

THE BEAT



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Did You Know...

- If you stretched the DNA from all the cells in the human body and laid it end to end, it would reach to the moon and back.
- The DNA from a single human cell contains about 3 billion "letters."
- Genes reside on the chromosomes. Humans have 46 chromosomes; chimpanzees have 48; dogs have 78; and horses 64. The number of chromosomes in an organism does not translate into the complexity of that organism.

IT'S IN THE GENES

PCD is a genetic disorder, but what does that mean? This article is a very simple explanation of the role of genes. It is not meant to be a comprehensive overview. For additional information, please see the resources listed at the end of the article. We will be posting a glossary of terms, including genetic terms, on the PCD Foundation website (currently under construction).

All living things are made up of cells. Groups of cells differentiate into tissues and organs that eventually make up a living human. How do the cells do that? The answer lies in a cellular component called the nucleus. Each of the approximately 100 trillion cells in the human body (except sperm, egg and red blood cells) contains two complete copies of the human genome comprising of 46 chromosomes, one set inherited from the father and one from the mother in the nucleus of every cell. Each copy contains 25,000 - 30,000 genes, arranged in a linear fashion (like beads on a necklace) on 46 different chromosomes (23 from each parent). Gene is a hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism. Genes may vary in their precise makeup between different individuals and species and that makes species and individuals unique.

In the book "Genome: The Autobiography of a Species in 23 Chapters," author Matt Ridley compares the genome to a book:

"There are 23 chapters called **chromosomes**.

Each chapter contains several thousand stories called **genes**. Each story is made up of paragraphs called **exons**, which are interrupted by Advertisements called **introns**. Each paragraph is made up of words called **codons**. Each word is made up of letters called **bases**."

The genome 'book' is written entirely in three-letter words, using an alphabet of only four 'letters' which stand for the four bases (a-for adenine; c-for cytosine; g-for guanine and t-for thymine). Specific combinations of these three-letter words—genes—code for the production of proteins and amino acids—the building blocks of life. Every tissue, cell, gland and neuron owes its existence to the various combinations of these genes, arranged in consistent patterns along the chromosomes.

Through a complex process of replication, genes are able to copy themselves and be passed from generation to generation. Replication is an ongoing process, and at times there are errors in the copy. When this happens, it is called a "mutation" that means the specific DNA sequence has changed. The word mutation has a negative connotation in modern language, but actually mutations occur all the time and some of them are beneficial. When we use the term mutation here, we are talking about disease-causing mutations. Mutations can take a number of forms: letters (bases) in the code can be transposed, added or missing; the message that starts or stops

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IT'S IN THE GENES (CONTINUED FROM PAGE 1.)

protein production may be faulty; the code may be on the wrong part of the chromosome, etc.

The function of the gene and the product (protein or amino acid) it codes for depends on many factors. Single gene defect disorders (homogeneous), such as cystic fibrosis (CF), are the result of mutations causing a loss of function in one particular gene and its product (in CF, it is the CFTR gene on chromosome 7, which codes for a chloride channel protein important for regulating salt and water levels across cell membranes). Using our book metaphor from above, we can see that genes are not single words or letters, but *stories* made up of paragraphs (exons), made up of words (codons), made up of letters (bases). This is a lot of information, and a mutation anywhere on the gene can result in a loss of function. Even though CF is a single-gene disease, there are more than 1,000 identified different CF-causing mutations on the CFTR gene!

In PCD, there are about 200 genes that make up the structure known as a cilium (closer to 700 if you count the ciliary basal body), making PCD a heterogeneous (multi-gene) disorder. Because many of the ultrastructural defects in PCD are related to inner and outer dynein arm proteins, researchers have been able to narrow the field a bit and concentrate on genes coding for the dynein protein (see Gordon Conference update). There are now two known locations where genetic defects result in PCD: *DNAI1* (on chromosome 9) and *DNAH5* (on chromosome 5). Multiple mutations have been identified on each of these genes in PCD patients, and both of these genes code for outer dynein arm protein. It is estimated that defects in these two genes account for

about 25% of all PCD cases. The identification of *DNAH5* is a very recent development and is the result of an international collaboration between UNC-CH and with Heymut Omran in Germany. His lab is also working on an immunofluorescent staining technique to identify outer dynein arm defects from biopsy samples (see Journal Watch).

So what is next on the genetic horizon? The race is on to identify mutations in the inner dynein arm proteins. This is a difficult task, because there is evidence to suggest that inner dynein arms are more complicated in structure and function than outer dynein arms. Using information from the *Chlamydomonas* (unicellular algae) gene sequencing project, researchers have been able to identify some excellent target genes for inner dynein arm that could be tested in patients with PCD.

Important Take Home Points:

- Genes code for specific proteins
- Genetic mutations result in the production of faulty or missing proteins
- Faulty or missing proteins result in disease-producing loss of function
- PCD is a heterogeneous disorder with known mutations on two genes: *DNAI1* and *DNAH5*

Additional Resources:

“Get a Grip on Genetics” by Martin Brookes
“Genome: The Autobiography of a Species in 23 Chapters” by Matt Ridley

Special thanks to Maimoona Zariwala, PhD, University of North Carolina, for her contributions to and review of this article.

PCD Wristband Fundraiser

Gina Manning has been busy coming up with fundraising ideas (see next article)! Through her efforts, the PCD Foundation has ordered a large number of teal-colored silicone wristbands (see example below), with the message “PCD—Keep Waving.” These wristbands will be available for purchase from the PCD Foundation for a minimum of \$1.00 each (feel free to donate/charge more per wristband if you wish). Gina has agreed to handle orders and distribution. An informational flyer about PCD will be available to distribute with each wristband.



This is an attempt to raise funds, but even more importantly to raise awareness about PCD in our local communities. If you would like some wristbands, contact Gina by e-mail at: manning_gina@yahoo.com, by phone 269-621-2702, or mail PO Box 161, Hartford, MI 49057.

Michigan PCD Walk-a-Thon by Kevin Langley

To the 47 volunteers, walking three miles on Saturday, April 2 was more than just another opportunity to gain good exercise. These dedicated souls were on foot to help raise money and awareness for an uncommon medical condition known as Primary Ciliary Dyskinesia, or PCD. PCD is a genetic condition affecting the microscopic hair-like structures normally found throughout many internal organs, which help the body remove infection causing debris from these areas.

Though the majority of walkers were from Van Buren County, a few traveled from as far as Battle Creek to meet at Hartford High School for the event. Student representatives from SADD and National Honor Society joined in the effort. Event coordinator and mid-west chairperson, Gina Manning stated, "This is the second year we have walked to help the PCD Foundation. We doubled last year's walker total and added 40 to 50 new sponsors. One of our primary goals of increasing public awareness was achieved through exposure on radio and in print. The Tri-City Record, and WSJM's 'In The Spotlight' program provided a good opportunity for us to educate the general public about the condition and available support services."

It is estimated that PCD afflicts as many as a half million people worldwide, and up to 25,000 Americans. It is a very difficult disorder to diagnose because it can mimic other diseases, and presents with a wide variety of symptoms. It takes a number of specialist's years to come to the conclusion that a person actually suffers from this particular genetic disorder. Ms. Manning credits her family physician, Dr. Ann Auburn from the Born Preventative Healthcare Clinic, with greatly adding to her quality of life. Dr. Auburn is an integrative physician, meaning that she implements a variety of natural as well as traditional methods to treat her patients. Dr. Auburn has been a terrific asset not only to Ms. Manning personally, but also has contributed her time, knowledge, and financial support to the PCD Foundation.

The monies raised through this walk will be used for research and education, thus enabling the PCD Foundation to accomplish their mission statement: The PCD Foundation seeks to promote research, increase public awareness, and provide information and support services for individuals with inherited ciliary disorders and their caregivers. Currently, research efforts at the University of North Carolina focus on locating all the genes involved in this disorder. These educational efforts center on equipping medical specialists and professionals to recognize PCD. Early diagnosis is extremely important to successfully manage the persistent respiratory infections that plague people suffering from PCD.

You still have an opportunity to get involved with the 2005 walk. The national Walk-a-Thon will take place in October. If you prefer, there is plenty of time to make your tax-deductible donation to Gina's walk. You may mail this year's contributions to: PCD Foundation, PO Box 19195, Minneapolis, MN, 55419.

Looking ahead to 2006, we need people to join us as walkers, and sponsors. Make plans now to be involved with next year's PCD Walk. We would love to reach the goal of 100 walkers, and increase our sponsor contributions by 50%. With your help, we can raise awareness of and benefit those individuals who are afflicted with this disorder. We invite you to visit the PCD website at www.pcdfoundation.org to learn more about PCD and how it affects the families who are dealing with this genetic disorder.



Gina Manning's Walk-a-Thon group,
April 2, 2005 at the Hartford High
School Track

Ask the Experts

What is Nitric Oxide (NO) and Why is it Important in PCD?

By Milan Hazucha, MD and
David Brown, III, MD, University of NC, Chapel Hill

Nitric oxide (NO) is a gas moderately soluble in water. It tends to concentrate within cell membrane. Its reaction with most biological molecules is slow. Because, by its structure, it is a free radical it strongly reacts with other free radicals. These reactions may produce oxidant species which will damage cells and lead to tissue injury.

In ambient air nitric oxide is a combustion by-product emitted as a primary pollutant. The major source is car exhaust. In human body it is a very important endogenously produced regulatory molecule. NO is generated at a cellular level by activation of an enzyme nitric oxide synthase (NOS) and subsequent oxidation of essential amino acid L-arginine to citrulline via complex chain of reactions. There are three variants of NOS, the neuronal NOS (nNOS or NOS I), the inducible NOS (iNOS or NOS II) and the endothelial NOS (eNOS or NOS III). The nNOS and eNOS are expressed in cells constitutively, i.e., they steadily produce a small amount of NO. The production of NO by iNOS has to be induced by various stimuli. These include mechanical stress such as shear stress (flow of blood in blood vessels or possibly beating of cilia and flow of mucus), as well as various mediators, e.g., oxygen, histamine, etc. Besides required activation of NOS, the successful synthesis of NO requires co-localization of key substrates (oxygen, L-arginine, nicotine amid adenine dinucleotide phosphate [NADPH]), along with essential co-factors (tetrahydrobiopterin [BH₄] and various nucleotides) and factors (calmodulin, zinc, and others) at the activation site. Nitric oxide is synthesized by activate NOS at the cell-specific sites when these substrates, co-factors and factors are presented in a certain sequence and concentration, and successfully bind to specific sites on the NOS enzyme. The enzyme activity and the concentration of these factors regulate the production rate of NO. Lower concentration or the lack of certain factors, e.g., BH₄, may divert NO biosynthesis into generation of superoxide and subsequently peroxyxynitrite and other oxidants. Excessive formation of these highly reactive and cytotoxic species may have potentially deleterious effects on cells if not ameliorated by scavengers and anti-oxidants.

Practically, every organ of the body produces NO through essentially the same mechanisms. Within the

respiratory tract, NOS is localized in the endothelial cells (very thin cells covering the inside of the lung capillaries), and in the apical surface and cilia of airway epithelial cells (the cells lining the airways, including nose and sinuses). Synthesized NO freely diffuses into surrounding tissues including airways where it is exhaled but also reabsorbed. Within tissues NO reacts with various chemical species, enzymes and substrates in and outside of the cells. These highly reactive nitrogen species may be transported into other tissues. Ultimately, it is metabolized into nitrite and excreted.

The concentration (measured in parts per billion [ppb]) and production (expressed as nanoliters per minute [nL/min]) of NO released into airway lumen and sinuses can be measured by high sensitivity NO analyzers. The most typical NO analyzers are based on NO reaction with high concentration of ozone in a dark reaction chamber. The reaction produces a faint light (chemiluminescence) whose intensity is proportional to the concentration of NO. To measure NO in biological liquids, e.g., epithelial lining fluid, plasma, etc., additional equipment is needed so as to release bound NO (nitrates, nitrites, S-nitrosothiols) from a liquid phase into a gas phase and subsequently measure its concentration or production by a gas analyzer. The air in the nose and paranasal sinuses contains the highest concentration of NO (up to 2,000 ppb). Concentration of NO produced in lower airways (referred to as pulmonary, exhaled or oral NO) is at least an order of magnitude lower (~20 ppb). The NO concentration in bound form in biological liquids may still be lower. In PCD patients, the average nasal NO production is ~ 10-20 nL/min. The NO production in parents of PCD patients (obligatory carriers) is intermediate between healthy individuals (~376 nL/min) and patients with cystic fibrosis (~185 nL/min), on the average. Although this suggests a relationship between carrier status and NO production, the measurement is not specific enough as compared to that in PCD.

Studies in the early and mid-nineties of the last century reported that NO decreases airway reactivity, causes relaxation of the airways and blood vessels, regulates ventilation and perfusion in the lung, decreases pulmonary artery pressure, and has antibacterial and antiviral effects. In 1993, Jain and colleagues (Biochem Biophys Res Commun, 191:83) reported that NO modulates airway epithelial cell ciliary beat frequency. Inhibition of NOS (resulting in

a lower production of NO) slowed ciliary beat frequency. The frequency was restored by administration of L-arginine, a key substrate for NO generation (see above). A year later Lundberg and collaborators (Eur Respir J, 7:1501, 1994) reported almost absent nasal production of NO in four children with Kartagener's syndrome (bronchiectasis, recurrent rhinosinusitis and situs inversus). They speculated that the impaired NO synthesis and the ciliary dysfunction could be interrelated, and if so, low NO production could be of diagnostic value in Kartagener's syndrome. Later studies have reported on a disorder clinically very similar to Kartagener's syndrome, *the immotile cilia syndrome*. Subsequently, it was recognized that the two syndromes show a substantial similarity and a new term **primary ciliary dyskinesia (PCD)** has been coined to describe the functional and anatomical abnormalities. Besides PCD there are only a few diseases which consistently show unusually low nasal concentration of NO; Cystic fibrosis, diffuse panbronchiolitis and systemic sclerosis with pulmonary hypertension.

There are many plausible causes for low pulmonary and nasal NO. Immunohistochemistry studies have shown that NOS protein is localized in the apical border of healthy epithelial cells and cilia. If abnormal, the NO synthesis may be reduced due to decreased or impaired activity of NOS. Even if produced in sufficient quantities, NO may be retained in the tissues or may degrade rapidly before diffusing into the airways. Some of the processes in synthesizing NO may be impaired either due to an insufficient supply of essential constituents (substrates, factors and co-factors) or weak stimuli (chemical or mechanical) to generate NO. Indirect evidence from numerous studies suggests that a low production of nasal NO due to abnormalities in NO synthesis may be one of the mechanisms involved in ciliary impairment. However, it is still unclear, particularly with PCD, whether such low nasal NO is a cause or a consequence of airway epithelial ciliary dysfunction.

Over the last decade several studies have explored the mechanisms of impaired production of NO in PCD. Administration of single or repeated large doses of L-arginine (one of the essential substrates) by intravenous infusion or by ingestion by healthy individuals, and patients with cystic fibrosis and PCD stimulated NO production in all three groups. However, the relative increase was small, about the same in all three groups and short lasting. The NO level though increased in PCD patients was still well below normal, even when compared to lower end values of a "healthy" NO range. Thus, administration of L-arginine

to boost NO production is not likely to be useful. Similarly, inhalation of oxygen (another essential substrate) by healthy individuals at or below ambient concentration of 21%, proportionally reduced both pulmonary and nasal NO production. Increased production and viscosity of mucus as in PCD, may slow the diffusion of oxygen to the epithelial cells. However, even during severe hypoxia (very low concentration of oxygen) of healthy individuals the NO production was still well above the concentration observed in PCD patients. The NADPH activity (the third essential substrate) was positively associated with the concentration of oxygen. Similar to oxygen, even at a very low concentration, the NADPH activity was still sufficiently high as to not limit NO production. Inhaled oxygen at concentration above 21% up to 100% had little effect on NO production. Although no studies have been done to examine the effects of other than ambient concentration of oxygen on PCD patients, it appears that the key substrates are unlikely factors limiting generation of NO in PCD. The effects of potential abnormalities in a critical co-factor BH4 or other co-factors on NO synthesis in PCD patients have not been investigated yet. Some studies have suggested that acute inflammation of sinuses may suppress NO production. Since NO has strong antibacterial properties insufficient concentration of NO may contribute to bacterial infection of sinuses.

In recent years much progress has been made elucidating genetics of PCD. This heterogenetic disorder is inherited as an autosomal recessive trait. We and others have identified mutation on two human genes as the cause of PCD. Some advances have been also made in our understanding of genetic structure and function of very complex NOS gene. For example, low nasal NO production in cystic fibrosis has been linked to polymorphism of NOS gene. It is plausible that NOS gene variants may be one of the contributing mechanisms to low NO in PCD.

Early diagnosis of PCD is instrumental in instituting an appropriate treatment, thus reducing future complications and improving the overall prognosis of the disease. Various studies, including ours, have convincingly demonstrated that PCD is associated with very low nasal concentration of NO. Although we do not know yet the mechanism(s) causing this impairment, the measurement is likely to prove to be a very sensitive method for screening and potentially diagnosis of PCD. Because of the simplicity of this test it can be adapted for use in infants and young children, complementing if not leading to an early diagnosis of the disease.

Letter from the President—PCD Foundation Update

First, let me express my apologies for the lateness (and the length!) of this newsletter. On occasion it's good to take some time to reflect on where we've been and where we are going. The past few months have been very busy for the PCD Foundation and I'd like to take this opportunity to recap the progress of the Foundation so far and invite your input into our strategies for the future.

As most of you are aware, PCD suffers from very low visibility in both the medical community and in the general public. A major thrust of activity for the PCD Foundation is to improve awareness of the disorder and our visibility as a patient group. This requires active participation in a number of meetings, conferences and research events. In my past career, I traveled extensively to pulmonary meetings on behalf of my company and understood the importance of "being there" to stimulate interest in research and to network with other groups facing similar issues. Frequently, my role at these meetings was to advocate for other rare pulmonary diseases—something I was happy to do, but it was frustrating to me that other patient groups had representation when PCD did not.

It became clear that the PCD community needed to organize. If we were going to be seen as a group with legitimate research needs, we had to develop a presence in the pulmonary community. This can be a slow process, but you start where you know you have support. I had been in contact with physicians Peadar Noone, Mike Knowles and Margaret Leigh from the University of North Carolina, Chapel Hill and knew of their active interest in PCD, but frankly I was not sure about the level of interest in the general pulmonary community. In 2002, thanks to a corporate sponsor and some volunteers, we were able to gauge the level of interest by having a booth at the American Thoracic Society (ATS) meeting in Atlanta. It was clear from the more than 200 contact leads we received from physicians and researchers all around the world that there was an interest in PCD. In fact, several physicians asked why it had taken us so long to get organized!

For the PCD Foundation, forward momentum started with that very first ATS meeting. We met a physician researcher from Miami, Matthias Salathe, MD who was active, along with several of the UNC researchers, in an international group called the Cilia, Mucus and Mucociliary International Interest Group (Mucus & Cilia Interest Group). The Mucus & Cilia Interest Group held meetings every two years. The efforts of this group had resulted in greatly expanded knowledge of the structure and function of cilia in humans and in non-human organisms. At the ATS meeting, UNC researchers, the Foundation, and Dr. Salathe discussed joining forces and having a scientific meeting focused on PCD. The Foundation raised funds through corporate sponsorship and co-sponsored the first PCD-focused scientific sessions at the Cilia & Mucus Interest Group meeting in Miami in November, 2002, attended by Lynn Ehrne and myself.

In Miami, we discussed goals for the future, including the Foundation's desire to establish standards of care for the treatment of PCD. It was at this meeting that Mike Knowles, MD from UNC began to discuss the possibility of creating a network of PCD "Centers of Excellence" similar to the model established by the CF Foundation. Around this same time, Congress passed the Rare Disease Act of 2002 which directed the National Institutes of Health (NIH) to "support centers of excellence for research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases." Based on the current definition of rare or "orphan" disease (affects fewer than 200,000 individuals in the U.S) there are more than 6,000 rare diseases affecting 25 million Americans.

By 2003, the NIH had devised a plan to comply with the Rare Diseases Act, and established the Office of Rare Diseases (ORD). ORD created the Rare Diseases Clinical Research Network (RDCRN), an umbrella organization that would be comprised of a number of research "consortia" which were small groups of diseases with similar features that could share research resources. The RDCRN also included a data and technology consortium to work with all the groups to get information about diseases and research updates to the public and interested healthcare providers. There were some requirements for participating as a consortia in the RDCRN; 1.) More than one disease or disorder had to be represented, 2.) There had to be a patient advocacy group associated with the disorders to represent patient interests and make sure the information collected was accessible to patients. The ORD sent out requests for grant application. The PCD Foundation agreed to support the effort and the Genetic Disorders of Mucociliary Clearance (MCC) was established in 2004 based on a grant written by Mike Knowles, MD, Margaret Leigh, MD, and others.

Also in 2004, Margaret Leigh, MD, arranged for a PCD workshop at the ATS conference in Orlando. This meeting brought together investigators from the four main research sites in the MCC (UNC, Washington U. St. Louis, Denver Children's and the University of Washington, Seattle) as well as clinicians interested in participating from other academic sites. The PCD workshop was funded by ATS for two years (2004, 2005) and is focused on creating publishable standards of care for PCD. Robert Gale and I attended the 2004 meeting, and preparations are currently underway for the 2005 ATS con-

ference in San Diego in May.

As the MCC study protocol was moving forward, some of our past contacts started to bear fruit. We were invited to participate as guests with another consortium, The Rare Lung Diseases Consortium (RLDC) at their first meeting in Cincinnati in 2004. This group included the Alpha-1 Foundation, the LAM Foundation, and the Pulmonary Fibrosis Association. It was a wonderful experience to see diverse patient groups willing to work together to advance the cause of rare lung diseases. We were invited to have a more active role in the next RDLC meeting in Cincinnati in 2005, and early in April, Jonelle Robertson, Meghan Manion and I met with investigators from the MCC there.

Late in 2004, Matthias Salathe informed me that the Cilia & Mucus Group had been awarded a grant by the Gordon Research Foundation. This is a very prestigious private group that sponsors scientific “retreats” focused on cutting edge science and the free interchange of information. We started to prepare for the second PCD-focused scientific session to be held at the Gordon Conference in California in February 2005. This entailed more fundraising to help bring in scientists from Europe who collaborated with our investigators here. Mary Kay Fowler-Wacholz and I spent four full days hearing about the latest research in mucus and cilia.

In addition to the clinical and research efforts we support, the PCD Foundation also develops and maintains close contacts with auxiliary groups. We are an affiliate member of NORD (National Organization for Rare Diseases), and are members of the Genetic Alliance, a group dedicated to protecting the legal interests of people with rare, genetic diseases. I am a member of C-PAG (consortium of patient advocacy groups) and serve on the CME (continuing medical education) committee of the RDCRN and am also active on the Genetic Alliance’s committees for genetic discrimination and insurance coding issues.

The PCD Foundation also sponsors educational events for patients and families. We are working on our third annual PCD Family Education Day scheduled for July 23, 2005. I receive e-mail inquiries for information from patients and healthcare providers on an almost daily basis, and attempt to maintain up-to-date contact databases and website information (despite my technological impairment!). Our newsletter is published (usually) on a quarterly basis. This is an important informational tool and one that we would like eventually to publish in hard copy form, but it is not within our current budget (it would cost between \$500-\$800 for publishing and postage for each quarterly 4-page newsletter).

There is also the “business” side of things to address. We are a non-profit corporation with State and Federal reporting requirements. The board of directors takes these obligations very seriously. We have the same needs for supplies and equipment that any other business would have, and someone needs to make sure things are stocked and running smoothly.

Obviously, there is a great deal of effort that goes into managing PCD Foundation activities and all of this activity is done by volunteers. The PCD Foundation has no paid staff. Board members (also volunteers) are all working PCD patients or parents who donate time and, and at times, sacrifice personal income to travel to important meetings. They do this because they are committed to improving the understanding of this disorder and because they know that we have an incredible opportunity right now to move PCD research forward.

So why am I sharing all this? 1.) It is important for members of the PCD community to know what we have been doing, and 2.) To assure you that that delays in communicating are due to extremely busy lives and are not a reflection of decreased interest or activity in PCD—in fact, just the contrary.

Our goal is to get the word out about PCD and we rely on our patient and parent members to assist with that. We are committed to improving communication through our printed materials, our website, and our Foundation activities. However, we work on a tiny budget with very limited time and resources, so please be patient—better things are coming soon!

Sincerely,

Michele

Here are some links for additional information about the above. Also, I am available to answer questions any time at info@pcdfoundation.org.

RDCRN:	http://www.rarediseasesnetwork.org/
ORD:	http://rarediseases.info.nih.gov/
Gordon Research Conferences:	http://www.grc.uri.edu/O5sched.htm
NORD:	http://www.rarediseases.org/
Genetic Alliance:	http://www.geneticalliance.org/

To Beat or Not To Beat... What is “Immotile Cilia Syndrome”?

Many patients with inherited ciliary disorders are diagnosed with “immotile cilia syndrome.” What is immotile cilia syndrome and how is it related to PCD? The answer to these questions lies in the history of the discovery of ciliary dyskinesia.

In 1933, Zurich pulmonologist Manes Kartagener published his observation of a number of patients who showed a specific triad of symptoms; sinusitis, bronchiectasis, and situs inversus totalis. This triad came to be known as Kartagener’s syndrome. Because he was not able to pinpoint the underlying cause for these symptoms, diagnosis relied on the presence of all three features of the triad.

In his paper, Kartagener did not address the male fertility issues that frequently plagued these patients, but in the 1970s, Bjorn Afzelius, a PhD ultrastructuralist from Sweden noticed that a number of male patients being evaluated for infertility had chronic respiratory problems, immotile flagella and about half of them also had the Kartagener syndrome with situs inversus totalis . Except for the situs issues, the clinical course of these patients was identical so Afzelius postulated that the underlying cause for the Kartagener syndrome and for the other infertile patients

was impaired motility of the cilia. Using available technology, he observed no movement in the respiratory cilia of these patients and coined the term “immotile cilia syndrome” to describe the pathophysiology. The term stuck for a decade.

As technology improved, it became clear that cilia which had at first appeared “immotile” actually did move—very poorly and with no coordination, but nevertheless they were not immotile. In the 1980s the term “immotile cilia syndrome” was replaced by “primary ciliary dyskinesia” to more accurately describe the genetic nature and physical features of the defect. There are extremely rare cases of truly immotile cilia—usually only if there is a complete absence of both outer and inner dynein arms. By far the majority of patients diagnosed with immotile cilia actually have dyskinetic cilia.

The terminology has changed to reflect greater understanding of inherited ciliary defects. Primary ciliary dyskinesia is the term currently preferred by most researchers. Whatever you prefer to call it, the important thing is to understand the underlying problem—dyskinetic cilia that can’t perform their intended function.

PCD Family Education Day July 23, 2005, St. Louis, MO

We have confirmed July 23, 2005 for this year’s PCD Family Education Day. Thanks to the efforts of Dr. Tom Ferkol and his staff at Washington University in St. Louis, we were able to reserve the Rivercamp Pavilion at the St. Louis Zoo for this one day event.

We are working on hotel and transportation details now, and will update the information through the PCD Foundation website and through the patient e-groups as it becomes available.

This year, we will have the opportunity to meet the investigators involved in the multi-center PCD study. Families may be able to participate in the study at Washington University either before or after the education event. For more information, contact the PCD Foundation at:
info@pcdfoundation.org

Upcoming Events

May 20-25, 2005:
PCD Standards of Care Workshop at the ATS conference in San Diego, CA

July 23, 2005
PCD Family Education Day, St. Louis Zoo, St. Louis, Missouri

In the Next Issue:

- Situs Issues in PCD
- Update on the Pseudomonas A. Vaccine
- PCD Family Education Day Information

Gordon Conference Update

Gordon Research Conferences are sponsored by a private organization whose mission is to provide an international forum for the advancement of scientific knowledge. The conferences are designed as week-long retreats with a focus on the presentation of “cutting-edge,” non-published research endeavors. The goal is to create an atmosphere that allows the free exchange of information, and for this reason, participants agree, in writing, not to publish the proceedings. Here is the policy from the Gordon website (<http://www.grc.uri.edu/whatis.htm>):

“To encourage open communication, each member of a Conference agrees that any information presented at a Gordon Research Conference, whether in a formal talk, poster session, or discussion, is a private communication from the individual making the contribution and is presented with the restriction that such information is not for public use.”

However, we can share general information about this year’s Gordon Conference on Cilia, Mucus and Mucociliary Interactions. As the title suggests, there were two distinct areas of focus—cilia and mucus—and then discussion about the interaction of these two areas and how they relate to disease.

For our purposes, we will focus on topics covered in the cilia section, which included the role of ultrastructure in ciliary dyskinesia, possible disease-causing sensory function defects, nodal (primary) cilia and situs determination, the role of nodal cilia in disease, and the significance of low nasal nitric oxide levels. Talks focused on what is known now and what areas are being targeted for research.

One of the most exciting things about the conference was to see how progress in basic sciences can translate into research on clinical disease in humans. For years, scientists have been studying a single celled algae called *Chlamydomonas* (*Chlamy*) which has motile flagella that are nearly identical in structure to human cilia. Studies of *Chlamy* ultrastructure and, more recently, sequencing of the *Chlamy* genome have had direct impact on our understanding of ciliary defects, and have helped to identify target genes for the human disease PCD. Because *Chlamydomonas* can be grown in abundance and defects that mimic PCD occur naturally or can be produced artificially, *Chlamy* provides an excellent source of genetic material for study. Future plans include using *Chlamy* gene sequencing information to identify target genes for inner arm dynein proteins.

In terms of ultrastructural evaluation of cilia, the difficulty with visualizing inner dynein arm defects was discussed at length. Inner dynein arm defects are much more difficult to evaluate because there are fewer inner arms, and it appears that they are more physiologically complex than outer dynein arms. In addition to improving the technology available for ultrastructure visualization, efforts are also underway to identify the proteins involved in inner arm defects and develop tests similar to the staining technique (see “It’s in the Genes”) being developed at UNC and Dr. Omran’s lab in Germany for inner arm defects.

Maimoona Zariwala, PhD and Heymut Omran, MD, discussed the current status of known genetic mutations in PCD. There are two confirmed PCD-causing genetic mutations, both on genes that code for outer dynein arm proteins:

- 1.) DNAI1—an intermediate chain protein located on chromosome 9. 17 distinct PCD causing mutations have been located on this gene.
- 2.) DNAH5—a heavy chain protein located on chromosome 5. 29 distinct PCD causing mutations have been located on this gene.

It is estimated that these two genes account for 25-30% of all cases of PCD. With the recent discovery of the DNAH5 defect, UNC is planning to re-test for this defect in research samples submitted by patients with outer arm defects. This will take some time. Patients will be notified of positive results. Please be patient with this process and allow the researchers to contact you, if appropriate.

This is a brief overview of some of the highlights of the conference. Much of what was presented will be published and available to the public in the near future. It was a wonderful experience to be with a large group of people who were intensely interested in dynein arms, ciliary ultrastructure, and PCD genetics. Because it is an international group, the next conference is tentatively planned for 2007 in Milan, Italy.



GORDON RESEARCH CONFERENCES
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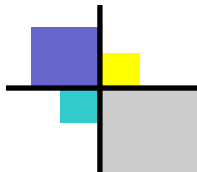
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*Education & Advocacy for
People with Inherited Ciliary
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Journal Watch NEW ARTICLES OF INTEREST TO THE PCD COMMUNITY

The National Library of Medicine (NLM) maintains a database of peer-reviewed articles from international medical journals. The peer-review process means that the article is subject to vigorous critical review by a panel of experts prior to being accepted for publication. This information can be accessed by the public at: <http://www.ncbi.nlm.nih.gov/PubMed> or by typing "entrez pubmed" into your internet provider search function.

When you enter a query (e.g. primary ciliary dyskinesia) into PubMed, a list of articles will appear, most recent at the top. Click on each article for a link to its **abstract**, or brief overview. Often, the abstract provides enough information and there is no need to get the full article. If the full article is desired, there are several ways to obtain it; 1.) universities with medical schools frequently maintain a large inventory of medical journals. Copies of articles from these journals are usually available to the public for a small fee, 2.) articles can be ordered from the publisher for a (typically large) fee, and 3.) the PCD Foundation maintains a bibliography of many articles and may be able to provide a copy.

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