2. Kenny T, Wilson RG, Purves IN, Clark J, Newton LD, Newton DP, et al. A PIL for every ill? Patient information leaflets (PILs); a review of past, present and future use. Fam Pract 1998;15:471-9.
3. Forliza LA. Adult literacy in the United States today. Report for the Institute for the Study of Adult Literacy. University Park (PA): Penn State University; 1989.
4. National Center for Education Statistics (NCES) National assessment of adult literacy (NAAL): a first look at the literacy of America's adults in the 21st century. Jessup (MD): US Department of Education; 2006.
5. McLaughlin GH. SMOG grading: a new readability formula. Journal of Reading 1969;12:639-46.
6. Ley P, Florio T. The use of readability formulas in health care. Psychology Health Med 1996;1:7-28.
7. Estey A, Musseau A, Keehn L. Comprehension levels of patients reading health information. Patient Educ Counsel 1991;18:165-9.
8. American Medical Association and American Medical Association Foundation. Health literacy—a manual for clinicians. Chicago: American Medical Association; 2003.
9. Sherman AL. Analytics of literature: a manual from the objective study of English prose and poetry. Boston: Ginn & Co; 1893.

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Helminthic infection as a factor in new-onset coffee allergy in a father and daughter

To the Editor:

We report a father and daughter who experienced a new onset of food allergy to coffee occurring after helminth infection (*Clonorchis sinensis*) contracted in China. M.G. is a 55-year-old white Italian man without previous allergy, and V.G. is a 22-year-old woman with allergic rhinitis to grass pollens treated with antihistamines as needed. In May 2005 the father and daughter journeyed to rural areas of China for several weeks. When returning, they were laid over in the Beijing airport for 9 hours. During this period in the airport, they drank a large quantity of green coffee without any other food. A few days later, in Italy, they developed abdominal pain, diarrhea, and urticaria that worsened daily. The feces were initially pultaceous then liquid, accompanied by abdominal colic primarily in the morning. Fecal analyses (parasitologic, cultures, and chemical) and serum tests (*Salmonella-Shigellae*) were negative, as was abdominal sonography. The only abnormal laboratory values were blood eosinophil counts, 1200/mm^3 (father) and 1050/mm^3 (daughter), and serum eosinophil cationic protein (ECP), 44 ng/mL (father) and 84 ng/mL (daughter). Both were treated with oral antihistamine (cetirizine 10 mg/daily) with remission of itching, but without effect on diarrhea. In subsequent months their body weight diminished (10 and 8.5 kg, respectively, for the father and daughter).

Intestinal endoscopy was performed on the daughter, and the histology of the biopsy revealed the presence of *Clonorchis sinensis*. On the basis of this finding, both father and daughter were treated with mebendazole (300 mg twice a day $\times$ 10 days). Subsequent fecal analyses specifically performed to detect *Clonorchis sinensis* (Kato-Katz method and formalin-ether sedimentation technique) were negative in samples taken for 3 consecutive days; however, clinical symptoms of diarrhea and urticaria continued. Liver and bile duct ultrasounds performed monthly were negative. Two months after mebendazole therapy, blood eosinophils (1150/mm^3 [father] and 1100/mm^3 [daughter]) and serum ECP (52 ng/mL [father] and 73 ng/mL [daughter]) remained elevated, reducing the chance that these abnormalities were caused by ongoing parasite infection.

Importantly, they reported that diarrhea and urticaria were more evident after meals, in particular after breakfast when they usually drank only coffee. Thus, they eliminated coffee, and the urticaria and diarrhea completely resolved. Three successive coffee challenges consistently induced immediate symptoms. Skin prick testing for coffee was positive, and elevated coffee-specific serum IgE was documented (4.8 and 5.9 kU/L, respectively; CAP-FEIA; Phadia, Uppsala, Sweden). Total IgE were 599 (father) and 600 (daughter). Sensitization to coffee was further studied by *in vitro* methods. Lymphocyte proliferation and cytokine production by peripheral blood lymphocytes were evaluated in allergen-stimulated and unstimulated 5-day cultures (freeze-dried coffee allergen 5 μg, to be diluted in PBS; Lofarma, Milan, Italy). Results of lymphocyte proliferation and cytokine production are summarized in Table I. After a diet that eliminated coffee, the symptoms disappeared, but skin prick tests were still positive. After 3 months of this elimination diet, blood eosinophil counts were normal (300/mm^3 and 600/mm^3, respectively) as ECP levels, presumably reflecting the lack of coffee as a trigger of eosinophilia.

We hypothesize that the helminth infection facilitated the new onset of food allergy to coffee. One mechanism may be that the infection caused increased intestinal permeability of allergenic molecules through the enteric wall, altering antigen presentation/processing with consequent sensitization. In fact, these cases are similar to a previous case concerning a woman with pollen allergy who developed food allergy after cobalt (^{60}Co) therapy that induced damage of the enteric mucosa.[1] The precise mechanisms remain unknown, but Katz's theory[2] would indicate that *Clonorchis sinensis* may produce a transient disturbance of immune tolerance, resulting in an "allergic breakthrough." Considerable swelling of the small intestine occurs a few days after helminth infection. The intestines, as shown in mice, have an increase in mucosal permeability (studied with mannitol) because of an abundance of mast cells in the small intestine after infection.[3] Enterocytes from human beings, rat, and mouse constitutively express MHC class II molecules, with enhanced expression in states of inflammation. These cells are mostly restricted to the basolateral membrane, where the enterocytes contact the intraepithelial and lamina propria lymphocytes. Endocytosis in the polarized epithelial cells from the apical surface differs from uptake from the basolateral face. The processing of luminal antigens normally exposed only at the apical surface might orchestrate a different immunologic outcome when these antigens gain access to the basolateral surface of the enterocytes via leaky tight junctions. An antigen that normally elicits no significant responses, or a tolerogenic response when processed apically, may become immunogenic after processing from the basolateral membrane. Furthermore, during inflammation, the enterocytes express the costimulatory molecules CD80 (B7-1) or CD86 (B7-2).[4] Thus, under pathologic conditions, the enterocytes function as professional antigen-presenting cells and stimulate mucosal CD4$^+$ T-cell responses.

This altered response may lead to an allergy to food proteins in patients with helminth infection characterized by an evident IgE response and a low regulatory T-cell activity; however, other patients with high regulatory cell activity during helminth infections are protected from allergy.[5] Indeed, conflicting findings have been reported in the literature with regard to enhanced allergy compared with reduced allergy associated with helminth infection, with populations living in areas of low prevalence of helminth parasites having a greater risk of allergic responses to environmental allergens, and populations living in areas of high prevalence having a reduced risk of allergy.[6]

TABLE I. ECP and eosinophils showing a marked reduction after diet*

	Father		Daughter	
	Before diet	After diet	Before diet	After diet
ECP (ng/mL)	44	12	84	28
Eosinophils (n/mL)	1200	300	1050	600
	Without allergen	With allergen	Without allergen	With allergen
IL-4 (ng/mL)	48.7	111.4	42.3	100.9
IFN-γ (ng/mL)	347.2	336.4	299.4	312.1
IL-10 (ng/mL)	8.9	6.5	10.2	7.8
Stimulation index of proliferation		155.4%		145.5%

*ILs in supernatants of PBMCs cultured with and without allergen: IL-4 strongly increased after allergen challenge. There was no increased production of IL-10 induced by allergen challenge. Allergens induced a marked proliferation as shown by stimulation index in both cases.

Despite the general consensus that helminth infections may protect individuals from allergic disease, not all experimental models support this notion. A study in China in an area with low helminth prevalence demonstrated a positive association between *Ascaris* infection and allergen skin test reactivity,[7] and studies in rural and urban areas of Ethiopia with high helminth prevalence have also shown positive associations between helminth infection and skin test responses.[8] Furthermore, it has been demonstrated that helminth infection may influence the allergic response to dietary allergens in mice.[9]

The timing of antigen (allergen) exposure during helminth infection may be pertinent to immunologic outcomes. During acute infection, antigen-specific T-cell responses are initially stimulated, and cells proliferate in response to parasite antigens, with the immune profile characterized by high IgE response and a low level of T-regulatory activity. With increasing exposure of the immune system to parasite antigens that are released from metabolically active worms, the immune system becomes increasingly hyporesponsive both to specific parasite antigens and subsequently, when high worm burdens occur, to bystander antigens, a stage characterized by a high level of T-regulatory cells.[10] It has been reported that in animals and humans, acute helminth infection may increase manifestations of allergy, whereas chronic infection with parasites decreases atopy.[11]

In summary, we postulate that the new onset of coffee allergy was a consequence of acute helminth infection that favored food allergy by damaging the enteric mucosa, allowing the absorption of allergens, and by enhancing T_H2 responses as demonstrated by T_H2 polarization (high IL-4 and eosinophilic cationic protein) and a defect of T regulation (low IL-10). Green coffee is known to have a high concentration of *Cos* (a major coffee plant allergen), and another determining factor for the coffee sensitization could be the large dose of this type of coffee consumed during the time of helminth infection during their last day in the Beijing airport.

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REFERENCES

1. Ciprandi G, Dirienzo W, Canonica GW, Fudenberg HH. ^{60}Co therapy as an "allergic breakthrough" in a case of food allergy. New Engl J Med 1984;311:861.
2. Bargatze RF, Katz DH. "Allergic breakthrough" after antigen sensitization: height of IgE synthesis is temporally related to diurnal variation in endogenous steroid production. J Immunol 1980;125:2306-10.
3. McDermott JR, Bartram RE, Knight PA, Miller HRP, Garrod DR, Grencis RK. Mast cells disrupt epithelial barrier function during enteric nematode infection. Proc Natl Acad Sci U S A 2003;100:7761-6.
4. Snoeck V, Goddeeris B, Cox E. The role of enterocytes in the intestinal barrier function and antigen uptake. Microbes Infect 2005;7:997-1004.
5. Maizels RM, Yazdanbakhsh M. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nat Rev Immunol 2003;3:733-44.
6. Hunninghake GM, Soto-Quiros ME, Avila L, Ly NP, Liang C, Sylvia JS, et al. Sensitization to Ascaris lumbricoides and severity of childhood asthma in Costa Rica. J Allergy Clin Immunol 2007;119:654-61.
7. Mao XQ, Sun DJ, Miyoshi A, Feng Z, Handzel ZT, Hopkin JM, et al. The link between helminthic infection and atopy. Parasitol Today 2000;16:186-8.
8. Dagoye D, Bekele Z, Woldemichael K, Nida H, Yiman M, Hall A. Wheezing, allergy and parasite infection in children in urban and rural Ethiopia. Am J Respir Crit Care Med 2003;167:1369-73.
9. Michels C, Goyal P, Nieuwenhuizen N, Brombacher F. Infection with Syphacia obvelata (pinworm) induces protective Th2 immune responses and influences ovalbumin-induced allergic reactions. Infect Immun 2006;74:5926-32.
10. Beiting DP, Gagliardo LF, Hesse M, Bliss SK, Meskill D, Appleton JA. Coordinated control of immunity to muscle stage Trichinella spiralis by IL-10, regulatory T cells, and TGF-beta. J Immunol 2007;178:1039-47.
11. Carvalho EM, Bastos LS, Araujo MI. Worms and allergy. Parasite Immunol 2006; 28:525-34.

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Patients' characteristics associated with unsuccessful sputum induction in asthma

To the Editor:

Sputum induction has been widely used to assess airway inflammation in patients with asthma.[1] An important limitation of sputum induction is that samples adequate for evaluation are often not obtained, unlike other materials for assessing airway inflammation, such as exhaled breath or serum.[2] Despite methodology of sputum induction might affect its success rate,[3] the association between the characteristics of patients and the results of sputum induction is unknown. We therefore retrospectively compared the characteristics of patients with asthma classified according to the success or failure of sputum induction.

At our outpatient clinic, sputum induction for clinical or research purposes was attempted a total of 1093 times from May 1998 through October 2005, including 576 examinations in 407 patients with asthma. These 407 patients were classified into 2 groups according to the success or failure of the first attempt at sputum induction on presentation and were compared with respect to age, sex, disease duration, ever-smoking and current smoking history, pack-year of smoking, serum total IgE, atopy, FEV_1, FEV_1/forced vital capacity, use and dosage of inhaled corticosteroids (ICSs), and disease severity. The protocol was approved by our Ethics Committee, and written informed consent was obtained from all participants.

Reproducibility of the success or failure of sputum induction was evaluated on the basis of data obtained from 124 patients in whom sputum induction was repeated. Sputum induction was performed twice in 86 patients, 3 times in 32, 4 times in 5, and 5 times in 1. We analyzed data from 66 of these subjects, who underwent 2 consecutive attempts at sputum induction while in a stable condition, as defined by stable disease for at least 1 month while receiving continuous treatment with ICS. This subgroup