The Primary Sclerosing Cholangitis/Inflammatory Bowel Disease Link: An informative and interactive workshop for medical professionals and Patients

University of Colorado, Denver, October 3, 2009

The workshop took place in Anschutz Medical Campus, the brand new research center at the University of Colorado, and brought together hepatologists, researchers, and gastroenterologists with the aim of discussing the intersecting paths that link IBD and PSC. The keynote speakers were Dr. Keith Lindor from Mayo Clinic and Dr. Tom Karlsen, project leader of NoPSC, the Norwegian PSC Research Center in Oslo, Norway. The exciting and promising research of Dr. Sean Colgan, head of mucosal inflammation research at UC and his team, (http://www.uchsc.edu/gastro/1_faculty/b_Colgan.php); the innovations in non-invasive techniques for staging liver disease led by Dr. Greg Everson, head of hepatology at UC; the animated discussions of Dr. Brian Doctor, Dr. Steve Helmke, Dr. Alan Baird, Dr. Lisa Forman, Dr. Raj Shah, Dr. Jeffrey Campsen, Dr. Jesus Rivera-Nieves and pediatricians Dr. Shikha Sundaram, , and Dr. Cara Mack displayed the vibrancy of the University of Colorado research center. *(Please note that all comments within parentheses are mine. Rachel Gomel)*

Dr. Keith Lindor, Dean of Mayo Medical School, head of Gastroenterology and Hepatology at Mayo Clinic, and current editor-in-chief of *Hepatology*, Dr. Lindor has studied PSC for decades. ***Current and Future Treatments for PSC***

Dr. Lindor, who was one of the two keynote speakers, organized his talk along the lines he used three or four years ago for his talk on novel therapies for PSC in an NIH conference. Though there are no solutions yet and we haven't learned much since that last conference in Washington, we have learned about what we do not yet know in PSC. He based his talk on some of the results of ideas that were discussed in the NIH conference. He discussed the mechanisms that could potentially be the cause of PSC, and how these mechanisms suggested possible targets for PSC research.

He started with a graph showing the risks for liver transplantation for PBC and PSC between the years 1995 and 2005 in the U.S. and said he wished PSC displayed the same statistics as PBC had, that is, a marked reduction in liver transplantation, probably due to the effectiveness of Urso in PBC. On the graph, PSC showed no decrease and in fact, a slight increase in the need for liver transplantation. Twenty years ago, PBC was the leading indication for liver transplant, and now it is an uncommon indication for PBC. The need for liver transplant went down from 250 per year to 200 per year in PBC. An effective treatment like Urso for PBC is precisely what we need to have for PSC.

Some of the areas that were considered in the NIH conference and that were reviewed in this talk, were the pathogenetic mechanisms in PSC, that is, genetic abnormalities, transporter defects, autoimmunity (particularly in IBD), infection agents (perhaps explaining the relationship between IBD and PSC), innate immunity, cholestasis and cell injury. And lastly, he said he would discuss his own

Urso study at Mayo as a warning about the importance of having well-controlled data before making therapeutic decisions. He said that what he would be showing would be pilot data, and that consequently, there should be caution before jumping into actual application.

When we think of *mechanisms*, we think of *targets*, he said. If bacteria are involved, there are all kinds of antibiotics we can use. Sometimes we can modify receptors that can cause problems such as cholestasis. For example, fibrosis had been considered a one-way street, with no hope of reversal. We now know that fibrosis can be reversed in Hepatitis C. Through these therapies, it was discovered that PSC, unlike PBC, is characterized by marked fibrosis with little inflammation.

Bacterial links in PSC were established by using an animal model. Steve Lichtman from the University of North Carolina (Gastro 1990; 98: 414-23) worked on rats and looped their intestine, creating a proliferation of bacteria. This excess of bacteria then led to liver inflammation. The inflamed liver and bile duct looked like human PSC, though animal models haven't been able to simulate human PSC. Through this mechanism of bacterial proliferation and inflammation, Lichtman was able to identify the peptidoglycan protein or murein that make up the cell wall of bacteria. His next step was to use metronidazole as therapeutic measure. He was also able to use antibodies targeting lipopolysaccharide that create tumor necrosis factor (TNF - regulates immune cells and induces cell death and inflammation). Lichtman used infliximab to inhibit TNF. Pentoxifylline (an antibiotic used for decades; an Anti TNF therapy) was able to prevent the bile duct injury that was occurring. This was considered promising. In a small pilot study, the effects of pentoxifylline on alkaline phosphatase and AST were observed: Nothing happened biochemically. There was little impact on TNF. What had proven to be effective with animal models was not applicable to humans.

Antibiotics nevertheless seem promising. A Finnish study looked at a fairly large number of patients. This randomized trial used a combination of UDSC (Urso) and metronidazole. It should be noted that Urso is still used in the majority of European PSC patients unlike in the U.S. A safe dose of Urso (15mg/kg/day) was used as baseline and combined with metronidazole. The trial went on for three years. It was observed that alkaline phosphatase improved in the first three weeks, then this improved level was sustained, and metronidazole added some improvement. This study was not replicated.

Other antibiotics such as tetracycline, short and long term vancomycin and azithromycin were tried on a small number of PSC patients, the largest study including 14 people. With some, changes in biochemistries could be dramatic. The results suggest that antibiotics should be further explored. It must be remembered that breakthroughs in medicine do not follow in orderly fashion. Often times these studies don't lead to therapy but can start elucidating the connection of bacteria to PSC. We have to be aware that looking for a treatment can be a two-way street.

Transporter defects. Steve Freedman's study of cystic fibrosis (http://www.bidmc.org/Research/Departments/Medicine/Divisions/TranslationalResearch/Faculty/StevenD,-d-,FreedmanMDPhD.aspx) is relevant to PSC as some of the features of PSC resemble those of cystic fibrosis. In PSC the CFTR gene (cystic fibrosis transmembrane conductance regulator – a glycoprotein with 1480 amino acids. Mutations of the CFTR are seen at the source of cystic fibrosis) can be defective as they are in cystic fibrosis. These were controversial papers because there may be a danger in thinking that PSC has a single cause. PSC is not characterized by a single injury. We see this because there are many subgroups in PSC, and these can display a limited response to injury. One abnormality is not present in all PSC. Steve Freedman tested how sodium chloride was being transported in cystic fibrosis. It was observed that the cystic fibrosis values were a lot less than normal, while PSC displayed intermediate values, higher than those in cystic fibrosis.

Steve Freedman is currently studying the impact of Omega-3 on PSC. Funded by the Morgan Foundation, this trial is at its first phase. (http://clinicaltrials.gov/ct2/show/NCT00325013). Thirty people are taking part in the study and are taking Docosahexaenoic Acid (DHA – in Omega-3). In this yet unpublished study, changes in biochemistry are being recorded. A fairly modest improvement of alkaline phosphatase has been observed. One result was particularly impressive, and that was the improvement of fatigue, a common disability in PSC. Up to date, there has been no effective treatment to reduce fatigue. Also, an uncontrolled study to be published this week showed improvement in biochemistry and fatigue with Provigil . As half of PSC patients complain of fatigue, provigil could be a helpful treatment for PSC induced fatigue.

Another angle for studying PSC is through the manipulation of nuclear receptors and by looking at reactions with biliary mechanisms. For PBC, the company Intercept Pharma developed *6*-ethylchenodeoxycholic acid, an urso like medication. This led to a lot of itching. Now there is effort to remove the factors that induce itching. We are waiting for results, he said, before trying it on PSC.

Some medications such as minocyclene (a second-generation tetracycline derivative that exerts anti-inflammatory effects) reduce iNOS (Inducible nitric oxide synthase whose function is that of immune defense against pathogens), inhibit DNA repair and inhibit apopteosis (programmed cell death). These showed modest improvement.

Immunomodulators that regulate immunologic abnormalities: mychophenolate (immunosuppressant drug to prevent rejection), tacrolimus (immunosuppressant drug that lowers the risk of organ rejection, reducing T-Cell and Interluken-2 activity), budesonide (fewer side effects than prednisone) have been studied with little success. Michophenolate produced a modest decline of alkaline phosphatase that was not impressive enough. Because of the numerous side effects, this drug will not be pursued. It was hoped that budesonide would improve biochemistry in PSC. Those that had elevated IGG4 (they have more aggressive disease) responded to

budesonide. In this study 10% of the 118 participants had elevated IGG4 and the liver enzymes were normalized in 2-3 patients. Overall there not much change was noted. Some got worse. As the disease itself has a fluctuating course, it is hard to plan these studies.

Anti-TNF agents.

Silymarin (milk thistle), 30 patients participated in this study. Alkaline Phosphatase and AST lowered. Silymarin could be used as adjunct therapy.

Antifibrotic therapy - ace inhibitors may be promising, due to their antioxidant, antifibrotic, and fibrosis-reducing properties in animal cholestasis models. ACE inhibitors such as Sirolimus (also known as rapamycin) deserve to be studied. There haven't been any good studies to date, but we have enough signals to suggest that they are worth studying.

UDCA – The Urso study at Mayo shows the importance of having well-controlled trials. Urso improves LFT's (liver enzymes), but are liver enzymes really the best indicators of liver protection? This is unknown since only biopsy can confirm whether Urso protects at the cellular level, and biopsy is only 70% reliable in predicting the status of disease. It is thought that urso improves histology, and decreases cancer risk. There are some thoughts that urso improves survival. Roger Chapman at Oxford saw a decrease in inflammation in a study with 21 participants and using 22mg/kg/day of urso. In a University of Washington study looking at dysplasia, with urso, the risk was 1 in 7. Urso looked protective. These studies were retrospective and prevented us from reaching such conclusions.

CCA (cholangiocarcinoma) is not common with PSC. We have no firm evidence that urso reduces the risk of cholangiocarcinoma (CCA). The higher dose lowered LFT's. It was tantalizing to think that high doses would improve survival. In Scandinavia, a study including 220 patients taking intermediate dose of urso was conducted. Mayo did its own trial and used a wide geographic distribution. Endoscopies were done every two years and ERCP's were to be performed every 5 years. During this trial, it was observed that the risk of dying or transplant was higher if the patient received a high dose of urso. The risk of varices was three times greater than those taking placebo. The PSC network expressed great concern. PSC Partners helped disseminate this information. We are still seeing patients who do not know about the study and are taking high dose urso. At this time, we are still ignorant about the best treatment for PSC. There are a lot of mechanisms to explore, a lot of agents to be tested for all forms of PSC.

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Q & A. *Dr. Greg Everson* (head of Hepatology at the University of Colorado) asked whether studies had been conducted on vascular injury. *Dr. Lindor* said that he was not aware of such studies and brought up the example of H. pylori which remained invisible to researchers for a long time. The same could happen with PSC, he said.

Q. *Sean Colgan*: On the connection between IBD and PSC. How sensitive are enzymes for showing the usefulness of urso?

A. With PSC, IBD is not severe and not very symptomatic. With the higher dose of urso, we had more loose stools, suggesting a link between the two. We don't have reliable markers to assess disease. We can validate an endpoint only after we have shown that a therapy is useful. The markers for fibrosis, serum markers or mechanical markers such as MRI are a conundrum. It is almost impossible to make a valid argument.

Most of the PSC patients have coexisting IBD (75%). In Scandinavia, the proportion is lower (50%), and in Japan even lower (30%).

Q. *Dr. Everson*: Is urso therefore an expensive placebo? Should we stop prescribing urso? Should we move from high to low dose?

A. *Dr. Lindor*: I don't have the answer, but the American Association for the Study of Liver Disease, in the November issue of the journal *Hepatology* will be recommending to stop the use of urso for PSC. Personally, I don't believe the data are strong enough to justify this recommendation. High dose, above 25mg/kg/day should not be used as it tripled varices and doubled the need for transplant. In the case of my patients, many have stopped, some have had liver enzymes rebound, so they went back to taking it. It is a question we do not have an answer to. Some studies showed that it doesn't prevent cancer. Some get AP lowered, and their outcome is very good, so I'm a little nervous about throwing all this out. Now that urso has gone generic, I don't think that pharmaceutical companies will want to continue to evaluate urso. The intermediate dose may have some benefit.

Q. *Dr. Everson*: On dose toxicity. On the possible mechanism of high dose urso – Perhaps high dose urso plays a role in the formation of toxic bile and in plasma elevation. In high doses, urso is not well absorbed and some of it turns lithocholic acid. In the high dose, we have seen lithocholic acid formation in the colon and the expansion of the total bile pool from 1 to 9%. Dr. Lindor said that we don't know if lithocholic acid is responsible for varices and transplant, though it is the most plausible explanation.

Dr. Lisa Forman, Assistant Professor of Medicine, hepatologist, UC Denver. ***Adult PSC at the University of Colorado***

Dr. Forman talked about the liver program at the University of Colorado and about a study on IBD post liver transplant she and her team led two years ago. Describing the liver transplant program at the University of Colorado which was established in 1988, she said that out of the 4500 patients followed in her department, over 450 were currently listed and that the center had performed 1350 transplants to date. Of the 80-100 transplants/year they perform, 12% was for PSC. She talked about an efficient post transplant database that was started in 1999 and that recently started

to include pre transplant information as well. It takes a click of a button to reach a patient's doctors, meds, labs. Through this system, doctors are currently able to follow a given patient on real-time basis.

Of the 155 transplants performed for PSC, 5 were relisted, 9 for cholangiocarcinoma (CCA), 22 were live donor transplants (LDLT), and 16% were for recurring PSC (rPSC). 75% had IBD. Of this group 89% already had IBD prior to transplant, and 11% at transplant. Of these patients, 85% had ulcerative colitis, 12% had Crohn's colitis, and 3% had indeterminate IBD. Though Dr. Forman's study on the IBD in post transplant PSC patients included the largest cohort among similar studies, their results were inconclusive. The various studies on the natural history of IBD post Tx reveal wide-ranging outcomes. 3-100% report disease improvement, 0-51% report worsening of IBD and 27% report *de novo* IBD (post transplant, new IBD). Dr. Forman's study, 38% of patients reported fewer IBD flares post transplant, 33% a worsening of IBD, and 5% could not tell. Most reported a significant improvement of quality of life (in a rating of 1-5, most reported a level of 4 or 5 post transplant), and in the *de novo* group there were more females than males and the IBD was milder with fewer flares. In the rPSC population there were no cases of *de novo* IBD.

Jeffrey Campsen, MD, Transplant Surgery Fellow, University of Colorado, ***Clinically Recurrent PSC Following Liver Transplant: A Time Course.***

Dr. Campsen gave statistics on recurrent PSC after liver transplantation (rPSC). Between 1988-2006, out of over 1000 liver transplants performed at the University of Colorado, 12% were for PSC. Out of the 130 transplanted PSC patients, 22 had rPSC. The risk seems to be 20% in 10 years with 61% surviva l at ten years. 7 received a second transplant. If PSC recurs, it is not benign and the course it follows is not as long as the original course. Out of the 22 who had rPSC, one had a third transplant and is doing really well. 4 had no recurrence in the graft. rPSC does well with a new transplant.

The second part of his talk focused on a procedure of choice used at the University of Colorado for hooking bile ducts with live donor transplants. Instead of Roux-en-Y, or duct-to-duct surgical reconstruction, they prefer using *choledochoduodenostomy*, in which ducts are hooked up to the duodenum instead of the jujenum. He said that this method allows the removal of the original injured bile ducts, makes it easier to get to stents, is more natural and requires minimal dissection. He said that at the U of Colorado they are advocates of live donor transplantation for PSC, they believe PSC patients to be excellent candidates for live donor transplants and very importantly, they achieve very good results.

Q & A: On live liver transplant. How long does it take for the donor's liver to regenerate itself?

Dr. Everson: At our center donor survival is 100%. The surgery of course has some risk to the donor. We prioritize the donor and we go all out to protect the donor's

liver. We assure that surgery is safe for the donor before we decide to accept the donor. For the donor, AST and INR normalize in 5-6 days, and 90% of the liver regenerates in 30-60 days.

Q & A: Could prednisone cause PSC and rPSC?

Dr. Everson: We avoid steroids after transplantation, but we could see no adverse impact of steroids on PSC progression and recurrence. Perhaps we thought that steroids speeded rPSC, but we gave steroids only to those who had aggressive IBD. And the faster recurrence of PSC might have been related to the inflammation in the body, so we could not reach any conclusion relating to the effect of prednisone. We found no clear link between steroids and recurrence, progression or severity of post-transplant PSC.

Dr. Lindor: We don't either, at Mayo. As for medications that may lead to PSC *de novo*, the usual medications like Tylenol, non-steroidals, etc. won't lead to PSC.

Q & A: In the Colorado series, did any of the IBD patients develop colon cancer after liver transplantation?

Dr. Everson: 3-4 did.

Q & A: Have you encountered anyone who developed CCA after re-transplant? How do you decide between Roux-en-Y and choledochoduodenostomy?

Dr. Everson: Of the 22, those with CCA with transplants, have not had CCA. If it looks easier than Roux-in-Y, we opt for choledochoduodenostomy.

Dr. Igal Kam (surgeon at U of C): Surgery is about controversies. If we don't try new ideas, we'll never improve. Our primary option here is choledochoduodenostomy. With Roux-in-Y, strictures form and we cannot do stenting and scoping. Literature is changing, and gradually choledochoduodenostomy will be the option of choice in cases where duct-to-duct is not a choice.

Dr. Everson congratulated Dr. Kam for his and his team's numerous innovations in liver transplant surgery. The U of C in Denver, where live donor liver transplation began, has refined the surgery procedures, and Dr. Kam and his team have contributed much to its progress. The fact that post surgery ICU is no longer used attests to the improved techniques in live donor transplantation at the U of C in Denver.

Dr. Raj Shah, Associate Professor, Therapeutic Endoscopy, UC Denver, ***Endoscopic Technologies in PSC.***

Common Bile Duct (CBD) stenosis (narrowing of duct) occurs in 10-20% of PSC patients. Dr. Shah explained that at the U of C, Denver, the approach to stenting is different from many of the liver centers in the nation. In this center, the approach is

balloon dilation followed by stenting. Multiple stents are used instead of a single large stent, and the stents remain for a short time, that is for 2-3 weeks instead of longer periods of time. He added that PTC (Percutaneous Transhepatic Cholangiogram) is reserved only for those with failed ERCP's.

The use of multiple stents placed side by side is meant to resolve stenosis and to improve cholestasis. Complications of stenting may be due to the use of PTC rather than an endoscopic approach or perhaps because the patients had advanced PSC. To date, all studies have been retrospective.

Every time we add dye, the chance of infection is increased, so the risks and the benefits are carefully weighed before such procedures. A decrease of jaundice and improvement of cholestasis have been noted following endescopic stenting.

Would pre-transplant stents or percutaneous drains delay the time to transplant? Neither for diagnostic or therapeutic purposes biliary interventions do not seem to delay the time to transplant nor do they increase post-transplant complications. They are a palliative bridge to transplantation, the treatment of choice.

In discussing endoscopic means used to detect cholangiocarcinoma, Dr. Shah said that the risk factor for cholangiocarcinoma is highest just after diagnosis and then declines. (For Dr. Shah's explanations of the various biliary intervention methods, please check his powerpoint presentation.)

Dr. Shikha Sundaram, Assistant Professor, Pediatric Gastroenterology, The Children's Hospital, UC Denver, ***Pediatric PSC at The Children's Hospital, UC Denver.***

Dr. Sundaram discussed the differences separating adult and pediatric PSC in understanding whether they are the same disease. She showed how pediatric PSC starts off with many of the bile ducts being inflamed and as the years go by, the number of bile ducts and inflammation decrease and cholestasis and fibrosis increase. From being reversible, the disease moves to being irreversible.

The frequency of PSC in the U.S. adult population is 1/100,000 (US); however, no such data exists on pediatric PSC patients, but it is assumed to be considerably less. Ten centers work together, and Denver is one of them. These centers follow 223 pediatric PSC patients. From the data coming from STOPSC, Dr. Sundaram said that PSC presents itself similarly in children and adults. However there exists a difference in the blood tests. The alkaline phosphatase, for example, can be elevated as it is in adults; however in children, the elevation in alkaline phosphatase could be due to growing bones. With children, the GGT is the more reliable figure. The preliminary data from STOPSC show that PSC in children is less cholestatic. 50% test ANA positive and 80% test pANCA positive. Though ANA and pANCA results are believed to be non-specific, Dr. Sundaram said that they are not so sure whether this is the case with pediatric PSC.

With children, dominant strictures are very rare and so is cholangiocarcinoma. Metabolic bone disease is of particular concern in pediatric PSC because this is the time for bone growth. In the pediatric population, IBD is evident in 50-60% of cases and therefore is less common than in adult PSC, but here again it may be due the fact that there is less screening for IBD in children.

Another important feature in pediatric PSC is autoimmune hepatitis which we now call *autoimmune hepatitis-PSC overlap syndrome*. Diagnosed in ¼ of pediatric PSC patients (only 8% of adults have overlap syndrome), this overlap disease responds to immunosuppressants and requires liver biopsy for diagnosis. In other words, pediatric PSC necessitates different evaluation.

30-35% of pediatric PSC patients have small duct PSC (versus 5-15% in adults). Ducts are too small to be seen with ERCP or MRCP, so again a biopsy is needed to diagnose PSC and to rule out autoimmune hepatitis. This form of PSC is much less aggressive than large duct disease, and Dr. Mylo at Mount Sinai in NYC suggests that overlap syndrome may be a different disease. Mayo Clinic studied 52 patients, and 11 of them required transplant, the mean being 6.5 years to transplantation.

Dr. Sundaram explained that the Urso debate is also going on in pediatric PSC. She said that children were never given high dose Urso (maximum 20mg/kg/day). They have witnessed prompt and important improvements in pediatric lab results with Urso, but they are questioning whether to stop Urso for children to prevent potential long-term problems. They are therefore doing a prospective pilot study of withdrawal and reinstitution of Urso in the pediatric PSC population, looking for disease flares, inflammatory markers and lab changes.

She concluded that children are not little adults. Pediatric PSC may be a variant of adult PSC as the disease behaves differently than it does in adults. Treatment and prognosis are different. There are more questions than answers.

Panel Discussion: Drs. Keith Lindor, Lisa Forman, Jeffrey Campsen, Raj Shah, Shikha Sundaram

1. What is the role of alcohol abuse in PSC? How do you monitor alcohol intake during treatment?

Dr. Lindor: We aren't adamant about abstinence unless there is cholestasis. My practice hasn't had alcoholic patients.

Dr. Lisa Forman: We *strongly* discourage alcohol consumption to pre-transplant patients.

Dr. Sundaram: Teenage week-end binge drinking is a problem. Teenage patients think they are invincible and experiment. We spend a lot of time talking to our teenage patients about alcohol consumption.

Dr. Karlsen (outside the conference) said he was opposed to alcohol consumption for PSC patients.

2. On the presence of homeopathic, alternative medicine such as milk thistle. Any studies on alternative medicine and PSC?

Dr. Lindor: No, other than the data we have on milk thistle, there are no such studies for PSC. We are very concerned about the combinations of compounds in alternative medicine. Alone, each compound may be safe, but together they might worsen the liver disease. Some of the proprietary products have a list that includes 20 products whose combinations can produce effects we cannot know. We see some of the patients whose disease was worsened by such compounds.

3. On the effects of pigs' tapeworm on IBD and PSC.

Dr. Everson: There is evidence that some organisms such as the tapeworm from pigs can tone down our immune system, and reduce inflammation. They infested IBD patients with tapeworm, and apparently the IBD inflammation improved. It has been used only for IBD. A German company made a purified product of tapeworm eggs that hatch in the colon. In a randomized trial, the eggs were given continuously - as their effect stopped shortly after intake. Colitis activity diminished through the suppression of the immune system.

4. Probiotics – any data for PSC?

Dr. Lindor: There aren't data but it is an interesting idea. Probiotics replace defiant microorganisms in our gut. VSL#3 is currently being used for Irritable Bowel Disease and IBD. If the theory of bacterial pathogenesis for PSC were to play out, altering the bacterial profile with benign probiotic bacteria might make sense.

5. Is there any limit to the number of ERCP's a patient can have, and is there work on making a stent that can last more than 6-8 weeks?

Dr. Shah: No, there is no limit to the number of ERCP's a patient can have. Our goal is to control dominant strictures. Stents can stay longer than 6-8 weeks. Metal stents are expandable unlike plastic stents. We don't leave large diameter stents for benign disease because the stent can get plugged and may not be able to be removed.

Dr. Lindor: Radiologically placed stents bring more complications and are harder to get in. We've changed our practice at Mayo and use short-term 2-3 week stents - if we use them. The long-term stents created complications.

6. Timing for transplant in PSC. Why not get transplants earlier while there is a window and the PSC has not yet spiraled?

Dr. Forman: This is one of the biggest challenges with PSC. If you have a low MELD, the risks of a transplant outweigh the benefits. Transplants are good for getting rid of disease, but patients can have complications. And with a transplant, a patient would be trading one disease for another. Chronic immunosuppression, high blood

pressure, kidney disease, kidney transplant and a second liver transplant are some of the consequences. Though the pre-transplant patients may have serious lifestyle issues such as severe itching and fatigue, their MELD score may be low. In that case we speak to them about live donor transplantation. The ways they acquire their MELD points is by having multiple organ failure and by being in ICU. And at that point, the window is extremely narrow. In the case of cholangiocarcinoma, if diagnosis is not yet made, does one wait for transplant and then find out that a transplant cannot be performed because the CCA is too advanced? It's not an easy question and it's quite controversial.

Dr. Lindor: 18,000 to 20,000 people are on the waiting list for a liver transplant. It's not about prioritizing who gets a liver. We perform transplants on our sickest patients, and the sicker the patient, the more re-transplants are required, and that shrinks the available donor pool. What we need is to expand our donor pool.

7. Do you see an option on the horizon to replace bile ducts only? If the problem is with the extra-hepatic ducts, is there a way to replace those?

Dr. Campsen: No, because the ducts are uniformly everywhere, and you can't replace just the bile ducts, and you can't replace just the segments. The problem with bile ducts is that they stay alive through arterial flow. The arteries that feed them are very fine, and that would be an issue in replacing tiny bile ducts.

8. Does prior serious surgery such as j-pouch or ostomy make live donor transplant less of a possibility?

Dr. Campsen: No, a lot of patients with PSC have had prior surgeries. More surgeries means more adhesions, and that makes the surgery more difficult, but that is by no means a reason for not operating on such patients.

9. How long have we been doing live donor transplant for PSC?

Dr. Campsen: Since 1998. Specially with the onset of the MELD score, there is a spattering of PSC patients every year.

10. Do processed foods, coffee or other foods exacerbate or even cause PSC?

Dr. Forman: We have no data. We recommend a regular healthy diet.

Dr. Everson: Coffee always comes up as a question. Does it hurt the liver? No, it absolutely does not. Have a cup of coffee on me!

Dr. Lindor: I agree with Dr. Everson. There is no reason to be restrictive about coffee.

11. Are there any studies for identifying triggers for flare-ups for cholangitis?

Dr. Lindor: Not that I am aware of.

12. Limitations and challenges for therapy in each of the disciplines.

Dr. Sundaram: In pediatrics, there is no data, so we extrapolate from adults.

Dr. Shah: To detect malignancy.

Dr. Forman: Treatment is endoscopy or surgery. There are no medicines. That's a challenge. And screening for CCA is a challenge.

Dr. Lindor: They say that the root of all evil is money, and that is our challenge. There are many therapies that could be tried, but PSC is not a common disease. There are about 30,000 people with the disease in the U.S. Pharmaceutical companies lack the money and prefer large markets. We have to come up with more clever ways of testing such drugs for PSC.

Ricky Safer, **president of PSC Partners** and **Don Safer** whom she introduced as her advisor and mentor, responded to the question, "How can we as a national organization, PSC Partners, help coordinate prospective multi-center studies?" She stated that this conference was a first-time collaboration between the medical and research communities at the University of Colorado and PSC Partners. We are a grass-roots national non-profit we created four and a half years ago in Denver, and our ultimate goal is to provide information and support for patients and help find new treatments and a cure, she said. The realization that little research and scary statistics were what patients were confronted with led them to create PSC Partners with the help of hepatologist Dr. Greg Everson. During these four years, PSC Partners has produced on its site, an online newsletter, *The Duct,* which includes medical research, reports on new research and support for lifestyle improvement. The PSC Partners' site includes a unique PSC literature database consisting of over 110,000 abstracts. With a new grant, PSC Partners is working on a new site. The Yahoo support group with Arne Mirabo as moderator includes over 2000members. An annual three-day conference unites many PSC Partners members and is as informative as it is life changing. The next conference will take place in Hartford, Connecticut in May 2010, and physicians from the Hepatology Department of Yale will be the presenters. Ricky Safer ended with, "We exist to help you."

Dr. Don Safer described the international research that PSC Partners has been funding. Currently, three grants were awarded, two in the U.S. and one in Holland, and there are more to come this year. PSC Partner also gives a prize during the annual meeting of the American Association for the Study of Liver Disease (AASLD). Last year the award went to Dr. Tom Karlsen, this conference's second keynote speaker. Dr. Safer invited physicians and researchers to apply for PSC Partners grants.

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Dr. Tom Karlsen – project leader of NoPSC, the Norwegian PSC Research Center, University Hospital, Oslo, Norway. ***Differences and Similarities between PSC-IBD and UC – Lessons Learned from Genome-Wide Association Studies***.

In his talk, Dr. Karlsen gave an update of the *Genome-Wide Association Studies* on PSC taking place in Norway. His talk included reports on in-press and even more current yet unpublished studies. The Oslo PSC group studies the relationship between genotypes and phenotypes in their focus on bile duct strictures. (Genotype is an organism's full hereditary information. Phenotype is an organism's actual observed properties, such as morphology, development, or behavior. This distinction is fundamental in the study of inheritance of traits and their evolution.) At the time PSC is diagnosed, there are already strictures and scarring in the biliary tree, and beyond these strictures, there can be cholestasis (when bile cannot flow from the liver to the duodenum), bile acids, bile acid toxicity and secondary events occurring on the cellular level. Insult may have started 10-15 yrs before diagnosis. The genetic constitution of the individual is not affected by the secondary inflammation and can be used to study primary events in PSC development.

An important aspect of PSC to keep in mind is that PSC is not a single disease. 80% of PSC patients also suffer from IBD, and 25% have additional autoimmune disease, and an increased risk of cancer. IBD phenotype in PSC – IBD is different from that of typical ulcerative colitis. Disease is extensive (with entire colon involvement), is more intense on the right side, 50% have ilial involvement, and no inflammation of the rectum. There is also a geographical gradiant to consider: Northern Europe and Northern U.S. experience a higher prevalence of PSC-IBD while PSC in Southern Europe and Southern U.S has a lower prevalence of IBD. And Japan is different from Europe and the U.S. In genetics the typical measure used as evidence is the heritability risk for siblings and relatives. One reliable study from Stockholm on the heritability of PSC shows that the relative risk in siblings is 10-40 fold as compared to the general population. Another important evidence is the increased frequency of ulcerative colitis without PSC in siblings of PSC ers. It is evident that there is shared genetics between PSC and IBD.

PSC genetic studies can be classified into 3 types. 1. HLA studies that were started in the 1980's by Erik Schrumpf (head of NoPSC) and that were further substantiated by 30 studies; 2. Studies of other genes (non HLA), and none of these studies have been replicated and therefore remain inconclusive. Up to last year, outside HLA, we had not discovered other susceptibility genes; 3. Studies on modifier genes (a gene that modifies the effect produced by another gene) - genes that modify disease

intensity without influencing the risk of getting disease. Further work is needed on these genes to find their effect on PSC.

Most of these studies are technology driven. In the first type, that is, the HLA Association studies, we now know that there exists no autoimmune disease that doesn't show an HLA association. On chromosome 6, containing 250 genes, we know that 50% of the genes are involved in autoimmune disease. Any one of these 250 genes could be responsible for this association.

When we look for PSC and IBD markers (Please see PowerPoint presentation diagram), we can see that there are significant associations throughout the genes. It is hard to tell which ones are specifically for PSC. When we look at PSC and ulcerative colitis together, we can see that PSC has stronger association with ulcerative colitis and that PSC and UC have different markers. What we can also see is that it will be difficult to a single HLA gene to PSC unlike in celiac disease which is associated with one HLA-variant.

With the recent technical innovations, ½ million to 1 million markers can be genotyped and variant genes in regions of genomes can be detected in healthy and PSC patients. These studies point to a rather surprising finding, that the 20-30 disease genes that have been detected and the variants coming out of these studies are of no value for genetic counseling. The focus should be on biological pathway detection. It is not a single molecule that is fulfilling a specific function but networks of molecules (pathways) that do. Biological functions are produced by networks of different molecules called pathways. For example, if something goes wrong with gene B, that gene in that pathway may be important in bringing disease; however, it may not be necessarily the genes that are relevant as there may be other components along this pathway that bring disease.

The difficulty with PSC studies is that populations will be limited, so the discovery of genome associations will also be limited and hard to find. It is disappointing that a specific PSC gene has not been found because the majority of genes are shared among a number of conditions. A general risk for inflammation can be conferred to certain genes. A commonality in genes is observed for asthma, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, MS, rheumatoid arthritis and Type I diabetes.

In summary: PSC displays strong HLA association; PSC shares at least 3 susceptibility genes with UC(TGR5, MST1 and GPC5/6); and no PSC-specific genes have been found. Norway is trying to improve research with larger experiments, , and newer and better technology. A major problem is that in the U.S. it is hard to recruit a homogenous PSC population, unlike in Norway and Nordic countries. German PSC patients and controls, for example, are clearly different from that of Norwegians. Lack of homogeneity has to be taken into account in these studies.

As for the limitations of the Genome-Wide Association Studies, the most important one is the limited number of PSC ers that can be recruited. The hope is that in two

years 4000 PSC patients will have been recruited. When compared to Type 2 diabetes studies that have tens of thousands of patients and controls, we can see why we may never find specific PSC genes. It is important to note that there may be many clinical effects "hiding" in other loci that may have closer therapeutical implications than the HLA tower does. The blind-spot of Genome-Wide Association Studies is that only a fraction of heritability of a condition can be explained by variants in statistical association analysis. A huge part of heritability variants cannot be explained. The missing heritability variants could be hiding in rare variants. That is why we cannot use variants found so far to predict disease.

The work of the large Norwegian team of NoPSC, Erik Schrump's leadership and work that go back to the 1980's, the $20 million donation the center received from Stein Erik Hagen, have given huge stimulus to the already expanding research activities at the center (for information on the center and its research, please open "Annual Report 2008", the first item on the google search, http://www.google.ca/search?q=nopsc+oslo+&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:en-US:official&client=firefox-a). Their philosophy for the center is that of international cooperation: The biobank in Oslo, says Dr. Karlsen, belongs to all centers wishing to do research and is not the sole property of the Norwegian PSC group. The center is also active with liver transplantation and cholangiocarcinoma projects. The bar code inventory system guarantees a most reliable system.

Dr. Karlsen ended with the hope that by pursuing the genetics of PSC, pursuing rare variants, performing functional enquiries on biobank material from patients, possibly the cause of this enigmatic disease will be elucidated.

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Q: Dr. Everson: In the diagram showing PSC genes, crohn's genes and colitis genes, you had one PSC gene in common with an ulcerative colitis (UC) gene, but there was no overlap between a Crohn's profile and PSC gene profile.

A. Dr. Karlsen: So far none of this data is surprising. There are some UC genes that overlap with PSC. That corroborates with the idea that PSC plus IBD is different from ulcerative colitis. But we classify it as UC. With Crohn's there may be some genes that we haven't been able to detect yet because of the small number of patients.

Q. Dr. Everson: When you look at colonic infection, we see bacteria stimulating immune response genes and inflammatory genes. But when we talk about PSC without IBD, you don't have that background of colonic bacterial superimposed factors altering immune inflammatory responses. So in a way PSC alone is a much purer condition to study in terms of genes associated with disease progression. Perhaps with PSC there are many secondary gene activations related to bacterial activity.

A. Dr. Karlsen: I totally agree. However, if we were to study PSC patients without IBD, we would have very few patients. PSC is a heterogeneous bag of different diseases, and what we are presently doing is looking at this bag as a whole. There exist different pathogeneses for different conditions within this bag. You can get IBD after a transplant. To say that you will have a PSC patient who will never have IBD is extremely difficult. The phenotyping becomes a problem.

Q. How can we participate in your research and donate samples for your institute?

A. Dr. Karlsen: This is best done on a nationwide basis because of complicated legal, ethical and practical issues. In Germany, participating centers are under strict agreement, otherwise samples are not shared. In the UK, Dr. Chapman's study depends on samples stored in Cambridge. In Scandinavia everything goes to the Oslo bank. Even though PSC groups are working together (STOPSC, the Mayo Clinic initiative led by Dr. Lazarides, and numerous European centers), the Infrastructure for this joint work has not yet been established.

Q. Dr. Everson: Just to elucidate. STOPSC was started by the Morgan family and has run out of money. We, both the adult and pediatric groups at the University of Colorado, are continuing with the project started by STOPSC. We are participating in the kids' urso withdrawal study. Locally, this is one of the STOPSC centers.

Dr. Brian Doctor , PhD, U. of Colorado Division of Gastroenterology and Hepatology, *Biliary physiology in PSC - Important Contributions of Animal Models in Understanding of PSC: Potential role of bile duct choleresis in PSC.*

If you want to find a treatment for a disease, you first have to understand the molecular underpinnings of that disease. The levels of mechanistic studies include, going from complex to simple, 1. human/clinical level, 2. whole animal models, 3. complex culture systems, and 4. molecular/biochemical studies. The less complex the level, the less relevant it becomes for human PSC, and the less we have the possibility for manipulation (Please see PowerPoint presentation). At the human/clinical level, relevance to the population is of course the greatest as these studies are directly applicable to PSC patients. However, on the downside, the disease is rare and consequently studies are rare; the disease is diagnosed later in the clinical course; there is a limited ability to study initiating pathogenic events; and it is a heterogeneous disease with large duct PSC and small duct PSC and other variants.

If we move one step down in the mechanistic ladder, and ask what animal models can do for us, the biggest con is that currently there is no animal model that faithfully recapitulates all the human conditions that we see with PSC. There are a number of pros: Firstly, there are now a large variety of models that may not be perfect for PSC but have many of the same characteristics. Secondly, we can study the full course of the disease, from its pathogenesis to disease progression.

We are investigating how we can use genetically modified mice to study PSC. Focusing on two studies, one using a Cftr knockout mouse and the other using Mdr2 knockout mouse, Dr. Doctor showed how the relationship between IBD and PSC was highlighted and how toxic bile could be an initiator of PSC. (*A knockout mouse is a genetically engineered mouse in which one or more genes have been turned off through a gene knockout. Knockout mice are important animal models for studying the role of genes which have been sequenced, but have unknown functions. By causing a specific gene to be inactive in the mouse, and observing any differences from normal behavior or condition, researchers can infer its probable function. Wikipedia*)

A clear and detailed explanation of the liver on PowerPoint slides followed (*Please see PowerPoint presentation*).

Studying a subset of cystic fibrosis patients who lose the function of Cftr, it was discovered that this subset had a PSC-like phenotype. However, all of these studies are underpowered - less than 20 PSC patients/study. Cftr knockout mice were used to test out the hypothesis. When Cftr remained intact, there were no signs of colitis and PSC when mice were fed colitis-inducing dextrane, but when dextrane was fed to Cftr knockout mice, they developed colitis and profound inflammation of the bile ducts. Bile ducts became inflamed when there was colitis-initiated inflammation.

The Mdr2 study supported the Cftr findings. Wild type mice remained normal while Mdr2 gene knockout mice, experienced bile-duct changes. And to this latter group, when Nor-Urso was fed to them, they remained protected from fibrosis and from the invasion of neutrophils. In summary, while PSC researchers call themselves half-empty guys, discouraged by the absence of definitive mechanisms, effective therapy and ideal animal models, Brian Doctor calls them half-full guys and reminds them that already numerous informative animal models were created out of which PSC can be teased out, and great strides were made in understanding PSC genetic human associations, pathology and immunology.

Steve Helmke. PhD, research instructor, U. of Colorado, ***Biomarkers of PSC.***

Dr. Helmke is a member of Dr. Everson's research group. He reported on a groundbreaking test that could have widespread consequences for PSC.

Dr. Helmke started his lecture by commenting on his title. Biomarker, he said, is a loosely defined term. It includes anything that measures disease. Currently biomarkers for PSC are liver function tests, histology, and earlier, whether the patient has IBD that was considered a risk factor for the progression of PSC. The Mayo MELD score uses biomarkers, and so does the Mayo risk score. These biomarkers have severe limitations, he said. Standard blood tests can vary widely. Biopsy is very invasive, painful and subjective. Sampling errors abound, according to where the samples are taken, and this is especially true with PSC which affects different regions of the liver. Currently biopsies are being avoided. There is a serious need for new ways to assess PSC disease progression. Methods that are more reliable, more accurate are needed. Ideally they should be non-invasive and safe. Currently there are a couple of new methods. One is called Fibroscan, which entails the use of a probe on the abdomen – the healthy liver is very soft and the fibrotic liver is very stiff. This test measures inelasticity. However, it is inaccurate with fibrotic livers and accurate only with cirrhotic livers. Another technique presently in trials, is a breath test. A patient drinks Carbon 13 which is absorbed by the liver and metabolized into C13 and carbon dioxide. The patient breathes into an instrument that measures the C 13, and thus measures the metabolic capacity of the liver. Other such tests display similar weaknesses.

Dr. Everson has developed a new technology, a new approach based on assessment of portal circulation. The advantage of this test is that it can measure patients early on in the disease. The team believes that portal circulation is the key to assessing liver function. As the liver receives injury, blood flow to the liver is impaired. In PSC, this impairment is serious and results in portal hypertension and in the blood being shunted around the liver, toxins not being filtered and in encephalopathy and varices. Dr. Everson and his team believe that all the major PSC complications are due to impaired blood flow and subsequently found a way to measure direct blood flow. Using a stabilized cholate compound (naturally present in bile), specific transporters take this compound specifically into the liver. Also there are

transporters that take it from the intestine into the portal circulation. In order to track the flow, stable isotopes such as Carbon 13 or heavy hydrogen are used. These are naturally occurring isotopes and are not radioactive. They have just been enriched to label these compounds so we can measure them through mass spectrometry. So the test uses safe, indigenous compounds. The C 13 compound is administered intravenously, and this is rapidly cleared by the liver through systemic circulation. This first step serves as the control for the basic capacity of the liver to take in cholate. The patient drinks the second compound which goes through the gastrointestinal tract, is absorbed by the portal circulation, and then taken up by the liver. This process directly measures the portal blood flow. Dr. Helmke is involved in the measurement of these compounds in human serums, while also considering interference from other medications. His aim is extreme accuracy and reliability so as to achieve the requirements of the FDA. The goal is to have this test available for widespread clinical use.

For the patient, this means having a catheter placed in the arm, and at time zero the intravenous dose is administered. Simultaneously, the patient drinks a compound and within 90 minutes, five blood samples are drawn from the same catheter at regular intervals. Within two hours, the patient can leave, without having been sedated and having undergone a very safe test. At the lab, mass spectrometry determines concentrations, which show the clearances of these compounds. The clearance for the intravenous compound is rapid and slower for the oral compound that needs to travel through the gastrointestinal tract before reaching the liver. In a healthy individual, the concentration of the oral compound is very low and 20% of the blood is shunted around the liver. In a patient having a compromised liver, a large amount of the compound escapes the liver and, in the example shown, 67% of the blood is shunted around the liver. Though in the example used by Dr. Helmke, the patient had moderate fibrosis and wouldn't have been tested for varices. The results of this test led to testing for varices, which proved to be serious in this case. In this trial there were 300 patients, and the test was run 500 times. 183 were tested every two years. The results show that,

1.The test correlates well with the extent of fibrosis; 20% for normal individuals, 25% at Stage I, 30% at Stage II and varices can be detected really early on.

2. The shunt measurement correlates with the size of varices in these patients.

3. A new yet unpublished result is the ability of the test to predict clinical outcomes. 183 patients were given the cholate shunt test every two years. When patients had clinical symptoms such as encephalopathy or varices, the shunt test reflected those symptoms accurately.

4. There was no adverse event following the two-hour test. The test is very safe and convenient for the patient.

5. The team believes that the cholate shunt test can be used for predicting disease progression. It identifies patients with risk of cirrhosis, varices. It predicts which patient would not respond to antiviral therapy.

6. Importantly, the test also predicts improvement of disease that responds to antiviral therapy - as in hepatitis - and when disease is gone. We can measure effectiveness of treatment, of the effect of medication over time.

7. The shunt test has great clinical utility in assessing patients with PSC. A shunt test of 35% is associated with significant fibrosis, of 40% is associated with cirrhosis and medium to large varices and predicts clinical decompensation. 45% over 6 years predicts clinical decompensation within two years.

Dr. Everson started a company called HepQuant and is planning to commercially introduce this test, but in the meantime the test is used for research purposes. Dr. Helmke invited physicians to try this test on their patients. In the future the hope is to use this test for therapy trials, as end-point, to measure and track whether patients are getting better when the effective therapies that everyone is hoping and working for arrive.

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Q How can we participate in this test?

A: When we are ready to enroll for these trials, Ricky will announce it in *The Duct,* the PSC Partners newsletter.

Dr. Jesus Rivera-Nieves. University of Colorado, researcher. ***Shared homing determinants between IBD and PSC***

Dr. Rivera-Nieves discussed another way of looking at the relationship of IBD and PSC. He talked about adhesion molecules that allow leukocytes to make it to sites of inflammation, and when they get out of control, they lead to chronic inflammatory conditions such as IBD, PSC, rheumatoid arthritis, multiple sclerosis. This recruitment of disregulated leukocytes plays an important role in both IBD and PSC. As IBD is not only focused in the intestines, its manifestations in different organs in the body show that it is a systemic disease with predominant manifestations in the intestines. IBD affects the eyes (uveitis), joints, skin (erythema nodulosum), and most relevant to us here, the bile ducts in PSC. Consequently, there are some shared pathogenetic mechanisms between IBD and PSC. We find disregulated leukocytes both in the liver and in the intestines in patients having both diseases. The inflammatory infiltrates (leukocytes) consist of granulocytes (basophile, neutrophil, eosinophil), phagocytes (monocytes and macrophage) and lymphocytes (T-cell and B-Cell), the latter of which through a rolling motion evade circulation and escape into the intestines and the liver, and roll back and forth through the body, hundreds of times during their lifespan. These lymphocites acquire memory and re-circulate.

They have "zip codes" that allow them to find their "home" after circulating through the body, all in the span of a couple of hours. The analogy showing the miraculous feat achieved by a leukocyte's motion is that of a hot air balloon which in a couple of hours must find its landing destination on earth. The second miracle achieved by leukocytes is that they are capable of escaping incredible forces with the help of other molecules.

Dr. David Adams in Birmingham has shown for the first time the links between the homing determinants of the liver and the intestines. He showed how the aberrant expression of the adhesion molecule MAdCAM-1, which takes place in the intestine, is also found in the liver of PSC patients. A few years later, Dr. Adams also showed that the CCL25 gene, which is expressed in the small intestine of Crohn's patients, is also expressed in the liver of PSC patients. In IBD many new drugs have been targeting such pathways, (Natalizumab for Multiple Sclerosis and previously for Crohn's until it was discovered that though IBD improved, a virus was reactivated) and if Dr. Adams is right, the same could be done for PSC and some of these inhibitors used for IBD can be tried for PSC. Dr. Rivera-Nieves hopes that European PSC trials will be trying these drugs on IBD.

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Panel Discussion with Dr. Karlsen, Dr. Brian Doctor, Dr. Steve Helmke, and Dr. Jesús Rivera-Nieves

Q & A

A. Dr. Karlsen: Commenting on the previous speaker's presentation - There are some concerns about the specificity of some of these mechanisms. Now we know that MAdCAM-1 is equally high in autoimmune hepatitis as it is in PSC. I doubt the specificity of this phenomenon in PSC pathogenesis. But I definitely believe that the data show the immunological connections between IBD and PSC. **Dr. Lindor** agreed.

Q. For Dr. Karlsen: For patients wanting to contribute blood samples now nationwide, if they participate in the Mayo database with Dr. Lazarides, will that information be automatically shared with your center?

A. Dr. Karlsen: We are already collaborating with Dr. Lazarides at Mayo, and he has already contributed his patients and his controls to the second phase of the genetic susceptibility to PSC study. Each center should voluntarily share its information nationwide in the U.S.

Q. For Dr. Helmke: Is the cholate shunt test a University of Colorado invention and will it be administered in other facilities?

A. Dr. Helmke: Yes, it is a University of Colorado invention and the technology has been licenced to HepQuant for commercially usage. We do want to set-up multi-center trials to be able to widely use it. I would like to stress that the test uses only stable isotopes and doesn't involve radioactivity. It is totally safe.

Q. For Dr. Helmke: Regarding the cholate shunt test, how would the results of the shunt test affect the management of the PSC patient?

A. Dr. Helmke: If, for example, the test results are very high, we would want to increase the frequency of screening. We would use it as a monitoring tool. If the test were to remain stable from one test to the next, that would be very reassuring and show that disease was not progressing and we would maintain the patient's current management.

Q. For Dr. Karlsen: Are you doing studies on twins or multiple births where there is a diagnosis of PSC and IBD?

A. Dr. Karlsen: We are only studying unrelated individuals and comparing them to unrelated controls. In our Norwegian database of approximately 400 PSC patients, we have only 2 or 3 relatives. An important point to stress, that these genetics studies are not tests for genetic testing. In the first place, the risk of PSC is very *very* low, so if the risk is increased by 10-40 times in relatives, that doesn't mean that you have a high risk of getting PSC even if your relative has PSC. However, I believe there are several variants of the disease. There is a subgroup of PSC that is more heritable. In Sweden, for example, there is one family that has 5-6 members with PSC.

Q. For Dr. Karlsen: In diabetes testing for HLA genotypes, how would you respond to a parent who wants to test the siblings of a PSC patient to see whether they have the HLA associated with PSC and whether they are at higher risk?

A. Dr. Karlsen: No, I wouldn't do it because you couldn't tell. You could have HLA associated PSC variants and no PSC and vice versa.

Q. For Dr. Everson: What is the status of organ cloning and pig liver transplants?

A. Dr. Everson: If you had asked me a year ago, I would have said nothing is happening in this country, but now, there is, with the activity in the stem cell research arena. We will probably see in the next few years interest kindling in stem cells for treating liver diseases. Regarding pig livers, there were two types of pigs, one was a complement deficient pig, and the other was a pig raised for donor organs, but that wasn't viable in the U.S. How about Norway?

Dr. Karlsen: We have a 1-month waiting time for liver transplantation in Norway!

Q. If live donor livers regenerate in 60 days, is it not possible to simply remove part of the patient's liver and let it regenerate? Does it regenerate with the PSC?

A. Dr. Everson: Whenever you do a resection on a diseased liver, it tends to regenerate back as a diseased liver and the resection ends up inducing liver failure. There are many different permutations of transplantation. One of them is the "domino transplant": You can use a liver of someone with a genetic disease other than PSC and transplant it into a PSC patient. This genetic disease will take 20-30 years to develop. Another kind of transplantation occurs when someone has acute

liver failure. An auxiliary transplant can be performed on that patient, whereby a liver graft is performed to temporarily maintain liver function. No immunosuppressant is given so that the graft is rejected and the original liver is allowed to regenerate. In special circumstances where liver function is good and perhaps there is regional structuring, focal cancer or abscesses , resectioning could be an effective option and subsequent regeneration of the liver can occur.

Q. What percent of children with PSC and ulcerative colitis contract other immune disorders?

A. The incidence of PSC is too low to have an accurate figure. But everybody knows that a person with one autoimmune disease is at risk for other autoimmune diseases. We have kids with PSC who have vitiligo and other autoimmune skin diseases, autoimmune thyroid disease, among others, but the incidence is not high enough to be able to give you a percentage.

Dr. Karlsen: The adult number is 25%.

Q. Can a healthy individual choose to voluntarily donate?

A. Dr. Everson: It can happen but we discourage it. How about in Norway?

Dr. Karlsen: Again, in Norway we have excellent cadaveric donor access, so we don't do live donor transplantation.

Dr. Everson: We have a very small fraction of "Good Samaritan" donors. We have performed 150 live donor liver transplants at the University of Colorado and probably 2500 live donor liver transplants in the U.S. We have to protect the donor, make sure there is no coercion. We worry about pecuniary issues when the recipient has no relationship to the donor. We have to assure ourselves of the psychological, social and mental health of the donor. To avoid the above factors, we prefer close family donors who have a real relationship to the donor.

Q. What is different about Norway that you have such great success with cadaveric donations? Is it a different system of organ donation?

A. Dr. Karlsen: No, it is similar to your system. We see a difference with Denmark in that they wait three to four times longer than patients do in Norway. I think it's a matter of efficient logistics, the hard work of transplant coordinators who have been working hard to advertise and to increase population awareness among Norwegians. It has nothing to do with the health care system. It's just a matter of being engaged.

Dr. Everson: If we didn't have as many Hepatitis C patients in the U.S., there would be enough liver donors in the U.S.

Q. Though the evidence is anecdotal and we hear that PSC patients fare well on a gluten free diet, can you comment on the basis for an inflammatory response to gluten?

A. Dr. Karlsen: There is definitely an HLA association between PSC and celiac disease. Clearly the celiac disease gene is on the same chromosome as PSC. Some of our patients have celiac disease. If the clinical evidence suggests celiac disease, then definitely gluten should be avoided. Otherwise I would be skeptical. **Q.** Do you see a disease comparable to PSC in livestock animals or other animals?

A. Dr. Karlsen: It wouldn't be PSC but infection cholangitis, that is, secondary cholangitis that mimics PSC.

Ricky and Don Safer concluded the conference. Ricky thanked Sean Colgan for coming up with the idea of holding this conference and Dr. Karen Ross for her role in organizing this meeting. On behalf of PSC Partners, Ricky thanked Dr. Karlsen and his team for passionately working to find a cure at the only PSC Center on the planet and for filling us with hope. She said that PSC Partners would continue to help researchers' efforts by fundraising. And for those who have PSC, she said that PSC Partners would announce each new trial, local or international, on their website, in the newsletter, and on the Yahoo PSC support group sites. **Don Safer** highlighted a question many asked during the conference: What can we do NOW to take part in the testing? Even though there has been a lapse of funding, the University of Colorado is maintaining a semblance of STOPSC that was started by the Morgan Foundation. Dr. Karen Ross said that they are continuing with the NIH-funded children's Urso withdrawal and re-introduction trial which is up and running and is welcoming samples. A member of the audience thanked Ricky and Don for all their great work and the researchers and physicians for their exciting research and excellent presentations.