Correspondence

The role of soil exposure in asthma prevention during neonatal period

To the Editor:

We read with great interest the article titled "Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model" by Ottman et al.[1] The study investigated the effect and mechanism of soil exposure–induced immune tolerance. However, soil exposure to adults might not be practical in asthma treatment and prevention.

Exposure to new microbiota might induce activation of innated and acquired immune system, which might lead to symptoms indicating intestinal inflammation, such as diarrhea.[2] Intestine microbiota of people from different areas varies greatly, and travel to a new area might cause traveler's diarrhea.[3] However, Ottman et al[1] did not show the pathology of intestine, severity of diarrhea, hematochezia, and weight loss during soil exposure and before sensitization and airway challenge in their study. The immune tolerance effect of soil exposure might be caused by rebalance of immunity and intestine microbiota.

The neonatal period is the most proper period for soil exposure. Neonates were born to a relatively safe environment with extensive safe antigens and little pathogens. Thus, one of the major targets of the neonatal immune system is to build immune tolerance to environmental antigens. Several immune-suppressive cells have been found to induce immune tolerance to environmental antigens.[4] Soil exposure begins right after birth for mammals, which might play a significant role in immune tolerance and prevention of allergic diseases including asthma.[5] Thus, soil exposure should be a given for pregnant mice and should remain persistent during the neonatal period, which might lead to a more significant effect in reducing ovalbumin-induced lung inflammation.

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REFERENCES

1. Ottman N, Ruokolainen L, Suomalainen A, Sinkko H, Karisola P, Lehtimaki J, et al. Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model. J Allergy Clin Immunol 2019;143:1198-206.e12.
2. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature 2012;489:231-41.
3. Giddings SL, Stevens AM, Leung DT. Traveler's diarrhea. Med Clin North Am 2016;100:317-30.
4. He YM, Li X, Perego M, Nefedova Y, Kossenkov AV, Jensen EA, et al. Transitory presence of myeloid-derived suppressor cells in neonates is critical for control of inflammation. Nat Med 2018;24:224-31.
5. von Hertzen L, Haahtela T. Disconnection of man and the soil: reason for the asthma and atopy epidemic? J Allergy Clin Immunol 2006;117:334-44.

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Reply

To the Editor:

We appreciate the interest from Jiang et al[1] regarding our article titled "Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model."[2] The readers' first question addresses the induction of a possible pathology in the intestines of the mice by the soil exposure. This is an important question, and one that we did not fully consider in the article.

Shifts in the composition of the gut microbiota, induced by, for instance, a change in the diet, or invasive pathogens, can disturb the balance of organisms and favor the outgrowth of potentially pathogenic constituents.[3] Traveling, for instance, involves exposing oneself to foreign microbes, and acute diarrhea is the most common travel-related condition, caused by bacterial, viral, or protozoal pathogens. Globally, *Escherichia coli* is the most common bacterial pathogen, followed by *Campylobacter* and *Shigella*, members of the phylum Proteobacteria. In the soil-exposed mice, we observed the enrichment of Proteobacteria, compared with the controls. Investigation at the species level, however, is hindered by the low taxonomic resolution provided by 16s rRNA gene sequencing.

The readers ask whether we could show any pathology of the intestine in the mice that were exposed to soil. Of note, most soil organisms pose no risk to human health, but represent rather the opposite: evidence is accumulating that soil biodiversity is of great benefit, and only a small minority of species living in soils can cause disease.[4] Regarding the soil-exposed mice, at the time of read-out, the mice appeared healthy and normally sized compared with their counterparts that were raised in control conditions. Moreover, we collected stool throughout the study, and were therefore able to follow up on stool texture. We did not observe any abnormalities, including diarrhea or hematochezia. Unfortunately, we did not weigh the animals. However, an important inclusion criterion in the experiment is the continued well-being of the animals, including normal feeding, drinking, and daily activities, a smooth fur, and normal growth. Any signs of ill health would have led to exclusion of the animal from the experiments.

Of note, the soil exposures in the mice started at a very young age, 3 to 4 weeks old, and continued for 6 weeks, before exposure to the asthma protocol. Presumably, this relatively long period of time, at least from a mouse perspective, may have allowed for adaptation to the colonization by new microbial species. This is spoken for by our observations of gene expression profiles in the ileum, finding no elevation in proinflammatory mediators in the intestinal epithelium at the time of read-out.

The reader also points out that the neonatal period would be the most proper period for interventions such as ours. In human studies, the first years of life appear to be critical in this respect,[5] and in animal models the timing of exposure relative to sensitization is critical.[6,7] However, our and others' previous work do also argue for the importance of a continued exposure to beneficial microbiota, to maintain a homeostatic balance and healthy immune responses.[8,9]

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REFERENCES

1. Jiang W-H, Qiao Y-D, Liu T, Chen J, Lu G. The role of soil exposure in asthma prevention during neonatal period. J Allergy Clin Immunol 2019;144:1139.
2. Ottman N, Ruokolainen L, Suomalainen A, Sinkko H, Karisola P, Lehtimaki J, et al. Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model. J Allergy Clin Immunol 2019;143:1198-206.e12.
3. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature 2012;489:231-41.
4. Wall DH, Nielsen UN, Six J. Soil biodiversity and human health. Nature 2015;528:69-76.
5. Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001;358:1129-33.
6. Tulic MK, Wale JL, Holt PG, Sly PD. Modification of the inflammatory response to allergen challenge after exposure to bacterial lipopolysaccharide. Am J Respir Cell Mol Biol 2000;22:604-12.
7. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol 1997;159:1739-45.
8. Brown EM, Sadarangani M, Finlay BB. The role of the immune system in governing host-microbe interactions in the intestine. Nat Immunol 2013;14:660-7.
9. Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, Laatikainen T, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. Proc Natl Acad Sci U S A 2012;109:8334-9.

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Regulation of allergen immunotherapy products in Europe and the United States

To the Editor:

We read with interest the CME review article "Understanding differences in allergen immunotherapy products and practices in North America and Europe,"[1] in which the authors compare the regulation of such products in Europe with their regulation in the United States. Unfortunately, the authors inaccurately describe the US regulatory framework for allergenic extracts. Here is a partial list of errors:

1. The section titled "Regulation and Clinical Development of New Products, US Regulatory Standards" includes a discussion of the Food and Drug Administration's (FDA's) procedures for classification/reclassification of allergenic extracts into category I, II, IIIA, or IIIB. These procedures, formerly specified in regulations (21 CFR 601.25 and 601.26) and rendered obsolete in 2016, relate to allergenic extracts regulated by the National Institutes of Health before transfer to the FDA in 1972 and *are irrelevant to regulation of new products*. The authors also omit that, consequent to the most recent review of these extracts, the FDA revoked licenses for 15 extracts in 2013 because of safety concerns.
2. The authors state, "There is no formal FDA guidance for clinical development of [AIT products]. Each product under development in the US is considered separately by the CBER." The authors communicate that, lacking a formal guidance document, the FDA is unable to provide consistent, proactive advice to manufacturers. This is untrue. The FDA routinely provides pre- and post-licensure advice to manufacturers, consistent with applicable regulations and statutes. Furthermore, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) documents described in Table E2 as European Union (EU) guidance documents are also considered as part of FDA's guidance regimen.
3. Fig 1 contrasts a detailed EU clinical development framework with a superficial US framework that suggests, erroneously, that the FDA *requires non-US phase II data for review of new products*. This is untrue. Furthermore, the authors assert (without reference) that "much [in the US regulations] has been borrowed from EU precedents." This is untrue as well. Although US and EU regulators appropriately learn from the other's experiences, their frameworks for pharmaceutical regulation evolved independently, the history of which is beyond the scope of this letter.
4. The authors state, again without reference, that in the EU, "… the pharmaceutical company has to provide evidence for *impeccable* [emphasis added] quality, efficacy and safety" of an allergenic product. The obvious implication is that US standards for manufacturing allergenic extracts are inferior to the EU standards. This is untrue. In the United States—no less than in the EU—the standards for licensure include a demonstration of safety, purity, and potency. Furthermore, the word "impeccable" is an odd choice in this situation, which implies perfection rarely attainable in science or regulation.
5. The authors state, "Only products with a positive benefit/risk ratio [can be licensed in the EU]." Obviously, this is also a requirement for US licensure.

In conclusion, rather than presenting a disinterested comparison of EU and US regulatory practices, the authors have substituted opinion for fact in an article that is inconsistent with the standards of the *Journal of Allergy and Clinical Immunology*, and inappropriate as a CME review.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest. This correspondence is an informal communication and represents the authors' best judgment. These comments do not bind or obligate the Food and Drug Administration.

REFERENCE

1. Mahler V, Esch RE, Kleine-Tebbe J, Lavery WJ, Plunkett G, Vieths S, et al. Understanding differences in allergen immunotherapy products and practices in North America and Europe. J Allergy Clin Immunol 2019;143:813-28.

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Reply

To the Editor:

Reviewing such a broad topic is formidable given many differences in extracts, manufacturing, clinical diagnoses, treatments, and regulation of new product development.[1] In our attempt to present a concise review of differences between continents, we did not intend to minimize the role of the US Food and Drug Administration (FDA) in assuring quality, safety,