Suppl. Fig 1. Impaired intestinal fluid homeostasis alters the morphology of ceca in *Cftr*-null and *Nhe3*-null mice. Ceca from untreated A: wild-type, B: *Cftr*-null, and C: *Nhe3*-null mice are shown. CF mice that are wild-type for the *Nhe3* gene typically have a coiled or "corkscrew" cecum (B). This appears to be due to dessication of intestinal contents resulting from the secretory defect, since the morphology of the CF cecum is uncoiled like that of a wild-type cecum if the mice are maintained on an osmotic laxative (Colyte). NKCC1 Na-K-2Cl cotransporter knockout mice, which also have a mild intestinal secretory defect, sometimes exhibit this phenotype (Flagella *et al*. *J. Biol. Chem* 274, 26946-26955, 1999). Ceca of *Nhe3*-null mice (C) and of *Nhe3*/*Cftr* double null mice (Fig. 3E) are typically swollen with fluid, with as much as 3 mL accumulating in adult animals. It is known that the rodent cecum serves a "reservoir" function and can hold considerable amounts of fluid in response to hypersecretion; this reservoir function of the cecum limits fluid losses since surgical removal of the cecum leads to an outwardly apparent diarrhea in response to secretogogues (Fondacaro et al. *J Pharmacol Methods* 24, 59-71, 1990). The occurrence of this phenotype in *Nhe3*-null mice shows that the cecum serves a similar function in response to excess lumenal fluid resulting from an absorptive defect.

Suppl. Fig 2. Goblet cell hyperplasia of the ileal villi of CF mice is corrected by loss of one or both copies of the *Nhe3* gene. Representative H&E-stained sections of ileum show the extent of goblet cell hyperplasia in villi from A: wild-type, B: $Cftr^{-/-}Nhe3^{+/+}$, and C: $Cftr^{-/-}Nhe3^{-/-}$ mice. Arrows indicate goblet cells, which exhibit light or no staining with eosin. Original images were taken at 20X magnification. D: cell counts of ileal goblet cells (shown as a percentage of total cells) indicate a ~3-fold increase in goblet cell numbers in CF mice that are wild-type with

respect to *Nhe3*. Only those goblet cells that had basal nuclei, reduced staining with eosin, and a wide apical pole were counted, which excludes a significant population of more narrow goblet cells (for example those that were thinly sectioned or those that had recently released mucus and collapsed). As shown in Figures 5A-5E, goblet cells were recounted after staining with alcian blue PAS, which increased the number of number of goblet cells identified by 3-5-fold in all mice. The quantitation of those cells in Fig. 5G is appropriately proportional to the quantitation in Supplementary Figure 2D, and did not alter the interpretation that goblet cell hyperplasia in this study is limited to $Cftr^{-/-}Nhe3^{+/+}$ mice. A minimum of 10 villi were counted for each mouse; n = 3-6 mice per genotype. * $p< 0.05$ compared to wild-type.