing-remitting multiple sclerosis than it does for progressive multiple sclerosis, and a provider of TSO explained that NA works better for some airway problems than does TSO.
(d) The information obtained from nonprovider users of helminths, both through survey and through evaluation of publically available information, agreed with the information obtained from the providers.

These factors support the view that the providers are confident that their product(s) are effective, and that they are forthcoming regarding the effectiveness or lack thereof of their products.

Given that approximately 6,000 to 7,000 individuals currently self-treat with helminths, the fact that only 58 surveys and 207 publically available anecdotes were obtained indicates a very strong selection bias of some sort. As pointed out by one provider, the level of concern regarding legal issues, noted by participants in our surveys, would probably deter many from openly discussing their situation on social media sites. However, other selection biases may affect the results. For example, one provider noted that patients who are effectively and satisfactorily treated rapidly cease to be active or even disappear altogether from the social media sites. Since the social media sites are important means of gathering publically available information and for disseminating surveys, this factor may bias the information obtained from those sources against helminth treatment. On the other hand, individuals who tried helminths without success might also cease to be active on the social media sites, making the effect of survivor bias difficult to assess. In contrast, other sources of publically available information, including books, magazine articles, films, and movies, may be biased toward the more sensational success stories. Despite the substantial potential for selection bias, the publically available information agreed well with information from the providers.

Although the publically available information was potentially fraught with selection bias in ways that might be expected, the survey results were altered by bias in ways that were not anticipated. As described in Section 3, surveys were biased strongly toward individuals receiving helminths free of charge. This selection bias favored HDC usage exclusively, but, at the same time, introduced another selection bias for participants using HDCs: the selection process used by the noncommercial supplier when asking individuals to fill out the survey. The noncommercial supplier reported a 100% success rate when asking individuals to fill out the survey, but selected about 50% of his "clients" to fill out the survey. He reported that his selection criterion was based on how comfortable he felt the client would be in disclosing very private information, and was independent of the actual effect of the self-treatment. In support of this assertion, the effects of HDCs as seen in the surveys were supported by interviews with commercial suppliers of the organism.

4.5. Helminths as a natural supplement rather than a drug

If the effects of helminths on neuropsychiatric function and a wide range of other common inflammatory-related disorders are confirmed by additional studies, helminths can be viewed as a necessary component of the human biome. Intuitively, if the population has widespread conditions (e.g., hayfever, anxiety disorders, and migraine headaches) which are readily resolved by the addition of a factor to their body that would have naturally been present prior to the industrial revolution, then it can be concluded that this factor, helminths, is much more of a necessary ingredient for our body to function normally than a drug to treat disease. In other words, the observations made herein parallel observations made by Christiaan Eijkman that led to the discovery of vitamins. Others share this view regarding helminths; as Anne Cooke and colleagues asserted, "In some not too distant futurity, there may come a day when we all take "helminth supplements" along with our Omega 3 fatty acids, vitamins, and whatever else goes to make up a modern balanced diet" [51]. Furthermore, helminth providers ($n = 4$) strongly asserted that helminths were a natural component of the human biome and should be viewed as such.

Three providers (none from the same company) cautioned that it will be counterproductive but yet very tempting for modern humans to view helminths as a drug targeted at specific disease. Indeed, the present study attempts to assess the effects of specific helminths on specific medical conditions. While such a view may prove useful in treating disease, an alternative view was expressed by the three providers: that exposure to helminths should be viewed as one aspect of healthy living, to be utilized

in combination with well-established immune stabilizing factors (e.g., a healthy diet, adequate exercise and vitamin D acquisition [57], reduction of chronic psychological stress, and maintenance of the microbiome). It is the authors' opinion that the providers' point is important; reductionist thinking as applied to helminths could indeed be counterproductive. The authors would suggest a more integrative approach whereby, at the very least, clinical trials with helminths are conducted so that every patient (either on helminths or on placebo) receives screening for vitamin D deficiency and counseling for behavioral factors which affect immune function. The potential pitfall of treating helminths as an immune-modulating drug while ignoring other risk factors for immune function was evident in the surveys, with 40% of the participants (23/57 that answered the question) having never checked their vitamin D level.

4.6. Future studies on helminthic therapy through clinical trials: considerations and hurdles

This study brings to light a number of rather fascinating considerations, perhaps even quandaries, regarding the potential design of clinical trials aimed at evaluating helminth therapy. The most apparent concern derives from the observation that the formulation of at least some helminths, including the conditions for growth and storage, appear to be important for therapy in humans. Given that dozens if not hundreds of potential formulations might exist for a given helminth, it becomes difficult to conceive of the financial burden of running the necessary phase 1 through 3 clinical trials. Furthermore, the potential to use various species in combination, suggested as beneficial by most providers, adds many more trials to the waiting list. When the potential for different isolates or strains of a given species to have different effects is considered, the idea of extensive testing for every possible treatment via clinical trials becomes untenable. In contrast, one might envision testing different helminth formulations much as chefs test various recipes. Indeed, this is essentially how the field of self-treatment with helminths has advanced.

A second quandary when considering clinical trials to test helminth therapy is presented by the fact that the use of helminth therapy may be very difficult to claim as intellectual property. The organisms are, like vitamins, naturally occurring and many are already widely characterized. If legal protection as intellectual property is not feasible, it becomes difficult to envision substantial funding from industrial sources to conduct clinical trials, and places the burden of those trials on governmental agencies. Additional quandaries were presented by helminth providers. Two providers pointed out that the effects of helminths on the human body are rather broad and often include improvement in a sense of well-being. Furthermore, all providers were united in their assertion that dosage is highly dependent on the individual. With this in mind, it seems quite possible that modern trials, aimed at treating one disease with one drug, may have difficulty in fully evaluating the effectiveness of helminthic treatment.

One possible way to reconcile the practice of helminth therapy with modern medical practice is to utilize the results obtained by those self-treating with helminths as a starting point for clinical research and trials. This approach has been previously suggested [21] and could utilize the flexibility of self-treatment practice as well as the quantitative aspects of modern clinical studies. Unfortunately, the realization of this ideal has not been achieved in many cases. Clinical trials are being conducted, but in some cases are apparently being conducted using inadequate doses of helminths. The use of hookworms is of particular interest in this regard. Self-treaters and providers alike generally agree that an effective treatment with hookworms involves a first dose of 25 to 50 hookworms, with subsequent doses aimed at achieving and maintenance of a colony of approximately 50 and 110 hookworms in the gut, depending on the individual. It is also agreed that treatment can take several months or even a year in some cases to fully take effect. Based on this "standard," formal studies at medical centers have under-exposed patients to hookworm, sometimes by a factor of 10 or more, and have not been sufficiently long in duration. For example, Feary et al. (2009) evaluated the effect of a single dose of 10 hookworms per patient on 32 patients with asthma for 16 weeks [22], and found no statistically significant effect on the disease. Daveson et al. (2011) used single doses of 5 to 10 hookworms per patient to treat 20 patients with Celiac disease for 21 weeks [58], and again found no effect on the disease. Croese et al. (2015), again using single doses, examined the effect of 20 hookworms for celiac disease with 12 patients and found no effect on celiac symptom indices after 52 weeks [59].

A separate issue, unrelated but equally as troublesome, is that the formulation of TSO currently used in clinical trials, based on available information (sources: publically available information and provider interviews) is noticeably less effective than the formulation originally used by Weinstock and currently sold to private individuals. (Note added in proof: all clinical trials with the potentially less effective formulation of TSO were terminated because of a lack of effectiveness.) Importantly, when clinical trials ignore the "standards of best practice" acknowledged by those self-treating, it should be widely appreciated that the results probably do not represent the full potential that helminthic therapy holds for public health.

4.7. To try the therapy or not to try the therapy?

It is readily apparent from a substantial number of anecdotes that self-treatment with helminths is effective for many people, probably even most people, in terms of alleviating a wide variety of inflammatory-related diseases. The more than 250 anecdotal observations described in this study

are supported by a few published clinical studies and are clearly in agreement with current scientific understanding of the immune system's dependence on the biome for proper function. At the same time, many of the risks to human health from biome depletion are readily apparent, with a wide range of allergic and autoimmune conditions attributed to biome depletion. Furthermore, diseases not currently confirmed to be associated with biome depletion, including Parkinson's disease and a variety of other neuropsychiatric problems, may be associated with biome depletion. With these factors in mind, it seems highly likely that self-treatment with helminths, despite its unknown risks, varied and changing practices, and poorly defined outcomes, is more beneficial than harmful to the average practitioner. With this in mind, the principle of *primum non nocere* (first, do no harm) dictates that the medical and scientific community avoid dogmatic de facto discouragement of self-treatment with helminths. At the same time, it is hoped that physicians will familiarize themselves with the field of helminthic therapy so that they can rationally discuss this emerging area with patients when questioned. In addition, it is hoped that the scientific community can utilize knowledge gained from those self-treating with helminths, bringing this form of therapy into mainstream medical use as safely, rapidly, and efficiently as possible.

Although it is untenable to rebuke patients for self-treatment with helminths when such treatment may in fact be their best course of action, specific recommendations regarding helminthic therapy may be difficult or impossible to make because of the limited data available. In addition, we have previously noted that, without more information, it is impossible to know whether exposure to otherwise beneficial helminths might be dangerous for patients with medical conditions such as HIV infection and hemophelia that potentially impair the body's response to helminths [9]. Unfortunately, this leaves individuals who often have no medical training to make decisions and judgment calls that are generally entrusted to medical professionals and regulatory agencies. Is a particular product the best product for a particular condition, is it safe, is it produced by a reliable source, and will it be effective? It is hoped that this study will provide information that may aid in that decision making process, and encourage health care professionals to educate themselves regarding current practice and experience in helminthic therapy. Importantly, it is hoped that an increased awareness of helminthic therapy, both of the benefits and the risks, by the medical community will encourage patients interested in helminthic therapy to make decisions regarding treatment in collaboration with their physicians.

4.8. The biology of the helminth's effects on human immune function

The question regarding the mechanism of action of helminths on immune function is frequently raised. One of the authors (WP) as well as many other investigators have devoted considerable time and energy to this question. What is clear is that helminths affect multiple immune components in the mammalian body, mostly likely through a wide range of complex interactions. What is perhaps less well appreciated is the inherent flexibility in this interaction; the original study evaluating the connection between multiple sclerosis and helminths demonstrated that the progression of multiple sclerosis could be halted by a variety of helminths, both flatworms and tapeworms [60]. In fact, no helminth was found which did not work. Consistent with this observation, the helminths described in this study (TSO, NA, TTO, and HDCs) represent not only all of the helminths currently in use by self-treaters, but also essentially all of the helminths that have ever been tried by self-treaters. (Exception: the bovine tapeworm has been tried at least once, but the "ick" factor was apparently intolerable.) The fact that all helminths are still in use and all have generally beneficial effects if used "properly" speaks directly to the potential for a wide range of organisms, perhaps including many that have never been evaluated, to help treat or avert human disease. The broad nature of the effects of eukaryotic symbionts on vertebrates is further supported by the observation that protozoans exert some of the same effects on immune function (e.g., induction of IgE production [61]) as do helminths. Thus, it seems likely that convergent evolutionary processes allowing eukaryotic organisms to live in the vertebrate GI tract have created a sort of "footprint of eukaryotic symbiosis" that is essentially required by humans for proper immune function. The molecular definition of this footprint of eukaryotic symbiosis is likely to be the subject of intense study in the future.

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