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GENETICS OF HEART DISEASE

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Over the past fifteen years, the genetic basis of various forms of heart disease have been studied and increased levels of understanding of the causes of these clinical disorders, the mechanisms of disease and clinical risk stratification have been gained. In this brief review, the current knowledge regarding the genetic basis of cardiomyopathies, arrhythmia disorders, and congenital heart disease will be described. In addition, insight into the use of this information for clinical care will be provided.

CARDIOMYOPATHIES

These disorders are classified into separate functional types including:

1. Dilated Cardiomyopathy (DCM).
2. Hypertrophic Cardiomyopathy (HCM).
3. Restrictive Cardiomyopathy (RCM), and (4) Arrhythmogenic Right Ventricular Dysplasia/cardiomyopathy (ARVD/C).(1) In addition, several other forms exist including Left Ventricular Noncompaction (LVNC) and overlap disorders with mixed functional types.(1)

The genetic basis of these disorders has been studied since the late 1980s and progress has been made for all forms.

Hypertrophic Cardiomyopathy (HCM): This disorder, characterized by left ventricular hypertrophy, systolic hypercontractility and diastolic dysfunction associated with myofiber disarray, is the most common cause of sudden death in young healthy subjects in the United States, particularly during athletics.(2) Genetic linkage studies initially demonstrated genetic heterogeneity; in other words, multiple different genetic loci on multiple different chromosomes and a variety of different mutant genes leading to clinically similar disorders.(3) The first gene, b-myosin heavy chain, located on chromosome 14, was first identified by the Seidman Laboratory in Boston and was followed by the identification of 9 other genes.(3) In all cases, these genes encode sarcomeric proteins and include cardiac actin, cardiac troponin T, cardiac troponin I, a-tropomyosin, myosin- binding protein C, titin, the essential and regulatory myosin light chains, and muscle LIM protein. Recently, non-sarcomere protein-encoding genes, including AMP kinase(4) and the a-iduronidase gene causing Fabry Disease,(5) have been identified.

Genotype-phenotype correlations were initially performed on b-myosin heavy chain, a-tropomyosin, myosin binding protein C, and cardiac troponin T and differences in age of onset, severity of hypertrophy, and survival

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was reported.(6),(7) However, the studies were performed on a small number of genotyped individuals and may not be representative. Recently, Dr. Michael Ackerman's laboratory has reported that many of these initial contributions are patient specific and not gene- or mutation-specific with clinical findings widely varying among mutated individuals.(8) Therefore, risk stratification on the basis of genotype is fraught with danger. In addition, no clinical test for genetic screening of the HCM-causing genes has been available to date, but a diagnostic laboratory in Boston is expected to begin to offer a fee-for-service genetics screen in the near future.

Dilated Cardiomyopathy (DCM): This disorder is characterized by a dilated left ventricle with systolic dysfunction.(1) Mitral regurgitation and ventricular arrhythmias may be associated. Studies of the genetic basis of DCM were relatively slow to get underway, in part due to the late recognition that this disease was genetically based. To date, nearly

twenty genetic loci have been identified and thirteen genes are now known.(1) We identified the first of these genes, dystrophin,(9) the cause of X-linked cardiomyopathy and speculated that the final common pathway for DCM is the cytoskeleton and the link between the sarcolemma and sarcomere.(10) Over the past decade, mutations in the genes identified include sarcolemmal/cytoskeletal genes (d-sarcoglycan, metavinculin, desmin), Z-disk protein-encoding genes (ZASP, a-actinin-2, MLP, titin), and sarcomeric protein-encoding genes (b-myosin heavy chain, a-tropomyosin, myosin binding protein-C, troponin T).(1),(10-13) In addition, mutations in lamin A/C, a nuclear envelope protein and G4.5/tafazzin (with uncertain function), have been identified.(14),(15) Little has been done regarding genotype:phenotype correlations.

Additional causes of DCM have been identified as well. In babies, abnormalities of mitochondrial function due to mitochondrial DNA (mtDNA) mutations, import protein-encoding genes of the genome and mutations in metabolic protein-encoding genes, particularly those of the fatty acid oxidation pathway such as the acyldehydrogenese genes (MCAD, LCAD, VLCAD and the trifunctional protein) are important causes, along with Barth Syndrome, caused by mutations in G4.5 (in boys).(16),(17)

Non-genetic causes of disease are also relatively common. In young children, myocarditis is particularly prevalent, although this certainly occurs throughout childhood and adolescence. The common viral causes of myocarditis and DCM include adenovirus, parvovirus and the enteroviruses, particularly coxsackieviruses B3 and B4.(18) Recently, we demonstrated that over 35% of cases of myocarditis can be identified etiologically using polymerase chain reaction (PCR) analysis of myocardial specimens(18) and previously showed the utility of PCR evaluation of tracheal aspirates in intubated children "too sick to biopsy".(19) Currently, we offer fee-for-service screening of viral genome in our diagnostic laboratory (CLIA-approved John Welsh Cardiac DNA Diagnostic Laboratory) with rapid report turn-around, as well as DNA screening for neonatal gene causes of DCM including G4.(5) and mitochondrial proteins SCO2 and SURF1 (See http://www.bcm.tmc.edu/pedi/cardio/research/welsh.html).

Left Ventricular Noncompaction (LVNC): This disorder, characterized by deep trabeculations in the LV endocardium, particularly in the apex and free wall, apical hypertrophy, with intermittent systolic dysfunction is an underrecognized disorder.(20) The disorder has an unpredictable course, with some patients developing progressive heart failure necessitating transplantation, others developing an "undulating phenotype" in which the echocardiographic features alternate between a DCM-like disorder and an HCM-like disorder, and still others having primarily diastolic dysfunction. In some cases, LVNC is associated with systemic disorders such as Barth Syndrome, mitochondrial or metabolic disorders.(17),(20)

The inheritance pattern in LVNC varies. The majority of cases are transmitted as autosomal dominant traits, but X-linked and mitochondrial transmission is also relatively common. We have identified the two autosomal dominant genes thus far reported (a-dystrobrevin, ZASP)(13),(17) and an X-linked gene, G4.5(17),(21) (the gene responsible for Barth Syndrome) has also been identified. As previously noted, mutation screening for G4.(5) in young males with LVNC is available in our diagnostic laboratory as a fee-for-service test (John Welsh Pediatric Cardiac Diagnostic Laboratory; See http://www.bcm.tmc.edu/pedi/cardio/research/welsh.html).

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C): This disorder is characterized by a thin-walled dilated RV with fibrofatty infiltration of the RV. These patients suffer from VT with a left bundle branch block morphology, right heart failure, syncope and sudden death.(22-24) ARVD/C is considered the most common cause of sudden death in young healthy adults and athletes in Italy, but has not been considered to be as common in the United States.

ARVD/C is inherited as an autosomal dominant disorder. Multiple genetic loci have been identified but only two genes have been discovered, the ryanodine receptor (RYR2, the same gene responsible for catecholaminergic polymorphic VT)(25) and desmoplakin,(26) an important protein of the adherens junction and desmosomes. An autosomal recessive disorder with complex phenotype, Naxos Syndrome, characterized by palmoplantar keratoderma, wooly hair, and ARVD/C, initially described in an inbred population on the Greek Island of Naxos,(27) results from homozygous mutations in another adherens junction protein called plakoglobin.(27) A similar autosomal recessive disorder in which the RV and LV are affected, called Carvajal Syndrome, is due to homozygous mutations in desmoplakin.(28) The search for the remaining genes, as well as for improved diagnostic and therapeutic approaches, is underway, funded by a grant from NIH/NHLBI funding for the ARVD Registry. This program includes the Clinical Coordinating Center in Tucson, Arizona (Dr. Frank Marcus), Data Coordinating Center in Rochester, New York (Dr. Wojciech Zareba) and Genetic Center in Houston, Texas (Dr. Jeffrey Towbin). Studies are ongoing.

ARRHYTHMIAS

Multiple arrhythmia disorders have been successfully studied regarding

genetic causes. The paradigm disorder, Long QT Syndrome (LQTS), was the first to be studied and set forth the concept that ion channel abnormalities result in these clinical phenotypes.(29) Since the initial studies in LQTS, studies of Brugada Syndrome, Sudden Infant Death Syndrome (SIDS), Sudden Unexpected Nocturnal Death Syndrome (SUNDS), AV block disorders, Sick Sinus Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia (CVPT) have provided insight into the genetic causes.

Long QT Syndrome (LQTS): These repolarization disorders, characterized by prolongation of the QT interval corrected for heart rate (QTc), T wave abnormalities, relative bradycardia, conduction system disease, and ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation, torsade de pointes), are thought to affect 1 in 5000 individuals in the population.(29) Syncope and sudden death are the dominant symptoms.(29)

Long QT Syndrome is inherited in approximately 50% of cases. In the most common form, Romano-Ward Syndrome, inheritance is in an autosomal dominant fashion. The other form, Jervell and Lange-Nielsen Syndrome, is inherited as an autosomal recessive trait and is associated with sensorineural deafness.(29)

The genes responsible for LQTS that have been described to date encode ion channels or ion channel modulating proteins. The genes for Romano-Ward Syndrome have heterozygous mutations (i.e., one of the two alleles is mutated and the other allele is normal) in one of several genes (i.e., genetic heterogeneity). These genes include KCNQ1 (LQT1, KVLQT1), KCNH2 (LQT2, HERG), SCN5A (LQT3), Ankyrin B (LQT4), KCNE1 (LQT5, minK), and KCNE2 (LQT1, MiRP1).(30-33) The genes encoding LQT1, LQT2, LQT5, and LQT6 encode potassium channels while the LQT3 gene is the cardiac sodium channel gene. The most recent gene, Ankyrin B, is important in localizing the channel to the membrane and plays a role in sodium channel function.(33)

The genes responsible for Jervell and Lange-Nielsen Syndrome include homozygous (both alleles mutated) or compound heterozygous (different mutations in the two different alleles) mutations in the LQT1 (KCNQ1) or LQT5 (minK) genes.(34),(35) The sensorineural deafness occurs due to total loss of function of the organ of corti in the middle ear due to loss of potassium channel function necessary to create the potassium-rich fluid bathing this structure.

The newest gene identified, Kir2.1, encodes a potassium channel protein and mutations result in a complex disorder known as Andersen Syndrome.(36) This disease is characterized by hypokalemic periodic paralysis skeletal abnormalities, dysmorphic features, QTc prolongation, and ventricular arrhythmias.

Genotype-phenotype correlations have been helpful in LQTS. Mutations in specific genes result in different T wave morphologies, different symptom triggers (i.e., LQT mutations commonly seen associated with sudden death while swimming, LQT2 mutations associated with auditory stimulation triggers, and LQT3 mutations associated with sudden death during sleep), outcome risk stratification, and potential specific treatments.(29),(34),(37)

Recently, a fee-for-service genetic test for these genes using direct gene sequencing was offered by Genaissance, Inc. No data currently exists as to whether this will be clinically useful or not or whether potential for errors in clinical decision-making will occur based on these tests. In addition, the cost of these tests may limit utility, particularly if insurance companies do not reimburse these tests.

Brugada Syndrome: Identified clinically by the electrocardiographic findings of ST-segment elevation in leads V1-V3 with or without right bundle branch block and episodic ventricular fibrillation resulting in syncope or sudden death, this disorder occurs most commonly in males.(38) Symptoms typically occur during sleep. It is usually not associated with structural heart disease.

Brugada Syndrome is genetically transmitted in approximately 50% of cases with autosomal dominant inheritance typical. In 1998, our laboratory identified mutations in the cardiac sodium channel gene SCN5A, the same gene as that causing LQT3.(39) Only 10-20% of patients with Brugada Syndrome have SCN5A mutations. A second gene, also on chromosome 3, has been reported but the gene has not yet been identified.(40) Other similar disorders in which sudden death occurs during sleep, including Sudden Infant Death Syndrome (SIDS)(41) and Sudden Unexplained Nocturnal Death Syndrome (SUNDS),(42) have also been shown by our laboratory to result from mutations in SCN5A. Another group of patients, those with conduction system disease and sick sinus syndrome, also occur due to mutations in SCN5A.(43),(44)

Catecholaminergic Ventricular Tachycardia: This disorder, first described by Coumel in 1976,(45) develops symptoms triggered by catecholamine surges as occurs with exercise and emotion. In addition to VT, these patients may develop bi-directional or polymorphic VT. This disorder was initially hypothesized by Coumel to be similar to digitalis toxicity and, therefore abnormalities in calcium handling has been considered a potential mechanism for many years.

Genetically, this disorder appears to be transmitted as an autosomal dominant trait. Recently, the genetic basis of this disorder was identified as mutations in

the ryanodine receptor (RYR2).(46) This is an enormous gene which makes it difficult and time consuming to screen for mutation.

CONGENITAL HEART DISEASE

Congenital Heart Disease (CHD) comes in many "flavors". The idea that CHD may be genetic-based has met with significant disagreement. For several decades, multi-factorial inheritance and not single gene disorders were thought to be the basis of disease. Recently, however, mutations in single genes in Heterotaxy Syndrome and in left heart obstruction have been identified, amongst other forms of CHD.

Heterotaxy Syndrome: Heterotaxy is a complex set of birth defects in which the normal concordance of asymmetric thoracic and abdominal organs is disturbed.(47) This class of birth defects, especially heart defects, originate from disturbance in early embryonic patterning. The classic combination of defects (cardiac looping defects with disturbance in abdominal organ asymmetry) is not rare and, if overlapping isolated defects are included , may explain birth defects in a much larger population of children. Heterotaxy, including l–transposition of the great arteries, accounts for ~3% of congenital heart defects, while d-transposition and related malpositioning of the great arteries accounts for 9-10% of heart defects. Other birth defects in this spectrum, such as intestinal malrotation, nonrotation, and reverse rotation are common, estimated at 1 per 500 births.

Heterotaxy arises from abnormal left-right embryonic patterning with consequent abnormal segmental arrangements of cardiac chambers, vessels, lungs, and/or abdominal organs. Incomplete or failed left-right patterning may lead to anatomic discordance (i.e., transposition of great arteries) loss of structures (i.e., asplenia), improper symmetry or lateralization (i.e., right atrial isomerism in which left atrial development is concomitantly lost), or failure to regress symmetric embryonic structures (i.e., persistent left superior vena cava). Hence, a wide variety of congenital anomalies of both lateralized internal organs and midline structures may occur.(47)

Nongenetic or environmental etiologies have been suspected in left-right patterning defects for many years but more recently genetic causes have gained favor. The occurrence of families with X-linked inheritance was demonstrated by linkage analysis to be localized to Xq26.2 and the causative gene, ZIC3, has been found in familial cases with Hypoplastic Left Heart Syndrome, as well as sporadic cases associated with VATER association and with Alagille Syndrome.(48),(49) In autosomal dominant and other sporadic cases, genes have also recently been identified. Left-right patterning of the lateral plate mesoderm requires the activity of the nodal signal transduction pathway and mutations in genes in this pathway cause Heterotaxy Syndrome.(50) In mice, ZIC3 deficiency causes improper nodal expression for instance. Similarly, mutations in ActRIIB and cryptic/EFG-CFC result in a failure of nodal signaling and predictably right isomerism. Mutations in lefty-1 result in failure to restrict nodal to the left and therefore, results in left isomerism.(51) Human gene mutations in LEFTY A, CRYPTIC, and ACVR2B have been identified to date.(52-54) The mechanisms resulting in these phenotypes is currently under study.

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Hypoplastic Left Heart Syndrome: This devastating and somewhat common disorder may occur alone or associated with complex phenotypes including dysmorphic syndromes. The cardiac abnormalities vary but generally include mitral and aortic atresia. Mutations in ZIC3 have been identified, but generally the underlying genetic basis is uncertain.(47)

Syndromes and Congenital Heart Disease: Two common syndromes, DiGeorge Syndrome and Noonan Syndrome, have recently been studied and genes identified. Noonan Syndrome, associated with pulmonic stenosis, septal defects, and hypertrophic cardiomyopathy has been shown to occur due to mutations in the chromosome 12q22-qter gene called PTPN11,(55) the protein-tyrosine phosphatase 11 gene. Mutations in this gene account for approximately 50% of patients with Noonan syndrome, particularly those with pulmonic stenosis. Mutations in this gene may also cause LEOPARD Syndrome (Lentigines, Electrotrocardiographic Anomalies, Ocular Hypertelorism, Pulmonary Stenosis, Anomalies of Genitalia, Mental Retardation, and Deafness), which is now considered to be an allelic disease with Noonan Syndrome.(56)

The DiGeorge complex (including Velcardiofacial Syndrome and Conotruncal Face Anomaly Syndrome) is a complex phenotype with clinical findings occurring due to abnormalities of the embryonic pharyngeal apparatus, neurobehavioral abnormalities, and multiorgan abnormalities including cardiovascular,

renal and skeletal defects.(57) The most common cardiovascular abnormalities affect the conotruncal region, predominantly in the outflow tract and aortic arch. Thymic and parathyroid hypoplasia or aplasia, as well as craniofacial abnormalities are common. Initial genetic abnormalities were noted to occur on chromosome 22q11 with large deletions noted. More recently, mutations in the gene TBX1 have been identified.(58-60) In the mouse, Tbx1 deficiency, affects the development of the fourth pharyngeal arch arteries, which contribute to the aortic arch (on the left) and the root of the right subclavian artery. The exact mechanisms resulting in the clinical phenotypes are currently being studied.

Holt-Oram Syndrome, an autosomal dominant condition, is characterized by bilateral forelimb deformities and congenital heart disease, and occurs in 1 in 100,000 live births.(61) This is the most common heart-limb syndrome. The cardiac phenotypes include septal defects, persistent superior vena cava, mitral valve prolapse, Hypoplastic Left Heart Syndrome, and atrioventricular block. Mutations in the T-box transcription factor TBX5 have been identified in these patients.(61)

Mutations in other genes causing congenital heart disease have also been described.(62) Mutations in NKX2.5 and CRELD1 lead to septal defects,(63),(64) as does GATA465 mutations. Other genes responsible for congenital heart disease will be identified in the near future. The key to understanding the causes of heart disease at the molecular level is now coming to the end of phase 1, the identification of the genes involved. The next phases, identification of the causative mechanisms and the interaction of mechanisms and genotype/phenotype correlation will probably last for the better part of the next decade, during which time the development of targeted therapies for patients (and probably fetuses) is likely to occur. The clinical utility of understanding the molecular basis of disease will then become apparent.

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MEDICAL CONFERENCES

Southeast Pediatric Cardiology Conference
Sep. 9-11, Howey-in-the-Hills, FL
www.sepcs.org/conference2004.html

NIH (National Heart, Lung, and Blood Institute) - Symposium on Cardiovascular Regenerative Medicine
September 13-14, Bethesda, MD
www.nhlbi.nih.gov/meetings/

8th Pediatric Interventional Cardiac Symposium (PICS-VIII) and 2nd Emerging New Technologies in Congenital Heart Surgery (ENTICHS-II)
September 19-22, Chicago, IL
www.picsymposium.com

2004 Annual Meeting - Western Society of Pediatric Cardiology (WSPC)
September 11-12, Napa, CA
www.wsopc.org/webpages/

Computers in Cardiology 2004
September 19-22, Chicago, IL
www.cinc.org/LocalHost/index.html

11th Paediatric Pacing Workshop
September 30 - October 1, Bristol, UK
www.bcs.com

9th Annual Meeting of the European Council for Cardiovascular Research (ECCR)
October 1-3, Nice, France
www.eccr.org

32nd Annual Meeting & Scientific Sessions of the North American Society for Cardiac Imaging (NASCI)
October 2-4, Amelia Island, FL
www.nasci.org

American Heart Association Scientific Sessions 2004
November 7-10, New Orleans, LA
scientificsessions.americanheart.org/portal/scientificsessions/ss/

5th International Symposium on Pediatric Cardiac Intensive Care
December 1-4, Miami, FL
www.pcics.com

HIGHLIGHTS OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY'S 15TH ANNUAL SCIENTIFIC SESSIONS

The American Society of Echocardiography's 15th Annual Scientific Sessions was held June 26 through June 30 at the San Diego Convention Center. Attendance was estimated at 3,200 professionals. Echocardiography, a five-decade-old technology, is the most widely used imaging tool for detecting heart disease.

The ASE Pediatric Echocardiography Council Luncheon was held during the Scientific Sessions on Monday, June 28, 2005. During this luncheon, Jack Rychik, MD; Director, Fetal Heart Program, Cardiac Center at The Children's Hospital of Philadelphia; Associate Professor of Pediatrics University of Pennsylvania School of Medicine, and the chair of the ASE Pediatric Council Board, gave the State-of-the Pediatric Counsel Address which included initiatives new and old. He also presented Stephen P. Sanders, MD and currently the Chair of the Departimento Medico Chirurgico di Cardiologia Pediatria at the Ospedale Pediatrico Bambino Gesù in Rome, Italy, with the *Founder's Award of the Pediatric Council of the American Society of Echocardiography* (Figure 1).

Founder's Award of the Pediatric Council of the American Society of Echocardiography

In his presentation speech, Dr. Rychik summed up Dr. Sanders' illustrious career. "For the seven years prior to accepting this position, Dr. Sanders was Professor of Pediatrics (Cardiology), Vice-Chair of the Department of Pediatrics for Extramural Relations and Chief of the Division of Pediatric Cardiology at Duke University Medical Center in Durham, NC, USA. Prior to that, Dr. Sanders was Associate Professor of Pediatrics (Cardiology) at Harvard Medical School and Senior Associate in Cardiology and Director of the Cardiac Noninvasive Laboratory at Children's Hospital Medical Center in Boston, MA, USA."

"The American Society of Echocardiography's 15th Annual Scientific Sessions was held June 26 through June 30 at the San Diego Convention Center. Attendance was estimated at 3,200 professionals."

Dr. Rychik continued, "Dr. Sanders is a world-renowned expert in pediatric cardiology and echocardiography. During his career he has produced relevant and outstanding clinical research on such topics as pre- and postnatal diagnosis and management of congenital heart defects, evaluation of ventricular function, assessment of health care cost and the determinants of cost, and race-based inequities in pediatric health care delivery. Dr. Sanders has strong interests in the morphology of congenital heart disease and has pioneered the use of cardiac ultrasound to study the vital anatomy of the heart. In 1985, along with Roberta Williams and Fred Bierman, he authored one of the earliest books ever published on the subject of echocardiographic diagnosis of congenital heart malformations, essentially establishing the approach and the standard for our current style of imaging in infants and children. He has

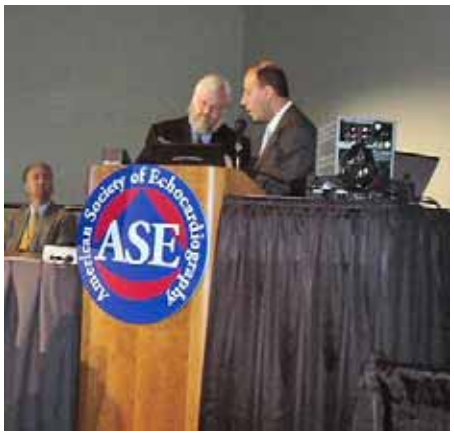

Figure 1. Dr. Rychik (right) presenting the "Founder's Award" to Dr. Stephen Sanders (left).

published over 130 peer reviewed articles and has authored or co-authored numerous abstracts, reviews, editorials and book chapters."

Starting in 2005, The ASE will give the *Founders Award* every other year, alternating with a *Teachers Award.*

Past winners of the "*Founder's Award"* include, David J. Sahn, MD; Dick Meyer, MD; Norman Silverman, MD; Roberta Williams, MD; Jeff Stevensen, MD; and Stanley Goldberg, MD.

The Core Curriculum track from the 15th Annual Scientific Sessions included introductory lectures that covered the basics and prepared the attendees for participation in the other Scientific Sessions program tracks. To review these Core Curriculum tracks visit ASE's website (www.asecho.org). ASE has made available selected slide presentations in PowerPoint. These include:

- *"The Technical Protocol: How Much is Enough?"* and "*Stress Echocardiography*," by Rick Rigling, BS, RDCS, FASE
- *"Hemodynamics,"* by Cris D. Gresser, RN, RDCS, FASE
- *"Coronary Anatomy,"* Judy R. Mangion, MD, FASE
- "*Dilated Cardiomyopathy*," by Edward F. Gibbons, MD, FASE
- *"Cardiac Arrest,"* by Alan D. Waggoner, MHS, RDCS

Next year, ASE's 16th Annual Scientific Sessions will be held June15-18, 2005 at the Hynes Convention Center in Boston, Massachusetts.

For comments to this article, send email to: AUGASE@PediatricCardiologyToday.com

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USEFUL WEBSITES

The American College for Advancement in Medicine (ACAM)
www.acam.org

The British Cardiac Society
www.bcs.com

Canadian Congenital Anomalies Surveillance Network (CCASN)
www.hc-sc.gc.ca/pphb-dgspsp/ccasn-rcsac/

Canadian Pediatric Cardiology Association
www.www.cardioped-canada.org/cpca.asp

Congenital Heart Surgeons Society
www.chssdc.org

European Council for Cardiovascular Research (ECCR)
www.eccr.org

The Heart Rhythm Society
www.hrsonline.org/Default.asp

International Registry of the Ross Procedure
www.saintpatrick.org/ihi/ross.html

Midwest Pediatric Pacemaker Registry
www.med.umich.edu/pdc/

National Pediatric Cardiology Study Group (NPCSG)
www.npcsg.com

PDA COIL Registry
www.med.umich.edu/pdc/pdacoil/pda_main.htm

Pediatric Cardiomyopathy Registry
www.pcmregistry.org/index.htm

Pediatric Electrophysiology Society
www.pediatricepsociety.org

Southeast Pediatric Cardiovascular Society
www.sepcs.org

HIGHLIGHTS OF THE 2004 BARTH SYNDROME INTERNATIONAL SCIENTIFIC/MEDICAL AND FAMILY CONFERENCE

By David G. Soergel, MD

Barth Syndrome (BTHS; MIM #302060) is an uncommon, but probably under diagnosed, X-linked genetic disorder characterized by dilated cardiomyopathy, skeletal myopathy, failure to thrive and neutropenia. The genetic defect in these patients involves mutation of the TAZ gene (also called G4.5) located at Xq28, which encodes the recently-described tafazzin protein.

The Barth Syndrome International Scientific/Medical and Family Conference, organized by the Barth Syndrome Foundation and held recently in Orlando, FL, brought together the world's experts in the many facets of Barth Syndrome (BTHS), including Peter G. Barth, M.D, Ph.D. who first described the disorder. In order to "give a face" to Barth Syndrome, the speakers were introduced by parents of boys affected by BTHS. The parents provided a brief description of the course of their family's diagnosis, progression of disease and treatment. This served to highlight the disorder's variability of presentation, as well as the frustrations of parents as they search for answers about treatment options and the clinical course of the disease. The scientific portion of the meeting was divided into the basic science presentations on the first day and the clinical aspects of the disorder on the second day.

The age of presentation of Barth Syndrome classically has been in the newborn or toddler years when the boys develop signs and symptoms of congestive heart failure or serious bacterial infection. However, the phenotype of BHTS is extraordinarily variable; some patients are severely affected as neonates, while others develop milder symptoms later in life. The determinants of this variability in presentation and clinical course are unknown. Patients with BTHS are hypotonic as neonates and may be neutropenic. They may have evidence of congestive heart failure, prompting initiation of digoxin and afterload reduction. In the toddler years, affected boys have failure to thrive and short stature. The cardiac dysfunction tends to improve or even normalize in the pre-pubertal years. By the teenage years, BTHS patients have a dramatic increase in their growth velocity. At this point, the cardiac dysfunction may recur. Throughout their lifetimes, patients may be affected by serious bacterial infections and recurrent mouth ulcers due to neutropenia. There are on-going issues related to the neurological manifestations of the disorder, such as hypotonia, weakness and myalgia, which limit the exercise capacity of even those patients with normal cardiac function. Patients with Barth Syndrome seem to have normal intelligence and, according to their parents, a "wise" sense of humor.

Physicians and patients posing at the Barth Syndrome International Scientific/Medical and Family Conference

The basic science portion of the meeting was composed of work on the genetics of the disease and the description of the functional disorder caused by the genetic abnormality. Iris Gonzales, Ph.D. of A.I. DuPont Children's Hospital and Frederic Vaz, Ph.D. of the Academic Medical Center in the Netherlands presented their work on the genetics of BTHS. The genetic sequence of the TAZ gene predicts multiple potential gene products of TAZ transcription; however, there is one predominant gene product expressed in humans and higher primates. The TAZ gene encodes tafazzin, which is homologous to members of the acyltransferase superfamily involved in complex lipid metabolism. A patient's particular gene mutation is, however, not predictive of their clinical course. In fact, patients within the same family may be affected differently.

As described by Michael Schlame, MD of New York University Medical Center and

Miriam Greenberg, Ph.D. of Wayne State University, the primary disorder in BTHS is a defect in the remodeling of cardiolipin, a critical structural component of the mitochondrial inner membrane. Mass spectroscopy performed on human cells as well as various genetic models of tafazzin deficiency show that the mature forms of cardiolipin are not present,

From left to right: Randall M. Bryant MD, University of Florida-Jacksonville/Gainesville; Robert Jack (RJ) Kugelmann, age 6, (held by Dr. Barry Byrne); Barry J. Byrne. MD, Ph.D, Shands Children¹s Hospital, University of Florida, Gainesville, FL; Carolyn T. Spencer, MD, University of Florida College of

and that there is a backlog of cardiolipin precursor products. Tafazzin plays a critical role in the three-dimensional orientation of fatty acid components of cardiolipin. Abnormal tafazzin results in a "stereochemical disorder" of the inner mitochondrial membrane, fundamentally changing the three-dimensional properties of cardiolipin and affecting how cardiolipin interacts with other components of the cell, e.g. proteins and other components of the mitochondrial membrane. This abnormal structure of cardiolipin results in a "leaky" mitochondrial inner membrane. The membrane potential, which provides the driving force for ATP generation, is low; therefore, ATP production may be lower than normal. In order to provide the cell with adequate amounts of ATP, these dysfunctional mitochondria proliferate. There are approximately twice the normal number of mitochodria in affected cells.

Work done in yeast using two mutant strains, one in which there is no cardiolipin produced and one in which the yeast homologue of TAZ is missing, demonstrate that these yeast do not grow in stressful conditions, e.g. high temperature or hypotonicity. Replacement of normal human TAZ in the yeast model corrects the phenotype.

"Barth Syndrome (BTHS; MIM #302060) is an uncommon, but probably under diagnosed, X-linked genetic disorder characterized by dilated cardiomyopathy, skeletal myopathy, failure to thrive and neutropenia."

The ATP production capacity of the respiratory chain components in an individual mitochondrion from a cell expressing mutated tafazzin is normal, supporting the hypothesis that the primary defect in ATP production is an inability to generate a driving force for ATP production at the membrane level. Arnold W. Strauss, MD of Vanderbilt University presented results from his experiments using a zebra fish model of Barth Syndrome. The fish are a "knockdown" model using antisense morpholinos to suppress production of tafazzin protein. The hearts of these fish are abnormally formed and function poorly. They develop large pericardial effusions and bradycardia. Work is progressing on the development of a transgenic mouse model of BTHS. Cardiolipin is also involved in the mitochondria's response to low oxygen states, which occurs in ischemia-reperfusion injury, for example. In fact, cardiolipin stores in the mitochondrial inner membrane are depleted during experimental ischemia-reperfusion injury. In addition, the abnormal structure of the mitochondrial inner membrane results in leak of certain mitochondrial components, such as cytochrome c and mitochondrial DNA, into the cytosol. Work by Mauro Degli Esposti, Ph.D. at the University of Manchester showed that there may be a link between the release of cytochrome c and the induction of apoptosis. This may play a role development of neutropenia in BTHS patients.

The cardiac manifestations of BTHS include left ventricular non-compaction, dilated cardiomyopathy and, possibly, a propensity to develop ventricular arrhythmia. Infants frequently present with signs and symptoms of congestive heart failure and require treatment, e.g. digoxin and afterload reduction. These medications may be weaned and even stopped as the patient may go through a "honeymoon" period between the ages of 5 and 10 years. The systolic heart function as measured by shortening fraction may be normal during this period. During puberty, there is again worsening of cardiac function followed by improvement in the teenage years. The reasons for this variation in cardiac function are not known. Carolyn Spencer, M.D. and Barry Byrne, MD, Ph.D. at the University of Florida, Gainesville are currently conducting a longitudinal study on the cardiac manifestations of BTHS. According to their data, cardiac function as measured by shortening fraction is in the mildly dysfunctional range on average. The wall thickness measurements are normal, as are the chamber sizes. The progression of the cardiac disease will be followed in their study. It should be noted that this study included only those patients well enough to travel to the study site, so patients experiencing exacerbations of cardiac function may be underrepresented.

The propensity of BTHS patients to develop arrhythmias is being addressed as a part of the study at the University of Florida, Gainesville. Randall Bryant, MD presented five cases of ventricular arrhythmia and two cases of prophylactic defibrillator implantation in patients with BTHS Syndrome. The patients ranged in age from 11 to 21 years. In most of the cases, patients experienced syncope with or without palpitations and had severe ventricular arrhythmia documented either during an event or at subsequent electrophysiological study. In general, BTHS patients with arrhythmia have mild left ventricular dysfunction that has been stable, with a shortening fraction in the 25-30% range. Vasovagal symptoms and chronic fatigue are common among BTHS patients and were present in all of the cases. Three of the patients had male siblings who died with cardiorespiratory symptoms and two of the three had other features of Barth Syndrome. Currently, signal average EKGs and microvolt T-wave alternans (MTWA) analyses are being performed on patients with BTHS who are old enough to cooperate with the test. A positive MTWA test has been shown in the adult population with non-ischemic cardiomyopathy to be predictive of adverse events (e.g. sudden death, ventricular tachycardia, ventricular fibrillation) occurring within one year. In general, patients with BTHS should be aggressively evaluated for ventricular arrhythmia as a cause for syncope, palpitations or vasovagal symptoms. Holter monitoring, event monitoring, tilt-table testing and EPS are all appropriate as clinically indicated.

Patients with BTHS have either a con-

genital or cyclic form of neutropenia according to Colin Steward, B.M., B.Ch., Ph.D. of the Bristol Royal Hospital for Sick Children. Those with the pattern of congenital neutropenia have an absolute neutrophil count (ANC) less than 500 frequently with mild-to-moderate anemia and a low platelet count. These patients generally experience serious bacterial infections. The cyclic form of neutropenia typically has an oscillating pattern with a 21 day cycle. The ANC nadir is in the 0 to 200 range and can be associated with mouth ulcers. The ANC typically peaks between 1500 and 2100. Some patients with BTHS also have recurrent lymphopenia, especially of the CD8+ subpopulation. It may be difficult to document neutropenia if there is a cyclical pattern, as the cycle duration is not necessarily the typical 21 days. In order to document the pattern of neutropenia, multiple samples may need to be tested over a period of 6 weeks. Patients with recurrent mouth sores or cyclic neutropenia may be treated with GCSF to stimulate neutrophil production. According to some parents, patients may respond to a very small dose of GCSF with an appropriate increase in ANC and resolution of any clinical symptoms.

The neurological aspects of BTHS were highlighted in a presentation by Tyler Reimschisel, MD of Johns Hopkins Hospital. Newborns with BTHS are frequently hypotonic at birth while older children have proximal muscle weakness, myalgias and fatigue. In this study, 75% of participants complained of weakness, usually localized to the upper and/or lower extremities. In many patients, prolonged sitting was very tiring which was explained by weakness of the neck, hips, and shoulders on neurological examination. Muscle weakness is not necessarily accompanied by a decrease in muscle bulk, as only one third of patients had subjectively decreased muscle bulk. Myalgias were common, occurring in 71% of patients, especially after a very vigorous day. Headaches were also common among the BTHS population studied, even in those with no family history of headache. Significant headaches occurred greater than once monthly in the majority of patients, and one third of patients experienced lightheadedness or felt dizzy. Approximately one third of patients had an abnormal gait (e.g. wide-based, everted ankles or toe walking); nearly half had ankle weakness and three-quarters had a flat arch. The neurological manifestations of the disorder may be quite variable in severity and presentation.

Barth Syndrome is a multifaceted disorder with great variability in course and presentation. The complexity of the disease makes a multi-disciplinary approach to patient care invaluable. Richard I. Kelley, MD of Johns Hopkins Hospital and Colin Steward, B.M., B.Ch., Ph.D. discussed the clinic model used at their respective institutions. In either case, the approach to the patient with Barth Syndrome involved evaluation by several subspecialists, including cardiology, hematology, neurology, development, metabolism and genetics. For certain patients, evaluation by a gastroenterologist or an endocrinologist may be of assistance. In addition, patients frequently require services from ancillary care providers such as physical therapy, psychology and nutrition and frequent education sessions on the genetic, nutritional and medical aspects of the disorder. The clinic model at the Bristol Sick Children's Hospital involved the use of play therapists to prepare the children for the more anxiety-provoking studies, such as MRI. In addition, the clinic was "family-led" and addressed the needs identified by the parents. The Bristol clinic is not held "too often" in order to minimize the inconvenience for parents who have to travel long distances to reach the clinic and thus encourage compliance with visits.

Great advances in the understanding of Barth Syndrome have been made since it was first described in 1983 by Peter G. Barth, MD, Ph.D. and colleagues. However, many aspects of the disorder remain to be explained, the more important of which are the factors predicting a more severe course and the link between the genetic defect and the clinical manifestations of the disease. In addition, there is, as yet, no disease-specific treatment for Barth Syndrome, a treatment that parents of Barth patients eagerly await. The Barth Syndrome Foundation is helping to move the process of discovery forward by organizing and participating in scientific meetings, funding research and educating parents and physicians about this challenging disorder.

For comments to this article, send email to: AUGBAR@PediatricCardiologyToday.com

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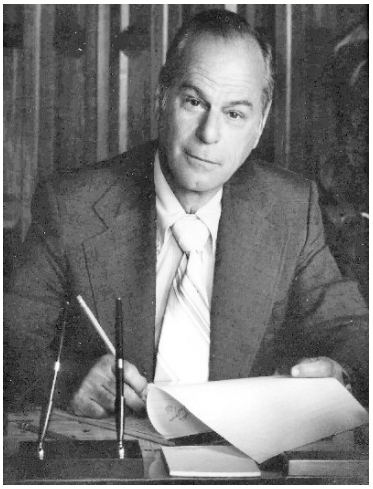
ARTHUR J. MOSS, UCLA PEDIATRIC CARDIOLOGY PIONEER, DIES AT 90

Dr. Arthur J. Moss, professor emeritus at the David Geffen School of Medicine at UCLA, who devoted five decades to the health of the young, died July 14, 2004. He was 90.



Moss was an internationally recognized authority in the field of pediatric hypertension and made many impressive contributions to the field of pediatric cardiology, among them his findings on cardiovascular changes in newborns. He also studied pulmonary artery pressure in newborns and the cardiopulmonary status of cystic fibrosis patients. His book, "Heart Disease in Infants, Children and Adolescents," has become the standard text in pediatric cardiology.

"He was a true pioneer and one of the founders of our field," said Dr. Thomas Klitzner, Chief of Pediatric Cardiology at the David Geffen School of Medicine and the Mattel Children's Hospital at UCLA.

Born in St. Paul, MN, in 1914, Moss attended the University of Minnesota in Minneapolis, where he earned his medical degree in 1938. He performed his internship at Minneapolis General Hospital from 1937 through 1939 and completed a pediatric fellowship at the University of Minnesota between 1939 and 1942. He served in the U.S. Army Medical Corps from 1942 through 1946, where he rose to the rank of major.

He came to California in 1946, and started a private practice in pediatric medicine in Inglewood, which he continued through 1960. He was chairman of the pediatrics department at Los Angeles Harbor General Hospital, now known as Harbor-UCLA Medical Center, in Torrance, CA., from 1948 through 1951. He also served as head of the department of pediatrics at Methodist Hospital in Los Angeles in 1951.

"Dr. Moss will be remembered as the consummate teacher who remained active in educating our pediatric residents until very recently," said Edward McCabe, physician-in-chief of the Mattel Children's Hospital at UCLA. "He was an outstanding leader who recruited young faculty to UCLA and nurtured their careers so they could become nationally recognized experts in the care of children."

Moss joined UCLA Medical School in 1952 as an assistant clinical professor of pediatrics. His other positions at the medical school included executive chairman of the department of pediatrics from 1967 through 1977 and chief of the pediatric cardiology division from 1977 until his retirement in 1981.

He won many awards, including the Los Angeles County Heart Association Award of Merit for three consecutive years (1964–66), the Susan and Theodore Cummings Humanitarian Award (1967), the Leadership Award from the National Cystic Fibrosis Research Foundation and the Outstanding Service Award from the American Academy of Pediatrics (both in 1973), the Outstanding Service Award from the American Journal of Cardiology (1978), the UCLA Pediatric Housestaff Teaching Award (1971–72 and 1977–78), and the Ventura County Medical Center Teaching Award (1992).

"'He was a true pioneer and one of the founders of our field,' said Dr. Thomas Klitzner, Chief of Pediatric Cardiology at the David Geffen School of Medicine and the Mattel Children's Hospital at UCLA."

He also is cited in Who's Who in America and is the namesake of the annual Arthur J. Moss Lectureship in the Mattel Children's Hospital at UCLA.

Moss was a major contributor to the activities of many professional organizations, including the American Academy of Pediatrics, the American Heart Association, the American Pediatric Society, the California Heart Association, the California Medical Association, the California Society of Pediatric Cardiology, the Los Angeles County Heart Association, the National Cystic Fibrosis Foundation, the Society for Experimental Biology and Medicine, the Western Association of Physicians, and UCLA's Jules Stein Eye Institute, which pioneered the field of pediatric ophthalmology.

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