



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

www.pscpartners.org

PSC Partners Seeking a Cure Newsletter

Vol. 3, Issue 1, July 2007

Edited by David Rhodes and Ricky Safer

PSC Partners Seeking a Cure Board Members:

Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Gregory Everson, Joanne Grieme, Chris Klug, Scott Malat, David Rhodes, Ricky Safer, and Deb Wentz

2008 Conference

The 2008 PSC Partners Seeking a Cure Conference will be held May 2-4, 2008 at the Mayo Clinic in Jacksonville, Florida.

In this Issue

- My Yearly Fix p. 1-4
- 2007 Conference Sponsors p. 4
- Conference Attendee Comments p. 5
- PSC Partners Seeking a Cure Fundraising News p. 6-7
- Update on the financial position of PSC Partners Seeking a Cure Foundation (through March 31, 2007) p. 7-8
- Update on the financial position of PSC Partners Seeking a Cure Foundation (through June 30, 2007) p. 8
- PSC Partners Seeking a Cure AASLD Award p. 8
- Update on STOPSC p. 8
- Next Issue p. 8
- Update on donations to PSC Partners Seeking a Cure (Jan - May, 2007) p. 9-11
- Largest Ever Study of Genetics of Common Diseases Published Today p. 11-12
- Commentary on Recent Genetic Studies p. 12-15
- Volunteers Needed p. 16
- eMail Address Correction p. 16
- Diet and Risk of Crohn's Disease in Children p. 16
- A Recent Review on PSC p. 16
- PSC 40 Years Ago p. 17
- Making Donations to PSC Partners Seeking a Cure p. 17
- Give Life p. 17
- Note to Readers p. 17
- Additional Contact Information p. 17
- Submitting Newsletter Articles p. 17

Please accept our sincere apologies for being late with this issue of the newsletter!

MY YEARLY FIX

Now that our 2007 conference is over and I've had time to begin absorbing the whole experience, I'm starting to come back to reality. That "magical something" that happens each time that we PSCers and caregivers get together to learn and share was evident in the faces of all the attendees, old and new! There is an indescribable yet palpable positive energy in our group, which continues to amaze and energize me. Our speakers were brilliant, the food delicious, the venue comfortable, but what truly made the weekend was all of you who participated. Thank you for giving me my annual fix!

As I think back to our conference weekend, here are some thoughts that I wanted to share with you:

- Our attendees this year came from nineteen different states and three foreign countries (Canada, the UK, and Sweden.) Although we are a diverse group, everyone is welcomed unconditionally. Where else in the world can you show up feeling fatigued, itching all over, jaundiced, and feel totally at home? The bonding that happens over the weekend is phenomenal.



Dr. Gregory Everson

- I would use this combination of words to describe our PSCers and caregivers: knowledgeable, questioning, positive, caring, compassionate, tenacious, and humorous. Together, we WILL find a cure for PSC!!!
- Thanks to Dr. Greg Everson, who helped us every step of the way in planning the conference, we had a superb conference with an unbelievable slate of speakers. On Saturday, the speakers covered the medical, scientific, and practical information that we all need to live positively with PSC. This variety of topics was covered by physicians from the University of Colorado Health Sciences Center, as well as these out of town speakers: Dr. John Vierling, Baylor College of Medicine, Dr. Doug LaBrecque, University of Iowa, Dr. Gregory Fitz, UT Southwestern, and Dr. Lyn Patrick. David Rhodes, gave another wonderful talk as well. Ivor Sweigler gave his yearly update on Dr. Roger Chapman's research in the UK. In the **next** issue of the newsletter, please check out David's summaries of these presentations. (If you attended the conference, you will be receiving a complimentary CD of all the PowerPoint presentations. If you didn't attend the conference and would like a copy of the CD, we will be selling them at a nominal cost once they are ready.)
- As always, Olympian Chris Klug was one of the highlights of the weekend. He was the keynote speaker at our Saturday evening banquet, and he was totally inspiring.
- On Sunday morning, when we broke into discussion support groups (males with PSC/females with PSC/parents of PSCers/spouses of PSCers and other caregivers), there were animated discussions of our experiences with PSC and concerns about how to deal with all the issues that we face. Thanks to feedback from the participants afterwards, we are going to schedule in more discussion time next year.
- I was encouraged by the many speakers who pointed out the progress that is being made by researchers who are studying PSC, immunity, and genetics. I'm proud that PSC Partners Seeking a Cure is supporting the STOPSC registry and the top PSC research fellow at this fall's AASLD meeting. As we continue to raise more funds, we will invest in more PSC research.
- After presenting, many of the physicians talked to me on Saturday, and they all passed on a similar message. They are very impressed with our group, especially with everyone's knowledge and proactive, positive stance. They mentioned that our group has now reached a "critical mass", where we can make our presence felt by working for more PSC awareness and research.
- Another success of the conference is the transformation of the new attendees. Most of them arrived on Friday evening, feeling anxious about their decision to come to the conference. By the time they left on Sunday, they were smiling and feeling confident and positive, thanks to the education they received and the new PSC friends that they made to help them through their PSC concerns in the future. How I wish this had been available to me when I was first diagnosed!
- Congratulations to Tim Wholey, who won our drawing for a free registration to next year's conference.



Drs. James Trotter, Lisa Forman, Raj Shah and Doug LaBrecque

Ivor Sweigler



Chris Klug



We are all very grateful to the following Corporate Partners who made this weekend possible through their sponsorship: University of Colorado Health Sciences Center, Axcan Scandipharm, Cook Medical, Procter and Gamble, Salix Pharmaceuticals, and Prometheus Labs. Please see the list of our individual sponsors following this article. We appreciate everyone's support!

(continued from p. 2)

Here are a few more thank you's to people who made our conference such a success:

- Thank you to our brilliant speakers, who gave up their weekend time to enlighten us about the latest information on PSC and related topics.
- Thank you to all the board members who continue to guide us in our progress: Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Greg Everson, Joanne Grieme, Chris Klug, Scott Malat, David Rhodes and Deb Wenthe.
- Thank you to Lee Bria, our always enthusiastic fundraising chairman, and Joanne Hatchett for organizing such a successful Virtual Walk!!! Thank you to all the walkers and their donors.
- Thank you to David Rhodes for your presentation at the conference, for creating the conference CD, and for continuing to put out our newsletters and update the PSC Literature site. Where would we be without you?
- Thank you to Joanne Grieme, who gave me advice throughout the year on conference details and who put together the name tags and attendee directory.
- Thank you to Joanne Hatchett for the wonderful handouts that you gave us at your display table: the lab/medication flow sheets, Advance Directive information, and the PSC medical cards.
- Thank you to Mark Stivers, who provided piano accompaniment during our Friday evening reception. You truly classed up our act!
- Thank you to Steven Deitch, our IT expert, who kept everything working smoothly.
- Thank you to Sue Safer, who designed our 2007 conference t-shirts.
- Thank you to Bettyann and Bud Harlow, Erin and Todd Litton, Deb and John Wenthe, and Nichole and Charles Rowland, who donated items for our Silent Auction.
- Thank you to all the volunteers who helped run the conference.
- **THANK YOU TO ALL OUR ATTENDEES!!!!** You set the tone for the weekend.

Mark Stivers



Steven Deitch

Saturday night, we were pleased to announce that our 2008 conference will be held May 2-4 in Jacksonville, Florida, and will be co-sponsored by the Mayo Clinic. Our keynote speaker will be Dr. Gregory Gores of Mayo/Minnesota. We are very excited about next year's conference, and we are already busy planning the details. If you couldn't make it to this year's conference, please try to join us in 2008!

As a kickoff for Jacksonville in 2008, we have started a new fundraising campaign to raise money for research, The Road to Jacksonville. Please join us in this effort. See Lee's article (p. 6 - 7) for details.

It will take me months to absorb all the medical information that I learned at the conference and to enjoy the warm vibes, courage, and compassion of our participants. I will miss all of you, but I look forward to seeing everyone again in 2008. I wish all our PSCers an asymptomatic and healthy year. May it be a year when we are able to support more PSC research in our search for a cure. We appreciate everyone's involvement.

Ricky Safer

Together in the fight, whatever it takes!

Adam and Sue Safer





Deb and John Wente

Helena and Nicklas Holmgren

Lee Bria

CONFERENCE FOR PATIENTS AND CAREGIVERS

APRIL 13 - 15, 2007

Hyatt Regency Tech Center, Denver, CO

We would like to thank our sponsors for making this conference possible:

- University of Colorado Health Sciences Center
- Axcan Pharma - Silver level sponsor
- Astellas - Silver level sponsor
- Cook Endoscopy - Bronze level sponsor
- Procter and Gamble - Bronze level sponsor
- Salix Pharmaceuticals - Bronze level sponsor
- Prometheus Laboratories



We are 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.



We also thank all those members of the PSC support group, and their family, friends and caregivers, who have generously donated their time and funds to the PSC Partners Seeking a Cure foundation.



CONFERENCE ATTENDEE COMMENTS

Here are some anonymous comments that we received post conference via email posts and evaluation sheets from various participants. They provide a flavor of the weekend.

- It was a wonderful, uplifting experience, as always. I hope that other conference attendees come away from the conference as energized as I was.
- I am very impressed by the resolve and organization of your group.
- Thank you everyone for being you. For being there and listening - I truly feel I'm not alone. I feel like someone out there understands....This conference was so worth the long distance to travel and dollars it took to get there - worth every penny and minute. I am so looking forward now to a positive and supported year and reunion of my new "family" next year.
- The conference in Denver was absolutely great. We always come away with so much more than we expect.
- The speakers were exceptional. The knowledge level of the speakers was evident and all could answer any of the questions asked. The camaraderie among the attendees was extraordinary.
- Seemed like much more new information this year. Nematodes research was brilliant.
- The people in this group are great, compassionate, caring, energetic. It helped lift my spirits.
- The time that the medical experts were willing to spend during and after the sessions was great.
- Overall, this has been the most informative and best organized conference I have ever attended.
- The presentations were extraordinarily good. They clarified and simplified some of the complexities of PSC. This is a wonderful organization and cause with very competent people.
- I never expected this conference to be so fantastic!
- The hardest part is going home!
- It was a great conference! For anyone who is wondering whether or not to attend next year, I vote that you go. You won't regret it. My husband and I were both revitalized. We learned a great deal, got some desired referrals, met truly wonderful people (new friends), and had an enormously positive experience.



Joanne Hatchett and Don Safer



Joanne Grieme and Ricky Safer

PSC Partners Seeking a Cure Fundraising News

In March we launched our second annual Virtual Walk which breezed in with an amazing \$26,536!!!! Walkers registered for kits that came with a PSC Partners tee shirt, permanent marker and signature sheets. They walked to gather signatures of support and donations for PSC research.

Our top three walkers raised:

1. **Joanne Hatchett** **\$8,014**
2. **Cindy Rogers** **\$5,106**
3. **Lee Bria** **\$2,500**

Thank you to all who participated and made this such a success. The shirts that come to the conference are displayed and are a real morale boost when all the signatures of support are seen. They are creative and heartwarming. Thank you to all our conference attendees who added their donations and signatures of support over the weekend. We are together in this fight, whatever it takes and it takes all of us working together. Next March we hope to have more walkers join us to help us fund the necessary research for a better treatment for PSC.



The Virtual Walk T-shirt created by Cindy Rogers in loving memory of her husband, Tom

Our 2007 conference has come and gone in a flash. Everything was wonderful and mixed in with business was a little fun. Our silent auction was a hit again. Conference attendees had the chance to bid on some great items and raised a total of \$755!!! Big thanks to Bud and Bettyann Harlow for the signed professional baseballs. What a great collectible for our winners. Big thanks to Nicole Rowland for the lovely blanket hand made by Nichole's aunt. Big thanks to Deb Wentz for the really cool Creative Memories Digital Photo Book donation. Big Thanks to Erin Litton for the two pretty table runners she made and for the beautiful bracelet and necklace her sister made.

Ali Lingerfelt-Tait, while not able to travel to the conference, was able to supply us with more of her wonderful artistic note-cards. We raised another \$250 from the sale of the note-cards and you can order them from our website whenever you need more. Thank you so much Ali.

Our AAA environmental program has brought in over \$1,710 so far. So please keep ordering envelopes and sending in old cell phones and empty ink cartridges because it really helps. Call 1-866-332-2234 to order. Ask for envelopes coded to PSC Partners Seeking a Cure. For more information see our PSC Partners web site.

Our Kroger program has brought in over \$9,861 by everyone working together. Please keep recharging those cards as this is so very generous of the Kroger Company to be such a great supporter of our foundation. I now have Kroger cards available for anyone who wants to order one. This is a free program to us with Kroger donating 5% every time we fill one of their rechargeable cards. It is so easy, free and tremendously helpful to the foundation. Please join us in the effort if you shop at Kroger stores. You can find the list of their different stores and more information on the PSC Partners web site or contact me at leedeubert@gmail.com

PSC Partners Seeking a Cure is hitting the road and raising money for PSC research.

The Road to Jacksonville

The Road to Jacksonville is ready for walkers, runners, bikers and any other means of travel you want to do.

Everyone is invited to join us on the road to Jacksonville, FL for our 2008 PSC Partners Seeking a Cure Conference! Along that road we will challenge ourselves to raise money for much needed PSC research. We have set a big goal to raise \$100,000 by the time we get to Jacksonville!!!

Let's pave that road together one mile at a time. Donate or raise \$50/mile and travel with us the 2,000 miles from Denver to Jacksonville. Watch our progress, participate and cheer us on! We need new studies for new therapies that

(continued from p. 6)

will change the future of PSC care.

Please help us advocate donor awareness along the way. Until there is better treatment available, liver transplants will still be necessary.

To watch our progress and for more details visit our "Road to Jacksonville" map at :

<http://www.pscpartners.org/RtJ.htm>

We are together in this fight, we will back new research for new treatments. The answers are out there, let's help start the search!!

On your mark, get set, go!!!!!!



More Exciting Fundraising

On May 6th Tina Rampino ran the Long Island Marathon in honor of Billy Colfer Jr. to raise funds for PSC Partners Seeking a Cure. So far \$4,459.43 have come in from this great effort!! Thank you so very much, Tina.

Quickstar Productions has donated \$500 and these generous musicians are now putting together a CD with a variety of bands that will raise yet more money for PSC Partners. Proceeds from the sales of the CD will honor their friend Kevin O'Hara who has PSC. Thank you so much, what great and caring friends you are.

We also want to thank the wonderful friends of Joe Warmbrodt who are preparing for a benefit concert in his memory later this year with all proceeds going to PSC Partners Seeking a Cure. Thank you so very much.

We are proving that by working together we can raise the funds necessary for research and better treatment. Please join us on the Road to Jacksonville with all your creative ideas for fundraising. Bookmark our website and watch our progress. We can all be a part of this effort. We can all feed the hope and feel the pride in helping ourselves. We can all fight for better PSC treatment!

Lee Bria

Update on the financial position of PSC Partners Seeking a Cure Foundation (through March 31, 2007)

Total income for 2006 was \$102,535. Donations contributed \$62,746 and net fundraising \$52,205.

There were 17 donations of \$1,000 or greater, with a total of 175 individual donations. The Virtual Walk was our most successful fundraising event, generating income of \$44,738.

The largest expenses of 2006 were conference expenses of \$17,488, offset by conference/sponsor income of \$26,188, fundraising costs of \$6,449, almost solely for initial gift card purchases and accounting expenses of \$3,595. Accounting expenses were offset by the generous inkind gift of accounting from Sima and Clifford Malat.

Administrative expenses for 2006 were slightly under \$1,500, or 1.5% of total income.

During 2006, a donation was made to STOPSC for \$20,000.

Total income for 2007 through March is \$92,676. YTD donations are \$36,209, predominately made up of 5 donations

(continued from p. 7)

each \$5,000 or greater. Fundraising has raised \$31,336 year to date, detail is provided in the article by Lee Bria.

Total assets through March 2007 are \$217,713, an increase of \$75,204 from Dec. 31, 2006. The largest changes since December 31 are noted in the preceding paragraph.

During 2006 the money invested at Charles Schwab earned \$199 in interest and \$1,021 in cash dividends. February 2007 YTD earnings were \$49 in interest and \$942 in cash dividends.

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

Deb Wentz

PSC Partners Seeking a Cure will award a \$3,000 prize at the annual meeting of the American Association for the Study of Liver Diseases (AASLD)

The following announcement of the annual award is from AASLD: 58th Annual Meeting of the American Association for the Study of Liver Diseases:

PSC Partners Seeking a Cure Award

\$3,000
(1 available)

This award shall be given to one investigator presenting the most promising PSC research at The Liver Meeting® 2007. All abstracts submitted to the Human Cholestatic and Autoimmune Liver Diseases Category, PSC descriptor will be considered for this award (there is not a formal application process for this award). Notification will be made in August. This award can be used to support travel and accommodation expenses associated with participation in the AASLD Annual Meeting, or for supplies and expenses for PSC research.

The awardee will also be invited to attend the PSC Partners Seeking a Cure Annual Conference (www.pscpartners.org).

AASLD gratefully acknowledges PSC Partners Seeking a Cure for their generous support of this award.

Update on STOPSC

David Rhodes has been invited to attend the Morgan Foundation Scientific Advisory Board Meeting in Memphis, TN, July 22-23, 2007. At this meeting it is expected that STOPSC progress will be a major topic of discussion. We'll keep you posted about significant developments in future issues.

Update on the financial position of PSC Partners Seeking a Cure Foundation (through June 30, 2007)

Following is an update of the current financial position through June 30, 2007 of PSC Partners Seeking a Cure Foundation.

Total income for 2007 through June is \$102,250. YTD donations are \$39,967, predominately made up of 5 donations each \$5,000 or greater and 2 donations of \$1,000 or greater. Fundraising projects have raised \$36,783 YTD.

Total assets through June 2007 are \$226,859, an increase of \$84,350 from Dec. 31, 2006. The largest changes since December 31 are noted in the preceding paragraph.

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

Deb Wentz

Next Issue

The next issue of the newsletter will include a detailed description of the talks presented at the 2007 Conference in Denver, CO. We anticipate that the next issue will be published in August, 2007, together with the conference CD. The next issue will also include an update on recent literature, donations since May, 2007, a report on fundraising progress, STOPSC progress, and additional conference photographs. Thank you for your patience as we assemble these materials.

Dave Rhodes

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE (January - May, 2007)

IN HONOR OF:

Samantha Wentz

Billy Bria

Susan Malat

Bill Wise

Paul Maranto

Steven Rhodes

Dike Ajiri

Ricky Safer

Joey Hatchett

Todd Clouser

Conference sponsorship

Birthday of Roy Gross

Jeffrey W. Brown

Casey Rountree

Brad Cvetovich/In memory of George Hall

Keep up the good work!

Ricky and Don Safer and David Rhodes for all of the incredible work, effort, support, love, comfort, hope and knowledge you give to those afflicted with PSC and their families.

PSC Partners Seeking a Cure

\$1 for each support group member

Kevin O'Hara

IN MEMORY OF:

Lauren Boiteau

Wesley Arjske

Milton Lukaczer

DONOR:

Deb and John Wentz

Darcy Ward

Lee and Bill Bria

Sima and Cliff Malat

Susan and Scott Malat

Eileen and Danny Langer

Goldman Sachs and Co. Matching Gift Program

S and S Cycle, Inc.

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Judy and David Rhodes

Rilee and Dike Ajiri

Steven Winber

Ricky and Don Safer

Joanne and Steve Hatchett

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Joanne and Steve Grieme

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Joanne Grieme

Faye Brown

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Tom O'Neal
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Mary Lynn Richards

Thomas Rogers

Robert B. Lloyd
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A BIG THANK YOU TO OUR NEWEST SPONSORS:

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Ricky and Don Safer
Susan and Scott Malat
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Teresa Maranto

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Bronze level sponsors:

Joanne and Steve Grieme
Jennifer and Jason Drasner
Judy and Arne Myrabo
Martha Marvin
Robert B. Lloyd
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Steve Winber

Copper level sponsors:

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Judy and David Rhodes

Sima and Cliff Malat
Quickstar Productions
Kim and Cameron Beck
Jeanne Cooper
Verna and Stanley Smith

*WE'D LIKE TO THANK OUR CORPORATE SPONSORS FOR THEIR
SUPPORT OF OUR 2007 CONFERENCE:*

University of Colorado Health Sciences Center
Axcan Scandipharm - Silver level sponsor
Astellas - Silver level sponsor
Cook Endoscopy - Bronze level sponsor
Procter and Gamble - Bronze level sponsor
Salix Pharmaceuticals - Bronze level sponsor
Prometheus Laboratories

Thanks also to our first group of donors to The Road to Jacksonville fundraising project (through May, 2007):

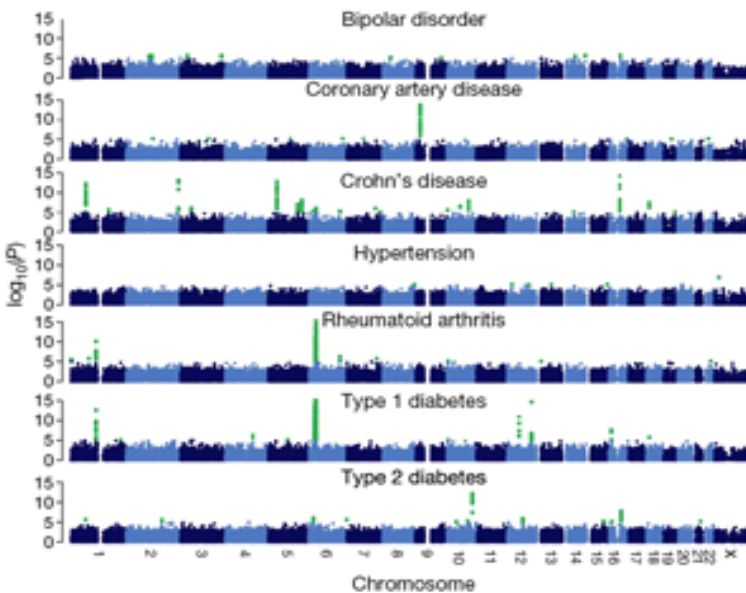
Lee and Bill Bria
Reggie and Jeff Belmont
Joanne and Steve Hatchett

Largest ever study of genetics of common diseases published today

Wellcome Trust Press Release: 6th June 2007

<http://www.wtccc.org.uk/info/070606.shtml>

The Wellcome Trust Case Control Consortium, the largest ever



Genome-wide scan for associations of SNPs with each of the seven diseases. Chromosomes are shown in alternating shades of blue, significant SNPs (p -values $< 1 \times 10^{-5}$) are highlighted in green.

study of the genetics behind common diseases such as diabetes, rheumatoid arthritis and coronary heart disease, today publishes its results in the journals *Nature* and *Nature Genetics*.

The £9 million study is one of the UK's largest and most successful

academic collaborations to date. It has examined DNA samples from 17,000 people across the UK, bringing together 50 leading research groups and 200 scientists in the field of human genetics from dozens of UK institutions. Over two years, they have analysed almost 10 billion pieces of genetic information.

"Many of the most common diseases are very complex, part 'nature' and 'nurture', with genes interacting with our environment and lifestyles," says Professor Peter Donnelly, Chair of the Consortium, who is based at the University of Oxford. "By identifying the genes underlying these conditions, our study should enable scientists to understand better how disease occurs, which people are most at risk and, in time, to produce more effective, more personalised treatments."

The study has substantially increased the number of genes known to play a role in the development of some of our most common diseases. Many of these genes that have been found are in areas of the genome not previously thought to have been related to the diseases.

"Just a few years ago it would have been thought wildly optimistic that it would be possible in the near future to study a thousand genetic variants in each of a thousand people," says Dr Mark Walport, Director of the Wellcome Trust, the UK's largest medical research charity, which funded the study. "What has been achieved in this research is the analysis of half a million genetic variants in each of seventeen thousand individuals, with the discovery of more than ten genes that predispose to common diseases."

"This research shows that it is possible to analyse human variation in health and disease on an enormous scale. It shows the importance of studies such as the UK Biobank, which is seeking half a million volunteers aged between 40 and 69, with the aim of understanding the links between health, the environment and genetic variation. New preventive strategies and new treatments depend on a detailed understanding of the genetic, behavioural and environmental factors that conspire to cause disease."

Amongst the most significant new findings are four chromosome

(continued from p. 11)

regions containing genes that can predispose to type 1 diabetes and three new genes for Crohn's disease (a type of inflammatory bowel disease). For the first time, the researchers have found a gene linking these two autoimmune diseases, known as PTPN2.

The study has also confirmed the importance of a process known as autophagy in the development of Crohn's disease. Autophagy, or "self eating", is responsible for clearing unwanted material, such as bacteria, from within cells. This may be key to the interaction of gut bacteria in health and in inflammatory bowel disease and could have clinical significance in the future.

"The link between type 1 diabetes and Crohn's disease is one of the most exciting findings to come out of the Consortium," says Professor John Todd from the University of Cambridge, who led the study into type 1 diabetes. "It is a promising avenue for us to understand how the two diseases occur. The pathways that lead to Crohn's disease are increasingly well understood and we hope that progress in treating Crohn's disease may give us clues on how to treat type 1 diabetes in the future."

Research from the Consortium had already played a major part in identifying the clearest genetic link yet to obesity and three new genes linked to type 2 diabetes, published in April in advance of the main study. It has found independently a major gene region on chromosome 9 identified by independent studies on coronary heart disease.

Researchers analysed DNA samples taken from people in the UK - 2,000 patients for each disease and 3,000 control samples - to identify common genetic variations for bipolar disorder, Crohn's disease, coronary heart disease, hypertension, rheumatoid arthritis and type 1 and type 2 diabetes. For each disease, the researchers will study larger population samples to confirm their results.

Although the human genome is made up of more than three billion sub-units of DNA, called nucleotides (or bases), most of these show little in the way of differences between individuals. A substantial part of the variation in DNA sequence between individuals is due to single-nucleotide polymorphisms (differences), also known as SNPs. There are approximately 8 million common SNPs in European populations. Fortunately, because SNPs that lie close together on chromosomes often tell quite similar stories, researchers in the Consortium were able to explore this variation through analysing a subset of these SNPs (in fact approximately 500,000).

"Human genetics has a chequered history of irreproducible results, but this landmark collaboration of scientists in Britain has shown conclusively that the new approach of analysing a large subset of genetic variants in large samples of patients and healthy individuals works," says Professor Donnelly. "We are now able to effectively scan most of the common variation in the human genome to look for variants associated with diseases. This approach will undoubtedly herald major advances in how we understand and tackle disease in the future."

Further analysis as part of the Consortium will be looking at tuberculosis (TB), breast cancer, autoimmune thyroid disease, multiple sclerosis and ankylosing spondylitis. The results are expected later this year.

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Notes to Editors

The Wellcome Trust is the largest charity in the UK. It funds innovative biomedical research, in the UK and internationally, spending around £500 million each year to support the brightest scientists with the best ideas. The Wellcome Trust supports public debate about biomedical research and its impact on health and wellbeing.

<http://www.wellcome.ac.uk>

The Wellcome Trust Case Control Consortium was supported by: the Medical Research Council, British Heart Foundation, Juvenile Diabetes Research Foundation, Diabetes UK, the Arthritis Research Campaign, the National Association for Colitis & Crohn's Disease and MDF The Bipolar Organisation.

<http://www.wtccc.org.uk>

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Wellcome Trust Case Control Consortium 2007 Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447: 661-678.

Commentary on Recent Genetic Studies

by David Rhodes

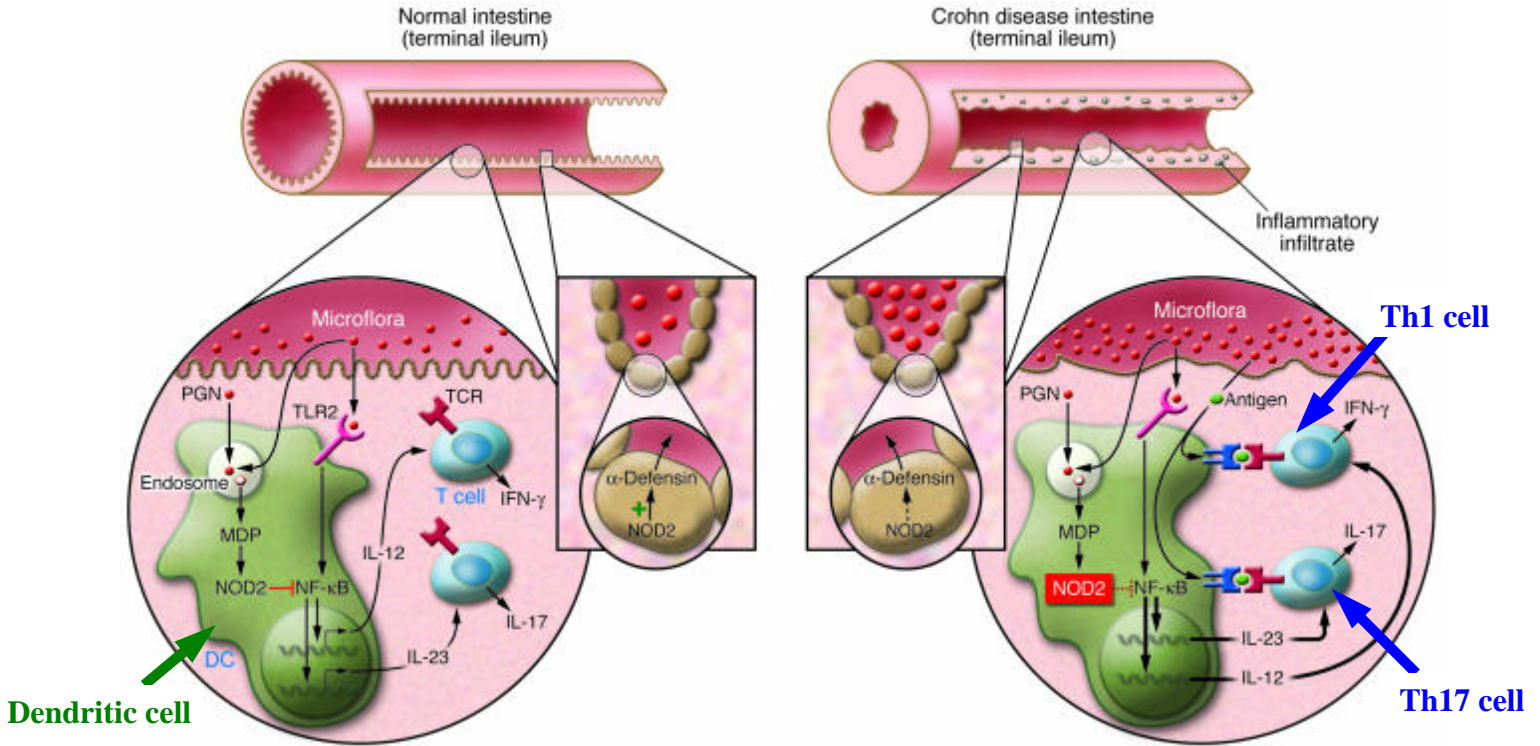
The preceding press release comes on the heels of several other large genome-wide scans for genes associated with inflammatory diseases. In 2006, Duerr et al found that in addition to the well-characterized Crohn's disease susceptibility gene, NOD2/CARD15 (on chromosome 16), the gene encoding IL-23R (interleukin-23 receptor) (on chromosome 1) was strongly associated with inflammatory bowel disease. This result was rapidly confirmed by Dubinsky et al (2007), Van Limbergen et al (2007), and Baldassano et al (2007). Moreover, the same gene was found to be involved in sus-

ceptibility to the inflammatory skin disease, psoriasis (Cargill et al., 2007; Capon et al., 2007). Other genome-wide scans also uncovered a gene associated with autophagy (ATG16L1) that appears to be central to susceptibility to inflammatory bowel diseases (Hampe et al., 2007; Prescott et al., 2007). Finally, a gene involved in regulation of prostaglandin metabolism (prostaglandin receptor EP4, PTGER4) has been identified as a Crohn's disease susceptibility gene (Libioulle et al., 2007) through genome-wide scanning of single nucleotide polymorphisms. Together with the Wellcome Trust results described in the preceding article, these publications represent truly outstanding progress in understanding the genetic basis of human diseases.

The IL-23R gene discovery is of particular interest because it suggests a critical involvement of interleukin-23 (IL-23) in inflammatory bowel disease, psoriasis, and perhaps rheumatoid arthritis (Farago et al., 2007). Indeed, Neurath (2007) has suggested that IL-23 be considered as a possible master regulator of

Crohn's disease. The current concept is that IL-23 produced by dendritic cells (DC) in the gut, activates naive T helper (Th) cells and promotes their differentiation into a newly described class of inflammatory T helper cells called Th17 cells (Neurath et al., 2007; Strober et al., 2007). IL-23R is a receptor that is expressed on Th17 cells. These Th17 cells go on to produce interleukin 17 (IL-17), a highly inflammatory cytokine (see Figure, below). IL-23 has been identified as a major driver of intestinal inflammation (Hue et al., 2006).

Th17 cells have recently been implicated in a number of inflammatory diseases, including experimental models of rheumatoid arthritis and multiple sclerosis. The reader is referred to the following key articles describing these associations: Bettelli et al., 2007; Cooke, 2006; Furuzawa-Carballeda et al., 2007; Iwakura and Ishigame, 2006; Kramer and Gaffen, 2007; Mucida et al., 2007; Sheibanie et al., 2007; Steinman, 2007; Stockinger and Veldhoen, 2007;



Critical features of the mucosal immune response of normal individuals and patients with Crohn disease with defective NOD2 function. (from: Strober et al, 2007)

Peptidoglycan (PGN) derived from the walls of commensal bacteria is sensed by Toll-like receptor 2 (TLR2) on the surface of dendritic cells (DC) in the intestinal lamina propria (left inset). This leads to TLR2 ligation and the downstream activation of nuclear factor-kappa B (NF-kB), the key transcription factor necessary for the differentiation of cells producing interferon-gamma (IFN-g) and IL-17, the proinflammatory cytokines responsible for Crohn disease. PGN, however, is also broken down in endosomes and is thus a source of MDP, a substance that is sensed by and activates NOD2. Such activation initiates a mechanism of inhibition of PGN-mediated NF-kB activation and thus causes downmodulation of TLR-induced cytokine production. In patients with Crohn disease bearing NOD2 mutations (right inset), the NOD2 modulation is impaired, and hence the innate immune "thermostat" of the intestine is set at a higher level of proinflammatory cytokine production. This, together with a tendency of T cells to react to mucosal antigens, leads to inflammation and disease. An additional factor relates to the function of alpha-defensins, antibacterial peptides produced by Paneth cells at the base of crypts in the terminal ileum (middle inset). Crohn disease patients with impaired NOD2 function manifest reduced alpha-defensin production in part because NOD2 in Paneth cells is an inducer of alpha-defensin production. Thus, it is possible that impaired NOD2 function also leads to increased bacterial density in the crypts of the terminal ileum and thus greater stimulation of a mucosal immune system already set at a higher level of function.

Weaver et al., 2007.

Th17 cells are a distinct subset of Th cells from the Th1 and Th2 cells described over 20 years ago (Steinman, 2007). Th1 cells produce interferon-gamma, and their differentiation is promoted by interleukin 12 (IL-12). Th2 cells are promoted by interleukin-4 (IL-4) (see image below).

The possible involvement of Th17 cells in inflammatory bowel disease may suggest new therapies, such as antibodies directed against IL-23 (Elson et al., 2007). Knowledge about these cells and the factors that regulate their differentiation, is growing rapidly. Recent studies suggest that prostaglandin E2 and retinoic acid (a derivative of vitamin A) play key roles in their development and/or activation (Mucida et al., 2007; Sheibanie et al., 2007). Other factors that are known to affect Th17 cell differentiation include interleukin-6 (IL-6), interleukin-27 (IL-27), and interleukin-21 (IL-21) (Korn et al, 2007; Nurieva et al., 2007; Zhou et al., 2007). Mudter and Neurath (2007) propose that IL-6 and Th17 cells may be intimately involved in a vicious circle of T-cell accumulation, finally leading to chronic inflammation. They suggest that this circle can be blocked by anti-IL-6 receptor antibodies.

Because Th17 cells have emerged as candidates to account for a number of inflammatory diseases, even cystic fibrosis is being re-evaluated in this light (Dubin et al, 2007). As yet, nothing is known about whether Th17 cells are involved in primary sclerosing cholangitis (PSC), but if we hear anything we'll be sure to let you know.

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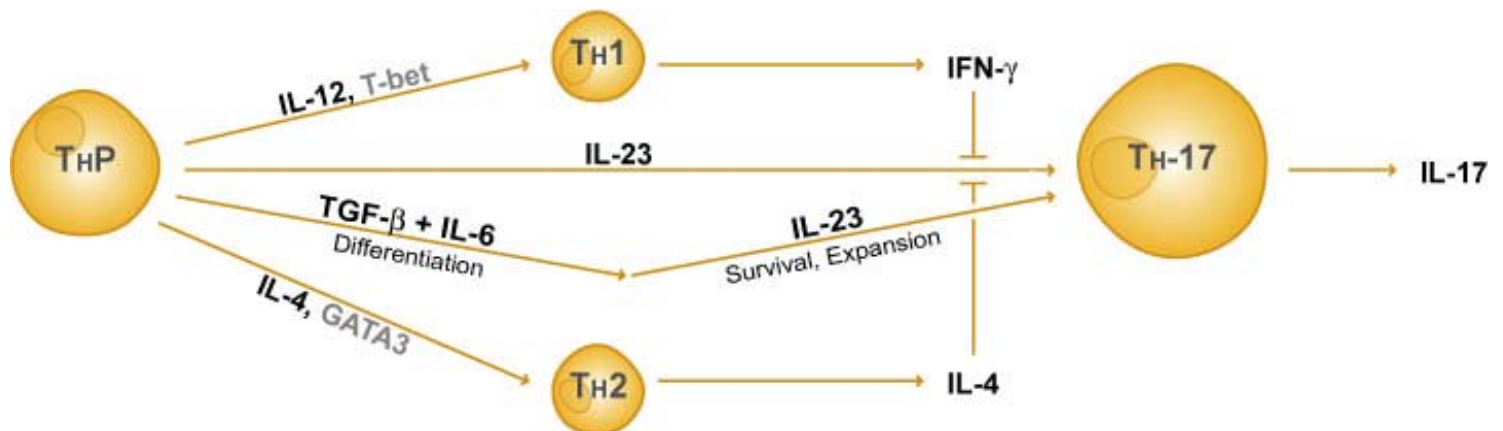
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The Th17 lineage of T helper cells is distinct from the Th1 and Th2 lineages. Differentiation of Th17 cells from naive ThP (progenitor) cells is influenced by transforming growth factor-beta (TGF-B), interleukin-6 and interleukin-23 (and other factors, see text). Th17 cells are characterized by production of interleukin-17 (IL-17) [image from www.ebioscience.com].

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Thanks so much for sharing your expertise.

Ricky Safer

eMail Address Correction

Nicklas and Helena Holmgren's email address was incorrectly listed on the conference list, so please correct your information. They would love to hear from other attendees at their correct email address: pdl541o@tinet.se

Ricky Safer

A Recent Review on PSC

Maggs JR, Chapman RW 2007 Sclerosing cholangitis. Curr. Opin. Gastroenterol. 23: 310-316

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Diet and Risk of Crohn's Disease in Children

Amre DK, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G, Israel D, Mack D, Ghadirian P, Deslandres C, Chotard V, Budai B, Law L, Levy E, Seidman EG 2007 Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am. J. Gastroenterol. Jul 7 [Epub ahead of print].

Department of Pediatrics, University of Montreal, Montreal, Canada.

BACKGROUND AND OBJECTIVES: The role of dietary factors in the etiology of Crohn's disease (CD) is inconsistent largely due to difficulties in acquiring valid information on consumption habits. We examined the impact of diet on new onset CD in children using a validated food-frequency questionnaire (FFQ). **METHODOLOGY:** A case-control study was carried out. Children ≤ 20 yr, newly diagnosed with CD, were recruited from 3 pediatric gastroenterology clinics across Canada. Population or hospital controls were selected matched to cases for time of diagnosis (± 6 months) and area of residence. Dietary consumption 1 yr prior to disease diagnosis was evaluated using a validated FFQ, administered within 1 month of diagnosis. Conditional logistic regression analysis adjusting for potential confounding variables (energy intake, age, gender, body mass index) was carried out. **RESULTS:** A total of 130 CD patients and 202 controls were studied. Mean age at diagnosis (\pm SD) was 14.2 (2.7). There were more male patients (59%). Comparing the highest to the lowest levels of consumption, higher amounts of vegetables (OR 0.69, 95% CI 0.33-1.44, $P = 0.03$), fruits (OR 0.49, 95% CI 0.25-0.96, $P = 0.02$), fish (OR 0.46, 95% CI 0.20-1.06, $P = 0.02$), and dietary fiber (OR 0.12, 95% CI 0.04-0.37, $P < 0.001$) protected from CD. Consumption of long-chain omega-3 fatty acids (LCN-omega-3) was negatively associated with CD (OR 0.44, 95% CI 0.19-1.00, $P < 0.001$). A higher ratio of LCN-omega-3/omega-6 fatty acids was significantly associated with lower risks for CD (OR 0.32, 95% CI 0.14-0.71, $P = 0.02$). **CONCLUSIONS:** Our findings indicate that an imbalance in consumption of fatty acids, vegetables, and fruits is associated with increased risks for CD among Canadian children. PMID: 17617201.

PURPOSE OF REVIEW: Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by strictures of the biliary tree complicated by cirrhosis and cholangiocarcinoma. It is immune mediated, although the precise aetiology remains unknown.

RECENT FINDINGS: Research into etiopathogenesis and epidemiology, diagnosis of cholangiocarcinoma, associations with inflammatory bowel disease and autoimmune pancreatitis, and medical therapy are discussed.

SUMMARY: Multiple gene polymorphisms associated with primary sclerosing cholangitis have been investigated. Common inflammatory bowel disease-associated polymorphisms do not confer any susceptibility to primary sclerosing cholangitis; the role of intercellular adhesion molecule-1 gene polymorphisms and CCR5 mutations remain unclear. Elevated IgG4 has been demonstrated in a subgroup of primary sclerosing cholangitis patients, which may indicate an overlap with autoimmune pancreatitis and possible responsiveness to steroids. Biliary brush cytology may assist in diagnosis of cholangiocarcinoma, although further clinical indicators are required. Animal studies suggest the superiority of 24-norursodeoxycholic acid over ursodeoxycholic acid in reducing histological disease progress; translational studies in humans are now required. PMID: 17414848.

PSC 40 Years Ago

Please take a look at this article from 1967:

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1552678>

Thorpe ME, Scheuer PJ, Sherlock S 1967 Primary sclerosing cholangitis, the biliary tree, and ulcerative colitis. Gut 8: 435-448.

SUMMARY

The clinical and pathological features of four cases of sclerosing cholangitis with ulcerative colitis are presented. The diagnosis can only be made at laparotomy. On clinical and laboratory findings the differentiation of sclerosing cholangitis from other intrahepatic biliary disease or large duct pathology is impossible.

The common duct is seen as a thickened fibrous cord with a markedly reduced lumen. Operative cholangiography and duct biopsy should be performed to confirm the diagnosis. Cholangiography localizes the site of any obstruction, demonstrates the extent of the intra- and extrahepatic duct involvement, and the appearance of beading appears to be diagnostic. The pathological changes in the bile duct are not specific in themselves. Gall bladder lesions were seen in three of the cases. The liver presented a variety of histological lesions including pericholangitis. The present study shows sclerosing cholangitis to be a general disease of the biliary tree that can affect both the intra- and extrahepatic ducts as well as the gall bladder. The findings also suggest that sclerosing cholangitis and pericholangitis may be part of a single disease process involving all or part of the biliary apparatus in ulcerative colitis.

The cause of sclerosing cholangitis is not known but none of the usual factors invoked were proven in the present cases. There was no relationship between either the severity or duration of the colitis and jaundice. Serum antibody studies gave variable and at the present time inexplicable results.

The prime requisite of treatment is decompression of the biliary tree to relieve any obstruction. Medical treatment is of use in the control of cholangitic episodes but is ineffective in altering the course of the disease process. Corticosteroids are of limited value. The prognosis is, however, considerably better than originally reported, patients frequently remaining asymptomatic for a number of years. One patient has developed a biliary cirrhosis but the only death was due to a complicating hepatic duct carcinoma.

Additional Contact Information

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

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