The Duct

Bringing you news on PSC

research, education, and Support

PSC PARTNERS SEEKING A CURE

PSC Partners Seeking a Cure Foundation Fall 2009 Special Focus

Special Focus Issue:

Oslo and Mount Sinai PSC Meetings, 2009

In this special newsletter edition, we are publishing detailed reports of the presentations from two recent PSC symposiums: the EASL symposium held in Oslo, Norway, June 21-23, and the Mount Sinai forum held September 8. As I mentioned in our Summer newsletter edition, it was an amazing experience to be a part of the EASL international conference where sixteen researchers and hepatologists from Europe and the United States gave presentations on the latest advancements in PSC research. In this edition, Ivor Sweigler of the UK Support Group has kindly shared his detailed report with us. Thank you so much, Ivor and also thanks to Rachel G., who helped with the editing of the report.

Posing at the beautiful Oslo City Hall where the mayor of the city welcomed the conference, are left to right: Nicklas Holmgren, Eve Jedrejewska, Peter Holmgren, Ricky and Don Safer, Ivor Sweigler, Rachel and Abe G.

As background information, the Norwegian PSC Research Center was established May 19, 2008 at Rikshospitalet in Oslo, Norway, thanks to a generous donation from Stein Erik Hagen of Canica A/S. Under the leadership of Drs. Schrumpf, Boberg, and Karlsen, the PSC Center has already established a modern biobank facility in conjunction with a new research database, set up laboratory facilities at the Institute of Immunology and Research Institute for Internal Medicine, and greatly strengthened their international collaboration efforts. They are at the forefront of PSC research internationally. I am pleased that Dr. Espen Melum from the center will speak at our 2010 conference in Hartford.

The September 8 public forum that we held in conjunction with the Mount Sinai School of Medicine, Division of Liver Diseases, was a very successful program attended by approximately 90 PSCers and caregivers. I'd like to thank Allan Luks of PSC Partners Seeking a Cure and Stephen Harris, a PSCer and medical student at Mount Sinai School of Medicine, who both were the impetus to hold this joint forum and to start a PSC support group in the New York metropolitan area. After very informative presentations by Dr. Douglas Dieterich, Dr. Joseph Odin, Dr. Nancy Bach, Dr. Franklin Klion, Dr. Miloh Tamir, and Stephen Harris, there was a chance to network with the physicians, PSCers and caregivers. Don and I were glad to see so many PSC Partners Seeking a Cure members who joined the forum to help us represent our foundation: Karen and Allan Luks, Susan and Scott Malat, Joanne and Steve Grieme, Reggie Belmont, Rachel and Abe G., and Theresa and Nick Valenti. Please take the time to read Rachel G's detailed report of the presentations beginning on page 25. PowerPoint presentations will be posted on our website soon.

The Mount Sinai PSC self-help group is being funded by the Women's Auxiliary of Mount Sinai Hospital. Their first support group meeting is being planned for October 19, from 6-7:30 pm, so if you are a PSCer or caregiver in the New York area, please plan to attend. Updated contact information will be posted on the PSC Partners website or is available by contacting Eileen Solomon at Eileen.Solomon@mountsinai.org.

I'd like to give a special thank you to the physicians who participated in this excellent forum and to the planning committee: Eileen Solomon, Special Events Coordinator at Mount Sinai Hospital, Dr. Odin, Stephen Harris, and Allan Luks. We are pleased to continue this partnership with the Mount Sinai School of Medicine in the future. We're also looking forward to welcoming many of the New York PSCers and caregivers at our annual conference in Hartford, CT, next May 14-16.

Ricky Safer, President of PSC Partners Seeking a Cure

2009 AALSD PSC Research Award to be Given This Fall

Dr. V.S. Teaberry will be the recipient of the PSC Partners-funded award for the most promising research in PSC that will be given at the upcoming American Association for the Study of Liver Diseases meeting. A full abstract will be available later in the fall. Her study is entitled:

Novel Role for Hedgehog Pathway Activation in the Pathogenesis of Primary Sclerosing Cholangitis. Authors are: V.S. Teaberry; G.F.Karaca; R.P. Witek; W. Syn; A. Omenetti; Y. Jung; S.S. Choi; A. Diehl.

Report from the Oslo PSC Conference, 2009

Under the auspices of EASL (European Association for the Study of the Liver)

Summarized by Ivor Sweigler, Chairman of PSC Support UK

This was the really big one, the most important conference on PSC ever held.

Twenty-seven papers were delivered over two days by the world's leading specialists in the research and clinical treatment of PSC. Around 97 doctors attended from Europe, the US, and the Middle East. There were eight PSC patients/caregivers, two from the U.S., three from Canada, two from Sweden and myself.

The meeting took place in one of Europe's most beautiful cities, in perfect weather. The organization was outstandingly efficient and the timing immaculate.

Thanks to the generous donation of 100 million Kroner and the additional 25 percent from the Norwegian Government to encourage scientific research, the Rikshospitalet in Oslo has the only center in the world devoted to the research and treatment of PSC.

I am concentrating here on papers that have more relevance to clinical treatment now or in the foreseeable future. It is not possible in the space available to summarize all papers. That would require a book! So there is a lot of editing in this account. I'm greatly helped by the book of abstracts provided to delegates.

Epidemiology (the occurrence and distribution of disease) and the Natural History of PSC

Dr. Paul Angulo, Gastroenterologist, Mayo Clinic, Rochester, US

(Note from Ivor: Unfortunately, this paper was inaudible on tape and had no available abstract.)

Dr. Angulo went through all the available research in an attempt to establish the incidence (frequency of new cases) and prevalence (total number of cases in a population). This is a very difficult exercise for reasons outlined in the next paper.

But on the evidence available, prevalence is highest in Northern Europe, especially in Scandinavia and in the US, while there is low prevalence in Southern Europe, Japan and most developing countries. These numbers explain why there is little PSC research in Italy, Spain, and Japan. In the developing countries where colitis and Crohn's are also very uncommon, then PSC appears even more rarely, perhaps because the kind of link between the gut and the liver, which characterizes PSC patients, is almost nonexistent in that population.

A Spanish study involving 23 medical centers serving 19 million people found a prevalence of only .02 per 100,000 (Es…cell et. al) which would add up to a PSC population of 800-900. A study in Japan of

388 medical centers revealed only 192 cases in total in 1995. Moreover, in these low-prevalence areas only 30 percent of PSC patients appear to have IBD (Inflammatory Bowel Disease) leading to the possibility that there may be a different variant of PSC in these areas.

The figures from existing studies indicate that for PSC patients in Singapore only 20 percent had IBD; in Japan, 21 percent; and in Italy, 54 percent had the disease.

While in the U.S. and Northern Europe the figure has always been given as 70 percent although it is now accepted that it may be as high as 80 percent or more.

One participant said there is evidence that PSC is increasing in prevalence. This was the impression in Europe. Since it is well known that IBD has been rapidly increasing, it would follow that the result would be an increase in PSC.

For some years Dr. Chapman (UK) has believed that PSC is less of a rare disease than we previously thought. He said the prevalence is probably much higher than is believed. He is about to publish a paper on this topic. Many people with UC have completely normal liver function tests (LFTs). When his patients undergo MRCP, the results reveal PSC-like changes in their bile ducts in 18 percent—a substantial number. These are mostly females of which a high number are smokers. Whether or not what they have could be called PSC, it is important to note that these patients were followed for five years, their disease showed no progression of their PSC, and their LFTs remained normal while their MRCPs showed abnormalities. We do not know what kind of consequences this kind of PSC has on their colon and on getting colon cancer.

Prof. Erik Schrump from the Oslo group concluded that we do not really know the true incidence and true prevalence of PSC. Dr. Angulo agreed.

PSC in Low-Prevalence Areas

Dr. Carlo Selmi, Department of Internal Medicine, University of Milan, Italy

Dr. Selmi said there would inevitably be some overlap between Dr. Angulo's paper and his. He said that the epidemiology is challenging because PSC is rare, often requiring specialized expertise. Therefore, population studies probably underestimate the true prevalence and incidence of PSC. Studies have been limited to specific geographical areas presenting a pattern similar to PBC. These show lower prevalence in Southern Europe, Asia and Alaska (where one study has been done).

In the case of Mediterranean countries this may be the result of a lack of solid data and underestimation of disease impact. He gave the example of his native Italy. There is a very large gastroenterological centre in Northern Italy where they have 3,000 IBD patients.

In working through the data, he could only find 14 cases of PSC, a ridiculously low number. The system does not use MRI imaging or Alkaline Phosphatase but only GGT for testing IBD. And in Italy not all patients have colonoscopies,

which must affect the appearance that IBD is much less common than in Northern Europe. In short, the Italian data is worth very little.

The evidence on the ethnicity of PSC patients is conflicting. He described some unpublished data from Northern California where African Americans were well represented in the PSC population of about 180. Asians were poorly represented. A study in Georgia where there is a substantial African American population found that they had 3 to 4 times higher IBD rates than other ethnic groups but they were most likely to receive a liver transplant (LTX) for Hepatitis C, a high burden for this group and much less likely to be transplanted (TX) for PSC.

He concluded with an appeal for much more accurate population studies and diagnostic markers for PSC to screen a large number of reportedly healthy subjects in a large series. "We can't even agree on definitions."

Pathogenesis (how a disease originates and develops) of PSC

Dr. Michael Manns, Department of Gastroenterology, Hepatology, and Endocrinology, Hannover Medical School, Germany

Dr. Manns said that he just wanted to set the stage for other speakers on this subject. In answer to the question, "What is the pathogenesis of PSC?" The answer is that WE STILL DON'T KNOW. Nevertheless he said he was asked to speak 20-25 minutes answering the question. The audience laughed along with him.

We can first of all discuss some aspects of the pathogenesis. We should look at inflammation, which develops, and this can give us some clues about the pathogen. And there are animal models that should throw light on the mechanisms we have seen in the study and treatment of PSC, a typical process of trial and error. The complex etiopathogenetic mechanisms involve genetic, autoimmune, inflammatory, and infectious aspects. From all these sources we could classify our ideas and approaches.

PSC may be seen as one of three autoimmune liver diseases. (The others are PBC and AIH, which is Autoimmune Hepatitis.) It has been regarded as an immune dysregulated disease in people who are genetically predisposed and also that it is a reaction against infectious agents triggered by this genetic predisposition.

A number of groups, in particular, Peter Donaldson (and associates, Freeman Hospital, Newcastle) have worked on the HLA background (Human Leukocyte Antigen and Histocompatability) of PSC.

On the genetics of PSC: The fact that first degree relatives and siblings of PSC patients have an increased risk of PSC emphasizes the significance of certain genetic predispositions. But the genetic architecture is complex and is based on the combination of multiple HLA and non-HLA genes (histocompatibility antigens: a group of proteins that have an essential role in the immune system. The antigens guide Killer T-cells into recognizing and killing foreign cells. Certain HLA types occur more frequently in particular diseases, including PSC.)

The fact that there is a higher risk of rPSC (recurrent PSC) after LTX in those who receive live donor liver transplantation from first-degree relatives is a further indication that genetics plays a role. But the genetic risk is weak, the architecture complex and involves HLA and non-HLA genes. There are now several groups across the world involved in genome-wide screening in PSC. Then we go back to the lab and look at genome analyses. There is a genetic association either with a risk of developing PSC or being protected against that risk. But the association is weak and certainly cannot explain all the genetic factors of PSC.

Then it still has to be considered whether PSC is an autoimmune disease. We have this clear picture of IBD involved in over 70 percent of PSCers (in Northern Europe and the US) and with the overlap syndrome AIH described by the London group (that is, Professor Mieli-Vergani and associates), especially in children. In addition we have the increased frequency of other autoimmune diseases, outside the liver, suffered by PSCers. Certain autoantibodies (an autoantibody reacts against the body's own cells) are increased in PSC compared to controls but they are very heterogenous unlike other autoimmune diseases. PSC does not respond to immunosuppressive treatment. It is also 2 to 1 male predominant, unusual in autoimmune diseases which are mostly female predominant.

The concept of PSC as an inflammatory reaction to infectious pathogens has not been confirmed by clinical data. Infectious agents probably do not directly cause PSC, but may activate an immune reaction by an enterohepatic (gut to liver) lymphocyte circulation. In addition bacterial or even fungal infections of the bile ducts are common in advanced PSC and probably accelerate disease progression. Helicobacter Pylori (a bacterium that is a main cause of peptic ulcers) has been found by several investigators in the gut of PSC patients, but this is not particular to PSC.

Since PSC is a cholangiopathy (disease of the biliary system), there has been research on the cholangiocytes (biliary cells) which are a primary target of the disease process: that is, in experiments with mice and the knockout of MDR2 (a gene which encodes a phospholipid transporter in the biliary system), then this leads in mice to hepatobiliary changes that resemble human PSC. The corresponding human MDR3 gene did not show significant variations in PSC patients, but this could be a valuable model for some pathogenetic and therapeutic principles in PSC.

Then there is the question of whether the inflammatory consequences that develop against infective agents in genetically predisposed people are a PSC trigger. There have been animal studies that indicate that this is particularly relevant because of the close association of PSC with IBD. Pathogens may enter the portal circulation causing damage in IBD and produce an autoimmune reaction and bacterial overgrowth leading to bile duct strictures. But studies with PSC patients have not shown significant bacterial growth.

Dr. Adams and the Birmingham group have documented the passage of leukocytes from the gut to the liver (where they can be seen to attack bile ducts), and long-lived memory cells enter the hepatic circulation and can then trigger hepatic inflammation. But this does not explain PSC in the absence of IBD and why most of those who have IBD do not suffer from PSC. The development of IBD does not correlate with the severity of PSC. (They are independent diseases with their own separate progression.) PSC can even develop after colectomy.

More recently the role of toxic bile acids that damage cholangiocytes is being studied (especially by Professor Trauner and colleagues.) But this cannot explain the overall spectrum of PSC.

I hope I have been able to show you that nothing is sure in the pathogenesis of PSC, that we have a number of hypotheses, which will be presented by other speakers. No single hypothesis will be relevant to all PSC patients. There is certainly a genetic susceptibility. We will await the final analysis of genome-wide screening. We certainly have an interesting hypothesis on gut-derived lymphocytes and saturation in the liver.

I believe that this is the most interesting liver disease we have been studying.

Pathogenesis of PSC II

Dr. Michael Trauner, Laboratory of Experimental and Molecular Hepatology, Medical University of Graz, Austria

Dr. Trauner has been studying bile acids in PSC for some years using knockout mice and the derivative of Urso, nor-ursodeoxycholic acid, on mice with induced PSC-like disease. The results are an improvement on urso. This is not new: nor-Urso (nor-UDC) has been used in experiments since the mid-1980's but Dr. Trauner has applied for a license from the manufacturers to use it in human trials. Nor-Urso has been used on several volunteers and the results have been an improvement on Urso in its effects on bile-flow and biliary lipid excretion. (Dr. Fickert, an associate of Dr. Trauner, who presented a paper at this conference, has found with mice, treated with Urso and nor-Urso, that nor-Urso was an improvement in every aspect. It increased the hydrophilicity (definition: having a strong affinity for water: tending to dissolve in it) of biliary bile acids: stimulated bile flow with flushing of injured bile ducts; induced detox and elimination routes for bile acids. P. Fickert et al. *24-norUrsodeoxycholic acid in the Treatment of Sclerosing Cholangitis in Mdr2 Knockout Mice,* Gastroenterology, Vol. 130, Issue 2, pp.465-481, 2009.)

Apart from the main detergent function of bile acids (BAs) in the digestive system in the process of absorbing food and lipid digestion, BAs also have signaling functions for several processes including hepatic and extrahepatic inflammation and carcinogenesis (cause and development of cancer). We have new insights into these processes and into inflammation driving fibrosis in the liver and biliary system and carcinogenesis. This may be particularly relevant for the cause of PSC and frequently associated malignancy in the biliary tract, colon, pancreas, and liver.

But bile acids have both malign and benign effects. Older studies concentrate on the pro-inflammatory effects but more recent work indicates that BAs can have anti-inflammatory effects, immunosuppressive effects. Of course, we do not know whether this helps PSC.

On the other hand, hepatocellular accumulation of high BA levels in cholestatis (stagnation of bile in the bile ducts, especially when we have dominant strictures) is clearly cytotoxic, contributing to inflammation and inflammation-driven cancer. But lower non-cytotoxic concentrations of BAs could have anti-inflammatory effects on hepatocytes (liver cells). So leaking BAs and retained BAs can contribute to immunosuppression. Of course, again, we do not know whether this helps PSC.

Cancer and bile acids: Again we have to integrate information about bile acids, some of which is quite old with recent insights. Bile acids have been linked to several types of cancer including cancer of the liver. It is a double-edged sword. Bile acids have both pro- and anti-inflammatory properties. We need more mechanistic evidence about cancer and liver injury in PSC. Some BAs may be beneficial in PSC.

A question was asked: It is proven that those with IBD and PSC have a higher risk of colon cancer (than with IBD alone). Can you see any prevention?

Dr. Trauner's answer: The short answer is, I haven't a clue. Of course it would be extremely attractive if we knew that this was due to toxic bile. (Because then we might be able to do something about it.)

Dr. Mann also answered: Of course there is also the possibility that while Urso might not do much for PSC, it may reduce the risk of colon cancer. The question is, what is Urso actually doing to toxic bile acids?

Dr. Trauner responded: The cholestasis of the patient, added to the exposure of bile acids, adds to the cancer risk, but to the best of my knowledge, it has not been worked out properly that the risk of cancer correlates with the degree of cholestasis in PSC. I think that would be one of the best things we need to look for. That's a good point.

The conclusion and a summary of the session would be the following: BA retained in cholestasis or leaking from injured ducts, may contribute to inflammation and carcinogenesis in PSC. Therapeutic strategies may aim at modifying BA pool composition, (e.g. Urso and its derivative nor-URSO) or may be directly targeted at BA receptors and signaling pathways, (e.g. PXR and FXR ligands.) The news was that Dr. Trauner will soon be able to proceed with a human trial of nor-Urso.

PSC in Children

Dr. D. Black, Pediatric Hepatology, University of Tennessee Health Science Center, Department of Pediatrics, Memphis, US

If PSC is a confusing disease in adults, it is even more so in children. Are they the same disease? The clinical course is different. Is it part of a continuum to adult PSC? Dominant strictures, recurrent cholangitis and CCA (bile duct cancer) are rare in children. One third will need LTX by early adulthood. There are other diseases that can mimic PSC. In childhood it is a very active autoimmune mediated disease with bile duct injury as it moves into adulthood. Very often it is seen as AIH (Autoimmune Hepatitis) and it may overlap with PSC.

As the patient enters adulthood, does it become a burned out stage of AIH with progressive damage from fibrosis, nutrient deficiency, bile duct distortion, and recurrent bacterial cholangitis? It then looks like PSC progression rather than continued AIH activity. The childhood diseases that can cause (or lead to) sclerosing cholangitis are extensive and include biliary atresia and cystic fibrosis. Biliary atresia is the most common reason for pediatric LTX and is really a type of sclerosing cholangitis. Thirty to fifty percent of children with PSC have a disease similar to that of adults.

We (STOPSC) are attempting to create a database with cohorts of 300-400: a basis for further studies including clinical trials.

The clinical features? There are no good numbers on prevalence. Incidence (new patients) is about one-fourth to one-fifth the incidence of adult patients. There isn't the male predominance; some studies report a female predominance. The median age of diagnosis is thirteen. IBD is within about 55 percent, mostly Ulcerative Colitis.

But there is a wide range: jaundice is not part of the presentation. Symptoms include fatigue, weight loss, abdominal pain, and pruritis. Typically, children may be asymptomatic and the disease has been picked up through blood tests. One third will require liver transplant by adulthood. About one third have large duct disease, and one third have small duct disease. About one third have PSC/AIH overlap syndrome—it is about 5 percent in adults.

We have to be cautious with these figures because there have been no prospective trials. Hard end-points such as portal hypertension, death, or liver transplant are not practical in children: Trials may have to run ten years or longer and hit the same end-points as adult trials. Pediatric PSC is more often associated with autoimmune features than is adult PSC.

There may be a unique subset of PSC/AIH overlap, "autoimmune cholangitis," that has a better response to immunosuppression and a better prognosis. But reliable criteria for overlap syndrome (histology, autoimmune markers, etc.) have not been conclusively established, especially for children. They are more responsive to Urso therapy. But we need reliable diagnostic criteria. Children do better with liver transplants than adults in the first year, but recurrence is 27 percent and may be higher. Professor Mieli-Vergani reports 67 percent.

PSC Overlap Syndrome

Professor Georgina Mieli-Vergani, Professor of Pediatric Hepatology,
King's College Hospital, London, UK

As you know, I'm a pediatrician, but I also represent an overlap between childhood and adult hepatology. There are different causes for Sclerosing Cholangitis and in fact one of them is what I call "Sclerosing Cholangitis without a Clue." This is the only one I call "primary."

What I want to talk about is what you call overlap syndrome but I prefer to call Autoimmune Sclerosing Cholangitis. We came to the conclusion some years ago that children who were being diagnosed as having Autoimmune Hepatitis actually had Sclerosing Cholangitis although we did not call it that then. *But* in all these studies, including my own, cholangiography had not been performed.

Since I have a very simple mind, I designed a very simple study. We aimed to investigate and differentiate what we then decided to call Autoimmune Cholangitis and AIH (autoimmune hepatitis), whether AIH could progress to PSC and what the response to treatment was. All children presented to us with a liver disease and serological features of autoimmune disease, autoantibodies with or without high IgG after excluding causes of liver disease. All of them underwent cholangiography, sigmoidoscopy, biopsy at presentation. And we repeated the cholangiogram, sigmoidoscopy and liver biopsy, etc. a while later.

This was a prospective study done over sixteen years. Half the children studied had changed bile ducts characteristic of SC but less advanced than in adult PSC. Hepatitis was present in all, while features of bile duct involvement were often absent. In the juvenile form of SC, treatment with steroids such as azathioprin, akin to that used in AIH, is beneficial in abating the inflammatory lesions, though it is less effective in countering the bile duct disease which progresses over time in about 50 percent of cases. At a median follow-up of 13 years (range 8-29 years) from the onset of the trial, those with SC needed a LTX or died more frequently than those with AIH. But recurrence occurred in two thirds of those with liver transplant.

"The juvenile form of SC, characterized by unambiguous serological and histological features of autoimmune disease and responsive to immunosuppressants, could represent the early stage of some adult primary sclerosing cholangitis. Contrary to juvenile PSC, adult PSC has an insidious onset, being often completely asymptomatic and could represent a late 'burn out' stage of the same condition, too advanced to respond to treatment…"

Lessons Learned from IgG4-Associated Cholangitis

Dr. Ulrich Beuers, Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, the Netherlands

(Note: IAC = IgG4-associated Cholangitis; AIP = Autoimmune pancreatitis)

IgG4: Immunoglobulins, abbreviated Ig, are antibodies, proteins in the blood used by the immune system to identify and neutralize or destroy foreign objects such as bacteria, viruses, etc. Five different antibodies or immunoglobulins have been identified. They perform different roles and help direct the appropriate immune response for each different type of foreign object they meet. IgG is the most common by far. As always things get more complicated! And there are subclasses like IgG4. Deficiencies and elevations of IgG are associated with many autoimmune diseases as well as allergies. And there are many immunodeficiency syndromes, defects of the immune system, so that now PSC is called an immunedysregulated disease.

With most PSCers IgG4 readings are normal, but in a significant minority, about 10 percent, they are elevated, and recent findings indicate that, if so, the prognosis may be worse. Most importantly, this can be treated with steroids while classic PSC cannot. If this is not correctly diagnosed, patients who could be treated, will remain untreated. This is another reason to be a patient in a liver center, NOT in a general practice, where they may not have specific knowledge and experience.

"A small proportion of PSC patients had elevated serum IgG4. In these particular patients, parameters of liver disease severity were more pronounced, and time to liver transplant was shorter, suggesting a more severe disease course. It is possible that this subset of patients behaves similarly to autoimmune pancreatitis patients with biliary strictures, and could potentially respond to corticosteroids. Testing PSC patients for IgG4 and treating those with elevated levels with corticosteroids in clinical trials should be

considered." (F.D. Mendes … K.D. Lindor. "Elevated serum IgG4 Concentration in Patients with PSC," *American Journal of Gastroenterology,* 2006, 101, 2070-75*)*.

Dr. Beuers said that the criteria for diagnosing IgG4–associated cholangitis was only proposed last year so don't expect too many lessons in the next twenty minutes. It is not such a new disease. Already in the early 1960s there were reports of IgG4-related systemic diseases (affecting the whole body rather than just a specific part).

In 1995 autoimmune pancreatitis (AIP) was seen as the main manifestation of IgG4-related disease. In 1999, four cases of sclerosing pancreatic cholangitis (now called AIP) were treated with Prednisolone by the Utrecht Group with considerable success, improving both intrahepatic stenosis (inside the liver) and extrahepatic (outside the liver) stenosis, using Prednisolone and Azathioprin. In 2001, there was a landmark paper and the main characteristics of Autoimmune Pancreatitis were identified. This is a recently defined disease with some similar features to PSC. *But*, unlike PSC, AIP responds to immunosuppressives, is not associated with IBD and mainly affects males over sixty.

IgG4-associated cholangitis is now seen as one variant of IgG4-related systemic disease of which AIP (autoimmune pancreatitis) is the most studied. The causes of IgG4-related disease are unknown. The most frequent symptoms include jaundice (75 percent of patients), weight loss (over 50 percent), mild to moderate abdominal pain (25 percent), steatorrhea (15 percent had pale colored fatty stools, also seen in pancreatitis and celiac disease), diabetes type II (8 percent), in the largest group of patients so far reported.

Diagnosis is based on biochemical, radiological and histological features, including elevated serum levels of IgG4, intrahepatic biliary structures, sclerosing infiltrations of the liver and bile duct tissue and association with autoimmune pancreatitis. A Japanese study (Nishino T. et al, "Clinicopathological Differentiation Between Sclerosing Cholangitis with Autoimmune Pancreatitis and PSC,"*J Gastroenterology*, 2007, 42:550-9) compared clinical features of IAC and PSC.

It was found that in IAC, there were more segmental strictures and strictures of the distal bile ducts (large ducts outside the liver) compared to the typical band-like strictures with a beaded appearance in PSC patients. Comparing liver biopsies, fibrous, obliterative cholangitis was seen only in PSC. In the IAC patients there was abundant IgG4 positive plasma cell infiltration which is typical in IAC. There were significant differences between IAC and PSC in age of onset, occurrence of diabetes type II, IBD and salivary gland swelling as well as IgG4 levels.

Immunosuppressive treatment may be effective in IAC, in reducing inflammation in contrast to PSC. Complete long-term remission after 3 months treatment has been reported. We must look more carefully at our PSC patients to understand the increase in IgG4-associated cholangitis and its differences with PSC.

The role of IgG4 remains unclear. Is this a bystander or a major component of the causes leading to IAG? We don't know. It is not a typical autoimmune disease. It is more in line with an allergic-type disease. And we don't have long-term data.

(Editorial comment: The literature on AIP and IAC has been increasing since it was first discovered in Japan in the mid-1990s. It has been recognized that chronic pancreatitis, usually caused by alcohol consumption, could also be caused apparently by an autoimmune condition: Since then it has been recognized as a world-wide problem. The Mayo Clinic in Rochester is studying a large group of AIP patients. In a patient information sheet, they say "the immune system mistakenly attacks healthy pancreas tissue, causing inflammation and hardening. Symptoms closely mimic pancreatic cancer . . . but the disease process is different. Other parts of the body can be affected, bile ducts, salivary glands, kidneys, aorta, etc." *Mayo Clinic Overview Autoimmune Pancreatitis*.

Recently in the U.S. media it was reported that a woman underwent surgery for cancer of the pancreas as the result of misdiagnosis. She had no malignancy but AIP. And most recently, George J. M. Webster, Pereira, Chapman, ("Autoimmune Pancreatitis/IgG4 Associated Cholangitis and PSC – overlapping or Separate diseases?" *J of Hep 51 (2009) 398-402*), conclude that AIP/IAC is probably not a new disease but "has masqueraded as others, and has been both under-diagnosed and, in some cases, wrongly labeled as PSC." Distinguishing between biliary involvement due to AIP/IAC and classic PSC is not just an academic exercise because AIP/IAC can be treated while PSC cannot.

It remains unclear whether PSC and AIP/IAC are separate conditions or variations of the same disease spectrum. This "reinvigorates the issue of the role of immunology in these conditions.")

Warnings about misdiagnosis are not that new, particularly from Japanese researchers, for example: "To avoid futile surgery in relatively elderly male patients with obstructive jaundice suggestive of pancreatic carcinoma, pre-operative clinical suspicion of AIP is mandatory. Indications of steroid therapy for AIP are thought to be obstructive jaundice due to stenosis of the bile duct, other associated systemic autoimmune diseases and DM (diabetes mellitus) coincidental with AIP." (T. Kamisawa et al., "Treating patients with AIP: Results from a long-term follow-up study," *Pancreatology.* Vol 5, no. 2-3, 2005)

Cholangiocarcinoma: Cancer of the Bile Ducts (CCA)

Three papers were presented to the meeting on this subject, two from the Mayo Clinic, Rochester, Minnesota, where, since 1993 Dr. Greg Gores and colleagues have developed a program for selected patients. It isn't easy to get into this program because there are strict criteria for inclusion, including age, size of tumor (less than 3 cm), etc., and any evidence that the tumor has spread, as it often does, into the lymphatic system, is an immediate contraindication. The tumor is first eliminated by powerful irradiation, chemotherapy and brachy-therapy (a type of internal radiotherapy), followed by liver LTX. The success rate is very impressive. One hundred eleven patients have undergone this program to date with 72 percent surviving five years. Other liver centers have begun to adopt this program or variations of it.

Cholangiocarcinogenesis

Dr. G.J. Gores, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, US

Most of the cases of CCA occur very rapidly, about four years after the diagnosis of PSC. CCA is extremely complex and quite confusing. The factors include bile acid leaks, pathogens, injury

to the bile ducts, a whole host of innate disease cells, etc., and inflammatory cells can do various things and this is part and parcel of CCA. And there are also genetic mutations and oxidative stress.

Dr. Gores mentioned Virchow's Hypothesis of 1863. "Lymphorectular infiltrates of cancer reflect the origin of cancer at sites of inflammation (i.e. the link between inflammation and cancer, the sites of inflammation in the colon, if we have IBD, and in the large bile ducts, are where we have cancer risks. Note that in small-duct PSC, which about 5 percent of us have, and in PBC, which is a small-duct disease, cancer is rare.) See "Inflammation and Cancer. Back to Virchow?" *The Lancet,* 24 May 2001.

But he also went into some detail on genetic factors and work in the Mayo labs. Apart from inflammation predisposing to the development of cancer, ILG appears to be a potent cancer-promoting inflammatory mediator; most cholangiocarcinomas over-express chomosome-7 which contains the ILG gene.

Surveillance and Early Diagnosis of Cholangiocarcinoma

Dr. Kirsten M. Boberg, Oslo University Hospital, Rikshospitalet, Oslo, Norway

The risk of CCA varies from 6 to around 20 percent depending on the patient population studied. Patients are usually young, in their 40s. Unfortunately most patients present with advanced cancer when treatment options are limited and prognosis poor. The aim should be to detect premalignant changes or early stage CCA when the cancer has not spread so that liver transplantation can be carried out before invasive cancer has developed.

We have no reliable prognostic markers to identify those at most risk. Genetic variation of the natural killer cell receptor G2D (NKG2D) has been associated with CCA susceptibility.

CCA is suspected when there is rapid clinical deterioration with abdominal pain, weight loss, jaundice, and pruritis (itching). Even when the cancer is advanced, it can still be difficult to differentiate malignant from benign lesions. The approach to diagnosis includes clinical evaluation with imaging modalities, serum biochemistry, histopathology/cytology, and molecular investigation. Ultrasound, CT scanning, and MRI can all reveal features indicative of CCA, especially the presence of mass lesions. But all these methods have limited ability to discriminate between benign and malignant bile duct strictures, and they do not detect very early stage tumors.

We still don't have a blood test with high sensitivity and specificity for detecting CCA. CA19-9 is most widely used. At a cutoff of 129U/ml, a sensitivity of 79 percent and specificity of 99 percent have been reported. But the cut-off levels have only detected advanced cancer.

The development of CCA is considered to follow a dysplasia (any abnormal cell features) tumor sequence. Systematic brush cytology sampling from bile duct strictures in PSC can have rather high sensitivity and specificity in the detection of malignant cholangiocyte changes. But conventional cytological assessment is often difficult and supplementing methods are needed. Fluorescence *in situ* ("in

place" i.e. a malignancy that is cancerous only in its surface cells and hasn't spread), Hybridization (FISH), and digital image analysis (DIA) detect chromosomal abnormalities and can enhance the diagnostic accuracy of brushing. Brush cytology technique does have the potential to diagnose CCA in situ. We in Oslo currently refer PSC patients with high grade and also low-grade dysplasia without evidence of advanced disease for liver transplantation.

In spite of high risk, there are no established guidelines for CCA surveillance, not with respect to patient selection, timing, or methods. At our center we currently recommend that (1) asymptomatic patients should be followed with serum biochemistry, including CA19-9 every 6 months. If we see a significant rise in bilirubin and/or CA19-9, referral for ERCP with brush cytology should be considered, and, (2) patients with a rapid deterioration of symptoms should be referred for ERCP without delay.

A physician commented: It would be really fine if we could divide patients into those who are most likely to develop CCA and those who are not. We are unable to confirm the Swedish finding that CCA occurs within a year of diagnosis because almost 50 percent of our patients are totally asymptomatic on diagnosis. So it really depends when you do the surveillance. But the comment is that we do brush cytology for every patient because the tumor markers cannot identify the sub-group who you refer for ERCP. So I think the only way is to do these systematic brushings and then act according to the findings. We have given up MRI for surveillance. It doesn't give us anything. It is a waste of money.

Colorectal Malignancies in PSC

Dr. Annika Berquist, Karolinska University Hospital, Stockholm, Sweden

PSC patients with IBD are at increased risk of colorectal cancer compared with those who have IBD alone. PSC is today a well-accepted risk factor for colorectal dysplasia in UC (ulcerative colitis). This risk increases with IBD duration. Colorectal dysplasia has been reported in as many as 30 percent of PSC patients after 20 years and 50 percent after 25 years of IBD in comparison to the corresponding risks of 5 and 10 percent in patients with UC alone.

We don't know why. In PSC the decreased bile acid excretion and relatively high proportion of secondary bile acids may play a role in the carcinogenesis of colorectal mucosa. This is supported by the fact that the cancers in PSC patients are more often located on the right side of the colon. Two reports have shown that treatment with Urso decreases the risk of colorectal dysplasia in those with PSC and UC (Pardi D.S., GE 2003; 124, 889-893: Tung B.Y. Ann. Inter Med. 2001; 134, 89-95.)

Treatment with Sulfasalazin/5-aminosalicylic acid (5-ASA) may decrease risk of colorectal cancer in those of us with UC. But the risk is still larger in those with PSC and UC compared with UC alone.

Surveillance programs for preventing colorectal cancer are widespread, but their effectiveness has been questioned. We need to identify patients at greatest risk, and PSC patients are such a group and we

should have annual colonoscopies following diagnosis. This risk remains after liver transplant, and colonoscopies should continue with regularity.

In summary, the risk of colon cancer with PSC is high. The risk may be reduced by treatment with Urso and well-performed surveillance with annual colonoscopies in this group is warranted.

Dr. Chapman commented that his experience with Crohn's Disease and colonic dysplasia is completely different. He indicated that in Oxford he has 59 patients with Crohn's and PSC, and remarkably there was not a single case of dysplasia over a ten-year follow up period. Whatever the role of Urso, he asked how many patients with PSC and Crohn's who have dysplasia are on Urso.

Ursodeoxycholic Acid for the Treatment of PSC: Who Benefits?

Dr. Keith Lindor, Mayo Clinic, Rochester, US

Dr. Lindor has been involved for many years in a variety of PSC trials, including trials on Urso for PSC. In his latest trial of 150 patients, divided into Urso and placebo treated groups, the Urso group was given high-dose, 30mg/kg/day. Until now, and even now, Urso has been considered a very safe drug with few side effects, none of them serious. But to everyone's surprise, those in the Urso group with advanced disease tended to do worse than those in the placebo group. Some became very ill and several had to be rushed to liver transplantation.

This caused shock waves throughout liver treatment centers. Some doctors stopped prescribing Urso and others reduced the dose. It should be said that it is unusual to give a dose as high as 30mg/kg/day. High dose is considered to be in the range of 20-25mg, and absorption studies have shown that at this level adequate amounts of Urso reach the gut. Higher levels lead to saturation. It is questionable whether Urso is of much use to patients in Endstage 4 PSC and in this trial 30mg/kg/day seemed to have tipped some of these patients into liver failure.

It should be stressed that no other liver centers have had such results, and those centers that have been prescribing high-dose Urso for two decades report low colon cancer and bile duct cancer rates. Dr. Lindor remains unconvinced by such clinical evidence. It appears that he is not currently prescribing Urso to his patients unless they request it.

He began by describing past Urso trials, the details of which are familiar to us. Most of these studies show improvement in liver biochemistries and improved histology as well as cholangiograms but none have produced convincing evidence of longer survival and/or time to liver transplant.

This latest study drew 150 patients from a number of liver centers, and they were dosed with 28-30mg/kg/day over 3 years. They also showed greater biochemical improvement compared to the placebo group. There were multiple endpoints: progression to cirrhosis, CCA, and need for liver transplantation or death.

Surprisingly more of the Urso group reached these endpoints than the placebo treated patients. The risk of death or liver transplantation as single endpoints were higher than in the placebo group. "Long-term, high dose Urso, although associated with improvement in liver tests, has not been associated with improved survival and is not recommended at this time." This, in spite of the fact that Dr. Lindor admits that Urso may have

benefit in reducing cancer risk, (and Urso should be taken for this reason alone). He mentions the Washington study showing reduced risk of dysplasia, the Cleveland study and Mayo's own study from the original PSC trial in which there was a several-fold reduction in the risk of dysplasia. Cancers were rare. (Pardi D.S… Lindor, K.D. *Gastroent* 2003; 124: 889-893*)*.

In a further description of the trial, he explained that patients represented a broad cross-section across the country. (Recruitment was not just from the Minnesota area, the usual state from which Mayo recruits its volunteers for trials.) Seventy percent of the patients were at Stage 3 or 4 of the disease and the Mayo Risk Score (MELD) was lower than in the earlier Mayo trial. As expected, liver biochemistry improved, but nevertheless accumulation of endpoints was more rapid in the Urso group compared to the placebo group.

"So this has been somewhat of a quandary for us to explain." Patients with more advanced disease on entry to the trial were more likely to approach the endpoints sooner. That was a surprise. The histological data, the biochemical improvement, the state of IBD, could not have led to a prediction of these outcomes. An independent review of the data and re-analysis has not provided the answers.

It is safe to say that Urso improves biochemistry but does not improve survival. Unfortunately, with advanced disease it can produce serious adverse events. One of our goals is to better understand why this happened so that we can better understand the role of Urso treatment for PSC.

Questions to Dr.Lindor:

Q: What were the main reasons for referral to LTX or death?

A: I think it was just advanced liver disease. The usual criteria: bilirubin level, ascites, etc. We didn't have many patients with CCA in this series.

Q: What was high dose Urso?

A: This study used 28-30mg/kg/day. The initial study used 13-15. The Scandinavian study, 17-23: so a broad range.

Q: In the high dose Urso group you had more females than in the placebo group. These people may have had autoimmune features. Have you looked for these features and the progression of disease, and have you been able to analyze the data for sex?

A: We did look at this. We didn't see a difference in gender. I can't answer the question on autoimmune features. Most of these patients didn't have many autoimmune features.

We have just received new data on blood tests, but I haven't had the chance to ask some questions on the analysis that has been done.

Q: Did you do any bile acid analysis?

A: We are looking at this. New data have been received: similarly with IgG4: sera are being collected.

Q: Can you explain the difference between the first and second Mayo study?

A: That is one of the concerns we have and why we are interested in bile acid analysis. High dose will deliver more Urso to the colon. With bacterial action this may change into more toxic bile.

Q: If you looked at those who reached the endpoints, presumably at some point their LFTs began to decline. Do you have any idea of the interval? If it was just three months, you might

assume it was just bad luck, but if there were consistent intervals across the endpoints, you might get an idea of the length of therapy that may be relevant to the development of toxicity. Have you had a chance to have a look at that?

A: We did initially. We need to look at it more closely. One of the things we wanted to know is that the patients who developed varices, in particular, did not seem to be associated with a worsening in biochemistry.

Q: On the question of Urso being absorbed in the intestines, do you have any ideas about that?

A. We don't. One of the things I wished I had done was to look more carefully at colonoscopy results. We haven't looked at the colonoscopy reports. Every time we want to look at something, we have to reprocess the data.

(Editorial comment: Dr. Lindor is to publish an article in a forthcoming issue of *Journal of Hepatology*, and there is to be an editorial by Dr. Chapman of the UK. Meanwhile PSC patients and their doctors have to decide what to do. Many of us are ignoring this study and continuing to take 20-25mg/kg/day on the grounds that no other studies have produced such surprising results. Others are more cautious and are reducing their dose. Meanwhile nobody appears to be in a hurry.)

Endpoints and Design of Future of PSC Trials

Dr. Roger Chapman, Oxford Radcliffe Hospital, UK

The topic is a difficult one, and I'll take you through the problems in the past and potential solutions in the future. Our ultimate aim is to cure the disease by medical therapy.

I have to say that the past has been a liturgy of failure. The results of trials by Dr. Lindor, Dr. Chapman,and others have been disappointing after thirty years of studying PSC and trying to find the pathogenesis. It gets very hard to design good trials. Looking at the natural history of the disease, it can be symptomatic and asymptomatic over a long time-span. Half the patients who are symptomatic reach the end point within 10-12 years.

But with asymptomatic patients 75 percent are still well and alive after 15 years.

These are the things you have to take into account when you design your study, and when it is a rare disease, it makes it even harder. And then the disease fluctuates very considerably for no discernable reason, unlike PBC (Primary biliary cirrhosis, which usually follows a regular course so that a more accurate prognosis can be made). This makes it difficult to design markers for this disease. The complications are very difficult to predict. It is virtually impossible to produce an accurate model to predict what is going to happen to the patient. Then we have the problem of strictures, malignancies, bile duct sludge, and also the complications of IBD. *This makes it a bit of a nightmare to research and study.*

On Urso: Slides were used to review previous PSC trials. Most of them are under-powered and too short. There is some possibility that Urso affects survival, but you don't expect to find much evidence in short trials. There is a clear trend in favour of Urso in moderate doses, 17-23mg/kg/day. Five years is too short, and there is a strong possibility of false negative results.

With a high dose of around 20-25mg/kg/day, Urso reaches a plateau. You can perhaps argue that high doses might lead to the possibility of toxicity in retrospect. But Dr. Lindor's study, using 28-30mg/kg/day, is a really surprising result.

How do we rationalize this trial? One clearly has to agree with Keith Lindor that high dose is not indicated because of the possibility of toxicity but we do know that Urso is safe at more moderate doses. When considering future trials, we require large sample size and/or long duration of therapy, which is very difficult in rare diseases.

We need this to assess effects on survival. Multicenter, randomized control trials remain mandatory (Since patients are aware that Urso may be beneficial, patients in a trial, may be unwilling to forgo such potential benefits for long periods. There is then the possibility of non-compliance, something suspected in the large Swedish study.) We need to take into account symptomatic and asymptomatic patients and need to exclude IgG4-associated cholangitis (probably a different disease) and those in end stage disease. We also need good surrogate markers. We are not really there at the moment.

In the light of the difficulties in carrying out these trials, pilot studies remain crucial, particularly in an uncommon disease, to assess potential new therapies. These can be improved by careful selection of phenotypically pure patients. We should include serum markers for fibrosis as well as standard LFTs and possibly prospective MRCP studies.

Norurso (NorUDCA, the C23 homologue of UDCA) is potentially, a very exciting compound, is more potent than Urso in an experimental mice model of cholangitis and cholestasis. It can prevent cholestasis completely. Two human studies are about to begin.

There is a great interest in targeting the nuclear receptors involved in the adaptive response of hepatocytes (liver cells) and cholangiocytes (bile duct cells) to cholestasis. These receptors include FXR, PXR, CAR and PPAR. The agonists of PXR and FXR appear to have most potential in the treatment of cholestasis. These agonists are now available for clinical use. In terms of cholestasis they offer hope in PBC. We are involved in using them for PSC patients, for improvements in IBD and reduction in CCA. Some of these seem almost too good to be true and appear to be ideal agents for these conditions. Only future research will tell us whether this can be used in PSC.

The antibiotic Rifampicin, widely used in the treatment of itching is also a potent inducer of PXR and therefore offers potential for treatment of PSC. Future studies are needed.

The case for studying FXR is even more compelling. FXR is the major/master regulator of bile acid metabolism in cholestasis. Activation of FXR is followed by a decrease of the import of bile acids into the hepatocyte, an increase of their influx from the hepatocyte and their biotransformation into more hydrophilic (attracting water) metabolites in bile or urine.

Further beneficial effects in PSC may include reduction in biliary fibrogenesis. FXR agonists are being studied in PBC and we hope these studies will extend into PSC. Consequently various antibiotics have been evaluated in small PSC studies. There has been a three-year Finnish trial of Metronidazole in which Alkaline Phosphatase becomes normal. This and Vancomycin in children have produced some promising results which need further investigation.

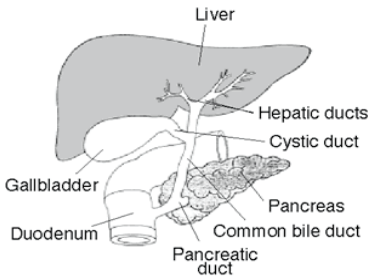
Where are we in 2009? We really don't know what causes the disease, and therefore we can't design treatments. The future lies in new biotics, new receptor agonists, adhesion molecule blockers, possibly long-term antibiotics.

Endoscopic Treatment in PSC: A Critical Appraisal

Professor A. Stiehl, Department of Medicine, University of Heidelberg, Germany

In PSC, progressive fibrotic inflammation frequently leads to dominant stenoses or strictures (DS, i.e. narrowings: Typically in PSC there are narrowings in the bile ducts. This can be followed by inflated areas of a bile duct where the bile acids back up, resulting in the typical beaded appearance in some bile ducts, like a string of beads. This concerns the extrahepatic bile ducts only, the large ducts outside the liver, particularly the common bile duct (CBD) through which the bile enters the small intestine and assists in the absorption of food.)

After endoscopic treatment, Professor Stiehl believes that survival is improved or time to LTX lengthened. DS can be treated surgically, bypassing the strictures. But after choledochojenunostomy, further endoscopic interventions in the biliary tree are not possible. A simple endoscopic dilatation of a DS may lead to temporary improvement of cholestasis and relief of itching. But restenosis usually occurs and the procedure needs to be repeated.



Professor Stiehl does this annually with his patients who have DSs. The method he prefers is balloon endoscopy that involves only one intervention. Temporary stenting involves placing the stent and then removing it. Repeated endoscopic dilatations allow the opening and preservation of the Common Bile Duct. In a recently completed study in our institution, five years after first endoscopic treatment of DS, 81 percent of patients were alive free of LTX and at ten year survival, we were at 52 percent (Of course we cannot know what the survival rate would have been without endoscopy.) The small bile ducts inside the liver cannot be endoscopically treated and fibrotic obliteration of bile ducts remains unaltered, leading to deterioration of liver function. This is the main determinant of survival or acceptance for liver transplant.)

A questioner asked how frequently are dominant stenoses in PSC seen.

Several centers have studied this and the figure is 40-50 percent. Those with DSs have a much worse prognosis if they are not treated. If you have a patient with cholestasis and you do not find the DS, you should look. This is after one year, and after five years, you see a perfect Common Bile Duct. This is what we can achieve. This is a typical situation.

With time the majority of PSC patients so treated will re-stenose. In order to get this result, you have to subject your patients to repeated annual procedures to keep the ducts open.

Q: What you do with asymptomatic DSs? Because I have seen real problems in patients with asymptomatic strictures.

A: We only treat patients where there is evidence of cholestasis.

Endoscopic Therapy in PSC: A Critical Appraisal

Dr. L. Aabakken, State University Hospital, Oslo, Norway

By alleviating the recurring strictures of the biliary tree, endoscopic therapy is arguably prolonging the transplant-free period of the patient when comparing to Mayo-based prognostics.

Symptomatic strictures are a good indication for ERCP and in general, there is a choice between balloon dilation and short-term stenting (one to two weeks). Both alternatives have been shown to be effective, but no direct comparison has been made to demonstrate superiority of either strategy. This may be because different strictures lend themselves differently to the two modalities. However, there is the obvious benefit of a single balloon dilatation procedure as compared to stenting, where a repeat procedure with stent removal is required.

It has also been suggested that stent therapy is associated with a higher number of complications although this has not been shown in the context of short-term PSC stricture stenting.

Either way, the effect of such dilation treatment is sometimes astonishing, with months or even years without recurrent symptoms of occlusion. Such therapy is mainly effective in central dominant strictures in the extrahepatic biliary tree. Multiple intrahepatic lesions are not amenable by endoscopic means.

But complications can result, especially in PSC patients. Recent figures from Mayo show a frequency of greater than10 percent. This may be partly due to longer procedures, more severe manipulation of inflamed bile ducts, and increased risk of purulent (containing or producing pus) cholangitis, post ERCP, in spite of antibiotic coverage, due to incomplete drainage of stricture ducts.

Q: How long does one go on doing this procedure?

A: When a patient is being considered for liver transplant, then you might have to stop. But if a patient has to wait six months, you might have to continue if DSs were causing problems.

MY WORDS, MY STORY

Our Visit to the EASL PSC Conference in Oslo, 2009

By Peter and Nicklas Holmgren, caregiver/father and PSC patient respectively, who live in Stockholm.

In November 2008 we found out, via PSC Partners I think it was, that there was to be a "Monothematic PSC Conference" in Oslo, Norway, in June 2009. The first ever of its kind aimed at PSC alone. This sounded very interesting. But looking at the homepage of Kenes International (who was the arranger) we thought that this was a conference not open for PSC-patients and caregivers – only for doctors and scientists. A short e-mail to Kenes to find out revealed that it was actually open for everyone wanting to attend!

Then we started to consider if this really could be something for us, since we are not really familiar with the nomenclature and the scientific language which surely would be used – and in English.

Nicklas did have an advantage over his father, since he had attended three PSC Partners conferences in a row he had caught up some more of the expected "hard to understand doctors language".

Nicklas' specialist Annika Bergquist was on the list of speakers and talking to her about attending made us even more positive as she thought it would be worthwhile for us to do so.

When I didn't have the opportunity to accompany Nicklas to the PSC Partners conference in Chicago, which I had in mind to do, I realized that the Oslo conference, being what it was to be, couldn't be afforded to miss out on. We simply had to go there. Living in the neighbouring country also made it a lot easier, reachable by car in few hours.

The week before the conference we met up with Ricky and Don Safer, spending some hours in Stockholm, on their way to the Oslo conference. Nicklas, of course, and Helena (his mother) had met them before, but my contact had so far just been by e-mail conversations with Ricky. Now we met, and it felt as we already knew each other! What a great couple!

Oslo, the capital of Norway! Nicklas and I arrived there in the early afternoon on Sunday the 21st of June, after a not too tiresome seven hour journey by car from Stockholm. Closing in to Oslo I said, "...after the next bend we should be able to see the "Holmenkollen" ski-jump tower up on the hill in the far end of Oslo, from where I was taking photos of the city 29 years ago. But the tower was not there to be seen? Funny, maybe it wasn't visible from here? Very well, we'll get up there on Tuesday afternoon, after the conference, on our way back home."

After taking some extra turns around the city, finding our way to the hotel, we checked in at about 3 pm. There was already a message for us from Don and Ricky who had arrived earlier. We called them up on the cell phone and joined them later in the evening at a Thai restaurant, after first registering for the conference.

Also attending the conference were Ivor from the UK, Eve, Abe and Rachel from Canada. Apart from Ivor they were together with Don and Ricky when we met up at the restaurant. The food turned out to be really nice, after some extended menu checking and negotiating with the Norwegian waitress (gluten free as well as vegetarian food was required). When we were about to leave we found out that this was actually a Swedish Thai restaurant (!) and everyone except our waitress were Swedish!

After the very good meal we went for a stroll in the city, first searching for a place to buy some much needed ice cream (Don's passion, we learned). Thereafter we found ourselves on quite a long walk to the Frogner Park where the sculptor Wegeland has created, basically all the sculptures in the whole park! They were all in granite and mostly made in one block for every sculpture, some of them very big. Very impressive work, a lifetime achievement! The park was well worth the walk!

After breakfast on Monday we sat down at the conference. We had the material we got at the registration: a full program with the abstracts from each speaker, minus two. We had looked through the list of speakers and the topics beforehand, printed all the information from the homepage. But this book we now had got was quite good. It showed to be a strong support when trying to keep up with the high pace kept by the speakers.

Our expectations for this conference were that we hopefully were about to see and listen to very initiated and knowledgeable doctors, specialists and scientists. If we could just catch the essence of it, that would be quite enough for us. The reason that really drew us to be there was the event as such: the first of its kind for PSC in combination with knowing that the very generous donation from Stein Erik Hagen had made it possible to set up a centre for research on PSC in Oslo. All this felt very promising, and coming to this conference where there actually attended some 140 specialists and doctors really lifted us in spirit!

The scientific aspects and content of this conference we believe is to be found in a report done by Ivor Sweigler, and we are not the ones able to put such a summary together, although we will highlight and give some reflections on some things that we found very interesting.

❖❖ ❖❖ ❖❖

For the following part Nicklas takes over the keyboard.

The first day of the conference was Monday, the 22nd of June. First up on the stage was one of the conference organizers, Dr. Erik Schrumpf of Norway. He gave a quick introductory speech to the conference, welcoming the attendees and let us know how the scientific presentations would work. After that it was right on to the next speaker, the schedule for this conference was very tight. Planning the whole thing must have been a tough job!

After each presentation there was a brief time for questions and answers, this sometimes helped to further clarify the scientific aspects for us laymen.

The first presentation was held by a Dr. Paul Angulo, a very interesting opening to the conference where he spoke about the epidemiology of PSC.

We learned many interesting statistics about the disease, starting with the number of PSCers per

100,000 people in different regions of the world. As we knew from before, the percentage is quite high for the Scandinavian countries.

The overarching themes for the first day were the following: Epidemiology and Natural History of PSC, Pathogenesis of PSC, and Overlap Syndrome and Autoimmunity in PSC.

All the presentations were very interesting and most of it was on a level of discourse that both me and my father could understand well.

As mentioned above we will not go over the specifics of any presentation but a few more of our favorites were:
Dr. Tom Karlsen who had the subject Genetic Epidemiology of PSC, Dr. David Adams, the subject, Aberrant Lymphocyte Homing in PSC: Only a Hypothesis? and (second day), Dr. Annika Berquist, Colorectal Malignancies in PSC, and Dr. Roger Chapman, Endpoints and Design of Future PSC Trials.

In the evening of the first day there was a reception at the Oslo City Hall, a really nice arrangement! The Mayor of Oslo held a speech directed to the conference. A buffet with much to choose from was presented.

The Oslo City Hall contains lots of art and wall paintings, and an interesting history of the building as such.

After the reception we visited a restaurant, which turned out to be not as expensive as we first believed, which in turn made us think the waiter maybe calculated wrong somewhere. Leaving the restaurant we went for a new quest for ice cream followed by a shorter walk this evening, and then we hit the sack quite exhausted!

The two themes for the second day, Tuesday the 23rd of June, were Malignancies in PSC, (with a minor change to the list of speakers, the speech by Dr. Hans-Gustaf Ljunggren was instead delivered by Dr. Yenan Bryceson) and a thoroughly excellent Clinical Practices session. One of the speakers this day was my specialist, Dr. Annika Bergquist, who held a very interesting presentation about the Colorectal Malignancies in PSC.

One of the things we could take away from the conference were that the great majority of the speakers hold fast that UCDA should be prescribed, for more than one reason, and then at a moderate dosage (roughly 17-23 milligrams per kilogram of body weight).

Another very interesting subject was the suspected relationship between PSC and T-Cells and that some sort of bowel inflammation, which later recesses, might be a trigger for PSC. This relationship could maybe also explain why so many PSCers have IBDs. The T-Cells may also prove to be a link in the recurrence of PSC in post-transplant patients. Further research on this topic might hopefully be relevant to future treatment techniques.

❖❖ ❖❖ ❖❖

Peter is back at the keyboard now.

After lunch we checked out from the hotel and talked a little more with our dear friends, Ricky, Don, Ivor, Eve, Abe, and Rachel, and promised to do our best to meet them at the next PSC Partners conference in the US. They were staying a couple of more days in Norway, but we had to get back home, Nicklas to work and myself to continue with some renovations on the house.

We were all very enthusiastic over this Oslo conference! For me and Nicklas it more than met all the expectations we possibly could have had. Then, we took farewell!

Before leaving the very nice city of Oslo for the journey back home to Sweden, we went up the hill to the Holmenkollen ski-jump tower. We wanted to take some nice photos and a video of the magnificent scenery, the Oslo Fjord. And for me to relive the last time I was there (fine memories), just to find that the tower was actually torn down!

There was now a huge construction site, and on some signs we could read that they were about to rebuild the whole ski-jump for the World Cup coming up in the winter of 2011.

As we were standing there, along came a motorcycle driving school, an instructor and some pupils on motorbikes. As Nicklas and I are bikers. too, we stood and watched them for a while. Suddenly the instructor said to his pupils, “Look out for the Swedes over there,” and I said “What?” smiling, of course. Then he came over to us and pointed to our license plate which spelled the three letters SYK, meaning ill in Norwegian, which we hadn’t reflected on up till then. It’s always nice being able to give people something to laugh about!

We did get some nice photos anyway as we went further up the hill to some high points with really nice views of Oslo and the Fjord.

Later in the afternoon, back on the Swedish side of the border, we passed outside a small village called Leverbyn, meaning Liver Village in English. This made me take a glance at the map, as Nicklas was driving, and I spotted one more place of the same kind, which we would pass nearby: Leverhoegen, that’s Liver Hill.

This in a car spelling ill on the license plate, on the way home from a conference all about a liver disease!

We will not forget this trip, for sure!

❄ ❄ ❄ ❄ ❄ ❄ ❄ ❄

Order Your PSC Partners ’09 Holiday Cards Before They’re Gone

Yes, it’s too early to think about the holidays--we haven’t even put Columbus Day behind us!

But the PSC Partners cards are available now, and there’s a deadline for ordering: November 4.

Check out the exclusive-from-us cards on our web site at:
http://www.pscpartners.org/2009_holiday_card_announcement.pdf
and order what you’ll need to spread holiday cheer as well as the word about PSC.

Report on the New York Symposium

at Mount Sinai Hospital, September 8, 2009

Reported by Rachel G.

The Mount Sinai School of Medicine Division of Liver Diseases, and PSC Partners Seeking a Cure jointly organized a symposium entitled, PSC: Treatment and Search for a Cure. Held at Mount Sinai Hospital on September 8, this meeting had the mission of establishing a New York City self-help group dedicated to educating and supporting those with PSC and their caregivers.

Approximately 90 PSCers and caregivers attended this first New York PSC meeting. Dr. Douglas Dieterich (Division of Liver Diseases, Mount Sinai School of Medicine) served as moderator for this event. The other participating physicians were Drs. Joseph Odin, Nancy Bach, Frank Klion, and Pediatric hepatologist Dr. Miloh Tamir. The PowerPoint presentations will soon be available online at our website: www.pscpartners.org .

Latest PSC Research

Dr. Joseph Odin, Director of the New York Autoimmune Liver Disease Program
at Mount Sinai School of Medicine

For newly diagnosed PSCers, Dr. Odin started with a slide presentation describing PSC and did not forget to remind us that many PSCers know more than their physicians. He explained that PSC goes hand in hand with IBD. Seventy-nine percent of PSC patients have IBD, and generally these patients experience mild colitis. However, only 7 percent of IBD patients have PSC, and either could occur first. Liver transplants do not prevent colitis, and removal of the colon does not prevent PSC, so the relationship between IBD and PSC remains obscure.
He presented the picture of a triangle narrowing down to a point, and on the largest side of the triangle, he placed the majority of PSCers who have been diagnosed through abnormal liver function tests (LFTs) and whose PSC does not show any changes for a long time. Below this group, a narrowing percentage have blockage of bile ducts, and 12 percent, have infections, (1 in 5) have cirrhosis at presentation, and at the very bottom of the triangle were the 5 percent that receive a liver transplant.

Though we do not yet understand the specific cause for PSC, the disease is described as originating from genetic polymorphisms triggered by environmental factors, which holds true for many diseases. We believe that subtle changes in DNA may predispose us to PSC, but at this time, these are not diagnostic of PSC but show pathways that have been interrupted. Some of these genes are the same as the cystic fibrosis genes, and it is of interest to note that patients with cystic fibrosis often develop a disease that resembles PSC. Of equal interest is the disconnect existing between ulcerative colitis and PSC polymorphisms in people who have both diseases. In other words, colitis polymorphisms are not found in PSC.

Though environmental causes have been suspected, there have not been many studies to specify the environmental culprits.

Curiously, smoking seems to be protective against getting PSC. On the other hand, obesity, gallstones, and diabetes predispose PSCers to cholangiocarcinoma (CCA). Research shows that chlorinated hydrocarbons may lead to PSC, or at least to the progression of PSC to cirrhosis. Hydrocarbons are of course found everywhere in the environment.

The main current clinical studies on PSC are:

1. PSC Partners sponsored a clinical study at Mayo entitled PROGRESS: The goal of this study is to find more genetic polymorphisms in PSC and to link those to disease outcome. By finding more DNA chains, the hope is to be able to identify disease progression.

2. In the Netherlands, the connection between colitis and liver disease is being studied. They are searching whether white blood cells from the colon migrate to the liver to bring on PSC.

3. A Mount Sinai Hospital study is trying to identify early histological (at cellular level) signs of PSC. Liver biopsies of patients with ulcerative colitis are collected to detect early changes that could develop into PSC.

4. University of California at Davis, supported by PSC Partners, is searching for PSC and cholangiocarcinoma predictors.

Who gets PSC? Children to adults, the average being 40 year-old adults. While autoimmune disease hits more women than men, PSC has more men than women. Ten out of 100,000 have PSC, so in NYC, there would be 800 PSCers. Clusters can be found in certain areas of the country. Dr. Nancy Bach discovered the existence of a cluster of cholestatic disease in Staten Island in New York City. The source of the hydrocarbon trigger originated from the fact that Staten Island has many toxic waste sites, that is, concentrated chlorinated hydrocarbons. Scandinavians have a high concentration of PSC, and in fact, in Sweden most liver transplants are from PSC. In the US cities in the Midwest that have a concentration of Scandinavians form other clusters (Saint Paul, Milwaukee, Chicago). The cluster in Denver, he explained, can be attributed to PSC Partners!

***Symptoms*:** Jaundice, dark urine, fever, chills, weight loss (look for CCA), no abdominal pain. As disease progresses, there may be vitamin deficiencies (fat soluble vitamins A, D, E, and K).

***Treatment*:** Though there is no treatment to stop PSC, milk thistle is helpful in lowering alkaline phosphatase. The controversy over Urso due to Dr. Keith Lindor's clinical trial of high-dosage Urso is now being studied. Urso is strongly recommended for Urso's cancer preventing properties. Symptoms are treated/relieved with antibiotics, stents, cholestyramine, etc. Tetracycline has shown little improvement; budesonide did not bring much benefit; milk thistle a little benefit in a Netherlands study; probiotics didn't show improvement. New techniques in endoscopy make diagnosis less invasive and clearer. Vancomycin trials at Mass General have shown improvement in children. Vitamin D3 seems to improve IBD and PSC.

Q & A followed Dr. Odin's presentation. Someone in the audience asked what would be considered high dosage of Vitamin D3? Dr. Odin responded that as in Urso, the optimal dosage is not yet known. He recommends 1000 IU/day.

Q: You say that few will need transplant. On the Internet, we are told that we have 13 years to transplant.

A: This is the problem with statistics. We have to remember that some never need it.

Q: Can you tell us what you mean by 5 percent needing transplant? Some reach cirrhosis or get cholangiocarcinoma.

A: Five percent have a transplant, but that 5 percent does not include, for example, serious cholangiocarcinoma that cannot have a transplant. However, it must be remembered that the largest percentage of PSC patients experience slow progression with mild disease.

PANEL DISCUSSION OF FOUR PSC CASES

Participants: Dr. Miloh Tamir (Pediatric hepatologist), Dr. Nancy Bach, Dr. Frank Klion, Mount Sinai Hospital, Hepatology

First Case: An 18 year old woman, borderline pediatric case, weighing 60 kg and jaundiced. Her serum alkaline phosphatase is very high. She was diagnosed with PSC by means of an MRCP.

Would you perform a liver biopsy on her?

Dr. Tamir: I would consider if her clinical history is consistent with PSC. In young people the alkaline phosphatase can be up because of bone growth. So elevated AP cannot be used as a marker. I would check for pregnancy as AP rises with pregnancy. I would test her GGT. In general, if the imaging findings are consistent with PSC, we would not perform a biopsy. We would screen for autoimmune hepatitis overlap because in pediatrics AIH is very typical with PSC. In that case, we would perform a biopsy.

Dr. Bach: Yes, I would perform a liver biopsy especially if his blood test does not confirm PSC. I would want to have a solid confirmation because I would want to screen for the three autoimmune liver diseases as each has a different treatment. Liver biopsy would differentiate, specially if blood tests do not specify autoimmune hepatitis. AIH is very treatable (especially in children), so I would definitely perform a liver biopsy.

Dr. Tamir: Fifteen percent have positive autoimmune markers and no sign of AIH. And these patients respond only to Urso. If the patient does have AIH, I treat it with immunosuppressants.

Would you use Urso?

Dr. Klion: There is absolutely no evidence that Urso has an impact on the progression of PSC. Urso is really a detergent and prevents sludge and stone, but even that is not proven in PSC. You would want to give Urso if the patient has overlapping IBD for colon cancer protection.

Dr. Bach: Dr. Klion said there is no evidence that Urso works. There are two studies that tell us otherwise. I would give Urso, but not high Urso. I would give the choice to decide to the patient.

Dr. Tamir: We have very good experience with Urso. A multi-center study is currently looking at Urso for pediatric patients. During the first month, Urso is decreased by 50 percent, in the second month, Urso is removed completely, and in the third month, Urso is reintroduced. We see that when we stop Urso, numbers go up. There is no downside to taking Urso, so I would definitely give it to children.

What would you do for itching for this 18 year-old?

Dr. Tamir: First, we look if we could do an intervention for a dominant stricture, so we use imaging. Then we give Urso that stops the itching with most. If that does not work, we add rifampin. As a third step, we try cholestyramine, sequestrin. We do not treat with opiate antagonists. If all three steps fail, we move to liver transplant.

Dr. Klion: I start with Urso. Then I move to cholestyramine(discovered 40 years ago, when it was used to treat elevated cholesterol. It binds bile acids). Though we do not know why people itch, we do know that there is no correlation between elevated quantities of bile salts in skin and itching. The risk of cholestyramine is that it binds with other substances such as vitamins. In an adult population, I recommend that it be taken before breakfast when bile salts are at high concentrations. When that fails, then I go to rifampin that has serious risks of liver toxicity. Last and rarely, do I use a morphine antagonist.

Dr. Bach: I use cholestyramine before rifampin. I recommend lotions, sauna, topical treatment, though these do not go to the root of the problem. I also try antidepressants such as Zoloft.

❍❍❍

Second Case: A 55 year-old fitness instructor, with mildly elevated alkaline phosphatase and abnormal ERCP. Otherwise feels fine. Wants holistic alternative treatments. He will continue to exercise.

Dr. Bach: There is no magic bullet. We do not discourage Omega 3s, fish oil, etc. There is no question that eating right is good for general health, but there is no evidence that such a regimen alters the course of disease, but it can't hurt.

Dr. Klion: We encourage the patient to follow the rules, urge him to take Urso and milk thistle. We urge them not to even go close to Chinese drugs that come in a box.

Dr. Tamir: We don't *recommend* anything. Regarding milk thistle, for example, we tell our patients that it has been shown to be beneficial, so we say we don't oppose it. We urge our patients to bring all alternative medication. We closely check all ingredients in any alternative medicine. We had two children who had liver failure because they ingested such herbs.

Dr. Klion: A Chinese professor at the University of Iowa checked the writing on the Chinese medicine boxes and reported they were all

gibberish. Just remember that in Chinese medicine anything white is called talcum powder.

Dr. Dieterich: Vitamin D3 is good for everything. Take it to prevent osteoporosis.

❍❍❍

Third Case: A 30 year-old woman, has had PSC for 5 years, taking 20mg/kg/day Urso and milk thistle. Should she get pregnant?

Dr. Klion: I would look at how severe her liver disease is. I would do an MRCP before advising her. I would check to see how much scarring she has. If the scarring is not significant, I would tell her to go ahead.

Dr. Bach: One study with 97 PSC patients shows that pregnancy does not increase complications. This is a personal decision. I do not advise anything.

Dr. Tamir: If pregnant, she would no longer be a pediatric patient. There is a four- to ten-time chance of PSC in first-degree relatives. The baby does not get screened. Only LFTs are checked.

Dr. Bach: I would recommend continuing to take Urso during pregnancy.

❍❍❍

Fourth Case: A healthy 60 year-old man, diagnosed with PSC 30 years ago, has mild PSC and IBD. He had his last colonoscopy 5 yrs ago and just had 2 brief cholangitis attacks. He reports a ten-pound weight loss.

Dr. Klion: I would suspect cholangiocarcinoma (CCA) or colon cancer or perhaps cholangitis, or blocked bile ducts. Antibiotics did not take care of his cholangitis. It was discovered that he had a liver abscess that is very unusual. I would perform an MRCP or a transhepatic cholangiogram.

Would you do brushings? Cholangioscopy?

Dr. Klion: He had surgery already, so I wouldn't do a cholangioscopy.

How frequently should he have imaging of his colon?

Dr. Bach: Ulcerative Colitis needs regular screening. I would do a colonoscopy for diagnosis, then I would recommend the next colonoscopy after five to eight years. Then I would increase the rate to one to three years because of increased risk of colon cancer.

I would screen for CCA by testing Ca 19-9 levels, with MRCP, and a PET scan. There is no study to show that having a PET scan increases the chance of survival.

Dr. Tamir: Cancer has not been reported in children under 18. MRCP is repeated every 5 years unless clinical changes are observed. And Ca19-9 is tested twice a year though it is not a great marker. Colonoscopies performed on asymptomatic PSCers show that a large percentage had quiescent IBD. I perform colonoscopies on these patients every three to five years as it is extremely rare to see colon cancer in children. If I see a single benign stricture, I use endoscopy and dilation.

Dr. Klion: Though cancer markers are not sensitive, if the tumor is small, long-term survival can be predicted.

Dr. Dieterich: I see there is no consensus.

Dr. Bach: We do have a consensus on the fact that we have to do aggressive screening.

Dr. Tamir: CCA can occur at any time during the course of the disease.

Dr. Dieterich: Let's assume the patient was hospitalized twice.

Dr. Bach: I would rotate antibiotics. I would give full dose during the cholangitis attack and would then reduce the antibiotics. I would also change the antibiotics. If there is no improvement, then I would consider transplant. The two hospitalizations would add 25 points to the MELD score.

Are the points removed with time?

Yes, after six months, they are.

Dr. Klion: Hopefully the ranking system will be corrected in the near future. I would hospitalize him for cholangitis even if he didn't need to.

Recurrent cholangitis is a common indication for transplant in the pediatric population. If prophylactic antibiotics don't work, there is a ten percent chance of recurrence.

Dr. Bach: We see more and more recurrence of PSC post-transplant as length of survival increases.

Dr. Klion: I tell a PSC patient with fever to first take antibiotics and then to call me.

Q & A Session

Q: What are the symptoms of cholangitis?

A: Fever, jaundice, a change or severe pain,

Q: There has been no study on the rate of recurrence of PSC in those who have received livers from live donors versus in those who have had cadaveric transplants.

Q: How long should one wait before going to the hospital? How long can you sit out feeling sick?

A: Don't sit out and wait. Take antibiotics and call.

Dr. Tamir: In pediatrics we admit children right away and give antibiotics intravenously.

Q: What can you tell us about small duct PSC?

A: Dr. Bach: Fifteen percent of PSCers have small duct PSC. Some say it is a different disease. The prognosis with small duct PSC is better than that for PSC. But small duct PSC is very much like classic PSC.

Q: In small duct PSC, is the alkaline phosphatase still elevated?

A: Yes, the liver function profile is the same. There is less risk of cholangitis.

Dr. Bach: Most studies say that small duct PSC does not evolve into PSC.

PSC in Children and Adolescents

Dr. Miloh Tamir, Department of Pediatrics and Surgery, Mount Sinai School of Medicine

The incidence of PSC is one fifth of that of adults. The average age of diagnosis is 11-12 years. In families, there is a 0.5 percent chance of having another family member with PSC. There are no more than two in a family. There is a risk of ulcerative colitis in another family member. Eighty percent also have IBD. Five percent of IBD patients have PSC. There is no correlation with the severity of either disease. PSCers have more quiescent IBD than those who do not have PSC. I do not do annual colonoscopies. PSC can be seen in infants who have autoimmune problems such as autoimmune hepatitis overlap.

Almost all are asymptomatic and only have elevated liver enzymes. Jaundice is less dominant in kids. Weight loss, arthritis, some abdominal pain can be seen. Bone loss could be present. Acute cholangitis is present only in 15 percent.

Clinical check-ups are unremarkable. Half have an enlarged liver, one third have enlarged spleens, 20 percent experience itching and one percent have fluid in the abdomen. Data from the STOP PSC group compares adults and children. Children have more elevated ALT. Adults have more elevated bilirubin. Twenty five percent have associated autoimmune disease. Usually the alkaline phosphatase is high due to bone growth. That is why GGT is also checked. MRCP (non-invasive), ERCP (the advantage is the possibility of intervention, sampling and stenting) is also used. Statistically survival to transplant ranges between 9 and 18 years. Some patients can be static for a very long time. Asymptomatic patients have a better prognosis, and among those, most have small-duct PSC and don't usually require transplant.

***Treatment*:** Treatment of children with PSC is extrapolated from that given to adults. But currently, this is being changed through multi-center studies. All children are given Urso. We adamantly follow the fat soluble vitamin supplementation (Vitamins A, D, E, K). We prescribe adult meds for stones, bone disease, and itching. We don't recommend milk thistle for children yet though we have seen improvement with it. We don't recommend Vancomycin longterm. We have very few liver transplants. The median from diagnosis to transplant is seven years. One-third of patients have needed transplant by early adulthood. Survival in children is good. Ten percent have recurrent PSC. The largest cohort involved 47 patients. Most were diagnosed through MRCP, ERCP, and liver enzyme tests. They had stage 3 and 4 at diagnosis. Urso improves liver numbers. Perhaps with Urso inflammation in the liver is subsiding. Seventeen percent of these patients were transplanted. Most were women because they also had autoimmune hepatitis overlap. There is no recurrence in this age group. But we lose track when they become adults.

Q: A vast majority did not need a transplant. Can there be kids who will remain stable?

A: Yes

Q: What about cholangitis fever?

A: Cholangitis fever will not resolve. There will be some days with fever and some days without. The fever should be treated aggressively with antibiotics.

Mt. Sinai Support Group Launched

Stephen Harris, Mount Sinai medical school student, was diagnosed with PSC a year ago. Seeing the danger of relying on false information on the Internet, and realizing the degree of variance existing on some of these sites, Steven Harris and Dr. Odin decided to start a new self-help group. One hundred people signed up for this first meeting. This number encompasses a large number of PSCers living in New York. Steve Crohn, the nephew of the Dr. Crohn who discovered Crohn's Disease, will be moderating the group.

The plan is to start meeting bimonthly. The first meeting will be on October 19. Each session will have a speaker who will be discussing a different facet of the disease. The group is funded by the Auxiliary Board of Mount Sinai. The aim of the group is to create a central hub for PSC Partners. Those seeking information about the group can write to this email address: Eileen.Solomon@mountsinai.org.

How Our National Foundation Helps PSC Patients and Caregivers

Ricky Safer, President, PSC Partners Seeking a Cure

Ricky thanked Allan Luks and Stephen Harris for making the seminar possible and gave a brief history of PSC Partners, explaining that the foundation started more than four years ago and developed as a grass-roots organization, that it has become worldwide with links to European and US liver centers.

Now at the forefront of PSC research, the foundation has been funding groundbreaking clinical studies. She invited the audience to read the online newsletter, *The Duct,* where new research, patient concerns, and member news are discussed. She also commented on the important database of PSC literature with its 118,000 articles and abstracts David Rhodes established on our site.

She described the life-changing experience the annual three-day conferences proved to be for many PSCers. She urged the New York group to attend the fifth annual conference in Hartford, Connecticut on May 14-15. She introduced Reggie Belmont and thanked her for co-organizing next year's conference. She expressed her excitement in working with Yale physicians to organize the conference. All the PowerPoint presentations presented in past conferences are on our site, are open to all, and free of charge.

Don Safer added that PSC Partners has given grants for two studies in the US, one in Holland, and three more will be funded by the end of this year. He highlighted the volunteer nature of the foundation by explaining that nearly 98 percent of its expenses are used for programs.

From PSC Partners, other attendees were Joanne and Steve Grieme of Pittsburgh, Allen and Karen Luks of New York, Reggie Belmont of Connecticut, Teresa and Nick Valenti of New York, Sue and Scott Malat of New York, and Rachel and Abe of Montreal.

Ricky and Don Safer discussed PSC Partners with the Mount Sinai attendees.

GENERAL DONATIONS TO PSC PARTNERS SEEKING A CURE
JUNE 2009 – AUGUST 2009

DONOR	IN HONOR OF
David Belmont	Jecy Belmont
Tim Brannigan	Sandy Wolf's Daughter
Sharon Carlson	
Wayne & Denise Chiodo	Erin Strauss
Katelyn Darna	Billy Bria
Steven & Elissa Deitch	Ricky Safer
Helga Dingman	Ian Roehrich
Kaitlin Genovese	Nancy Douglas Beck
Dr. Jenny Heathcote	
Jeremy & Courtney Houser	Houser/Tucker Wedding
Dr. Chris & Jan Karras	Ricky Safer
Daniel & Karen Lipscomb	
Valerie McManus	Erin Strauss
Bob Mikulak	Peder Hedburg
David & Brenda Nevins	Erin Strauss
Paula Oberndorf	Ricky Safer
Michael & Eileen Pearlman	Anniversary
David Rhodes	Steven Rhodes
Angela Roehrich	
Virginia Stivers	Jennifer Soloway
Ronald & Rhonda Strauss	Erin Strauss
Darcy Ward	Billy Bria
Von Welch	

DONOR	IN MEMORY OF
Craig & Kelly Austin	John Ross
Thomas & Robin Belsha	Thomas C. Belsha
Eugene & Gay Crowley	John Ross
Robert & Mary Fugett	John Ross
Hayes Management Consulting	John Ross
Francis & Dorothea Henninger	John Ross
Jeremy & Courtney Houser	Katy Miller
Andria & Lucienne Ibrahim	Abraham Kesden
Robert & Marikay Kovac	Abraham Kesden
Cliff & Sima Malat	Esther Grossman
Cliff & Sima Malat	Al Malat
Paul & Dolores Nugent	John Ross
Anita Rummel-Ttee	John Ross
Don & Ricky Safer	Henry George Deubert

FUNDRAISING DONATIONS
JUNE 2009 – SEPTEMBER 2009
ITCHING FOR A CURE/ROAD TO CHICAGO FUNDRAISER

DONOR	IN HONOR OF
Teresa Abrahams	Wim Ruyten's Bike Ride
Keith Anspach	Wim Ruyten's Bike Ride
ATA Aerospace Testing Alliance	Wim Ruyten's Bike Ride
Yolanda Belmont	Wim Ruyten's Bike Ride
Eric & Valerie Bjorn	Wim Ruyten's Bike Ride
William & Lee Bria	Wim Ruyten's Bike Ride
Jane Cholminsky	Becky Long
Lloyd & Linda Davis	Wim Ruyten's Bike Ride
Richard & Jean Dorris	Joey Hatchett
Traci Downs	Wim Ruyten's Bike Ride
Euclidean Optics, Inc.	Wim Ruyten's Bike Ride
Charles Fisher	Wim Ruyten's Bike Ride
Scott & Cynthia Freese	Wim Ruyten's Bike Ride
Abe & Rachel Gomel	
Wayne Gregory	Wim Ruyten's Bike Ride
Judith Hanson	Wim Ruyten's Bike Ride
Arthur Hargrove	Wim Ruyten's Bike Ride
Highland Baptist Church	Wim Ruyten's Bike Ride
Internal Medicine Associates	Wim Ruyten's Bike Ride
Stephen & Anne Jacobsen	John Joseph Shepherd
Henry P. Kern III	John Joseph Shepherd
Randy & Abigail Kozel	Tyler Ostos
Pam Ledford	Wim Ruyten's Bike Ride
Jere Ledsinger	Wim Ruyten's Bike Ride
Michael & Barbara Marvin	Wim Ruyten's Bike Ride
Michael & Marguerite Moyers	Tyler Ostos
Hudson & Miriam Nichols	Wim Ruyten's Bike Ride
Julie Olexa	Becky Long
Jeffrey & Barbara Ottum	Samantha Wente
Edward & Joan Pavlik	Peder Hedberg
Abigail Pribble	Wim Ruyten's Bike Ride
Mary Pribble	Wim Ruyten's Bike Ride
Todd & Carrie Reinholtz	Wim Ruyten's Bike Ride
Patty Russell	Wim Ruyten's Bike Ride
Don & Ricky Safer	Wim Ruyten's Bike Ride
Irene Shepherd	John Joseph Shepherd
Carlos & Fatima Simoes	John Joseph Shepherd
Daryl & Trellis Sinclair	Wim Ruyten's Bike Ride
Mark & Linda Smith	Wim Ruyten's Bike Ride
TD & LM Spitzer	John Joseph Shepherd

Dennie & Anita Sutherland	John Joseph Shepherd
Jason Lee Umphress	Joey Hatchett

ITCHING FOR A CURE/ROAD TO CONNECTICUT FUNDRAISER

DONOR	IN HONOR OF
Jeff & Reggie Belmont	Jecy Belmont
William & Sara Brazo	Jackson Brazo
Lee Bria	Billy Bria
Patrick & Trina Hapgood	Jackson Brazo
Graham & Heather Milligan	
Thomas & Jeany Park	Joey Hatchett
Scott & Linda Schrader	Jackson Brazo
Rev. Arthur & Ann Yost	Jecy Belmont

DONOR	IN MEMORY OF
Mr. & Mrs. Alan Andeen	Henry George Deubert
Norman Andeen	Henry George Deubert
Virginia Andeen	Henry George Deubert
Burton & Lorraine Anderson	Henry George Deubert
Margaret Annino	Henry George Deubert
Paul Annino	Henry George Deubert
ATT & T Co-workers of Darcy Ward	Henry George Deubert
Bernard & Anne Auger	Henry George Deubert
Robert & Aileen Bannon	Henry George Deubert
Jeff & Reggie Belmont	Henry George Deubert
Edward & Mildred Berggren	Henry George Deubert
Nancy Berggren	Henry George Deubert
Marjorie & Rita Bertolini	Henry George Deubert
Lee Bria	Henry George Deubert
John & Elizabeth Cernan	Henry George Deubert
Philip & Margaret Crombie	Henry George Deubert
John & Jeanne Helenek	Henry George Deubert
Mary Ann Herrmann	Henry George Deubert
Diane Labedzki	Henry George Deubert
Richard & Linda Mardirosian	Henry George Deubert
Rosalind Martin	Henry George Deubert
G.K. & Vreni McMaster	Henry George Deubert
John & Marianne Metcalf	Henry George Deubert
Sharyn Mitzo	Henry George Deubert
William & Mary Quirk	Henry George Deubert
H.E. Reilly	Henry George Deubert
Jack & Carla Shanks	Henry George Deubert

Richard & Mary Todzia	Henry George Deubert
Richard Towns	Henry George Deubert
Robert & Josephine Vandermark	Henry George Deubert
Terence & Nanette Weaver	Henry George Deubert
Beatrice Webb	Henry George Deubert
Wayne & Jill Wenstrom	Henry George Deubert
Andrea Zeffiro	Henry George Deubert

GENERAL FUNDRAISING

DONOR	IN HONOR OF
Chrissy Newcomb	Nicola Parry

PSC Partners Seeking a Cure Treasurer's Report: July 31, 2009

Following is an update of the current financial position through July 31, 2009 of PSC Partners Seeking a Cure Foundation.

Year to Date 2009

Total net income for 2009 through July 31 is $72,111, compared to last year for the same time period of $101,181. The biggest difference between last year and this year to date is that we were able to donate $60,000 for research in 2009, our contributions to research in 2008 was $20,000.

Year to date donations are $19,404 compared to 2008 YTD of $13,526.

Fundraising projects have raised $127,103 YTD, compared to $81,230 in 2008 YTD, detail can be found below in the Fundraising Income Detail. Please note that the Road to Chicago total only includes dollars donated in 2009.

Total assets through July 2009 are $492,697, an increase of $74,746 from Dec. 31, 2008.

As always, please direct any questions/comments to Deborah Wente, Treasurer at debs_3@charter.net.

	Jul 09 YTD
	Act. Revenue
Capital Gains	0.00
Cash Dividend	1104.46
CD	0.00
Fundraising Income Detail	26311.00
Donations	19403.93
Grocery Cards	952.25
Holiday Cards	75.00
Miscellaneous Fundraising	444.11
Money Fund Dividend	10.55
Notecards	210.00
Other Sponsors	0.00
Pay Pal Fee	-290.32
Road to Chicago	121412.15
Road to Connecticut	3999.00
Silent Auction	0.00

Sponsors		11500.00
Wristband		0.00
	TOTAL	185132.13

	Dec 08 YTD	Jul 09 YTD	Difference
Income			
300 · Donation Income	20410.23	19403.93	1006.30
301 · Conference Income	20618.95	26220.64	-5601.69
302 · Sponsor Income	21160.00	11500.00	9660.00
303 · Fundraising Projects	125270.41	127103.28	-1832.87
304 · In-Kind Contributions	5171.51	0.00	5171.51
305 · Interest Income	20.34	3476.03	-3455.69
306 · Cash dividends	6665.96	1115.01	5550.95
307 · Capital Gains	57.91		57.91
Total Income	199375.31	188818.89	10498.51
Expense			
500 · Admin Fee	1660.39	360.80	1299.59
502 · Conference Expenses	14877.80	56055.76	-41177.96
503 · Pay Pal Expenses	194.48	290.32	-95.84
509 · Insurance	295.00	0.00	295.00
508 · Licenses and Taxes	1150.00	0.00	1150.00
521 · Expendables	188.95	0.00	188.95
525 · Fundraising Project Expenses	2307.49	0.00	2307.49
530 · Advertising	5165.00		5165.00
555 · Donations	26000.00	60000.00	-34000.00
66900 · Reconciliation Discrepancies	0.00	0.64	-0.64
Total Expense	51839.11	116707.52	-64868.41
Net Income	**147536.20**	**72111.37**	**75424.83**

	Dec 31, 08	July 31, 09	Difference
ASSETS			
Current Assets			
Checking/Savings			
101 · Checking Account	48812.37	116332.70	67520.33
102 · Cash	0.00	0.00	0.00
103 · Pay Pal	-17.67	-17.67	0.00
104 · Charles Schwab	369156.25	376381.94	7225.69
Total Checking/Savings	417950.95	492696.97	74746.02
Total Current Assets	417950.95	492696.97	74746.02
TOTAL ASSETS	**417950.95**	**492696.97**	**74746.02**

LIABILITIES & EQUITY	
Equity	
299 · Retained Earnings	285258.63
3000 · Opening Bal Equity	-0.10
401 · Investment Adjust to FMV	-10360.18
402 · Income Reinvested this Period	-4483.60
Net Income	147536.20
Total Equity	417950.95
TOTAL LIABILITIES & EQUITY	**417950.95**

Itching for a Cure

PSC Partners Seeking a Cure

Note to Readers:

Articles in this newsletter have been written by persons without formal medical training. Therefore, the information in this newsletter is not intended nor implied to be a substitute for professional medical advice.

Please consult with your doctor before using any information presented here for treatment. Nothing contained in this newsletter is intended to be for medical diagnosis or treatment. The views and opinions expressed in the newsletter are not intended to endorse any product or procedure.

PSC PARTNERS SEEKING A CURE

PSC Partners Seeking a Cure is a 501(c)3 nonprofit foundation that endeavors to find a cure for Primary Sclerosing Cholangitis.

The three-fold purpose of the **PSC Partners Seeking a Cure** foundation is to: raise funds for research on the causes and cures of PSC, promote PSC and organ donation awareness, and provide education and support to PSC patients and their families.

Ricky Safer is the principal contact person for the PSC Partners Seeking a Cure Foundation. Reach her at: contactus@pscpartners.org

Tax-deductible donations can be sent to: PSC Partners Seeking a Cure, 5237 South Kenton Way, Englewood, CO 80111 with a check made out to: PSC Partners Seeking a Cure.

Website

www.pscpartners.org

PSC Partners Seeking a Cure Board Members

Dike Ajiri, Lee Bria, Becky Long, Dr. Gregory Everson, Joanne Grieme, Chris Klug, Scott Malat, David Rhodes, Ricky Safer, and Deb Wente

Medical/Scientific Advisory Committee

Dr. Greg Everson, Dr. Richard Green, Dr. Denise Harnois, Dr. Aubrey Goldstein, Dr. Dennis Black, Dr. Kapil Chopra, Dr. Don Safer, Dr. Steven Deitch, Dr. Chris Bowlus, Dr. Gideon Hirshfield, and David Rhodes (Chair)

The Duct Newsletter

Editor: Pat Bandy (newsletter@pscpartners.org)

Contributors to this issue: Ricky Safer, Ivor Sweigler, Rachel G., Peter and Niklas Holmgren, Joanne Grieme, Deb Wente