PSC Partners Seeking a Cure

Newsletter

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Edited by David Rhodes and Ricky Safer

www.pscpartners.org

In This Issue:

August Update

We are pleased to announce that PSC Partners Seeking a Cure will hold our 2006 conference in Pittsburgh, and our 2007 conference in Denver. Joanne Grieme of Pittsburgh has been kind enough to offer to host our yearly conference in Pittsburgh next spring (exact dates to be confirmed soon). Joanne has been working hard and has already lined up a wonderful slate of renowned and talented hepatologists and GIs led by Dr. Thomas Shaw-Stiffel, Medical Director, Liver Transplantation at University of Pittsburgh Medical Center, and also transplant surgeons at the Thomas E. Starzl Transplantation Institute. For those of you who attended this year's conference and who were uplifted by Dr. Greg Everson and his colleagues' highly informative talks, we know that you will benefit greatly from also hearing a different perspective in Pittsburgh in 2006. By choosing Pittsburgh as our venue for 2006, we are hoping that our PSCers and caregivers who live on the east coast and in the Midwest will find it easier to attend in 2006. We will keep you updated as our planning continues. I know that I, personally, benefitted enormously both from the incredible knowledge that our speakers shared with us last year, and also from the time spent getting to know the other PSCers and their caregivers. What a compassionate, upbeat, enthusiastic group you are! I can't wait to see you all again in person and to meet the new PSCers and caregivers who will join us in 2006.

Here's a continuing thank you to all of you who are helping us to achieve our foundation goals in so many different ways: providing education and support, promoting organ donation awareness, and raising funds for research. I'd like to highlight three creative members who have recently started projects for us that will make a difference. Alice Bennell, a sixteen year-old PSCer from London, England, has created her own company named 'Simple Gifts'. Alice was diagnosed with PSC in February 2003, and she started 'Simple Gifts' "to help give people with PSC a second chance at life. I really wanted to help raise funds for PSC research." Alice's logo is shown on the right. Alice has been teaching transplant patients how to make beaded butterflies to help in their recuperation. Now, she is making beaded butterflies, knitted purses, and aprons to sell at her summer school shop in Dorset, England. All proceeds will be sent to the foundation. We're also going to work out a way to sell her wonderful handmade crafts in the U.S.

Help me find a cure for Primary Sclerosing Cholangitis

Melanie Scherder's vibrant daughter Andrea returned from our conference in April, and felt motivated to get involved. She and her boyfriend are going to have an unusual fundraiser-a battle of the bands concert next spring in St. Louis. They already have a soundman, a lights man, a generator, musicians, and many ideas for fundraising at the event and spreading the word about PSC and organ donation.

Carolyn B. in South Carolina has become a true activist in the cause of promoting organ donor awareness. She has contacted the South Carolina Gift of Life Trust Fund to start working on getting organ donor license plates made available in South Carolina. She is writing to all 170 state legislators in South Carolina. Because of Carolyn's interest and willingness to write letters, make phone calls and send e-mails, the SC Gift of

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Life Trust Fund has invited her to join their Advisory Board. Way to go Carolyn! A thousand thank yous to Alice, Andrea, and Carolyn for their creativity and commitment!!!!

I'd like to suggest that our readers think about subscribing to the wonderful newsletter that Ivor Sweigler puts out in the U.K. His newest edition, which is coming out soon, summarizes Dr. Roger Chapman's yearly update on PSC research in the U.K. To subscribe, please visit:

http://www.psc-support.demon.co.uk/page8.html

If you have any questions about the foundation or ideas to suggest to us, please feel free to contact any of the board members: Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Gregory Everson, Chris Klug, David Rhodes, Ricky Safer, and Deb Wente. Thank you for everyone's continuing input. You keep us all revved up.

Ricky Safer

Chris Klug On Board!

The PSC Partners Seeking a Cure Foundation is very pleased to announce that Chris Klug (Professional Snowboarder, Olympic Medal Winner, PSC Liver Transplant Recipient, and Author) has agreed to serve on the PSC Partners Seeking a Cure Foundation Board. He will make a great spokesman for our cause. Chris is excited about being a part of the foundation and looks forward to contributing in the future We wish him success as he strives towards his goal of 'Gold in Torino'.

Auto-antibodies and Autoimmune Liver Diseases

(by David Rhodes)

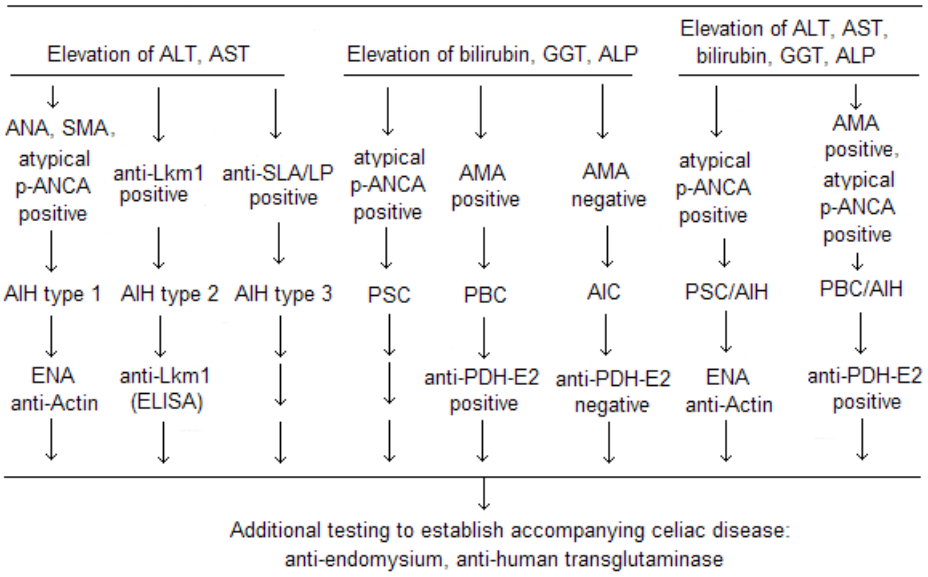
Diagnosis of autoimmune liver diseases often begins with the observations of elevated liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP)), and sometimes elevated bilirubin in serum. However, this is not always sufficient for accurate diagnosis. Often a series of antibody tests are performed to assist in diagnosis (see adjacent figure). For instance, anti-mitochondrial antibodies (AMA) (usually directed against the pyruvate dehydrogenase E2 subunit (anti-PDH E2)) are frequently characteristic of primary biliary cirrhosis (PBC). Smooth muscle antibodies (SMA) are characteristic of autoimmune hepatitis (AIH) type 1. Liver/kidney microsomal type 1 (anti-Lkm1) antibodies are characteristic of AIH type 2. Soluble liver antigen/liver pancreas antigen (anti-SLA/LP) are associated with AIH type 3. Primary sclerosing cholangitis (PSC) is associated with atypical p-ANCA antibodies, where p-ANCA stands for perinuclear-antineutrophil cytoplasmic antibodies. Extractable nuclear antigens (ENA) and anti-Actin antibodies can help confirm AIH type 1 diagnosis, and when occurring with atypical p-ANCA, might suggest a PSC/AIH overlap syndrome. Similarly, AMA antibodies, together with p-ANCA, might suggest a PBC/AIH overlap syndrome. Absence of most of the above antibodies might suggest autoimmune cholangitis (AIC). There is some evidence that AIC is a form of biliary cirrhosis (PBC) without anti-mitochondrial antibodies (AMA), but it is also speculated that AIC might be very similar to small duct PSC [a variant of PSC that does not affect the large ducts].

Where PSC is suspected, based on liver function tests and antibody profile, imaging of the biliary tree is essential for accurate diagnosis. Two imaging techniques are now extensively used for this purpose:

- endoscopic retrograde cholangiopancreatography (ERCP)
- magnetic resonance cholangiopancreatography (MRCP)

In ERCP a flexible tube, or endoscope, is inserted into the upper gastrointestinal tract (via the mouth and esophagus), and a dye is then injected into the bile and pancreatic ducts. An X-ray is then taken to image the bile and pancreatic ducts. In MRCP, no contrast dye is used, no radiation is involved, and no endoscope is employed. Rather, patients are simply exposed to a strong magnetic field and the bile ducts are visualized because the stationary fluid in the bile ducts produces a higher intensity signal in comparison to the surrounding tissue. A 'beaded' appearance of the bile ducts revealed by these imaging techniques would strongly suggest PSC.

Auto-antibodies in autoimmune liver diseases



From: Terjung B, Spengler U (2005) Role of auto-antibodies for the diagnosis of chronic cholestatic liver diseases. Clin. Rev. Allergy Immunol. 28: 115-133.

Clinical Trials on the Genetic Bases of Primary Sclerosing Cholangitis and Primary Biliary Cirrhosis at Mayo Clinic

Unraveling the Genetic Predilection to Primary Sclerosing Cholangitis (PSC)

IRB Number : 670-02

Trial Status : Open for Enrollment

Why is this study being done?

This research study is being done to unravel the genetic predisposition to primary sclerosing cholangitis (PSC). Evidence indicates that the inherited genetic material passed from parents to their children as well as environmental factors contribute to the development of PSC. This study will help us develop novel ways to prevent, diagnose and treat PSC. Because we look at how PSC may be passed down in families, we are also interested in studying family members of PSC patients who are not affected by PSC.

Who is Eligible to Participate in the Study?

Men and Women between the ages of 18-90 who have a history of PSC are eligible to enroll in this study. PSC patients who have undergone liver transplantation are also eligible to participate. Family members of enrolled PSC patients between the ages of 18-90 can participate in this study. Women of childbearing potential and pregnant women will be offered enrollment because there is no risk to an unborn child in this investigation.

Minimum Age: 18

Maximum Age: 99

What is Involved With this Study?

As a study participant you will be asked to:

1. Read and sign a written consent form if you wish to participate in this study.
2. Complete a questionnaire about your health status, diet, exercise, lifestyle/habits and medical history at the start of the study.
3. Provide information about your family history, contact information for living relatives and your permission to contact other available family members of yours, that are either affected or unaffected by PSC.
4. To provide a sample of your blood (approximately three tablespoons) for genetic testing.

Do I have to visit the Mayo Clinic in order to participate in this study?

No, you do not. If you agree to participate in this study, we will send you a mail-in blood kit and we will ask you to go to your local medical facility to obtain the blood collection. All blood tests and collection of blood specimens will be performed at NO cost to the participants.

How long will the Study run?

This is a one time participation study

Whom can I Contact for Additional Information on this Trial?

If you wish to participate in this study or if you have any questions related to this study, please contact Mrs. Gwen Boe at 507-284-1738.

What is/are the Locations of this Clinical Trial?

Rochester, MN

To find information about both of these trials on the www, please visit:

http://clinicaltrials.mayo.edu/

and then search for the key word: 670-02

Understanding the Genetic Predisposition to the Development of Primary Biliary Cirrhosis (PBC)

IRB Number : 670-02

Trial Status : Open for Enrollment

Why is this study being done?

This research study is being done to better understand what causes Primary Biliary Cirrhosis (PBC). Current evidence suggests that both genes (the inherited genetic material passed from parents to their children) and environmental factors play a role in the development of PBC. This study will help us better understand the cause(s) of PBC and hopefully find new ways to its prevention, diagnosis and treatment. Because we are also looking at how PBC may be passed down in families, we are identifying families in which more than one family member has a history of PBC. We are also interested in studying family members of PBC patients who have anti-mitochondrial-antibodies in their blood. These antibodies are present in almost all persons with PBC and are also found in some of their family members who, however, have no evidence of PBC.

Who is Eligible to Participate in the Study?

Men and Women between the ages of 18-90 who have a history of PBC are eligible to participate in this study. PBC patients who have undergone liver transplantation are eligible to participate in this study. Family members of the enrolled PBC patients are also eligible to participate. Men and women between the ages of 18 to 90 who have a history of PBC are eligible to participate in this study. Women of childbearing potential and pregnant women will be offered enrollment because there is no risk to an unborn child in this investigation. The diagnosis of PBC for the patient will be based on standard PBC criteria including clinical and biochemical evidence of chronic cholestasis of at least six months duration, positive anti-mitochondrial antibodies (>1:40 titer) and compatible liver biopsies if available.

Minimum Age: 18

Maximum Age: 90

Additional Requirements / Information

As a study participant you will be asked to:

1. Read and sign a written consent form if you wish to participate in this study.
2. Complete a questionnaire about your health status, diet, exercise lifestyle/habits and medical history at the start of the study.
3. Provide information about your family history, contact information for living relatives and your permission to contact other available family members of yours, that are either affected or unaffected by PBC.
4. To provide a sample of your blood (approximately three tablespoons) for genetic testing.

Do I have to visit the Mayo Clinic in order to participate in this study?

No, you do not. If you agree to participate in this study, we will send you a mail-in blood kit and we will ask you to go to your local medical facility to obtain the blood collection. All blood tests and collection of blood specimens will be performed at NO cost to the participants.

Whom can I Contact for Additional Information on this Trial?

If you wish to participate in this study or if you have any questions related to this study, please contact Mrs. Gwen Boe at 507-284-1738.

What is/are the Locations of this Clinical Trial?

Rochester, MN

Gender, Smoking, and PSC/UC ... What are the Links?

(by David Rhodes)

One of the peculiar features of PSC is that it is more prevalent in males. It has been widely reported that males are more frequently affected by PSC than females. This observation has led to the suggestion that PSC is not a typical autoimmune disease, since most autoimmune diseases are more frequently found in females (see Figure 1).

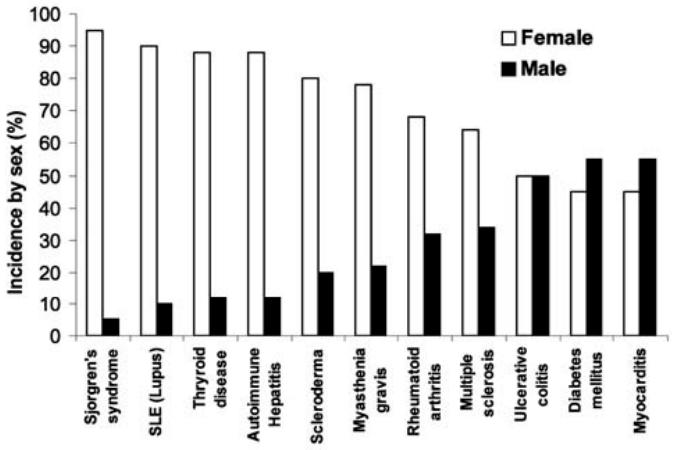


Figure 1. Major autoimmune diseases, comparing the incidence of disease in women (white bars) to the incidence in men (black bars) by percentage. *From*: Fairweather D (2004) Women and autoimmune diseases. Emerg. Infect. Dis. 10: 2005-2011.

If primary biliary cirrhosis (PBC) were to be included in the above figure, it would be similar to autoimmune hepatitis (with a female : male ratio of 10:1). If PSC were to be included in this figure, it would be on the far-right, with a female : male ratio of 0.5 to 1.

PSC is frequently associated with inflammatory bowel disease, and most often with ulcerative colitis (UC). Because UC is equally frequent in men and women (see Fig. 1), this suggests that males with UC must be twice as likely to develop PSC as females.

One possible explanation of this association is that there might be genes determining susceptibility to PSC that are male-specific. We know that there are such genes that influence susceptibility to inflammatory bowel disease, and one or more of these male-specific genes is in the major histocompatibility complex (human leukocyte antigen (HLA)) region of chromosome 6 (Fisher et al., 2002).

> "The major histocompatibility region on chromosome 6p, referred to as IBD3, showed evidence of male-specific linkage with a maximum LOD score of 5.9 in both CD and UC male-affected families." (Fisher et al., 2002).

This genetic region deserves special attention because genes determining susceptibility to PSC have also been mapped here (Donaldson, 2003).

What are some important metabolic pathways in the liver that are known to be regulated in a sex-specific manner, and what are their key regulators? Are any of these regulators known to be located in the HLA region?

It's known that retinoid X receptor-alpha (RXRA) is responsible for determining expression of a number of enzymes of xenobiotic and bile metabolism in male hepatocytes (Cai et al., 2003). Could the retinoid X receptor-beta (RXRB), located in the major histocompatibility complex on chromosome 6 (Fitzgibbon et al., 1993), represent a candidate gene in the HLA region for providing male-specificity? RXRB is highly related to RXRA, and plays a key role in regulating genes responsive to retinoic acid, thyroid hormone and vitamin D (Yu et al., 1991).

Could retinoid metabolism (and control of metabolism by retinoid X receptors) also provide an opportunity to link PSC and UC to smoking behavior? PSC, like UC, is a disease of non-smokers: the odds of having PSC were significantly decreased among current and former smokers (Mitchell et al., 2002). It has been recently shown that a nicotine metabolite alters retinoid metabolism (Brogan et al., 2005).

References

Brogan AP, Dickerson TJ, Boldt GE, Janda KD (2005) Altered retinoid homeostasis catalyzed by a nicotine metabolite: implications in macular degeneration and normal development. Proc. Natl. Acad. Sci. U.S.A. 102: 10433-10438.

Cai Y, Dai T, Ao Y, Konishi T, Chuang KH, Lue Y, Chang C, Wan YJ (2003) Cytochrome P450 genes are differentially expressed in female and male hepatocyte retinoid X receptor alpha-deficient mice. Endocrinology 144: 2311-2318.

Mitchell SA, Thyssen M, Orchard TR, Jewell DP, Fleming KA, Chapman RW (2002) Cigarette smoking, appendectomy, and tonsillectomy as risk factors for the development of primary sclerosing cholangitis: a case control study. Gut 51: 567-573.

Donaldson P (2003) HLA system and other genetic markers in PSC. Falk Symposium 136. XII FALK LIVER WEEK (Part I) In Honour of Hans Popper's 100th Birthday. Cholestatic Liver Diseases: Therapeutical Options and Perspectives. Freiburg (Germany). p. 71-72. October 15-16, 2003.

Fisher SA, Hampe J, Macpherson AJ, Forbes A, Lennard-Jones JE, Schreiber S, Curran ME, Mathew CG, Lewis CM (2002) Sex stratification of an inflammatory bowel disease genome search shows male-specific linkage to the HLA region of chromosome 6. Eur. J. Hum. Genet. 10: 259-265.

Fitzgibbon J, Gillett GT, Woodward KJ, Boyle JM, Wolfe J, Povey S (1993) Mapping of RXRB to human chromosome 6p21.3. Ann. Hum. Genet. 57: 203-209.

Yu VC, Delsert C, Andersen B, Holloway JM, Devary OV, Naar AM, Kim SY, Boutin JM, Glass CK, Rosenfeld MG (1991) RXR beta: a coregulator that enhances binding of retinoic acid, thyroid hormone, and vitamin D receptors to their cognate response elements. Cell 67: 1251-1266.

Keeping Up with the Johne's

(by David Rhodes)

Here are some important recent abstracts of papers on the controversy concerning whether or not *Mycobacterium avium* subsp. *paratuberculosis* is responsible for Crohn's disease, and whether this organism might be transmitted to humans from ruminants with Johne's disease:

Johne's disease is a chronic diarrhea affecting all ruminants. *Mycobacterium avium* subsp. *paratuberculosis* (MAP), a slow growing mycobacteria, is the etiologic agent. There is also a concern that MAP might be a causative agent of some cases of inflammatory bowel disease in humans, especially Crohn's disease. Food products including pasteurized bovine milk have been suggested as potential sources of human infection. This review addresses microbial factors that may contribute to its pathogenicity. In addition, the experimental evidence defining MAP as the cause of Johne's disease and the issues and controversies surrounding its potential pathogenic role in humans are discussed.

Chacon O, Bermudez LE, Barletta RG (2004) Johne's disease, inflammatory bowel disease, and *Mycobacterium paratuberculosis*. Annu. Rev. Microbiol. 58: 329-363.

BACKGROUND AND AIMS: Conflicting results exist about the presence of *Mycobacterium avium* subspecies *paratuberculosis* (MAP) specific IS900 DNA in Crohn's disease (CD) tissues. Therefore, we examined IS900 in a large number of gut samples from patients with CD (n = 100) and ulcerative colitis (UC, n = 100), and in non-inflamed control tissues (nIBD, n = 100). We hypothesised that IS900 DNA detection might be associated with distinct clinical phenotypic characteristics in CD. METHODS: The prevalence of MAP DNA in surgically resected tissues was examined using a mechanical-enzymatic disruption technique and nested IS900 specific polymerase chain reaction (PCR). CD patients were stratified according to the criteria of the Vienna classification and other clinical characteristics. RESULTS: IS900 PCR detection rate was significantly higher in CD tissue samples (52%) than in UC (2%) or nIBD (5%) specimens ($p<0.0001$). In CD patients, IS900 DNA was detected in samples from both diseased small bowel (47%) as well as fro the colon (61%). No firm association between MAP specific IS900 detection rates and clinical phenotypic characteristics in CD could be established. However, corticosteroid medication constituted a factor which tended to have a negative influence on IS900 DNA detection rates in CD ($p<0.01$). CONCLUSIONS: The presence of MAP specific IS900 DNA is a predominant feature of CD. Therapeutic intervention against MAP might represent a potential target for disease mitigation in Crohn's disease.

Autschbach F, Eisold S, Hinz U, Zinser S, Linnebacher M, Giese T, Loffler T, Buchler MW, Schmidt J (2005) High prevalence of *Mycobacterium avium* subspecies *paratuberculosis* IS900 DNA in gut tissues from individuals with Crohn's disease. Gut 54: 944-949.

In South Wales, United Kingdom, a populated coastal region lies beneath hill pastures grazed by livestock in which *Mycobacterium avium* subsp. *paratuberculosis* is endemic. The Taff is a spate river running off the hills and through the principal city of Cardiff. We sampled Taff water above Cardiff twice weekly from November 2001 to November 2002. *M. avium* subsp. *paratuberculosis* was detected by IS900 PCR and culture. Thirty-one of 96 daily samples (32.3%) were IS900 PCR positive, and 12 grew *M. avium* subsp. *paratuberculosis* bovine strains. Amplicon sequences from colonies were identical to the sequence with GenBank accession no. X16293, whereas 16 of 19 sequences from river water DNA extracts had a single-nucleotide polymorphism at position 214. This is consistent with a different strain of *M. avium* subsp. *paratuberculosis* in the river, which is unculturable by the methods we used. Parallel studies showed that *M. avium* subsp. *paratuberculosis* remained culturable in lake water microcosms for 632 days and persisted to 841 days. Of four reservoirs controlling the catchment area of the Taff, *M. avium* subsp. *paratuberculosis* was present in surface sediments from three and in sediment cores from two, consistent with deposition over at least 50 years. Previous epidemiological research in Cardiff demonstrated a highly significant increase of Crohn's disease in 11 districts. These bordered the river except for a gap on the windward side. A topographical relief map shows that this gap is directly opposite a valley open to the prevailing southwesterly winds. This would influence the distribution of aerosols carrying *M. avium* subsp. *paratuberculosis* from the river.

Pickup RW, Rhodes G, Arnott S, Sidi-Boumedine K, Bull TJ, Weightman A, Hurley M, Hermon-Taylor J (2005) *Mycobacterium avium* subsp. *paratuberculosis* in the catchment area and water of the river Taff in South Wales, United Kingdom, and its potential relationship to clustering of Crohn's disease cases in the city of Cardiff. Appl. Environ. Microbiol. 71: 2130-2139.

Reassessing this persistent theory in light of advances in molecular microbial detection and genetic pathogenesis of disease. Similarities between chronic idiopathic granulomatous ileocolitis and mycobacterial infections have been noted since the original descriptions of the clinical syndrome now called Crohn's disease. Interest in a possible infectious origin of this disorder was renewed in 1989 when Chiodini et al cultured apparently identical *Mycobacterium avium* subspecies *paratuberculosis* (MAP) from three patients with Crohn's disease. This controversy increased in intensity following the detection of the specific DNA insertion sequence, IS900, of MAP in relatively high numbers of patients with Crohn's disease relative to ulcerative colitis and normal controls, and is now raging as several different groups have detected this organism in the food chain and water supply, proposed maternal-fetal transmission in human milk, reported long term responses to antimycobacterial antibiotic combinations, and even cultured viable *M paratuberculosis* in blood samples of Crohn's disease patients.

Sartor RB (2005) Does *Mycobacterium avium* subspecies *paratuberculosis* cause Crohn's disease? Gut 54: 896-898.

(contd. on p. 6)

Keeping Up with the Johne's (contd. from p. 5)

OBJECTIVES: Sardinia is an island community of 1.6 million people. There are also about 3.5 million sheep and one hundred thousand cattle in which Johne's disease and *Mycobacterium avium* subspecies *paratuberculosis* infection are endemic. The present study was designed to determine what proportion of people in Sardinia attending for ileocolonoscopy with or without Crohn's disease were infected with this pathogen. METHODS: *Mycobacterium avium* subspecies *paratuberculosis* was detected by IS900 PCR on DNA extracts of fresh intestinal mucosal biopsies as well as by isolation in culture using supplemented MGIT media followed by PCR with amplicon sequencing. RESULTS: Twenty five patients (83.3%) with Crohn's disease and 3 control patients (10.3%) were IS900 PCR positive ($p = 0.000001$; Odds ratio 43.3). Mycobacterium avium subspecies paratuberculosis grew in cultures from 19 Crohn's patients (63.3%) and from 3 control patients (10.3%) ($p = 0.00001$; Odds ratio 14.9). All patients positive by culture had previously been positive by PCR. *Mycobacterium avium* subspecies *paratuberculosis* first appeared in the liquid cultures in a Ziehl Neelsen (ZN) staining negative form and partially reverted through a rhodamine-auramine positive staining form to the classical ZN positive form. This resulted in a stable mixed culture of all 3 forms illustrating the phenotypic versatility of these complex chronic enteric pathogens. CONCLUSIONS: *Mycobacterium avium* subspecies *paratuberculosis* was detected in the majority of Sardinian Crohn's disease patients. The finding of the organism colonizing a proportion of people without Crohn's disease is consistent with what occurs in other conditions caused by a primary bacterial pathogen in susceptible hosts.

Sechi LA, Scanu AM, Molicotti P, Cannas S, Mura M, Dettori G, Fadda G, Zanetti S (2005) Detection and isolation of *Mycobacterium avium* subspecies *paratuberculosis* from intestinal mucosal biopsies of patients with and without Crohn's disease in Sardinia. Am. J. Gastroenterol. 100: 1529-1536.

The heterogeneity of Crohn's disease suggests that it would be unwise to dismiss an infectious contribution to the pathogenesis in a subset of patients. The most enduring infectious candidate has been *Mycobacterium paratuberculosis*, which appears to be widespread in nature and appears to have the potential to infect humans. However, there are many counterarguments to the notion that MAP causes Crohn's disease, and numerous observations are seemingly at variance with this concept.

Shanahan F, O'mahony J (2005) The mycobacteria story in Crohn's disease. Am. J. Gastroenterol. 100: 1537-1538.

BACKGROUND: Crohn's disease, a form of inflammatory bowel disease, resembles some aspects of tuberculosis, leprosy, and paratuberculosis. The role of *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in Crohn's disease is controversial. METHODS: We tested for MAP by PCR and culture in buffy coat preparations from 28 individuals with Crohn's disease, nine with ulcerative colitis, and 15 without inflammatory bowel disease. FINDINGS: MAP DNA in uncultured buffy coats was identified by PCR in 13 (46%) individuals with Crohn's disease, four (45%) with ulcerative colitis, and three (20%) without inflammatory bowel disease. Viable MAP was cultured from the blood of 14 (50%) patients with Crohn's disease, two (22%) with ulcerative colitis, and none of the individuals without inflammatory bowel disease. Current use of immunosuppressive medication did not correlate with a positive MAP culture. Sequencing of PCR products from MAP cultures confirmed the presence of the MAP-specific IS900 fragment. Among 11 MAP isolaes assessed, we identified nine strains that were not identical. INTERPRETATION: We detected viable MAP in peripheral blood in a higher proportion of individuals with Crohn's disease than in controls. These data contribute to the evidence that MAP might be a cause of Crohn's disease.

Naser SA, Ghobrial G, Romero C, Valentine JF (2004) Culture of *Mycobacterium avium* subspecies *paratuberculosis* from the blood of patients with Crohn's disease. Lancet 364: 1039-1044.

Living Donor Liver Transplantation

Living donor liver transplantation (LDLT) has become a viable option for many patients with end-stage liver disease. In fact, about 5% of all liver transplants performed in the United States last year were performed using a live donor. The first adult-adult right hepatic lobe LDLT was performed at the University of Colorado Health Sciences Center in 1997. Over the subsequent five years, about ½ of the liver transplant centers in the United States have begun to offer this procedure to selected patients.

LDLT is performed by removal of the entire diseased liver from the recipient followed by transplantation of the right hepatic lobe (approximately ½ of the donor liver) from a live donor. The surgery on the donor and recipient takes about 4 - 8 hours to complete. Amazingly, the remnant liver in the donor and the transplanted organ in the recipient grow back to near-normal size in a matter of weeks. Survival statistics for the LDLT recipient are similar to conventional transplantation.

LDLT significantly reduces the waiting time for transplantation. Once the living donor is identified and adequately tested, the transplant can occur in a matter of hours to weeks. An expedited transplant with LDLT prevents patients from dying while waiting for a conventional transplant and prevents clinical deterioration which could jeopardize the success of the transplant.

The greatest area of controversy surrounding this procedure is the risk to the donor. A donor death that occurred in New York focused the attention of the medical community and media on this important issue. In response to concerns related to LDLT, the National Institutes of Health has funded an eight-year study to measure the outcomes of donors and recipients of LDLT to determine the value of this procedure. The LDLT Cohort Study began in July 2002 and will continue to follow donors and recipients until 2010. The results of this study will help future donors and recipients to benefit from LDLT.

James F. Trotter, M.D
Associate Professor of Medicine
Division of Gastroenterology/Hepatology
University of Colorado Health Sciences Center, Denver, CO

Update on Donations to PSC Partners Seeking a Cure

(by Ricky Safer)

Here is a list of our recent individual donors (since July 2005)

In honor of:	Donor:
"In honor of and with thanks to my husband/donor, my family, organ donors everywhere, the PSC Support Group, and the medical personnel who have helped me" (Denise Boyd)	Denise Boyd & Michael Jenkins
William F. Bria III	Galen & Anita Toews Dr. Rosemarie Bria-Levine Darcy Ward Friends and colleagues of Bill Bria at University of Michigan Hospital
Daniel Kantor	Vincent & Janice Cianciulli
Garrett Leach	Sheila Leach
Ricky Safer	Paula Oberndorf-Ullman Stephen Winber
Tim Wholey and the PSC cause	Kimberly Walsh
All those dealing with PSC	Tim and Mary Wholey

Thank you to all our donors for helping us reach our ultimate goal of finding a cure for PSC!

Making Donations to PSC Partners Seeking a Cure

Tax-deductible donations can be sent to:

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

with a check made out to:

PSC Partners Seeking a Cure

Alternatively donations can be made on-line via PayPal (**https://www.paypal.com**) to **pscpartners@yahoo.com**

Please include a note to indicate whom the donation is in honor and/or in memory of, and your return address.

We offer several levels of sponsorship

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

Thank you for your generosity!

Thank you to our new silver level sponsors:
Dr. Stephen Winber
Friends and colleagues of Bill Bria at University of Michigan Hospital

Thank you to our new bronze level sponsors:
Tim and Mary Wholey

Thank you to our new copper level sponsors:
Denise Boyd and Michael Jenkins

Did Ludwig van Beethoven have PSC and IBD?

Ludwig van Beethoven (1770-1827) had a number of medical conditions, including deafness and a chronic liver disease. An autopsy was performed on the day after his death. Physicians and historians have tried to reinterpret original sources to determine the causes of his deafness and systemic illnesses. Clinical and post-mortem findings point to renal papillary necrosis and liver cirrhosis of unknown aetiology (Hui et al., 2000). It has been speculated that the combined additive, toxic effects of alcohol and iron were the most likely cause of Beethoven's cirrhosis (Davies, 1995).

However, Beethoven's abdominal symptoms that began in his teens are highly suggestive of inflammatory bowel disease (IBD). IBD is an umbrella term that includes a number of named entities such as ulcerative colitis and Crohn's disease. IBD is now considered to be a problem of immune regulation with extra-intestinal manifestations that include sensorineural hearing loss and primary sclerosing cholangitis (PSC). PSC eventually causes cirrhosis and failure of the liver. A diagnosis of IBD therefore provides a single entity that explains most of the composer's symptoms and was finally the cause of his death. Karmody and Bachor (2005) conclude that Beethoven's sensorineural hearing loss was an immunopathy associated with IBD.

Davies PJ (1995) Was Beethoven's cirrhosis due to hemochromatosis? Ren. Fail. 17: 77-86.

Hui AC, Wong SM (2000) Deafness and liver disease in a 57-year-old man: a medical history of Beethoven. Hong Kong Med. J. 6: 433-438.

Karmody CS, Bachor ES (2005) The deafness of Ludwig van Beethoven: an immunopathy. Otol. Neurotol. 26: 809-814.

PSC Partners Fundraising Update

Dear All,

Just an update on Partners Seeking a Cure. We are committed to funding research for PSC, providing patient education and promoting organ donation. First, for all those who are new , you can find out about our PSC foundation by visiting: www.pscpartners.org. There you can find out all the latest that our foundation is working on. We are continuously looking for ways to help all our PSC members. If you have any comments or ideas please email me at: ldbria@comcast.net

Our Kroger gifts cards are off to a good start. Thank you to all our members who have signed on to raise money while buying our groceries at Kroger and its affiliates listed in the right column. We appreciate everyone who is spreading the word to family, friends, neighbors and colleagues. Now if you would like to give them as a gift, you can buy the rechargeable gift cards in any amount! Just email me to let me know what amount you would like on the card and mail me a check to cover the amount. On my next order I will fill your request and then send it out to you. For all regular cards the check should be made out to PSC Partners Seeking a Cure for $20.00. My email is: ldbria@comcast.net and my address is: Lee Bria, 2720 White Oak Dr., Ann Arbor, MI. 48103.

Tim Wholey is also looking to get his local grocery store on board with a similar fundraiser project. Since these tend to be regional, please see if your grocery store has a program we can join. For more details on how it works you can email me at the address above.

Our AAA environmental fundraiser is up and running. Great news! The following states now have at least one of our members participating in our recycling program: MI, NE, NJ, NH, SC, VA, KY, OH, CO, CT, IL, DE, TX, PA, WI and IN! Hooray! Our recycling program is gaining momentum! Thanks to our members who are signing up to raise money for PSC Partners and to help our environment at the same time. Just call 1-866-332-2234 and tell them you are with PSC Partners Seeking a Cure, or go on line to register at:

http://www.aaaenviornmentalinc.com (our organization's code # is **PSC PARTNE 001)**

They send you the free plastic mailers to recycle your ink cartridges and used cell phones. For more details contact Tim Wholey at: timwholey@cox.net

Jeff Belmont is looking into supplying us with Home Depot certificates to benefit the foundation.

Fall is coming probably sooner than anyone wants it to and with it comes the United Way campaign. Please check with your employers to see if you can direct your contribution to PSC Partners Seeking a Cure. At the University of Michigan and Purdue University, all you need to do is write in on your pledge card that you would like your donation to go to PSC Partners Seeking a Cure and then they will verify our 501[c]3 status and direct the money to PSC Partners.

If you or anyone you know works for SBC you can also direct your donation to PSC Partners Seeking a Cure. Instead of payroll deductions to United Way you can choose your local CSF [Community Services Fund] and ask that the money be directed to PSC Partners Seeking a Cure. Proof of our 501[c]3 status has already been provided to the SBC offices in Connecticut. Let us know at pscpartners@yahoo.com if you need to supply proof to your local office.

Raising money for medical research is an ongoing endeavor. Please contact me if you have any ideas or if you need help getting a fundraiser started. I thank all of you for your commitment and efforts.

It's summer time and a great time for fundraising. Having a family get together? Consider having a raffle to benefit PSC. Want to put together a sporting event? How about a run, walk, bike or boating event? Contact me if you want a company to supply sporting raffle items.

Once again, thanks to all of you who make this possible. We will make a difference.

Best regards to all,

Lee Bria

Kroger
Ralphs
King Soopers
City Market
Dillons
Smith's Food & Drug Stores
Fry's
QFC Quality Food Centers
Baker's
Cala Foods Bell Markets
Owen's
Jay C Food Stores

Re-birthdays

by Denise E. Boyd

When I joined the PSC Support group, I would always take heart from the "Happy Re-birthday" postings sent out to our transplanted members. It gave me hope that I would one day join this group of transplanted individuals. When I first read the term "re-birthday," though, I had no idea of its accuracy. It wasn't until my husband, Mike, donated 60% of his liver to me on May 19, 2005 that I learned exactly what the term meant.

Following transplant, my body has metamorphosed into a completely different being. Upon waking from the surgery, I felt exactly what our members at the conference this May told me I would - BETTER. Despite the well-managed surgical pain, I could tell that my body had a working liver. My jaundice immediately began to improve. By the time I was released from the hospital, most of it had cleared, and my eyes were white. The day after I transferred out of ICU or my third day post-surgery, I started walking the halls. At first, I only did one third of a lap, but I quickly worked up to as many as five or ten laps at a time. When I switched to oral pain medications and my pain started to creep in before my next dose, I would get up and walk. The movement helped me make it to the next dose.

On the order of the bizarre, I have a newfound liking for milk, a beverage I have loathed my entire life. My husband, who was my donor, is a heavy milk drinker. Perhaps, there was some transfer with the liver? Who knows! The only true negative, is that I also received my husband's allergy to cats. (Okay, perhaps it is the immunosuppression allowing an already present allergy to come to the fore, but it is real nonetheless!) Whenever I'm in a home with cats now, my nose starts to run and I feel like I'm coming down with a cold. Once I leave the cat, I begin to improve. Also, I now know that the insomnia I endured when I last took the antibiotic Levaquin pre-transplant was due to encephalopathy and not the drug itself. This is a big relief because I am limited in the number of antibiotics that I can take because of a sensitive stomach.

My one regret during this period of immense change is that I did not provide my medical advocate with a tape recorder to record what the doctor said just after surgery. Everyone present was in such an emotional state that they failed to remember the doctor saying that there were three bile ducts from Mike's liver and they were extremely narrow. Had I known this fact, I would have pressed harder that I was feeling cholangitis-type symptoms when they cropped up a few weeks ago. As it turns out, during surgery the doctor had stented those ducts, and my MRI shows some dilatation behind one of the ducts. After identifying that there was a blockage, my family recalled that my surgeon had suggested that this was a likely complication for me. Perhaps I could have been spared one or even both biopsies had I known this information. Luckily, this type of blockage is related to the surgery itself and does not represent a PSC recurrence.

Other changes post transplant? I now wear a watch with three alarms to help me remember to take my carefully timed medications. I never leave the house without sunscreen. My energy level has risen to new heights. Perhaps the best things are that I have my mind back and I no longer itch. Looking back on my final year post-surgery, the encephalopathy started even sooner than I had realized. Prior to surgery, I wondered if I was sick enough, and if I was ready for transplant. Now, I am certain that I made the right choice to accept Mike's amazing gift, small bile ducts and all. Already our son has said, "Mommy, I'm so glad you had your transplant." It is amazing to be able to be a full parent and a full person. I am already looking forward to next year's May 19th, because I, too, will have a re-birthday to celebrate.

Laughter is the Best Medicine

Sorry, we had to withdraw our “Laughter is the Best Medicine” column this month because of this paper:

Liangas G, Morton JR, Henry RL. (2003) Mirth-triggered asthma: is laughter really the best medicine? Pediatr. Pulmonol. 36: 107-112.

PSC Partners Seeking a Cure Notecards

Notecards can be purchased from "PSC Partners Seeking a Cure":

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

Alternatively, notecards can be ordered on-line via PayPal (https://www.paypal.com/) email:
pscpartners@yahoo.com

If choosing this route, please indicate the number of notecards you wish to purchase, and give your name and shipping address.

The purchase price of the notecards is dependent upon the number ordered, as follows:

- 1 bundle of 6 cards ..... $10.00 plus $1.00 shipping and handling
- 2 bundles (12 cards) .... $20.00 plus $1.75 shipping and handling
- 3 bundles (18 cards) .... $30.00 plus $2.00 shipping and handling

These S&H numbers are for domestic orders only. For international orders please email

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and a shipping quote will be provided.

(*Notecard concept by Ali Lingerfelt-Tait*)

Probiotics and Inflammatory Bowel Disease

(by David Rhodes)

Probiotics can be defined as microbial cells that have a beneficial effect on the health and well-being of the host (Fioramonti et al., 2003). There is growing evidence that probiotics can be useful in inducing remission in patients with active ulcerative colitis (UC). A recent paper by Biblioni et al (2005) has shown that the probiotic called VSL#3 resulted in induction of remission in a significant number of patients with active UC who were not responding to conventional therapy. No adverse effects were reported (Biblioni et al., 2005).

VSL#3 consists of a mixture of eight lactic acid bacterial species: four strains of *Lactobacillus*, three strains of *Bifidobacterium* and one strain of *Streptococcus*. It is marketed by VSL Pharmaceuticals, Inc., Ft. Lauderdale, FL. (Biblioni et al., 2005). The mixture is reported to have anti-inflammatory activities, and has previously been demonstrated to be effective in preventing flare-ups of refractory pouchitis (Akerlund and Lofberg, 2004). Moreover, probiotics are reported to reduce intestinal inflammation in children with cystic fibrosis (Bruzzese et al., 2004).

The possible mechanisms of action of probiotics may include a decrease in the secretion of pro-inflammatory cytokines such as IFN-gamma (interferon-gamma), TNF-alpha (tumor necrosis factor-alpha) and IL-12 (interleukin-12), and interference with bacterial adherence to the epithelium (Dotan and Rachmilewitz, 2005).

Fedorak and Madsen (2004) postulate five possible mechanisms of action of probiotics:

(1) competitive exclusion, whereby probiotics compete with microbial pathogens for a limited number of receptors present on the surface epithelium;

(2) immunomodulation and/or stimulation of an immune response of gut-associated lymphoid and epithelial cells;

(3) antimicrobial activity and suppression of pathogen growth;

(4) enhancement of barrier function; and

(5) induction of T cell apoptosis in the mucosal immune compartment.

What are prebiotics and synbiotics? A “prebiotic” is a dietary carbohydrate selectively metabolised by probiotics. Combinations of probiotics and prebiotics are known as “synbiotics” (Fooks and Gibson, 2002). Furrie et al (2005) have recently reported that synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active UC. Synergy 1 is an inulin-oligofructose growth substrate that is preferentially used by the probiotic strain *Bifidobacterium longum* (Furrie et al., 2005).

References

Akerlund JE, Lofberg R (2004) Pouchitis. Curr. Opin. Gastroenterol. 20: 341-344.

Bibiloni R, Fedorak RN, Tannock GW, Madsen KL, Gionchetti P, Campieri M, De Simone C, Sartor RB (2005) VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. Am. J. Gastroenterol. 100: 1539-1546.

Bruzzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, Guarino A (2004) Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Aliment. Pharmacol. Ther. 20: 813-819.

Dotan I, Rachmilewitz D (2005) Probiotics in inflammatory bowel disease: possible mechanisms of action. Curr. Opin. Gastroenterol. 21: 426-430.

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Fooks LJ, Gibson GR (2002) Probiotics as modulators of the gut flora. Br. J. Nutr. 88 Suppl. 1: S39-S49.

Furrie E, Macfarlane S, Kennedy A, Cummings JH, Walsh SV, O'neil DA, Macfarlane GT (2005) Synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. Gut 54: 242-249.

CCFA Educational Brochures

The Crohn’s and Colitis Foundation of America (CCFA) has published a series of newly revised Education Brochures on inflammatory bowel diseases:

- Living With Crohn's Disease
- Living With Ulcerative Colitis
- A Guide for Parents
- A Guide for Teachers and Other School Personnel

Other CCFA brochures include:

- Medications
- Maintenance Therapy
- Diet and Nutrition
- Emotional Factors
- Complications
- Understanding Colorectal Cancer
- Surgery
- Sexuality
- Women's Issues
- A Guide for Children and Teenagers

All of these brochures are available as .pdf files from the CCFA web site:

http://www.ccfa.org/info/brochures/

2005 Conference CD

Copies of the 2005 Conference CD ($25 each in the U.S./ $30 abroad; this includes shipping and handling) can be purchased from:

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

Please make checks out to: **PSC Partners Seeking a Cure**
Please include your name and mailing/shipping address when you place your order! Thank you!

Conference CD Disclaimer

PSC Partners does not provide specific medical advice, is not engaged in providing medical or professional services and does not endorse any medical or professional service obtained through information provided on this CD. Use of this CD does not replace medical consultations with a qualified health or medical professional to meet the health and medical needs of you or a loved one.

Additional Contact Information

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

pscpartners@yahoo.com

Submitting Newsletter Articles

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

or use the "Submit Newsletter Article" form on the www.pscpartners.org web site.

A wise man should consider that health is the greatest of human blessings, and learn how by his own thought to derive benefit from his illnesses.

Hippocrates
(460 BC - 377 BC)

GiveLife

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."

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.

Facilitating Contacts Between Conference Attendees

If a conference attendee would like to be placed in e-mail contact with someone else who attended the conference, please write to Ricky Safer (pscpartners@yahoo.com) with your request, and she will forward your message to the person in question.