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Letter to the Editor

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Address for correspondence:
Bernadette S. de Bakker, Department of Medical Biology, section Clinical Anatomy & Embryology, Amsterdam UMC, University of Amsterdam, Amsterdam Reproduction & Development Research Institute, Meibergdreef 9, Amsterdam, The Netherlands.
Email: b.s.debakker@amsterdamumc.nl

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Reconsidering the "non-recanalization theory" of the gut

Bernadette S. de Bakker, Aleena Babar and Kees C. N. Tol

Department of Medical Biology, section Clinical Anatomy & Embryology, Amsterdam UMC, University of Amsterdam, Amsterdam Reproduction & Development Research Institute, Amsterdam, The Netherlands

Dear Editor,

With this letter, we would like to raise concerns about the manuscript entitled *Gut lumen formation defect can cause intestinal atresia: evidence from histological studies of human embryos and intestinal atresia septum*, written by Liu et al., published in your journal in April 2021.[1] In this paper, the authors claim to be the first to show the presence of vacuoles in the occluded gut lumen, which would further support the non-recanalization theory that was first proposed by Julius Tandler in 1900.[2] We truly appreciate the fact that the authors have studied original histological sections of eight human embryos, but we have reservations about the conclusions that are drawn from the presented sections.

Careful assessment of Fig. 1, revealed that only a single specimen was presented, whereas the figure caption mentions multiple human embryos. Be that as it may, we are presented with an image of the gut, in which the authors claim that the visualized vacuoles are located. While the designated structure indeed appears to be situated within the abdominal cavity, careful exploration makes us believe that it is not an occluded gut, but the embryonic kidney (mesonephros) that is shown. In the lowest panel of Fig. 1, the middle arrowhead indicates not a vacuole, but a Bowman's capsule including glomerulus.[3] The typical segmental presence of tubules is also clearly recognizable on the presented section. We presume that this misinterpretation arises from the fact that in this particular section, the presented longitudinal structure is completely surrounded by coelom. When adjacent sections would be studied, the mesonephros would show attachment with the dorsal body wall as it is a retroperitoneal organ. Unfortunately, the complete datasets of histological sections or (3D-)datasets were not presented.

Our second concern regarding Fig. 2 again suggests that histological sections of multiple human embryos of two developmental stages are shown, whereas we are actually shown one section of a single specimen per stage. Based on the two sections presented, the reader is encouraged to appreciate remnants of the mesenchyme that obliterated the intestine. However, if the authors had studied adjacent sections, they would have observed that the "vacuoles" marked with an asterisk are in fact just tangentially sectioned mucosal folds. The same holds for the gut presented in Fig. 3. The brown "intestinal canal" in the 3D-reconstruction is actually the intestinal wall. The actual intestinal lumen is, though difficult to see, undeniably present in between the densely packed mucosal folds.

The above-described erroneous assumptions that the authors support with a few histological sections have far-reaching consequences for their conclusion and the title of their article. Based on our own insights, gained during the creation of the *3D Atlas of Human Embryology*,[4] which included the manual annotation of the complete gut in 34 human specimens between three and eight weeks of development, we found no evidence supporting the non-recanalization theory. The gut is formed as an open tube, which remains open throughout embryonic development. Gut atresias can be explained by insufficient vascular perfusion throughout the development of the gut, leading to narrowing or obliteration of the gut lumen.[5] Readers are encouraged to study the open source histological datasets of all 34 embryos on our website http://www.3Dembryoatlas.com.

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