Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

drugs such as proton pump inhibitors or potassium-competitive acid blockers for treating gastroesophageal reflux disease—regardless of whether they have blood type A, chronic gastritis, or *H pylori* infection—may be similarly at risk.

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References

1. Xiao F, et al. 2020;158:1831–1833.e3.
2. Darnell MER, et al. J Virol Methods 2004;121:85–91.
3. Chen XY, et al. J Clin Pathol 2001;54:367–370.
4. Sung J, et al. Gut Liver 2018;12:158–164.
5. Russell RM, et al. Gastroenterology 1986;91:1476–1482.
6. Zhao J, et al. medRxiv preprint doi: https://doi.org/10.1101/2020.03.11.20031096
7. Nakao M, et al. Cancer Epidemiol Biomarkers Prev 2011;20:1665–1672.
8. Wang Z, et al. Int J Mol Sci 2012;13:13308–13321.

Conflicts of interest
The author discloses no conflicts.

Most current article

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Gastrointestinal ACE2, COVID-19 and IBD: Opportunity in the Face of Tragedy?

Dear Editors:

We read with interest the articles by Xiao et al[1] and Du et al[2] regarding severe acute respiratory syndrome coronavirus-2 (SARS Co-V 2) shedding in feces, staining of viral nucleocapsid protein in the cytoplasm of gastrointestinal epithelial cells, and the characterization of angiotensin-converting enzyme 2 (ACE2) receptors across tissues in the human body. The relationship between coronavirus disease 2019 (COVID-19), intestinal ACE2 expression, and gastrointestinal symptoms is worth exploring further, and may offer unique clues to the pathogenesis of intestinal inflammation.

We have previously characterized multiple components of the renin–angiotensin system (RAS) in the terminal ileum and colon in patients with and without inflammatory bowel disease (IBD).[3] Notably, all of the components of the classical and alternative RAS were expressed in the mucosa, demonstrating the presence of a locally active intestinal RAS. In particular, ACE2 was localized by immunohistochemistry to the brush border and epithelium, and ACE2 messenger RNA expression was 10-fold higher, and ACE2 activity 7- to 10-fold higher, in terminal ileal biopsies when compared to colonic biopsies in patients without IBD.[3] ACE2 activity was lower in inflamed colonic biopsies than non-inflamed biopsies from patients with IBD, and angiotensin (Ang) 1–7 immunohistochemical staining intensity was lower in colonic biopsies from patients with IBD when compared with healthy controls. Ang 1–7 has been shown to exert anti-inflammatory, antifibrotic, and antiproliferative actions in various tissues, and decreased myofibroblast proliferation and collagen secretion in cultured colonic myofibroblasts.[3] ACE2 knockout mice had increased susceptibility to colitis and an altered microbiota profile, which was associated with higher colonic Ang II levels, the putative peptide of the classical RAS pathway that exerts proinflammatory and profibrotic effects.[4] Plasma ACE2 activity was higher in patients with IBD, especially Crohn's disease, than non-IBD controls, perhaps representing a compensatory mechanism.[5]

Intestinal ACE2 is also required for absorption of tryptophan, an essential amino acid required for niacin production. Pellagra, caused by the deficiency of niacin (vitamin B_3), is characterized by intestinal inflammation and protein malnutrition.[4] Serum tryptophan levels were lower in patients with IBD, especially Crohn's disease, than controls without IBD.[6]

SARS-CoV-2, which, like the original SARS-CoV of earlier this century, infects humans via its spike proteins binding to ACE2 on mucosal membranes.[7] Multiple mucosal surfaces express ACE2, including alveoli, esophagus, stomach, small bowel, and colon. The original transmission of COVID-19 from an animal reservoir to human, initially described in Wuhan, China, likely occurred by the oral route, perhaps mediated via intestinal ACE2.[1,7] SARS-CoV was shown to induce shedding of the ACE2 ectodomain following cellular entry, dependent on tumor necrosis factor (TNF)-α converting enzyme production.[8] This was also associated with increased TNF-α production and tissue damage.[8]

Conceivably, if SARS-CoV2 also induces reduction of mucosal ACE2 after entry, intestinal inflammation may result via multiple mechanisms: elevated Ang II, reduced Ang 1–7 levels, increased TNF-α, and tryptophan deficiency. Gastrointestinal symptoms, including diarrhea, occur in approximately 4%–20% of patients with COVID-19, and severe colitis has recently been described. Hence, multiple potential targets for therapy for COVID-19, and intestinal inflammation in IBD, may result from further investigation of these pathways.

In our studies, we have additionally analyzed whether conventional therapies for IBD were associated with altered intestinal mucosal ACE2 expression. No association between steroids, mesalamine, thiopurines, or anti–TNF-α medication use and terminal ileal or colonic ACE2 messenger RNA expression, ACE2 activity, or ACE2 immunohistochemical staining intensity was noted (Supplementary Figure 1). Furthermore, no effect of these drugs on plasma ACE2 activity was noted (Supplementary Figure 2). Whether the use of these drugs alters the risk of acquiring COVID-19, or developing gastrointestinal symptoms or other complications, remains to be elicited, as data are acquired in an international registry.

Nonetheless, our understanding of IBD and intestinal inflammation may increase significantly after further investigation into ACE2 and its effects, potentially leading to new treatments for these conditions, and providing us with opportunities in the context of this tragic global pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.04.051.

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References

1. Xiao F, et al. Gastroenterology 2020;158:1831–1833.
2. Du M, et al. Gastroenterology 2020;158:2298–2301.
3. Garg M, et al. Gut 2019;69:841–851.
4. Hashimoto T, et al. Nature 2012;487:477–481.
5. Garg M, et al. J Renin Angiotensin Aldosterone Syst 2015;16:559–569.
6. Nikolaus S, et al. Gastroenterology 2017;153:1504–1516.
7. Zhang H, et al. Intensive Care Med 2020;46:486–590.
8. Haga S, et al. Proc Natl Acad Sci U S A 2008;105:7809–7814.

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Presence of SARS-Coronavirus-2 in the Ileal Mucosa: Another Evidence for Infection of GI Tract by This Virus

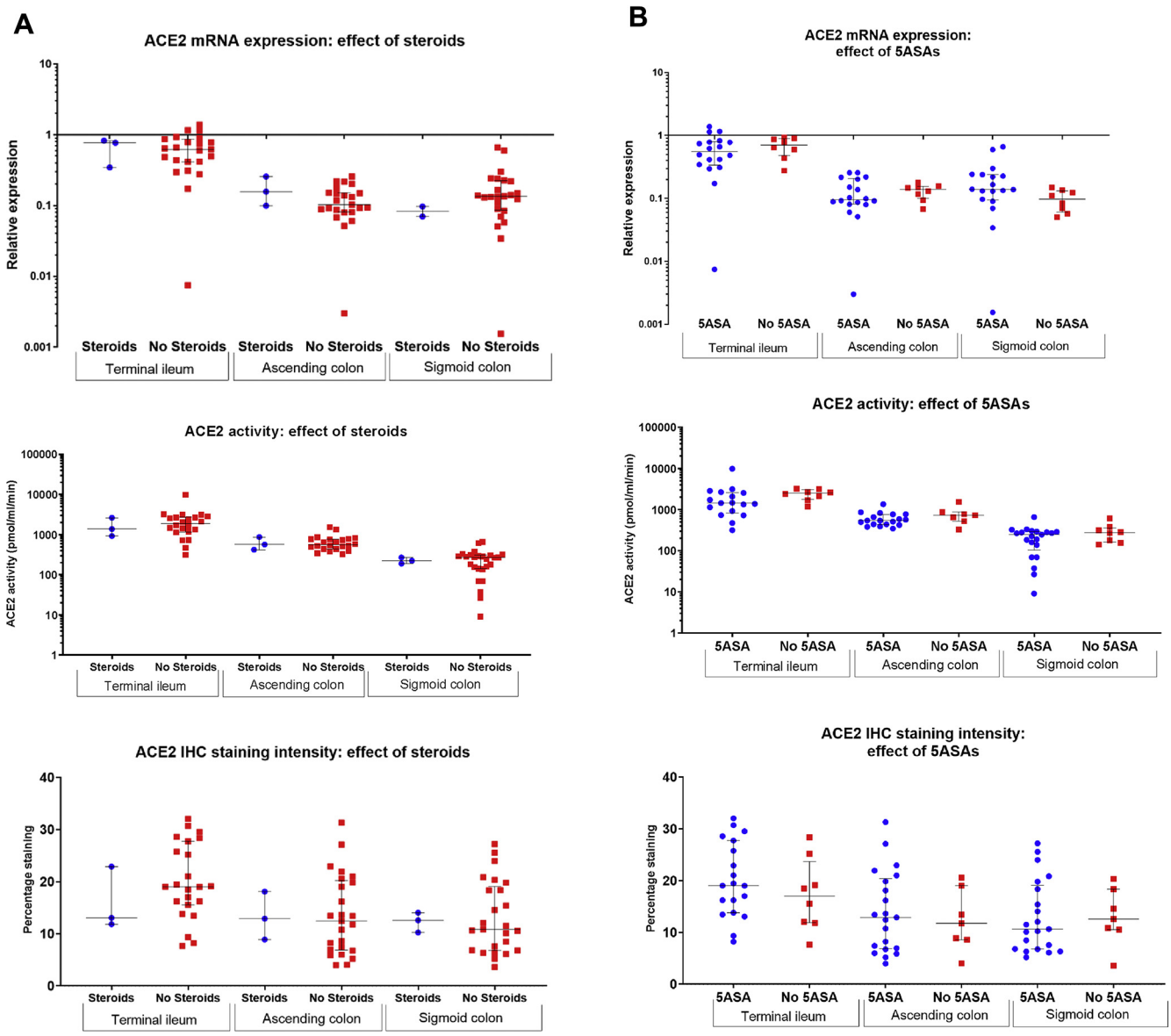
Dear Editors:

We have read with great interest the recent article published entitled "Evidence for Gastrointestinal Infection of SARS-CoV-2." In this article, Xiao et al[1] report how ≤20% of patients with negative viral RNA in their respiratory tract present positive RNA in feces. They present a case of a patient with severe pneumonia owing to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and gastrointestinal bleeding, with viral RNA in the gastrointestinal mucosa, as well as the presence by immunofluorescence of abundant angiotensin-converting enzyme (ACE) 2 receptors in the gastrointestinal tract. These findings could indicate the gastrointestinal tract tropism of the virus, and its persistence, even after the RNA in the respiratory tract has been cleared.

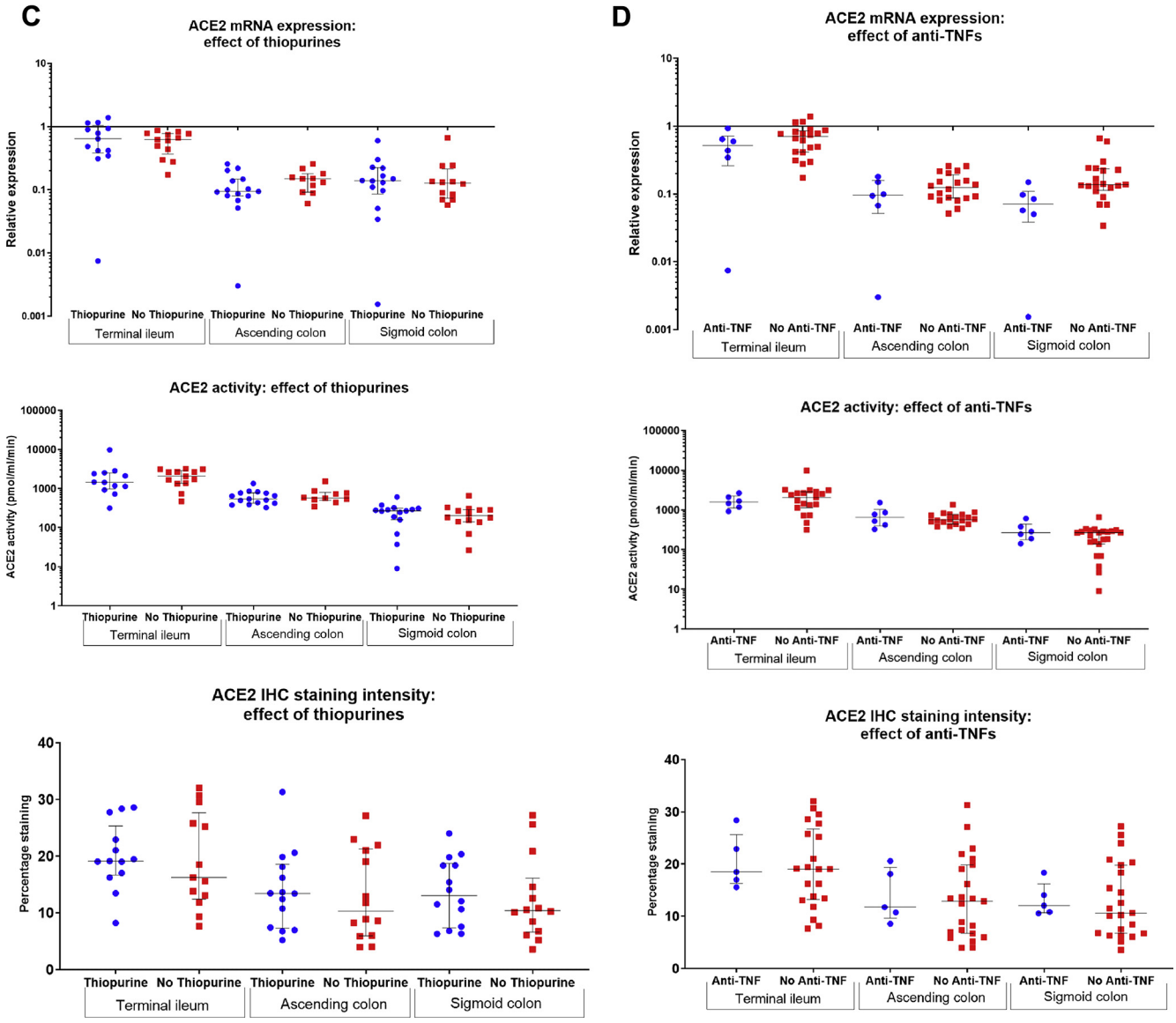
We present a case of a 54-year-old male ex-smoker with a medical history of hypertension, supraventricular tachycardia ablated in 2015, and Nissen fundoplication in early March 2020. On March 15, the patient presented with fatigue, myalgia, and fever, without respiratory symptoms. The SARS-Cov-2 real-time polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab was positive on March 27. IgM for SARS-CoV-2 was indeterminate and IgG was positive with ELISA test. He received symptomatic treatment with acetaminophen. On April 20, he started with diarrhea, nausea, and vomiting. In the emergency room, he was hemodynamically stable, and his temperature was 37.4°C. Laboratory data showed elevated C-reactive protein and D-dimer levels, with mild lymphopenia. IL-6 levels were also elevated. A chest radiograph was normal and SARS-CoV-2 RT-PCR test on nasopharyngeal swab was negative currently. In the abdominal computed tomography scan, a thickening of the terminal ileum was observed suggesting the presence of acute ileitis. The patient received empirical treatment with ciprofloxacin and metronidazole without any improvement. Microbiological stool examinations were negative for SARS-CoV-2 RT-PCR test. On April 29, the study was completed with an ileocolonoscopy with ileal biopsy. The mucosa of ileum and colon was macroscopically normal, and the biopsy showed no damage. However, RT-PCR test on ileal tissue was positive for SARS-CoV-2 RNA. We repeated the SARS-CoV-2 RT-PCR test on nasopharyngeal swab and it again came back negative. The patient improved over the next few days without any specific treatment.

Since the novel coronavirus was identified in China, scientists know that the virus mainly affects the respiratory system. However, more and more data are also suggesting significant involvement of the gastrointestinal tract, even in patients who do not have respiratory symptoms,[2] as in our case. Recent studies have shown a high prevalence of ACE2, not only in AT2 lung cells, but also in the upper esophagus, ileum and colon[3]; showing a higher expression of ACE2 in the small bowel.[4] These findings could explain the vulnerability of the gastrointestinal tract, specifically, of the ileum, to SARS-CoV-2.

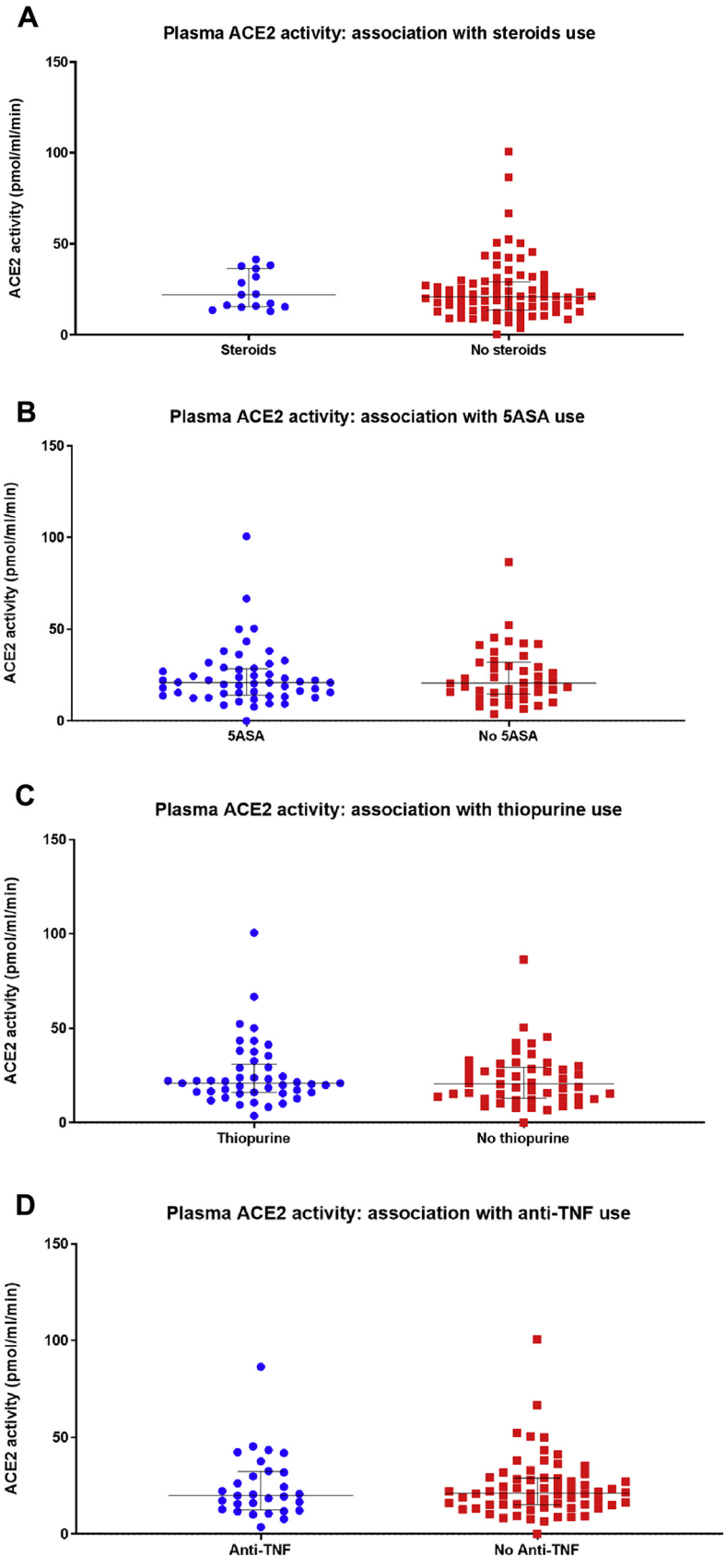
Gastrointestinal symptoms have been detected in ≤20% of patients with SARS-CoV-2.[2] Similarly, viral RNA has been isolated from stool samples in ≤50% of patients with SARS-CoV-2, regardless of the presence of digestive symptoms. In addition, 70.3% of the stool samples were collected after viral clearance in the respiratory tract.[2] In our case, RNA in nasopharyngeal swab was already negative, but RNA in



Supplementary Figure 1. Association between (*A*) steroids, (*B*) mesalamines (5-ASA), (*C*) thiopurines, and (*D*) anti-tumor necrosis factor (TNF)-α agents and mucosal ACE2 messenger RNA (mRNA) expression, angiotensin-converting enzyme 2 (ACE2) activity, and immunohistochemical (IHC) staining intensity in colonoscopic biopsies in patients with inflammatory bowel disease (IBD). No statistically significant differences were noted.



Supplementary Figure 1. (*continued*).



Supplementary Figure 2. Association between (*A*) steroids, (*B*) mesalamines (5-ASA), (*C*) thiopurines, and (*D*) anti-tumor necrosis factor (TNF)-α agents and plasma angiotensin-converting enzyme 2 (ACE2) activity in patients with inflammatory bowel disease (IBD). No statistically significant differences were noted.