Multiple sclerosis and the hygiene hypothesis

John O. Fleming, MD; and Thomas D. Cook, PhD

In 1966 Leibowitz et al.[1] first suggested that the prevalence of MS was correlated with a childhood environment characterized by a high level of sanitation. Similar observations have led to the formulation of the hygiene hypothesis, which holds that a relative lack of "evolutionarily normal" childhood infectious exposures may predispose susceptible individuals to allergic and autoimmune diseases later in life. Recent findings that are consistent with the hygiene hypothesis have come from studies in epidemiology, immunology, and animal models, as well as successful clinical trials of probiotic treatment for allergic and autoimmune diseases.[2-4] In this regard, many observers have noted that the prevalence of MS in the developed world far exceeds that of regions characterized by widespread childhood infection or poor sanitation. Nevertheless, to the best of our knowledge, to date the global relationship between MS incidence and parasitic exposure has only been addressed in qualitative terms.

To address this issue quantitatively, we first noted the global prevalence of *Trichuris trichiura*, a common human helminth with world-wide distribution and a surrogate marker for 1) infection with other macroparasites as well a marker for 2) low levels of community sanitation. Initial data were obtained from the definitive review[5] of *T trichiura* prevalence by country or region, supplemented by primary scientific reports. After this information was complied, corresponding estimates of MS prevalences were obtained from a comprehensive survey,[6] which was supplemented by data from primary references when necessary. A detailed account of the methods and published surveys used in our analysis may be found on the *Neurology* Web site (www.neurology.org).

As shown in the figure, the prevalence of MS appears to fall steeply once a critical threshold of *T trichiura* prevalence (about 10%) is exceeded; surprisingly, there is a virtually dichotomous relationship (Kendall tau test, correlation −0.53, p value =

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the December 12 issue to find the title link for this article.

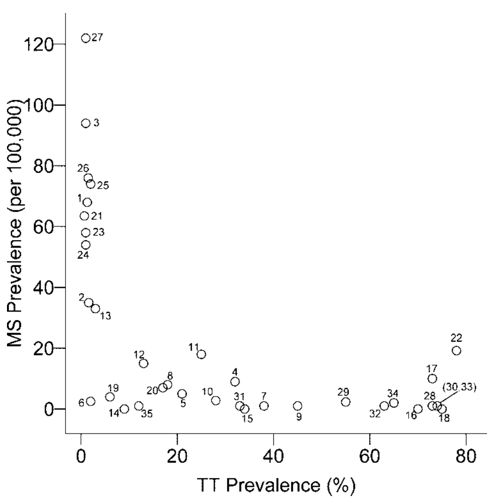

Figure. The prevalence of MS (patients per 100,000 general population) and T trichiura (percentage of surveyed population infected) by country or region. North America: northern United States (1), southern United States (2), Canada (3). Latin America: Brazil (4), Mexico (5), Paraguay (6), Honduras (7), Cuba (8), Jamaica (9), Panama (10), Argentina (11), Chile (12). Oceania: Australia (13). Africa: Ethiopia (14), Kenya (15), Cameroon (16), Nigeria/Ghana (17), Ivory Coast/Senegal (18). Middle East: Iran/Iraq (19), Lebanon/Jordan (20), Jerusalem–Jewish (21), Jerusalem–Arab (22). Europe: Italy (23), Poland (24), Belgium (25), East Germany (26), United Kingdom (27). Asia: Indonesia (28), Japan (29), Korea (30), Malaysia (31), Taiwan (32), Philippines (33), China (34), Central India (35).

0.00001) between MS prevalence and prevalence of *T trichiura*, with almost no regions of intermediate prevalence for both parameters. Note that the *T trichiura* data cited reflect the prevalence of a single parasite at one time point or survey date. Thus, it is possible that a "spot" prevalence of *T trichiura* in the order of 10% corresponds to a state of affairs in which exposure to multiple parasitic infections over the entire period of childhood will be almost universal in a given population. In this instance, according to the hygiene hypothesis, most children will experience a strong protective effect, possibly favoring a modified Th2-type immune response or an increase in T regulatory cell activity,[2] such that subsequent allergy and autoimmunity in adulthood will be uncommon.

Prior studies have demonstrated a direct relationship between absolute latitude and MS; however, in our survey, there were several exceptions to this relationship. For example, MS was relatively infrequent in countries such as Korea (data point 30), Argentina (data point 11), and Chile (data point 12) characterized by substantial latitude and high *T trichiura* prevalence. Also, in a survey conducted in Jerusalem, the prevalences of MS were inversely linked to differing prevalences of *T trichiura* in Jewish (data point 21) and Arabic (data point 22) populations, despite residence at the same latitude. Further studies are necessary to evaluate variables that may have confounded our analysis, such as race, migration, medical surveillance, sunlight exposure, diet, or other factors. Also, it is obvious that association does not prove causality. Possibly, both excellent sanitation and increased latitude may simply be markers for more fundamental social, genetic, or environmental factors in developed countries that are directly linked to MS etiology and pathogenesis.

There are many methodologic differences and limitations in the epidemiologic studies we have relied upon for our comparisons (table E-1). However, the striking and consistent findings shown in the figure are intriguing and indicate the need for further, rigorous investigations assessing the possible relevance of the hygiene hypothesis to MS. Longitudinal studies, including those tracking the prevalence of MS in response to changing sanitation and levels of parasite infection, would be very informative tests of the hypothesis. In this regard, the increase in MS prevalence in the French West Indies (FWI) from 1978 to 1994 was recently correlated with a significant reduction in intestinal parasitism during the same period.[7] They also found that the prevalence of MS was twice as high in returning migrants (islanders who returned to FWI after childhood emigration to France) in comparison with nonmigrants (persons remaining in the FWI throughout childhood). The authors discounted genetic variation to explain their findings, as no significant differences in ABO groups and HLA-1 allelic frequencies were observed between the two populations; instead, it was suggested that environmental factors, possibly including childhood infectious exposures, may be crucial in determining relative MS risk, either in terms of a MS-promoting influence in France or a MS-protective factor in FWI.

From the Departments of Neurology (J.O.F.) and Biostatistics and Medical Informatics (T.D.C.), University of Wisconsin Medical School, Madison.

Disclosure: The authors report no conflicts of interest.

Received June 26, 2006. Accepted in final form September 5, 2006.

Address correspondence and reprint requests to Dr. J.O. Fleming, Department of Neurology, H6/564 CSC, 600 Highland Ave., Madison, WI 53792-5132; e-mail: fleming@neurology.wisc.edu

References

1. Leibowitz U, Atonovsky A, Medalie JM, Smith HA, Halpern L, Alter M. Epidemiological study of multiple sclerosis in Israel. II. Multiple sclerosis and level of sanitation. J Neurol Neurosurg Psychiatry 1966;29:60–68.
2. Maizels RM, Yazdanbakhsh M. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nat Rev Immunol 2003;3:733–744.
3. Wickelson I. Can worms tame the immune system? Science 2004;305:170–171.
4. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911–920.
5. Bundy DAP, Cooper ES. Trichuris and trichuriasis in humans. Adv Parasitol 1989;28:107–173.
6. Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurol Sci 2001;22:117–139.
7. Cabre P, Signate A, Olindo S, Merle H, Caparros-Lefebvre D, Bera O, Smadja D. Role of return migration in the emergence of multiple sclerosis in the French West Indies. Brain 2005;128:2899–2910.

Table (E) T-1. Primary Sources for Comparison of Prevalences for *T. trichiura* and Multiple Sclerosis (please see notes and bibliography that follow)

Country/Region	**Datapoint in Figure**	***T. trichiura* Prevalence**		**Multiple Sclerosis Prevalence**		**Comments**
		Citation	Date of Survey	Citation	Date of Survey	
North America						
Northern United States	1	8	1978	3	1976	States above 37th parallel
Southern United States	2	8	1978	3	1976	States below 37th parallel
Canada	3	9	1979	27	1975	
Latin America						
Brazil	4	6	1971	27	1999	
Mexico	5	6	1966-76	27	1985	
Paraguay	6	6	1975	25	1990?	
Honduras	7	30	1998	16	1960	
Cuba	8	26	1993	27	1984	
Jamaica	9	31		29	1973	
Panama	10	26	1987	25	1990?	
Argentina	11	4	1999-00	27	1996	
Chile	12	6	1972	19*	1990?	*E
Oceania						
Australia	13	11	1993	27	1981	*E
Africa						
Ethiopia	14	12*	2000 1998	16	1957	*mean of two surveys available
Kenya	15	10, 22*	1998 1998	29**	1952-1969	*mean of two surveys; **E
Cameroon	16	6	1982	29*	1970?	*E
Nigeria/Ghana	17	1,6*	1981 1992	29	1960-1970	Nigeria for TT, *mean of two surveys; Ghana for MS
Ivory Coast/Senegal	18	20	1979	29	1970?	Ivory Coast TT; Senegal MS
Middle East						
Iran/Iraq	19	6	1980	27	1969	Iran TT; Iraq MS
Lebanon/Jordan	20	6	1955	27	1977	Lebanon TT; Jordan MS
Jerusalem-Jewish	21	13	1957	14	1995	representative studies from complex literature
Jerusalem-Arab	22	13	1957	14	1995	
Europe						
Italy	23	28*	2000	27	1975/1995	*CM
Poland	24	24*	1999	27	1966/1981	* average two regions
Belgium	25	6	1961	27	1992	*CM
East Germany	26	5	1980	27	1984-1992	*CM
United Kingdom	27	17	1972	27	1980-1996	*CM UK mainland, excluding N Ireland & islands

Asia						
Indonesia	28	6	1968-78	15*	1975	*E
Japan	29	18	1950?	27	1973-85	*CM
Korea	30	6	1971	2	1950's	
Malaysia/Thailand*	31	6	1980	15*	1965	*E, Thailand used for MS
Taiwan	32	6	1977	15*	1960-70	*E
Philippines	33	6	1968-78	15*	< 1975	*E
China	34	7	1993	27*	1986	* representative study from complex literature
Central India	35	6	1967-83	27*	1988	* representative study from complex literature
E = estimated prevalence; CM = mean prevalence for a country, combining results for regions. Please see explanations below.						

Note: The starting point for the analysis above was the review of *T. trichiura* prevalences provided by Bundy and Cooper (6); this source was chosen because it was one of the most authoritative and comprehensive quantitative surveys of the world-wide distribution of a common human macroparasite. We next attempted to find corresponding estimates for MS prevalences in the review of Rosati (27); this source was chosen because of the relatively recent date of publication, the objective summary of prior surveys, and attention to all world regions. After this initial comparison, we searched the Medline database for any publication relating to *T. trichiura* prevalence, and, for these papers, any corresponding publication relating to MS prevalence, if this data was not already available in our primary source, Rosati. As indicated in the table, in some cases our analysis was supplemented by reference to neurological texts or from personal communications of experts in neuroepidemiology of a given country or region.

Specific methodological points of our analysis are as follows:

1. Choice of surveys: Our general approach is described above. In the case of multiple surveys for a region or country, to be as consistent as possible, we used the data in our two primary sources (Bundy and Cooper for *T. trichiura*; Rosati for MS) when available, or, when necessary, the published report that most closely corresponded to the dates and methodology of our primary sources. Unfortunately, in some countries (e.g. South Africa) which would be very informative and for which extensive research existed for the prevalence of *either* MS or *T. trichiura*, it was not possible to find reliable, published reports for *both* prevalences. In some countries (e.g., Israel, China, and India, as noted) the relevant epidemiological literature is very extensive and complex; in these cases, we chose the reference or references that most closely corresponded to the dates and methods of Bundy-Cooper and Rosati, acknowledging that the choice of citations is to some extent arbitrary and over-simplified.

2. Date of surveys. Most of the data for *T. trichiura* prevalences in Bundy and Cooper were based on surveys prevalences conducted in the decades from 1970-1980, and most of the MS prevalences cited by Rosati were obtained approximately a decade later. According to the "time lag" implied by the hygiene hypothesis, as indicated in the text of the note, these survey times are appropriate. Unfortunately, as indicated in the specific entries for survey date in the table, in some cases it was not possible to group surveys by these ideal or target dates. In some citations the date of the survey was not stated explicitly; in these cases we have estimated the date of the survey, based on publication date, and indicated the uncertainty by means of a question mark (?) after the date.

3. Estimated prevalences. Insofar as possible, we based our analysis on epidemiological surveys for a specified region or country. In some cases, indicated by the letter "E" and explained in the table comments, an estimated prevalence was employed; usually this corresponded to circumstances in which published medical reports reliably indicated that the prevalence of parasite or MS was extremely low in that area. In other cases, indicated by the letter "CM", a mean estimate for a country was given; for example, in the case of Italy, a country-wide estimate for MS prevalence was determined by taking a mean of individual Italian regions cited in Rosati. While the CM determination does not take into account population structure and therefore does not provide an exact country-wide determination of MS prevalence, for the purposes of our survey, this procedure provided a reasonable estimate of MS in a given country, such that an exact determination, even if available, would not appreciably change either the appearance of the figure or the conclusions in the text.

4. Neighbor country determinations. In some cases, excellent correspondence, usually from our two primary sources (Bundy and Cooper; Rosati) was only available for one parameter (i.e., *T. trichiura* prevalence or MS prevalence for one country, but not both for one country). However, as noted, valid corresponding data, appropriately matching geography and socio-environmental characteristics, were available for a neighboring country (e.g. Malaysia/Thailand paring). In these cases, we have indicated the countries which were coupled, as well as the published studies on which the comparison was based.

5. Measures of Prevalences. Please see Rosati and individual citations for epidemiological methods used to determine MS prevalences; in virtually all cases the prevalences were determined in the general population. *T. trichiura* prevalences were usually determined by microscopic analysis of fecal specimens, though in the report of Sablich for Italy (28), endoscopy was employed. We made no attempt to list intensity of infection or co-infection with other parasites, though biologically these variables may be important. In some cases, the prevalence of *T. trichiura* was determined in the general population or extrapolated from hospital-based studies; however, in the majority of surveys, subjects were school aged children, and this age group is appropriate for the current analysis, since the hygiene hypothesis posits that *childhood* exposure to infectious agents is a critical influence for the risk of subsequent autoimmunity.

6. Other limitations of Cited Studies. There are other several limitations to our meta-analysis, including: 1) The most rigorous investigations of MS occurrence have been performed in developed countries where this disease is common; by contrast, the best epidemiological investigations of *T. trichiura* have been conducted in the developing world, where parasitism is frequent. 2) There were minor, and occasionally major, variations in epidemiological methods which were used in the different surveys (please see table and primary references for details) , 3) Since the prevalences of MS and parasitic infection are known to vary within countries and subregions, more informative analyses would be expected from studies conducted on a finer scale, for example, during investigations of rural versus urban areas within a given country, 4) To simplify our analysis we limited our comparisons to the prevalences of MS and a single parasite; ideally, a more complete assessment in future surveys would consider multiple infections (e.g. Ethiopia, data point 14, has an unexpectedly low prevalence of *T. trichiura*, but a much higher prevalence of other macroparasites (12); this country represents an exception where *T. trichiura* prevalence is not a good surrogate measure for sanitation and all-over childhood infection). 4) As the hygiene hypothesis posits that childhood infections influence subsequent autoimmunity in adulthood, in an ideal comparison, the date of a MS prevalence survey should be offset by 1-2 decades relative to the corresponding survey of parasitism or sanitation in the country or region under study. To the extent possible, we have attempted base our analysis on available, published reports which minimize these methodological difficulties.

In summary, we acknowledge the methodological limitations and variations in the studies cited in our review and have tried to present these forthrightly in the text and electronic supplement. Certainly, there is a need for more rigorous epidemiological studies to be performed which will employ uniform methodology in order to compare the prevalences of parasitism and MS in carefully-defined populations and regions. Nevertheless, the compilation above represents the best available published data, the majority peer-reviewed, bearing on the relative prevalences of *T. trichiura* and MS in the countries or regions cited. These observations form an informative dataset bearing on the hygiene hypothesis of autoimmunity, and hopefully, this first quantitative analysis, with its limitations, will be a basis and an impetus for definitive future studies.

Primary References for Prevalences of *T. trichiura* and Multiple Sclerosis.

1. Asaolu SO, Holland CV, Jegede JO, Fraser NR, Stoddard RC, Crompton DW. The prevalence and intensity of soil-transmitted helminthiases in rural communities in southern Nigeria. Annals of Tropical Medicine and Parasitology. 1992; 86: 279-287.

2. Barlow JS. Multiple sclerosis in North Korea and China, Neurology 1967; 17: 802-812.

3. Baum HM, Rothschild BB. The incidence and prevalence of reported multiple sclerosis. Ann Neurol 1981; 10: 420-428.

4. Beltramino D, Lura MC, Carrera E. Selective vs. mass treatment with antihelminthic drugs: experience in two hyperendemic communities. Pan American Journal of Public Health 2003; 13: 10-18.

5. Bernhard K, Semlow A. Intestinal helminths in the DDR district of Rostock. [German] Angewandte Parasitologie 1980; 21: 6-10.

6. Bundy DAP, Cooper ES. *Trichuris* and trichuriasis in humans. Adv Parasitology 1989; 28: 107-173.

7. Cai SC, et al. Studies on the changes in infection rates of whipworm and ascaris in population after continuous chemotherapy. [Chinese] Chung-Kuo Chi Sheng Chung Hsueh Yu Chi Sheng Chung Ping Tsa Chih Chinese Journal of Parasitology & Parasitic Diseases. 1993; 11: 282-285.

8. Center for Disease Control: Intestinal Parasitic Surveilance Annual Summary 1978. Atlanta, 1979.

9. Croll NA, Gyorkos TW. Parasitic disease in humans: the extent in Canada. Canadian Medical Association Journal 1979; 120: 310-312.

10. Geissler PW, Mwaniki D, Thiong F, Friis H. Geophagy as a risk factor for geohelminth infections: a longitudinal study of Kenyan primary schoolchildren. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998; 92: 7-11.

11. Grove DI. Worms in Australia. Medical Journal of Australia. 1993; 159: 464-466.

12. Jemaneh L. The epidemiology of schistosomiasis mansoni and soil-transmitted helminthes in elementary school children from the South Gondar zone of the Amhara National Regional State, Ethiopia. Ethiopian Medical Journal. 2000; 38: 105-118.

13. Jjumba-Mukasa OR, Gunders AE. Changing pattern of intestinal helminth infections in Jerusalem. American Journal of Tropical Medicine and Hygiene. 1971; 20: 109-116.

14. Karni A, Kahana E, Zilber N, Abramsky O, Alter M, Karussis D. The frequency of multiple sclerosis in Jewish and Arab populations in greater Jerusalem. Neuroepidemiology 2003; 22: 82-86.

15. Kuroiwa Y (ed). Multiple sclerosis in Asia. Baltimore: University Park Press, 1975.

16. Kurtzke JF. A reassessment of the distribution of multiple sclerosis. Acta Neurologica Scandinavica 1975; 51: 110-136.

17. Lynch DM, Green EA, McFadzean JA, Pugh IM. *Trichuris trichiura* infestations in the United Kingdom and treatment with difetarsone. British Medical Journal 1972; 4: 73-76.

18. Morishita K. Parasite control activity in Japan – a brief review. In: “Collected Papers on the control of soil-transmitted Helminthiases”. Tokyo: Asian Parasite Control Organization. 1980; 1: 223-231.

19. Nogales-Gaete J. University of Chile. Personal communication. 2005.

20. Nozais JP, Donand J, Le Brigant S. Distributions of *Ascaris lumbricoides*, *Necator americanus*, and *Trichuris trichiura* in six villages of Ivory Coast. [French] medicine Tropicale 1979; 39: 315-318.

21. Nunez Fernandez FA, Sanjurjo Gonzalez E, Ramon Bravo J, Carballo D, Finlay Villalvilla CM. Trichuriasis in Cuba. Revista Cubana de Medicina Tropical. 1993; 45: 42-45.

22. Olsen A. The proportion of helminth infections in a community in western Kenya which would be treated by mass chemotherapy of schoolchildren. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998; 92: 144-148.

23. Jemaneh L. Comparative prevalences of some common intestinal helminth infections in different altitudinal regions in Ethiopia. Ethiopian Medical Journal. 1998; 36: 1-8.

24. Plonka W, Dzbenski TH. The occurrence of intestinal parasites among children attending first classes of the elementary schools in Poland in the school year 1997/1998. [Polish] Przeglad Epidemiologiczny. 1999; 53: 331-338.

25. Rivera VM, Department of Neurology. Baylor College of Medicine, personal communication, 2005.

26. Robertson LJ, Crompton DW, Walters DE, Nesheim MC, Sanjur D, Walsh EA. Soil transmitted helminth infections in school children from Cocle Province, Republic of Panama. Parasitology 1989; 99: 287-292.

27. Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurological Sciences 2001; 22: 117-129.

28. Sablich R, Vitalba A, Benedetri G, Lacchin T, Guido C. Endoscopic prevalence of whipworm infestation in northern Italy. Digestive Diseases and Sciences. 2002; 47: 2106-2107.

29. J.D. Spillane (ed). Tropical Neurology. London, Oxford University Press, 1973.

30. Smith H, Dekaminsky R, Niwas S, Soto R, Jolly P. Prevalence and intensity of infections of *Ascaris lumbricoides* and *Trichuris trichiura* and associated Socio-demographic variables in four rural Honduran communities. Memorias de Instituto Oswaldo Cruz. 2001; 96: 303-314.

31. Wong MS, Simeon DT, Powell CA, Grantham-McGregor SM. Geohelminth infections in school-aged children in Jamaica. West Indian Medical Journal. 1994; 43: 121-122.