Vincent’s Seasonal Sense

For this seasonal issue—the last issue of 2013—the Pathology, the Pharmacy and Pharmacology and the Junior Faculty and Trainees Councils spotlight the sunsational highlights tuning us in for the 2014 meeting in San Diego from Faces, Explorations, and Highly-Sensitized Patients to Blood, Bugs, Drugs, Dishes or Lishes and Pulmonary Hypertension as well as Coming of Age, Drills, Pressurized Pipes and Pumps, Capsules and Dilemmas. There are several Cores and of course there is the Masters in Mechanical Circulatory Support.

We also have some Weighty Issues for our candidates for Lung Transplantation by Beth Coplan and Christina Migliore from Beth Israel in Newark and an interview with our very own living legend, the inimitable Paul Corris by Christina. Also, Miae Kim from the Brigham and Women’s gives us a treatise on the newly FDA approved, extended-release tacrolimus, and Chris Ensor of the University of Pittsburgh Medical Center updates us on the challenges of Pneumocystic jiroveci prophylaxis with the incomparable trimethoprim-sulfamethoxazole.

Dylan Miller from Intermountain Central Lab in Murray, Utah draws our attention to the recently published definitive reference cardiac antibody mediated rejection. Margaret Burke of London, Ornella Leone of Bologna and Clair Toquet of Nantes show us the clustering of an integrated network of European Cardiovascular Pathologists and their evolving efforts to promote quality control studies, undertake multicenter investigations, and link-up with other groups to discuss current and evolving practices in heart transplant pathology.

Then there remains our Special Interest stories, News and Announcements, and of course Links from Outta This World and those that Tattle for us into the upcoming New Year.

Happy Holidays!

Vincent Valentine, MD
Editor-in-Chief, ISHLT Links Newsletter
IN THE SPOTLIGHT:
ISHLT 2014 in Sunsational San Diego!

Featuring meeting highlights in:
- Pathology
- Pharmacy & Pharmacology
- Junior Faculty & Trainees

The ISHLT is very excited to return to the beautiful, sunny city of San Diego in April 2014 for the ISHLT 34th Annual Meeting & Scientific Sessions to be held at the Manchester Grand Hyatt hotel. A wealth of information about the meeting can be found on the Annual Meeting website, including Abstract Submission, Registration & Housing information, the Daily Timetable, the Preliminary Scientific Program, the Schedule At-A-Glance, and much more. Please note that the Annual Meeting begins on Thursday, April 10, one day later than usual, and concludes at mid-day on Sunday, April 13.

Since this month's newsletter focuses on Pathology, Pharmacy & Pharmacology, and Junior Faculty & Trainees, below are highlights of the upcoming meetings related to these disciplines.

PATHOLOGY HIGHLIGHTS:

Pathology will provide some very important content again at ISHLT 2014 in a number of symposia. Lung allograft dysfunction occurs in many different ways; these present and progress in differing fashions; treatment, although not well developed, could be different between different types. Thursday's Pre-meeting Symposium 10: The Many Faces of Chronic Lung Allograft Dysfunction will address these issues.

Events and mechanisms in T-cell mediated immunity are distinct from those of B-cell mediated immunity, but the two are not mutually exclusive. Saturday's Sunrise Symposium 10: Exploring Interactions Between Cellular and Humoral Immunity in Cardiac Allograft Rejection deals with interactions between the two arms of the immune system at the basic science level (using NK cells and innate immunity as one possible contributor) and reviews what is available with respect to "mixed rejection" in terms of outcomes and management.

The Pathology Scientific Council Meeting will take place on Saturday, April 12, from 12:05 PM - 12:55 PM during the lunch break.

Sensitization (circulating HLA-antibodies) in patients awaiting heart transplantation may lead to prolonged waiting times and possibly increased complications/death while on the waiting list. Saturday's Concurrent Symposium 29: Approach to the Highly Sensitized Patient Awaiting Heart Transplantation is designed to provide attendees with practical information and strategies to manage sensitized patients awaiting heart transplantation. Recent research publications and program experience will inform this session.

PHARMACY & PHARMAOLOGY HIGHLIGHTS:
The Pharmacy & Pharmacology content of the Annual Meeting kicks off on Thursday with Pre-meeting Symposium 7: Making Bloody Sense of Anticoagulation. Anticoagulation is common in most practice areas represented by the ISHLT membership. Although most clinicians use anticoagulation therapies, questions often arise around how these medications compare with others within this class, interpretation of labs testing, and the function of new and future medications. The goals of this symposium are to discuss: 1) where anticoagulation therapy has been, 2) the status of anticoagulation in 2014, and 3) appropriate interpretation and application of anticoagulation monitoring; and then use this information in discussion of MCS recipients and their thrombotic and bleeding risk after implantation where multiple different regimens, goals and management strategies that employed across centers and between devices.

Pre-meeting Symposium 15: Bad Bugs: Optimize the Drugs! combines brief illustrative case presentations followed by state-of-the-art lectures reviewing issues and controversies in antiviral, antibacterial, antifungal and antimycobacterial therapeutic drug monitoring (TDM). Although there is a small amount of published information on TDM and azole antifungal agents in heart lung transplantation, the antibacterial and antiviral drugs have been very neglected. Inappropriate dosing may lead to treatment failure, toxicity and the development of resistant organisms, both of which can be catastrophic in the transplant setting.

The Pharmacy & Pharmacology Scientific Council Meeting will take place on Thursday, April 10, from 12:30 PM - 1:30 PM during the lunch break.

The infectious disease sessions at ISHLT traditionally have focused on adults rather than children. Some of the pediatric responses to infections are quite disparate from those of adults. Pre-meeting Symposium 23: State of the Art Update on Infectious Disease Issues in Pediatric Thoracic Transplantation will provide a state of the art update based on the latest data in pediatrics.

Friday morning begins with Sunrise Symposium 5: What You Always Wanted To Know About LISH (Laboratory Tests, Infectious Agents, Special Situations, Hidden Infections) But Were Afraid To Ask. In the field of infectious diseases there are many accepted standards for treatment and diagnoses. However we do not always know the real explanation for them nor do we question them. This symposium will attempt to clarify several main topics in ID from laboratory to therapy.

After the successful symposium, "A lifecycle journey in cystic fibrosis and lung transplantation" at ISHLT 2013, we propose to continue this innovative session for the 2014 meeting. Traditional symposia are presented either in pure didactic tracks or cases with panel discussions during Friday's Concurrent Symposium 25: A Lifecycle Journey in Pulmonary Hypertension. This series is a practical hybrid depicting an enduring case interspersed with a best practice based discussion at predefined key "journey intervals." The symposium will be rounded off by a panel assisted and audience supported anchoring discussion. The lifecycle of pulmonary arterial hypertension will include special emphasis on 4 "journey points:"
1) Appropriate evaluation and diagnosis, 2) Management of acute decompensated PAH, 3) Long term management, and 4) Invasive options for bridging and palliation. The focus of this series will be on therapeutics that uniquely involves emerging or established knowledge in the pharmacology and pharmacy aspects of the interval disease states or situations.
Saturday begins with Sunrise Symposium 7: The Effects of Prostaglandin Therapy in Pulmonary Arterial Hypertension: The Seen and Unseen Risk/Benefit Profile. Although treatments have improved symptoms, exercise tolerance, and quality of life for patients with pulmonary arterial hypertension, PAH remains a progressive, life-limiting disease. The purposes of this symposium are to raise awareness of the physical (seen) and psychological (unseen) effects of IV prostaglandin, the current mainstay for treatment for PAH, culminating in a case presentation/panel discussion.

Sensitization (circulating HLA-antibodies) in patients awaiting heart transplantation may lead to prolonged waiting times and possibly increased complications/death while on the waiting list. Saturday’s Concurrent Symposium 29: Approach to the Highly Sensitized Patient Awaiting Heart Transplantation is designed to provide attendees with practical information and strategies to manage sensitized patients awaiting heart transplantation. Recent research publications and program experience will inform this session.

**JUNIOR FACULTY & TRAINEES HIGHLIGHTS:**

The Junior Faculty & Trainee Council (JFTC) submitted 14 proposals for symposia for ISHLT 2014, most of which were developed jointly with other councils. The JFTC is excited to have had 6 of these symposia selected for ISHLT 2014.

Transition is defined as "the process by which adolescents and young adults with chronic childhood illnesses are prepared to take charge of their lives and their health in adulthood". Effective transition programs have the potential to decrease morbidity and mortality associated with transfer of care and can improve quality of life. Thursday's Pre-meeting Symposium 6: Joint ISHLT/IPTA Symposium: Here They Come: Preparing Pediatric Patients For Transition To Adult Care will discuss issues essential to successful transition of pediatric patients to adult care, including patient and family challenges, as well as potential strategies/interventions to meet these challenges.

Mechanical circulatory support, through the advent of continuous-flow left ventricular assist devices, has dramatically altered our management of patients with advanced heart failure. Despite over a decade of experience with continuous-flow pumps, we only have a basic understanding of the human cellular and molecular response to mechanical support. Gene expression, metabolomics and other translational techniques should provide some key insights into the human response to continuous blood flow and will perhaps lead to strategies to predict and prevent the morbidities of VAD therapy. Finally, the "holy grail" of MCS is myocardial recovery which may indeed involve therapy with stem cells, but only if aided by an integrated analysis of the entire human genome and its downstream transcriptional and translational products. Pre-meeting Symposium 13: Drilling Down on Myocardial Recovery—Basics and Clinical will review our current understanding of translational research in the setting of MCS with an emphasis on its clinical utility and translation.

Friday's Sunrise Symposium 2: Under Too Much Pressure: Challenging Cases in Pulmonary Hypertension Management is meant to be a multidisciplinary symposium (cardiology, pulmonary, PH) discussing management of challenging patients who have complicating pulmonary hypertension. Three cases will be presented by junior faculty members. The case presentations will include challenges to the discussants (in an open forum) regarding next steps in evaluation, management, etc of pulmonary hypertension. The objectives of the symposium are 1) Evaluation and management of challenging cases
in PH, 2) Discussion of controversial techniques in PH evaluation, 3) Pre- and post-transplant evaluation of patients with PH, and 4) Post-transplant pharmaceutical management of cardiac transplant patients with preexisting PH.

Endothelial function is increasingly recognized as a general barometer of health. There is extensive data that endothelial function is impaired in patients with heart failure, and it may be a marker of development of allograft vasculopathy in transplanted patients. A better understanding of the pathophysiology of endothelial dysfunction in heart failure, VAD and transplanted patients, the methods of endothelial dysfunction assessment, and its relation to outcome following VAD and transplant is crucial for specialists caring for patients undergoing advanced heart failure management. It is also critical for scientists working in the field of vascular physiology and outcomes research to understand the interaction between the different modalities and endothelial function in order to further enhance research in this arena. The first discussions in Sunrise Symposium 3: Endothelial Dysfunction in Advanced Heart Failure, Mechanical Circulatory Support, and Heart Transplant: It's a Pipe and Pump Issue will provide a general overview of the pathophysiology of endothelial dysfunction. The subsequent talks will provide in depth analyses of the development, treatment, and morbidity of endothelial dysfunction development, treatment, and morbidity in patients with heart failure, transplant, and MCS.

Saturday's Concurrent Symposium 28: JHLT at ISHLT: The Year in a Capsule will summarize the best research presented in the Journal of Heart and Lung Transplantation.

And finally, the JFTC is planning a return of the popular concurrent abstract session, Clinical Case Dilemmas in Thoracic Transplantation. The Junior Faculty Mentor Lunch will take place on Thursday, April 10, from 12:15 PM - 2:00 PM. The Junior Faculty & Trainees Council Meeting will take place on Friday, April 11, from Noon - 1:00 PM.

Prior to the Annual Meeting, the ISHLT will be conducting five Academies. The first two will be held simultaneously on Monday and Tuesday, April 7-8, at the Loews San Diego Bay Resort in Coronado, California:

1. ISHLT Academy: Core Competencies in Mechanical Circulatory Support
2. ISHLT Academy: Masters Course in Mechanical Circulatory Support

Then, on Wednesday, April 9, the ISHLT will host three additional Academies simultaneously at the Manchester Grand Hyatt Hotel in San Diego:

3. ISHLT Academy: Core Competencies in Basic and Translational Science
4. ISHLT Academy: Core Competencies in Heart Failure and Cardiac Transplant Medicine
5. ISHLT Academy: Core Competencies in Nursing, Health Science, and Allied Health

Detailed information about each academy is available on the ISHLT Academy website, including course descriptions, registration and hotel information, and scientific programs.
Helping Your Patient Achieve an Adequate Weight to be Suitable for Lung Transplant

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Most people have struggled with their weight at some point in their lives. Some people need to lose weight, while others have difficulty gaining weight. Women may want to lose weight to fit in a specific dress, to feel more attractive and confident, or to become healthier, while men may want to build muscle and become more physically fit. But what happens when you are not most people? What happens when you are the person with a life-threatening pulmonary disease, requiring continuous oxygen, taking high dose steroids daily, cannot exercise on a regular basis, and needing a lifesaving procedure such as a lung transplant, but are too obese to be a suitable transplant candidate? It is very easy to tell someone that he/she has to lose weight, but how do we help our patients achieve and then maintain these weight loss goals in order to be a suitable transplant candidate?

Transplant centers have specific weight guidelines in place to ensure that each patient is well nourished prior to transplant, will be able to heal properly and timely, and will be able to thrive after transplant. Weight guidelines tend to include a BMI between 17 – 30 kg/m2 or that a patient must weigh at least 70% of ideal body weight or no more than 130% of ideal body weight. (Weight guidelines may vary slightly at each transplant center.) Since obesity has been a factor for mortality post lung transplant, following the weight guidelines will help to ensure the best outcomes for our patients.

Weight can be a sensitive subject for some people, especially if they have been trying to lose weight, gain weight, or their weight has changed dramatically since becoming ill. The transplant physician, the registered dietitian, and the patient should all be agreeable on the determined goal weight. The patient needs to have a clear understanding of why the weight guidelines are in place and why it is imperative for that patient to reach his/her individual goal weight. It is also important to stress to the patient that even though weight loss is required, staying nourished while losing the weight is key to ensuring the patient will heal properly after transplant.

Losing weight can be extremely difficult, but gaining weight can be just as challenging. Some patients with pulmonary diseases struggle with keeping their weight up. For those patients, reaching a BMI of 20 is just as challenging as patients trying to achieve a BMI of no higher than 30.

Below are lists to help each patient achieve his/her weight goals in order to become a suitable transplant candidate. Continuous follow up with the registered dietitian is always essential to help the patient overcome any obstacles and to keep the patient motivated in order to achieve and maintain the goal weight.
### When a Patient Requires Weight Gain

- Eat at least 3 meals with 3 – 4 snacks daily.
- Consume high calorie, high fat, high protein meals and snacks.
- Drink high calorie beverages with meals and throughout the day such as milk, flavored milk, and juice.
- Between meals consume commercial supplements, nutrition bars, and homemade milkshakes.
- Enjoy high calorie snacks such as smoothies, whole milk yogurt, puddings, ice cream, custard, and yogurt parfaits (made with whole milk yogurt, fruit, and granola).
- Always pack snacks when going out for several hours including a peanut butter and jelly sandwich, trail mix, and granola bars.
- Add butter, margarine, or oil to soups, breads, potatoes, rice, pasta, and vegetables.
- Use dressings and spreads freely – mayonnaise, nut butters, salad dressings, cream cheese, sour cream, bean dips, and guacamole.
- Enjoy cream sauces on pasta and veggies. Eat cream soups instead of broth based soups.
- Add protein powder or dry milk powder to milkshakes, smoothies, hot cereal, soups, stews, and mashed potatoes.
- Add cheese to any meal and snack.
- Sprinkle nuts and seeds on both hot and cold cereal, salads, fruits, and desserts.

### When a Patient Requires Weight Loss

- Eat consistently throughout the day, at least 4 times per day (3 meals with 1 snack).
- Be sure to eat within 1 hour of waking up (if possible), and then eat every 4 – 5 hours throughout the day.
- Drink low calorie or no calorie beverages including water, seltzer, unsweetened teas and coffee, and skim or 1% milk.
- Consume lean protein with each meal such as skinless poultry, lean ground beef, lean ground turkey, sirloin, tenderloin, or pork loin, fish, eggs, egg whites, egg substitute, and tofu.
- Eat complex carbohydrates with each meal including whole grain cereal, oatmeal, 100% whole wheat bread, brown rice, whole wheat pasta, beans, corn, and baked potato or sweet potato with the skin.
- Do not fry foods. Always bake, broil, boil, grill, sauté, roast, poach, or stew.
- Enjoy only low fat or fat free dairy products.
- Choose broth base soups, tomato sauces, and vinaigrettes instead of cream soups, sauces, and dressings.
- Divide the plate into 3 portions – ¼ of the plate consists of a complex carbohydrate, ¼ of the plate consists of a lean protein, and ½ the plate consists of vegetables.
- Enjoy a piece of fruit for dessert instead of cake, pie, cookies, or ice cream.
- Be sure to eat slowly and enjoy the food. Always put the fork down between bites.
- Keep a daily food record or journal.

**Disclosure statement:** The authors have no conflict of interest.
Transplant Greats: An Interview with Paul Corris

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To continue our series on the legends in the field of heart and lung transplant we get to know a little more about Dr Paul Corris. Dr Corris needs no introduction. He can always be found at every ISHLT meeting with his trademark scarf and turned up collar. His accomplishments in the field are extraordinary. He served as the President of the ISHLT from 2007-2008 and president of the European Society for Heart and Lung Transplant from 2006-2008. He was elected to the office of President of the British Thoracic Society in 2009-2010. I have included some questions that I thought would let us get to know this prominent and praised physician.

What was your direction in Medical school?

I went to University College London then the Westminster Medical School. I qualified in 1976 and had been taught surgery by the legendary Harold Ellis. I wanted to be a surgeon, though other mentors such as Duncan Geddes who was my tutor (very well respected London respiratory consultant) and the Medical School Secretary Robin Forrest always said I should be a physician. I did the Physician’s job first so I would be good at looking after patients post op, then did surgery but realised that surgical interest certainly at that stage was all about what went on in the great THEATRE of Dreams, ie Operating Theatre. I could tie knots and did an emergency appendix on day 7 but soon realised that using my brain as a physician was more exciting than surgery, so I switched to medicine. Respiratory Medicine came from Duncan Geddes – I can be like him or so I imagined.

Were you always interested in transplant or was there another field that sparked your interest?

After completing my training and research I was appointed to the Newcastle Teaching Hospitals and my research and training became more biased toward lung cancer. I was handy at interventional bronchoscopy at that time. The true story is that I was appointed in 1986 and the Toronto results for SLT just published. One of our CT surgeons, Chris McGregor, knocked on my door one afternoon very early after I had started and said, “Why don’t we start a lung transplant programme?” He had started the heart transplant programme in Newcastle so—always on the lookout for excitement—I said why not? We visited Toronto then started and that is how I became involved in the subject that dominated my professional life.

Who were your Mentors?
Harold Ellis, Duncan Geddes, Alastair Brewis, and John Gibson.

**What are some of you earliest experiences in transplant?**

Explaining to a cardiothoracic surgeon I was going to do a transbronchial lung biopsy early after transplantation (one of the early experiences of this technique). He was worried!

Seriously, there were no rules or rule books in those days and we had a great time integrating research with clinical management and writing the various algorithms for patient management. It was a steep learning curve and great fun but in the pioneering spirit—you had to have the courage to fail. The early transplant folks were all great at sharing information and we helped each other out.

**What keeps your interest in the field?**

Well we still have not cracked some of the early problems like OB and are seeing new problems to keep us on our toes. There is still so much to try and understand.

**What are some “fun facts” about yourself?**

- I’m in Who’s Who in UK
- Born May 1953 (Taurus) in Bebington near Liverpool
- No medics in Family
- Scholarship to very good school (Birkenhead School)
- Played Rugby and Cricket
- Saw the Beatles
- History and Geography were my best subjects but I wanted to be a doctor from as long as I could remember and chose science subjects pre-University
- I attended medical school at the University College and Westminster Medical School where I played too much Rugby and too little Medicine at first!

**What are some of your favorite films?**

*The Shawshank Redemption*: Hang in there and use your brains, motivate and inspire; all good characteristics for a Transplant Physician.  
*Casablanca*: Try to do the right thing.

**What are some of your hobbies?**

- I’m a member of the Newcastle Film Club so I am able to see non-major films. War of the Buttons is one I remember—go see it if you can.
- I follow all sports but in particular, the Newcastle United soccer team known as the Toon. I have season tickets. Rugby is still my favourite team game but I no longer play!!
• Love skiing
• Enjoy music, good food and good wine

**Have you read any good books lately?**

I’m currently reading a biography of a physician called *Bodkin Adams* who murdered a whole number of rich widows in Eastbourne! It’s a fascinating court case. He had a brilliant defense lawyer but justice prevailed.

I appreciate a wide number of authors from Charles Dickens to James Elroy.

The author would like to thank Dr Corris for letting us get to know him a little better. He is as generous with his knowledge as he is with his time.

**Disclosure statement:** the author has no conflicts of interest.
Extended Release Tacrolimus (Astagraf XL™, Advagraf®): Same Old Drug in a Different Package?

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Tacrolimus extended-release capsules (Astagraf XL™, Astellas Pharm US, Inc. Northbrook, IL) were approved in the US by the Food and Drug Administration (FDA) in July 2013. The development of this new formulation garnered interest due to a possible improvement in immunosuppressive medication compliance. This formulation has been approved for use in European countries since 2007 under the trade name Advagraf®, and it has been approved for use in 73 countries worldwide.

Astagraf XL™ or Advagraf® is modified to be released slowly by adding ethylcellulose, hypromellose, and lactose monohydrate in order to modify water penetration and form a protective polymer coating around the drug. Extended release tacrolimus has different dissolution properties and is delivered in a more distant area of the gastrointestinal tract [1]. Comparable trough levels but lower peak levels were seen with the extended released formulation compared to regular release tacrolimus in two industrial sponsored clinical trials. The trials showed an equivalent overall drug exposure between the two formulations in spite of the lower peak levels with extended release tacrolimus, and suggested a 1:1 conversion from the regular tacrolimus formulation to extended released tacrolimus and the same therapeutic drug monitoring strategy.

Subsequent clinical trials have, however, consistently reported low trough levels and area under the curve (AUC) with the extended release formulation [2]. On average, the trough tacrolimus level with the extended release formulation was 40% lower than that of regular release tacrolimus at 6 weeks post transplant [2]. The total daily dose requirement also tended to be at least 10% higher with extended release tacrolimus as compared to the regular release tacrolimus at 1 year post transplant [2]. One conversion trial among heart transplant recipients used a 1:1.25 dose conversion ratio between regular tacrolimus and extended release tacrolimus to avoid under-immune suppression post conversion, but this did not prevent the need for subsequent dose modifications [3].

Additionally, although a high correlation between trough and AUC was reported with the extended formulation in phase I trials with healthy subjects, significant inter-subject variability in PK profiles and the trough to AUC ratio has been observed with extended release tacrolimus in solid organ transplant recipients, which leads to a concern that monitoring troughs of this drug may not
represent the overall exposure to it [1].

Studies have also presented concerning results on more biopsy-proven acute rejections with extended release tacrolimus [4-6], and there was speculation that this may be related to the lower peak concentrations [1]. However, a recent meta-analysis of 6 randomized controlled trials and 15 observational studies found a non-significant difference in biopsy proven acute rejections and graft/patient survivals at 12 months between the two formulations [2].

Considering the relatively low peak obtained from using extended release tacrolimus, it was hypothesized that there may be a beneficial impact on preventing peak-related complications of tacrolimus. In an animal model, reducing tacrolimus peak levels was related to a lower incidence of hyperglycemia [7]. A meta analysis, however, showed that the observed incidence of new-onset diabetes after transplantation was not different [4]. Some studies reported better renal function with the extended release tacrolimus formulation early post renal transplant, but the benefit did not last until 1 year post transplant [4,8]. Additionally, the incidence of bacterial infection was significantly lower among patients receiving extended release tacrolimus [4].

There have been a small number of studies that investigated whether the once daily regimen with extended release tacrolimus instead of twice daily dosing actually improved patient compliance to immunosuppressive regimens. There are no data to suggest that extended release daily tacrolimus improves medication adherence compared with the twice daily tacrolimus formulation in kidney transplant recipients [2], but improved adherence rates were reported with the use of extended release tacrolimus in liver and heart transplant recipients [9,10].

Finally, there is a new formulation of extended release tacrolimus, LCP-Tacro™ (Veloxis Pharmaceuticals, Hørsholm, Denmark), being developed for use in kidney (Phase III) and liver (Phase II) transplant recipients. LCP-tacrolimus has greater bioavailability than regular release tacrolimus, and only requires about 70% of the daily dose of regular release tacrolimus on average [11]. The release of LCP-tacrolimus, which has small size particles of the drug embedded in the tablet being absorbed consistently over a full day, provides a time-to-concentration plot that is similar to that of a continuous infusion of intravenous tacrolimus, with significantly lower peak to trough variations [11,12]. It will be interesting to see how this medication impacts transplant outcomes, safety, and medication compliance.

Nonadherence to immunosuppressive medications is not uncommon in organ transplant recipients, and it can significantly worsen long-term outcomes. It is known that choosing a simpler yet effective regimen is preferred by patients and improves adherence. Utilizing once daily extended release tacrolimus products may be beneficial for improving immunosuppressive medication adherence without compromising graft/patient survivals or patient safety in patients at a high risk of medication noncompliance. More studies are needed to confirm this.
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References:

Pneumocystis jiroveci is an opportunistic fungus that is recognized as a major public health hazard, particularly for recipients of solid-organ transplantation (SOT) [1]. Pneumocystis jiroveci exists in three known forms: trophozoite, cyst, and sporozoite. Its primary mode of transmission is aerosolization from host-to-host; after which it remains indolent until a period of opportunity for reactivation, such as that experienced during enhanced immunosuppression immediately after transplantation. Risk factors for PJP in lung transplant recipients include immunosuppression intensification, periods of neutropenia, and airway complications. Cytomegalovirus disease enhances the virulence of PJP, increasing the adhesion and replication at least 5-fold over 5 days. Unlike other solid organs, the risk of PJP in lung transplant recipients does not decline over time. The morbidity and mortality experienced after Pneumocystis jiroveci pneumonia (PJP) after lung transplantation is significant; thus, prevention is critical.

The Challenge...

There exists considerable variability in pneumocystis jiroveci pneumonia (PJP) prophylaxis practices amongst lung transplantation programs worldwide [2]. Opinions and practices amongst providers regarding the optimal prophylaxis strategy are generally poorly informed by case experiences and toxicities of one dose or regimen vs. another. Despite recognition that oral sulfamethoxazole/trimethoprim (SMX/TMP) provides optimal prophylaxis, one consistent regimen has not emerged (table) from the breadth of literature [1-6]. Expert opinions generally favor 1 single-strength SMX/TMP tablet daily as a balance between efficacy and toxicity; though, they acknowledge that less-frequent regimens are equally effective [1].

The Data...

First, the study published by Gordon and colleagues from The Cleveland Clinic group describes their experience in 1299 recipients of SOTs between 1987 and 1996 [4]. PJP prophylaxis consisted of 1
double-strength SMX/TMP tablet daily for 1 year in lung transplantation recipients. Of all patients, 25 cases of PJP were identified (4.8 cases per 1000 person-transplant-years [PTY]). Ten of these cases occurred after the first transplanted year, and no cases developed while on PJP prophylaxis. The overall risk of PJP was the highest in lung transplantation (22 cases per 1000 PTY). Risk of PJP within the first year after lung transplantation was 26 cases per 1000 PTY, and subsequently 19.6 cases per 1000 PTY, which indicates that the risk of PJP after lung transplantation does not decline over time. This is a critical point as it supports the practice of life-long PJP prophylaxis after lung transplantation as employed by many centers.

Second, the study published by Wang and colleagues from the Vancouver British Columbia group describes their experience in 1241 recipients of SOTs between 2001 and 2011 [2]. PJP prophylaxis was not defined but was continued for 1 year in lung transplantation recipients. Of all patients, 14 cases of PJP were identified; 7 of which were lung or heart-lung transplant recipients. No cases developed while on PJP prophylaxis. The range of time to diagnosis in lung or heart-lung transplant recipients was 645-1583 days. Here, again, is further substantiating evidence for the unabating PJP risk over time in lung transplant recipients.

Third, and the study that speaks most relevantly to the optimal SMX/TMP regimen, is the meta-analysis (MA) published by Ioannidis and colleagues [6]. This MA included 35 trials and 6583 patients, mostly with human immunodeficiency virus. Irrespective of dosing regimen, SMX/TMP was near universally effective for PJP prevention in patients who did not experience treatment-limiting toxicities. SMX/TMP prophylaxis was clearly more effective than any other regimen (TMP/SMX vs. aerosolized pentamidine [AP]: OR 0.58, 95% CI 0.45-0.75; TMP/SMX vs. dapsone: OR 0.61, 95% CI 0.34-1.1). Toxicities of SMX/TMP were dose-related, and the risk of discontinuation due to adverse effects declined 43% when 1 double-strength tablet was given thrice weekly vs. daily. Moreover, there was a counterintuitive trend towards more PJP cases with higher doses of SMX/TMP (5.9 vs. 1.8 per 100 patient-years) which could be due to suboptimal adherence or discontinuation due to toxicities. Indeed, the discontinuation rate of any oral PJP prophylaxis regimen was higher when compared to AP (OR 5.38, 95% CI 3.69-7.83).

The Conclusion...

Much of these data suffer from three glaring and inalienable limitations: retrospective designs, study location (endemic vs. non endemic areas), and lack of sufficiently large case groups [1-6]. It becomes increasingly difficult to draw meaningful conclusions from these data given these; however, three overarching maxims relevant to PJP prophylaxis lung transplant recipients do emerge: First: life-long prophylaxis should be considered the standard-of-care, Second: SMX/TMP
is better than all other agents, and Finally: lower doses of SMX/TMP are reasonably effective with less risk of toxicity when compared to higher doses. At present, each individual center should continually evaluate their local risk-patterns in the context of these data. Consequently, the PJP prophylaxis regimen will, in all likelihood, remain variable across the field.

Table: PJP prophylactic agents [1-8]

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<th>Agent</th>
<th>Dosing</th>
<th>Toxicity</th>
<th>Mechanistic Targets</th>
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<tr>
<td><strong>First line</strong></td>
<td>Sulfamethoxazole/ trimethoprim (Bactrim, Septra)</td>
<td>1 SS tab PO daily</td>
<td>++</td>
<td>Dihydrofolate reductase and dihydropteroate synthase</td>
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<td></td>
<td></td>
<td>1 DS tab PO daily</td>
<td>+++</td>
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<td>1 SS/DS tab PO thrice weekly</td>
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<td>1 SS/DS tab twice weekly</td>
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<td><strong>Second line</strong></td>
<td>Dapsone (Aczone)</td>
<td>100 mg PO daily</td>
<td>++</td>
<td>Dihydropteroate synthase</td>
</tr>
<tr>
<td><strong>Third line</strong></td>
<td>Aerosolized pentamidine (Pentam)</td>
<td>300 mg monthly</td>
<td>+</td>
<td>Thymidyate synthase and nucleic acid binding</td>
</tr>
</tbody>
</table>

SS, single strength. DS, double strength.

Disclosure statement: The author has no conflicts of interest to disclose.

References:

What's New in the Pathology Council?

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This has been a productive year for the Pathology Council, with our attention focused primarily on solidifying our work in cardiac AMR over the past few years and expanding efforts to define and understand AMR in lung allografts. Here are a few highlights, forthcoming papers, and symposia from the Pathology Council as 2013 wraps up:

2013 Working Formulation for Cardiac AMR - "Standardization of Nomenclature"

The December issue of JHLT, now available online, features the latest ISHLT Consensus document regarding the pathologic diagnosis of AMR in Cardiac allografts. This document builds on the latest revisions published in 2011. While the primary tenets established in the 2010 consensus conference have not changed, this new paper fills in some of the gaps, clarifies some contradictions, and provides tables and lavish color illustrations addressing salient features in the new working formulation classification scheme in an atlas-like fashion. We hope this will serve as the definitive reference for the ISHLT cardiac AMR working formulation for many years to come.

2014 Annual Meeting Scientific Sessions

Please join us in San Diego at any of these pathology-oriented sessions:

The Many Faces of Chronic Lung Allograft Dysfunction: exploring the clinical, radiologic and pathologic aspects of obstructive and restrictive pulmonary allograft disorders.

Exploring Interactions between Cellular and Humoral Immunity in Cardiac Allograft Rejection: AMR and cellular rejection are not mutually exclusive. When they occur simultaneously, how should the patient be treated? Which is a greater short term and long term threat to the graft? Can one trigger the other? These questions and others will be the focus of this session, incorporating immunologic, histopathologic and clinical aspects of mixed rejection.

Approach to the Highly Sensitized Patient Awaiting Heart Transplantation: examining the diagnostic and therapeutic strategies for presensitized patients. The new 2013 Working Formulation document for Cardiac AMR will feature prominently.

For more details about these and other symposia, visit IN THE SPOTLIGHT: ISHLT 2014 in Sunsational San Diego!

Disclosure statement: The author has no conflicts of interest to disclose.
The AECVP Cardiac Transplant Pathology Network


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A Cardiac Transplant Pathology Working Group was established under the auspices of the AECVP in 2008 by Margaret Burke and Annalisa Angelini, and was given Steering Committee status in 2012 with the addition of Ornella Leone and Claire Toquet as members.

Our aims are to create a European network of pathologists to discuss current and evolving practice in cardiac transplant pathology; to promote quality control studies in both diagnostic and technical fields; to undertake multi-centre studies on cardiac transplant pathology; and to establish working relationships with sister societies involved in cardiac transplantation. We also seek to establish a referral network for postgraduate educational purposes, especially for pathologists new to this area of practice, and to establish links between cardiac transplant pathologists and transplant cardiologists, immunologists, surgeons and researchers. To date, over 50 pathologists in 17 European countries have registered as Network members.

You are welcome to check out our recently updated Cardiac Transplant Pathology web page on the AECVP website. We have carried out a number of multi-centre projects, including a reproducibility study of the 2005 Working Formulation for cardiac allograft rejection [1], and a survey on technical aspects of C4d immunostaining and its interpretation in the diagnosis of cardiac antibody-mediated rejection (AMR) [2]. Other collaborative projects such as a study of intravascular mononuclear cells in AMR [3] and a survey of autopsy practice in cardiac transplantation are underway. Our website now contains helpful information on diagnostic criteria and laboratory practice in AMR. All European transplant pathologists are welcome to join, whether or not they are members of the AECVP. A membership form can be accessed on the website.
Our work also informed the 2013 ISHLT Working Formulation for pathologic diagnosis of cardiac AMR published in the December 2013 issue of the *Journal for Heart and Lung Transplantation* [4]. The paper is the result of 5 years of trans-Atlantic collaboration by Pathology Council members, led by Gerry Berry (Stanford, CA) with Margaret Burke and Annalisa Angelini.

Many of us are also members of the North America-based Society for Cardiovascular Pathology (SCVP) and the AECVP Cardiac Transplant Pathology Network. The last 5 years has also seen fruitful collaboration between these two groups several other projects relating to both cardiac and transplant pathology. One is a consensus paper on interpretation of the endomyocardial biopsy in cardiac and transplant pathology [5]. Another is an image-rich web-based tutorial on assessment of endomyocardial biopsies for acute cellular rejection, led by Marc Halushka (Baltimore, MD) of the SCVP and hosted on its website. A tutorial on cardiac antibody-mediated rejection, led by Dylan Miller (Salt Lake City, UT) will follow now that the Working Formulation has been published.

We hope that these ventures will provide opportunities for all ISHLT members to learn about the pathology of cardiac disorders and transplantation as well as stimulate opportunities for collaborative research.

**Disclosure statement:** The authors have no conflicts of interest to report.

**References:**

AHA 2013: Highlights of Interest to ISHLT Members

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The 2013 Scientific Sessions of the American Heart Association were held in Dallas, TX from November 16-20, 2013. The sheer size of the meeting makes it impossible to discuss all abstracts of importance for ISHLT members. Below are a few of the highlights from another great meeting.

Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) Trial
This multicenter, double-blind, placebo-controlled trial studied 360 hospitalized patients with acute heart failure and renal dysfunction randomizing these patients, compared to placebo, in a 1:1 allocation ratio the addition of low dose dopamine (2mcg/kg/min) or low-dose nesiritide (0.005 mcg/kg/min) to diuretic therapy and whether decongestion is enhanced and renal function is preserved. Within each strategy, there was a 2:1 ratio to active treatment or placebo. Coprimary endpoints included 72-hour cumulative urine volume (decongestion endpoint) and change in serum cystatin C to 72 hours (renal function endpoint). Ultimately neither strategy enhanced decongestion or improved renal function when added to diuretic therapy.

Mitral-Valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation
This study randomized 251 patients with severe ischemic mitral regurgitation to undergo mitral-valve repair or chordal-sparing replacement in order to evaluate efficacy and safety. The primary endpoint was left ventricular end-systolic volume index at 12 months. There was no significant difference in left ventricular reverse remodeling or survival at 12 months between either strategies. The rate of moderate or severe recurrence of mitral regurgitation at 12 months was higher in the
repair group than in the replacement group suggesting a more durable correction of mitral regurgitation with replacement. However, there was no significant between groups in outcomes. NEJM; DOI: 10.1056/NEJMo1312808

Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)
In this randomized placebo controlled trial, patients with heart failure with preserved ejection fraction were randomized to spironolactone (titrated up to 45mg). Primary endpoint was time to first event mortality, aborted cardiac arrest or heart failure hospitalization. There was no significant difference in heart failure hospitalization, all-cause hospitalization or all-cause death. Compared with placebo the spironolactone group exhibited more hyperkalemia and were 50% more likely to experience doubling of creatinine above the upper limit of normal. This study failed to demonstrate a benefit in heart failure with preserved ejection fraction patients.

Diastolic Pulmonary Artery Pressure to Pulmonary Capillary Wedge Pressure Gradient (DPG) in over 5700 Patients with an Elevated Transpulmonary Gradient does Not Predict Survival after Cardiac Transplantation – Abstract 7084
(Tedford RJ, Beaty CA, Shah AS, et al.)
Using the United Network for Organ Sharing (UNOS) database, Tedford and colleagues from Johns Hopkins University studied the ability of the pre-transplant diastolic pulmonary gradient (diastolic pulmonary artery pressure minus pulmonary capillary wedge pressure) to predict survival after cardiac transplantation. All patients with pulmonary hypertension and an elevated transpulmonary gradient (n=5777) were included in the analysis. The results show no difference in survival between high (defined as >3, >5, >7, or >10mmHg) and low DPG groups (≤ 3, ≤5, ≤7, or ≤10mmHg), p = 0.94, 0.76, 0.29, 0.66, respectively. DPG did also not predict survival in those with pulmonary hypertension and an elevated pulmonary vascular resistance (PVR). The authors urge caution before DPG is incorporated into pre-transplant or pulmonary hypertension-related clinical decision making.

High Pre-Operative Right Atrial Pressure to Pulmonary Capillary Wedge Ratio is Not Associated with Right Ventricular Dysfunction After LVAD Implantation – Abstract 7086
(Cogswell RJ, Masri, SC)
Studying the pre- and post-LVAD hemodynamics of 69 patients, Cogswell and colleagues from the University of Minnesota found that an elevated right atrial pressure (RAP) to pulmonary capillary wedge pressure (PCWP) ratio did not predict right ventricular dysfunction after implantation. In fact, the tertile with the highest pre-LVAD RAP:PCWP ratios showed the greatest decline in RAP after LVAD implantation (p<0.0001). Overall, there was no difference in cardiac index, RAP, or PCWP in the three tertiles post-LVAD. This study suggests that an elevated RAP:PCWP ratio should not alone preclude LVAD implantation.

Incidence and Outcomes Related to Pre-Transplant Anti-Vimentin Antibodies in the Cardiac Transplantation Population – Abstract 5126
(Young R, Dale B, Tedford R, et. al.)
Young and colleagues from Johns Hopkins University analyzed 50 adult and pediatric patients who underwent de novo cardiac transplant for the presence of pre-transplant anti-vimentin antibodies (AVA). The incidence of AVA in pre-transplant samples was found to be high (34%). Pre-transplant AVA positivity did not predict rejection in the 1st year post-transplant, including time to first episode (31 vs. 13 days p=0.41) compared to AVA negative patients. There was no difference in rejection-free graft survival (53 vs. 52%, p=0.85), graft survival at 1 year (82 vs. 88%, p=0.56) or graft survival at a median follow up of 23 and 26 months (76 vs. 85%, p=0.41). The significance of pre-transplant AVA on outcomes should be validated in a larger cohort and with longer duration of follow-up.

**Comparison of Difference Strategies of LVAD implantation for Bridging Patients to Heart Transplantation: An Analysis of the United Network for Organ Sharing – Abstract 5125**  
(Schulze PC, Kato ST, Mancini DM, et al)

Schulze and colleagues from Columbia University Medical Center utilized the UNOS database to study the impact of early versus late left ventricular assist device (LVAD) support on likelihood of successful heart transplant and post-transplantation outcomes. Patients (n=14,198) were classified into three groups: patients listed UNOS status 1A and 1B medically treated from the time of listing until heart transplantation (Group M), patients medically treated at listing but requiring LVAD implantation while listed (Group M-to-V), and patients on LVAD support at the time of listing for heart transplant (Group V). Patients on medical therapy had the highest waitlist mortality. Group M-to-V had similar waitlist mortality compared to Group V. Among the 1A status candidates Group M-to-V showed the highest likelihood of heart transplant (OR: 3.59 95% CI: 1.073-11.993; p=0.038). Post-transplant 1-year survival was worse in Group V compared to Group M (89.4% vs. 91.1% p=0.036). LVAD support at the time or during listing as a bridge to transplant was associated with lower waitlist mortality. The authors conclude that LVAD implantation in response to clinical deterioration during heart transplant listing is safe and not associated with increased mortality compared to patients with prior LVAD placement.

**Echocardiographic Normalization in Children With Idiopathic Dilated Cardiomyopathy: Results From the Pediatric Cardiomyopathy Registry – Abstract 9783**  
(Everitt MD, Sleeper LA, Lu M, et al)

Everitt and colleagues analyzed the Pediatric Cardiomyopathy Registry (PCMR) database for the incidence and predictors of echocardiographic normalization of ventricular size and systolic function in children with idiopathic dilated cardiomyopathy (IDCM). The study cohort consisted of 773 children from 98 pediatric cardiac centers in the United States and Canada. Echo normalization occurred in 25% by 2 years, at a median of 9.4 months. About half (51%) of the cohort died or received a heart transplant by 2 years. Younger age (RR=0.9, 95% CI=0.86-0.94, p<0.001) and lower LVEDD z-score (RR=0.74, 95% CI=0.66-0.82, p<0.001) were independent predictors for normalization. Interestingly, 9 patients who had echo normalization within 2 years of diagnosis later went on to either die or undergo heart transplantation, suggesting that continued follow-up is needed in these children even after echo normalization.

**Outpatient Milrinone Therapy as a Bridge to Pediatric Heart Transplantation: A Large Single Center Experience – Abstract 18457**
Auerbach and colleagues from Children’s Hospital Colorado presented a retrospective review of all their pediatric patients that have received outpatient milrinone between February 2000 and June 2013. A total of 53 patients were on milrinone as an outpatient as a bridge to heart transplantation. The median age was 9.7 years [IQR=2-16] and included infants with single ventricle physiology after failed stage 1 palliative surgery. The cardiac diagnoses included graft failure (n=17), dilated cardiomyopathy (n=16), congenital heart disease (n=15), and restrictive cardiomyopathy (n=5). The mean dose of milrinone was 0.5+0.02 mcg/kg/min. There were few complications and all patients survived to transplantation, with a median duration of milrinone infusion of 28 days (IQR=2-16). This study supports the use of home milrinone therapy as a bridge to transplant, even in our youngest patients.

Use of Sirolimus in Pediatric Heart Transplant Patients: A Multi-Institutional Study From the Pediatric Heart Transplant Study Group – Abstract 11572

Rossano and his colleagues analyzed the Pediatric Heart Transplant Study (PHTS) registry for the use of sirolimus in pediatric heart transplant recipients. There were 2,085 patients from 46 pediatric heart transplant centers in the United States, Canada and England who underwent transplant between 2004 and 2010. Overall, 18% of patients were on sirolimus at some point (8% at 30 days post-transplant, 10% at 1 year, and 16% at 5 years). The use of sirolimus has increased over time, from 13% in 2005 to 17% in 2011 (p=0.02). Some factors associated with sirolimus use at 1 year included renal insufficiency and a history of rejection (p<0.05). Sirolimus treated patients had similar overall survival, 1-year conditional survival, and 5-year conditional survival in propensity matched analysis. Sirolimus use by 30 days post-transplant was associated with a decreased freedom from rejection (p=0.02) and infection (p=0.02), suggesting that early use of sirolimus may be associated with an increased risk of rejections and infections.

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The Magical, Mystical and Mythical Music of Mozart: The Mere Mortal

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It’s December, it’s the time for merriment and celebration and for the third time in three years the ISHLT Links gives you another treatise a selected composer of Great Music and his influence on the World and the ISHLT. We began with Dvorak, the pride of Prague in the (ISHLT Links 2011, Volume 3, Issue 7) who gave America its own Classical music. Last year, we gave you the intense, passionate, individualistic and fearless self-expression of Beethoven (ISHLT Links 2012, Volume 4, Issue 8) whose alcoholic father tried to futilely beat him into being a child prodigy to rival Mozart. We need no reminder that there is only one Mozart. Johannes Christian Wolfgang Gottlieb Mozart, the most comprehensively gifted musician who has ever lived, was born January 27, 1756. A child prodigy, who began to play the harpsichord by the age of three, completed his first musical compositions by age five. During his obscenely abbreviated life, Mozart composed enough musical master works, suffered many illnesses, traveled many miles, and experienced enough psychological stress for many full lifetimes, let alone one brief existence of 35 years. Although, there have been other prodigies, none has approached Mozart’s ability to combine the elegant and dazzling musical imagination with a total mastery of style and form with matchless beauty, clarity and expression. The great 19th century German music critic and composer, Robert Schumann appropriately asked, “Does it not seem as if Mozart’s works become fresher and fresher the oftener we hear them?”

For example:

- Eine Kleine Nachtmusik, K. 525
- Rondo in A Minor for Piano, K. 511
- Symphony No. 40 K in G minor, K. 550
- Piano Concerto No. 21 in C Major, K. 467
- Piano Sonata in A Minor, K. 310
- Clarinet Concerto in A Major, K. 622
- Opera, The Marriage of Figaro, K 492
- Opera, Don Giovanni, K 527
- Opera, The Magic Flute, K 620
- Requiem in D minor, K 626

Need I provide more? How about letting “The Great Dane” or “The Clown Prince of Denmark” share his dream on Mozart. “In my dreams of Heaven, I always see the great Masters gathered in a huge hall where they all reside. Only Mozart has his own suite.”
Mozart’s mysticism and magic stem from his inexplicable and extraordinary ability to write more than 600 pieces. Nearly every year, he wrote more music than the Beatles recorded in their entire career composing 21 piano sonatas, 27 piano concertos, 26 string quartets, 41 symphonies, 18 masses, 13 operas, 9 oratorios and cantata, 2 ballets, 40 plus concertos for various instruments, trios and quintets, violin and piano duets piano quartets, and the songs. Also, he could sight read anything written, remember the most complex music after a single hearing and write it down. Above all, he was not mystical. His biographers deified him long after he died. Mozart referred to himself as Amade, never Amadeus which was adopted after his death by other writers. The name Amadeus implies a God-like deity derived from his third name, Theophilus or Gottlieb, “loved of God.”

He was a talented performer, composer, and genius, but most of all he was a mere mortal. His music was not popular during his time and like other great artists he had his enemies. His music was criticized as being too rich in ideas, too “artful” and too complex. His compositions did not arise from divine inspiration, but came from an intelligent and hard-working man with monstrous talent. This talented man was the product of a domineering father, Leopold Mozart, who was also Wolfgang’s teacher, booking agent, publicist and tormentor throughout his life. Most of all, he was his creator not unlike Dr Frankenstein. The small, frail and desperate-to-please young Mozart became his family’s main breadwinner. The Mozart family toured Vienna and all of Europe as a traveling musical circus in the 1760s. Mozart was showered with expensive gifts and became the pet of royalty with his prodigious performances. His musical training came from his father and the leading composers of the European musical scene, most notably, Johann Christian Bach, whom he met while in London in 1764. Mozart did serve an apprenticeship, not unlike other composers, however Wolfgang began his apprenticeship at a very young age and by age 20 he was a seasoned composer, an age when other composers are just starting their apprenticeships.

Over Leopold’s objections, Mozart married Constanze Weber in August 1782. From 1782 – 1786, he reached the peak of his career as a pianist and composer with Constanze in Vienna. His income depended on commissions by wealthy aristocrats which he needed because he spent money as fast as he made it (why not, he was in his mid-twenties). Nevertheless, he worked very hard to earn a great deal of money to support himself and Constanze who were theatergoers with a rich and busy social life with many affluent friends. At the same time he had very little respect for rank and position with deep skepticism of enlightened despots and of all authority, and unlike Beethoven, Mozart was not fooled by Napoleon or other tyrants because he knew these men personally. His disrespect for authority through The Marriage of Figaro and its critical portrayal of the ruling class among other works offended many members of the Viennese aristocracy, who had been Mozart’s primary source of income. Through the opera’s critical portrayal of the ruling class, Mozart was biting the hand that fed him. While he was falling from grace in Vienna, Prague opening it arms to him. The new opera for 1787, Don Giovanni, was commissioned for premiere in Prague. According to legend, Mozart composed the overture the night before the final dress rehearsal. Don Giovanni was a bigger success than The Marriage of Figaro. Unfortunately, Mozart wanted to return to Vienna, he would have enjoyed a very successful and profitable career had he made Prague his home.
Between 1788 and 1791, Austria became engaged in a costly and unpopular war with the Ottoman Turks. The war resulted in drastic cancellations of concerts and opera performances in Vienna. Wolfgang and Constanze’s extravagant lifestyle and loss of income put them into debt. They had fallen ill and lost their baby daughter. By late 1790, near destitute and in poor health with deepening depression, Mozart had a compositional renaissance culminating in the opera, *The Magic Flute*. In 1791, he was commissioned to write a Requiem Mass which was unfinished at the time of his death on December 5, 1791. Of course there was a great deal of speculation as the cause of his death. The most famous myth was that he was poisoned by the Italian composer Antonio Salieri. Another theory claims he died as the result of a Jewish-Roman, Catholic-Masonic conspiracy. Other speculations include mercury and arsenic poisonings, milletary or military fever, or a chronic subdural hematoma. All of these theories more than likely contributed to the riches gained by his wife and surviving children. He most likely died from rheumatic fever and shock induced by massive bloodletting.

Mozart was buried in a common unmarked grave without a ceremony and its exact location was lost. Fortunately for us, his music was not lost.  

In memoriam we have:  

Gioacchino Rossini, the great master of Italian opera, lived in awe of Mozart. He said, “The Germans have always been the greatest harmonists, and the Italians the greatest melodists. But from the moment the North produced Mozart, we of the South were beaten on our own turf, because this man rises above all nations, containing in himself the charm of Italian melody and the profundity of German harmony. He is the only composer who had as much knowledge as genius, and as much genius as knowledge.” Rossini also exclaimed, “Beethoven I take twice a week, Haydn four times, and Mozart every day!”

"The sonatas of Mozart are unique: too easy for children, too difficult for adults. Children are given Mozart to play because of the quantity of notes; grown-ups avoid him because of the quality of notes." – Artur Schnabel

“Mozart encompasses the entire domain of musical creation, but I've got only the keyboard in my poor head.” – Frederic Chopin

Disclosure statement: the author has no conflicts of interest to report.
Death Of Para Given A Faulty Heart Prompts 'Marginal Organs' Concern

With an Introduction by John Dark

"We will put you on the list for a transplant, give you a new heart;" typical words to a newly listed potential recipient. It's the same for any organ transplant. We talk about these "new organs" as if the analogy is the 2013 model, just rolling out of the showroom, no miles on the clock, free servicing and a 7 year warranty on the bodywork.

The reality is very different; these organs are all used, all have some imperfections, perhaps worse after brain death. For the heart, the donor may have hypertension, LVH, maybe smoked (and not just tobacco). Some of these risks can be quantified, but some are entirely unpredictable, as the blocked LAD in a donor below anyone's age cut-off for an angio.

We are making big steps, certainly in the UK, in formally explaining the donor related risks. The whole transplant thing is a gamble, and the majority of our patients realize this. On our donor risk consent form, most tick the "I-will-take-any-organ-the-team-thinks-is-good-enough-for-me" box, implying that most still trust that same team. Only when that goes wrong, do we find ourselves facing the media; time to roll out your most eminent surgeon... Link to Article
ISHLT 2014 QUICK LINKS:

- Annual Meeting website
- Academy website
- Online Registration
- 2014 Preliminary Program (PDF)

NEWS AND ANNOUNCEMENTS:

ISHLT Grants and Awards Applications Now Online - APPLY TODAY!
The 2014 ISHLT Grants and Awards applications are now available online at www.ishlt.org/awards. Deadline for receipt of applications is Wednesday, January 15, 2014. Grants will be awarded at the ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California. Also, view a Special Invitation for JFTC members.

IMACS Registry Meeting — SAVE THE DATE!
Thursday, April 10, 2014, 7:15-8:30 PM (PST)
The IMACS Registry Meeting will take place at the Manchester Grand Hyatt Hotel in GASLAMP A-C Room. All are invited to attend! Thank you in advance for your participation and we look forward to seeing you!! RSVP: Please confirm your attendance by emailing Sharmene Smith at IMACS@uab.edu.

WORD OF THE MONTH:
"Triturate"

trɪtʃərɑːt – To pulverize or to crush, grind, pound or rub into fine particles or a powder;

Synonyms include comminute, granulate, levigate, masticate and pulverize

To pulverize and to triturate are essentially interchangeable and suggest reducing something to fine particles or powder. Pulverize comes from Latin pulvis, dust and by derivation suggests reducing something to dust. Triturate comes from Latin meaning to thresh grain or tread out corn. By derivation it suggests the violent beating, pounding, crushing, rubbing or grinding action. The corresponding noun is trituration. In medicine and pharmacy a mortar and pestle are important tools to triturate herbs and pills.
Outta This World Links
Interesting, Inspiring and Intriguing Links from Around the Globe

FROM CANADA:

# 45 - World's First Successful Single Lung Transplant
YouTube, 4 Nov, 2013

Early in the morning of Nov. 7, 1983, a team of Toronto General Hospital surgeons began a surgery that would make medical history. It was an experimental human procedure — a single lung transplant. The patient was Tom Hall, the 45th patient worldwide to undergo the risky procedure — risky because none of the previous 44 attempts had been successful. This is the story of a world first ... the story of a courageous patient and medical staff, and, how the legacy of their achievement lives on today at UHN's world leading Toronto Lung Transplant Program, led by Dr. Shaf Keshavjee, who is also Surgeon-in-Chief at UHN's Sprott Department of Surgery.

Watch video →

Inspiring Lung Transplant Recipient to Host Boot Camp
ChrisD.ca, 31 Oct, 2013

The unofficial face of organ donation in Canada is travelling to Winnipeg next week to inform the community on the importance of donating an organ. You may have seen Helene Campbell on the "Ellen DeGeneres Show." The 21-year-old received a double lung transplant last year and has attracted some high-power endorsements for her outreach efforts, including from Justin Bieber. She's even been a recipient of the Queen Elizabeth II Diamond Jubilee Medal in recognition of her work.

Read full article →

New Legislation allows Albertans to consent to donate their organs when they renew their drivers' licences
EdmontonSun.com, 8 Nov, 2013

New legislation Friday means Albertans can now easily consent to donate their organs upon death when they renew their drivers' licences. They will also be able add their name to an online consent-to-donate registry. When Karen Korchinski was diagnosed with Budd-Chiari syndrome in 2011, her greatest fear wasn't surviving the blood clot lodged in the hepatic vein of her liver—it was surviving the liver transplant waiting list. "To have the cure (a transplant) be inaccessible because there weren't enough organs in our health system just made me frustrated and sad," said the 46-year-old Edmonton mother of two.

Read full article →

FROM CHINA:

No Quick Fixes for China's Overwhelmed Organ Transplant System
The New York Times, 10 Nov, 2013

Suffering from bile duct cancer and with no family to support him and little money for treatment, Xu Bao, 35, vowed that if he suffered an early death he would give something back to society. He decided that he would donate his corneas to fellow Chinese waiting for transplants. It was a remarkable gesture in a country where organ donations are rare, and executed prisoners have been the main source of transplant organs. Local news media in Hefei, the city where Mr. Xu was
being treated, gathered at his hospital bedside in April to report as he signed documents declaring his intentions. Read full article →

FROM UNITED KINGDOM:

Importance of organ donation hits home at volleyball contest
ChronicleLive.co.uk, 11 Nov, 2013

A battle on the volleyball court was nothing for these players who have had to battle for their lives. Transplant patients descended on Tyneside for a tournament hosted by the Freeman Heart and Lung Transplant Association (FHLTA) and Transplant Sport UK, which aims to highlight the importance of organ donation. Most of those taking part—who had travelled from all corners of the country—were close to death before they received their transplants but they are all fighting fit today thanks to those who have signed up to the organ register. Gateshead Leisure Centre welcomed teams from Addenbrookes in Cambridge, Wythenshawe Hospital in Manchester, Royal Berkshire Hospital in Reading and Newcastle's Freeman Hospital. Read full article →

FROM UNITED STATES:

Riggs to speak for Red Cross
MtairyNews.com, 3 Nov, 2013

The Cana youth who just a few short months ago was awaiting a heart transplant will become something of a celebrity next month. Samantha Riggs, 10, received a heart transplant in April, and after months awaiting the heart, Riggs will be featured in hundreds of television commercials, her mother said Friday. It all began last December. "It was very sudden," mother Randi Riggs, a nurse, said. "She became short of breath, and I realized her heart was beating really fast so I took her to the emergency room." There doctors discovered that Riggs' heart was enlarged. Read full article →

SDSU receives $8.5M for heart research
Phys.org, 6 Nov, 2013

The National Institutes of Health has awarded a prestigious Program Project Grant totaling more than $8.5 million over five-years to San Diego State University to better understand how the heart heals and ways stem cells can help the heart repair itself. "Regenerative medicine using stem cells has changed the way researchers and clinicians are thinking about and trying to treat heart failure," said Mark Sussman, Ph.D., a distinguished professor of biology at SDSU. Read full article →
Tattling Links
ISHLT Members in the News

FROM AUSTRALIA:

Peter MacDonald, MD, PhD
St. Vincent's Hospital
Sydney

Advancements made in treatment for heart disease

Organ-donation rates have increased dramatically over the past few years but there simply aren't enough to meet a growing demand. For every 1000 people in this country, only one is a potential donor and only 30 per cent of that one per cent will become a successful donor.

But new technology looks set to change these odds. Cardiologist Peter Macdonald has created a way to reduce that damage once the heart is removed from the donor by keeping it working while waiting to be transplanted. "The heart just isn't able to withstand the insults that occur during the withdrawal of life support and just isn't usable, Dr MacDonald said. Read full article →

Allan Glanville, MBBS, MD, FRACP
St. Vincent's Hospital
Sydney

Australia ranks 21st for organ donation
Herald Sun News, 12 Nov, 2013

Spain is the world leader, and France, the US, UK, Belgium and Norway are among the countries with higher proportions of donors than Australia. The figures compiled by Sharelife Australia draw on international donor data published by the Council of Europe. The data shows hundreds of Australians are missing out on life-saving transplants every year. This is because a $151 million, four-year package announced by the federal government in 2008 has failed to achieve its goal of establishing Australia as a world leader.

There has been an improvement, says ShareLife spokesperson Sara Irvine, but Australia's progress is slower than many other countries. Australia's rate of organ donation is half that of the leading countries, and 1000 more transplants could be performed a year if it reaches the level of the top five countries. "We are still not in the top 20 nations and have long way to go," says ShareLife director Professor Allan Glanville, medical director of lung transplantation at St Vincent's Hospital in Sydney. "Organ donation saves lives, saves money and improves quality of life. "You only need to talk to people who have been on kidney dialysis to see how well and productive they are after a kidney transplant." Read full article →

FROM CANADA:

Shaf Keshavjee, MD
Toronto General Hospital
Toronto, Ontario
# 45 - World's First Successful Single Lung Transplant
YouTube, 4 Nov, 2013

Early in the morning of Nov. 7, 1983, a team of Toronto General Hospital surgeons began a surgery that would make medical history. It was an experimental human procedure — a single lung transplant. The patient was Tom Hall, the 45th patient worldwide to undergo the risky procedure — risky because none of the previous 44 attempts had been successful. This is the story of a world first ... the story of a courageous patient and medical staff, and, how the legacy of their achievement lives on today at UHN's world leading Toronto Lung Transplant Program, led by Dr. Shaf Keshavjee, who is also Surgeon-in-Chief at UHN's Sprott Department of Surgery.

Watch video →

Lori J West, MD, DPhil
University of Alberta
Edmonton, Alberta

Alberta MLAs approve bill to boost organ donations

Transplant advocates, doctors and patients are hailing the approval of new legislation designed to improve Alberta's abysmal organ donation rates. The Human Tissue and Organ Donation Amendment Act, which will create a new provincial agency to oversee donations, passed third reading in the legislature late Tuesday after receiving support from all parties.

"Alberta has not only failed to move forward with the rest of the world, but we have actually fallen behind," said Dr. Lori West, an Edmonton cardiologist serving as director of the Canadian National Transplant Research Program. "So this is a real step forward to helping hundreds of patients who are waiting on transplant lists." Read full article →

FROM UNITED STATES:

Thomas M. Egan, MD, MSC
University of North Carolina School of Medicine
Chapel Hill, NC, USA

'Lungs don't die when you do': New transplant program might ease shortages
NBC News, 17 Nov, 2013

The pair of lungs sits inside a clear dome, gently inflating as doctors measure how well they'll breathe if implanted into a patient who desperately needs a new set. It's a little-known twist of nature—your lungs can live on for a while after you die. The air left inside keeps them from deteriorating right away as other organs do.

An innovative experiment now aims to use that hour or more window of time to boost lung transplants by allowing donations from people who suddenly collapse and die at home instead of in a hospital.

"There aren't enough lungs. We're burying them," said Dr. Thomas Egan of the University of North Carolina, Chapel Hill, who is leading the project. "It turns out your lungs don't die when you do." Read full article →
Breathing new life
Iowa Now, 22 Nov, 2013

On Thanksgiving Day 2011, the Nacks found hope. It came in an email—from Iowa. For Dennis Nack of Nelson, MN, the previous two decades had not been easy. Since his mid-40s, his health had been in a slow, steady decline. He’d spent nearly 20 years working with industrial chemicals, inhaling noxious fumes daily. He’d also smoked for a number of years before quitting in 2011.

"It was from the University of Iowa," Sharon Nack says. "They asked us to send his medical records." The request for Dennis' medical records was only a requisite first step and not a guarantee, but for Sharon, it was a glimmer of hope. "It was all I had to go on," she says, "and I believe in miracles."

A few weeks later, gathered around the table for Thanksgiving dinner, Sharon asked the Nacks' son-in-law, Bill, to read Beaver's email to the family, which included Dennis' 90-year-old mother. "No one knew what to say at first," Sharon says. "And then one of the kids asked, 'What does this mean, Mom?' I said, 'It means we're going to Iowa.' "It was a ray of light, and we aimed right for it." Read full article →

New Transplant Tech Keeps Lungs Warm, Ready To Work Immediately
CBS Minnesota, 21 Nov, 2013

Last week, a new lung transplant procedure was performed at the University of Minnesota, and for the first time in the Midwest. The new technology keeps the lungs warm and breathing from the time they leave the donor. Common practice has been to keep the organs on ice before transplant. We spoke with the doctor who performed the new procedure, using the Tans Medics Organ Care System. "It's almost like landing on Mars," Dr. Gabriel Loor said.

On Nov. 13, a 50-year-old man received two transplanted lungs. And those organs were never put on ice for the two hours they were outside a human body. The lungs were kept sterile, perfused with blood, and breathing inside the portable machine. "Before this, we relied on ice, so we'd bring a cooler out to a donor hospital, and after the procurement, we would place the lungs on ice," Loor said. Read full article →

Mechanical hearts hold death at bay for patients on transplant list
The Chicago Tribune, 4 Nov 2013

There were 5,500 machines, known as left ventricular assist devices, implanted worldwide last year, said Doug Godshall, chief executive officer of Framingham, Mass.-based Heartware. The benefits of the pump are clear, said John Stulak, a cardiovascular surgeon at the Mayo Clinic in Rochester, Minn., who studies and implants the devices. Every trial comparing them with the best drug therapy, often the only treatment available, shows they lengthen and improve lives, he said.

"As we are learning more about LVADs, and we’re getting more experience and people are living longer, we are starting to see it's not completely a walk in the park," said Randy Starling, head of heart failure and cardiac transplant medicine at the Cleveland Clinic in Ohio. "We are starting to see some of the other potential complications," including bleeding in the stomach, infections and erratic heart rates. Read full article →

Michael Hess, MD
Virginia Commonwealth University Medical Center
Richmond, VA, USA

Nelson A Burton, MD
Cardiac Vascular Thoracic Surgical Associates
Falls Church, VA, USA

Devices have changed heart transplants
Milwaukee Wisconsin Journal Sentinel, 11 Nov 2013

As many as 500,000 people suffer heart failure in the United States each year. Yet the number of hearts available for transplant plateaued at around 2,500 in 1995. Medicine is getting better at transplanting hearts and the need for them is growing larger, but the number of organs available is static. So devices are filling some of that gap. "The whole field is being dominated today and tomorrow by LVAD and artificial hearts, and is becoming a problem of engineering, miniaturization and, believe it or not, batteries," says cardiologist Michael Hess, who directs the Pauley Heart Center's heart transplantation program—one of the world’s oldest—at the Medical College of Virginia in Richmond. "The next big breakthrough is going to come out of engineering schools such as MIT and not medicine."

"Mechanical circulatory support has been a real game-changer," says Nelson Burton, chief of heart and lung surgery at Inova Fairfax. He says he implants twice as many LVADs as hearts these days, and "I'm sure that ratio will increase as the technology improves. We'll be putting in more and more of them." Read full article →

Frank Smart, MD
LSU School of Medicine
New Orleans, LA, USA

Frank Smart, MD: Bringing engineering know-how to HF care
healio.com, Nov 2013

Frank Smart, MD, always had a fascination with technology, so cardiology—and mechanical circulatory support systems for HF patients, in particular—was a natural focus when he decided to switch his course of study from engineering to medicine.
A prominent transplant cardiologist, he has been a lead researcher on studies of immunosuppression in transplantation and in transplant CAD. He has advised many medical device companies on how to support device design. His passion for engineering and building systems extends to his free time as well, in the form of refurbishing cars and welding.

What else sparks his interest? Mark Twain, Abe Lincoln and Clancy's restaurant in New Orleans—all subjects near and dear to the heart of our Links editor! Read full article →

**Alfred Asante-Korang, MD**  
**Pediatric Cardiology Associates**  
**St. Petersburg, FL, USA**

**Young heart transplant patient faces rejection with a smile**  
**ABC Action News, 4 Nov 2013**

Ask 9-year-old Jayden Langan why he's in the hospital, and he doesn't really know, but his father does. Will Langan is Jayden's father. "It scared me to death. It's, I mean, since he had his heart transplant we knew at any time he could go into rejection."

But the fact is, heart transplant surgery is still relatively new and no one knows how long these unique kids will survive. So when Jayden came in Friday in stage 3 rejection, his parents feared it was life threatening. Dr. Alfred Asante-Korang is the Medical Director of the Heart Transplant Program at All Children's Hospital. "If the heart function is severely affected, then it can be life threatening." Read full article →

**Mariell Jessup, MD**  
**University of Pennsylvania**  
**Philadelphia, PA, USA**

**Derek Fitzgerald: Cancer, Heart Transplant, IRONMAN**  
**phillymag.com, 6 Nov, 2013**

In 2003, Fitzgerald was your typical 30-year-old, focused more on his career than his health. His perspective quickly changed when doctors found a large, grapefruit-sized tumor in his stomach and, after removing it surgically, diagnosed him with non-Hodgkin's lymphoma. Fitzgerald immediately underwent several rounds of chemotherapy. The treatment destroyed the cancer and Derek was given a second chance at life. However, the treatment had also destroyed his heart.

In his many trips to the ER for shortness of breath and suspected pneumonia, Fitzgerald learned that he had dilated cardiomyopathy and heart failure. His ejection fraction—the levels at which the heart pumps oxygenated blood through your body—was at 18 percent. The ejection fraction for the average healthy person is between 55 and 70 percent, according to the American Heart Association.

After completing the compatibility process for the heart transplant, Dr. Jessup met with Fitzgerald and explained that the healthy organs surrounding his damaged heart were compensating well now, but that would soon change. He recalls her explaining that when that happened it would be like falling off a cliff. "But don't worry," she added. "When that happens, we'll be there to catch you." Read full article →
**Joseph M Pilewski, MD**  
*University of Pittsburgh Medical Center*  
*Pittsburgh, PA, USA*

**Double lung transplant gives cystic fibrosis patient second chance at life**  
*AltoonaMirror.com, 10 Nov, 2013*

Proud parents watch as 4-year-old Gavin carefully writes first his name on lined paper in marker, and then his dad's name, Jeremy, and finally, his mom's name, Joy. Such simple things for a family of three, except for this Altoona family, nothing is taken for granted anymore. Jeremy Weyandt, Gavin's father, almost lost everything when Jeremy came as close to death as anyone could come, his doctor said. Jeremy doesn't remember anything of that harrowing time, he said. "The last thing I remember is the nurse saying I think we need to talk about a transplant," Weyandt said.

"They almost ran out of time," said Dr. Joseph Pilewski, medical director for the UPMC lung transplant program in Pittsburgh. "There's a limit to how long people can be on the ECMO machine and Jeremy had almost reached that limit," he said.  

**Cesar A Keller, MD**  
*Mayo Clinic Transplant Center*  
*Jacksonville, FL, USA*

**Pulmonary rehab: Healing with music**  
*MySunCoast.com (Ivanhoe newswire), 11 Nov, 2013*

Playing a musical instrument can be fun, but for people with lung problems it can also offer a health benefit. Music has always been a huge part of Larry Rawdon's life. "I think it transports people to a different, a better place," Larry Rawdon told Ivanhoe. Larry was a professional cellist for 30 years. More recently, he took up the harmonica. "I love playing the harmonica. It's a great outlet," Larry said. However, for Larry, it's been much more than that. After surviving two lung transplants, he noticed that his passion could also be a form of therapy. "My scores were always substantially elevated after playing the harmonica," Larry said.

Larry told his doctor about what he observed on his lung tests. "I knew I could not just ignore what he was saying because this guy knows what he's talking about," Cesar Keller, MD, Professor of Medicine Medical Director, Lung Transplant Program, Mayo Clinic Florida, told Ivanhoe.

**Dr Ali Nsair, MD**  
*David Geffen School of Medicine at UCLA*  
*Los Angeles, CA, USA*

**UCLA doctors test stem-cell therapy to improve blood flow in angina patients**  
*HealthCanal.com, 13 Nov, 2013*

Marty Greenfield lives with crushing pain every day due to angina, a condition that is caused by an inadequate supply of blood to the heart. He has suffered a heart attack, and a coronary bypass procedure and angioplasty have provided little relief. His doctor referred him to UCLA to be considered for a heart transplant. Dr. Jonathan Tobis, a UCLA clinical professor of cardiology, performed an angiogram and angioplasty on Greenfield, 64, but found that the patient was not a candidate for a heart transplant because his heart muscle function was still good. Instead, Tobis
suggested that Greenfield consider participating in a Phase 3 clinical trial that uses a patient's own blood-derived stem cells to try to restore circulation to the heart.

"We're hoping to offer patients who have no other options a treatment that will alleviate their severe chest pain and improve their quality of life," said Dr. Ali Nsair, an assistant professor in residence of cardiology at the David Geffen School of Medicine at UCLA and the study's co-principal investigator. Read full article →

Michael M. Givertz, MD
Brigham & Women's Hospital
Boston, MA, USA

Tethered to a machine, R.I. man awaits a new heart
Providence Journal, 11 Nov, 2013

To save Steve DiSumma's life, doctors had to remove his heart. The surgery was in July, and since then the 44-year-old husband and father has been connected to a machine that keeps him alive at Brigham and Women's Hospital in Boston. He is waiting for a donor heart. He says he's at the top of the list, but his wait could be as long as eight months.

His doctor, Michael M. Givertz, said some patients can leave the hospital with the device, but DiSumma's condition keeps him tied to Brigham and Women's. Steve was born with transposition of the great arteries, a type of congenital heart defect in which the two main arteries going out of the heart—the pulmonary artery and the aorta—are switched in position. Instead of pumping oxygen-rich blood from his lungs to his body, his heart pumped oxygen-depleted blood from his body back into his body. Oxygen-rich blood, meanwhile, was cycled in and out of his lungs. If he hadn't had holes between the chambers of his heart, he could not have survived, Givertz said. Read full article →
As we continue our journey to improve communication for our patients through the Links, we move from the Hellenistic influence to the language of the Roman Empire. Latin is not dead. Actually, along with Greek, Latin elements are very much alive and quite active in many English words today from speech to writing. Knowledge of Latin unveils the relics of Latin roots, prefixes and suffixes that compose much of English. A valuable resource and a must for all of us is Donald Ayers’ book *English Words from Latin and Greek Elements*. In his book, a careful review of the Latin base or root, “spir-” means “breathe” and its web of words created with different Latin prefixes is just one of many examples that enrich our vocabulary.

In English there is no verb spire, however because of Latin we have aspire, aspirate, conspire, expire, inspire, respi
re, perspire and transpire. With these words, the prefixes give us an idea how these words relate to breathing. The prefix “ad-” means “to” or “toward” and from here we have the word aspire meaning to breathe toward or pant after something which can be interpreted as something we want, when we aspire. From here aspirate and aspiration become obvious. The prefix “con-” means “together with” or “in union” therefore conspire means to breathe together or has a meaning related to uniting for a specific purpose. Today, conspire has evolved with a more negative connotation, should I dare have you think of the word conspiracy.

"Ex-" means “out” therefore expire has us thinking about breathing out until it becomes our last breath. When we breathe air in and out, today we inhale and exhale. We could be inspiring and expiring while breathing, but these meanings have evolved. *Hale*re is another Latin root referring to breathe. But today, from one's last breath expire refers to the end of time periods, such as expiration dates. However, in the pulmonary function lab we do have inspiratory and expiratory limbs of the flow volume loops. “In-” means “into” so the word inspire means to breathe in or breathe spirit or feeling into once we are motivated or inspired to accomplish a task. “Re-” means “back” or “again” and can show how respire refers to the act of breathing in and out again and again. The related verb respi
rate refers to artificial breathing or other kinds of ventilation. “Per-” means “through.” Perspire therefore means to breathe through or it can refer to material passing through pores like sweat or vapor. “Trans-” means “across.” Transpire therefore refers to breathe across. But in the 18th century, Samuel Johnson defined transpire “to escape from secrecy to notice.”

It was also in the 18th century when many people believed that wet clothing and dampness in the air caused the common cold. But our enlightened Benjamin Franklin observed that sailors constantly wore wet clothing and remained healthy. After years of consideration he eventually
concluded: “People often catch cold from one another when shut up together in small closed rooms, coaches, etc. and when sitting near and conversing so as to breathe in each other’s transpiration.” Franklin had determined that the common cold passed across from the infirmed to the healthy through the air before any knowledge of germs or viruses existed.

So, let’s turn our attention to the Latin base “firm-,” which means “strong” or “firm.” In English we have the words firm, affirm, affirmation, affirmative, confirm, confirmation, infirm, infirmity and infirmary. The prefix “ad-” with its meaning defined earlier assimilates to “af-” before the “f” to give us the word affirm meaning a movement toward strength or firmness when we affirm something. Confirm suggests a union with what is strong or firm meaning to make firm. The Latin privative prefix “in-” gives negative meaning to the word infirm when we are not strong, sick, ill or unwell. An infirmary is a place for the infirm. The suffix “-ary” gives us the sense of a place for as in the words aviary, dictionary and vocabulary.

Donald Ayres book is replete with many devices that can only improve our vocabulary. At last, the only way I can bring this bit of a disquisition to a closure is to give you a brief glimpse of some Latin phrases that have made their way into the English vernacular. The expression ad hoc means for a specific purpose or to fill a specific need. Ad infinitum means to infinity or without limit. This essay could go on ad infinitum to the point of ad nauseam. Don’t you want to just puke? A non sequitur is an inference or conclusion that doesn’t follow the premises or evidence. A quid pro quo is something given in return for something else, an equal exchange and finally a sin qua non literally means without which not or something absolutely necessary or indispensable.

Disclosure statement: the author has no conflicts of interest to disclose.