

Vincent's Veritable Sense

This issue is all about getting to the truth. Science, the systematized knowledge that has been accumulated through observation, experimentation and reasoning, mandates truthfulness of the answers from testable hypotheses. In this month's Spotlight, we have our fine, energetic, resourceful, creative and truly European [President's 100 Days](#) and [Program Chair's Quarterly Report](#), respectively. The venue in Nice is shaping up nicely. Their challenge is to assure us that the ISHLT sessions will keep our attention away from the French Riviera. [Pamela Combs](#) explains to us that VAD programs drive on with bioengineering students aboard. We are given an overview of the necessary pharmacotherapy of right ventricular failure in LVADs by [Roy Lee](#). We are swiftly accumulating more data on the importance of Tregs and *Ex vivo* lung perfusion to the point we must start asking the practical and proper questions. [Rebecca Shilling](#) updates us about Tregs in lung transplantation and the promise of potentially ONE truth or the truth of ONE. [Marcelo Cypel, Dirk Van Raemdonck, and Shaf Keshavjee](#) keep us aboard the freight train on what we think is the proper path from where we are to what's next with *ex vivo* lung perfusion? Hopefully, the rails remain in place and we don't steam ahead without tracks. [Bryan Boling and Katie Burns](#) move us forward with ambulatory ECMO and share with us how safe it can be especially for those resistant to change and afraid to pursue such an endeavor. [Erin Schumer](#) shows us how an ISHLT International Traveling Scholarship Award provided her the opportunity to travel across the ocean to advance research on the biohybrid lung project. Finally, with a nod to our upcoming meeting in France and the dignity and grace of a pirouette in ballet we round out this issue with [Tereza Martinu's](#) *adieu* to Duke's Schwartz Center Rounds that grounds us in the truth and humanity of what's best for our patients.

IN THE SPOTLIGHT: ISHLT President's Report: The First 100 Days in Office

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So far, I have really enjoyed my first 100 days in office! Although my email-inbox volume increased by about 200%, I still enjoy reading them. However, I have noticed a marked change in the job since Cape Town in the late 80's, when I watched my former chief, Bruno Reichart, become President of the ISHLT. At that time, there were no emails, only some occasional phone calls or letters. Now, I receive emails at 2 a.m. in the morning and another three hours later wondering why I have not responded yet. Ideally, an ISHLT president should work simultaneously at all different time zones. I am sure that Allan Glanville can report on this as well, from his time in office, working from Sydney, Australia last year.

The two highlights of my first 100 days were, first, the signature of the Memorandum of Understanding between IMACS, an ISHLT-owned international registry and EUROMACS, a European-based registry, which was founded several years ago by Roland Hetzer and Reinhardt Koerfer. In the future, the data entered into the EUROMACS registry will automatically be transferred to the IMACS registry as well. For centers preferring to interact directly with IMACS, this will also be possible, although we would recommend that all European centers go to EUROMACS first.

The second highlight certainly was the site visit for next year's annual meeting site in Nice, France. First, Nice is one of the most attractive and spectacular cities in Europe, located beautifully at the Côte d'Azur of the Mediterranean. Particularly, the old part of the city is very beautiful and, of course, the beaches are spectacular. Weather in April is usually mild, but this doesn't matter, since everybody will go to the annual meeting anyway. The Acropolis Congress Center is one of the best congress centers to ever host our meeting, with an extraordinary exhibit hall allowing for many great parallel sessions. Since the meeting is pretty much concentrated in one location, there will be lots of opportunity to interact with other members and colleagues. Currently we are planning the annual gala reception and, although I cannot say too much at that moment, rest assured it will be spectacular.

Therefore, I would like to encourage all members to plan the trip to Nice next year in April and to book your hotel accommodations early. Information on hotel reservations will follow soon.

I have planned quite a few more strategic developments while I am in office and will report on the progress regularly.

Once again, I am very happy to serve as your President and I am happy to receive even more emails from our members.

Have a great summer!

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IN THE SPOTLIGHT: Program Chair's First Quarter Report

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What makes a good program chair? I asked myself this question a thousand times before the board officially appointed me. You never know if, or when, you may be selected for this job. Fortunately, I got the call from the incoming president way ahead of the meeting; January 2013. This is important, as you need to plan your private life as well as your normal working life at the university.

After receiving the 'baton' from Jason Christie in San Diego earlier this year I have learned a lot of things about my job; things I never thought I would have to deal with. Naming Jason is significant, as he is one of the people who has helped me tremendously over the last months. He taught me how to plan and think ahead. Our President is the next important person I must mention, as Hermann acts like a big brother, helping with tough decisions, and offering wisdom and creative ideas.

However, the biggest help to me are ISHLT's response to Wonder Women. Amanda, Susie, Lisa, Phyllis and Lee Ann know so much about the meeting and are its heart and soul. Without them I would have struggled a thousand times more.

So the big questions now are: What is the best way to utilize all these great people helping me? And what *really* makes a good Program chair?

I guess the recipe consists of these ingredients: a huge amount of creativity, mix it with tons of persistence, then stir it deliberately and slowly to include more and more time before topping it off with diplomatic skills

Right off the bat, I had to choose a committee of experts who would help me put together the meeting content. I tried to convince Amanda to expand the committee roster to 500 people, but she surprisingly rejected this idea so I had to cut down and skeletonize the committee until the final number was reached. There are so many great people I could not include and I apologize for that.

The next important step was a sight inspection in Nice. We had to check out the congress center and possible locations for the Gala. These were two great but very exhausting days as we rushed from place to place and tried to discuss every aspect of the meeting in the congress building. However, we immediately recognized our big mistake in bringing the meeting to Nice; the city (as the name tells it) is so nice, we will have to organize a very enticing meeting with excellent

content and speakers, otherwise all participants will do their own sessions on the promenade or the beach. Nevertheless, President Reichenspurner and I are optimistic that we will put together a great meeting for you!

As it will be an international meeting, we will try to reach out to our members, especially the ones who are not able to attend the meetings in the USA. The globalization of the ISHLT and all that it stands for (the only organization that tackles end-stage heart and lung failure and pulmonary hypertension in a real interdisciplinary way) is the foundation on which the meeting will be built. Right now we are in the process of constructing the symposia and we will be sure to update you soon.

Looking forward to see you in Nice in 2015!

PS: Let us Read and let us Dance - two amusements that will never do any harm to the world.
(Voltaire)

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VAD Programs Driving Ahead with the Inclusion of Bioengineering Students

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"The discipline of creation, be it to paint, compose, write, is an effort towards wholeness."

(Reflections on Faith and Art by Madeleine L'Engle) [1]

Due to a significant improvement in survival rates following implantation of ventricular assist devices (VADs), the number of patients with implanted VADs has increased considerably [2]. Considering this increase in implants, the VAD team composition is evolving into a mixture that includes other members besides cardiologists, surgeons, VAD Coordinators, and perfusionists [3]. This brief discussion will describe the three key factors to consider when transitioning a Bioengineering student into the VAD program in order to add to the program's "wholeness."

- 1) Stay within the Lines: The third-year student hired from the [University of Texas School of Bioengineering](#) had little knowledge of VADs but was eager to learn. Orientation began with a comprehensive and intensive training period consisting of one-on-one training with the VAD Coordinators, shadowing the surgeons and physicians, and formal training with industry.

Clear delineation and explanation of scope was explained regarding the role. An explanation of scope of service was provided to the Bioengineering student which was not to provide hands-on care for the patient, since typically the patient believes anyone who is not a physician is a nurse [4]. The duties of the student were listed as the following:

- 1) Serve as support staff for patients with VADs
 - 2) Be responsible for the care and maintenance of the VAD equipment
 - 3) Coordinate VAD equipment care and maintenance activities with VAD procedures/physicians/ teaching
 - 4) Provide patient teaching regarding equipment.
- 2) Add fuel for Motion: Initially, simple learning goals were established and as those goals were achieved, higher goals were set. Each achievement in knowledge goal was a step to a higher knowledge level. This learning process takes time and patience and is crucial to provide mentoring with a continuum of communication. The team's long-term goals were to foster growth and to keep the student in the field of VADs.

Initially, basic foundational learning was performed with VAD equipment and as confidence and knowledge expanded, the duties broadened to teaching the patient and community.

- 3) The Compass remains on the Patient: The **primary** focus of the VAD team is the patient. One of many attributes the student represented was a strong work ethic with a personable demeanor that worked well with patient interactions. This positive demeanor allowed the building of student-patient relationships. These positive relationships led to extra monitoring of the VAD patient. Many patients provided positive feedback towards the students stating she added energy and time for equipment focus to our care.

In conclusion, the integration of the Bioengineering student has added to the positivity of the dynamic while adding not only a technical “go to” but a chance to mentor young innovators. This experience has allowed the team to foster a newcomer into the field who is now graduated and will forge ahead into the VAD industry. Understanding changes in the composition of the VAD team is imperative in order to proceed towards the destination of positive patient outcomes. Changes like those described above will only add to our own strength in knowledge and deliverance of care to the VAD patient. This experience was particularly rewarding in fostered mentoring, sharing of knowledge, building teamwork, and positive patient outcomes.

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Brief Overview of Pharmacotherapy of Right Ventricular Failure in LVADs

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Until recently, patients with advanced heart failure had few options other than cardiac transplantation. With advances in left ventricular assist devices (LVAD), however, these patients now have a viable, long-term alternative with the HeartMate II and Heartware. Unfortunately, right ventricular failure (RVF) is a common complication following implantation of an LVAD and can be associated with increased morbidity and mortality. The incidence of RVF post-implantation has been reported to be between 20%-50% [1]. Risk factors include both patient characteristics and hemodynamic parameters, but definitive risk factors are unknown. Some risk factors may include gender, underlying disease state, increased central venous pressure (CVP), decreased right ventricular (RV) stroke work index, pulmonary hypertension, and signs of end organ damage [1].

Unlike left heart failure, which has been studied extensively and for which many pharmacologic therapeutic options are available, very few options with high quality of evidence exists for RVF. Additionally, no viable long-term right ventricular assist devices exist. Aggressively supporting the right ventricle post-operatively, therefore, is of paramount importance and is achieved by tailoring therapy to its suspected cause. When pharmacologic agents are used, their mechanisms and some aspects of pharmacokinetics should be understood to try and achieve a desired outcome. These agents typically modulate volume status, preload, afterload, inotropy, and rhythm.

Post-operatively, achieving optimal volume status is important and is accomplished mainly by diuretics (e.g. loop diuretics and thiazides) [2]. Underdiuresis is important to avoid, as an increase in preload and central venous pressure (CVP) can lead to RVF which can be difficult to recover from. Continuous infusion of loop diuretics, or a combination of diuretics may be required, especially if intermittent use of diuretics fails to achieve adequate response. Overdiuresis, on the other hand, will prevent adequate preload to the left ventricle, thereby, potentially causing left septum deviation and left ventricular collapse [2]. With this, not enough forward flow from the pump will be achieved and, in the case of the HeartMate II, may lead to a decrease in the PI (pulsatility index). In either case, both scenarios can lead to hemodynamic instability.

There is a dynamic interplay and interdependence between the LVAD and the RV. Successful filling of the left ventricle and LVAD (and, therefore, adequate flow and systemic circulation) also requires the right ventricle to match the LVAD flow. If the problem is increased RV afterload, as evidenced by increased pulmonary vascular resistance or pulmonary artery pressures, then a reduction in afterload on the RV can be achieved by methods that can include the use of inhaled nitric oxide, inhaled epoprostenol, oral sildenafil, nesiritide, or milrinone (which has the added benefit of

increasing right-sided inotropy) [3]. (Note: Not all of these agents, nor all possible agents, will be discussed.)

Inhaled epoprostenol in the critically ill is an ideal agent, as it acts locally on the pulmonary vasculature without systemic vasodilation. Epoprostenol, also known as prostaglandin I₂ or prostacyclin, activates adenylate cyclase by prostaglandin I receptor stimulation, resulting in the intracellular production of cyclic adenosine monophosphate (cAMP) in vascular smooth muscles and, therefore, vasodilation [4-5]. Originally approved as an intravenous (IV) medication for pulmonary arterial hypertension, it should not be given intravenously in the critically ill, as systemic hypotension will ensue leading to decreased RV perfusion and, thus, decreased RV contraction. Epoprostenol can be titrated rapidly as it has a very short half-life (plasma half-life of 3 minutes) and, unlike inhaled nitric oxide, is substantially cheaper, does not require dedicated equipment, and does not form toxic metabolites (e.g. methemoglobinemia) [4-5].

Milrinone, a phosphodiesterase type 3 inhibitor specific to cardiac and smooth muscle, leads to increased levels of cAMP and, therefore, increased cardiac contractility and vasodilation [6]. The beneficial effects come from increased right heart inotropy and decreased pulmonary vascular resistance (PVR) [7]. It is important to note, however, that milrinone has a particularly long half-life in patients with renal dysfunction and in those on dialysis (up to 20 hours in patients on CVVH) [8]. It should be used with extreme caution in these situations and the dose should be reduced. Additionally, it is important to note milrinone's effect on vascular resistance is not limited to the pulmonary vasculature, but also the systemic vasculature and additional agents may be required to maintain systemic vascular resistance. It is available as an IV medication.

Sildenafil (Revatio) is an oral phosphodiesterase type 5 inhibitor of smooth muscles cells in the pulmonary vasculature that leads to increased levels of cyclic guanosine monophosphate (cGMP). This results in pulmonary vasculature relaxation and, to a lesser degree, relaxation of the systemic vasculature [9-11]. Although no dose adjustment is needed for renal dysfunction, sildenafil is metabolized hepatically via CYP3A4 (major) and CYP2C9 (minor) and close monitoring should be applied in patients who are started on other medications that inhibit these enzymes (e.g. azole antifungals and nondihydropyridine calcium channel blockers) [9]. Although oral tadalafil (Adcirca) also falls in the same class as sildenafil and is metabolized by CYP3A4, its long half-life of ~15-35 hours (vs. ~4 hours for sildenafil) may not make it the most suitable candidate in the acute setting [12]. Onset of action for both drugs is expected within 1 hour and may be used to transition patients off inhaled or IV medications. Sildenafil can be used in cases of severe renal dysfunction or those requiring dialysis, while tadalafil is not recommended.

Nesiritide (Natrecor) is a recombinant B-type natriuretic peptide of cardiac origin that causes an increased level of intracellular cGMP, resulting in vasodilatation and natriuresis [13]. It has been shown to produce a dose-dependent reduction in pulmonary capillary wedge pressure (PCWP) in as quickly as 15 minutes [14]. Unlike milrinone, nesiritide is not eliminated renally. Thus, accumulation of the drug and prolongation of its effects is not expected in patients with renal dysfunction. Unfortunately, questions remain regarding the safety of nesiritide. While initial studies in patients with left ventricular failure have shown improved hemodynamics and symptoms,

other studies have suggested deterioration in renal function and mortality concerns [15-16]. Less information exists for patients with isolated RVF, though one retrospective study suggests a worsening of kidney function [17].

Finally, managing arrhythmias is important, as this can cause a decrease in right ventricular output and, therefore, cause a decrease in flow. Additionally, arrhythmias can lead to thromboembolic events. One common arrhythmia is atrial fibrillation, which can be managed pharmacologically (e.g. with amiodarone) or via electrical cardioversion. Acutely, beta-blockers will want to be avoided as they are negative inotropes and can depress right ventricular function.

Until more research and data becomes available, management of RVF must be tailored based on cause, understanding of drug mechanics, and the dynamic interplay between the LVAD and right ventricle.

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Pirouetting with Humanity in Lung Transplantation

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With contributions from **Lynn Bowlby, MD, Shane Nolan, Lynn O'Neill, MD** and **Bill Taub, MSW**

Introduction (by Lynn Bowlby, MD)

This text is from a recent session of Schwartz Center Rounds®, entitled *There and Back Again: A Transplant Journey*, which took place at Duke University Medical Center on July 9, 2014. Schwartz Center Rounds is a monthly interdisciplinary conference offering clinicians a regularly scheduled time during their fast-paced work lives to openly and honestly discuss social and emotional issues that arise in caring for patients. Schwartz Center Rounds began at Duke University in September 2012 and has generated a tremendous response from participants. An initiative of the [Schwartz Center for Compassionate Healthcare](#), the rounds take place at 320 sites in the U.S. and U.K. including Massachusetts General Hospital, Brigham & Women's, Vanderbilt, Mount Sinai, Emory, Cleveland Clinic, UNC-Chapel Hill, and Duke University Medical Center. For more information about Schwartz Center Rounds please refer to www.theschwartzcenter.org

The focus in these Rounds is to explore the patient-provider relationship and the emotions that surround it. A panel of 3-4 caregivers shares their experiences in taking care of patients. With the increasing challenges in medicine, reduced time with patients and augmented more administrative responsibilities, time can be limited for focusing on the patient and the impact of illness on their life. In the midst of a medical world, which is growing increasingly technical and complex, Schwartz Center Rounds is an opportunity to acknowledge and mature our human perspective in caring for patients.

For the first time at this institution, a family caregiver was invited to participate in the panel discussion along with professional staff.

Medical History (by Tereza Martinu, MD):

Ms. Ann was a 61 year-old woman with a past history of emphysema who underwent a bilateral lung transplantation in May of 2011. She had a prior history of depression and bipolar disorder, which had been well managed, as well as a lung infection of *Aspergillus* fungus. Her early post-transplant course was complicated by multiple admissions for issues such as dehydration, depression, post-surgical wound infection, respiratory viral infection, and severe headaches. She also had two early lung rejections, which were successfully treated with high-dose steroids.

Subsequently, Ann had a relatively good year, with great lung function and minimal collateral issues. During this time, her quality of life was still somewhat compromised by recurrent headaches and depression. In June of 2013, two years after her transplant, she developed late-onset acute rejections. The first rejection episode was treated with high-dose steroids, but Ann's lung function continued to deteriorate. We then treated her with Campath, a very aggressive form of immunosuppression, which can be associated a multitude of side effects. In spite of this treatment, Ann's lung function deteriorated further with worsening oxygenation and increasing carbon dioxide levels. She became oxygen dependent and also developed altered mental status and anxiety. At that time we had discussions about end of life care. After two hospitalizations, Ann was transferred home with hospice and later transitioned to an inpatient hospice setting where she died in September of 2013, a year, three months, and 19 days after her transplant.

Ann's Journey (by Shane Nolan, Ann's husband):

Our journey began when a doctor said to my wife "your lungs have been damaged irreparably and the only solution would be a double lung transplant."

I recall feeling a bit surreal as I had never heard of anyone getting a lung transplant. Generally, I felt quite happy, as this was going to be a solution to my wife's deteriorating pulmonary problems. It all seemed pretty amazing.

The side bar to this was also the realization that I would have to resign my job to take care of Ann. There was no way she could do this without a full time caregiver and advocate. Even then, I am not sure I realized completely what lay ahead.

Waiting for transplant

From the time the pre-transplant coordinator called us in December 2010 to tell her she was accepted into the program to receiving the transplant, both of us felt that we were on a path with a lot of unknowns. As the Duke pre-transplant process played out with the countless tests and patient physical preparedness, both of us worked at trying to see this as an "adventure". Ann's spirit faded on more than a few occasions, but I was always convinced that we could do this. Coming to the clinic for months before the surgery, slowly but surely, one begins to think that at Duke "all things are possible". We both fed on that very distinct feeling.

The transplant

When the coordinator called to say that this was it, I think we both were in that intoxicating cocktail of emotions (anxiety, joy and fear) and just trying to make sure the other was going to be "okay".

Seeing her in ICU just after the surgery and in the early days, I began to see that "getting the transplant" was just the beginning of a changed life. And that was the first time that I worried.

After 12 days in the hospital, we went back to our locally rented apartment. Despite counseling that it may be difficult, nothing prepared me for the full on, seemingly 24 hour care of the first days at home. Though thrilled that she was being released, the short ride home was quiet and anxiety filled, especially after stopping at the drugstore to pick up a grocery bag with \$2000-worth of time-dependent drugs.

This is where the real test began. Those first days could only be described as "drinking from a fire hose."

Caregiving

Clearly, the biggest job - it seemed - was keeping Ann motivated and positive when side effects like depression and migraines developed. Fortunately, Ann never fell into that self-conversation of regret.

Ann's last 12 months had various significant health ups and downs. I recall wondering then if I was just watching Ann die slowly or observing her living poorly.

Rejection and diagnosis

A few early rejections and their quick fix may, in retrospect, have given us (or just me) a false sense of security. Rejection was not that scary, just very inconvenient.

That being said, as Ann went into what would ultimately be her last series of rejections, I surely sensed the graveness of the event. I think Ann did as well, even before she was hospitalized and subsequently diagnosed with chronic rejection. She had also now presented with shortness of breath and a series of dropping PFT's. Things did not look good.

The final yeoman efforts in the hospital to turn things around began to weigh heavily on us both as Ann got sicker quickly ... our transplant solution began slipping away.

I recall how crushing that felt like and not wanting Ann to know.

Nearing the end of the Journey

My first reaction to being visited by the Palliative care team was resentment. In Ann's case it was even more so.

How could they be giving up? This is Duke ... "all things are possible" here. It seemed like we had just changed buses and now we were on a new bus speeding to the edge of cliff. We just didn't know where the edge was.

Ann's deterioration, however, was rapid so I really didn't have much time to dwell on anything, instead focusing only on Ann.

The word "hospice" was now used in open discussion; like squeezed toothpaste, we couldn't put it back in.

The final days of Hospice were amazingly pleasant. The home nurses that came were just what Ann (and I, for that matter) needed. Ann was moved to the Smithfield location where she knew 50% of the volunteers and was now within miles of all of her siblings. After the controlled clinical environment of Duke, Ann didn't want chaos in her last days. Hospice answered that need perfectly.

Ann's pulmonary team from Duke stayed by our side to the end.

From a caregiver's perspective, I knew that, in the end, we did everything we could have done.

On September 7, 2013, the caregiving role was suddenly over. The need to manage her meds, meals and even laundry, stopped. As my daughter so insightfully stated, "you not only lost your mate of 30 years, but also just lost your caregiver job."

Ann and I had been on quite a journey; one that had enriched us both. Despite the outcome, I think it made us better people in the end.

The Transplant Pulmonologist Perspective (by Tereza Martinu, MD):

I like the word "adventure" that Shane used to describe the lung transplant. It really is an adventure, with times of excitement and times of fear. I often warn our patients, both before and after transplant, that they will be going through a physical and emotional roller coaster. But I rarely acknowledge to myself that the emotional roller coaster takes place in my mind as well. Preparing for the Schwartz rounds made me reflect upon my own emotions and feelings that accompany each patient through their lung transplant journey.

Initially, when I met Ann and Shane, things were a little rocky with frequent admissions. But at the same time, Ann's lungs were improving. To describe my feelings during this time, I would depict myself as swaying like a pendulum between two sets of emotions. On one hand there was a feeling of satisfaction, a feeling of awe regarding the miracle that can be accomplished, really, in transforming a breathless person into someone who can breathe peacefully; a feeling of hope that this will last for a long time and that things will get even better. But on the other hand, there is the realistic "me" with feelings of gnawing worry. The transplanted lungs, in almost all of our patients, will fail at some point. So I can't help but have a constant sense of temporariness and inevitability.

When Ann developed her late onset rejections and her lungs started to fail, I definitely had a sense of frustration and helplessness. As Shane mentioned, this is Duke, and this is lung transplant; we want everything to be possible. We never want to give up. I always feel like, along with my patient,

I go down kicking and screaming, coming up with every possible intervention. But at the same time, with Ann, I sensed that things may not go well and that Campath may not work.

I think Ann helped me a lot when she told me "I'm not afraid of dying but I'm afraid of dying in pain." I really appreciated her voicing, out loud, that death was ok ... but that she was scared of the dying process. She emphasized that we needed to talk about quality of life during these last days.

I always try to have discussions about the end-of-life sooner rather than later, often even when patients are still doing well ... but it doesn't change the fact that I find it hard to have these talks and that it's uncomfortable to bring up the topic. There is this fear of disappointing the patient and their loved ones; a fear of failure. Ann sent me a note just a few weeks before her death. I would like to relay her note to you:

"Tereza,

On my last visit with you at clinic, I told you 'you are to blame for this.' Though said in jest, I have worried about those misspoken words since then. Please accept my apologies. Your care for me has been wonderful. I could not have hoped or wished for a better doctor over the past two years."

I remember very clearly that clinic visit. I never thought Ann really blamed me. In fact, we both laughed and joked about "everything being all my fault" during that visit. But the thing is, I blamed myself. I always blame myself on some level. Did I miss something? Should I have treated her differently ... earlier? Did my treatment actually make her more miserable? As much as I have learned to deal with these feelings of guilt on my own, her note really helped me come to terms with them in her particular case and it helped me refocus on the positive.

I think that what made Ann and Shane so memorable was their persistent positivity. In spite of the migraines and the up and down depression, they always remained extremely appreciative of the time they had together. In spite of all the complications that Ann had, she was always very thankful and smiley. We always had time for jokes and laughter during clinic visits. And I would like to thank Ann and Shane for those precious times.

A Palliative Care Clinician Perspective (by Lynn O'Neill, MD):

As is often the case in my work in palliative care, I met Ann and Shane towards the end of their journey at Duke. Before I speak specifically about Ann and Shane, I want to speak more generally about my work in palliative care. The most common response I receive when I tell people in healthcare that I'm in palliative care is, "Wow...that must be hard." My response, ever the optimist, is usually something like, "Actually, it is very rewarding. We have the opportunity to help patients and families at a time of great need." And this response that I repeat to someone at least once a week is true. However, the initial response of my healthcare colleagues--the "Wow...that must be hard" response--is also true. Yes, it is hard. It's hard to shine the light of clarity on a terminal diagnosis for a patient who might have been told this before but, for whatever reason,

was unable to hear it. It's hard to work amidst family dynamics that are complex even in the good times and much more complex when the family is confronted with the serious illness of one of its members. It's hard to broker conflict between colleagues in our own healthcare system, people who all have the best interest of the patient at heart but who have strong opinions about how to achieve the best for the patient.

I will say, however, that I don't think I'm alone in this--this hard work. And I don't think we're alone in palliative care in the hard work. All of our work is hard. The important thing for me is figuring out a way to balance the hard with the rewarding. The way I describe it to students who work with me is that there are some encounters that completely deplete you--those that open up the spigot and let all of the water drain out. And then there are those that fill you back up.

This is where I finally get back to Ann and Shane. What I remember most about meeting Ann and Shane is that my first encounter with them was one of those that filled me back up. They were so quick to share their own experience with the transplant journey that I almost immediately felt like I had known them for months, rather than minutes. I remember how Ann's face lit up when she talked about being able to shed some of the transplant restrictions; no longer off limits were things like enjoying a glass of wine and going out in public in a place where germs might abound. While I knew that this shift in the focus of her care was a major one for her and Shane, it also seemed that she was facing it with the same composure that she had possessed during the entirety of her transplant journey. And that encounter is why I do the work I do. It filled me back up and allowed me to go about the rest of my day and week, meeting each patient and family right where they were and providing them with what they needed in the moment.

Wrap-up (by Bill Taub, MSW):

Today's Schwartz Center Rounds focused upon the themes of loss and hurt. It is so difficult for us in life (and at work too) to fall in love with people and then to lose them. In the case of our patient, loss meant Ann's death. Loss also meant the difficulty of dealing with the fact that Ann's double lung transplant wasn't going to keep her alive for decades as we had all wanted and hoped. Similar situations often force upon us an unwanted necessity to learn to function with an empty spot in our lives. Life just isn't fair, is it? And losing the people we love and count on is one of the hardest challenges of all. Are we up to continuing on and making life the best it can be without these loved ones? Maybe we can, if we truly can be supportive of and understanding toward one another.

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Are Tregs the ONE for Lung Transplantation?

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The balance between infection and immunosuppression is never trickier than with the organ responsible for filtering the air we breathe and for oxygenating the body. Is it possible to flip the balance back to homeostasis and away from constant immune suppression? The normal immune homeostasis of the lung involves multiple regulatory mechanisms, from multiple cell types that are only beginning to be understood [1]. One major mechanism is CD4+ T regulatory cells (Tregs), characterized by expression of the transcription factor Foxp3 [2-4]. Tregs are able to prevent activation of other T cells and are necessary to avoid autoimmunity [1]. They are known to prevent, or delay rejection in solid organ transplant models and have been associated with improved outcomes after human lung transplant ([5,6]; nicely reviewed in [7]). Data from mouse models also suggest Tregs may be beneficial for inducing tolerance to lung allografts [8,9]. Could they be used as therapy for human transplant recipients? The ONE Study (www.onestudy.org), funded by the European Commission's Seventh Framework, hopes to start answering this important question [10].

Foxp3+ Tregs can be broken down into two major groups and include natural Tregs (thymic-derived) and induced Tregs (iTregs, produced in the periphery). Both subsets can suppress other T cells, although the mechanisms in vivo are not entirely clear. The "suppressor cell" concept is not new to immunology, and was first proposed by Gershon and Kondo in 1971 and was established in transplant by Kilshaw in 1975 (reviewed in [11]). Suppressor cells generally fell out of favor until the mid-80's, when their importance was reasserted in transplantation and in the prevention of autoimmunity [11]. Waldmann and colleagues established that tolerance to allografts could be transferred and "infectious," as regulatory CD4+ T cells could recruit other T cells to promote allograft tolerance [12]. Subsequently, the transcription factor Foxp3 was established as necessary for the development and function of Tregs [2-4]. Since the affirmation that suppressor cells were real and potent regulators of the immune response, the challenge has been to harness the power of Tregs for human therapy.

The number of Tregs naturally occurring in humans is a small percentage of the total T cell repertoire. Thus the focus has been on ex vivo expansion of either natural or induced Tregs [11]. Multiple regimens have been reported, but the challenge has been to expand a stable suppressive population [11,13,14]. Especially with natural Tregs, which are mostly specific for self-antigens, loss of Foxp3 expression and the possibility of being reactive and dangerous to self is a real concern. For this reason, iTregs, which are not thought to be self-reactive, may be an important alternative (for a more thorough discussion ref. [14]). In addition to maintaining stability, the numbers needed to treat for efficacy are not insignificant and require substantial expansion in the laboratory [11,13]. There are also good data that while Tregs are globally suppressive, they are more potent when they are antigen-specific [13]. Donor-specific expanded Tregs would be

preferable, but this is obviously a challenge for cadaveric donors, such as in lung transplant. Further, the mechanisms by which Tregs function in vivo are not completely understood and the location where they function, either in the graft or lymphoid tissue, is also unknown. Thus, there are many challenges to overcome before Tregs are widely available for therapy, not the least of which, are the GMP compliant protocols required to generate cellular therapy for clinical use [14].

Nevertheless, the promise of using suppressor cell therapy for allotransplantation is getting more and more real. Early phase clinical trials of human Treg therapy to treat graft versus host disease (GVHD) or Type I diabetes have been reported [11]. Even more exciting, the ONE study has begun in eight sites in Europe and in the U.S. [10]. The ONE study is a multicenter Phase 1/11a trial evaluating the safety and feasibility of transferring Treg, compared to seven different regulatory cell based therapies, in living donor kidney transplant recipients [10,11]. The aim is to have results by 2016 to smartly choose the most feasible and safe cell therapy for a larger trial to determine efficacy. This is not long to get a hint of whether the promise of 40+ years of basic research on suppressor cells will be realized. While the lung will be a considerable challenge for Treg therapy, the relative magnitude of immunosuppression required, compared to other solid organs, such as kidney and liver, suggest the potential benefits could be even greater. Let's hope for some good regulation to arrive in a timely fashion for lung transplantation.

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Ex Vivo Lung Perfusion: Where are We... and What's Next?

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Since the inception of the first successful clinical lung transplantation in Toronto in 1983, very few innovations in the field have garnered such attention and excitement in the lung transplant community as Normothermic Ex vivo Lung Perfusion (EVLP). Stig Steen published his work in 2001 when he used EVLP for short term assessment of function of a DCD lung, which was ultimately successfully used for transplantation [1]. Between 2001 and 2007, many experimental EVLP studies were performed in Europe again with the focus of short term lung evaluation in the DCD context [2,3]. In 2007, our group in Toronto presented, at the ISHLT annual meeting in San Francisco, the first concept and feasibility of prolonged EVLP (12h) in association with an active treatment strategy (IL-10 gene therapy) to repair injured donor lungs ex vivo [4]. Subsequent publications, demonstrated the benefits of having a period of normothermic EVLP during the lung preservation process [5] and a seminal prospective clinical trial demonstrated the feasibility and safety of EVLP to assess and improve function of injured donor lungs or lungs from donors after cardiac death [6]. An explosion of EVLP research has occurred since then, and EVLP became one of the major topics of our annual meetings. As expected, in parallel with this, there has been a heightened interest from industry in related technology with at least four companies producing devices for lung perfusion, each however with different characteristics.

In Toronto, EVLP has been an integral part of our clinical lung transplant program since 2008. In 2012, Health Canada approved this strategy and subsequently the ministry of health started to reimburse our hospital for EVLP costs. In 2013, our lung transplant activities increased by 28% in one year, with EVLP being the major responsible factor for that, considering that our multi-organ donor pool number and characteristics did not change. We now have significant experience with over 110 patients that have received EVLP lungs in Toronto. This group of patients enjoys very low rates of severe PGD, and a 5-year survival of 70% in comparison to 63% in contemporaneous conventional transplants.

Several prospective studies of various EVLP techniques are underway or have been recently completed in Europe and North America. This includes the HELP trial (Toronto; sponsor XVIVO Perfusion), the NOVEL trial (USA; sponsor XVIVO Perfusion), the INSPIRE and EXPAND trial (Europe and USA; sponsor Transmedics), the Develop UK (England; sponsor Vivoline), the Vienna trial (Vienna, sponsor XVIVO), and the Perfusix Trial (USA; sponsor Perfusix). Important differences between these studies besides the different technologies and techniques are the specific indications. While the HELP, NOVEL, Develop UK, Expand, and Perfusix trials include extended criteria lungs, the Inspire and Vienna trial are evaluating the impact of EVLP in standard criteria donor lungs. Some of the preliminary results to date of these studies have been presented at the

last ISHLT annual meeting, and in general the results are encouraging - both with respect to the ability to rescue declined lungs as well as to provide improved outcomes after transplantation.

Despite all this significant activity and optimism, many questions still remain unanswered and careful further scientific research and investigation is still needed. To highlight a few, first is the controversy about routine or selective use of EVLP in controlled DCD lungs, and second, the attempt to minimize or avoid cold ischemic time by transporting the organ with machine perfusion rather than having a stationary EVLP system. In regards to the first, robust data from highly committed DCD centers have demonstrated the ability to safely transplant category III DCD without the routine use of EVLP [7]. However, EVLP seems to have an important role in extending utilization of DCD lungs when other concerning situations occur such as a prolonged agonal period or concern regarding donor aspiration. It is certainly a mandatory step with categories I and II DCD donor lungs.

Some have proposed that cold ischemia could be minimized or abolished by perfusing the organ from the donor to recipient hospital [8]. However, there is currently no experimental evidence to support that periods of cold ischemia of several hours before and/or after EVLP lead to deleterious effects. In fact, Mulloy and colleagues demonstrated added benefit of 4h of static cold preservation time before EVLP in comparison to normothermic EVLP without cold ischemia [9]. Our group has recently demonstrated both in large animals and humans that long periods of CIT before or after EVLP in fact does not have an adverse impact in recipient outcomes. Whereas, the partial results of the INSPIRE trial presented at the annual meeting demonstrates a benefit to recipients receiving standard criteria donor lungs that underwent machine perfusion during transportation versus cold ischemia alone, this will not answer whether the minimization of cold ischemic times before EVLP had any impact on observed patient outcomes. The randomized study currently under way in Vienna, where no minimization of the first cold ischemic time (CIT-1) will occur (stationary system) will help to further clarify this question. It is very likely that the "intervention of normothermic EVLP" at some point during the total preservation period is the major driver of donor lung quality improvement that we are seeing.

Finally, with the completion of all these important clinical studies, and an increasing body of experimental studies with EVLP, in the near future we hope to see the initiation of clinical trials with active targeted treatment strategies such as drug or molecular interventions during EVLP come to fruition [10]. This will realize the true potential of EVLP in improving both short and long term outcomes of lung transplantation.

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Moving Forward: Safely Walking Patients on ECMO

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Venovenous extracorporeal membrane oxygenation (ECMO) is an effective and often necessary therapy for end-stage pulmonary disease patients awaiting lung transplant [1]. Even though newer cannulation techniques, such as the use of a dual lumen cannula in the internal jugular vein, allow for greater patient mobility, ambulation of patients on ECMO remains rare. Immobility of critically ill patients, particularly those with pulmonary disease, is a significant problem, often leading to physical deconditioning [2], prolonged mechanical ventilation [3], and skin breakdown [4].

Despite the benefits of mobility, there are safety concerns regarding the ambulation of patients on extracorporeal support. In our experience, staff concern for patient safety presents the largest barrier to ambulation of these patients in many institutions. However, this can be done safely. In the [Cardiothoracic and Vascular Intensive Care Unit](#) (CTVICU) at the University of Kentucky Hospital, we have been ambulating ECMO patients for three years with great success [5].

Initially, there was significant resistance on the part of the CTVICU nursing staff towards the ambulation of ECMO patients. Fears of decannulation, major bleeding, falls, and other patient safety issues were the primary concerns expressed by the nurses. From talking with staff at other centers, these fears are a common impediment to the routine ambulation of ECMO patients nationwide. With time, our experience has shown these fears to be unwarranted and ECMO ambulation is now a commonly accepted standard of practice in our institution [5].

Proper planning and execution are essential to ambulating these patients safely. The use of a multidisciplinary team, led by the CTVICU nurses and consisting of physical therapy, perfusion, and respiratory therapy, ensures that all needed support is available. In addition to our team, we also employ special equipment such as a self-contained mobile ECMO cart and specialized thoracic walker to ensure the safety of the patient.

Prior to being ambulated patients are classified as either high or low-risk based on a number of factors, including their ability to bear weight independently, hemodynamic stability, and the distance they are able to walk without seated rest periods (see Box). Those patients who are physically debilitated to the point they require two or more people to assist them with walking are also considered to be high-risk.

At least two nurses, typically the patient's nurse and the ICU charge nurse, accompany all high-risk patients with additional nurses and/or nursing care technicians assisting as needed. In addition to the nurses, either the cardiac perfusionist or ECMO specialist accompanies the patient and is responsible for the ECMO cart and protection of the integrity of the ECMO circuit. If the patient needs manual ventilation via bag valve mask or if they are receiving inhaled nitric oxide, one or more respiratory therapists may be involved. Physical therapy staff may also assist, if available. To ensure that the cardiothoracic surgeons and operating room staff are available, should there be the need for any emergent surgical intervention, these high-risk patients are only ambulated during the hours of 0700-1900.

Low-risk patients, however, may be ambulated at any time, provided the needed staff and resources are available. Because these patients are more independent and require less physical support, the additional staff is often unnecessary and only two nurses are required to accompany the patient. While one of the nurses assists and monitors the patient, the second is charged solely with managing the ECMO cart and monitoring the securement of the cannulas.

The primary nurse works with the patient to determine the optimal time for ambulation and then coordinates with the rest of the team. Each session is tailored to the needs and abilities of the individual patient, but frequently consists of distances up to 300 feet or more, with many patients walking two or three times per day. Patients are ambulated both within the CTICU and in the adjacent hallways outside the unit. In some cases, staff or family members may push a recliner chair behind the patient to allow for seated rest periods. In addition to the ECMO pump and circuit being contained on the mobile cart, a special thoracic walker that facilitates optimal patient positioning, along with providing attachment for oxygen tanks, chest tubes, foley catheter drainage bags, portable monitors and other equipment, is used.

In the past three years, we have successfully ambulated over 50 patients undergoing ECMO therapy without any major adverse events [5]. We attribute this outstanding safety record to good planning, proper equipment, and a dedicated staff willing to move beyond traditional thinking in order to provide the best care for our patients. Ambulating ECMO patients is safe, if done correctly, and we feel that it ultimately leads to improved outcomes.

Box – Classification of ECMO Patients

High-Risk

- Requires > 1 person to assist with ambulation (independent of ECMO)
- Unable to ambulate > 100 ft or requires frequent seated rest periods
- Becomes unstable with exertion requiring additional support (i.e. vent, bagging, etc.)

Low-Risk

- Patient currently ambulating >100 ft. with minimal difficulty
 - Able to bear weight and ambulate with ≤ 1 assist (independent of the ECMO)
 - Hemodynamically stable
-

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International Traveling Scholarship Report: Research Contributions on the Biohybrid Lung Project

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In January, 2014, I was awarded the ISHLT Travelling Scholarship Award which provided me the opportunity to spend May 2014 at the [Hannover Medical School](#) (MHH) in Hannover, Germany, contributing to research efforts on the [biohybrid lung project](#). As a general surgery resident, my goal of becoming an academically active cardiothoracic surgeon creates a strong interest in lung transplantation and lung transplantation research.

Starting in July 2013, I dedicated two years to research with the Advanced Heart Failure Research Group at the University of Louisville to work on cardiac assist device Research and Development and develop an *ex vivo* lung perfusion model. Following that experience, I knew that the [ISHLT Travelling Scholarship Award](#) presented an invaluable opportunity for me to obtain a wealth of knowledge in these research areas.

With this in mind, I approached my mentor, Professor Mark Slaughter, who felt we should collaborate with Hannover Medical School. MHH has one of the world's largest lung transplantation programs and a very active research program in artificial organs and *ex vivo* perfusion, which coincided perfectly with my research and career interests. Throughout the application process, both Professor Axel Haverich and Dr. Bettina Wiegmann at the Hannover Medical School were generous of their time and effort; and after very graciously being given this award, I was able to discover that this generosity was characteristic of the entire Department of Cardiothoracic Vascular and Transplantation Surgery at MHH.

My primary role during my visit was to conduct and complete an experiment as part of the biohybrid lung project with the intent to submit the data as a manuscript. When I was not in the laboratory, I participated in daily rounds in the intensive care unit and acted as an observer in the operating room. In addition, I had the opportunity to attend the "Breath meets Rebirth" conference upon arrival to Hannover. This conference demonstrated a varied breadth of research and innovation from international investigators on the topic of end-stage lung disease.

Following the conference, we began our experiments as part of the biohybrid lung project [1]. The research team, headed by Professor Haverich, at Leibniz Research Laboratories for Biotechnology and Artificial Organs, is currently developing a biohybrid lung for the treatment of end-stage lung disease. His group has made significant progress in the field of artificial organs in the last few years, and fortunately, my background in the development of an *ex vivo* lung perfusion model allowed me to participate in this project role.

In order to develop the biohybrid lung, we needed to determine the smallest acceptable surface area capable of adequate oxygenation and ventilation. We created a mock circuit by using a cardiopulmonary bypass roller pump to circulate human blood first through an oxygenator to deoxygenate the blood and then through three sizes of oxygenators to test their capabilities. We tested the oxygenators by achieving various desired conditions using a carbon dioxide/nitrogen gas mixture, oxygen, and carbon dioxide. Preliminary analysis indicates that the pediatric oxygenator will likely be sufficient for adequate gas exchange.

I also spent time with the cardiac surgery residents assigned to the intensive care unit, the intermediate care unit, and in the operating room observing the care delivered to patients with heart and lung disease. The lung transplantation program at MHH is truly impressive, not only by volume at greater than 120 cases annually, but through the care delivered by the transplant team. I was able to observe several cardiac procedures, including the minimally invasive approach to ventricular assist devices originally developed at MHH. I enjoyed discussing the similarities and differences in patient care and training programs with the clinicians. The pride of the residents and attending surgeons was clearly demonstrated through their careful and enthusiastic explanations.

This visit was a truly memorable and valuable experience that I will carry with me as I progress through my training and career. Furthermore, we plan to continue this collaboration between University of Louisville and Hannover Medical School.

I would like to thank ISHLT for providing this award, Professor Mark Slaughter and the University of Louisville for their support and guidance, and Professor Haverich and Dr. Wiegmann in the Department of Cardiothoracic, Vascular, and Transplantation Surgery at MHH for this opportunity.

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

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Links Travel Awards: Go! Write! Win!

With the support of W.O. and Joan Leach (Gadsden, Alabama, USA), Mrs. Sue Abramson (Birmingham, Alabama, USA) and Mr. Larry Imhoff (La Place, Louisiana, USA), ISHLT has been able to offer the **Leach-Abramson-Imhoff Links Travel Awards** to support the growth and development of our future leaders from within our society. From physicians to nurses to other health care professionals, anyone motivated enough by investigation, communication, and dissemination of new ideas for the betterment of patients with failing lungs and/or a failing heart should be rewarded for their efforts. Whether writing about conditions such as pulmonary fibrosis, cystic fibrosis, emphysema, pulmonary hypertension, and from ischemic, nonischemic to congenital heart diseases, those who work tirelessly to educate themselves, their patients and their field should not go unnoticed or unmentioned.

Eligibility requirements include:

1. Any healthcare professional including but not limited to nurses, nurse coordinators, social workers, pharmacists, therapists, dietitians and early career physicians are eligible and must be a member of the ISHLT regardless of duration in their career.
2. An imposed restriction on physicians is that they must be in their Early Career—within 7 years of training, Assistant Professor equivalent, or junior faculty level with rare exceptions.
3. Individuals must display some form of research interest, basic, clinical, translational or outcomes investigations or at a minimum display some skill in journalism best exemplified by their contributions to the Links Newsletter engendering fresh and creative ideas.

Each year, winners are selected from a pool of nominees by the ISHLT Links Travel Award Committee (LTAC) which includes: the Links Editor-in-Chief, ISHLT Executive Director, ISHLT President, ISHLT Program Chair, and the Links Managing Editor. Past and present award winners are announced on the [Links Newsletter Awards](#) page of our website.

By submitting one (or more!) article(s) for publication in any of the 2014 ISHLT Links Newsletter issues AND meeting the above eligibility requirements, any author can be considered for one of these awards. Please visit [Links Schedule & Deadlines](#) for upcoming issue deadlines and content information.

So go! Write! Win! And don't forget to tell us all about it when you get back, as we do so enjoy hearing from our members!

ISHLT Editorial Staff

JHLT Impact Factors Reach New High

Hot off the press, the 2013 Impact Factors for the Journal of Heart and Lung Transplantation (JHLT) were released on July 29th, 2014:

- JHLT's Impact Factor increased from 5.11 to 5.61
- The Journal's total citations jumped from 7139 last year to 8078 this year
- Our Article Influence Score (a measure of prestige of publishing in the JHLT) has risen consistently from <1 (2010) to 1.41 this year
- We are now ranked 3rd in the category of ANY SURGICAL journal (out of 202); remain 2nd in the Transplantation category and we moved up to 17 in the Cardiovascular Category (out of 125)

Congratulations to Editor-in-Chief Mandeep Mehra, the entire editorial staff of the Journal, and the ISHLT for this impressive accomplishment.

EDITOR'S CORNER: Descartes, Bacon, Locke and Newton: The Journey of Scientific Inquiry to Truth

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In the Editor's Corner for Volume 6 of the ISHLT Links we have immersed ourselves into 18th Century France and specifically, Voltaire. In the previous issues, we reviewed the influence his Jesuit education and the Lady Newton (the Divine Émilie) had on shaping Voltaire into what he would become; the Patriarch of the French Enlightenment. Here we examine one of his most influential works, *Letters on the English* (or *Lettres Philosophiques* in France), a series of essays drawn from his experience in England which served to define his intellectual life and attract the Divine Emilie.

While in England, Voltaire learned that the world worked according to one set of laws of physics in France, and by another set in England. He believed the events of the 17th Century philosophical and scientific English revolutions were more important not only for French readers, but for all of mankind. France had recognized the importance of these revolutions but not for their merit. Voltaire argued that France favored Descartes and his philosophy simply because he was French, and that French readers favored French authors. This was not the way of philosophy. Through his philosophical letters, Voltaire proclaimed the obvious superiority of English over French natural philosophy, and above all the French achievements of the 17th Century. The aim of his philosophical letters was to popularize and glorify English thought with open-minded critical inquiry and without prejudice. Most importantly, he sought to emphasize that human thought or philosophy knows no national boundaries and that philosophers are more important to society than political or military heroes, without discriminating against one particular culture or society.

In [Letter XII](#), he started his discussion of philosophy with a tale about discussants debating who was the greatest of all human heroes. Was it Caesar, Alexander the Great, Tamerlane (who conquered much of the world) or Oliver Cromwell, who brought down the 17th Century monarchy and established the British Puritan Commonwealth? Voltaire's answer to this question was Sir Isaac Newton, simply because, while others conquered by force, violence and slavery, Newton enlightened the world. But it was not only Newton; other philosophers had changed the world by the force of truth and thus deserved to be ranked amongst the world's greatest. He asserted that these philosophers, unlike religious enthusiasts, posed no danger to society. Voltaire further posited that philosophers worked peaceably and enriched mankind by voluntary enlightenment, using Michel de Montaigne, Pierre Bayle, Baruch Spinoza, Thomas Hobbes, John Locke and Sir Isaac Newton as examples. And yet, he asserted, France celebrated the 17th Century revolutions of Science and Philosophy on the basis of chauvinism, confining themselves within their national boundaries for the sake of national pride. Their hero, and appropriately so, was Rene Descartes, who brought down Aristotle and promoted the revolution in physics.

Voltaire did give Descartes much credit, for he had freed the human mind from the past by teaching that all things were open to doubt and re-examination; to skepticism. Mankind must pursue knowledge from the beginning by taking nothing for granted from their upbringing and education. Mankind must think clearly and analytically. As a brilliant mathematician and the founder of analytical geometry, Descartes' advances in logic also immortalized him in the history of human thought. However, his error was thinking one could do science in the manner of geometry and, by finding the axioms that were true, one could deduce all other forms of knowledge from the known axioms. The genius of Descartes that glorified France was his logic, his mathematics and freedom of the human mind. "I think, therefore I am."

Voltaire, on the other hand, took France outside the box, from the top down under the inductive reasoning of Sir Francis Bacon, or by the deductive reasoning of Descartes, to the bottom up. Both provided the seeds for the modern scientific method. Voltaire elevated Bacon's status to that of a great theoretician of the new inductive experimental science. Unlike Descartes, he was not a mathematician; he was a lawyer, and promoted an "eye witness" account of empirical observations, as he would if he were accumulating evidence required in building a case in a court of law. Both Descartes and Bacon believed in reducing problems to their smallest constituent parts, but Descartes began with intuition while Bacon began with empirical observations. Like Descartes, Bacon's method emphasized the importance of taking nothing for granted from past knowledge. However, he assumed error is more likely to survive the test of time than truth. He recognized the need to harness the human mind to the facts of this world and to experimentation rather than abstract reasoning. He further emphasized an avoidance of abstract philosophy and beginning with patient observations of nature to construct a hypothesis that is testable. Voltaire concluded that Bacon provided the scaffolding of the new philosophy. He was not a scientist; he did not discover any laws or operations. Instead, what he provided was a method of securing knowledge by seeking knowledge. In Bacon's metaphor, **method** is the proper path to take one from where one is to where one wants to be. Bacon defines genius as fleetness of foot; the fastest person on the wrong path gets farther and farther away more quickly from where he desires to finish, a warning against action before thought. On the other hand, the one who thinks before he acts, the tortoise, or the plodder on the proper path, ultimately arrives at the truth. Bacon gave us the method of philosophy. For Voltaire, Bacon represented the pinnacle of the new philosophy, whose superiority to Descartes needed to be known.

Next, Voltaire turned to John Locke's empirical sensationalism, the gathering of knowledge by the experience of our senses, which began with a blank slate on which experience prints ideas. Voltaire took us away from the doctrine of innate ideas, as suggested by Descartes. From the influence of religion and innate ideas, it was believed that the principles of thought were placed there by God and, thus, inquiry ends. Locke studied how the mind *actually* behaves, instead of theorizing about the nature of it. Descartes believed the mind was immaterial substance. According to Descartes, the mind was not body, and it could not be an act of the body because **matter** was lifeless and without thought. Only soul could think. Locke's counter argument came under theological attack, for in professing to believe as Descartes believed, the mind could not be material; it would be the same as saying the Almighty God in his omnipotence was incapable of creating matter that could

think; that God was impotent in creating matter capable of thought. "How could any human being, limited to the knowledge we gathered from the difficulty of the senses, prescribe to God what the world must be or what it must be made of based upon human philosophical ideals?" Locke's argument was honest skepticism and his only conclusion on metaphysical matter was to admit ignorance when human knowledge does not allow us, on the basis of experience, to note something about the world. In Voltaire's famous phrase, "I'm proud to be as ignorant as Locke on this **matter**," he described his pride in his ability to admit what he did not know, and what human beings could not know, thereby accepting, with appropriate humility, the limits of human knowledge. Voltaire concludes that Locke taught us to avoid unresolvable metaphysical problems but instead, to study the world and its behaviors through the limited natural faculties God provided us.

With Bacon's inductive methodology and Locke's empirical sensationalism, Newton was able to accomplish what Voltaire explained and popularized as proof of his superiority. With Bacon's scaffolding and Locke's approach, Newton discovered the nature of light and its separation into primary colors, and derived his laws of motion. He also had inferred, from the data of nature, one simple law—a sensational law: of any two masses in the world with mass M_0M_1 , there is a force which increases according to the sizes of the masses and decreases according to the square of the distance between the two masses. This was Newton's Law of Gravity. Descartes' could not grasp this universal law of gravitation. His physics assumed that everything occurred by matter touching matter in the manner of the world as one vast fluid in which everything effects everything else by motions; a "butterfly effect." Nevertheless, Descartes did get us on the road to truth, but it was Newton who took us to the end of that journey. Newtonian science redefined what knowledge of nature was all about by removing it from abstract speculation. This Newtonian achievement, in the opinion of Voltaire, was a result of the application of the genius of Newton, Lockean empiricism and Baconian methodology to the study of nature, which altered the human relationship to natural knowledge into one that knew no national boundaries and not unlike the ISHLT.

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