Anson W. Lowe and Richard H. Moseley, Section Editors

Colonic Polyps in a Porcine Model of Human Familial Polyposis

Familial adenomatosis polyposis (FAP) syndrome is a genetic disorder characterized by numerous adenomatous polyps that first appear in the large intestine and in later years in the stomach and duodenum. About 90% of all patients with classic FAP develop colon cancer by age 45.

Mutations of the APC gene represent the primary pathogenetic mechanism for FAP. APC serves an essential role in the constitutive degradation of β-catenin in the cytosol. In the absence of APC function, β-catenin remains intact whereupon it will translocate to the nucleus and promote Wnt signaling by interacting with the Tcf and Lef transcription factors. The most common APC mutations that result in FAP are those that result in truncation of the APC protein, thus rendering it ineffective in binding β-catenin for degradation.

APC truncation mutations similar to their human counterpart have been introduced into mice. Most murine models harboring APC mutations result in the formation of adenomatous polyps distributed mainly in the stomach and small intestine and not the large intestine. The murine model rarely, if ever, progresses to invasive adenocarcinoma unless a second mutation, such as a Kras mutation, is introduced.

In this issue of GASTROENTEROLOGY, Flisikowska et al along with an accompanying editorial by Randall Burt and Joanna Groden report on the development of a porcine model for FAP. Using transgenic technology, two APC mutations, $APC^{1061/+}$ and $APC^{1311/+}$, consisting of premature stop codons, were introduced into the pig model. $APC^{1311/+}$ corresponds to the $APC^{1309/+}$ in humans, which results in early onset and severe polyposis. The $APC^{1061/+}$ mutation represents a similar change in humans and induces a much milder phenotype. After 1 year, the animals were humanely killed and their gastrointestinal tract evaluated. Both the wild-type control and the $APC^{1061/+}$ pigs exhibited no polyps in the gastrointestinal tract. The $APC^{1311/+}$ pig, however, displayed numerous adenomatous polyps in the large intestine. The polyps varied in size and histology. Aberrant crypt foci were observed that contained features of dysplasia. Thus, in contrast with the murine model, the $APC^{1311/+}$ porcine model resulted in features that were closer to their human counterpart. An important point is that only early adenomatous lesions were observed. Later time points will have to be assessed in the future to determine whether advanced cancers will develop.

One of the advantages afforded by the porcine model is the opportunity to evaluate technologies and therapeutic approaches that are not feasible in the murine model. An example provided by the study is the use of high-resolution magnification chromoendoscopy designed for humans. Evaluation of the porcine model produced results comparable with what is observed in humans (Figure 1).

Thus, the early results reported by this study suggest that the porcine model for FAP results in a phenotype that is closer to its human counterpart and may represent an improved animal model with which to study the biology and therapy of FAP.

See page 1173; editorial on page 1133.

Burden of Gastrointestinal Disease in the United States: 2012 Update

It has been >3 years since the burden of upper and lower gastrointestinal (GI), liver, and pancreatic diseases in the United States was last reported. In this issue of GASTROENTEROLOGY, using a variety of publicly and privately held databases on GI symptoms, outpatient diagnoses, quality of life, hospitalizations, cost, cancer, mortality, and endoscopic utilization, Peery et al provide an updated analysis of the impact of GI disease in the United States. Abdominal pain was the most common GI symptom prompting outpatient evaluation. Gastroesophageal reflux was the most frequent outpatient diagnosis. Diverticular disease (including diverticulitis and diverticulosis with hemorrhage) was the most common inpatient principal GI discharge diagnosis, although acute pancreatitis was the most common single GI diagnosis with an estimated inpatient cost of $2.6 billion per year. Hospital discharges with a principal diagnosis of infection with *Clostridium difficile* increased 237% from 2000 to 2009 (Figure 2) and accounted for a proportion of in hospital deaths (3.7%) similar to GI hemorrhage. Although not among the top 100, hospital discharges with a principal diagnosis of chronic liver disease and viral hepatitis increased 14% from 2000 to

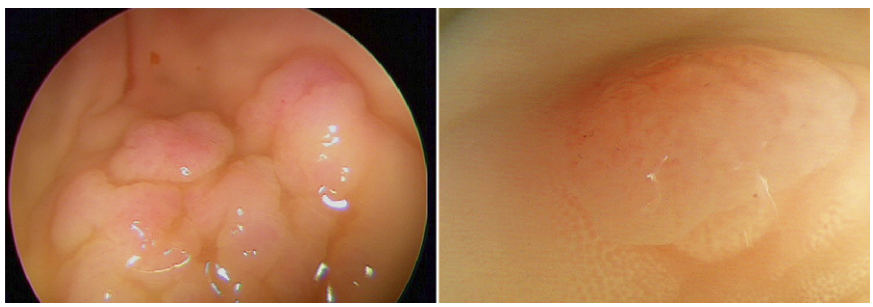

Figure 1. Endoscopic appearance of sessile colonic polyps in the $APC^{1311/+}$ pig.

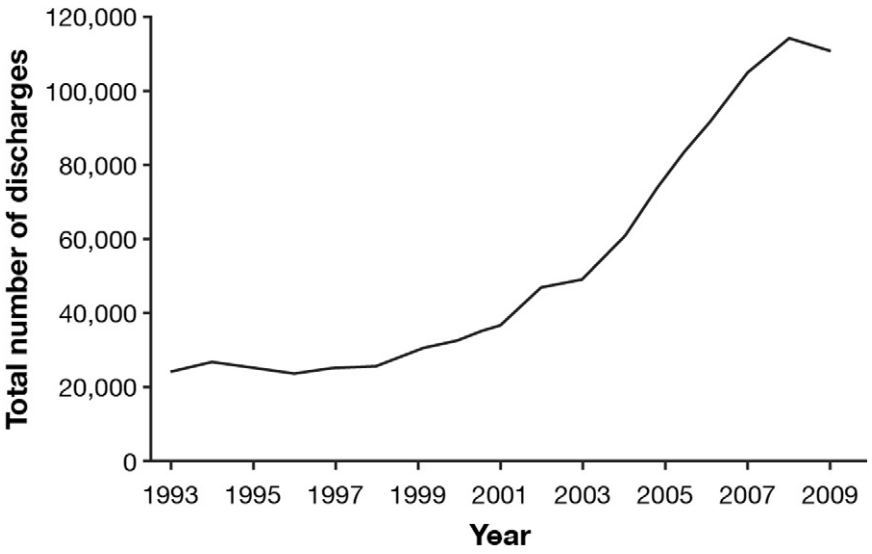

Figure 2. Number of annual hospital discharges with a principal diagnosis of *C difficile* infection, 1993–2009, from the National Inpatient Sample.

2009 and accounted for 6% of in hospital deaths and cost an estimated $1.8 billion per year. Hospitalizations for nonalcoholic fatty liver disease and morbid obesity increased 97% and 314%, respectively, from 2000 to 2009. Ten percent of all deaths in the United States in 2009 were attributable to an underlying GI disorder, with colorectal cancer the leading cause of mortality, followed by pancreatic and hepatobiliary neoplasms. Infection with *C difficile* was the 9th leading GI cause of death, with a 230% increase in mortality from 2002 to 2009. Between 2000 and 2009, there was a 54% and 17% increase in the number of upper and lower GI endoscopic procedures, respectively, performed in commercially insured patients. Substantial increases in endoscopic volume were also observed in Medicare recipients, with a 53% and 50% increase in the number of upper and lower GI endoscopic procedures, respectively. Increases in endoscopic retrograde cholangiopancreatography volume were less substantial, although magnetic resonance cholangiopancreatography use increased 8-fold and was performed twice as much as endoscopic retrograde cholangiopancreatography in this patient population. This comprehensive and updated analysis of the burden of and trends in GI and liver disease in the United States should help to inform decisions by payers, policymakers, and others interested in resource allocation and utilization.

See page 1179.

Utility of Enoxaprin in Patients With Advanced Cirrhosis

Although uncommon in compensated cirrhosis, the incidence of portal vein thrombosis (PVT) increases with the severity of liver disease. The development of PVT may precipitate clinical decompensation as well as affect post-transplant survival. Anticoagulation is effective in reversing acute PVT in the absence of cirrhosis. However, despite reports of the efficacy of anticoagulation in PVT in patients with cirrhosis, particularly in patients listed for liver transplantation, there have been no randomized, controlled trials comparing the safety and efficacy of anticoagulation with no treatment in preventing PVT in patients with advanced cirrhosis. In this issue of GASTROENTEROLOGY (accompanied by an editorial), Villa et al investigate the role of a 48-week trial of a low-molecular-weight heparin, enoxaprin, in preventing PVT in 70 patients with Child–Pugh class B and C cirrhosis from a single tertiary care center in Italy. In addition, the potential role of enoxaprin in reducing bacterial translocation and inappropriate activation of coagulation by improving the intestinal microcirculation was evaluated with measurements of intestinal fatty acid binding protein, a marker of enterocyte damage, and 3 markers associated with bacterial translocation (16S ribosomal DNA, soluble CD14, and interleukin-6). No patients in the enoxaprin group (n = 34) developed PVT while on treatment or at 2 years compared with 16.6% and 27.7%, respectively, of patients in the control group (n = 36). In addition, decompensation (ascites, sepsis, variceal bleeding, and encephalopathy) and hospitalizations occurred significantly less frequently among the enoxaprin-treated patients. Furthermore, survival rates were higher in enoxaprin-treated patients compared with controls (Figure 3). The rate of either spontaneous bacterial peritonitis or bacteremia while on treatment was significantly lower in enoxaprin-treated patients and this decrease was associated with decreases in intestinal fatty acid binding protein, 16S ribosomal DNA, soluble CD14, and interleukin-6. Enoxaprin was well-tolerated with no difference in the occurrence of bleeding in the 2 groups and only 1 patient in whom enoxaprin was discontinued early for thrombocytopenia. These findings demonstrate that anticoagulant treatment with enoxaprin significantly reduces the risk of PVT in patients with advanced cirrhosis and may have an additional protective effect against hepatic decompensation that is mediated by improvement in intestinal microcirculation.