REPLY:

TO THE EDITOR:

We appreciate the commentary on our study.[1] We do not contest the Sperber hypothesis of osmotically driven water influx in bile formation per se. Rather, our data contests the belief that this water influx occurs in canaliculi to cause a "canalicular flow." We refine the Sperber hypothesis by showing that (1) the anatomical site (Sperber's "bile capillaries") where basal and secretin-induced as well as bile acid (BA)-stimulated water influx occurs is the intralobular bile duct and (2) canalicular bile flux is dominated by diffusion through the network and not by fluid flow.

The cited transient reduction in extrahepatic bile flow induced by estradiol-17-glucuronide (E17G)[2] is not in conflict with the refined Sperber hypothesis because E17G induces several changes in hepatocytes and cholangiocytes that could explain this effect. E17G inactivates the canalicular bile transporter BSEP by direct inhibition from the apical side[3] and endocytic removal from the canalicular membrane,[4] leading to reduced BA concentrations in the canalicular and ductular lumina. This in turn reduces BA-TGR5–mediated ion secretion and bile flow in the duct.[5] A simultaneous decrease in ductular BA concentration and water excretion explains why the bile volume decreases without an increase in BA concentration. Other possibilities include direct effects of E17G on cholangiocytes, e.g., inhibition of $HCO3^-$ and Cl^- channels in the gastrointestinal tract,[6] which are considered important for ductular water influx.

The mechanisms of the complex and nonlinear E17G-induced temporal changes in bile flow, BA output, and BA concentration are not yet fully understood. However, neither the Sperber hypothesis nor the cited data mandate that the site of osmotic water influx must be the canalicular network. The refined explanation we propose is equally consistent with the cited previous data and a diffusion-dominated canalicular flux.[1]

In contrast, the (unproven) simplistic "osmotic canalicular flow" model runs into inconsistencies: (1) The E17G-induced decrease in postulated canalicular water influx implies a decreased extrahepatic bile flow with a simultaneous increase in BA concentration, provided the rate of BA secretion remains constant. Instead, the data cited show that the BA concentration did not increase. (2) The recovery of bile flow is delayed compared to the recovery of BA amount, contradicting an osmotic 1:1 relationship.

When the technology (or eclipses) allows for hypothesis verification, we are compelled to accept general relativistic complexity in lieu of Newtonian simplicity. To paraphrase Einstein from his Herbert Spencer Lecture (1933), everything should be made as simple as possible, but no simpler.

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[correction added on August 17, 2021 after first online publication: Reference 1 was added. All subsequent references were renumbered.]

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Potential conflict of interest: Nothing to report.

[Correction added on August 17, 2021, after first online publication: The article title was revised.]