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# The Duct

Bringing you news on PSC



PSC PARTNERS  
SEEKING A CURE

research, education, and Support

PSC Partners Seeking a Cure Foundation  
Part 2, Summer 2009

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## Special Issue

# 2009 Annual Conference Presentations

### A Message from Ricky Safer, President of PSC Partners

This portion of the newsletter contains all the wonderful educational materials that were presented to us during the weekend. I hope you'll find the time to read through the presentation summaries and an update of PSC progress in the UK that were kindly prepared for us by Ivor Sweigler and Rachel. Also, feel free to study all the PowerPoint presentations that are found in our 2009 conference website ([www.pscpartners.org/PSCConf09/index.htm](http://www.pscpartners.org/PSCConf09/index.htm)).

I am incredibly proud and thrilled about our progress in the last year in supporting PSC research. David Rhodes, the head of our Medical Advisory Committee, is the driving force behind our amazing progress. All our members have helped us raise the money to support these projects, and now our Medical Advisory Committee has awarded our first three PSC research grants.

This is a huge and vital step for PSC Partners Seeking a Cure!! Thank you to the members of our Medical Advisory Committee who spent hours studying all the research proposals that were submitted in order to choose the three top grants for us to award. In addition to David Rhodes, the committee consists of Drs. Greg Everson, Denise Harnois, Rich Green, Dennis Black, Kapil Chopra, Steven Deitch, and Don Safer. Please read the article about our continuing research grants program on page 2.

### A Note from the Editor

There's so much to report from the annual conference that we broke this Summer issue into two parts. We've produced this special issue on the medical/technical presentations, thanks to our good friend Ivor Sweigler of PSC-Support UK, who took excellent notes for all of us to recall the valuable information given by the Northwestern University team. Part 1 focuses on news from PSC Partners, photos of events, recollections of the weekend, and commentary on the conference. There's a lot going on in the world of PSC. We're together in the fight, whatever it takes!

Pat Bandy

We are on the way to finding that elusive cure, and as a group, we WILL succeed!

Also included here are summaries from the three researchers that we have supported through our awards given out via the AASLD (American Society for the Study of Liver Diseases):

Dr. Karlsen (2007), Dr. Blanco (2008), and Dr. Tornai (2008)

We are watching all these research projects closely and encouraging more PSC research.

Another development is an announcement of the recently published PBC genetic discovery that Dr. Heathcote of the University of Toronto, in conjunction with Dr. Lazaridis of the Mayo Clinic/Rochester have made. Dr. Lazaridis attended our 2009 conference to discuss PROGRESS, his important PSC research project. Many of our attendees signed up to volunteer for this project, and I hope that non-attendees will consider joining. This is an easy way that we can have a huge impact on helping researchers get closer to solving the mysteries of PSC. Dr. Lazaridis' PROGRESS information is found on page 12, and his PBC research results are found on page 26 .

This is an exciting time for us. When we started four and a half years ago, there was little PSC research worldwide, but it's changed now. Don and I were at the EASL international PSC researchers' conference in Oslo, Norway, June 21-23. We were joined by Ivor Sweigler, Rachel and Abe, Eve Jedrzejewska, and Nicklas and Peter Holmgren. We spoke personally with several researchers and handed out PSC Partners Seeking a Cure brochures to let researchers know that we exist. What an opportunity this was for PSC researchers throughout the world to share their knowledge and research results! There's more on page 28.

## Successful Fundraising Enabled Three Awards for PSC Researchers

David Rhodes, Chair of the Medical/Scientific Committee, announced at the conference that recent high-result fundraising efforts made possible more awards than anticipated.

Details of the grant projects are at this address: [www.pscpartners.org/2009Awards.htm](http://www.pscpartners.org/2009Awards.htm) .

In our recent 2009 grants competition, PSC Partners Seeking a Cure made three awards of \$40,000 each to the following investigators and projects:

- Konstantinos N. Lazaridis, MD, Assistant Professor of Medicine, Center for Basic Research in Digestive Disease, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905. *Examining the Disease Impact of Genetic Variation in Logical Candidate Genes for PSC: a PROGRESS Study.*
- Pietro Invernizzi, MD, PhD, Assistant Professor of Medicine, Division of Rheumatology, Allergy, and Clinical Immunology, University of California, Davis GBSF suite 6515, Davis, CA 95616. *Cholangiocarcinoma-associated serum microRNAs in primary sclerosing cholangitis: Identification and prognostic potential.*
- Cyriel Y. Ponsioen, MD, PhD, Department of Gastroenterology & Hepatology, Academic Medical Center, C2-112, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. *Aberrant homing of lymphocytes to the liver in patients with primary sclerosing cholangitis; the missing link between colon and liver.*

2009 PSC Partners Conference  
Medical Presentations are on the  
Website

Slides of medical presentations made at our conference, are available on the web at this address:

[www.pscpartners.org/PSCConfo9/index.htm](http://www.pscpartners.org/PSCConfo9/index.htm)

Conference attendees as well as non-attendees now have full access to the slides of ALL conferences at no charge.

Next PSC Partners Conference:  
May 14-16, 2010 in Hartford,  
Connecticut

Held in conjunction with the Section of Digestive Diseases and Yale Liver Center at Yale University School of Medicine

Co-Chairs: Jeff, Reggie, and Jecy Belmont with Ricky Safer

Details to be announced in early 2010. Check the newsletter and website then!

## 2009 Conference Sponsors

We'd like to thank the physicians at the Northwestern University Feinberg School of Medicine, especially Dr. Rich Green and Dr. John Martin, who have worked closely with us in planning the conference.

Many thanks as well to all our wonderful speakers who will broaden our perspectives and understanding of PSC. We are also indebted to our conference sponsors:

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### Special Thanks To:

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# Conference Session Summaries

by Ivor Sweigler, Chairman of the UK group, PSC Support

*Ivor attended the Chicago conference on behalf of his organization and graciously offered us his summaries of the sessions. These summaries also appear in that group's newsletter, PSC Support News, which is available by subscription at [pscsupport@aol.com](mailto:pscsupport@aol.com). The newsletter is not written by medical personnel and readers are advised to seek their doctor's advice concerning any changes in their treatment. The following summaries are written from a layman's understanding. If the presentation you are looking for is not summarized here, our website includes slides from all speakers and you may find more information there.*



Ivor Sweigler

## Looking Ten Years Ahead: Potential Therapies for PSC

Dr. Jenny Heathcote, University of Toronto, Canada, Head of the Patient-Based Clinical Research Division at Toronto Western Research Institute

The keynote speaker, a specialist in viral hepatitis and cholestatic liver disease (especially PBC), trained under Dame Sheila Shirlock at the Royal Free Hospital in the UK.

What are the causes of PSC? You've mostly heard about *Primary* Sclerosing Cholangitis, but there is also *Secondary* Cholangitis. It is a complex disease. There are probably many genetic abnormalities. There are many causes: Some are reversible and others are not. In end-stage AIDS, the biliary system can also become distorted, having the same appearance as PSC. This is related to very unusual infections of the biliary tree. You can even have very rapidly developing sclerosing cholangitis after a liver transplant (LTX) relating to a clot, which is cutting off the arterial supply.

Are there differences between primary and secondary sclerosis or are they all part of the same pathogenesis? I think probably not. In Secondary Sclerosing Cholangitis (SSC) the causes and the outcome are quite different. But the most likely cause is infection.

Keynote speaker  
Dr. Jenny Heathcote

Some patients may have autoimmune hepatitis (AIH). Patients can have inflammation of the pancreas, associated with high levels of IG4. We now call this Autoimmune Cholangitis. It looks exactly the same as PSC. But it can respond to a course of prednisolone. This, therefore, is a treatable form of Sclerosing Cholangitis.

What about therapy for PSC? The question was answered by referring to previous drug trials. She also mentioned research by Prof. David Adams, QEH, Birmingham, into recurrent PSC (rPSC). His theory, she said, concerned the consequences of a leaky colon at the time of a LTX. White blood cells, in particular lymphocytes continue to migrate to the new liver. They are re-activated by immunosuppressive agents and steroids leading to higher levels of inflammation and damage to both



liver and biliary system. Removal of the colon before LTX led to zero rPSC.

Urso, a bile acid our body produces, is about three percent of our bile acids. It is therefore a natural substance although the Urso we take is manufactured. The first trial by Keith Lindor at Mayo was very disappointing because of no survival benefit. Ohlssen, et. al., in Scandinavia increased the dose, and again no survival benefit. In the recent Lindor trial the survival was actually reduced. Nobody knows why. Eventually we will work out why this was the case.

My question is why does medical therapy fail to date in PSC? In part because little can get through heavily scarred bile ducts. Meds taken by mouth may be blocked. To the question as to where we go in the next 10 years, she said that we needed to go backwards, that is, back to basics. She said, "I'm sorry that I cannot offer you new treatments for PSC."

### **Attendees' Questions and Answers**

#### ***Discuss accessing bile ducts through the skin (PTC: Percutaneous Transhepatic Cholangiogram)?***

We prefer not to go directly into the liver because if you get into a bile duct which cannot be adequately dilated, then the bile in the area poked with the needle may decide that the only way to get out is through that needle tract and you can get a fistula which is not a great situation. We all try to avoid PTCs in any of our PSC patients.

#### ***How do you screen for Crohn's and Crohn's ileitis?***

It is the same as for UC. We make sure that there is no microscopic inflammation. If you take biopsies and you see inflammation, I would put that person in the same risk category as active colitis.

#### ***What about stem cell research?***

Certainly in the future, stem cell research is going to lead to new therapies. These will be much more effective treatments for liver disease and IBD. This is one of the areas that is going to explode and may come from areas we haven't even imagined. We have to be careful and make sure we know what we're doing.

It was then explained that there are pluripotent stem cells and embryonic stem cells that can become any cell in the body.

#### ***Does a dominant stricture need stenting?***

It doesn't necessarily need to be stented, but it does need to be investigated. Let me clarify what a dominant stricture is. If you have a tight narrowing anywhere in the tree trunk, part of the bile duct or the lower part of the biliary tree where the ducts are relatively large, any tight narrowing is called a dominant stricture (DS).

We're interested in them even if they're not causing problems, not causing jaundice because we know that some DSs could be harboring an occult cholangiocarcinoma. So we always feel compelled to investigate. If we see them on an ERCP, we're going to brush across it to collect cells and send them to be examined by a pathologist.

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A stent is a temporary plastic tube placed into a stricture to keep it open. But we know from multiple studies, primarily from the European literature, that particularly with PSC patients, don't tend to have one DS and nothing going on upstairs in the branches. Most people who have tree trunk strictures have lots of strictures upstream and they don't drain well, either. So no surprise that if you put a pipe across the dominant stricture, that's going to act as a siphon to suck up bacteria that normally are in the liver and intestine.

Your immune system should be able to handle this for about a week and a half, but for much more than that, the results can be much worse. In many cases a stent is therefore not a good idea in PSC. It may be a good idea if we're trying to open a stricture but not for more than a couple of weeks. You therefore take them out. You only put in permanent stents when a patient is not expected to live much more than 6 or 12 months. So avoid stents. If you really need one, it should be temporary. (Many hepatologists will use balloon endoscopy instead.)

### ***Could you discuss cancer of bile ducts?***

Although there's a lot of talk about cholangiocarcinoma (CC), most patients do not get CC. Keep it in perspective. (It's a difficult thing to see, and there are lots of false positives.) Very often the procedure to follow is not to go for a LTX if tests appear positive but to have a repeat ERCP in the suspect area and see that area more clearly. Most of the time, the area is seen as clear and the anxiety is removed.

## **Live Donor Transplantation for PSC**

**Dr. Michael Abecassis, Chief, Division of Organ Transplantation Surgery  
Northwestern Memorial Hospital**

I'm going to talk about liver transplant (LTX) for PSC. It's just good to know that when things get bad, we have a really good solution for you, and that is the purpose of LTX.

So what kind of PSC patients do I get to work on? It's PSC patients with cirrhosis. But not just cirrhosis; cirrhosis with life-threatening complications in end-stage liver disease. But sometimes PSC patients get into trouble without having advanced cirrhosis.

You can have recurrent infections of the bile ducts or cholangitis. You can also have backed up bile that needs to be drained and treated with

antibiotics, but we don't have any other options, and if cholangitis continues to recur, then that may be an indication for LTX.

Sometimes there are strictures that even magicians can't open. These are strictures that just can't be managed and cause a lot of significant problems.

Cholangiocarcinoma (CC) is another indication for LTX. The natural history of CC is really not well defined at all.

There was an old study by a French group years ago that basically said that over a thirty-year period, a PSC patient had a 30 percent chance of

getting PSC. That has been translated as being one percent per year. That is really not accurate, but that is what we use because we do not have better numbers.

It is very easy to screen for colon cancer in ulcerative colitis (UC), but it is very difficult to screen for cancer in PSC. It is not easy to get to the bile ducts, and it is very difficult to biopsy the ducts. The concern is not to miss the carcinoma. Once you have CC, the options are extremely limited. And CC very often recurs post transplant. So we are always watching out for it.

If it is advanced, LTX is not an option. And CC does not have to be very advanced. If the tumor is 2cm, it is already too far-gone. You have to catch these cancers when they are *in situ* (“in place,” where only the surface cells of the tissue are cancerous) or when they have not gone through the wall of the bile ducts, and that is an extremely difficult thing to do.

We are getting better with MRIs (Magnetic Resonance Imaging). Sometimes we can pick up CC on MRI. Some blood tests can indicate that you have CC, but these are totally unpredictable.

And even if we find CC at an early stage, you cannot just have a TX because the recurrence is almost 100 percent, so you have to undergo very aggressive neo-adjuvant therapy before the TX.

The group at Mayo has done a lot of work on this process, and we, at Northwestern, have also worked on it. We exclusively go to LDLT (Live Donor Liver Transplant) for those with CC, and have some fantastic results with therapy and LDLT. But this is a problem you do not want to be facing because it is really very challenging.

The problem with LTX and PSC (in the US) is that there is one score that consists of the results of three blood tests: the MELD score. This determines your priority on the waiting list. It is

your blood type and your MELD score that determine your status.

The problem is that cholestatic diseases like PSC and PBC are the worst diseases to have in terms of the MELD score because the score is determined by the bilirubin level which is one of the least weighted values in the logarithmic calculation that is the MELD score.



Dr. Michael Abecassis

And to get priority when you need a LTX with PBC or PSC is difficult, and there is no significant upgrade you are entitled to. The race is on, the clock is ticking, and you need to get a liver before the disease advances. In our Region 7, we tried to get an upgrade with CC and could get only a small upgrade. So with PSC or PBC, priority status could be a real problem in the US.

Our problem as surgeons is deciding what process to follow when we suspect that a PSC patient has CC. We may not be able to prove it, though we have the suspicion, and there is not really any other reason to do a LTX.

You can assume there is a cancer and do a TX, or you wait, but it is possible that in a short period of time the cancer may advance to the point where a TX is no longer an option. This is a

dilemma that our group may discuss several times a year with specific patients.

For adults in the U.S., we tend to take the right lobe of the donor for a LTX. This is 55-60 percent of the surface of the donor's liver. The donor, left with 40 percent of his/her liver, will recover 90-100 percent of the liver within a couple of months.

And the piece of the liver that is given to the recipient also grows to its normal size. But with children we only take a little tip of the liver. It is a much bigger deal to take 60 percent of the liver, and that is why LDLT has taken such a long time to get off the ground.

About seven years ago, there was a lot of concern about LDLT in the US. A lot of centers were starting to perform them. They were involved in a consortium study that would once and for all answer us about the safety and efficacy of LDLT.

We had to decide whether a LDLT was better or worse than a LTX with a cadaver organ. How much better can you do with a LDLT than a regular LTX if you need LDLT?

It is not as if you could get a LTX tomorrow. You have this long waiting list, and you are much more likely to die waiting for one than you are to get one. To compare the efficacy of one with the other makes no sense because you can have a LDLT tomorrow if you have a donor.

So the question in this study was the following: Assuming you need a LTX, is it better to have LDLT rather than not to have one? Not everyone who needs a LDLT can have one, because not everybody has a suitable living donor.

[Points to slide] This is the chance of dying; this is not only for PSC but LTX in general. The yellow line represents staying on the waiting list. Over time the chances of dying go up.

It turns out that it takes 20 LDLTs for a transplant center to get over the learning curve, to learn from their mistakes, surgeons need to perform 15-20 LDLTs to really get good at it. And once the center reached this threshold, then the results of LDLT were far superior to those who were waiting or getting a deceased donor transplant.

This is what has now led to resurgence in LDLT for when it is highly unlikely that a PSC patient will be getting a deceased donor TX.

These results have been published in the last couple of years. If you just compare the operations themselves: it used to be that post-LDLT survival was worse, but now they're equivalent. But if you need a LDLT, your survival is much better because you avoid the waiting list.

The second question we need to ask is what about the donors?

This is a big surgery. At Northwestern, we have the largest kidney donor TX program in the US. I can tell you that being a kidney donor is easy in comparison to being a liver donor. You go home the next day and back to work the next week. You give up a kidney but in terms of morbidity (illness), there is no comparison with taking 60 percent of the donor's liver.

What is the risk to the donor? Even though we are the only center in the world to do the operation microscopically, it is still a pretty big operation. We ask ourselves, is it ethical to put the donor through this kind of risk?

Remember, the donor is a healthy individual whose only crime in life is that they know someone who needs help! And we took an oath as physicians to help and not to hurt. This is contrary to everything that we believe in, but it is something that we have come to agree, saves lives. The issue hit the headlines when a brother



who was a donor died in NY. At about the same time, there were a total of six donor deaths. What was going on essentially was that the selection of donors was not good and every operation has risks.

Let's define the risks and minimize them. Let's make sure that every donor that goes through this, puts emotions aside and understands the risks. We defined the surgical complications and their significance from least to worst.

Grade 1 complications are basically a nuisance and do not really hurt anyone. You may have to stay in the hospital an extra couple of days.

Grade 4 complications occur when you donate 50-60 percent of your liver, you have liver failure and you need a liver TX yourself. We have had two such cases in the US, but not in Chicago.

We wanted to know about the incidence of complications but also about their significance. We did this introspectively, and the bottom line was that in 230 living donors if they sneeze we have to report it as a complication. There was a three percent incidence where the donors went to the operating room, got the incision, and then the decision was made to abort the operation for whatever reason. That's a complication.

Or the operation can't be done for some reason. You have gone through an unnecessary operation. That is also a complication.

Twenty nine percent of donors had at least one complication. The vast majority involved biliary infection complications, and recovery for this complication takes place within thirty days. This was a seven-year study.

If clearly you were a good donor, most of the complications were Grades 1 and 2, which are defined as needing some kind of intervention, but leaving no residual problem. But there were four

Grade 3 complications. Luckily we had no deaths and no need for TX.

There were another 500 donors that we reported on. For over 666 donors in this cohort the results have been very consistent.

The bottom line is that this is an operation that has complications but these are nearly all Grades 1 and 2 complications. Even in Grade 3, a complication might be a hernia that needs to be fixed. So these are not huge complications. But we consider any complication a significant complication. It was nice to know that those in the second set had gone down in complications. There's that learning curve: we get better at it as we do more operations.

The livers in donors regenerated to 90-100 percent over two to three months. These are the participating centers [on the screen] and the primary investigators.

PSC has become one of the primary indications for LDLT because PSC patients have low MELD scores when they need a TX. We opt for LDLT for those patients we really suspect of having CC, and those are patients who would need TXs down the road anyway. We have had good results with such patients, especially using photodynamic therapy and radiotherapy.

The program has been so successful that it is now being renewed for the next five years. The interest has now shifted. We are no longer just interested in what percentages of patients get complications. We are still interested in that, of course. But we are also studying the post-transplant quality of life of LDLT patients in relation to those receiving cadaver livers. We are currently designing instruments to measure quality of life accurately. We have seen that LDLT is safe and effective, that problems and complications decrease especially once a center goes beyond the learning curve of 15-20 cases.

## **Discussion with Panel of Drs. Heathcote, Abecassis, Green, and Baker**

### **Who are the donors? Are they necessarily family members?**

No. In the pediatric department, they are usually parents, but with adults, it is siblings, spouses, neighbors, a priest donating to a parishioner, friends, etc. We call it being emotionally related.

### **What sorts of procedures are used to maintain ethical responsibility?**

LDLT presents significant ethical questions. About four years ago we created the Chicago Transplant Ethics Resource Center, a multi-center, inter-disciplinary group that meets weekly. We had a conference in 2008. The center addresses specific issues that come up.

### **What are the specific blood tests for screening for CC?**

Unfortunately, there is no specific and sensitive blood test. We would like a blood test that could identify CC early and would be specific for CC and not give us false positives. The CA-19-9 blood test is frequently used as a tumor marker. If we see increasing elevations over time, we will screen. It is not very specific as a test. We will combine this with screening, MRCPs, etc.

### **What signs or symptoms make your suspicions fact?**

There are no specific signs or symptoms, and that's the dangerous part of it. But any kind of decompensation of a very stable situation, that is, any kind of sudden change, jaundice, changing color of stool or urine. These indicate there may be obstructive jaundice even though this may not yet appear in the eyes. Sudden pain, weight loss or any kind of sign suggesting that things are different, are indications to check for CC.

### **Should a patient diagnosed with PSC, but having never experienced bacterial cholangitis, carry antibiotics while traveling?**

Part of the reason for this conference is to help people lead a normal life. Ascending or bacterial cholangitis is really very rare. But if you have repeated bouts of bacterial cholangitis in your bile ducts, yes, it is important, but for the overwhelming majority of patients, I don't think it's necessary.

### **I understand that doctors can advocate for exceptions to MELD scores, based on issues like CC, ascites, varices. Which physician does the advocacy? Is it the surgeon, the hepatologist, or can the patients advocate for themselves?**

There are certain rules and exceptions. For PSC, CC is already in the book, so we write a standard form and it gets upgraded. Unfortunately, PSC doesn't get enough points. If we have PSC patients with a bunch of biliary drains, and that's another way they can live, but their MELD score is not elevated, then the team, comprised of both hepatologists and surgeons, get together and write a compelling letter asking the Regional Review Board to give this patient the necessary points so that they can have access to a LTX.

A Regional Review Board is made up of representatives from all the TX centers in the region. But there are also lay people on the Regional Review Board. The patients have no way of being their own advocates other than having their physicians advocating for them. We often ask if we can have some points to avoid LDLT. If the answer is no, which it usually is, then we go to LDLT.

### **Does early medical attention for cirrhosis help slow down progression of PSC from one stage to another?**

Cirrhosis just means scarring. It is often associated with alcohol, but it really may have nothing to do with alcohol. The progression of the disease from “compensated cirrhosis,” meaning your liver is functional, to “decompensated cirrhosis,” meaning you are having liver failure, is probably not affected by medical therapy.

What’s important is having cirrhosis. There are certain ways to avoid the complications, especially variceal bleeding in the esophagus. It can be predicted by screening endoscopies, and by recurrent screening and imaging. It may be necessary to do repeated screening and imaging. It may be necessary to do screenings and perhaps biopsies just to see if patients need to be studied with screening.

**It often seems that you need more than one study to answer a question. It is frustrating when you are looking for an answer. You get one test and it is a kind of answer. You get another test and you may have a little bit more of an answer but not a definitive one. With PSC it is even truer than with most liver diseases.**

I’m probably not supposed to say this, but we’re people *and* we’re doctors. We do the best we can. When there’s a definitive way to answer a question, we will always use it. But there is also a grey area. Screening for CC is a perfect example. Often we will clinically suspect something but not definitely know. Sometimes you get a second opinion. We can repeat tests three months later and get different results.

**Should somebody who has been taking high-dose Urso think of reducing the dose based on the Lindor study?**

Opinions differ.

[Dr. Heathcote] We don’t know the reason why they found what they found. I suspect it was something to do with the recruitment. Most of the patients were on Urso and they had to come off it to go into the study, and why would they want to go off it if they see Urso improving their LFTs? So it may have been people who were not responding to Urso treatment in any way. We have to wait for the answer.

I asked Keith Lindor, we know that 20mg/kg of body weight per day appears to be quite safe so I would lower the dose. I say to my patients, “I don’t want you to be on high dose because there’s some disturbing data, but based on previous studies, I don’t think there’s any disturbing data on taking lower doses.”

The other study from Scandinavia did not show this toxicity. In fact, had more patients been recruited to that study, these may have seen improvement in survival. Those on high-dose Urso did better but it wasn’t significantly different statistically. The problem could have been sample size. Two hundred patients (in the Scandinavian study), is not a very big sample. In PBC studies we need to have at least five hundred to show if there are any improvements.

[Dr. Richard Green] There is some evidence that Urso may reduce the risk of colon cancer in UC, so I am continuing to treat my patients with Urso.

**Talk about activism from public and patient support groups.**

There has to be some kind of allocation system for organs. The fact that the MELD score disadvantages patients with cholestatic liver disease was discussed at meetings considering the MELD score.

There were groups of patients lobbying and interest groups pleading with the federal government to take into account the interests of

PSC and PBC patients. This obviously didn't help. There aren't enough organs and therefore somebody gets rationed out.

The MELD score seems to work for most people but that's why we offer LDLT to those who are disenfranchised by the allocation system.

There's always a role for activism and being engaged, and there are a lot of different ways in which this group can influence and maybe inform policy. I think the problem is going to get worse with the introduction of this sodium measure in the MELD score, and PSC patients don't have this indication.

I think the best possible action is to try to mobilize patients who don't fit the MELD model well to get priority through the Regional Review Boards. And one of the issues is that there is an incredible amount of variability between Regional Review Boards.

Some say yes to everything and some say no to everything. There are no standards. All the UNOS meetings are public and the public is invited to participate. They meet three to four times a year and they generate policy. It would be

important to have representation at those meetings when an issue like this is being discussed. Go on the UNOS website and look at the liver committee and find out when they're meeting and what the issues are going to be.

It's an open forum and the public is encouraged to comment, and every rule that UNOS makes goes through a public comment period and they have to address every public comment. So there's a lot of opportunity for people to be active and advocate policy making.

Another area is to be active in increasing organ donation. This is the central thing along with prioritizing PSC. Our secretary of state has a brother who got a kidney TX. That was fundamental in the way we changed our laws here. You can now get a driver's license clearly stating that you will donate your organs.

The best example of patient advocacy is the dramatic improvement in HIV treatment in large part due to the continuous political lobbying of patients.

## Update on PROGRESS: PSC Resource of Genetic, Risk, and Synergy Studies Dr. Konstantinos Lazaridis, Assistant Professor of Medicine, Mayo Clinic

Dr. Lazarides presented a report on current developments in this important project, which is to be large-scale and long term. It parallels the genome-wide project that Dr. Chapman and the Cambridge group are working on, but this Mayo project is to be much bigger. It is also going to be long term, and there will be an attempt to

investigate environmental factors in the etiology of PSC.

The overall rationale of the project is to better understand what causes PSC in order to improve diagnosis, condition of the patient, treatment, and more clearly understand the complications of PSC. There is strong evidence from

Scandinavia and the US and other studies that genetic factors are involved in PSC. DNA will be collected and studied from all participants to understand the genetics of PSC.

To do all of this, we have to go back to basics. There is most likely something in the

environment, an infective agent, a chemical, or something else, unknown, which affects some individuals who have a genetic predisposition to get PSC. We therefore have to understand how that genetic predisposition works together with relevant environmental factors.

PSC is complicated in nature, and there are going to be complex multiple, small, genetic defects that interact with each other and with the environment.

PSC is highly variable. Once we understand the genetic factors as to why some have PSC developing faster and others slower, we can produce improved diagnoses, including who is likely to need a LTX, who may develop CC.

Our approach is to collect DNA from patients, their family, and also from the population without PSC. We then find what is unique about PSC patients compared to the non-PSC population. We can then individualize treatment. We also recruit first-degree relatives. We have been treating PSC patients for over forty years. And the Registry that we started to build in 2005 will have both old and newly diagnosed patients. We

consider this particularly important because if we only use newly diagnosed patients, it could take 10-20 years to observe the outcome of the disease and its complications.

In general then, these are aims. The questionnaire is more than 37 pages long and takes an hour to complete. This is a tool to help us understand the characteristics of the disease and it will also help us to assess the environmental risks, as far as we can.

So far we have collected specimens from 400 patients and received their completed questionnaires.

There is collaboration with Dr. Tom Karlsen of the Oslo group and the sharing of information on the specimens, unless patients object to sharing. Currently most of our cases are from the Midwest, but we do have cases as far as Alaska and in several other states. We need to expand this because we are also assessing the role of the environment. This is a long-term participation, and after five years, we will return to participants to ask more questions about how they have been doing.

So far, from the 400 who have currently participated, most of

the cases are male, which is what we expect of course, given that PSC is a male-dominated disease. Most are Caucasian. We need as many non-Caucasians as possible. As we would expect, the length of the disease, from diagnosis, is variable. From recently diagnosed, to one patient who has had the disease for 42 years and is still doing well. The average is over 10 years.

Ages vary from 8-83. There is a wide spectrum because of the heterogeneous nature of the disease. About 80 percent have IBD. Eight percent have, or have had CC. It appears that if CC is going to develop, it is most likely to be within the first five years after diagnosis. We don't know why.

Dr. Konstantinos Lazaridis



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Most PSC patients first present with IBD, then, around 14 years later present with PSC. About 17-18 percent develop the two diseases concomitantly. And about the same number, 18 percent, present with PSC first and IBD later.

We initially sent off 2,000 letters, and we use websites for recruitment. This project has taken many years to establish, and we are thankful to those who have so far participated. We need more of you.

## Know Your Rights: An Overview of Health Insurance and Federal Disability Law

Jennifer Jaff, Advocacy for Patients with Chronic Illness, Inc.

I'm going to give you a very short overview relating to your legal rights as PSC and IBD patients. I've had Crohn's Disease (CD) for 34 years and I've also had gastroparesis. This is in the *Know your Rights Handbook*, which I will leave as a donation to PSC Partners. It is available also on our website at <http://www.advocacyforpatients.org/>.

I'll start by answering the question I get most often: *Is my disease a disability?*

The answer is, it depends—not a fully satisfactory answer but it is the truth. It depends on what you can do, not on the name of your disease. It depends on your ability to function, regardless of the context.

For each context there's a different definition. For example, if you have private disability insurance, you need to look at the definition of disability under

your policy. If you cannot perform the essential functions of your occupation (these are *own occupation policies*), it can say that you cannot perform the essential functions of *any* occupation. Then there are policies that start out as *own occupation policies* and then after two years, they turn into *any occupation policies*.

A lot of people think they're going to get their disability benefits forever but there are several steps: The first one is, "Do you need a listing?" There is a detailed listing on liver disease: PSC is included.

But having PSC is not enough to get you Social Security Disability. You have to meet the technical requirements of very specific categories relating to liver disease. If you don't meet the listing, it doesn't necessarily mean that you'll fail the Social Security Benefits for Disability.

They will look at whether you retain the residual functional capacity to work. This is the same as the definition I just gave you. It's not the name of your disease; it is what you can do.

If you, for example, have a light, sedentary job as a receptionist, an example they like to quote, and you can do it, you are not disabled. You have to be substantially impaired in the performance of the major life activities; that's in the Americans Disabilities Act. This includes walking, talking, seeing, hearing. These were Amendments in 2008. It also includes major bodily functions such as digestion, immune function, etc.

I'm asked so often if these amendments make it easier to get Social Security Disability. No—the definition, which has been broadened, has not affected the ease of getting disability. Even if you meet the definition of

disability, you are not covered by the Act if you can perform the essential functions of your job.

For most jobs attendance is an essential function (unless you can work from home). This attendance loophole is particularly

important. If you can't turn up on a regular basis, you can be fired even if you have a disability because you can't perform the essential functions of your job.

Unfortunately the Family and Medical Leave Act (FMLA) applies only to employers with fifty or more employees but this varies between states and you need to check. The FMLA gives you twelve weeks of unpaid leave out of any twelve-month period. But it is very important for people with chronic illnesses and a lot of people don't know this: that FMLA can be taken on an intermittent basis, for example, if you need a couple of days off every eight weeks for your Remicade treatment, it's no problem: You can use FMLA for that. The beauty of FMLA is that you can't be fired even if you miss twelve weeks in one year. You have job protection under the FMLA.

The last part of the question, "Is my disease a disability?" Under



Jennifer Jaff, Esq.

for Medicare. There are a whole set of problems here. It is very difficult to show that you are disabled. There was a 2005 report that showed that 67 percent of applicants with IBD are denied on their first application for Social

Security Disability.

I suspect that the numbers for PSC are probably better because it is easier to meet the listings, but I couldn't find a figure. The listings for IBD are extremely narrow. But if you have both IBD and PSC, they must look at the combination of impairments: So don't tell them that you have just one of the two if you have both. Make sure that they get records from both of your doctors.

If you are denied, you absolutely must appeal. You must have a lawyer. You cannot go to an appeal and not know how to cross-examine. A lot of people here do not even know what a Vocational Expert is. It is the person who comes into your hearing. They'll come up with jobs that they think you are perfectly capable of performing. Therefore, you're not entitled to Social Security Disability.

You need someone who can cross-examine that person,

Section 504 of the Rehabilitation Act of 1973, otherwise known as Section 504, the definition of disability is exactly the same as the American Disabilities Act, that is, substantially impaired major life activity. We have every reason to believe that the new amendments will apply to Section 504, but the courts have not yet decided the question.

I'm giving you a very rapid and oversimplified account of a very complicated subject. The second question I very often get is, "Is there assistance for me if I don't have private disability insurance?" The only really good answer is Social Security Disability (SSD). That is the form of assistance that is available. There are two forms: SSDI: you have to have worked forty quarters for a total of ten years. If not, you might qualify for SSI. Your income has to be at the poverty level.

If you get on SSD, after two years of benefits, you are eligible

someone who can take time to understand your disease. We don't ever charge for our services, but we don't handle appeals. We work with lawyers who do, and we help them understand the disease. These lawyers don't get paid unless they win. Federal Law establishes the fee. It is the lesser of \$6000 or 25 percent of a retroactive lump sum that you get. This goes back at least to the date that you applied for social security or earlier. You get this lump sum benefit when you first win your appeal. That's the only easy source of financial assistance.

Unfortunately, there isn't any temporary benefit that would be good if you have a sudden flare-up. It's all or nothing.

Under the Disabilities Act, you can try to get an accommodation with your employer but you don't always get what you ask for. For example you might ask for permission to work at home full-time. Your boss might agree if you can come in for team meetings weekly. It's an interactive process. You negotiate.

If your employer will not negotiate, that violates the American Disability Act. You can file a complaint.

That's the easy stuff. Now what does it mean to be HIPAA eligible? This also covers pre-existing conditions. If you've had continuous group insurance for 18 months and this has not lapsed for 63 days or more, you are HIPAA eligible.

This gives you a guaranteed issue option. This means they can't turn you down. This will cover your pre-existing condition. This is very good news for all of us. The problem is that the guaranteed issue option is different in every state. Insurance companies are allowed to discriminate and premiums are often higher for women. They can use gender, age, where you live, etc. to discriminate.

If you lose your job or change it, COBRA means you're allowed to continue the insurance you have for 18 months, whether you lose your job voluntarily or involuntarily. You have to be in premium but they have to let you keep your insurance. This would generally be your best option and in order to be HIPAA eligible, you have to have exhausted your COBRA. If you have COBRA, you have to use it. Otherwise, in most states, they're allowed to turn you down because you have a pre-existing condition. Or you can call me and I'll do some research for you.

There are other options for insurance. For example, you might join your local Chamber of Commerce and join a group health insurance through them. There is the National Association of the Self-Employed, which can be joined for a low membership fee, and they have group health insurance that you can sign up for. These kinds of things are out there and they're changing all the time. We really have to ask a lot of questions about whether your pre-existing conditions will be covered and what your benefit limits will be.

When you are denied what you need, you must appeal. Only four percent of people do appeal. Write using your medical data. Don't just write an informal letter to your insurance company. They want to see the underlying medical records, even if it is your doctor writing it. Take the time to get these medical records.

If they deny you your application because of some medical question, you are also going to have to do some medical research to see if there are studies to support the particular medical treatment that you need. You must identify the reason for denial. If it is medical necessity, you need medical records. If it is experimental, you need medical journal articles. What you say in the appeal will be dictated by the reason they give for denial.



Most importantly, you must always include objective medical evidence in the form of medical records: not just a letter from you or your doctor. As for you doctors, insurance companies are not really persuaded by your letters.

Some policies have lifetime dollar maximums. The most common is \$1 million maximum. But with the kind of illnesses we are talking about, it is a joke. I know people who have had to change jobs to get new insurance, so they can get a clean slate. It does not follow you around, unless you stay with the same insurance company. If, for example, you are with Blue Cross, Illinois, and you change jobs to another employer in Illinois who has Blue Cross, you are still at that lifetime maximum.

If you have no insurance, there is no single answer. You have to take a little from here and a little from there.

Free prescription drugs are one of the easiest things to get. Every pharmaceutical company has a patient assistance program. They provide meds for free for those who meet their income guidelines. If you don't have insurance and you are having trouble paying for medication, look into this. The website that I like best is [www.neednet.org](http://www.neednet.org) and you follow the instructions.

Non-profit hospitals have to provide charity care. They get money from the federal government, but our experience is that they often don't use it. It is meant for "uncompensated care" for those unable to pay. This is not a favor the hospitals do you. They are required to do it by federal law because they are already receiving that money. They are supposed to spend it on your care. They often sit on that money, and they don't spend it where they should. You have a right to tap into it. If you don't get 100 percent, there are hospitals

which give discounts. You can negotiate with hospitals. They are used to doing that.

But doctors are the hardest to get for free. There are Fed-financed health centers. There's a wonderful website: [www.Findahealthcenter.HRSA.Gov](http://www.Findahealthcenter.HRSA.Gov) . You first put in your address, and you will get the centers near you.

But it is very difficult to get care from a specialist if you have no insurance and cannot pay. At most of these clinics, you are looking at primary health care physicians. You work with your doctor, make a payment plan, stick by it, have that constant dialogue, and don't make them send your claim to a collection agency. You are then going to have to negotiate for something you will be unable to afford.

What about protecting the rights and needs of college students regarding their workload? A Section 504 requires schools to provide reasonable accommodation for students with disabilities. And this applies to all members in education. You also have the protection of the American Disabilities Act once in college and for post-grads. So you have two layers of protection. But it's again, a negotiation process. The parents negotiate.

You can, if you have to, go through a complaints procedure under Section 504, but don't expect a lot. If you have a serious problem, come to me and I'll see if I can help you. We could spend hours on this topic.

Please find me personally at [www.advocacyforpatients.org](http://www.advocacyforpatients.org) and my phone number is right in the middle of the homepage. You can call me and I will try to help you. We've never turned anyone away.

# Breakout Session Summary: Pre-Transplant

Dr. Alfred Baker, Professor Emeritus, Department of Hepatology, and  
Katie Turpin, Transplant Coordinator

*reported by Ross Heil*

Three things you need pre-transplant are a physician that you have confidence in and one that knows your disease; reliable information, and a friend that listens in addition to your spouse.

He gave an overview of the incision of a liver transplant. Put your right hand over the right side of your body with your middle finger on your xiphoid process. Notice where your fingers are laying, this indicates the right lobe of your liver. With your hand in the same position, slide it along your rib cage around to your back.

This area is about the size of your whole liver. The remaining area is the left lobe of the liver. If you do the same thing on the left side of your abdomen, this is where your spleen lies. Both the spleen and liver are very important in a liver transplant.

The main criteria for a donor liver match, both living and cadaveric liver are: blood type and size of liver (notice that

HLA is not required to match as in kidney transplant).

The centers, found on the UNOS website that perform living donor transplant, will turn to a living donor when the patient is not going to survive long enough to obtain a cadaveric liver transplant.

Having said that, there are always exceptions, but this is the rule that is followed. The reason that the living donor option is not pursued first is due to the risk to the living donor.

The relative, not absolute, age limit for live donation is around 60-65. This is due to the liver not working as well post transplant in addition to the risk to the donor increases as the age increases.

It is important to make sure that no one feels forced into being a living donor. An extensive psychiatric evaluation will be done on the living donor.

**Questions Asked of Dr. Baker and Kate Turpin**  
Are you confident in the MELD score with respect to PSC?

The MELD score reflects the progression of PSC less well than in other liver disease. The score is comprised of the serum bilirubin, PT time/INR (best measure of overall liver function), and creatinine (kidney function test), since liver failure can affect the kidneys.

These components go into an equation and yield a score. This score can be compiled on the UNOS website and gives an expected survival over the next three months.

**Should a living donor be lined up in advance?**

First, you should check with the transplant surgeon. If the patient has a low MELD score then do not worry about a living donor yet.

**How is a split cadaveric donor liver utilized?**

The left lobe is given to the child and the right lobe goes to the adult. This rationale is due to the size of each lobe.

**Are there any drawbacks to a PSC patient if he doesn't get the whole liver?**

Studies suggest that survival is about the same. Having said that, patients with severe liver disease, with a high MELD score, need the whole liver. Fortunately in PSC the surgeon can generally time a living donor transplant where you avoid the patient becoming too sick.

**What about being listed for a liver transplant in more than one region?**

A patient can be listed in different regions at the same time. There are ten regions currently in the US. It might be advantageous if one region has more organs that would provide an organ donor sooner at the same MELD score.

**Why shouldn't you push to have a transplant when you have a low MELD score?**

Studies show there is an increased risk of death when a patient is transplanted at a low MELD score. Only with a

MELD score of 15-16 does it make sense to have a transplant.

**How do you determine who gets a liver?**

Allocation is based on size and blood type. Donors with group O blood go to the recipient with highest MELD score and type O blood. Blood type O, however is universal and can be used by persons with non-O blood types.

**Can previous surgeries affect the viability of a liver transplant?**

It depends on the size and site of the surgery. However in general most surgeries should not prevent a liver transplant.

**Does a liver transplant include transplantation of the bile duct?**

With PSC, they try to remove the recipient's entire bile duct and take as much of the donor bile duct (assuming cadaveric), to attach to the small intestine.

**Would it be best to find a transplant center that does both live and cadaveric donor transplantation?**

Here at Northwestern, we believe the answer is yes. To

find a live donor center, look at the UNOS website which states the number of living and cadaveric donor transplants that occur at each center. The more experience a center has, the better the outcome will be.

Look for a surgeon with 20-30 live donor transplantations and many years of experience to feel comfortable. A few of these centers include University of Chicago, Nebraska, and Emory. Also the insurance a transplantation center takes will give you a good idea of how it stands. If the center does not take Blue Cross Blue Shield, you should be concerned.

**Is there a strong enough link with genetics and PSC that if a living donor is needed that a member from outside the family should be sought?**

There is no evidence that a patient with PSC will do worse or will have recurrent PSC if a live donor is taken from the family, even if it is from their parents or siblings. There are similar rejection rates for transplants that come from close family versus outside of the family.

# Open Forum Discussion Summaries

*reported by Ivor Sweigler*

## Post-Transplant Group

On Sunday the meeting broke up into separate groups, that is, post-transplant, pre-transplant, parents of adult PSCers, parents of pediatric group, PSCers in their 20s and 30s (female group and male group), PSC men over 30, PSC women over 30.

I chose firstly to sit in with the Post-Transplant Group. There is no doubt that a liver transplant (LTX) is life-saving when your own liver is near the end of its useful life and you're into end stage for PSC with a cirrhotic liver. Survival depends on your being evaluated and then entering the waiting list. The group of six in this session agreed that having a new liver was not the Holy Grail or the Elixir of Life. "You have a different set of problems. You just change one set for another."

You know you're so much better than before and you get used to the effects of taking anti-rejection drugs for the rest of your life. All these drugs come with problems.

Some of the side effects mentioned include loss of taste, and you may not want to eat. Muscles may not gain their previous strength. It can take two years to gain normal muscle control. There can be nausea but without throwing up. Tremors, back pain, and hallucinations were also mentioned. The drugs tire you out and can affect your mind.

None in the group would have wanted to change their decision, and they were all extremely grateful for their "Gift of Life." They would not want people to think they were complaining, but

said they should be realistic about living with a transplanted liver. And while PSC patients have the highest success rates among the various liver disease groups, PSC can return in a minority of cases, though usually in a milder form.

*Additional notes reported by Denise Boyd*

- \*Everyone has a different transplant experience
- \*The "healthier" you are when you get your transplant, the better your recovery will be so try to maintain general health pre-transplant and try to transplant earlier if possible.
- \*Even immediately in the ICU after transplant the recipients felt better.
- \*It's completely feasible to have children post-transplant but it's important to find an obstetrician who is familiar with transplantation and to check possible effects of medication before getting pregnant.
- \*Staying positive post-transplant is also important for a good recovery; get help if you need it.
- \*Early diagnosis of cholangiocarcinoma can be treated and then you can be transplanted, i.e., transplant is not ruled out because of CCA.
- \*Recurrence of PSC, if it occurs at all, is usually a milder form and rarely requires a second transplant.
- \*Getting back to work post-transplant is so variable. Don't judge your recovery by others' experiences.

\*You may wish to consider a change or shift in career post-transplant that doesn't expose you to very sick people or require long shifts, etc.

\*Some surgeons are reluctant to conduct other, non-transplant surgery on transplant recipients. This notion should be questioned since it may just be their lack of familiarity with transplant recipients.

\*It can be a delicate balance between taking enough immunosuppressants to avoid infection and taking a low enough amount to limit side effects.

\*Short-term memory loss is a significant side effect of Prograf and can be related to blood levels of the drug.

\*Immunosuppressants can cause headaches and pouchitis problems, among other side-effects.

\*Always carry medications in your carry on suitcase and bring extra meds when traveling.

\*You can arrange to have extra supplies of medications provided from the pharmacy if you are going to be away for a long period of time

## Young Male PSCers

*reported by Ivor Sweigler*

I then sat in at the tail-end of Young Male PSCers in their 20s and 30s. Thanks to Jecy Belmont for giving me the gist of what had been discussed. It's not surprising that a major concern was the question of dating and how and when you discussed your health once you got into a serious relationship with a woman, although several in the group were already married and had small children.

A further topic was that of finding a living donor and the pressures that might be placed on a sibling. They talked about the potential problem of dealing with drinking with one's peers and the difficulty of finding life insurance.

## Parents of Adult PSCers

*reported by Mary Ann Long*

\*We are our own advocates

\*Need ideas for getting PSC information to medical professionals in the community

\*PSC patients need to be seen at a major medical that sees a number of PSC patients!

\*Each PSCer needs both a gastroenterologist and a hepatologist

\*Tell doctors about PSC Partners website

\*FAQs on website: please ask members to contribute answers and helpful tips as well as questions (similar to Wikipedia)

\*Academic meetings may have helpful information. Let us know when and where. Get our info to academic meetings

\*Encourage adult patients to participate in studies

\*Seek second opinions if not satisfied with doctor or facility.

\*Get the word out to newly diagnosed via brochures, public service announcements directing patients to information

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## Current PSC Research in the UK

*by Ivor Sweigler, Chairman of PSC Support, who graciously offered PSC Partners his written presentation for publication when events precluded him from speaking during Sunday morning's session.*

The paramount PSC researcher in the UK remains Dr. Roger Chapman at the John Radcliffe Hospital, Oxford. He's been seeking the cause, that elusive trigger, for 36 years and has by no means given up.

The problem is lack of funds. He has a "Liver and Gut" fund, which is often empty. Our PSC-Group tries to raise funds but we have managed to collect only £10,000 per year. We hope we can raise it to £15,000 this year after two sponsored races, including this year's London Marathon.

Dr. Chapman is pursuing many areas of research He provided me with the following list of active projects.

1. A British Nationwide Genome-wide screening of 1,000 PSC patients. So far they have collected data on 300 patients. Half million pounds was required for this study. This funding is being provided by NoPSC in Oslo. We gave £10,000 to cover the cost of collecting DNA.

2. Studying pouch function in PSC. A large study examining all aspects of pouch function. Funds urgently required.

3. Study looking at PSC prevalence in UC patients and those with colon cancer and pre-cancer using MRCP Funds urgently required.

4. Study looking at Crohn's and PSC. Funds urgently required. (He believes that those with Crohn's have a lower rate of colon cancer than patients with ulcerative colitis. In discussion with Dr. Terry Barratt he questions this. Dr. Barratt said that he's seen colon cancer in several Crohn's patients at Northwestern Memorial Hospital.)

5. Quality of Life (QoL) study including fatigue in PSC. . It is increasingly believed that fatigue in cholestasis is derived from central neurological origin, In addition with collaboration with Prof Simon Taylor Robinson at Imperial College MRS brain-scanning has been performed PSC patient volunteers. The results will be published soon

6. Collaborating with University College London and Imperial College, London on bile duct cancer projects.

Dr. Chapman believes that PSC is much more prevalent than was

previously supposed, that if you look more carefully at ulcerative colitis patients using MRCP scanning you find PSC-like features even though they're asymptomatic and cause no problems. It's more likely that 90 percent of PSC patients have (or have had) IBD, if you look very carefully.

He presently has over 250 PSC patients being followed at the John Radcliffe Hospital.

*University College London Institute of Hepatology, under the direction of veteran Hep, Prof. Roger Williams.* They have 50 PSC patients and are involved in important liver disease research. Relevant to PSC are ongoing research projects in cirrhosis and producing new tumor markers for CC. (I assume they must be in contact with the similar ongoing project in the US.)

*Queen Elizabeth Hospital, Birmingham, Prof. David Adams.* This Liver Unit has developed over the last two decades and more into a major center of research into cholestatic liver disease. David Adams has received grants totaling £6.5 million, beyond his wildest dreams.

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For a full account see the nine page report in our *PSC – News*, April 2009, #42. He is involved in leading-edge microbiological studies into autoimmunity and liver disease. He told us in our meeting with him on February 7, “We have a unique combination of facilities.” These facilities include:

1. A clinical liver unit;
2. A center for liver research, which includes his group working on inflammatory liver disease, and
3. A stem-cell center which brings together large groups of scientists. We have some wonderful research facilities totally dedicated to research (not dedicated to standard patient care), where we can do everything from colonoscopies, to infusing cells, to monitoring patients, all very carefully controlled and well-staffed.
4. In the Blood Transfusion Services Centre we have a GMP, Good (clinical data) Management Practice, where you can make these cells under immaculate conditions...
5. The Clinical Trials Unit. They advise us on how to carry out studies and trials. They have world expert statisticians and trial designers.

“It is a very exciting time in Birmingham. All these facilities are (now) in one place,” he said.

Asked when we could really start curing PSC, he said, “... I don’t know; it is going to be years. The one hope is that these currently tested new drugs for IBD . . . can be also used to treat PSC. That could happen over the next year or so. Perhaps at this kind of meeting in five years time, we may be able to say that there’s a cohort of you who are suitable for using new drugs like Infliximab and other agents for treating PSC.

*Liver Unit, Edinburgh, Scotland.* Under Prof. Donaldson and his team, genetic research into PSC and PBC has been ongoing for several years. There are some publications.

*Liver Unit, Freeman Hospital, Newcastle, North England.* This is a well-known center of PBC research, but under Prof. Julia Newton, there is an increasing interest in PSC and some trials are being planned, no details were offered.

*Institute of Hepatology, King’s College, London.* This is the biggest liver unit in Europe. They have around 50 PSC patients and perform around 220 LTXs per year. It is sad that here hasn’t been any adult PSC research for years, but under Prof. Giorgiana Mieli-Vergani who is a leading authority on pediatric PSC, there is important ongoing research and many publications.

It may be surprising that there is so much research into a rare disease like PSC, but doctors have told me that they find the link between the gut and the liver “fascinating,” a word they use, although we wouldn’t! And by studying PSC and PBC, they are learning much about autoimmunity.

The above topics are regularly reported in our quarterly U.K. newsletter, *PSC-News*. Anyone wanting copies should contact me (Ivor Sweigler) directly at [psc-support@aol.com](mailto:psc-support@aol.com).

## 2008 AALSD PSC Partners Research Awardees Report on Their Progress

PSC Partners Seeking a Cure has awarded \$3,000 prizes annually at the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

The recipients of the 2008 PSC Partners Seeking a Cure AASLD Awards were Dr. I. Tornai (2nd Department of Medicine, University of Debrecen, Debrecen, Hungary), and Dr. P. G. Blanco (Beth Israel Deaconess Medical Center, Boston, MA, USA).

Below are summaries describing each research award.

From Dr. Istvan Tornai:

### **The possible role of haptoglobin in the pathogenesis of primary sclerosing cholangitis (PSC)**

Haptoglobin is a protein synthesized by the liver and known to play a role during the destruction of erythrocytes and hemoglobin. Haptoglobin protects the tissues from the toxic effects of the hemoglobin metabolites. The cellular receptor of haptoglobin is found on the surface of the monocytes and macrophages, which have an important role in the immune system.

Haptoglobin has three main forms (1-1, 2-1 and 2-2) and only one of them is present in a person.

The type of haptoglobin is genetically determined. Since the receptor of haptoglobin is found on immune cells (monocytes and macrophages), haptoglobin most probably

influences the function of these cells.

Furthermore, since the structure of the three types of haptoglobin differ significantly from each other, their functional activity on the immune cell can be different as well, however this is not well characterized.

First we investigated the three types of haptoglobin in patients with Crohn's disease and among them we had 18 patients with PSC. We have observed that there was no 1-1 type of haptoglobin in patients with PSC. Since this was not a sufficient number of patients, we collected 75 patients with PSC in Hungary.

We have collected serum samples as controls from healthy volunteers (n:384) and patients with alcoholic liver disease (n:153), chronic hepatitis C (n:155) and hepatitis B (n:45), as well as other autoimmune liver diseases: primary biliary cirrhosis (n:173), autoimmune hepatitis (n:103) and overlap syndromes (n:51).

Overall we have collected nearly 1000 samples, which is the biggest cohort investigated, to our best knowledge. Every control group showed a similar distribution of the three types of haptoglobin, however in the PSC group we did not find a single case with 1-1 type.

We suggest that the presence of 1-1 type of haptoglobin provides a protection against the development of PSC. Since the receptor of haptoglobin is found on immune cells, this should be the key event in this effect. However, this still needs further research.



This is the very first report on such a remarkable genetic alteration, which influences the susceptibility of PSC.

From Dr. I. Tornai:

### **Novel therapeutic approach to Primary Sclerosing Cholangitis (PSC)**

The etiology of Primary Sclerosing Cholangitis (PSC) is unknown and there are no proven effective therapies or early markers of the disease to predict which patients with colitis may be at risk to develop PSC. Primary Sclerosing Cholangitis (PSC) and Cystic Fibrosis (CF) liver disease are slowly progressive cholestatic diseases and are characterized by fibro-inflammatory inflammation of the biliary tract. We have shown that there is an increased prevalence of CFTR alleles (the gene responsible for Cystic Fibrosis (CF)) in patients with PSC.

These data suggested that colitis, in the setting of CFTR dysfunction, may lead to bile duct inflammation and fibrosis. As proof of concept, we subsequently demonstrated in *cftr*<sup>-/-</sup> mice that (1) colitis leads to the development of bile duct injury and (2) this is prevented by correction of the CFTR related fatty acid defect with oral Docosahexaenoic Acid (DHA). Preliminary data in these mice indicates that low PPAR expression in the liver may predispose to inflammation. Pretreatment of CF mice with oral docosahexaenoic acid (DHA) resulted in a decrease in both bile duct injury and in serum alkaline phosphatase levels. This was associated with an increase in PPAR- $\alpha$  expression.

Based on these data, we hypothesize that DHA, through its effects on fatty acid composition and the innate immune response might be an effective therapy for patients with PSC.

In collaboration with the Mayo Clinic, we conducted a 12 month pilot open-label trial of DHA in the treatment of patients with PSC. We enrolled 28 adult patients (age 18-80). Based on data in mice and saturation kinetics in humans, we used 800 mg of DHA (4 capsules) orally twice per day for 52 weeks. The primary outcome measure was change in serum alkaline phosphatase during the treatment period. Secondary outcomes included changes in biliary tract disease based on cholangiograms, liver biochemistry, fatty acid profile, serum/plasma liver fibrosis markers, innate immune assessment, and clinical data based on signs and symptoms.

Preliminary data showed a decrease in mean alkaline phosphatase levels following DHA administration which were statistically significant compared to results at baseline and at all subsequent assessments through month nine. 70 percent of the subjects had an improvement in fatigue and in well being. There was no change in fibrosis or apoptosis markers during this period of time.

These encouraging preliminary results demonstrate that an increase in serum DHA levels is possible and results in a significant decline in alkaline phosphatase and a clinical improvement in fatigue and well being. Given these promising results, we intend to do a randomized double-blind control trial with DHA therapy in patients with PSC.

The recipient of the 2007 PSC Partners Seeking a Cure AASLD Award was Dr. Thomas H. Karlsen (Medical Department and Institute of Immunology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway).

## PBC Study Clarifies Genetic Link

We'd like to draw attention to the news that a recent study published in *The New England Journal of Medicine* has reported that two genes are involved in primary biliary cirrhosis (PBC). This major new discovery concerns the genetic basis of PBC, a disease that affects the small bile ducts of the liver, mostly in women.

“Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants” was published May 20, 2009, in the international medical journal.

Several hospitals in Canada, the University of Toronto and the Mayo Clinic/Rochester in the US used blood samples to analyze the links. The significance of the research is that the finding can begin to serve as a basis for targeted treatment of the disease.

These web links describe the study in more detail: <http://sev.prnewswire.com/health-care-hospitals/20090527/DC2335427052009-1.html> and <http://www.torontoliver.ca/hcp/Publications/NEJM2009.html>

Dr. Kostas Lazaridis, who spoke at the conference and who is a co-author on the journal's manuscript, has said, "We are making great progress with PBC. We are on the same direction of research for PSC with Dr. Tom Karlsen from Norway."

Dr. Lazaridis asks us to remind the PSC community that it is important that as many PSC patients as possible participate in PROGRESS (PSC Resource Of Genetic Risk, Environment and Synergy Studies) by providing blood samples. Information on how to participate is at the following link: [http://mayoresearch.mayo.edu/mayo/research/lazaridis\\_lab/genomics\\_of\\_psc.cfm](http://mayoresearch.mayo.edu/mayo/research/lazaridis_lab/genomics_of_psc.cfm)

Thanks to all of your contributions, the PROGRESS study has recently been funded by PSC Partners Seeking a Cure. See Research Grants Awarded (2009) <http://www.pscpartners.org/2009Awards.htm> for more details.

## New PSC Partners Brochures Available on Diagnosing and Living with PSC

Attendees at the annual conference were the first to receive copies of two new PSC Partners brochures.

*Diagnosing PSC*, a new brochure, offers answers to common questions newly-diagnosed patients have about the disease. These questions include a description of blood tests typically used to diagnose and imaging tests via ERCP and MRI. Biopsies and how they are used to help stage the disease are described. In addition a list of diseases associated with PSC are included. *Living with PSC* is an update of the original brochure and describes symptoms, treatments, and origins of the disease.

Both brochures include a listing of useful support and information sources. A third brochure on PSC medications is in development and will be available later this year. All brochures are available for download on the web or by contacting PSC Partners. Members often take copies of the brochures to their physicians for waiting room displays.

## ***PSC IN TWINS: HELP NEEDED***

Genetically identical twin pairs in which one or both siblings have PSC are an enormous resource to determine the environmental factors contributing to the disease.

Researchers at the Division of Rheumatology at UC Davis are searching for patients with PSC that have a twin, whether identical or fraternal.

Dr. Carlo Selmi is leading a study on these issues and is interested in such twins whether they both have PSC or not and whether they are identical or not. The search for twins is ongoing throughout the world, if you know of anybody who is a patient with PSC and has a twin, please contact us at [cfselmi@ucdavis.edu](mailto:cfselmi@ucdavis.edu).

The study will only include a blood draw and a simple questionnaire for both twins.

## Have you always wished that you could tell your health care story? Here's your chance . . .

Advocacy for Patients with Chronic Illness, Inc., and the University of Michigan Center for Managing Chronic Disease have been awarded a grant by the National Institutes of Health (NIH) to study the obstacles facing the chronically ill and caregivers, interventions that do and do not work to surmount those obstacles, and ways in which the work done by the NIH, including research and clinical trials, may be helpful to patients with chronic illnesses.

With the help of twelve patients and caregivers, we

have drafted a survey which is available online at: <http://chronicdisease.sgzmo.com>.

If you have a chronic illness such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, fibromyalgia, multiple sclerosis, immune deficiency, or other chronic illness or are a caregiver of someone with a chronic illness, are at least 18 years old, and would like to take the survey, please do so.

If, for any reason, you are unable to take the survey

online, or you would prefer to be interviewed by telephone, or if you have any questions at all about the research, please contact Jennifer Jaff at (860) 674-1370. She will answer any questions you may have, provide more details about the study and arrange for an interviewer to call you to schedule the telephone interview at a time convenient to you.

Any services you or the person you care for may receive from Advocacy for Patients will not be affected by your participation or decision to not participate.

## The EASL Conference: One Last Word from Ricky

Don and I attended the EASL international conference for PSC research held in Oslo, Norway, June 21-23, where we were joined by six other members: Ivor Sweigler, of the UK, Nicklas and Peter Holmgren, of Sweden, Eve Jedrzejewska, of Toronto, and Rachel and Abe, of Montreal. The conference was an opportunity for all of us to hear brilliant presentations from researchers from the U.S., but mostly from Europe.

Although no huge breakthrough was announced, we were encouraged by the large number of PSC researchers who attended (143) and also by the brilliance, intensity and passion of the researchers. We were also impressed by the organization and future plans set in place by the Norwegian PSC Center headed by Drs. Erik Schrupf, Kirsten Boberg and Tom Karlsen. They coordinated this excellent conference and are also very successful in encouraging present and future collaboration between the European researchers. I liked the phrase coined by Dr. Michael Manns of Germany: "PSC is the only black box of hepatology left." PSC is the last mystery for researchers to unravel.

We left the conference overwhelmed with new knowledge and with a spirit of optimism and hope to find that elusive cure for PSC. Watch for our fall newsletter; we will provide a detailed account of conference presentations. I'm also excited to announce that Dr. Espen Melum will fly in from Norway to give a presentation at our 2010 conference in Hartford, giving us the latest update on the progress of the Norway PSC Center. Stay tuned!

Ricky Safer

### 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** 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](mailto: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](http://www.pscpartners.org)

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