COMPANION MEETING

25th Anniversary of the Society for Cardiovascular Pathology: an update on endomyocardial biopsy

ROOM THURGOOD NORTH EAST

Sunday, March 21, 2010
h.08:30 – 12:00
25 years elapsed since the foundation of the Society for Cardiovascular Pathology. The Session of the Companion Meeting 2010 will be a celebration of the event and endomyocardial biopsy was chosen as the topic of the Symposium.

The possibility to study the myocardium in living patients through endomyocardial biopsy made a revolution for the discipline of Cardiovascular Pathology. It is accomplished in cases of acute, non ischemic heart failure, especially when myocarditis is suspected, in ventricular arrhythmias of otherwise unexplained cause, in cardiac masses and in the monitoring of cardiac transplantation. Dallas criteria for diagnosis of active myocarditis and classification of cardiomyopathies will be revisited. The need to include molecular investigations in the cardiovascular pathology armamentarium will be discussed as well clinical implication of bioptic findings in terms of treatment and prognosis.

**Moderators:**

Michael C. Fishbein, *Los Angeles-CA, USA*
Gaetano Thiene, *Padua, Italy*

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Modern Classification of Cardiomyopathies

Cristina Basso, MD, PhD; Gaetano Thiene, MD, FRCP

University of Padua Medical School, Padua, Italy

Numerous systematic classifications of cardiomyopathies have been advanced through the years, designed for physicians and basic scientists, and based on different taxonomic criteria, including origin, anatomy, physiology, symptoms, therapy, diagnosis, and histopathology. However, an inevitable limitation of any classification, either etiologic or functional, is the considerable overlap encountered between different groups into which diseases have been categorized. In fact, from the functional viewpoint, some cardiomyopathies do not always have the same static phenotype, but may dynamically evolve, as a consequence of remodeling, from one category to another during their natural clinical course. Moreover, also etiologic classifications of cardiomyopathies are imperfect, given that diseases with similar genotype can have different phenotypes and pathogenetic pathways and vice versa. Therefore, although the objective is a classification that can be appreciated by all interested parties and disciplines, it is universally accepted that no past, present or future classification of cardiomyopathies is likely to satisfy the purposes of all users.

The advent of cardiac transplantation and the renewed interest on sudden cardiac death have arisen exciting opportunities in the clinico-pathologic study of cardiomyopathies, as to allow the discovery of new entities. The availability of sophisticated methods of investigation like molecular biology techniques, other than the traditional tools in morphology, opened extraordinary avenues in the understanding the causes, other than the substrates of cardiomyopathies. The major advances were achieved in the last twenty years and pathologists played a major role as to highlight their key position in producing new knowledge: the discovery of new cardiomyopathies (see for instance primary restrictive and arrhythmogenic right ventricular cardiomyopathies), the understanding of the etiopathogenesis and the updates of classification. In particular, the 2006 American Heart Association (AHA) definition and classification scheme recognizes the rapid evolution of molecular genetics in cardiology, as well as the introduction of several recently described diseases, and it is unique in that it incorporates ion channelopathies and conduction disorders as a primary cardiomyopathy.

The AHA expert consensus panel proposed this definition: “Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability”.

From this definition, it appears clear that the major difference from prior efforts (1980 and 1995 WHO Classifications) is the genomic and molecular orientation of this proposed cardiomyopathy classification. It is based upon the hypothesis that causative mutations in genes encoding proteins regulating the transport of ions (“channelopathies”) across the cell membrane are responsible for electrical dysfunction that triggers primary life-threatening ventricular tachyarrhythmias. They ultimately may evolve in a structural disease. However, the authors themselves admit that it is probably still premature and
inadvisable to formulate a classification that is entirely dependent on genomics. The molecular genetics of myocardial disease is not yet completely understood, and more complex genotype–phenotype relationships will continue to emerge for these diseases. For example, several sarcomeric gene mutations are now known to cause both dilated and hypertrophic cardiomyopathies. Furthermore, troponin I mutations have been found to underlie both hypertrophic and restrictive cardiomyopathies.

On the other hand, an important goal of the 2006 AHA document is that myocardial dysfunction, that is a direct consequence of other cardiovascular abnormalities such as valvular heart disease, systemic hypertension, congenital heart disease, and atherosclerotic coronary artery disease, have not been considered anymore as cardiomyopathies.

As far as classification is concerned, cardiomyopathies are now divided into 2 major groups, i.e. primary or secondary, based on predominant organ involvement.

*Primary cardiomyopathies* (further subdivided into genetic, nongenetic, and acquired) are those solely or predominantly confined to heart muscle (Fig.). *Secondary cardiomyopathies* present myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders. In the WHO 1980 and 1995 classifications, these systemic diseases associated with secondary forms of cardiomyopathies have been referred to as "specific cardiomyopathies" or "specific heart muscle diseases", respectively.

An update of the 1995 WHO/ISFC classification has also been proposed as a position statement of the ESC Working Group on Myocardial and Pericardial diseases in 2008. In the definition, it is clearly stated that cardiomyopathy is ‘a *myocardial disorder in which heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart diseases*’. While accepting and reinforcing the idea advanced by the AHA statement to divide cardiomyopathies into familial/genetic and non-familial/non-genetic, the traditional division of primary and secondary (specific) cardiomyopathies was abolished, probably with the erroneous belief that primary means idiopathic and secondary means of known aetiology. Moreover, the concept of pure electrical dysfunction was denied, thus ruling out ion channel and conduction system diseases from the umbrella of cardiomyopathies.

Basically, five types of cardiomyopathies are recognized according to the morphofunctional phenotype (hypertrophic, dilated, arrhythmogenic, restrictive, and unclassified), either familial or non-familial, whether or not the heart is the only target of the disease. This approach is certainly a simplification of a complex nosographic puzzle, but does not yet fully answer the question raised by emerging evidence. While removal of specific cardiomyopathies such as ischaemic, hypertensive, and valvular should be greeted with cheers, as the AHA document first did in 2006, it is not convincing at all why myocarditis should be grouped ‘tout court’ among dilated cardiomyopathies. Moreover, the AHA position statement abolished the so-called non-classified cardiomyopathies, whereas the ESC position statement still regards forms such as non-compaction and Tako Tsubo in search of a room. Finally, only cardiomyopathies with structural deformities were included, renewing the purely morphofunctional approach, without considering the problem of possible evolution of a disease phenotype into another during the natural history and leaving electrical disorders without a taxonomic location.

Although we are well aware of the complexity of disease phenotype in the setting of a nosographic framework, an agreement to update the 1995 WHO/ISFC classification is deemed necessary, with merging views of worldwide scientists, based upon the
breaking news coming from genomics and proteomics of molecular cardiovascular medicine.

**Key Words:**

**Figure:**

**PRIMARY CARDIOMYOPATHIES**
(predominantly involving the heart)

- Genetic
  - HCM
  - ARVC / D
  - LVNC
  - PRKAG2
  - Danon
  - Glycogen storage
  - Conduction Defects
  - Mitochondrial myopathies
  - Ion Channel Disorders
    - LQTS
    - Brugada
    - SQTS
    - CVPT
    - Asian
    - SUNDS

- Mixed*
  - DCM
    - Restrictive
      (non-hypertrophied and non-dilated)

- Acquired
  - Inflammatory (myocarditis)
  - Stress-provoked
    (“tako-tsubo”)
  - Peripartum
  - Tachycardia-induced
  - Infants of insulin-dependent diabetic mothers

**Selected References:**


**Bullet Points:**

• Since 1980, date of the first WHO classification of cardiomyopathies, major advances have been achieved, such as the discovery of new cardiomyopathies (primary restrictive, arrhythmogenic right ventricular cardiomyopathies, non compacted myocardium, etc), the understanding of the etiopathogenesis mainly thanks to molecular biology and the updates of classification.

• Pathological myocardial dysfunctions that are a direct consequence of other cardiovascular abnormalities (i.e. valve disease, systemic hypertension, congenital heart disease, and coronary artery disease) should be ruled out from the classification of cardiomyopathies.

• The myocardium has both an electrical and a mechanical function. Thus, should primary myocardial electrical dysfunction without structural abnormalities be considered a cardiomyopathy?

• Some myocardial disorders (see non-compactied myocardium and Tako Tsubo) are still in search of a room; should we maintain a group of so-called non-classified cardiomyopathies?
The utility of endomyocardial biopsy has been questioned and in many centers is not a common procedure any longer. If one asks why this is so, issues of non-specific pathological diagnoses and significant complication rates are mentioned. In skilled operator hands the complication rate is low (1). With decreasing performance of the procedure, and the resulting lower expertise, such a cycle is self perpetuating. We also risk loss of pathological expertise in the interpretation of these biopsy specimens.

In the past heart biopsies were used for diagnosis and monitoring of Adriamycin drug toxicity, with treatment decisions based upon the degree of cardiomyocyte damage. (1) Such decisions are now made with non-invasive monitoring and imaging. Endomyocardial biopsies continue to be the gold standard for monitoring of cardiac transplant allograft rejection. Even this application is being challenged with the advent of biomarkers.

As pathologists, in this time of translational medicine and personalized health care, we should assume responsibility to provide input concerning the utility of the cardiac biopsy for specific diseases, and provide guidance for tissue triage and investigations including histology, ultrastructural examination, immunohistochemistry or fluorescence, and molecular and genetic investigations, when these are warranted or desired.

The cardiac biopsy should be regarded as complimentary to new developments in cardiac imaging and electrophysiological investigations that may increase biopsy utility. Endomyocardial biopsy for sarcoidosis or arrhythmogenic cardiomyopathy traditionally are considered low yield as sarcoid tends to involve the base of the heart, which is not the area biopsied, and biopsy of the right ventricle free wall and infundibulum is thought to be too risky. (2) Imaging and electrophysiological guided biopsy may change this reluctance.

Cardiac biopsy is useful for differentiating chronic cardiomyopathy from myocarditis in the setting of acute heart failure. Many patients actually have an acute exacerbation of a chronic cardiomyopathy. (1) Although the biopsy findings may not always be specific for a type of cardiomyopathy, such a finding has implications for reversibility, likelihood of recovery, future investigations and perhaps treatment. Giant cell myocarditis can produce a severe acute clinical picture and may be responsive to immunosuppression. Molecular biology and immunological workup of myocarditis and cardiomyopathy are of use in certain situations and if performed should always be accompanied by histology. With developing molecular biology techniques, judicious use of cardiac biopsy may be relevant to decide whether antiviral or immunosuppressive therapy is indicated. (3)

Knowledge concerning the genetics and molecular biology of primary cardiomyopathies are also evolving. Much of the genetic diagnosis will almost certainly be possible by peripheral blood analysis, but somatic mutations do occur, as illustrated by the recent discovery of somatic mutations in connexins in atrial fibrillation. (4)

Endomyocardial biopsy may be helpful for the differentiation between constrictive pericarditis versus restrictive cardiomyopathy. If the hemodynamics or imaging studies
are not clear, an endomyocardial biopsy may demonstrate a myocardial cause for restriction such as eosinophilic and non-eosinophilic primary restrictive cardiomyopathy, amyloid, or iron storage. In constrictive pericarditis such a biopsy specimen would be normal or the myocytes may show atrophy. The cardiac biopsy may spare the patient an unnecessary surgery.

Amyloid may be diagnosed and typed, with treatment implications. Amyloid may be deposited solely in the heart, so a negative extracardiac biopsy (such as a fat aspirate or rectal biopsy) does not rule out cardiac amyloid. Differentiating the amyloid type is relevant. (5,6) AL amyloid is seen in primary amyloidosis and plasma cell dyscrasia, including myeloma. Cardiac transplant in such individuals usually does not have a good outcome, unless the underlying plasma cell problem is also aggressively treated. (7) Transthyretin type amyloid is often age related and is becoming more commonly noted. It is mainly incidental, however this type of amyloid may cause heart failure and be localized solely to the heart.

Fabry disease may be diagnosed by endomyocardial biopsy. Heterozygotes may have unexplained left ventricular hypertrophy and there may be cardiac predominant Fabry’s. With enzyme replacement available, such a diagnosis may have implications for therapy and altering disease course. (8) Neoplasms and cardiac drug toxicity, such as chloroquine toxicity, may also be diagnosed. (2)

The endomyocardial biopsy procedure should not be forgotten. It is important to maintain clinical interest and expertise. Pathologists should lead and actively participate in investigating the utility and cost effectiveness of the biopsy specimen and the modalities to obtain the specimen and ultimately a diagnosis for the patient. Future applications are promising and judicious use of this procedure remains an important contributor to care of our patients.

Key Words:
Amyloid
Biopsy
Cardiomyopathy
Genetics
Molecular
Myocarditis
Myocardium

Selected References:


**Bullet Points:**

- Endomyocardial biopsy is a safe procedure
- It is useful in selected indications
- Always interpret the endomyocardial biopsy with clinical information
- Interpret the cardiac biopsy as a “medical” biopsy similar to a liver or kidney biopsy
- Molecular biology and genetics tests should be used with histology, not alone
- Imaging and electrophysiology advances may change how biopsy specimens are obtained and their utility
- Pathologists should lead in determining the utility of cardiac biopsy for patient diagnosis, work up and concurrent use of diagnostic modalities
In 1984, the Myocarditis Panel met in Dallas to set forth criteria and guidelines to characterize the morphologic diagnosis of myocarditis. The panel was convened by Dr. Margaret Billingham with the major purpose of developing a practical set of pathological criteria to diagnose myocarditis on endomyocardial biopsies. The success of the endomyocardial biopsy in monitoring of cardiac transplant patients for rejection had been established. However, the diagnosis of myocarditis on endomyocardial biopsy was problematic with published rates of myocarditis ranging from 5% to 80% in patients clinically suspicious of having myocarditis. Clinical cardiologists were frustrated and needed reproducible criteria to carry out clinical trials of immunosuppressive therapy for patients with biopsy proven myocarditis.

The central tenet of the Dallas criteria is that myocarditis is defined as the presence of a cellular inflammatory infiltrate in direct association with myocyte degeneration or necrosis not typical of ischemic necrosis. In clinical trials, application of this criteria revealed that the incidence of Dallas criteria myocarditis was uncommon in patients clinically diagnosed as having myocarditis. In the multi-institutional Myocarditis Treatment Trial, of the 2000 plus subjects entered in the trial with a clinical suspicion of myocarditis, only 111 patients had myocarditis based on the Dallas criteria as applied by local pathologists. Furthermore, only 66 of the 111 patients in the trial were diagnosed as having Dallas criteria myocarditis by the trial’s expert panel of pathologists.

The Dallas criteria were considered to be inadequate in the diagnosis of patients with clinically suspected myocarditis. It was recognized that the Dallas criteria were still limited by variability in interpretation, lacked prognostic value and had low sensitivity due to sampling error. However, it was also realized that clinically suspicious myocarditis was a heterogeneous disorder caused by a myriad of mechanisms. These limitations have led to the application of PCR to determine virus involvement, immunohistochemical stains of endomyocardial biopsies for leucocytes and surface antigens, such as ICAM or HLA-DR as well as serum immunological studies for circulating antimyocardial antibodies.

In a study of 181 consecutive patients with clinically suspected myocarditis-endomyocardial biopsies were examined for inflammation using the Dallas and immunohistological criteria. Virus genome was detected by polymerase chain reaction. Immunohistological detection of inflammation was shown to be a significant predictor of poor outcome in the univariate analysis, whereas Dallas criteria myocarditis and detection of viral genome were not significantly related to outcome.

Finally, the recently published TIMIC study evaluated the efficacy of immunosuppression in patients with virus-negative inflammatory cardiomyopathy. The diagnosis of myocarditis was performed according with Dallas criteria and confirmed by immunohistochemistry. Clinical improvement in the immunosuppression treated subjects with myocarditis was reflected in significantly lower average New York Heart Association (NYHA) class at 6 months.
Endomyocardial biopsy remains an important diagnostic tool in patients with clinically suspicious myocarditis. The Dallas criteria identify a subset of patients with cellular myocarditis. In addition to the Dallas criteria, studies of endomyocardial biopsies based on markers of immune upregulation, antimyocardial antibodies and evidence of viral infection by PCR are needed to diagnose additional subsets of this patient population. With the application of more sophisticated testing, we will be in a better position to define the actual pathophysiological basis for the ventricular dysfunction in individual patients with clinically suspicious myocarditis and to provide rational therapeutic options.

**Key Words:**
- Myocarditis
- Inflammatory dilated cardiomyopathy (iDCM)
- Endomyocardial biopsy
- Histopathology
- Immunohistochemistry
- HLA
- Viral PCR

**Selected References:**
The past decade has been witness to some remarkable advances in the early diagnosis of myocarditis and unexplained cardiomyopathy, leading to better prognostic information, enhanced triage of patients, and a greater willingness to consider immunomodulatory treatment. This new era began, in 2000, with the classic description from the Hopkins group, “Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy” published in the New England Journal of Medicine. In this paper, a specific cause of cardiomyopathy was identified in 614 of the 1230 patients (50%). The remaining 616 patients were classified as having idiopathic cardiomyopathy despite having undergone a comprehensive clinical evaluation. Endomyocardial biopsy provided a specific histological diagnosis in only 188 patients (15%). This relatively low diagnostic yield, coupled with the data from the Myocarditis Treatment Trial published in 1995 showing little efficacy of immunosuppressive treatment in patients with myocarditis, and a high degree of improvement in both treatment arms, reinforced the prevailing view in the United States that endomyocardial biopsy was of little value given the paucity of evidence based treatment. This was codified in the ACC/AHA guidelines for the management of chronic heart failure.

Nevertheless, outside the United States, substantial effort continued to further describe some important subsets of the clinical manifestations of viral myocarditis, including 1) those patients who have an acute inflammatory response to viral infection that serves to clear the virus, following which the inflammatory response subsides, or 2) those patients who fail to clear the virus despite an acute inflammatory response, with a subsequent smoldering viral infection, or 3) the group of patients who clear the viral infection but with an ongoing inflammatory response. In the patients in group 2 and 3, evidence suggests that either ongoing viral infection or inflammatory reaction leads to deteriorating myocardial function and chronic dilated cardiomyopathy. Various treatment strategies have recently culminated in a randomized clinical trial, the TIMIC study, that demonstrated the clinical efficacy of immunosuppressive drugs in a patient population carefully chosen to be free of viral genome but with immunocompetent cells on myocardial biopsy signaling ongoing inflammatory response. Complementary to these early trials has been the recent publication of the AHA guideline statement, “The role of endomyocardial biopsy in the management of cardiovascular disease”. At long last, the stage has been set for more intensive scrutiny of the information contained in the endomyocardial biopsy of patients presenting with new onset cardiomyopathy.

Finally, it should be noted that, parallel to the histological developments of the past decade, has been the significant advances in the management of the patient with heart failure, including the patient with fulminant myocarditis. This includes a better understanding of how to integrate drugs which antagonize the neurohormones responsible for ventricular remodeling with implanted devices, such as defibrillators (ICD) and cardiac resynchronization therapy (CRT), leading to survival in many patients heretofore only managed with emergency heart transplant. Most importantly, the increasing utilization of ventricular assist devices (VADs), either as temporary support or
fully implantable devices, has made it possible to keep patients alive long enough to search for a specific treatment plan, based on careful viral and immunologic surveys.

**Key Words:**
Myocarditis
Cardiomyopathy
Ventricular assist devices
Endomyocardial biopsy
In 1990, an international grading system for cardiac allograft biopsies was adopted by the International Society for Heart and Lung Transplantation (ISHLT) to improve communication between clinicians and investigators, to enable comparison of treatment regimens and outcomes, to facilitate multicenter clinical trials, and to promote further studies to determine the clinical significance of various histologic patterns. The grading system was widely adopted and served the transplant community well for over a decade. In 2004, under the direction of the ISHLT, a multidisciplinary review of the grading system was undertaken to address challenges and inconsistencies in its use, to consider changes in rejection incidence and treatment practices, and to incorporate advances in medical knowledge.

The outcome of the consensus conference was revision of the 1990 working formulation for cellular rejection as outlined below with "R" after the rejection grade indicating the 2004 revision:

- Grade 0 R: No rejection (No change from 1990)
- Grade 1 R: Mild rejection (1990 Grades 1A, 1B, and 2)
- Grade 2 R: Moderate rejection (1990 Grade 3A)
- Grade 3 R: Severe rejection (1990 Grades 3B and 4)

In addition, non-rejection biopsy findings, including early ischemic injury (perioperative), late ischemic injury (related to allograft coronary disease), and Quilty effect were further discussed. Early ischemic injury is an extremely common finding up to six weeks (or more) post-transplant, characterized by myocyte necrosis which often extends to the endocardial surface. As healing ensues, a mixed inflammatory infiltrate including neutrophils as well as lymphocytes, macrophages, and eosinophils must be distinguished from acute rejection. Late ischemic injury resulting from allograft coronary disease may be detected by secondary myocardial changes since vessels large enough to demonstrate this process are rarely present in biopsy material. Myocyte vacuolization and/or microinfarcts are characteristic of this process and may be helpful in determining the cause of late cardiac failure or, more importantly, ruling out other potentially treatable etiologies. Quilty effect (nodular endocardial infiltrates) may be confined to the endocardium (1990 ISHLT Quilty A) or extend into the underlying myocardium where associated myocyte damage may be present (ISHLT 1990 Quilty B). However, because the sub-typing of Quilty A and B were never shown to have clinical significance, the designations "A" and "B" were eliminated in the 2004 revision.

Antibody-mediated rejection (AMR) is an evolving and controversial issue in cardiac transplantation. While mentioned only briefly in the 1990 grading system, the 2004 revision recommends reporting whether AMR is absent (AMR 0) or present (AMR 1). AMR is recognized as a clinicopathologic entity that has been characterized by (1) cardiac dysfunction in the absence of cellular rejection or ischemic injury, (2) characteristic histologic features on endomyocardial biopsy, (3) positive immunoperoxidase staining for...
the complement component C4d, and (4) presence of circulating anti-donor antibodies. It often occurs in sensitized patients (including those with previous transplantation, transfusion or pregnancy, and previous ventricular assist device use) and is associated with worse graft survival. The incidence of AMR is highly variable between transplant centers, but most agree that the incidence is low (<5%).

Histologic features have been described, including interstitial edema, endothelial cell swelling, and intravascular macrophages, however these finding are not uniformly present and are not entirely specific. For this reason, the use of histologic criteria for screening biopsies (as stated in the 2004 grading system revision) has been questioned. Immunohistochemistry using antibodies directed against C4d is the most widely used marker for AMR and may be performed on formalin fixed, paraffin embedded tissue. C4d positivity, however, must be correlated with the presence of donor specific antibodies in the serum.

Due to the many unanswered questions regarding AMR, the heart transplantation section of the Tenth Banff Conference on Allograft Pathology in August 2009 focussed solely on AMR, specifically to address (1) appropriate tests and interpretation of histologic findings and immunohistochemistry, (2) use of serologic data, specifically donor specific antibodies, and (3) correlation of allograft dysfunction and histopathologic-serologic findings. In addition, due to the multifactorial nature of AMR, it is not clear who should be making the actual diagnosis of AMR. Pathologists can report biopsy findings (histologic and C4d status) but may not have access to serologic and/or clinical data at the time of the report.

Treatment of AMR is also controversial. Most transplant centers treat AMR (positive C4d staining on endomyocardial biopsy and positive serum antibodies in a hemodynamically compromised patient) with plasmapheresis. Less clear is the appropriate clinical response for a patient who is clinically doing well yet has positive C4d staining on endomyocardial biopsy with or without positive donor specific antibodies. Does this represent "subclinical" AMR which may impact allograft/patient longevity and/or contribute to allograft vasculopathy? Developing standardized criteria and techniques for diagnosing AMR will be necessary before these questions can be answered.

Key Words:
Cardiac transplantation
Endomyocardial biopsy
Cellular rejection
Antibody-mediated rejection

Selected References:
**Bullet Points:**

- The International Society for Heart and Lung Transplantation (ISHLT) grading system for acute cellular rejection revised in 2004 consists of 3 grades: 1R (formerly Grades 1A, 1B, and 2), 2 R (formerly Grade 3A), and 3R (formerly grades 3B and 4).

- Non-rejection biopsy findings, such as early and late ischemic injury, Quilty effect, and old biopsy sites, are common and must be distinguished from acute rejection.

- The diagnosis of antibody-mediated rejection (AMR) remains controversial and continues to evolve. The most commonly used marker is C4d staining by immunoperoxidase.
DISTINGUISHED ACHIEVEMENT AWARD LECTURE

Molecular Basis of Heart Muscle Disease
Insights from Endomyocardial Biopsies,
Whole Hearts, Body Fluids and Model Systems

Bruce McManus, MD
St. Paul's Hospital, University of British Columbia, Vancouver, B.C., Canada

The Cardiovascular Pathologists and Experimentalists

In the past several decades there have been many improvements in the care and prevention of cardiovascular diseases. Through the period of these developments, the opportunities for cardiovascular pathologists and experimentalists to contribute to progress have been unlimited. As the utility of the endomyocardial biopsy became clearer, in the setting of transplantation medicine, in the monitoring of anthracycline toxicity, and in the assessment of acute heart failure, and other clinical situations, the role of cardiac pathologists increased. Similarly, as registries and biobanks evolved in their sophistication, explanted hearts at the time of transplantation became important resources for studies of bio-mechanisms involved in heart failure and its relief by mechanical assistance. While our understanding of how to utilize the biopsy and explants tissue has progressed towards the possibility of much more biologically refined classification systems, attention has also been drawn to the potential that blood and urine analyses offer for discerning cardiac disease or risk in the periphery with minimal invasion of patients. The cardiac pathologist has a wonderful position, sitting in the very heart of this maelstrom. And, beyond this, many cardiovascular pathologists also take advantage of the many tools, techniques and model systems that can answer questions which at times are very difficult to answer in human materials alone.

Our Efforts to Learn and Discover

In our search for better ways to inform clinical colleagues about the nature of heart muscle diseases, especially enteroviral heart disease, cardiomyopathies and allograft rejection, we have used multiple approaches. Characterizing the face of human myocarditis from a pathological standpoint has included gross, histochemical, immunohistochemical, in situ hybridization and polymerase chain reaction tools. We have also typically utilized various morphometric analysis strategies to provide a quantitative basis for observations. In order to carry our work forward, we established a Registry 38 years ago. The Registry became the home for ethics-approved biospecimens and related clinical data for patients with heart and blood vessel diseases, including those with acquired ailments and those with congenital disorders. The Registry was computerized in 1987 and a locally derived nosology/ontology was built based on SNOMED and other knowledge that provided the kind of granularity necessary to conduct translational studies and to support educational activities. The Registry holds various collections of exquisitely phenotyped specimens, especially those related to transplantation and allograft rejection. Protocols for fresh retrieval of explanted hearts and valves on a 24/7 basis have allowed the systematic triage of tissues for culture, flash freezing, frozen blocks, and microscopic assessment. These materials have proved invaluable for studies
of pathogenesis. The tradition of archiving, photographing, annotating, and analyzing the tissues, cells and fluids using multiple techniques and approaches, allowed us to transition to full-scale molecular studies when discovery could no longer be sufficient with still-life appraisal alone. Now the programs have grown to fully embrace molecular strategies for predicting, diagnosing, tracking and better treating and managing cardiovascular diseases. We are fortunate to be a part of the effort to better understanding mechanisms, pathways and networks that underpin risks, disease initiation and progression and responses to clinical interventions including pharmacological and engineering innovations. We have been able to open doors to the basis of inflammatory heart muscle disease through the study of model systems in vivo and in vitro, and through the application of genomic tools to blood, urine and tissues over the life cycle of disease, especially allograft rejection and heart, lung and kidney failure. We have harnessed the power of genetics in trying to understand degenerative aortic valve disease, while spawning other programs focused on proteolytic determinants of aortic injury and aneurysm formation, and potential molecular pharmacological strategies for interruption of the pathogenic processes. We are, like many others, trying our best to make the “personalization” of health care a reality.

**Reflection on the Journey**

We are all very fortunate to have the luxury of asking tough questions about human health and disease. This precious gift of free thought and exploration is made richest by the students, by the learners, the passionate seekers, all of whom make the journey more exhilarating than could have been imagined in the beginning. Warmest thanks to many colleagues and friends from wide-ranging geographies, disciplines and viewpoints. My professional life as a cardiovascular pathologist, experimentalist and translational researcher has been buoyed by traveling the road together. My family keeps me connected to the world in a broader and deeper sense than science or medicine can do by themselves, although the privilege of riding these curious waves hand-in-hand with my wife and closest colleague Janet Wilson-McManus has been something unusual and extraordinary.

**Selected References:**

**Bullet Points:**

- Classical and molecular pathology, as well as other disciplines in and out of the medical sciences, must be embraced in order to make progress and for cardiovascular pathologists to have a central role in advancing the understanding and management of cardiovascular diseases.
- Standardized approaches to biospecimen accrual, handling and analysis are essential for new information to arise from all forms of interrogation, whether microscopical, cell biological or molecular.
- Combined training in clinical medicine, biological sciences and pathology may be the path of the future for rising stars who wish to make a difference in fighting the burdens of heart and blood vessel disease.