The importance of serotonin in gastrointestinal biology is often overlooked given the intense interest of investigators focused on neurotransmitter (mal)functions of the central nervous system. Regardless, the gastrointestinal tract is the major site of serotonin (5-hydroxytryptamine, 5-HT) production (95%) and its crucial role as a paracrine mediator and neurotransmitter in regulating gastrointestinal function has been well established (2). Its functions range from modulating visceral sensation, neuronal protection and regeneration to stimulating secretion, motility, and proinflammatory responses. Serotonin elicits its varied effects by the coordinated action of multiple receptor subtypes exhibiting cell-specific localization and signaling cascades as well as the regulation of the NaCl-dependent serotonin transporter, SERT. Furthermore, serotonin’s interplay with the gut microbiome and its role as a key intermediary in the gut-brain axis is gaining prominence. These multiplex roles have led serotonin to earn the moniker, the “sword and shield of the gut,” where Dr. Gershon ascribes the sword function to mucosal serotonin and the shield function to neuronal serotonin (3).

In this issue of the *American Journal of Physiology-Gastrointestinal and Liver Physiology*, the work of Bhattarai and colleagues (1) adds a twist to this, suggesting that the sword function could be manipulated by the microbiome. With a view to gain an insight into the human microbiota, the authors compared serotonin-sensitive ion secretion in age-matched Swiss Webster Germ Free (GF) mice with those colonized with human gut microbiota (HM). They focused on the proximal colon and measured ion transport by transepithelial short-circuit current (Isc), an index of Cl- secretion in this segment of the colon. While there were no differences in baseline transepithelial resistance, Isc or cAMP-stimulated secretion, the GF mice had a significantly greater secretory response to serotonin than their HM counterparts, suggesting that the presence of gut microbiota specifically tempers the secretory response to 5-HT. The prevalent 5-HT receptors in the intestine are 5-HT3, the cystic fibrosis transmembrane conductance regulator (CFTR), the ligand-gated ion channel, and 5-HT4, a G protein-coupled receptor. Although not specifically defined in the mouse colon, 5-HT3 is known to exist as a heteropentamer of 5-HT3A and 5-HT3B isoforms. There was an increase in colonic 5-HT3B, but not 5-HT4, transcript in GF versus HM animals. The serotonin response in GF persisted in the presence of tetrodotoxin, suggesting a nonneuronal component of regulation. In contrast, the 5-HT4 antagonist, GR113808, decreased Isc both in GF and HM, even in the presence of tetrodotoxin, suggesting that the GPCR signaling cascade has a role in the nonmicrobial-dependent response to serotonin. An intriguing observation is that both human microbiota (HM) and conventional mouse microbiota (CR) can overcome the 5-HT3-mediated response seen in GF animals, suggesting this was a common effect of commensal microbiota regardless of host species. It still begs the question as to whether the alpha diversity of the HM mice is similar to that of CR. Clearly all these point to a role of the microbiota in tempering the serotonin response, but how is the signal conveyed? Suggestive hints are provided that need further proof. First, as a proof of concept, the authors use 5-HT3A-GFP (not 5-HT3B) mice to demonstrate the presence of these receptors in nerve fibers as well as enterochromaffin cells of the proximal colon. Second, in colonoids derived from GF mice, acetate at a single concentration, but not butyrate, decreased the levels of 5-HT3B mRNA, hinting that the signal may be via short chain fatty acids, in particular, acetate.

As with many good studies, the findings raise more questions: What is the diversity and composition of the protective commensals? While treating all mice with samples from one human allows for a well-controlled study, it begs the question of what effects β-diversity will have on the response? What is the trigger? Is the microbiome profile altered in disease states, and does it use the same or different triggers? There is some hint to the trigger in nondiseased states, in that the short chain fatty acid, acetate, attenuates the 5-HT3 mRNA levels in GF-derived colonoids. It is interesting that acetate is effective at a very narrow concentration range and perhaps evokes, suggestions of a niche effect in the intact animal.

Here it is helpful to set it in the larger context of what other changes are seen in the serotonin signaling scenario. In a 2015 paper by Reigstad et al. (5), this investigative group reported that there was no difference in the contractility seen in GF mice or those exposed to humanized microbiota (HM) or conventional mouse microbiota (CR). The HM and CR mice, however, exhibit an increase in serotonin production, which was related to an increase in its rate-limiting synthetic enzyme, tryptophan hydroxylase (Tph), but there were no changes in 5-HT4, SERT, or monoamine oxidase. Again in a proof of
concept, acetate and butyrate had a biphasic effect on altering Tph transcript, with stimulation at low and inhibition at high concentrations in the BON cells, an in vitro model of enterochromaffin cells. In an earlier study, these authors (4) also demonstrated the influence of diet on gut transit time in GF and HM mice, but its effects on serotonin-mediated I_sc are unknown. Finally in diseased states, consideration has to be given to other members of the 5-HT signaling cascade. Thus in another AJP-GI paper earlier this year, Singhal et al. (6) showed that enteropathogenic E. coli co-opted the host cell protein tyrosine phosphatase SHP2 to directly inhibit SERT and thereby increase extracellular 5-HT by preventing its reuptake. Does that allow more extracellular 5-HT to wreak proinflammatory havoc?

In summary, Bhattarai et al. (1) suggest that gut microbiota temper host cell response to a pleiotropic signal, by attenuating the more proinflammatory signaling cascade. Thus, while gut microbiota promote 5-HT production through their metabolic products, SCFA, the potential for deleterious actions is curtailed by two means. First, SCFA have a biphasic effect on TPH the rate limiting enzyme of 5-HT production, by inhibiting it at high concentrations and thereby reducing 5-HT production; second as shown in this study, SCFA probably decrease 5-HT3B receptor expression, thereby reducing the capacity for 5-HT to stimulate Cl− secretion. Finally, all these findings need to be related to the effects of serotonin on other aspects of gut function like contractility and sensation.

The gut possesses a variety of regulatory mechanisms that coordinate the diverse actions of 5-HT to maintain homeostasis of fluid transport and contractility; and this paper adds the gut microbiota to that armamentarium. As it is already well established that disruption of 5-HT homeostasis underlies diarrheal and inflammatory bowel diseases, extending the observations of this paper to how microbiome dysbiosis alters 5-HT function can lead to the development of innovative biotherapeutics to treat intestinal disorders.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
E.B.C. and M.C.R. drafted, edited, revised, and approved final version of manuscript.

REFERENCES