A History of the "Discovery" of VCFS (Or Whatever You Choose to Call It): A Trainee's Perspective

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In his eloquent article in the inaugural issue of ***The Velo-Cardio-Facial Syndrome Journal,*** Dr. Shprintzen notes that an infant born in Boston with tetralogy of Fallot who, after an evaluation, is found to have a deletion in chromosome 22 in the q11.2 region, would be given a diagnosis of velo-cardio-facial syndrome (VCFS), while a baby with a similar phenotype and chromosome deletion born in Philadelphia might receive a diagnosis of DiGeorge syndrome, another born in the Czech Republic with identical features might be described as having Sedlačková syndrome and a fourth such infant born in Japan would be labeled as having contruncal anomaly face syndrome.[1] All of these infants have the same condition. However, the name that is assigned to that condition differs in different locales, based on the "Local Hero," the clinician who initially described that set of symptoms and signs, and who has served as an advocate and champion for the disorder in that region.

It is clear that simply being the first to describe a syndrome is not enough to qualify for Local Hero status. Dr. Shprintzen cites the case of William Strong, a pediatric cardiologist who described a family with what he called "…a syndrome of right-sided aortic arch, mental deficiency, and facial dysmorphism" a full decade before the article by Shprintzen et al. coined the term velo-cardio-facial syndrome.[2,3] Apparently, after he wrote his article, a case report that appeared in the Journal of Pediatrics, Dr. Strong moved onto the next subject that interested him. Following this, he rarely, if ever, gave the syndrome he described a second thought. On the other hand, after his article that described VCFS was published, Dr. Shprintzen dedicated the remainder of his professional life to furthering the study of this condition, organizing both a strong clinical research focus, developing strong ties with basic scientists, educating the public, including families of individuals affected with the disorder, and training the next generation of leaders in multiple disciplines to recognize, treat and perform research into the disorder.

It is the latter of these tasks, the training portion, which is perhaps the most important. Because when you think about it, in Philadelphia, it would have been a disciple of Angelo DiGeorge who made the diagnosis of DiGeorge syndrome in that infant with tetralogy of Fallot, while in the Czech Republic, it would have been a student of Eva Sedlačková who described the baby as having Sedlačková syndrome. In the Bronx, it would have been me, or one of my colleagues, professionals who had been trained directly by Dr.

Shprintzen to search for and recognize the constellation of findings that we know as velo-cardio-facial syndrome. Training the next generation of clinicians virtually assures that the title favored by the Local Hero, the one that in some way honors him or her, the Local Hero will live on (because, as M. Michael Cohen, Jr. has stated, clinicians would rather use the same toothbrush than the same nomenclature).

Dr. Shprintzen is well known to the readership of this journal for his clinical acumen, his devotion to providing the best care possible to individuals with VCFS and their families, and for his prodigious research output over the past 35 years. However, outside of the local professional communities in Syracuse and the Bronx, little is known about his role as an educator and mentor. In this commentary, by describing my personal experience, I will explore Dr. Shprintzen's role in the training of the next generation of scientists from multiple disciplines.

Teacher and Mentor: A Personal Appreciation

I first met Bob Shprintzen in 1980. At that time, he was Director of the Center for Craniofacial Disorders (CCFD) at Montefiore Medical Center (MMC), a full professor in Plastic and Reconstructive Surgery at the Albert Einstein College of Medicine (when he was first promoted to professor, Bob held the distinction of being the youngest person at that rank in the entire medical school faculty), a clinical researcher who had already described two "new" syndromes (VCFS and Shprintzen-Goldberg syndrome)[3,4] and who had an article describing a third "new" syndrome (which would be called Goldberg-Shprintzen syndrome) in press.[5] In short, he was an academic clinician who was near the top of the academic totem pole. As a second year resident in pediatrics at Jacobi Medical Center who had a strong interest in medical genetics, I was near the bottom of that pole. I had arranged to do an elective rotation at the CCFD.

Under these circumstances, many people in Bob's position would have chosen to have little to do with me; they would have assigned me to work with an assistant or with a trainee from another discipline who was spending time at the center. But as was the case with most of us who came to him for training, Bob took me under his wing. He also had a major interest in genetics (he was interested in virtually every discipline that touched craniofacial disorders), desiring to educate himself about the genetic basis of the conditions he had described. As a result, even though I was coming to him at such a junior level, he welcomed my input, treating me as if I were an equal. To this day, I appreciate how Bob treated me. Throughout my career, when dealing with trainees, I've always tried to emulate his approach.

During that first elective experience, which occurred over a year after the first article on VCFS appeared in ***The Cleft Palate Journal***, I came across the article by Strong that Dr. Shprintzen discusses in his lead article in the first issue of this journal (1). Although it had come from a virtual clinical research rookie, Bob did not dismiss my contribution; he took it seriously, triggering his search for, and ultimate phone call to Dr. Strong.

For the remainder of my training and into my early years as a faculty member at Einstein, I worked closely with Bob, who, at every step of the way, continued to value what I had to offer. This was not true just for me, but was true for every trainee from dentistry, orthodontia, oral surgery, ophthalmology, plastic surgery, otolaryngology and other disciplines. During those years, Bob and his colleagues made great strides in identifying the expanding phenotype of VCFS and understanding the impact that the rapidly enlarging list of clinical features had on the individual patient. Personally, while working with Bob and the rest of his team, I made a few contributions. For instance, during this period, we did the preliminary work that led to the identification of the chromosomal basis of the condition.

This came about through some simple clinical observations, essentially having the "right clinicians" in the "right place" at the "right time." In the early 1980s, the overlap between VCFS and diGeorge syndrome had not yet been appreciated. However, during those years, we noted that following cardiac surgery, some children with VCFS manifested transient hypocalcemia. Evaluation revealed that this hypocalcemia was due to hypoparathyroidism. In addition, because of the history of multiple upper and lower respiratory tract infections that occurred in many young children with the disorder, we studied the immune systems of a few children. This led to the observation that these children had mild dysfunction of the T-lymphocytes.

Because hypocalcemia due to hypoparathyroidism and T-lymphocyte dysfunction are prominent features of the DiGeorge malformation sequence, we made the case that these two entities overlapped.[6] Simultaneously, following the original observation by de la Chapelle et al.,[7] evidence was accumulating that a microdeletion in the long arm of chromosome 22 was responsible for diGeorge syndrome.[8,9] Because of these two observations, using high resolution chromosome analysis, a search was conducted looking for the presence of the deletion in patients diagnosed by Bob with VCFS; in greater than 90% of cases, the deletion was identified.[10]

It was also during the 1980s that Bob and his research group began to become concerned about potential psychiatric manifestations of VCFS. Having described the condition in the late 1970s, Bob had had the ability to follow the population longitudinally for over a decade. He and the group observed that with increasing age, serious behavioral manifestations such as schizophrenia, schizo-affective and bipolar disorders, and cyclothymia were seen in a higher frequency than would be expected by chance. The first publication reporting this observation appeared in 1992.[11]

Because Bob's interest in VCFS transcended the clinic, his role as a mentor and teacher reached beyond clinical trainees. Soon after the deletion in chromosome 22 was established as the etiology of the condition, Dr. Shprintzen reached out to Dr. Raju Kucherlapati, then Chair of Department of Molecular Genetics at Einstein, asking for help in identifying the molecular basis of the clinical features that occur in the condition. At that time, Dr. Bernice Morrow, a young post-doctoral student who had recently begun working in Dr. Kucherlapati's lab, was searching for a project. Bob arranged for Dr. Morrow to visit

him at the CCFD while he was evaluating a patient with VCFS. This experience changed Dr. Morrow's life. Now, more than 20 years later, after publishing dozens of articles about deletions from 22q11.2, Dr. Morrow is one of the world's leading experts on the molecular basis of VCFS. She cites Dr. Shprintzen's role as an early mentor and teacher as a major cause of her success.

As a young trainee, Bob both offered me the opportunity and encouraged me to take my work in any direction I wanted to go. Although he was protective of his patients and made sure to safeguard the clinical information he had gleaned from caring for them, whenever possible, he was willing to share data. He was also willing to share his time and expertise in furthering the interest of those who looked to him for guidance. As such, he proved to be the perfect teacher and mentor for dozens, perhaps hundreds of trainees.

Sadly, my time working directly with Bob came to an end in 1997 when he left the Bronx for Syracuse. However, the impact that Dr. Shprintzen had on my life has lasted for my entire career. I owe him a debt of gratitude. And so, as a result of that impact, whenever I encounter a patient with the constellations of findings that are caused by a deletion of the q11.2 segment of chromosome 22, I will refer to that patient's conditions not as DiGeorge syndrome nor as Sedlačková syndrome, not as conotruncal face syndrome nor as 22q11.2 Deletion Syndrome; instead, I will always call the condition "velo-cardio-facial syndrome." Thank you, Bob!

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COMMENTS FROM THE EDITOR:

Dear Readers,

The Editor has been placed in the uncomfortable situation of publishing an article that sounds like a festschrift (a celebratory publication in honor of an academic person) for himself. I am very grateful to Dr. Marion for his kind words. It is difficult to walk the fine line between false modesty, true embarrassment, and what may seem like self-promotion prompted by Dr. Marion's submission of this commentary to the Journal. However, as I stated when we launched this journal, it is an open access journal that eschews the process of peer review, and we have pledged to publish everything submitted. While I anticipated we might be placed in the position of publishing material that represented bad science, or material with which we did not agree, I never dreamed I would be faced with going to press with something like Dr. Marion's submission. I can assure you that I knew nothing of it until I saw it this morning. I think the last time I spoke with Dr. Marion was over a year ago and I had not yet thought of starting this journal. When I communicated my embarrassment to Dr. Marion, he insisted on its publication and suggested that he could change my name in the article to "Dr. Robert X." I replied immediately that I had seen worse misspellings of my last name (perhaps the worst being Dr. Schlepson).

I am very grateful to Dr. Marion for his very generous and gracious comments. They are especially poignant when they come from someone of his level of achievement. Dr. Marion is not only a prestigious clinician holding a prominent position in the world of

pediatrics and genetics, but he is also a writer with several best-selling books to his credit, including *Learning to Play God: The Coming of Age of a Young Doctor, The Intern Blues: The Private Ordeals of Three Young Doctors, Genetic Rounds: A Doctor's Encounters in the Field that Revolutionized Medicine, The Boy Who Felt No Pain, Rotations: The 12 Months of Intern Life, Born Too Soon, and Was George Washington Really the Father of Our Country? A Clinical Geneticist Looks at World History*. There is no source of pride in teaching greater than being surpassed by a student.