
REGISTRY NEWS

Volume 9 Newsletter for the Pediatric Cardiomyopathy Registry Spring/Summer 1999

THANKS FROM THE PCMR
OUTREACH TEAM!



As we pass the April 30th deadline, The Outreach Assistance Team would like to extend our thanks to all our participating sites. With your help, we have currently reached over 90% capture of all outstanding forms. We are striving for 100%, so if you receive a call from our helpful team, you will know that you still have some outstanding forms.

This has been a very busy year for our Outreach Assistance Team. In the past two months alone, we have traveled to over fourteen sites encompassing over ten states and part of Canada. At times we met some unexpected and unique experiences – delayed flights, New York traffic, hurricanes, Texas humidity, and a blizzard or two.

However, what overwhelmed us the most was the hospitality we have received at each site visit. For that, we would like to take this opportunity to thank you. The ease with which you let us into your institutions is truly amazing. We appreciate your taking the time out of your busy schedules to have the charts and medical records ready when we arrive. Your efforts in making our site visits a success are unparalleled. It was also nice to finally put a face to a site number and voice on the phone!

Not only has the Outreach Team been busy, but all the sites have been busy as well. Those sites that did not receive a site visit have submitted a considerable number of forms. We know that these forms can be somewhat time consuming (believe us, we know!), but it is because you have taken the time to complete the forms that the Registry is a success. We could not have achieved such a high capture rate without your data submissions. Everyone who participated should know that his or her role was important. No part is insignificant. Even something

as small as pulling one echo report from a patient's records or looking up a patient's race is important. PCMR's Data Coordinating Center, New England Research Institute, can vouch for that.

In February, we established three main goals to attain by April 30, 1999. Our goals included the complete capture of all the prospective data through December 1998 in New England and the Central Southwest, the complete capture of the retrospective patients from all sites through April 1999, and reaching our target of 1,000 *retrospective patients* (patients newly diagnosed with cardiomyopathy between January 1, 1990 and December 31, 1995). As of May 1999, we have reached a 95% completion rate of all the retrospective forms. In addition, we have 83% of the New England and 79% of the Central Southwest prospective forms completed. NERI has received more forms in April of this year than in any other month since the registry's inception! Clearly, a job well done by all!

From our conversations with you during our site visits and on the phone, it is evident that we all understand the importance of this registry in improving the course of care for cardiomyopathy patients and the necessity for its continuation. Not only has this been our investigative objective, but we have personal reasons involved as well. Some of us have family members and friends who are affected by cardiomyopathy. In addition, some of us have clarified our career goals as a result of the experiences and interactions we have had with you. Three members of our Outreach Assistance Team are now applying to medical school or graduate school for public health and epidemiology.

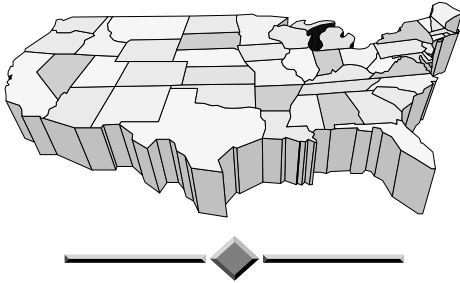
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ENROLLMENT REPORT

PCMR Enrollment as of March, 31 2000 1,965 Eligible Patients

As of June 14, 1999 we have **1,965** eligible patients enrolled in the Registry!



Of the 182 sites that have agreed to participate, the following 90 sites have submitted Enrollment Forms:

- Duke University, Durham, NC, *Dr. Resai Bengur*
- Strong Memorial Hospital, Rochester, NY, *Susan Truesdell, P.A.*
- University of Maryland Medical System, Baltimore, MD, *Dr. Janet Scheel;*
- Oregon Health Sciences University, Portland, OR, *Dr. Mark Reller*
- Babies and Children's Hospital, New York, NY, *Dr. Daphne Hsu*
- The Children's Heart Center of West Texas, Lubbock, TX, *Dr. Charlie Sang*
- TC Thompson Children's Hospital, Chattanooga, TN, *Dr. John Morgan*
- Children's Hospital, Buffalo, NY, *Dr. Robert L. Gingell*
- St. Louis Children's Hospital, *Dr. Arnold Strauss and Dr. Vernat Exil*
- University of Iowa Hospitals and Clinics, Iowa City, IA, *Dr. Mary Jeannette Hagan Morriss*
- The Hospital for Sick Children, Toronto, Ontario, Canada, *Dr. Lee Benson*
- Children's Hospital of Los Angeles, *Dr. Alan B. Lewis*
- Primary Children's Medical Center, Salt Lake City, UT, *Dr. Bob Shaddy*
- Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada, *Dr. Martin Hosking*
- University of Texas Medical Branch, Galveston, TX, *Dr. William Pearl*
- Children's Associated Medical Group, San Diego, CA, *Dr. Rob Spicer*
- Vanderbilt University, Nashville, TN, *Dr. Debra Dodd*
- Mt. Sinai Medical Center, New York, NY, *Dr. Bruce Gelb*
- Michigan State University, East Lansing, MI, *Dr. Monica Goble*
- NYU Medical Center, New York, *Dr. Michael Artman*
- Children's Hospital of Wisconsin, Milwaukee, *Dr. Stuart Berger*
- Children's Hospital, Omaha, NE, *Dr. Ameeta Martin*
- Dartmouth-Hitchcock Medical Center, NH, *Dr. Nancy Drucker*
- Yale University, *Dr. Peter Bowers*
- University of Alberta Hospital, Edmonton, Alberta, Canada, *Dr. John Dyck*
- Children's Hospital of Michigan, Detroit, MI, *Dr. Robert Ross*
- Tulane University Hospital and Clinic, New Orleans, LA, *Dr. Arthur Pickoff*
- UC Davis Medical Center, Sacramento, CA, *Dr. Mark Parrish*
- Capital District Pediatric Cardiology Assoc., P.C., Albany, NY, *Dr. Eric Spooner and Dr. Harm Velvis*
- Texas Children's Hospital, Houston, TX, *Dr. Jeffrey Towbin*
- Children's Hospital, Boston, MA, *Dr. Steven Colan*
- Metro Health Medical Center, Cleveland, OH, *Dr. David Connuck*
- Elliot Hospital, Manchester, NH, *Dr. Sol Rockenmacher*
- Rhode Island Hospital, Providence, RI, *Dr. John Werner*
- Children's Hospital of Pittsburgh, PA, *Dr. Steve Webber*
- Connecticut Children's Medical Center, Hartford, CT, *Dr. Harris Leopold*
- Hasbro Children's Hospital, Providence, RI, *Dr. Robert Corwin*
- Children's Hospital Medical Center, Cincinnati, OH, *Dr. Tom Kimball, Dr. William Lewis, and Dr. David Schwartz*
- Loma Linda University Medical Center, Loma Linda, CA, *Dr. Ranae Larsen*
- UCSD Medical Center, San Diego, CA, *Dr. Abraham Rothman*
- Children's Memorial Hospital, Chicago, IL, *Dr. Elfriede Pahl and Dr. Sam Gidding*
- Cleveland Clinic Foundation, OH, *Dr. Maryanne R. Kichuk*
- Johns Hopkins School of Medicine, Baltimore, MD, *Dr. Jean Kan and Dr. Janet Scheel*
- University of Texas Health Science Center, Houston, TX, *Dr. Steven Wolfe*
- University Hospital, Oklahoma City, OK, *Dr. Kent Ward*

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- Children's Medical Center of Dallas, TX, *Dr. Matthew S. Lemler*
- UMASS Medical Center, Worcester, MA, *Dr. Phyllis Pollack*
- Children's Hospital Heart Center, Albuquerque, NM, *Dr. J. Deane Waldman*
- University of Kentucky College of Medicine, Lexington, KY, *Dr. Bradley Keller*
- Marshall University School of Medicine, Huntington, West Virginia, *Dr. Mahmood Heydarian*
- Wichita Clinic of Kansas, *Dr. Steve W. Allen*
- New York Hospital, Cornell Medical Center, New York, NY, *Dr. Myles Schiller*
- University of Miami School of Medicine, Miami, FL, *Dr. Delores Tamer*
- University of Florida, Gainesville, FL, *Dr. F. Jay Fricker*
- Montefiore Medical Center, Bronx, NY, *Dr. Carl Steeg*
- Pediatric Cardiology, San Antonio, TX, *Dr. Kenneth Bloom*
- Loyola University Medical Center, Maywood, IL, *Dr. Elizabeth Fisher*
- Presbyterian Professional Building, Dallas, TX, *Dr. Ed Neufeld*
- Cook Children's Heart Center, Fort Worth, TX, *Dr. J. Hudson Allender and Dr. Steve Lai*
- Healthcare Professional Associates, Amarillo, TX, *Dr. Jorge Garcia*
- The Children's Heart Clinic, Minneapolis, MN, *Dr. Robert Gajarski*
- East Carolina University School of Medicine, Greenville, NC, *Dr. Michael McConnell*
- Children's Hospital of Orange County, CA, *Dr. Melville Singer*
- Texas Tech University, El Paso, TX, *Dr. Jeffrey Schuster*
- Children's Cardiology Associates, Austin, TX, *Dr. Stuart Rowe*
- Arkansas Children's Hospital, Little Rock, *Dr. Elizabeth Frazier and Dr. Paul Seib*
- PEDIAPEX Heart Center for Children, Dallas, TX, *Dr. Patrick Callahan*
- Wilford Hall Medical Center, Lackland Air Force Base, TX, *Dr. John Brownlee*
- Alberta Children's Hospital, Calgary, Canada, *Dr. David Patton*
- Univ. of Alabama, Birmingham, *Dr. Bennett Pearce*
- Pediatric Cardiology Associates, Portland, ME, *Dr. Maribeth Hourihan*
- Children's Heart Network, San Antonio, TX, *Dr. James Rogers*
- Pediatric Cardiology, Bayside Medical Building, Providence, RI, *Dr. Patricia Rompf*
- Massachusetts General Hospital, Boston, MA, *Dr. Baruch Ticho*
- Royal University Hospital, Saskatoon, SK, Canada, *Dr. Michael Tyrrell*
- BC Children's Hospital, Vancouver, BC, Canada, *Dr. Derek Human*
- Boston Floating Hospital, MA, *Dr. Jonathan Rhodes*
- Driscoll Children's Hospital, Corpus Christi, TX, *Dr. John Pastorek*
- Children's Hospital of Montreal, Quebec, Canada, *Dr. Charles Rohlicek*
- University of Illinois Medical Center, Chicago, IL, *Dr. S.P. Kumar*
- Eastern Maine Medical Center, Bangor, ME, *Dr. Angela Gilladoga*
- Medical College of Virginia, Richmond, *Dr. William Moskowitz*
- Children's Heart Center, Las Vegas, NV, *Dr. William Evans*
- SUNY Downstate Medical Center, Brooklyn, NY, *Dr. Dov Nudel*
- UCLA Children's Hospital, Los Angeles, CA, *Dr. Samuel Kaplan and Dr. Juan Alejos*
- Columbus Children's Hospital, OH, *Dr. Hugh Allen*
- University of Vermont, Burlington, *Dr. Nancy Drucker*
- The Sanger Clinic, Charlotte, NC, *Dr. Donald Riopel*
- 3200 SW 60th Ct., Miami, FL, *Dr. Richard Zakheim*
- The Children's Heart Center, Atlanta, GA, *Dr. Margaret Strieper*

Please submit your Enrollment Post Cards as soon as possible. Every contribution strengthens the database of information for future use in clinical and scientific environments.



DATA MANAGER CORNER

The following are a few important things to remember before sending data to the DCC:

- 1) Make sure **ALL** questions are answered on the data collection forms, even if the answer is "No." If you **cannot** answer a question, write a *brief* explanation in the margin as to why you left it blank. Please write legibly! I think edit reports are as much of a nuisance as you do!
- 2) If a transplant was performed during the year of a requested Annual Follow-Up Form, only *pre*-transplant information is requested. No further Annual Follow-Up Forms should be completed after the year of transplant.
- 3) A W-9 form is necessary to receive reimbursement for forms completed and returned to the Data Coordinating Center. Please complete and send them to the Administrative Coordinating Center in Rochester, NY, attention Kristen Lewis. It should take two weeks for checks to be processed - reports are run at the end of every month.
- 4) Once the initial Enrollment Post Card has been sent to the DCC, a pre-labeled Supplemental Enrollment Form (02) will be forwarded to your site. This form serves as a compliment to the initial enrollment form, and should be submitted at the earliest opportunity to complete the database on the new patient. Pre-labeled Annual Follow-Up Forms (03) will be forwarded to sites for each enrolled

patient at the yearly anniversary of the date of diagnosis. This form should be submitted within a one month window of the patient's annual follow-up date.

5) If a patient does **NOT** meet the inclusion criteria (question 8 on the enrollment postcard), the patient is ineligible for the registry. Please do not send postcards for these patients to the DCC.

6) It is extremely important that the ID assignment log is kept in a secured and well-organized place at each site. (Never send this log to the DCC as it contains the names of patients. Remember, patient confidentiality is crucial!) This log is the only link in the registry between ID #'s and patients. **DO NOT LOSE IT!!!**

My phone number is (617) 923-7747 ext. 366. Please leave a message on my voicemail if I do not answer, and I will get back to you as soon as possible. You can fax or e-mail requests for additional forms and labels to Kristen Noonan at (617) 926-0144 or KNoonan@neri.org.

Thank you for your continuing effort to keep the Pediatric Cardiomyopathy Registry as complete and accurate as possible.

FREQUENT QUESTIONS ... ANSWERED!



Q: *There is no code for this particular diagnosis, what should I do?*

A: If there is no diagnosis code available for the diagnosis of a patient on the Enrollment Form, please write a brief diagnosis name in the blank area (i.e., viral myocarditis, IDCM with EFE, etc.).

Q: *What is the reporting period for the Supplemental Form (02)?*

A: The reporting period is listed on the label attached to the top right corner of the form. Results recorded on the Supplemental Form should be from tests and procedures done at the time of diagnosis.

Q: *What if there are several tests and procedures done over the period of a year - which do we record on the Annual Follow-Up Form (03)?*

A: The reporting period is listed on the label attached to the top right corner of the form. Results recorded on the Annual Follow-Up Form should be from the most recent tests and procedures during the year requested. (For example, if 09/96 - 09/97 is requested, then tests taken in

August 1997 as opposed to those taken in December of 1996 would be documented.) However, if the patient has become acutely ill during the reporting period, please record these test results instead.

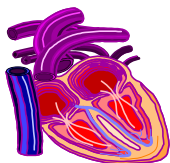
Q: *I don't have the time to complete the follow-up forms. Who can help me?*

A: Consider having a nursing student, medical or patient technician, or someone with a medical background. To attract such an individual consider a flexible working arrangement (i.e., flex hours, an autonomous environment, and an adequate and appropriate compensation).

Q: *Where on the follow-up forms do we indicate if a patient's cardiomyopathy has resolved?*

A: If a patient's cardiomyopathy has resolved and is no longer present, please answer "**no**" to the question, "*Is cardiomyopathy present at this time?*" (Function Type of Cardiomyopathy section) on the appropriate annual follow-up form.

RELEVANT ABSTRACTS



Detection of Adenoviral Genome in the Myocardium of Adult Patients with Idiopathic Left Ventricular Dysfunction

Matthias Paushinger, MD; Neil E. Bowles, PhD; F. Javier Fuentes-Garcia, BS; Vanlinh Pham; Uwe Kuhl, MD; Peter L. Schwimmbeck, MD; Heinz-Peter Schultheiss, MD; Jeffrey A. Towbin, MD

Past studies have established the importance of enterovirus infection of the myocardium in the pathogenesis of myocarditis and DCM in adult patients and both adenovirus and enterovirus infection in children. However, few reports of adenoviral DNA detection in myocardial samples from adult patients with myocarditis have been made. The goal of this study was to determine, by use of nested PCR (nPCR), whether adenoviral genomic DNA can be detected in endomyocardial biopsies of adult patients with impaired left ventricular function of unknown origin.

The frequency of adenoviral DNA was compared to that of enteroviral RNA in myocardial tissue samples of 94 adult patients (age ≥ 17 yrs) with idiopathic left ventricular dysfunction and 14 control patients. Of the 94 enrolled subjects, 12

(13%) were adenovirus positive by nPCR, and another 12 (13%) were enterovirus positive. None of the 14 control samples was positive for either virus. In addition, in all 12 samples positive for adenovirus, the serotype detected was type 2. This is similar to findings in pediatric patients with myocarditis or DCM in whom the major serotype of adenovirus was also type 2, with the remainder being type 5.

This study shows that while enteroviruses are an important causative agent in the pathogenesis of myocarditis and DCM, adenovirus infection is also important in the pathogenesis of left ventricular failure in adults.

[*Circulation*. 1999; 99: 1348-1354]

Tracheal Aspirate as a Substrate for Polymerase Chain Reaction Detection of Viral Genome in Childhood Pneumonia and Myocarditis

Noorullah Akhtar, MD; Jiyuan Ni, MD; Daniel Stromberg, MD; Geoffrey L. Rosenthal, MD, PhD; Neil E. Bowles, PhD; Jeffrey A. Towbin, MD

Infectious respiratory disorders are important causes of childhood morbidity and mortality. Viral causes are common and may lead to rapid deterioration, requiring mechanical ventilation; myocardial dysfunction caused by myocarditis may accompany respiratory decompensation. The etiologic viral diagnosis may be difficult with classic methods such as bacterial and viral cultures of blood and respiratory secretions, serologic studies,

rapid antigen tests, bronchoalveolar lavage (BAL), lung biopsy, and endomyocardial biopsy (EMB). This study evaluates polymerase chain reaction (PCR) as a rapid and more sensitive diagnostic method for identification of causative agents in cases of viral pneumonia with or without accompanying myocarditis.

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RELEVANT ABSTRACTS, *Continued*

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This study analyzed a purely pediatric population, 1 day to 18 years of age. The principal study group identified patients who had recently been endotracheally intubated for respiratory decompensation (n=32), a subset of which also had myocarditis (n=8). These patients provided tracheal aspirate samples for PCR analysis. In addition, three different control groups were used for comparison of PCR findings.

Oligonucleotide primers specific for a variety of common respiratory tract viruses were used on each sample (DNA viruses: adenovirus, cytomegalovirus, herpes

simplex virus, and Epstein-Barr virus; RNA viruses: enterovirus, respiratory syncytial virus, influenza A and B). Tracheal aspirate (TA) PCR results were then compared to results obtained from conventional diagnostic methods. Comparisons revealed that TA PCR is predictive of etiology with 79% sensitivity and 96% specificity. In subjects with myocarditis sensitivity of TA PCR for predicting the PCR results on EMB specimens was 100%. These results suggest that TA PCR may provide a safer means of arriving at an etiologic diagnosis in viral myocarditis than the currently used, more invasive method of EMB.

[*Circulation*. 1999; 99: 2011-2017]



Etiologies of cardiomyopathy and heart failure Evidence for a final common pathway for disorders of the myocardium

Jeffrey A. Towbin, Karla A. Bowles, and Neil E. Bowles

This issue of *Nature Medicine* presents two studies that characterize the pathogenic mechanisms underlying hypertrophic cardiomyopathy (HCM) and associated heart failure and a third that provides new information on the development of dilated cardiomyopathy (DCM).

Mutations in genes encoding sarcomeric proteins have been shown to cause familial HCM. Georgakopoulos *et al.* used a mouse model to study one of the more severe mutations, the Arg403Gln β -MHC mutation. Alterations in contraction kinetics were noted, similar to the diastolic dysfunction of the human disorder. Increased calcium sensitivity was suggested to be underlying the diastolic dysfunction.

Related to this conclusion, a paper by Lim and Molkenin describes the interaction of calcium handling, cardiac hypertrophy, and heart failure. Calcineurin, a calcium-regulated phosphatase, mediates cardiac hypertrophy in transgenic mouse hearts when overexpressed and regulates the hypertrophic response through action on the transcription factor NF-AT3. The authors also found that calcineurin inhibitors can prevent cardiac hypertrophy and DCM as well as cause a

hypertrophic dilated myopathy when mutated. Lim and Molkenin show that calcineurin is activated during mouse heart failure, suggesting an essential role in the progressive nature of human heart failure as well.

Bardorff *et al.* define the development of myocarditis and its sequela, DCM. Myocarditis is commonly caused by viruses, particularly adenoviruses and enteroviruses. In over 2/3 of patients it develops into DCM. Dystrophin mutations and mutations in cardiac actin, an important component of the thin filament of the sarcomere (the contractile apparatus), have been identified as causes of DCM. These two proteins interact with each other and ultimately link up with the basal lamina. Therefore, anything that disrupts these proteins or other molecules that interact with them further down the cascade of events has the potential to produce DCM. In their study, Bardorff *et al.* demonstrate that enteroviral protease 2A cleaves dystrophin directly, resulting in the development of post-myocarditis DCM.

[*Nature Medicine*. 1999; 5; 3: 266-267]

MAUDLIN REFLECTIONS

When there's a space to be filled and nothing important to say I lapse into reflection. "Nothing important" -- because the Registry staff is anxiously awaiting the result of the recently submitted competitive renewal application. If it is successful we can all rejoice. If not, we will have to start panhandling to maintain the momentum we have achieved with the cooperation of most of the pediatric cardiologists of North America. 1,965 patients registered at last counting!

There is on my desk a copy of a book I recommend to any of our readers who may feel they need it -- "Molecular Biology Made Simple and Fun" (Clark DP, Russell LD, 1997, Vienna IL, Cache River). It is my latest attempt to acquire an understanding of genetics sufficient to grasp the significance of the increasing number of papers describing genes implicated in cardiomyopathy. It penetrates this octogenarian brain, but not very far and it doesn't stay there long. I envy today's students to whom this stuff looks easy. But they should really envy me. I experienced first hand the thrill of performing one of the first cardiac catheterizations for congenital heart disease, one of the first selective cineangiograms, the introduction of the Seldinger percutaneous insertion technique into the USA, and echocardiography when it was just barely able to make out pericardial fluid and a dilated, poorly contractile heart. What's more, we didn't have to worry about charging for any of these wonders--they were "just research".

Now that I've done my ego-strengthening exercise for today and have filled the space, I can go back to figuring out how to continue the Registry if we don't get funded.

Paul R. Lurie, MD

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So to all 237 sites, we wish to say thank you for your support in your efforts to make the Pediatric Cardiomyopathy Registry so successful. And on a personal level, we thank you for all we have learned in working with you.

The Travelers --

Eran Muto, Renee O'Brien, Christy Cianfrini, Melissa McDonald, and Marcie Keesler

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Clinical Centers!!!

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Staff Editorial

Registry News

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