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A strategic vision to promote advances in biliary tract disorders

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Biliary tract disorders are ubiquitous in large tertiary care gastroenterology practices. These disorders are complex, and associated with significant morbidity and mortality. Their management requires an integrated multidisciplinary approach involving radiologists, oncologists, endoscopists, hepatologists, gastroenterologists, pathologists and surgeons. Indeed, the authorship of this issue of *Current Opinion in Gastroenterology* reflects this disciplinary diversity. Advances in biliary tract disease have been aided by dramatic improvements in imaging modalities (e.g. magnetic resonance cholangiography, cholangiography by computer-assisted tomography, etc.) and device development (e.g. biliary stents, direct cholangioscopy, etc.). Many tertiary care centers have organized multidisciplinary teams and/or centers to care for patients with biliary tract and pancreatic disorders in order to coordinate care and optimally employ those diagnostic and therapeutic modalities. In this regard, this issue of *Current Opinion in Gastroenterology* focused on biliary tract disorders is timely and topical. Despite these technical developments, the care of patients with biliary tract disorders remains frustrating. We have been hampered by a lack of mechanistic insight regarding disease pathogenesis and the absence of coordinated, multidisciplinary, multiinstitutional studies. These are also insufficient numbers of investigators to help propel this field forward. I will explore our current deficiencies in biliary tract disorders and provide an action plan to help remedy this gap in medical knowledge.

When I was a Gastroenterology Trainee (1983–1986), there was a rich and vibrant community of investigators focused on biliary tract disorders. The disease primary sclerosing cholangitis (PSC) was being defined, the prevention of and/or dissolution of gallstones was a national priority, and endoscopic retrograde cholangiography (ERC) was emerging as a widespread, relatively safe and accurate technology for biliary tract visualization. State-of-the-art seminars on biliary tract disorders were frequent at national meetings. Unfortunately, this wave of interest in biliary tract disorders quickly dissipated; the tide went out to sea and has not returned. The national gallstone dissolution study with chenodeoxycholic acid was disappointingly negative, laparoscopic cholecystectomy rendered gallstone disease a more easily remediable condition and therapeutic ERC became the purview of talented endoscopists, more focused on their craft than biliary tract pathobiology. Finally, biliary tract cancers were viewed as the domain of oncology, although these cancers are an orphan disease for oncologists who are often overwhelmed with the more common breast, lung, colorectal and prostate cancers. We need a strategic plan to engender enthusiasm for investigation of biliary tract disorders. I will use the articles in the issue as a platform to help formulate a strategic vision.

Inflammatory disorders of the biliary tract remain extremely problematic to treat. In this issue, Dr Björnsson (pp. 389–394) has nicely summarized a new inflammatory disorder of

the biliary tract, IgG4 cholangiopathy. This disorder has previously been masquerading as biliary tract cancer, a mimic of PSC, and idiopathic biliary strictures. The diagnosis of this syndrome is now straightforward (elevated serum IgG4) and it responds to corticosteroid therapy. In this regard, we have a new treatable biliary tract disease. How many other types of inflammatory cholangiopathies exist? We know so little regarding biliary tract inflammation, a critical unmet need in biliary pathobiology. Despite rapid gains in our knowledge regarding the pathogenesis of inflammatory bowel disease, which is strongly associated with PSC, this information has not been translated into a better understanding of PSC. There have been no recent medical therapeutic advances in the management of PSC. In his article on PSC, Dr Roger Chapman (pp. 377–383) eloquently reviews recent advances regarding the genetics of PSC; however, this information can only be placed into context with more fundamental information on immune-mediated biliary tract injury. The strategic plan to remedy this deficiency involves additional animal models of PSC and further studies of cholangiocyte injury by the immune system. In particular, the role of the innate immune system in biliary tract injury needs clarification.

Three articles in this issue involve biliary tract neoplasia. Dr Heimbach (pp. 384–388) discusses the implementation and outcome of a novel protocol employing neoadjuvant chemoradiation followed by liver transplantation for highly selected patients afflicted with cholangiocarcinoma. Dr Thomas (pp. 372–376) reviews new information on emerging targeted therapies relevant to gallbladder cancer. Dr Sripa (pp. 349–356) reviews new information on inflammation driven carcinogenesis in the biliary tree. What emanates from these thoughtful and erudite reviews is how devastating those cancers remain. Further work is necessary to examine chemoprevention and targeted therapies for these cancers. Effective medical therapies could be employed in adjuvant and neoadjuvant protocols, potentially expanding the role of surgery and liver transplantation for these cancers. What is necessary to test these therapies is an organized consortium of investigators, infrastructure support and access to novel drugs coupled to well-designed clinical trials. Additional information is also needed in regards to patient stratification to help design such trials. The latter is an urgent need.

In contrast to PSC, recent genetic studies have provided considerable insight regarding gallstone disease pathogenesis. The majority of gallstones are comprised of cholesterol. Cholesterol transport in epithelial cells, including biliary tract cholangiocytes and gallbladder epithelia, is regulated by the ABC G5/G8 transport proteins. A number of polymorphisms including single nucleotide polymorphisms (SNP) of these proteins are associated with cholesterol gallstone disease. This new information is aptly reviewed by Dr Lambrecht in this issue (pp. 363–371). With the increasing feasibility of cost-effective screening of SNPs of an individual's genome, patients at risk for gallstones can be identified. We, as a profession, are now uniquely poised to once again think about gallstone prevention in high-risk groups. The practicality of chemoprevention studies depends upon a cheap chemopreventative agent and a safe drug whose efficacy could be validated and established. Investigators motivated to conduct such studies will also be needed.

Significant strides in technology to investigate the biliary tree have occurred. We now have the ability to perform intraductal ultrasound and direct cholangioscopy. Drs Small and Baron (pp. 357–362) do a terrific job in exploring these technical advances. While the technology exists, however, manufacturers have shown little interest in developing drug-eluting stents for the biliary tree; such stents are widely available and employed for coronary artery disease. Drug-eluting stents could be ideal to treat malignant strictures and/or to help preserve bile duct stent patency. As a profession, we need to advocate for this technology on behalf of our patients.

We have substantial unmet needs in biliary tract disease (Table 1). Additional investigators with an interest in biliary tract disorders are necessary to accomplish the above goals. Those of us engaged in this field need to attract junior investigators and nurture their career development. Biliary tract disorders must be portrayed as an opportunity. Senior members of our community must be proactive in this regard. Finally, the distinctions between disciplines must blur if we are to prevent and cure biliary tract disorders. Perhaps customized training tracks within gastroenterology focused on biliary tract disorders should be developed (Fig. 1). I believe we must train focused academicians in a manner distinct from training subspecialty practitioners. The focused academician need not be competent in general gastroenterology nor should they be trained with this objective. For example, a tract to potentially train an individual in cholangiocyte biology, clinical trial design plus the technical skills to perform advanced and therapeutic ERC could be developed. The ability to obtain tissue at the time of ERC by an investigator would promote translational studies. Only with a re-engineering of academic training pathways will we have the necessary investigators to advance the field to prevent and cure biliary tract disorders. The current separation between proceduralists and experimentalists is not optimal if we are to further advance the field of biliary tract disorders.

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Year 3	Clinical trial design	Advanced endoscopic retrograde cholangiography	Care of patients with biliary disorders
Year 2	Cholangiocyte biology	Endoscopic retrograde cholangiography	
Year 1	General gastrointestinal training		

Figure 1.
A customized program for training in biliary disorders.

Table 1**Strategic vision to enhance progress in biliary tract disorders**

Discovery research
Development of animal models relevant to primary sclerosing cholangitis
Development of cholangiocyte-specific genetic animal models
Development of animal models to explore immune-mediated cholangiocyte injury
Development of animal models of gallbladder and extrahepatic bile duct cancers
Translational research
Development of drug-eluting biliary stents
Development and validation of biomarkers for biliary tract inflammation
Identification of genes predisposing to biliary tract disorders
Clinical research
Multiinstitutional trials for primary sclerosing cholangitis
Multiinstitutional trials for gallbladder cancer and cholangiocarcinoma
Multiinstitutional trials for gallstone prevention