VINCENT’S SEASONAL SENSE:

In this issue of the Links, we reminisce over this Holiday's hallmarks in heart and lung transplantation, a 20th century marvel. 100 years ago, there were many technological advancements that simplified our lives but altered our perception of space and time. Marking the 75th anniversary of what some consider 20th century’s greatest technological achievement from our greatest minds Einstein, Fermi, Compton, et al, was the CP-1 (Chicago Pile-1), a part of the Manhattan Project. These initial efforts and criticism brought to the world nuclear power plants and humanoid robots. Today, we decorate the 50th anniversary of heart transplantation with Jim Kirklin’s spotlight on the history of heart and lung transplantation by reviewing the transition from animal to human candidacy. With tidings from Alyssa Perez and Steven Hays, we re-examine lung transplantation in patients with Mycobacterium Abscessus. Lindsay Caldarone explores the sprinkles of neutrophil extracellular traps (NETs) in lung transplantation, while Georgina Waldman unwraps the new shingles vaccine. Claire Aguilar gallops to a winter wonderland in her article, “When You Hear the Drumming of Hooves, Think Horses... (But Don’t Forget Unicorn): Hyperammonemia Associated with Ureaplasma spp. Infection in Lung Transplant Recipients.” Javier Carbone carols the season with his article, “European Day for the Prudent Use of Antibiotics. A European Health Initiative.” To wrap it all up, Maryl Johnson caters an update from the ISHLT Governance Committee and our President Andy Fisher untangles the tinsels in his halftime report. In keeping with the December Yuletide of the ISHLT Links, yours truly provides a chorale and corrals the 20th Century’s achievements reflected by the delightful Debussy.
IN THE SPOTLIGHT:

Introduction to the ISHLT e-monograph on the History of International Heart and Lung Transplantation

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The developmental history of human heart transplantation is laced with innovation, prescient persuasion, intense competition and courageous convictions. When all is written and the controversies laid to rest, Norman Shumway will always rise above the rest as the true Father of Heart Transplantation. But he wasn't the first. That landmark event in the history of medicine is inexorably linked to Christian Barnard, the charismatic cardiac surgeon from Cape Town, South Africa, who on December 3, 1967 took the heart from Denise Darvall, the deceased victim of a hit-and-run motor vehicle tragedy. The recipient was Louis Washkansky, a 53-year-old former sports enthusiast in the terminal phase of heart failure. The simple recognition of this amazing and historic accomplishment belies the intensely competitive struggle involving four heart surgeons and their teams, each of whom would be acclaimed in the early history of heart transplantation.

The experimental prelude and surgical preparations, shrouded in the drama of human ambition and quest for immortality, is a beautifully woven story written by the widely acclaimed writer Donald McRae in the first chapter of this monograph. Norman Shumway, Richard Lower, Adrian Kantrowitz and Christian Barnard became the principle antagonists in this fascinating race to perform the first human heart transplant. With all of his monumental contributions to the field, Norman Shumway, with his usual grace and good humor, accepted his shared place in history as he reflected about the journey in his final interview with Donald McRae (see Chapter 1): “Maybe, in the end, it all worked out for the best...yeah, I think it worked out just fine...” It was fitting that he was selected Honorary Life President of the International Society for Heart Transplantation in 1981.

Nevertheless, long before Shumway, Alexis Carrel planted the seeds for future heart transplantation in the early 1900’s. An experimental surgeon, Carrel was inspired to provide surgical solutions to prevent fatal hemorrhage from wounds such as the lacerated portal vein in the assassination of French President Carnot in 1894. Carrel would later win the Nobel Prize in Medicine (1912) for his work with Charles Guthrie on vascular anastomoses.

Vladimir Demikhov staked the Russian claim to relevance in developing this field with his pioneering experimental work in canine heart and heart-lung transplants. The surgical techniques evolved with the experimental work of Webb, Goldberg, Akman and Reemtsma in the 1950’s and 60’s. In 1964, James Hardy at the University of Mississippi etched his name in the historical annals with his ill-fated xenotransplant of a chimpanzee heart into a dying 68-year-old man.
Shumway and Lower provided the critical experiments that paved the path for a rational approach to heart transplantation. In 1960, they first demonstrated that an animal could recover with its circulation entirely supported by a transplanted heart. Kantrowitz extended these experiments to puppies and achieved survival exceeding 100 days. Following eight years of experimental work with Richard Lower and the Stanford research team, Shumway was quoted in a JAMA article in the late fall of 1967, “We think the way is clear for human heart transplantation.” Two weeks later, Christian Barnard shocked the world.

The chronology of those first few heart transplants is fascinating. Three days after the first transplant, Adrian Kantrowitz performed the first infant heart transplant on baby Jamie Scudero, dying from Ebstein malformation. Like Shumway and Lower, Kantrowitz had a strong experimental background in heart transplantation, but it was not enough for this baby. The donor heart failed and the baby died eight hours after the transplant. Louis Washkansky began showing signs of infection at the end of his second week, later dying of pneumonia 18 days after his historic transplant.

The year 1968 began with great optimism in the transplant world, but it would be short-lived. Barnard performed the world’s third human heart transplant on January 2nd, and the recipient, Philip Blaiberg, became the first long term survivor, succumbing after 18 months. Shumway performed his first (the world’s fourth) on January 5. Kantrowitz completed the fifth on January 9. Two weeks later, four of the first 5 heart transplants were dead, then the dark epoch shrouded heart transplantation. These three pioneers were followed by Cabrol, Ross, and Cooley. By the end of 1968, 102 heart transplants had been performed in 50 different institutions in 17 countries. The mortality was 60% by the eighth postoperative day, with a mean patient survival of only 29 days! With the sobering reality that available immunosuppression modalities were not reliably controlling rejection and infection, the global experience in cardiac transplantation fell to 17 during 1969, 13 of which were in the U.S.

By 1970, nearly all centers worldwide, with the exception of Shumway’s group at Stanford and Lower’s team at Medical College of Virginia, had declared a moratorium on heart transplantation because of dismal survival. Shumway’s group quietly worked away during the dark decade of the 70’s, gradually improving outcomes and increasing the science and knowledge of heart transplantation. During this enshrouded time frame, many events occurred that provided the scaffolding for later success. Even before Barnard’s first heart transplant, DeBakey successfully supported a patient with a left ventricular assist device in 1966. In 1968, JAMA published a recommended definition of brain death from the Ad Hoc Committee of Harvard Medical School, setting in motion establishment of a legal definition of brain death. Cooley implanted the first total artificial heart in 1969, just a few months after man walked on the moon. In the early 1970’s, Phillip Caves built on contributions of Sakakibara and Konno to develop endomyocardial biopsy of the transplanted heart. With allograft tissue provided by this technique, Margaret Billingham, also at Stanford, established pathologic criteria for the diagnosis for cellular rejection. Distant procurement of donor hearts began in 1973 at Stanford.

The 50 years that have elapsed since the first Cape Town transplant are really demarcated into 2 epochs by the availability of cyclosporine in 1983. Prior to the introduction of cyclosporine, heart transplantation had descended into an abyss by a public splash in the late 1960’s to an irrelevancy
during the 1970’s. Despite important ongoing activity at a few centers, in 1980, less than 10 centers worldwide had active heart transplant programs.

As a young cardiac surgeon just 2 years out of training, I was fortunate enough to be in at the beginning of the second epoch of heart transplantation. The University of Alabama at Birmingham (UAB), like most institutions, was discouraged at the unpredictable and frequently poor outcomes in the late 1970’s and early 1980’s. The heart transplant program had been shut down, joining the nearly worldwide moratorium on heart transplantation while awaiting more effective immunotherapy. With the first availability of cyclosporine, we were poised to re-engage, and I jumped into the heart transplant world with our first cyclosporine heart transplant in 1983. Soon thereafter, the field exploded. Centers throughout the U.S. and Europe rapidly joined the fray. The International Society for Heart Transplantation had been established in 1981, but was a small niche organization until the unveiling and rebirth of the field in 1983. Soon the Society [later renamed the International Society for Heart and Lung Transplantation (ISHLT)] flourished - mirroring, recording and facilitating the dynamic evolution of the field.

Yes, the ISHLT has showcased the incredible evolution of this revolution, providing the world’s dominant platform for scientific and clinical progress, education, innovation and analytics in heart and lung transplantation and mechanical circulatory support.

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NEWS & ANNOUNCEMENTS:

An Update from Your ISHLT Governance Committee

Maryl Johnson, MD
Governance Committee Chair

In the ISHLT Strategic Plan for 2016 – 2020, under the Strategic Imperative: Ensure Organizational Vitality, one of the prioritized goals was to “Improve Governance.” A starting point for this goal was the establishment of a formal Governance Committee, charged with tasks related to not only the Nominations and Elections processes of the Society, but also to the development of job descriptions for volunteer leaders in the Society, a process necessary prior to beginning an assessment of Society infrastructure and projects. As your past-president, I am the current chair of the Governance Committee, which also includes the president (Andy Fisher), president-elect (Jeff Teuteberg) and four at large members serving staggered three years terms (currently Duane Davis, Joe Rogers, Stuart Sweet and David Taylor). Over the past 6 months, we have been working diligently on the required job descriptions as well as defining a more deliberate process for electing Council vice-chairs. Many of these documents have now been reviewed and approved by the ISHLT Board of Directors, and I wanted to call your attention to them. They can be accessed through the links below and available on the ISHLT web site for future reference.

Board of Directors
President, President-Elect, and Past-President
Treasurer
Secretary
Finance Committee and Chair
Governance Committee
Standards and Guidelines Committee and Chair
Scientific Councils and Council Officers

The Committee is still working on the job description for the Annual Meeting Program Committee and Chair, the Executive Committee and the Council Workforce Leaders, and these documents will be uploaded to the website when available. A reassessment/possible reorganization for the Grants and Awards Committee, I2C2 Committee and the Registries and Databases Committee is currently in progress with the intent to develop job descriptions for these groups when the way forward is defined.

The Board has also approved the following process for the selection of Council Vice-Chairs, with the first stages of this process currently in progress and the intent to follow this process for the elections of Council Vice-Chairs in 2018.

Process for Council Vice-Chair Selection

The hope is that the defined job descriptions and processes will improve ISHLT governance and assist in ensuring the ongoing vitality of the ISHLT. We look forward to your continued participation in the ISHLT.

Disclosure statement: The author has no conflicts of interest to disclose.
Protecting Our Protected Characteristics: ISHLT President’s Mid-Term Report

Andrew J. Fisher, FRCP, PhD
ISHLT President

As we enter December 2017 and those of us in the Northern hemisphere start to feel the cold chill of winter arrive and those of you in the Southern Hemisphere look forward to the warmth of the summer, we must take a few moments to remember the events that occurred 50 years ago in South Africa when the first human heart transplantation was performed. This momentous event in modern medical history is being celebrated in many ways this month and certainly, at the ISHLT we are making our own contribution. The December edition of JHLT is dedicated to this anniversary and contains a number of fascinating articles and is well worth a cover to cover read (http://www.jhltonline.org/current).

As I pass the mid-point of my term as ISHLT President and knowing in detail all the productive activities our community is involved in, I have taken a moment to reflect on how far the field of Thoracic Organ Transplantation has come in this momentous half century.

I strongly believe that the same incredible multi-disciplinary teamwork that generated critical breakthroughs in turning an experimental surgical procedure into a semi-routine therapy and lifelong care is alive and well in the International Society for Heart and Lung Transplantation in 2017. Indeed, it is that very teamwork that allows thousands of hearts and lungs to be successfully transplanted, thousands of mechanical circulatory support devices to be successfully implanted and thousands of patients with advanced cardiopulmonary disease to be successfully treated each year around the world.

Yes, the Society has changed since it started back in 1981, it has grown as our clinical disciplines and the science underpinning them have equally grown in stature. The diversity of the ISHLT membership continues to increase as all the professions, disciplines and specialties who are committed to improving the lives of people with advanced heart and lung disease see the Society as their professional home. It’s this melting pot of skills, experiences and professional cultures, which makes the ISHLT unique as a professional society as is a characteristic we must celebrate but also protect. Our membership is increasing year by year and our Annual Meeting footprint continues to grow with increasing attendance and more abstract submissions for our 2018 meeting than ever before.

At a time when global tensions are running high and relations between many countries are strained, it is essential we also remember that other protected characteristic of ISHLT – the fact we are an international society. As an ISHLT member from Europe myself (and yes, I will always consider the UK as part of Europe despite the “B” word!), then one of my aims as President has been to make sure we protect the international diversity of the Society. This was a major focus at our recent ISHLT Leadership Retreat held in London in October 2017, when the Board of Directors
and the Chairs of all our Scientific Councils and Standing Committees came together for 2 days to evaluate our performance and strategy in our protected characteristics.

As an indication of our wish to be a global society, I am pleased to report that this year we have held joint symposia with regional societies in South America (Brazil) and Southeast Asia (Singapore) which have been hugely well received, and we already have a number lined up for 2018. In addition, translation of selected key ISHLT guidelines into other languages, initially Spanish, is underway.

Our 2018 Annual Meeting is being held in Nice on the southern coast of France, and I am grateful to our Programme Chair, Chris Benden and the entire Programme Committee for their continued efforts to pull together an exceptional programme.

Furthermore, I am delighted to inform you that the Board of Directors at their recent meeting in Europe agreed to host the 2021 ISHLT Annual Meeting in Sydney, Australia. This is a clear indicator of the Society’s commitment to engage our global community and respects of the significant contribution to our mission made by our colleagues in the Asia-Pacific region.

Finally, as we approach a period of annual holidays and festivals, I hope all our members have some quality time with their families and loved ones, and may I take this opportunity to wish you all a very happy and healthy 2018. Hope to see you in Nice!!

Disclosure statement: The author has no conflicts of interest to disclose.
ISHLT Call for 2018 Grants & Awards Applications

ISHLT is currently accepting applications for all major 2018 awards. Application links and eligibility information for all awards can be found on the [Grants and Scholarships](#) page of the ISHLT website.

**ISHLT Norman E. Shumway Career Development Award** - ISHLT issues one Norman E. Shumway Career Development Award every year. Each award is in the amount of $160,000. The funding period is for two years ($80,000 per year). The Norman E. Shumway Career Development award is aimed to support the rising stars of basic, clinical or translational research at a critical time in their independent research career. The awardee will have already established a track record in the field of heart or lung transplantation, the failing heart or lungs or mechanical circulatory support and will aim to further develop their career in one of these areas.

**ISHLT Joel D. Cooper Career Development Award** - ISHLT issues one Joel D. Cooper Career Development Award every year. Each award is in the amount of $160,000. The funding period is for two years ($80,000 per year). The Joel D. Cooper Career Development award is aimed to support the rising stars of basic, clinical or translational research at a critical time in their independent research career. The awardee will have already established a track record in the field of heart or lung transplantation, the failing heart of lungs or mechanical circulatory support and will aim to further develop their career in one of these areas.

**ISHLT Nursing Research Grant Award** - ISHLT issues two grants annually, each in the amount of up to $12,000. The PI must be a member of ISHLT. The PI must be at least bachelor's prepared. The PI may be a beginning or established researcher. An individual who is a PI on multiple studies is eligible for funding for any of the studies. The grant may be for new or ongoing research. A grant will be awarded to the same study for a maximum of two times.

**ISHLT Research Fellowship Award** - ISHLT issues one Research Fellowship Award annually in the amount of $40,000. The funding period is for one year. The applicant or the applicant's chief of staff/research project director must be a member of the ISHLT in good standing at the time of application and throughout the period of funding. The applicant must have either an MD or PhD/DSc or equivalent degree and be in a clinical or post-doctoral training program and not yet have attained specialty Board certification / accreditation / faculty level appointment (Assistant Professor equivalent or above)/salaried senior staff position (or equivalent) during the period of the award.

**ISHLT Transplant Registry Early Career Award** - ISHLT issues up to five Transplant Registry Early Career Awards annually. Each award is in the amount of up to $7,500. The funding period is for one year. The applicant or the applicant's chief of staff/research project director must be a member of ISHLT in good standing at the time of application and throughout the period of...
funding. The applicant must have attained fellowship or junior faculty level (Instructor or Assistant Professor Equivalent) appointment prior to the period of award. Please refer to the "Past Recipients" page on this website for examples of funded projects.

**NEW! ISHLT/Enduring Hearts Transplant Longevity Research Award** - The purpose of this award is to further the scientific understanding surrounding the topic of improving pediatric cardiac graft outcomes and patient quality of life. The areas of scientific interest to which the awards will be directed, in order of priority, are: Technology Application, Transplant Immunology, Organ Matching, Nutrition and Exercise Physiology, Medication Compliance, and Education. The applicant and the applicant’s chief of staff / research project director must be members of the ISHLT in good standing at the time of application throughout the period of funding. The applicant must have completed a clinical or post-doctoral training program. Candidates must have completed their clinical or postdoctoral training no more than 7 years prior to the date of application. The research project must be conducted at an accredited university, college, medical or dental school, school of public health, hospital, laboratory, or other non-profit institution. No awards will be made for projects that receive overlapping funding from other sources (unless supplementary in nature) or that duplicate other projects already funded.

**ISHLT/O.H. Frazier Award in MCS Translational Research Sponsored by Medtronic** - The purpose of this Award is to support research utilizing MCS that would result in an increased understanding of the biologic effects, use as sole or combined therapy, insights into patient/MCS management, innovative use/application or improved outcomes for the treatment of heart failure. The Award is aimed to support rising stars in the field of mechanical circulatory support at a critical time in their career. The Award recipient will have already established a track record in the field of mechanical circulatory support and will aim to further develop their career in this area. The intent is that the Award will be for a junior faculty position dedicated to a career in the use of MCS as a treatment option for heart failure. It is anticipated that the individual will be clinician or clinician scientist at an active VAD/transplant program with a faculty appointment in either cardiology or cardiac surgery. The applicant must have Board certification or be Board eligible (within their stated field). The applicant must have achieved such no more than 3 years prior to the date of application, and the applicant must have an academic appointment at a University or other accredited institution of higher learning.
European Day for the Prudent Use of Antibiotics: A European Health Initiative

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A recent high profile report estimates that by 2050, 10 million people will die every year due to antimicrobial resistance (AMR) unless a global response to the problem of AMR is mounted. On November 17, a meeting related with the European Antibiotic Awareness Day 2017 was held at the Spanish Ministry of Health in Madrid, Spain.

Belen Crespo, Director of the Spanish Drug Agency (AEMPS), talked about recent advances of the Spanish National Plan against AMR (PRAN). Infection-related death rates due to AMR are increasing in Spain with antibiotic resistance causing 2,500 deaths each year. This situation generates an additional health spend of 150 million euro. The focuses of PRAN are human and animal health. One Health recognizes that the health of people is connected to the health of animals and the environment.

Actions of Human Health in Spain are oriented to primary and specialty care, health care associated infections, definition of indicators of AMR, critic antimicrobial lists, the need of an increasing role of microbiologist and infectious disease specialists, awareness campaigns for professionals and public in general, communication and education. A program for the optimization of the appropriate use of antimicrobials (PROA) in primary care and hospitals is in due course in 10 regions of Spain. A web page for surveillance of AMR has been designed and will be available in the next days. Voluntary reduction of colistin use in veterinary medicine in Spain is an example of the actions that are ongoing in veterinary medicine.

Jean Baptiste Rouffet, member of the coordinating group of the European Joint Action of Antimicrobial Resistance and Healthcare Associated Infections (EU-JAMRAI), gave a conference entitled Antimicrobial Resistance, yes we care! According to the European Center for Disease Prevention and Control, across Europe, infections caused by multiresistant bacteria are responsible of 25,000 deaths and 1,500 millions of euros in losses each year. Rouffet presented updated information of the context of the Joint Action, general objectives and inclusive governance. The challenges of the Joint Action are the awareness of the general public and healthcare professionals, education of health professionals on appropriate use of antimicrobials, research and innovation in the field, surveillance and monitoring and governance and intersectorial policy. Thirteen measures are ongoing including an intersectorial communication campaign, providing support to proper prescribing and incentivize healthcare professionals. An important challenge is to reach consistency between the objectives of WHO and other international organizations and the Joint Action work packages. Inclusive governance of the Joint Action includes 28 countries and partners including university, patient associations, scientific societies and international organizations (ECDC, WHO, OECD, FAO, OIE).

The participation of distinct specialties is necessary for the development of efficient tools and guidelines for antimicrobial use and surveillance of resistance in humans and animals.

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Re-Examining Lung Transplantation in Patients with Mycobacterium Abscessus

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A 26F with a history of cystic fibrosis (FEV1 0.89) and Mycobacterium abscessus (diagnosed in 2006) presents for pre-lung transplant evaluation at your center after being turned away from multiple programs due to M abscessus infection.

The prevalence of nontuberculous mycobacterial (NTM) pulmonary infection is increasing worldwide among patients with structural lung disease and importantly, among our pre-lung transplant population [1]. Infection with NTM poses numerous challenges to lung transplantation as the organisms are difficult to eradicate, therapies are difficult to tolerate, and infection with NTM is associated with worse outcomes if present pre or acquired post lung-transplantation [2,3]. Particularly worrisome is Mycobacterium abscessus, which is considered to be a relatively strong contraindication to lung transplantation given association with poor outcomes [4].

NTM are ubiquitous in the environment and are found in water and soil. M abscessus is the most common cause of rapidly growing mycobacterium (RGM) pulmonary infection and is considered a virulent pathogen [1,5,6]. M abscessus is becoming increasingly prevalent among patients with structural lung disease, particularly in those with cystic fibrosis and bronchiectasis [1,7]. Part of this may be due to its ubiquitous nature in the environment as well as increased rates of detection; however, there is also evidence of patient to patient transmission among the cystic fibrosis population [5]. Among patients with cystic fibrosis, chronic infection with M abscessus portends a more rapid decline in FEV1 compared to patients with non-M abscessus NTM [2].

Why is M abscessus considered a relative contraindication to lung transplantation?

These recommendations stem from case reports in literature that describe a high post-transplant mortality associated with pre-lung transplant infection with M abscessus and a high rate of recurrent and refractory infection with M abscessus post-transplant [2,8,9]. In general, post-lung transplant infection with NTM is associated with increased mortality as well as the development of chronic lung allograft dysfunction (CLAD) [9,10]. Several retrospective studies have identified M abscessus as the most common mycobacterium causing NTM disease post-transplant [3,4]. Post-transplant, extra-pulmonary M abscessus infection involving the skin and soft tissue has also been observed, and the general recommendation has been for surgical debridement [11].

There is evolving, albeit limited, data to suggest that good outcomes are possible in patients with pre-transplant infection with M abscessus. There are two case series, one from Denmark and the other from Sweden, that describe successful transplantation of patients with pre-transplant infection...
with *M. abscessus* [12,13]. One recent retrospective case study from the University of North Carolina by Lobo et al, found no difference in mortality between cystic fibrosis transplant recipients with pre-lung transplant infection with *M. abscessus* and those without *M. abscessus* infection [14].

*M. abscessus* is notoriously difficult to treat, however, improving treatment regimens have helped treat these infections successfully. Generally speaking, the treatment of *M. abscessus* is undertaken in a biphasic approach beginning with an intensive phase lasting 1-4 months (until smear conversion), comprised of multiple IV and oral drugs followed by a consolidation phase usually compromised of daily oral and inhaled medications. Drug choice is tailored to patient micro sensitivities as much as possible; however, generally includes a macrolide backbone, amikacin, cefoxitin and imipenem [15]. Tigecycline, inhaled amikacin and linezolid are other agents being used to treat *M. abscessus* [5]. A recent study in the *Journal of Cystic Fibrosis* by Da Costa et al showed that treatment of *M. abscessus* in cystic fibrosis patients significantly improved lung function at 30 and 60 days and may prevent progression of lung function decline beyond this time period [15].

**Should we transplant patients with pre-transplant infection with *M. abscessus***?

The patient was referred to our program in March of 2012 and initially treated with PO azithromycin, IV cefoxitin and IV amikacin for smear positive *M. abscessus*. Inhaled amikacin was added in August of 2012. In November of 2012, due to hearing loss noted on screening audiology exam and recurrent positive smear, amikacin was stopped and linezolid and tigecycline were started. Tigecycline was held temporarily due to GI intolerance. Linezolid was transitioned to tigecycline several months later due to the development of peripheral neuropathy. The patient was actively listed for transplant when AFB smear became negative although she was intermittently culture positive leading up to transplant. The four-drug regimen of PO azithromycin, IV cefoxitin, inhaled amikacin and IV tigecycline was continued until the time of transplant on 1/16/14, and a four-drug regimen was continued for eight months post-transplant. Cultures from bronchoalveolar lavage immediately post-transplant were positive for *M. abscessus*, but have otherwise been negative to date. She developed an incisional infection due to *M. abscessus* approximately one month following her transplantation. This was managed medically with PO azithromycin, IV cefoxitin, inhaled amikacin and linezolid. No surgical debridement was needed and the incisional wound healed well. Currently, the patient has intact graft function with no evidence of CLAD.

While pre-transplant infection with *M. abscessus* can pose a therapeutic challenge and potentially place the recipient at high risk for recurrent infection and CLAD, improved antibiotic regimens and emerging data suggest that *M. abscessus* can be adequately treated pre-transplant, managed post-transplant if recurrent and may not result in increased mortality post-transplant. Further studies are needed to help standardize the approach to the treatment of *M. abscessus* infection pre-lung transplant, ensure infection eradication post-transplant and ensure that this patient population is not uniformly excluded from lung transplantation.

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References:

New Shingles Vaccine

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Vaccination is a core component of preventing infection. However, immunosuppressed patients have a reduced response to vaccination which is multifactorial, influenced by type of immunosuppression, time from transplantation and type of graft. Due to this blunted response, we optimize all vaccinations prior to transplant, particularly post-transplant contraindicated live vaccines. However, not all patients are able to be fully immunized prior to transplant or may not have developed full immunity, leading to risk of infection post-transplant. This has been an issue especially with herpes zoster (HZ), a reactivation of varicella-zoster virus (VZV) in the posterior dorsal root ganglion.

Prior to the approval of the zoster vaccine live (Zostavax®) in 2006, reported incidence of HZ infections was 8-12% for lung and 20-25% for heart transplants, though there was wide variance likely due to differences in protocols across centers [1,2].

Development of HZ post-transplant is associated with higher healthcare costs, VZV hyperimmune gamma-globulin is not currently widely available and may be cost prohibitive [3]. Therefore, when the live zoster vaccine was approved, its use in the pre-transplant phase was highly recommended. Currently, the 2013 IDSA guidelines recommend zoster vaccine live at least 4 weeks prior to transplantation in candidates aged ≥60 years and varicella-positive candidates (aged 50–59 years) but not in immunocompromised patients [4].

Recently, a new zoster vaccine was approved for use in immunocompetent individuals –the inactivated HZ subunit vaccine (HZ/su), Shingrix®. In October 2017, Shingrix® was approved in the United States and Canada while regulatory filings in the European Union, Australia and Japan are underway [4]. It is a recombinant, adjuvanted combination subunit vaccine that mixes a lyophilized surface glycoprotein E antigen with a AS01b adjuvant [6]. The ZOE-50 trial first paved the way to approval and found an 97.2% efficacy against HZ in patients over the age of 50, a marked improvement over the zoster vaccine live reported efficacy of 51% [7,8]. The most common side effects of HZ/su are injection site pain, redness and swelling. Muscle pain, headache, fever, shivering and GI upset have also been reported with most lasting less than 3 days.6 Two doses of the vaccine are required to gain immunity for immunocompetent patients at 0 and 2 - 6 months.6 However, one study in adult hematopoietic stem cell transplant (HSCT) recipients studied HZ/su in three doses at 0, 1 and 3 months [9]. This vaccination schedule gave acquired humor and cellular immunity equivalent to immunocompetent individuals post two doses of vaccine, even when initiated two months post-transplant.

Per GSK, a phase III, observer-blinded, placebo controlled study to evaluate efficacy, safety and immunogenicity of HZ/su vaccine administered as a 2-dose schedule, in autologous HSCT recipients 18 years of age and older has been completed (ClinicalTrials.gov identifier: NCT01610414) [10]. Study results will be available in December 2017.

Shingrix® has been found to be effective in patients that have previously received the live vaccine, Zostavax® as well [11,12]. Another study assessed the impact of co-administration of HZ/su and inactivated influenza at the same time and found no significant difference efficacy with co-administration [13].
Questions of transplant patients and their household contacts often arise. Current recommendations from the IDSA state that healthy immunocompetent individuals who live in a household with immunocompromised patients should receive their vaccinations, including live vaccines, based on the CDC annual schedule recommendations [4]. However, our patients should avoid contact with persons who develop skin lesions following the varicella live vaccine or the zoster vaccine live until the lesions clear, though risk of transmission is low.

After years of difficulty in management of this painful infection post-transplant it appears that we will now have a safe and effective preventative vaccine for our transplant patients. Further studies are always needed to truly assess the safety in our unique population, and it is uncertain the financial burden on our patient’s will be but at the moment, the future is looking bright.

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References:
When You Hear the Drumming of Hooves, Think Horses... (But Don’t Forget Unicorn): Hyperammonemia Associated with Ureaplasma spp. Infection in Lung Transplant Recipients

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When I started my fellowship in Transplant Infectious Diseases in Toronto two years ago, I was expecting to order numerous tests to find unusual infections in those very immunocompromised patients.

As an example, the differential diagnosis for neurological symptoms in immunocompromised hosts includes various infectious etiologies. In fact, I quickly realized that after transplant, a lot of patients had delirium. My staff, Dr. Husain, asked me if I knew the proportion of cases due to infections. Less than 5% quite low. Think horses: medications, metabolic disorders, psychological stress post-transplant.

Few weeks after the beginning of my fellowship, Dr. Michael Ison from Chicago was an invited professor in Toronto and presented new data about hyperammonemia syndrome, a rare but very severe disease in lung transplant recipients. Firstly described in the 90’s, hyperammonemia syndrome is characterized by increased ammonia levels in blood, usually in the early post-transplant phase, associated with neurological symptoms, and results in high mortality rates [1, 2].

Ison’s team found evidence of infection with Ureaplasma urealyticum, Ureaplasma parvum and Mycoplasma hominis in respiratory samples and blood from lung transplant recipients suffering from hyperammonemia syndrome [3]. Surprisingly, Ureaplasma sp. and Mycoplasma hominis are classically responsible for urogenital tract infections in immunocompetent patients, without neurological symptoms. Ureaplasma spp. and Mycoplasma spp. are urea splitting organisms. Recent experiments in mice models showed that inoculation of Ureaplasma urealyticum or Ureaplasma parvum in immunosuppressed mice resulted in high ammonia levels in blood compared to infected control mice [4,5].

This association also raises the question of the transmission mode. Fernandez et al. reported a case where the donor sample was positive for Ureaplasma urealyticum [6]. In a prospective study including 28 donors, Fernandez et al. found that 14% of respiratory samples from donor had a positive PCR for Ureaplasma spp. These positive donors were mostly young male patients who had an aspiration pneumonia [7].

This finding raises the question of screening systematically donor samples for those pathogens to administer appropriate antibiotics to the recipients, and consequently avoid the occurrence of
hyperammonemia syndrome. Such screening test should be done by PCR to provide a quick result, as hyperammonemia tends to occur shortly after transplant.

Nowadays, in the Toronto Lung Transplant Program, all patients are monitored for ammonia levels during the first month post-transplant, and if ammonia is elevated, an empirical treatment with Moxifloxacin and Doxycycline is administrated, associated with the prompt initiation of dialysis to reduce ammonia levels. Recently, we retrospectively studied the samples from 8 patients who had hyperammonemia syndrome in the last 5 years, and found a positive PCR for Ureaplasma and/or Mycoplasma in donor or recipient samples in 6 cases. Interestingly, we also studied 2 recipients with cerebral edema without hyperammonemia, and *Ureaplasma urealyticum* was found in their respiratory samples.

This example highlights the difficulty of transplant infectious diseases, where we have to prioritize the diagnostic assumptions and think first to the most common etiologies, but at the same time keep in mind that unusual infections, with unexpected presentations, can require a quick and accurate diagnosis in order to appropriately treat our patients.

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Exploring Neutrophil Extracellular Traps (NETs) in Lung Transplantation

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A “suicide bomber” that undergoes “cellular kamikaze” to produce a “spider’s web” – and these are just a few of the many colorful descriptions used to explain the process of neutrophils undergoing NETosis [1,2,3]. NETosis was first described in 2004 by Brinkmann et al. as an innate immune response to bacterial invasion [4]. Since that time, research into the mechanisms and consequences of NETosis has exploded. NETs have been described as beneficial agents that fend off viruses and fungi, in addition to bacteria. They have also been implicated in a wide variety of inflammatory disease states, from autoimmune disease to acute lung injury.

The specific mechanisms of NETosis are not yet fully described, but there is a general consensus that key steps include the activation of peptidylarginine deiminase 4 (PAD4) that assists in the citrullination of histones resulting in decondensation of nuclear chromatin. This chromatin co-localizes with granular proteins such as neutrophil elastase and myeloperoxidase, before being actively extruded into the extracellular space. NETosis can be NADPH oxidase-dependent or -independent, and can be either "suicidal," wherein the neutrophil dies after producing NETs, or "vital," where the NET is extruded through vesicles, the neutrophil membranes are preserved and the resulting anuclear neutrophil retains phagocytic function[2, 5].

Of special note to our community is the discovery by Sayah et al. that NETs are pathogenic in primary lung graft dysfunction [6]. This group showed that NETs were detectable in mouse lungs after both a hilar clamp model as well as orthotopic lung transplantation, indicating that NETosis occurs as a result of the ischemia and reperfusion of the lung, as well as in the more clinically applicable scenario of orthotopic transplant. In fact, many steps in the NETosis pathways are well described as mediators in ischemia-reperfusion injury (IRI); for instance, generation of reactive oxygen species, autophagy and influx of intracellular calcium [7, 8].

IRI occurs in the recipient; however, donor lungs may also sustain various types of injury. Many of these injuries trigger inflammatory pathways that may also lead to NETosis; for instance, brain death can lead to increased levels of the neutrophil activator interleukin-8[9]. NETs are thought to propagate neutrophil recruitment and activation, thus contributing to a positive feedback cycle of NETosis at the site of injury. NETs found in the donor lung could be an artifact of the injury sustained by the donor lung and presumably, if these donor NETs are transplanted into the recipient they could amplify the IRI post-transplant. Examining the donor lung for NETs could a) give a quantifiable assessment of inflammatory injury in the donor lung and b) provide a potential therapeutic target so NETs could be removed or degraded prior to transplant, resulting in reduced IRI.
How could this be done? Ex vivo lung perfusion (EVLP) provides the unique opportunity to assess the viability and functionality of donor lungs prior to transplantation. EVLP has been successfully implemented clinically in our center and others around the globe. Furthermore, the perfusate from the circuit can be analyzed for markers of biological processes occurring in the donor lung. Understanding what is happening in the donor lung on a cellular level offers an entirely new insight into how a lung will perform post-transplant. More precise, objective donor lung assessment can lead to an expansion of the donor pool and alleviate the intense shortage of donor lungs, as lungs that may otherwise be too risky to transplant can be proven to be safe. Likewise, donor lungs that may seem acceptable based on the current practice of visual, physiological and functional assessment can be rejected if cellular markers of injury are apparent, thus preventing adverse outcomes in the recipient.

If we can assess NETs in the donor lung, we can understand more about the type of injury sustained by each individual lung as well as learn more about how this novel, programmed neutrophil response impacts lung injury pre- and post-transplant. EVLP provides the ideal opportunity for quantifying NETs in the donor lung. Just two decades ago, the use of “clinical ex vivo lung perfusion” or the phrase “neutrophil extracellular traps” did not exist; by continuing to build on the rapid advancements in research in this field, we can continue to have a greater and greater impact on clinical outcomes and patient lives.

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References:
EDITOR’S CORNER:

Paintings, Words and Wines: Blurred Reflections of France and Debussy

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The 20th century marks an epoch of phenomenal progress in virtually every aspect of Western society, including the genesis of heart transplantation and birth of the ISHLT. With music as a mirror, musical style has also gone through a period of accelerated change during the 20th century. Many turn to concert music as a refuge from the complexities, ironies and difficulties of modern life with much that might appear to be ugly, confusing and incomprehensible. To those who feel this way, would they prefer vanilla over chocolate; coke over a 100 year old single malt; scrambled eggs over caviar or a Ford over a Ferrari? Most of the best things in life, including the music of the 20th century, are acquired tastes. If this were not true, then every child would be as sophisticated as every 50-year-old, which is an abomination. Something must set the aged apart from the youngsters. The youth may have their teeth, their eyesight, their hearing and their knees, but the refined aged can distinguish the finest wines from grape juice and the great cuisines of France. Life experience counts.

Into the early 1900s, the average listener had a problem with most 20th-century concert music and most 20th-century concert music had a problem with the average listener. For example, Johannes Brahms’s Symphony no. 1 in C Minor, op. 68 of 1876, music had become a mainstay of the orchestral repertoire. This symphony premiered in Boston on January 3, 1878, with local critics who didn't sugar-coat their rejection. The Boston Courier wrote, “The Brahms C-minor symphony sounds, for the most part, morbid, strained and unnatural, much of it even ugly.” Not to be outdone, the Boston Gazette wrote, “The symphony is an ungraceful, confusing and unattractive example of dry pedantry without a glimmer of soul.” These bad reviews are not the sort we would send home to our parents to validate our questionable career choice. Examine the book entitled, Lexicon of Musical Invective, assembled by Nicolas Slonimsky. It's a compendium of the worst reviews of many great composers. We read these reviews and wonder how someone would write such things about Beethoven, Brahms, Mahler and so many others. The same thing that makes a piece of art new and exciting also makes it different. Lacking a context to understand its differences, a contemporary critic will lash out and dismiss such works even when what he should be doing is lashing out at himself for not having the insight or tools to understand it. The critics of Brahms' time had no context to comprehend his first symphony, never having heard it before. Some, did what stupid critics have done from time immemorial. They attack when faced with the unknown. Ideally, a critic would reserve any critical judgment of any piece of new music until he or she examines the score, attends rehearsal and hears the piece performed several times.
How we approach the music of the 20th and the 21st century tells us that we should treat such music carefully and with as much respect as we can muster because what is new, different and difficult in a piece of music is very often what makes it original, powerful and enduring. This means we must be patient with ourselves with anything new such as the innovations in heart or lung transplantation. We shouldn’t expect to fully understand a new piece of music when first heard, any more than Brahms, Bach’s, Mozart’s and Beethoven’s first listeners experienced. Admittedly, what is new is not necessarily good, but it is often different, and within its differences might lie a world of expression and experience previously unexplored.

Across the span of western musical development, music served the spirit and the church, both Catholic and Protestant. Music, at different times and places, served the intellect, the spoken word, the stage, the aristocracy and the middle class. Music was also intended to entertain or enlighten or educate its listeners. It wasn’t until the early 19th century when the principal aim of concert music was to serve the emotional and self-expressive needs of the composer himself. Glorification of the individual marked the Enlightenment, along with the growing social and economic power of the middle class, the profound societal disruptions caused by the French Revolution and the subsequent Napoleonic age—these and various other circumstances combined to create the preconditions for an expressive musical revolution, a revolution that would see one or more middle-class-born composers, unwilling to maintain the musical status quo, and assert that musical expression “must serve the individual,” meaning the composer himself.

The late 19th and early 20th century was the time for incredible intellectual, scientific and technological advancements. If music is a mirror, then we would expect the evolving environment at the turn of the 20th century to have influenced the cutting-edge composers. With the first big break at what we might consider the German-Australian-Italian tonal tradition occurring in France, let’s examine the setting on how both French art and music evolved during the second half of the 19th century.

The humiliating French defeat by Prussia during the Franco-Prussian War of 1870-71 drove a huge wedge between France and German-speaking nations. As a result, French culture turned more insular with the nationalist cultivation of everything French already evident for hundreds of years in French culture, it took on a new intensity. The inspiration at the core of this cultivation of things French was the French language. From mid-19th century on, national and ethnic self-identification became for many non-German, non-Austrian and non-Italian composers, an increasingly important mode of personal self-expression. Folkloric nationalism became both a political and an autobiographical statement, "This is who I am, this is where I am from and I am proud of it." Self-expression or the abortive gesture, the increasingly extreme range of Romantic expression required increasingly extreme musical means to depict that expression. The challenge of finding new modes of compositional discourse, of replacing the principles and structures of traditional tonality with new approaches to melody, harmony and rhythm, occupied many of the best musical minds at the turn of the 20th century.

French born, bred and dead, Claude Debussy was a modernist composer who created a nuance of music reflecting French language and culture. He wrote, “I want my music to be as relevant
to the 20th century as the airplane.” In a new century, dominated by a sea of change, the desire to be relevant was overwhelming. The traditional tonal language had proven itself to be increasingly outmoded, as cutting-edge composers, ever more, had to resort to the abortive gesture to achieve their expressive aims. The time was ripe for a new musical syntax, for new ways to approach melody, harmony and rhythm. Hello 20th century music!

The comparison of music by Brahms and Debussy illustrates the essence of French music and culture during this time. Brahms’s music is a manifestation of the German language, with clarity of articulation at every level. [Musical selection: Brahms, Violin Concerto in D Major, op. 77 (1878), movement 3.] Clarity at all levels is obvious: beat, meter, theme, accompaniment, bass line and harmony. Like the German language itself, and typical of almost all German music, this music is nothing if not clearly articulated. It’s also music of great intrinsic substance. In contrast, in Debussy’s Prelude to the Afternoon of a Faun (1892), there are no clearly expressed beats, groupings of beats and harmonic progression, no expressed themes with clear phrase structures and no clear differentiation between theme and accompaniment. Brahms’s music was music of articulation, of consonant whereas Debussy’s is music of vowel, music that reflects utterly the French language. Instead of clarity of articulation, we hear blend; instead of individual events, we hear diphthong, we hear blur. What makes up the theme in Debussy’s piece is as much as pitch and rhythm, as is the actual sound of the instruments, alone and in combination.

Today, Debussy is one of the most original and influential composers in the history of Western music, he had, of course, virulent critics, but among the younger generation of composers who owed much to him was Igor Stravinsky. A great anecdote, told by Alma Mahler in her biography of her husband Gustav, depicts Debussy accurately—the Mahler’s were in Paris in April 1910 for a performance of Mahler’s Symphony no. 2. Alma refers to his double forehead saying:

Debussy brought his second wife, who was said to be very wealthy. He sat next to me at dinner and I noticed that he took only the minutest helping of any dish. When Madame Pierné tried pressing him, his face took on a look of pain. Dukas told me in an undertone that when they were schoolboys together and provided, by their mothers, with money to buy their mid-morning lunches, they all selected the largest confections, except Debussy. He always chose the smallest and most expensive, for even as a child he was nauseated by bulk. That evening too, we were told of Debussy’s ill treatment that had almost been the death of his first wife. It was a youthful marriage and they were very poor. She couldn’t endure her life with him or life without him, so she took poison. Debussy found her apparently unconscious on the floor. He went up to her very calmly and took what money she had on her before sending for a doctor. She heard and saw all of it, for she was not unconscious but simply temporarily paralyzed. She recovered from the poison and was cured too, of her love of Debussy, from whom she was divorced.

The writer, Collette, referred to, “His pan-like head; in his unrelenting gaze the pupils of his eyes seemed to dart from one spot to another, like those of animals of prey hypnotized by their own searching intensity.” Like a cat, Debussy thought only of himself. Of Debussy, his friend, Paul Vidal,
wrote, “I don’t know whether his egoism will ever be subdued. He is incapable of any sacrifice whatsoever. Nothing has any hold over him.” We leave the final word on Debussy’s character to Harold Schonberg, “The chain-smoking Debussy was a sybarite, a sensualist, an ironist and not the most pleasant of men.”

Debussy may have had the morals of a tomcat, but he had the compositional imagination of an angel. His compositional influences are four in number: and one, the French language, with its blurred edges and infinity of nuance; next, Romanticism: Debussy grew up during the 19th century and the overwhelming bulk of his music is programmatic. The third influence: Romantic literature extolling expression and descriptive images of the symbolist poets, Mallarmé, Verlaine and Rimbaud. Finally, French Impressionist painting. Impressionism is a visual manifestation of the French language, an art movement that celebrates light, blended and nuanced color, blurred edges and objects in flux. In Impressionism, the idea of an image is much more important than the image itself. For that reason, there is little Impressionist portraiture, because Impressionist art is not so much about the object being depicted as it is about light, color and the artist's immediate feelings about the object.

The term Impressionism was originally a critical pejorative to Monet's painting, “Impression, Sunrise” of 1874, but the word stuck. For Debussy he hated the word Impressionism and wanted no association with the movement. Frédéric Chopin claimed to have hated Romanticism. Both Chopin and Debussy “protesteth too much” probably. Whether Debussy liked the term Impressionism or not, his music evokes the same water-dominated, brilliantly-colored, subtly-shaded, blurred-edge imagery as an Impressionist painting.

Debussy’s innovative approach to timbre, rhythm, melody, harmony and musical form created music to the likes of which no one had ever heard before. In 1889, Debussy wrote, “To a Frenchman, finesse and nuance are the daughters of intelligence.” Debussy’s music, characterized by finesse and nuance, is the French language in musical action. And while, by the late 19th century, French music had already moved well away from traditional German techniques, the big break with both German and tonal tradition came with Claude Debussy. His music grew from French language with a proclivity for color, nuance and blurred sound. He expressed his musical worldview when he wrote:

I am more and more convinced that music, by its very nature, is something that cannot be cast into a fixed form. It is made up of colors and rhythms. The rest is a lot of humbug invented by frigid imbeciles riding on the backs of the masters who, for the most part, wrote almost nothing but period music. Bach alone had an idea of the truth.

Debussy’s Nuages (Clouds) from his Trois Nocturnes for orchestra of 1899 is a musical impression of moonlit clouds scudding across a night sky. When listening to Nuages, we imagine a more impressionistic image than vague, puffy, moonlit clouds scudding across a night sky. As much as anything else, the opening theme consists of the actual physical sounds of the instruments: the
undulating winds, the piercing, nasal sound of the English horn, the icy strings and the rolling timpani.

Timbre, instrumental tone color, becomes a thematic element, as important, if not more important than melody, rhythm and harmony. *Nuages* is stunningly different from anything ever heard in Concert music until the 20th Century. This music organizes time very differently from traditional tonal music. Tonal music organizes time through tonic, subdominant and dominant harmonies, through rest, through departure or subdominant harmonies. There’s no such temporal linearity in *Nuages*, no harmonic urgency, no sense of global harmonic motion from point A to point B and back. Instead, like a series of freeze frames, this music seems to exist out of linear time. Without linear time, this music explores, observes and wallows in the coloristic nuances and infinite details. Like a French meal, we dine. With a German meal, we eat. The point here is not so much to eat but to experience a heightened sensory of reality through the medium of the music.

Debussy does not conceive of the orchestra in the traditional manner, as an instrumental ensemble consisting of four large instrumental families: woodwinds, brass, strings and percussion. Rather, he approaches the orchestra as a huge chamber group consisting of 85 or 90 individual instruments that can be used singly or grouped as sparingly or as grandly as he wishes. Debussy has an entire orchestra of 85 or 90 players sitting there not performing, but listening with the audience to just three players, one violin, one viola and one cello to play the pentatonic theme of *Nuages*. He is not maximizing the group, like a German, rather he wants the delicacy and intimacy of a string trio, and delicacy and intimacy are delivered. His approach to the orchestra offered him infinite possibilities of instrumental combinations and colors. There’s not a single orchestral composer in the last 100 years who hasn’t studied Debussy’s scores and stolen from them, which is exactly as it should be.

Claude Debussy was, simply put, one of the most shockingly original and influential composers in the history of Western music. Whether the critics or academes liked Debussy’s music or not, the next generation of composers saw him as a compositional Moses, as someone who could lead them from the bondage of traditional tonality to a promised land of new music, music relevant to the new truths and realities of the 20th century.

PS: For more great masterpieces of Debussy enjoy:
1. The quiet chords of opening melody and the rippling arpeggios that follow evoking the silvery moonlight of “Clair de Lune”
2. The ever graceful and dainty “Arabesque”
3. The timeless and exquisitely beautiful “La mer” for orchestra; Images, Book 1, for piano.

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