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Innovation and hard work: The 2015 George E. Palade Medal Award Lecture

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Abstract

The George E Palade Medal is the highest honor awarded by the International Association of Pancreatology and is given to an individual who has made outstanding contributions to the understanding of the pancreas and pancreatic diseases. Professor David C Whitcomb, University of Pittsburgh, is the 2015 recipient. The Palade Lecture, presented in Shanghai, China on August 28, 2015, included 5 personal stories that provide perspective from a life-time of achievement: “My life in a nutshell”; “Two old ladies”; “7777”; “I helped put a man on the moon”; and “Rugby”. Together, the stories provide encouragement to a younger generation, struggling to find their way as physicians and scientists who are working on pancreatic or other diseases in a challenging world.

Keywords

Pancreatitis; Trypsin; Trypsinogen; Genetics; Dyslexia; Chronic pancreatitis

Introduction

The George E Palade Medal is the highest honor awarded by the International Association of Pancreatology to an individual who has made outstanding contributions to our understanding of the pancreas and pancreatic diseases. As the 2015 recipient of this honor, I accept it with gratitude and humility because my story is not just about my own work and accomplishments – it is about vision, collaborations and hard work by teams of dedicated people, some of whom I have never met.

My lecture is divided into 5 personal stories: “My life in a nutshell”; “Two old ladies”; “7777”; “I helped put a man on the moon”; and “Rugby”. Together they tell a larger story of a man with disabilities dedicated to a hopeless cause and joined by friends and volunteers to accomplish impossible tasks through innovation and hard work.

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My life in a nutshell

I was born and named David Clement Whitcomb on December 7, 1955 in the small Midwestern town of Warsaw, Indiana – nestled in the rural vacuum formed by a triangle with points anchored by Chicago, Detroit, and Indianapolis. My father was a world-famous academic theologian, and, as a brilliant Princeton University graduate (with honors), remained one of the most revered men in the tiny town of Winona Lake, Indiana (population 4000). He had four children, of whom I was the oldest.

My mother died of liver cirrhosis when I was 14 years old. Although she never drank a drop of alcohol, I remember being taken aside by doctors and nurses at various referral hospitals and questioned as to how much alcohol she *really* drank. “She does *NOT* drink alcohol!”, I emphatically and honestly answered. The medical professionals had no other explanation. Some of them I saw walking away, shaking their heads in disbelief.

As the oldest of 4 rambunctious children, things did not go well from me in school. I “flunked” kindergarten. Grade school became a nightmare, pitting unrealistic expectations of being my father's son with difficulty sitting still, paying attention, and following instructions. On the other hand, manual labor jobs were easy to obtain because I developed a reputation as a hard worker with endurance and commitment to the task with the ability to contrive creative solutions to unexpected problems.

My report cards typically included comments such as, “Appears bright but is unable to read, write, or spell at grade level”, “not trying hard enough”, “a behavior problem”, “does not listen well”, “trouble copying sentences” and “his handwriting is sloppy”. Things worsened in high school, and I was expelled from two schools for various “creative” reasons. Standardized aptitude test showed signs of genius, but the exams were never finished in the time allotted. Abilities seemed to be concentrated in the areas of art, mechanics, design, engineering and creative story telling, but not in reading, writing, spelling or memorization. Taken together, my high school guidance counselors concluded, “David is *not* college material” and, “He should consider a career in landscaping”.

Our local liberal arts college accepted me as a student on probation, and I ended up on the deans “other” list. I struggled to maintain a “C” grade point average, which was required to play soccer. But I also determined to remain in school because, “to get a good job you need a good education”. However, everything changed for the better on an ice-cold night in snowy Indiana when I returned to my dorm with frozen fingers, warmed them around two cups of hot coffee. Then I opened my textbook. It was as if the blinders came off, because for the first time I could read and fully comprehend the written words. The caffeine was a wonder treatment for something linked to effective reading. My grades leaped to straight “A”s, and I went on to graduate school for a PhD in physiology and to medical school.

While in medical school I diagnosed the disease that killed my mother: primary biliary cirrhosis. The medical community, years before, had misdiagnosed the etiology of my mother's condition out of scientific and medical ignorance.

In 2010, as a tenured professor and accomplished scientist at the University of Pittsburgh, I received an unexpected phone call from the Chancellor's Office. One of the top administrators asked me if I would be willing to join the board of directors for a new school for dyslexic children. When I asked her why she was calling me, the answer was direct, "... because you have dyslexia". After a brief online search, I found that she was right – and these descriptions of dyslexia perfectly depicted my life story between early childhood and college.

Dyslexia is a disorder of language processing. Some of the major manifestations include inability to read and process written material normally, phonetic spelling, difficulty processing verbal instructions, poor handwriting, etc. Dyslexia and attention deficit disorder (ADD) often overlap, compounding the challenges. Children with dyslexia typically fall behind in grade school and lag further behind in high school where academic achievement is primarily linked to lectures, reading and writing. However, dyslexic people often have unusual strengths in mechanics, high-level mathematics, physics, and problem solving. Albert Einstein, for example, struggled in grade school because of dyslexia but understood that $E = mc^2$. But success for dyslexics also requires more time and effort to accomplish routine things than is required by their peers. As Thomas Edison, the famous dyslexic inventor of the light bulb noted, "genius is one percent inspiration and 99% perspiration". Edison epitomized the principles of *innovation* and *hard work*.

The lesson from this story is that everyone has strengths and weaknesses. Successful people find a role in life where their strengths are maximized and their weaknesses are minimized, often relying on teamwork with colleagues possessing complementary talents. In my case, success required innovation, determination, coffee, long hours, supportive people and an extra dose of hard work. And I did join the Board of Directors of Provident Charter School for Children with Dyslexia. My goal is to help dyslexic kids with encouragement, rather than criticism and punishment for failure to read well or understand complex instructions, and to teach them effective strategies to maximize their strengths and become successful in this complex world.

Two old ladies

As a first year GI fellow at Duke, I examined two older ladies for whose diagnosis I had no explanation. As a tertiary referral hospital, Duke University Medical Center was the last hope for them. They suffered from painful, calcific chronic pancreatitis. After finishing my evaluation, I presented the cases to my mentor, who immediately concluded that they had developed *alcoholic* chronic pancreatitis – no other explanation considered. "These women do NOT have alcoholic pancreatitis!", I responded, adding "They are Conservative Baptists. They do not drink, and they do not lie."

After a short discussion of possible pathophysiology, I was told that very few people wanted to work on pancreatitis since the diagnosis could only be made in irreversibly damaged tissue. The attending physician must have read some non-verbal response on my face, as he added, "Do not throw your career away working on chronic pancreatitis – it is a hopeless disorder!". Indeed, the leading experts from Harvard, after reviewing a century of research,

concluded that “chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment” [1a].

I returned to the exam room. As these desperate patients focused their eyes on me, I could clearly see two righteous women that suffered greatly from both a terrible disease and from an obstinate medical community who believed they were just secret alcoholics. At that moment I told them that I had no explanation for their condition, but that as a physician and scientist, I would dedicate my career to find the cause of this disease, and then a cure. A hopeless cause needs a champion, and to the best of my ability, for *this* hopeless cause, I would strive to be that champion.

Although I never saw these ladies again, I can see them today as clearly as any person in front of me. And I could say to them without shame, “I kept my promise”. “My friends and I exposed the secrets of your viscous enemy, chronic pancreatitis, and her days of unrestrained destruction are numbered. She will soon come to an end”. Then I would add, “And as for her evil sister, pancreatic cancer ... she is next!”

The lesson is that dedication to a noble cause is an important thing. The road has been rough, and many dead ends were encountered. But tremendous progress was made through *innovation* and *hard work*. Not only are methods to prevent chronic pancreatitis possible, but our work on this complicated disorder also opened new doors that will make precision medicine for other complex disorders possible [1b].

7777

The number “7777” suddenly flashed on the display panel along with a strong vibration as my hospital beeper sprang to life. It was early May 1995 – years before personal cell phones were reliable or affordable. This particular number alerted the physician to immediately call the operator at Presbyterian University Hospital in Pittsburgh, Pennsylvania USA so that they could connect the doctor to another physician for urgent matters. A familiar voice greeted me, “Dave, this is Larry Gates calling from Lexington, Kentucky. I need to speak to you right now!”

Larry was a friend of mine, and a colleague from my internal medicine residency training at Duke University. After residency, I stayed at Duke University for a gastroenterology fellowship, while Larry studied gastroenterology at Mayo Clinic in Rochester, Minnesota. We both focused our clinical and research training on the pancreas. After training, I joined the faculty at the University of Pittsburgh while Larry went to the University of Kentucky, and his lab partner, Charles (Chuck) Ulrich MD went to the University of Cincinnati. Sadly, the academic leaders in the field of pancreatic disease research dismissed our offers of service and rejected our ideas. As one famous leader told me, “If you hope to have a future in pancreatic research, then you must first work with me – and *you are not working with me!*” Larry and Chuck related similar experiences.

Rejection led to redirection. Larry, Chuck, Steve Martin MD (my first fellow) and I got together to plan the future. First, we agreed that there needed to be better integration of science and clinical research in pancreatic diseases. Second, adequately powered multicenter

pancreatic studies were needed. Third, we committed to work together as a team, to rigorously support each other's ideas and plans, and to form the *Midwest Multicenter Pancreatic Study Group* (MMPSG).

The principles of the MMPSG were friendship, to include anyone who wanted to join us, to support and train young investigators, and to execute audacious plans. My plan was to discover the gene for hereditary pancreatitis (HP), even though I had no training in genetics and never (knowingly) saw a patient with HP in my life. I reasoned that whatever the HP gene turned out to be, it would be a key to understanding *human* pancreatitis. Furthermore, I heard rumors that a few families with HP lived somewhere in the Midwestern USA. Larry chose to study pediatric acute pancreatitis [2], and Chuck and Steve developed other plans.

I asked Larry, in my response to the 7777 page, why he called. He replied, "I just saw a man with hereditary pancreatitis!"

The man, sitting next to Dr. Gates during the call, came to the University of Kentucky outpatient clinic that day with a scroll constructed by him and his family representing an HP kindred of hundreds of people spanning 7 generations. Larry handed the phone to the patient. Within minutes we determined where the family members lived and agreed to sponsor a picnic to meet them. The MMPSG team members met the family in West Virginia and collected detailed histories and blood samples. Within one year we identified the gene for HP, which turned out to be cationic trypsinogen (*PRSSI*) [3–6] (Fig. 1). The rest is history.

This story again illustrates the importance of *innovation* and *hard work*. We developed the MMPSG as a new type of working group based on friendship and audacious plans. The hard work included launching multicenter research programs across multiple institutions without guidance or prior experience, and in mobilizing friends and family to recruit patients from rural Kentucky and West Virginia with no funds. In Pittsburgh, we founded the *Center for Genomic Sciences* as a way to obtain DNA sequencers for our work. We ploughed through hundreds of genetic markers that were synthesized and tested primer by primer. And we got lucky. The result of our audacious plan was the discovery that *PRSSI* mutations cause HP – a finding that revolutionized our understanding of the mechanisms of acute [7,8] and chronic pancreatitis [3,9], and the role of inflammation as a risk factor for pancreatic adenocarcinoma [10–12]. These revolutionary advances may not have occurred for years without Larry Gates MD and a 7777 page.

"I helped put a man on the moon"

My father occasionally took me with him for weekend speaking engagements at various churches in the small towns and cities of the Midwestern United States. As a young teenager I remember going to a specific, small, simple home somewhere in rural Indiana for Sunday afternoon lunch after church. Everyone was in the kitchen except an older working-class gentleman and me. He sat across from me as we awkwardly stared at each other.

"What kind of work did you do?" I asked. "Glad you asked!" he said with sudden engagement and a broad smile, "I helped put a man on the moon!" (Fig. 2)

His story was profound. Growing up during the Great Depression, he finally landed a job as a welder, an industrial job joining two pieces of metal together. He explained that, although it was not the job he wanted, he determined to be the best welder that he could be – and welding became his career.

When the US government was building the Saturn V rocket to send the first man to the moon, his company got a contract to build some parts, and they assigned the welding to him. He went on to say, as he gazed upward and raise his hand toward the sky, “When that rocket was speeding to the moon with our astronauts on board, and those parts were called upon to do their function, *my welding did not fail!*”. “And therefore, because of me”, he added, “a man walked on the moon.”

After a moment of reflection, I realized that he was right! Even though his name is not written on the American Flag still standing on the moon, or on a prominent plaque somewhere, and although few people would have ever heard his name, he knew that he had done his job well, that his small contribution was important. Indeed, he contributed to one of the greatest achievements in recorded history.

This story also applies to the physicians, scientists, technicians, nurses and others who contributed to the *North American Pancreatitis Study II* (NAPS2). The study represents a historic achievement, based on multiple innovative ideas and the hard work of many individuals. Innovations include, using a reverse engineering applied to decipher CP as a complex disorder [1], development of the SAPE hypothesis as a new, progressive model of disease to organize dozens of variables [9,13,14], the TIGAR-O classification system to manage multiple risk [15], use of modeling and simulation applied to understand complex processes (e.g. modeling the pancreatic duct to understand the role of CFTR in bicarbonate secretion [16–18]), organizing the North American Pancreatitis Study Group [19], and establishing *PancreasFest* (www.pancreasfest.com) as an annual meeting of investigators & friends. In addition, the entire Division of Gastroenterology, Hepatology and Nutrition of the University of Pittsburgh, where I became Chief, was reorganized to become a model for translational research [20], and proved to be the most efficient and effective recruitment center of all.

The results are fantastic and many more remain to be published. They include finding that alcoholism is the etiology of CP in a *MINORITY* of cases [19,21,22], smoking is a major, independent risk factor for CP [21,22], chronic pain drives poor quality of life [23], pain does not correlate with gross pancreas morphology [24], and both medications [25] and therapeutic endoscopy are effective in selected cases [26,27]. The first genome-wide association study (GWAS) in pancreatic disease was conducted [28], genes associated with risk, progression and complications of pancreatitis [17,29–40], genes linked to alcoholic pancreatitis risk [28], and smoking risk [41] were discovered or further defined. And the discoveries continue.

The NAPS2 study included more than 30 centers and over 100 investigators working for more than a decade to recruit 3000 deeply phenotyped subjects and to collect biological samples for biomarkers and genotyping. Most of the contributors to the NAPS2 study,

including the patients, nurses and technicians, remain anonymous, or have their names buried in a long list of authors or acknowledgments. But the analysis proves that the effort and quality of work reflected pride and commitment to the cause – and when their contributions were tested, they did not fail. I expect that this historic achievement, which is much more important to those with pancreatitis than a moon walk, is appreciated for what it is – and that the forgotten workers can say upon reflection – “because of me, this historic mission was a success!”

Rugby

I never played rugby. Rugby is a violent game that is best described as a cross between soccer and American football, but without protective gear. In the United States, rugby is not played in front of large cheering crowds or for large sums of money. In fact, playing rugby costs the rugby player their own money and time, risks injury, and has a low chance of success given that only one team in a rugby league can win. So why play rugby?

I believe the answer is simple. If a bloody participant were asked, they would answer, “Because I am a rugby player”, and “Because I am a member of *our* rugby team.” The answer reflects personal identity, community, friendship and the celebration after the game – win or lose.

Academic medicine is like rugby. It costs you your time and money (compared to other jobs), and has many setbacks, disappointments and losses. But we do it because we are academic physicians and scientists, because we are part of a team, and because we are dedicated to winning. I also believe that it is important to come together to celebrate great ideas, new innovations and the fun of *being a member* of hard working teams – where winning matters!

The July meeting of our little MMPSG has grown into one of the most exciting and collaborative annual meetings, attended by over 200 academic gastroenterologists, surgeons, pathologists, epidemiologists, scientists and pancreatologists, and now know as *PancreasFest*. The basic concepts of friendship, cooperation, encouraging trainees and tackling audacious plans of the MMPSG also spawned many new working groups through *PancreasFest* including NAPS2 [19], the *Collaborative Alliance for Pancreatic Education and Research* (CAPER, www.caperpancreas.org), the pediatric working group *INSPIRE* [42,43], and others. Have we made a difference? The answer is yes – but it required years of *innovation and hard work*.

Conclusions

I have related 5 stories from my life that provides a perspective on the accomplishments leading to the honor of receiving the George E. Palade Medal. The stories are admittedly personal but are meant to be an encouragement to the young people struggling to find their way as physicians and scientists working on pancreatic or other diseases. The lessons are that by using strategic partnerships you can overcome disabilities and weakness – but it takes innovation and hardwork. Find a worthy cause and become a champion. Develop friendships with colleagues of *your* generation and work together to achieve audacious,

long-term goals. Be sure to celebrate the advances and successes of *your* team – at *PancreasFest* or at your own research-celebrating meeting. And while you may never be awarded the Nobel Prize or the Palade Medal, appreciate the fact that you have been part of an important team and that your dedication to excellence matters, even if only a few people recognized you for your commitment and effort. But when anyone asks you what you did with your career – you should be able to say the equivalent of, “I helped put a man on the moon!”

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Biography

David C Whitcomb MD PhD, 2015 George E. Palade Medal awardee

Fig. 1. Ribbon diagram of the cationic trypsin molecule interacting with SPINK1 (red). The trypsin molecule is colored yellow and blue, with the transition at the R122 site where trypsin auto-digestion occurs in solutions with low calcium concentrations. In hereditary pancreatitis there is substitution of histidine (H) for arginine (R) resulting in loss of protection from trypsin through the self-destruction pathway. (The original report was an R117H substitution, based on the chymotrypsin numbering system prior to consensus numbering base on the gene).

Fig. 2.

One of the great achievements in the history of mankind was the national effort of the people of the United States to send men to the moon. The first human stepped onto the moon on July 20, 1969. The event is commemorated with an American postage stamp, issued on September 9, 1969.