

PSC Partners Seeking a Cure

Newsletter

Vol. 1, Issue 3, Mar 2005

Edited by David Rhodes and Ricky Safer



Working together to provide research, education, and support for people affected by Primary Sclerosing Cholangitis.

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There's Spring in our Steps

By Ricky Safer

Thanks to the help and wonderful suggestions from so many of our PSC online group members, the PSC Partners Seeking a Cure foundation, after only three months in existence, is already taking on a life of its own. Here are some of our beginning steps:

- The IRS just approved our 501(c)3 status.
 - David Rhodes continues to expand our invaluable PSC literature site, which includes over 23,900 research abstracts. Physicians studying PSC have already consulted the site as a resource, and requested files.
 - Through our website <http://www.pscpartners.org>, we are reaching new PSCers throughout the United States and in many foreign countries.
 - This is the third edition of our PSC newsletter that is being distributed for free on our website.
 - National CCFA has created a link from their website to our PSC literature site, which will greatly increase our visibility on the web.
 - Dr. Eric M. Gershwin at the University of California at Davis has contacted us because he is expanding his genetic research study on PBC to include PSC and AIH. Interested PSC patients are signing up to give samples for his important research study.
 - We have contacted Dr. Dennis Black of the Morgan Foundation, and hope to discuss possible future collaboration between our two groups. The Morgan Foundation is partnering with the NIH NIDDK to sponsor a PSC Research Workshop for physicians at the NIH in September (<http://www.scgcorp.com/primariesclerosing/>).
 - Our first educational project will take place the weekend of April 29-May 1 in Denver, Colorado. We are sponsoring a PSC conference for PSC patients and caregivers, with an outstanding group of presenters from the University of Colorado Health Sciences Center including Dr. Greg Everson and Dr. Igal Kam. Chris Klug will also be giving a presentation. To see more conference information, log on to <http://www.pscpartners.org> and click on Conference 2005. We still have three weeks until the conference, but we are thrilled with responses so far.
 - We have 58 attendees registered. They are coming from 16 different states, Canada and the United Kingdom.
 - Ivor Sweigler, who represents a group of 300 PSCers in the UK, will be attending. We're lucky to be connecting with his group.
 - Shelley Eater, a representative from the PBCers' organization will be attending, and she is eager for our two groups to work together closely.
 - We have three pharmaceutical sponsors for the conference: Axcan Pharma, Gold Level Sponsor, Procter and Gamble, Copper Level Sponsor, and Salix, Copper Level Sponsor.
 - Thanks to Lee Bria, our fundraising chairman, our fundraising campaign is off to a great start.
 - We continue to receive many individual donations.
 - Bill Wise is spearheading our PSC bracelet project. The attractive PSC Partners bracelets have just arrived, and are being mailed out. The bracelets can also be ordered online from our website.
 - Mike Boyle is spearheading our PSC polo shirt project. Soon, you will be able to order a variety of embroidered PSC shirts.
 - Nichole Rowland is working on an alternate plan for a football fundraiser, perhaps in the fall, which includes Ricky Manning Jr. and other Panthers' players.
 - Joan Kantor and Deb have created a distinctive letter requesting corporate donations, and they will be working on a letter writing campaign.
 - PSC online group members are working on organ donor awareness programs at their place of work, schools, and within their communities.
- Thank you again to so many of our unnamed members who continue to encourage us and give us suggestions. We are looking forward to meeting many of you in person at the conference, if not this year, then maybe next year. We would never have progressed this far without all of you!

Update on Donations to PSC Partners Seeking a Cure

By Ricky Safer

Here is a list of our recent individual donors and honorees (since Feb, 2005):

In honor of:	Donor:
Billy Bria	CitiCards
Billy Bria	Darryl Albright
Tim Wholey	Scott Wiley
Billy Bria	Victoria and David Sarah
Billy Bria	Greg and Pamela
Billy Bria	Hollingsworth Cary and Suzy Engleberg
Ricky Safer	Art Robbins
Ricky Safer	Marsha and Stanley Stein
Billy Bria	Mark and Madalyn Kaminski
Ricky Safer	Kent and Liz Kreider

Thank you to all our donors for taking the first step in helping us to reach our ultimate goal of finding a cure!



Selecting a Medical Agent

By Denise E. Boyd

When I was diagnosed with PSC, my husband Mike was in the hospital room with me post-ERCP. We both looked blankly at the doctor not even knowing what questions to ask. We heard the dire prediction that I would need a liver transplant to survive within ten to fifteen years, and we were stunned. Since then, Mike has accompanied me to doctor's appointments; he has helped me learn what to ask, and he has asked the questions I was afraid to ask. He has been an excellent medical agent, partner, and advocate. Now that my health is deteriorating, Mike is undergoing testing for living liver donation. This adds another layer to the liver transplant process if he is approved. Not only will my husband be putting himself at risk as my donor, but also neither of us will be able to make decisions for our care during the time after surgery. We find ourselves in search of effective, understanding, and qualified medical agents.

What exactly is a medical agent? A medical agent is someone who makes medical decisions for you if you are unable to do so. Each state has its own laws concerning how someone does this, but if you do not choose an agent, then your family members make your decisions. Family members may differ in their opinions about what you want, decisions can be delayed, and feelings can get hurt. Worse than that, you may have medical care chosen for you that you did not wish to receive. Terri Schiavo's much publicized case in Florida is an extreme example of what can happen when relatives fail to agree on care. Regardless of whom you feel is correct in her case, her example shows that failing to name an agent is risky.

Choosing a medical agent is a complex task since there are so many issues to consider. Not only does the individual need to be someone you can trust, he/she needs to be immediately available. Given the commitment required, selecting someone who is far away, who cannot take time off of work, or who has significant family/financial issues could be a mistake. Additionally, you need to consider the personality of your agent. Is this individual assertive enough to engage in thoughtful discussions with your doctors? Can this person stand up to bullying from family members or even from medical staff?

Another criterion I find important is that the agent has the intellect to grasp medical concepts. If the agent cannot comprehend medical information, then you are at risk. Once you select an agent, plan to give him/her basic information about PSC and your surgical/therapeutic options. While the agent doesn't need to know everything, reading articles with the PSC/liver medical vocabulary is good preparation. I am suggesting that my agent join the PSC Support group to take advantage of the articles the group posts.

According to PeaceHealth, a Catholic hospital system in the Pacific Northwest that focuses on compassionate care, "Not everyone will be comfortable taking on this responsibility, so talk openly with the person you choose before completing the process. Consider choosing someone who:

- Is at least 18 years old.
- Knows you well and understands what makes life meaningful for you.
- Understands your religious and moral values.
- Will honor your wishes and do what you want, not what he or she wants.
- Will be able to make difficult choices at a stressful time.
- Will be able to refuse or stop treatment, if that is what you would want, even if it may result in your death.
- Will be assertive with health professionals if needed.
- Will be able to ask questions of doctors and others to get the information needed to make decisions.
- Lives near you or is willing and able to travel if needed to make decisions for you

(Amy Fackler, MA PeaceHealth website article Choosing a Health Care Agent May 14, 2004; <http://www.peacehealth.org/kbase/topic/special/aa114352/sec1.htm>).

Nolo.com (<http://www.nolo.com/>) a web site specializing in making legal information available to the public for free, states that you should not name a medical provider as your agent, "In fact, the laws in many states prevent you from naming such a person to make decisions for you (Irving, Shae, JD Nolo.com website article Choosing Your Healthcare Agent 2005)" (<http://www.nolo.com/article.cfm/objectID/8E4016BA-472D-4BD5-8D551B93E56EE6BD/309/292/295/ART/>). However, in absence of any next of kin, medical providers do make decisions for you.

Finally, you need to verify that the person will accept the responsibility and understands the duties of being a medical agent. A good way to do this is to present the agent with the legal documents that make the selection official. Depending on the your state's laws, a medical power of attorney, a living will or an advance directive can name your medical agent. Often medical centers have copies of the documents for your state. Have the document reviewed by an attorney and get it notarized to help ensure it will survive any legal challenges. Also, complete your documentation prior to becoming markedly ill, because "The person creating the medical power of attorney and living will must be mentally competent when signing it and it must be witnessed. Just as healthcare providers and staff can't be appointed as agents, they also can't act as witnesses to these documents (American Heart Association website article Insurance, Legal Issues and Advance Directives, 2005)" (<http://www.americanheart.org/presenter.jhtml?identifier=11084>). As a last step, discuss your choice with family and friends so that they are not surprised later. Explaining your selection and your faith in your agent could promote harmony if difficult and controversial decisions arise.

After much consideration, I'm choosing a long-time friend if Mike is approved as my living donor. This friend has undergone her own medical journey with a different disease. She has spent time in hospitals, she understands how the system works, and she's one of the smartest people I know. I'm using the web to educate her about liver therapies, and I am certain that she'll know enough to communicate effectively with the doctors and with my family during the transplant journey. Just in case, I have an alternate agent selected, too.

I have drafted an advance directive that is approved in my state, and I am working on making it official. We plan to hold a family meeting once the living donation process is finished to announce the outcome. Should Mike be my donor, I will announce and explain my agent's selection then. In the meantime, we're waiting, something we've gotten very good at doing since I was listed for transplant in 2001.

Denise E. Boyd (aka: Deb in VA)
PSC 1998, UC 1999, Listed Ltx 2001

If you would like to contribute an article to a future issue of this Newsletter, please e-mail it to David Rhodes:

rhodesdavid@insightbb.com



Give Life!

One of our foundation goals is to increase organ donor awareness. We encourage U.S.A. readers to visit www.donatelife.net and click on their state. This site gives a state by state guide to the organ donation process. This would be a good place for our members to start thinking about how to help locally, if they are interested....“While donated organs and tissue are shared at the national level, the laws that govern donation vary from state to state. Therefore, it is important for you to know what you can do to ensure your decision to be a donor is carried out.”

Update on Bracelets/Wristbands

By Lee Bria

We have bracelets/wristbands on the way that we can all sell not only to our friends and family, but also through local groups such as high school Key Clubs, Rotary groups, Lions Clubs and even the Boy Scouts and Girl Scouts. Think about where you have a personal contact and then ask if they might help you to sell some bracelets/wristbands. These can be ordered by contacting or messaging Bill Wise.



Bill Wise
2300 N. Preston Dr.
Richland Center, WI 53581
PayPal/email: gmoobad@yahoo.com

Please contact Bill Wise for details of purchase and suggested retail prices.



Judy, Mandy, Arne, and Rowdy

Arne Myrabo

Arne has been a member of the PSC support group (Yahoo) since 2000. He is our chief statistician (using information that people have provided in group e-mails), and is the main contact person for any details about support group membership and data. For instance, Arne keeps records of all group member transplant dates. He can be reached at the following e-mail address: psc@myrabo.com. He also maintains a wonderful, pictorial website at: <http://www.myrabo.com/>

Additional Contact Information

Ricky Safer is the principal contact person for our PSC Partners Seeking a Cure Foundation. She can be reached at:

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5237 S. Kenton Way
Englewood, CO 80111

e.mail: pscpartners@yahoo.com

National Donate Life Month

In 2003, President Bush first announced that the month of April will be observed as National Donate Life Month, a time to raise public awareness of the critical need for organ, tissue, marrow, and blood donation.

Originally known as National Organ and Tissue Donor Awareness Week and celebrated for one week in April, that observance was the result of smaller, independent efforts around the Nation to recognize the altruism and generosity of organ and tissue donors.

<http://www.organdonor.gov/donatelife.htm>

Genetic Association Database (GAD)

A growing database of human genetic association studies of complex diseases and disorders can be found at the following URL:

<http://geneticassociationdb.nih.gov/>

GAD is intended for use primarily by medical scientists and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While GAD is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.

Useful Links:

Crohn's and Colitis Foundation of America: <http://www.cdfa.org/>
PSC Literature: <http://www.psc-literature.org/>
PSC Partners Seeking a Cure: <http://www.pscpartners.org/>
American Liver Foundation: <http://www.liverfoundation.org/>
PSC Support U.K.: <http://www.psc-support.demon.co.uk/>
PSC Support (Yahoo): <http://health.groups.yahoo.com/group/psc-support/>
Canadian Liver Foundation: <http://www.liver.ca/english/index.html>
Clinical Trials: <http://www.clinicaltrials.gov/ct>

Coalition on Donation – Donate Life: <http://www.donatelife.net/>
IBD Patient Community: <http://ibd.patientcommunity.com/>
United Network for Organ Sharing: <http://www.unos.org/>
Falk Foundation: <http://www.falkfoundation.com/>
British Liver Trust: <http://www.britisHLiverTrust.org.uk/>
PBCers: <http://pbcers.org/>
Centers for Disease Control and Prevention: <http://www.cdc.gov/>
TransWeb.org: <http://www.transweb.org/>

NIDDK Action Plan for Liver Disease Research

NIDDK

Liver disease is an important cause of morbidity and mortality in the United States, affecting persons of all ages, but most frequently individuals in the productive years of life, between the ages of 40 and 60 years. Liver disease also disproportionately affects minority individuals and the economically disadvantaged. Medical research on liver disease is critically important and further progress in research promises to bring under control the major toll of liver disease on human health and well-being. Indeed, the last 25 years of medical research in liver disease has resulted in major improvements in the survival and quality-of-life of patients with liver disease. The next 25 years should bring even more profound and important changes.

To address the burden of liver diseases in the United States, the National Institutes of Health has developed an Action Plan for Liver Disease Research.

Mission Statement

The goal of the Action Plan for Liver Disease Research is to advance research on liver and biliary diseases with the aim of decreasing the burden of liver and biliary diseases in the United States.

The Action Plan for Liver Disease Research is available in both electronic (PDF) and print formats:

http://www.niddk.nih.gov/fund/divisions/ddn/ldr/ldr_action_plan.htm

For an introduction to genetics, please visit:

Genetics Home Reference
<http://ghr.nlm.nih.gov/>

Examples of Research Goals of the NIDDK Action Plan for Autoimmune Liver Disease Research (PSC, PBC and AIH)

- To develop animal models for each of the autoimmune liver diseases
- To convene an international, interdisciplinary research workshop on the development of animal models of autoimmune liver diseases.
- To utilize animal models of autoimmune liver diseases to define the roles of the innate and acquired immune systems in these diseases and identify environmental and/or genetic triggers for induction of autoimmune hepatitis
- To develop multicenter clinical research networks of investigators to study the natural history, clinical course, pathogenesis, etiology, and therapy of AIH, PBC, and PSC.
- Identify genetic linkages in PBC and refine the HLA associations in AIH and PSC.

Dr. Eric Gershwin's PSC/PBC/AIH Research

Dr. M. E Gershwin (U.C. Davis, Davis, CA) is conducting genetic studies on PSC/PBC/AIH. Dr. Gershwin has a group of 30 scientists from all over the world that specifically study the immune system and genetics of PSC, PBC, and AIH. Although Dr. Gershwin's group is able to find many people with PBC to enter into their studies, they are currently having a very difficult time finding people with PSC or AIH. They need blood samples from people with PBC, PSC, and AIH that are very fresh. The only way for them to obtain these samples is by holding regional meetings on the West coast. Dr. Gershwin and his Staff Research Associate, Marcy Crees, have been having meetings in Seattle, WA, Portland, OR, San Francisco and the bay area in California, Davis, CA, Los Angeles, CA, San Diego, CA, Phoenix, AZ, and Las Vegas, NV. The reason they have meetings in these cities is because they are within a 1-2 hour flight from Davis and the blood that is collected for their research at these meetings has to get back to the laboratory in Davis before the immune cells start to deteriorate. At these meetings, Dr. Gershwin and other members of his research staff talk about their current research on PBC, PSC, and AIH. Dr. Gershwin also holds a question and answer period, which has been so beneficial to everyone who attended. During all of this, Marcy Crees collects a small blood sample from anyone that is willing to donate to their research. Without this blood, their current research would come to an abrupt halt. Marcy Crees would appreciate if anyone with PBC, PSC, or AIH that lives in or around these cities listed above, could send her your name, address, and phone number so she can contact you when she has a meeting in your area. She currently has a meeting planned for Saturday, April 30 in Davis. Marcy usually has one meeting a month in a different city. She is going to plan meetings for Los Angeles and Seattle very soon. Please contact Marcy at:

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Primary Sclerosing Cholangitis Conference

September 19-20, 2005
Lister Hill Conference Center
National Institutes of Health
Bethesda, MD

This conference will assess current knowledge about primary sclerosing cholangitis (PSC) focusing on its prevalence and incidence, diagnosis and staging, pathogenesis, disease associations, management, and treatment, including use of surgery and liver transplantation. The meeting will be sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Rare Diseases, and the Morgan Foundation. The aims of the meeting are to stimulate clinical and basic research interest in PSC and identify gaps in knowledge and challenges for medical research in this disease. The meeting will include poster sessions with noon and evening attendance of speakers, presenters, and participants. The meeting summary will be prepared for publication by members of the organizing committee.

<http://www.scgcorp.com/primarysclerosing/>

PSC Partners Seeking a Cure Sponsorship Levels

We offer several levels of sponsorship at the corporate level:

Platinum level:	\$10,000
Gold level:	\$5,000
Silver level:	\$2,500
Bronze level:	\$1,000
Copper level:	\$500

and at the individual member level:

5 Star Partner:	\$1,000
4 Star Partner:	\$500
3 Star Partner:	\$250
2 Star Partner:	\$100
1 Star Partner:	\$1-50

Please send donations to:

Michael Schaffer, CPA
Schaffer and Associates
2020 South Oneida Street-Suite 201
Denver, CO 80224

With a check made out to:

Fdn.Bio.Ed.Res./PSC

Thank you for your generosity!

Ricky Safer

www.pscpartners.org

PSC, Pancreatitis and Cystic Fibrosis

By David Rhodes

Portincasa et al. (2005) have noted that PSC is often accompanied by cystic fibrosis or pancreatitis. What are the relationships between these diseases?

Cystic fibrosis has long been known to be caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an "ABC" chloride transporter, encoded by the ABCC7 gene (gene map locus 7q31.2). Interestingly, this gene is highly expressed in bile duct epithelial cells (Cohn et al., 1993), and the bile duct lesions seen in liver disease associated with cystic fibrosis show striking similarity to that seen in PSC. Both cystic fibrosis associated liver disease and PSC are currently treated with ursodeoxycholic acid (Colombo et al., 1992; Angulo, 2002).

While Girodon et al. (2002) observed that the proportion of CFTR mutations is not significantly higher in PSC patients than in the general population, Sheth et al. (2003) observed that CFTR (ABCC7) mutations were found more frequently in PSC patients. While the contribution of CFTR mutations to PSC is still controversial (Gallegos-Orozco et al., 2005), there seems to be growing evidence to support the idea that CFTR mutations are responsible for idiopathic pancreatitis (Choudari et al., 2004). The pancreas normally generates high concentrations of bicarbonate in the pancreatic fluid. CFTR interacts with a chloride/bicarbonate exchanger in pancreatic duct cells to achieve these high concentrations of bicarbonate. CFTR mutations that predominantly affect bicarbonate permeability lead to a predisposition to pancreatic dysfunction in humans (Whitcomb and Ermentrout, 2004).

The severity of liver disease in cystic fibrosis is in part determined by the mannose binding lectin gene (Gabolde et al., 2001), which has also recently been implicated in Crohn's disease (Seibold et al., 2004).

One of the promising animal models of PSC is the CFTR-deficient mouse. Blanco et al. (2004) recently showed that when mice defective for CFTR (*cftr*^{-/-}) are induced to have colitis, this results in bile duct injury resembling PSC in humans. This bile-duct injury in *cftr*^{-/-} mice is associated with the marked down-regulation of PPAR α (peroxisome proliferator-activated receptor alpha). This bile-duct injury is reversed by feeding docosahexaenoic acid (DHA) [a component of fish oil that acts as a PPAR α activator] (personal communication from Dr. Harpreet Pall, Children's Hospital Boston, Boston, MA). In the last issue of this newsletter (Volume 1(2) Feb 2005) the role of fibrates in treatment of PSC and PBC was discussed; fibrates also activate PPAR α .

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Inflammatory Bowel Disease Genetics (Part 2)

By David Rhodes

In the last article in this series, the genetic association between the NOD2/CARD15 gene on chromosome 16 (the IBD1 gene), and Crohn's disease was described. The product of this gene, the NOD2/CARD15 protein, participates in the pathways that sense bacterial cell wall products in the gut. Absence of a properly functioning NOD2/CARD15 protein leads to inflammation (via activation of nuclear factor-kappa B (NFkB) and tumor necrosis factor alpha (TNF α)).

During the last month some new publications have re-emphasized the importance of the NOD2/CARD15 and TNF α genes in inflammatory bowel disease (IBD). Polymorphisms in the TNF α gene (gene map locus 6p21.3) have been shown to influence the inter-individual variation in susceptibility to, and manifestation of, Crohn's disease caused by NOD2/CARD15 mutations (Linderson et al, 2005; Ferreira et al., 2005).

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.

Newman et al. (2005) have recently shown that polymorphisms in a pair of genes encoding solute carriers (the SLC22A4/22A5 gene cluster on chromosome 5q31, corresponding to the IBD5 gene locus), act together with the NOD2/CARD15 disease susceptibility gene to increase risk for Crohn's disease and ileal disease among Crohn's disease patients in the Canadian population. However, the SLC22A4/22A5 gene cluster does not contribute to risk for ulcerative colitis in this Canadian cohort (Newman et al., 2005). Grundemann et al. (2005) have recently shown that the SLC22A4 gene encodes an ergothioneine transporter.

A highly significant new discovery reported this month is the association between a complex insertion/deletion polymorphism in the NOD1/CARD4 gene and susceptibility to inflammatory bowel disease (McGovern et al., 2005). The NOD1/CARD4 gene is located on chromosome 7p14.3, in a region of known linkage to IBD, and encodes an intracellular bacterial pathogen associated molecular pattern (PAMP) receptor that is closely related to NOD2/CARD15.

Additional genes contributing to Crohn's disease and ulcerative colitis will be discussed in subsequent articles in this series.

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We would like to thank Axcan Pharma (www.axcan.com), Procter and Gamble (www.pg.com) and Salix Pharmaceuticals (www.salix.com) for generously providing funds to support our conference in Denver in April, 2005. We are also indebted to all the speakers who have agreed to contribute to this conference; especially Dr. Gregory T. Everson and his colleagues from the University of Colorado Health Sciences Center (UCHSC), Denver, CO. We also thank all those members of the PSC support group, and their family, friends and care-givers, who have generously donated funds to the PSC Partners Seeking a Cure foundation.

MDR1 and Ulcerative Colitis

By David Rhodes

The human multidrug resistance 1 (MDR1) gene encodes P-glycoprotein 170, an efflux transporter that is highly expressed in intestinal epithelial cells. The MDR1 gene is also known as ABCB1 (gene map locus 7q21.1). Polymorphisms/variations of the MDR1 gene determine disease extent as well as susceptibility to ulcerative colitis in the Scottish and German populations (Ho et al., 2005; Schwab et al., 2003). Schwab et al. (2003) have proposed that P-glycoprotein plays a major role in the defense against intestinal bacteria or toxins. Schwab et al. (2003) suggest that impairment of its function could render patients more susceptible to the development of ulcerative colitis.

References

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Schwab M, Schaeffeler E, Marx C, Fromm MF, Kaskas B, Metzler J, Stange E, Herfarth H, Schoelmerich J, Gregor M, Walker S, Cascorbi I, Roots I, Brinkmann U, Zanger UM, Eichelbaum M 2003 Association between the C3435T MDR1 gene polymorphism and susceptibility for ulcerative colitis. *Gastroenterology* 124: 26-33.

Conference Reminder

The PSC Partners Seeking a Cure – 2005 Conference will be held in Denver, CO from April 29 – May 1, 2005. Please visit www.pscpartners.org for details of the conference and how to register.

Connections Between Multidrug Resistance Proteins, PSC and Cystic Fibrosis

By David Rhodes

The multidrug resistance 1 (MDR1) gene is clearly implicated in ulcerative colitis (see article above). Ulcerative colitis is frequently associated with PSC (over 70% of PSC patients have ulcerative colitis). Ulcerative colitis is also associated with down-regulation of expression of MDR1 (via down-regulation of the pregnane X receptor) [Langmann T, Moehle C, Mauerer R, Scharl M, Liebisch G, Zahn A, Stremmel W, Schmitz G 2004 Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes. *Gastroenterology* 127: 26-40]. In theory, either a mutation in the MDR1 gene or a down-regulation of this gene associated with ulcerative colitis, could result in accumulation of substrates of MDR1. An intriguing report [Linsdell P, Hanrahan JW 1999 Substrates of multidrug resistance-associated proteins block the cystic fibrosis transmembrane conductance regulator chloride channel. *Br. J. Pharmacol.* 126: 1471-1477] suggests that accumulation of such substrates could inhibit the cystic fibrosis transmembrane conductance regulator. Could this cascade then trigger bile-duct injury, and account for the similarity between PSC bile-duct damage and bile-duct damage associated with liver disease of cystic fibrosis (see article on p. 5)?