



UNIVERSITÀ DI PARMA

**Conferment of the Honorary Master's Degree
in Medicine and Surgery**

to John Alex Elefteriades

Lectio Magistralis

“Fortune Favors the Prepared”

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Great Hall of the Central University of Parma Headquarters

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It is my great honor to be with you today for this ceremony. I am deeply grateful to the University of Parma for this opportunity and to the audience for your attendance.

In a lecture at the University of Lille on 7 December 1854, the great scientist Louis Pasteur, who originated vaccination, sterilization, and the germ theory of disease, gave us the famous quote “Fortune Favors the Prepared”. More fully, he stated specifically, “In the fields of observation, chance favors the prepared mind.”

This quotation is very meaningful to me because I have experienced this play during my clinical and scientific career as a cardiothoracic surgeon specializing in diseases of the aorta, the main artery of the body. Indeed, in my life and my career, I have noted that specific, apparently random occurrences guided me to further fruitful investigations and insights—just as the Pasteur quotation signifies.

I will recount for you today a number of such apparently random instances from my life and career, any of which I could easily have overlooked, that subsequently provided opportunities for clinical and scientific advances. My hope is to sensitize young students here at Parma to be alert to and recognize similar opportunities that “fortune” will provide to you. Recognizing these opportunities may lead to clinical and scientific advances. But, without being alert and noticing and pursuing these opportunities—with a *prepared* mind—you may forfeit the potential that such opportunities present.

I will recount several such experiences from my own life and career as examples of the importance of being alert to opportunities that life naturally provides to us.

Fortune offers Opportunity #1: Coach Seibert: Fortitude

When I was 12 years old, my best friend and I wanted to go out for a school sport. By coincidence, wrestling tryouts were coming in a few days, and we decided—essentially randomly—to attend. From that day on, for the six years of my High School education, our remarkable coach, Mr. James Siebert, forged our young minds and personalities. For two hours every day—from 3 pm to 5 pm—he worked us mercilessly—to make us the best athletes and wrestlers we could possibly be. We ran, lifted weights, and wrestled to the point of sheer exhaustion—and we were transformed from children into battle-hardened young men. For me, this experience with “Coach” provided an inner resolve and strength that would stay with me lifelong.

Every day, Coach Siebert would tell us, *“Nothing you do in life will be harder than the time you spend wrestling on my team.”* And, I can confirm for you his prediction has been absolutely true. No matter how hard circumstances ever became for me during my training or during my career in the operating room, I could hear Coach’s voice in my mind. And Coach was right. No matter how hard the circumstances, whatever I was facing was easier than those overwhelming training sessions in the wrestling room.

Cardiac transplantation and aortic surgery can be challenging. I show you here photographs of two large aneurysms, one in the ascending aorta and one in the thoracoabdominal aorta. Even when facing the most challenging cardiac surgical cases, such as the aortic arch replacement, which I will show you in the upcoming video, Coach’s training allowed me always to remain calm, focused, and determined. In such operations, the patient and the brain are preserved by Deep

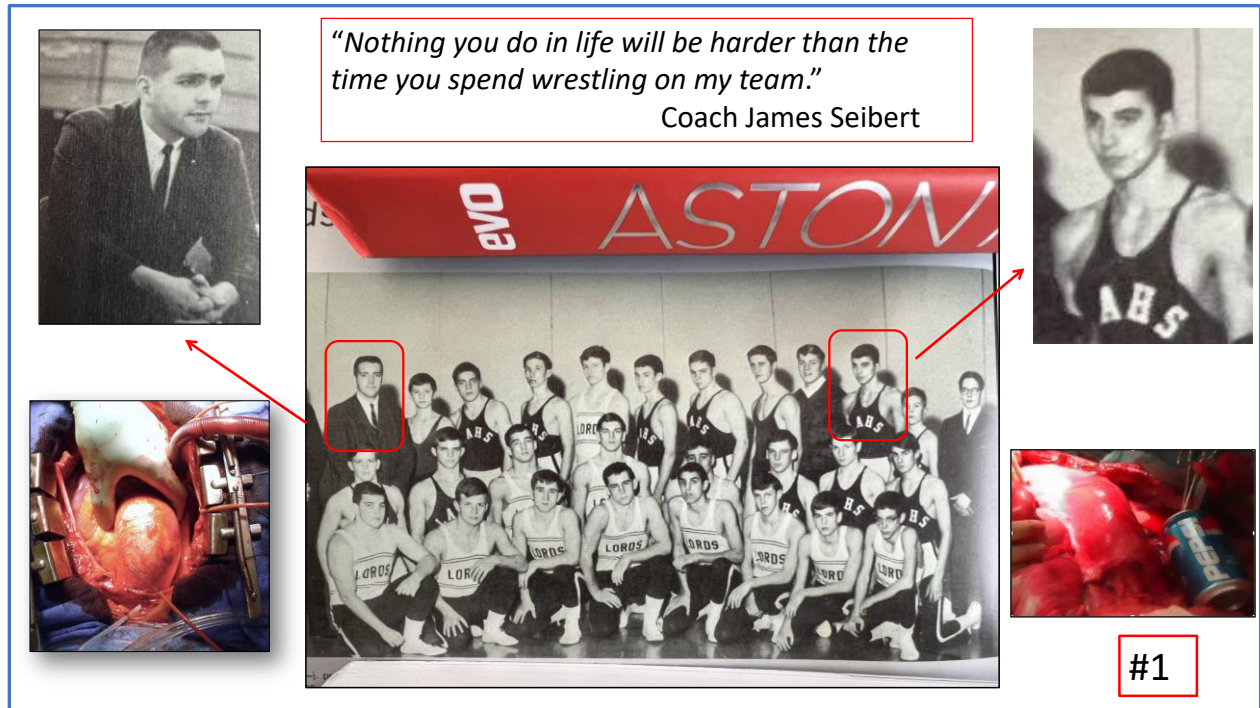
Hypothermic Circulatory Arrest—cooling the entire body to 18°C. This provides 45 minutes of excellent brain protection. However, we *must* finish within 45 minutes, or brain function will be lost. Let's watch a short video clip of an aortic arch replacement. Please note from the time stamp in the lower right corner that we finished well within the 45-minute safety interval.

This has been my “office” for the last 40 years—in the operating room all day, every day. RAI Italian Televisions spent a week with me here in this room. I will play for you now a 30 second clip from the program they filmed on the technique of Deep Hypothermic Circulatory Arrest.

Now, to show you how well this technique protects the brain, I will play the video of an elderly woman at 7 am after her aortic arch replacement under Deep Hypothermic Circulatory Arrest. Please note how well she does spelling my difficult name. I am sure I am the only one in this room who can spell my long name properly, and even I cannot spell it backwards.

I do believe that being hardened under Coach's direction gave me the calm I have always had during these technically demanding and time critical procedures.

Coach Siebert, “Thank You”. As I look back, coming under your tutelage might easily never have happened. Joining your team was seemingly a matter of chance. But, even at the young age of 12 years, somehow, I recognized that the battle hardening you imbued in us might be important later in life. You taught us to find more when our bodies and minds told us there was no more to give. I truly believe that, perhaps subliminally, my years with Coach have influenced my world view and my conduct every day since then.



Fortune offers Opportunity #2. Inception of our aortic research

It was a Saturday afternoon, my wife was away, and I was, by myself, entrusted with the care of our two young children. I was almost never alone with my children, as my work is all-encompassing, and I could be needed on a moment's notice.

Sure enough, an ultra-emergency came up in while I was out at the park with my children. Unexpectedly, I received an urgent call about a critically ill patient in distress in the Emergency Room. "John, this young woman is deteriorating rapidly. I need you here right away", said our premier Cardiologist. Dr. Cohen was always a supremely calm, composed, brilliant clinician. If he was worried, that meant a lot. A patient of his, a 31-year-old woman, had suffered an internal splitting of the aorta—which is called an "aortic dissection". This is shown schematically in the drawing you can see here. The falling blood pressure indicated that her aorta was in the process of rupturing completely into the heart sac. This is the highest-level

cardiac emergency imaginable. Furthermore, said Dr. Cohen, “Her husband is *a Professor* here at Yale.” His name was Dr. John Rizzo, and he was a Professor of Epidemiology. I dropped the children off at the house of a neighbor whom I barely knew and headed for the Hospital.

As my wife had the family car, I needed to take the car you see in the picture— a Chevrolet Corvette. I am, of course, also very partial to Italian sports cars. To make a long story short, I arrived very quickly to the Hospital, where we operated immediately, giving Carmella a new aorta, and leading her from desperate circumstances to good health, an excellent recovery, and future longevity.

While Carmella was in the hospital recovering from surgery, each day on Rounds, Dr. Rizzo would quiz me for more information about aortic aneurysm and aortic dissection. He is a supremely talented epidemiologist. “It should be possible,” he said, “to predict when a terrible event like Carmella’s aortic dissection is likely to occur.” On the third day after Carmella’s urgent operation, as we stood by her door discussing aortic disease, Dr. Rizzo and I said to each other, “Why don’t we combine our expertise (epidemiology and cardiac surgery) to see if we might someday write a collaborative paper about aortic aneurysm and its susceptibility to aortic dissection.”

Several months later, that paper was written, demonstrating that bad events happen when the aorta has grown to 6.0 cm, thus leading to our recommendation that prophylactic surgical intervention be done at an aortic diameter of 5.5 cm— before aortic dissection becomes likely.

Those events, with Carmella’s illness and meeting her husband, Dr. Rizzo, formed the basis through which the Aortic Institute at Yale University was born.

From that very first paper, we have at this stage progressed to 291 collaborative scientific publications on all aspects of aortic disease.

Thus, the Aortic Institute was born via the random occurrence of an aortic dissection in one specific patient that brought together two scientists with disparate but mutually constructive disciplines.

In the next slide, you can see Carmella when we celebrated the 25th anniversary of her aortic surgery. She became a still life artist, and the painting that you see her presenting to me now hangs on a wall in our house.

Was this all an accident—my meeting Dr. Rizzo via caring for his wife after her suffering a dramatic aortic event? Was this somehow meant to occur? Fortunately, I sensed immediately, in the moment, how important it could be to work collaboratively with Dr. Rizzo. The subsequent collaboration that life had offered—apparently randomly—proved important for my career and also for progress in the care of thousands of patients worldwide suffering from aortic aneurysms.



Carmella and her husband, Dr. John Rizzo, the superb epidemiologist who was instrumental in the founding of the Yale Aortic Institute. This is the celebration of the 25th anniversary of her extremely urgent aortic root replacement for acute aortic dissection. It was through Carmella's urgent operation that Dr. Rizzo and Dr Eleferiades first met—before conceiving and forming the Aortic Institute.

Fortune offers Opportunity #3. Recognition of role of exercise or stress in triggering aortic dissection.

About two decades ago, our long-term Nurse Coordinator, Ms. Maryann Babcock, tugged unexpectedly on my sleeve while we were making rounds. We were just outside the bed of a young man on whom we had operated urgently for an acute aortic dissection. He had survived and was doing well. “Why,” Maryann asked, “have we operated on 3 young men this year who dissected while lifting weights in the gym?”. I did not even recognize that we had done so. Here again, it turns out, “Fortune” was offering me another opportunity, via Maryann's perceptive observation.

Here you see the specific patient who caught Maryann's attention, the 3rd weightlifter in one year to suffer aortic dissection while exercising. Do not get the wrong idea from the bandana and the tattoos. He is a responsible young man and a high school teacher. You can see my scar on his chest from his urgent aortic replacement. As you can see, he has returned to the activity that triggered his aortic event.

My team and I went to work immediately. I have been a weightlifter since the age of 13, as was my son. For my son's 9th Grade Science Project, our anesthesiologists and I set up an experiment in my home gym, with equipment that could monitor the *instantaneous* blood pressure during a weight lift of different proportions of our own body weight. We were astounded at the results. As you see in the chart, our Anesthesiologist hit 320 mmHg lifting 75% of his body weight. For safety, we stopped him at that level. The rest of us hit very high pressures as well, when lifting 100% of our body weight. This recognition of astronomical elevations of blood pressure represented totally novel information, gathered because of Maryann's perceptive recollection of a pattern of young weightlifters suffering acute aortic dissection.

My Son's science project received a mediocre grade, but at the age of 15, he became an author on the corresponding scientific article in the highly respected journal *JAMA*.

Our team immediately went a step further: We interviewed all our aortic dissection patients to determine *what they were doing* at the moment that the dissection pain came on. Aortic dissection represents the most severe pain a human

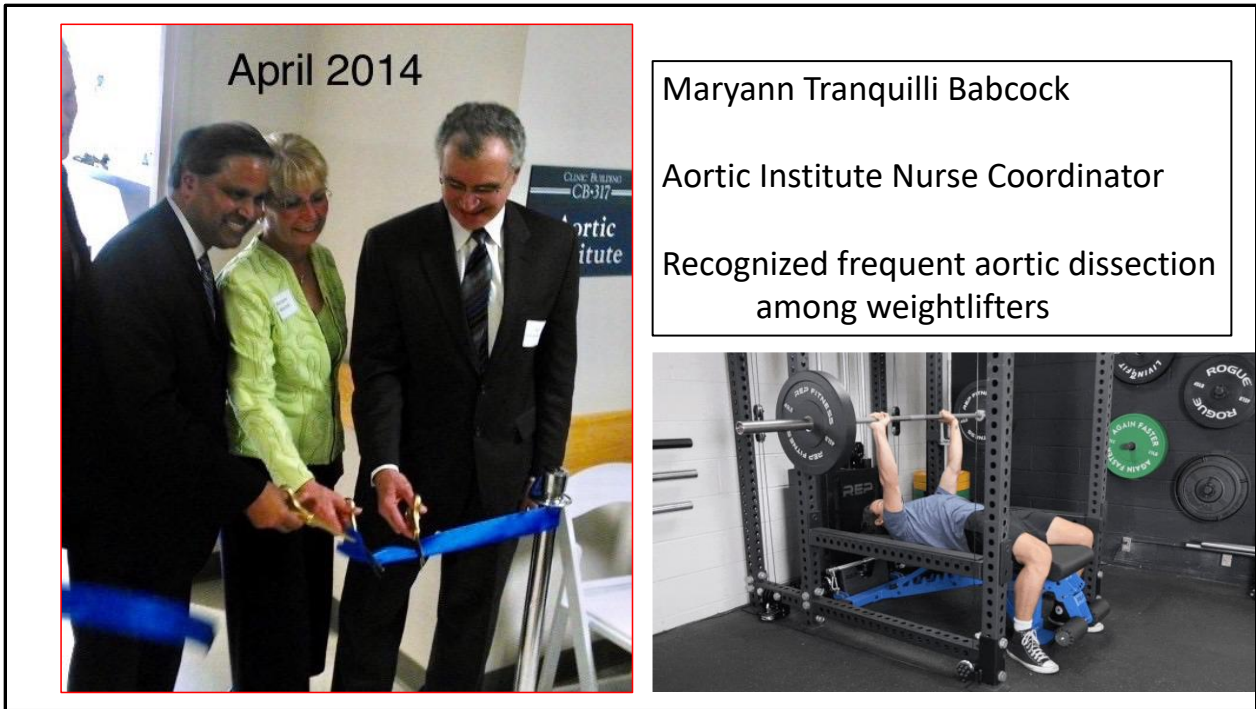
being can feel. So, their recollections were vivid and detailed. Remarkably, two-thirds of our patients recalled a specific, severe physical or emotional strain.

These observations allowed us to formulate the first pathologic analysis of how aortic dissection picks *a specific time and place* to occur. First, these patients have an inherited genetic defect that allows formation of an enlarged, thinned out aortic aneurysm. Then, a specific severe exertion or emotion intervenes, and the dissection occurs—as the weak aortic wall is overwhelmed by the astronomically high blood pressure from the physical or emotional strain.

For over two decades since we published this scenario, no one has challenged this general understanding of the sequence of events leading to aortic dissection at one specific year, month, day, hour, and moment in time.

Subsequently, we chronicled 33 unfortunate cases of young men experiencing aortic dissection during strenuous physical exertion. One of the affected young men was a heart surgeon. My team and I love and respect weightlifting and other physical exercise and endorse them fully—but only after the athlete has been tested by cardiac ECHO to make certain he does not, unknowingly, harbor an ascending aortic aneurysm.

Fortune gave me the benefit of Maryann's keen recollection of our three young athletic dissection patients. All I had to do was to pay attention and to recognize the importance of her recollection. From there, it was easy to carry forward into scientific investigation.



Long-term Nurse Coordinator Ms. Maryann Babcock Tranquilli, who called to attention her observation that we were encountering a disproportionate number of weightlifters suffering acute ascending aortic dissection. She is seen here cutting the ribbon at the opening of a new Aortic Institute facility.

Fortune offers Opportunity #4. Three generations in one family: The recognition that thoracic aortic aneurysm runs in families.

In 1998, medical science knew that Marfan Syndrome, in which great physical height is associated with aortic aneurysm, was inherited in families. The vast majority of aneurysm disease and aortic dissection, however, was thought to be random in occurrence and of uncertain origin.

One morning, in 1998, I was making rounds with my team. We were at the bedside of a middle-aged woman who had dissected (internally torn) her aorta. Two days earlier, I had replaced her aorta in a very urgent, high-risk surgical procedure. She was well enough this morning to carry out a short conversation. “Has anyone in your family had a similar problem,” I asked her. “Doctor,” she said, “don’t you remember? You operated on my mother 12 years ago for the very same problem.”

Of course, I did not remember that case among the many thousands performed since that time. I was surprised to hear that I had operated on the patient's mother. Medical science had, at that time, no inkling that aortic dissection was anything but a random event. "Has anyone else in your family been affected," I asked. That is when the tears began to flow. She was un-consolable. "It was my little girl," she said. "I don't know. They told me it was her heart." We looked up the hospital records, and, indeed, her young daughter, at 12 years of age, was the youngest individual ever to die of aortic dissection at Yale University.

This recognition hit me like a ton of bricks. I was flabbergasted that three generations in one family had been affected.

Immediately, we conducted interviews of all our prior patients with aortic dissection. Here you see the 26 positive pedigrees, indicating familial inheritance, among the first 100 patients whom we interviewed.

Thanks to that one lady with the three affected generations, medical science suddenly found out that thoracic aortic aneurysm and dissection are inherited in a familial, genetic pattern.

From that point on, our team, and others, have been able to characterize the genetics of aortic aneurysm with great precision—saving countless lives by prophylactically investigating family members of affected patients.

Fortune offers Opportunity #5. A Dwindling Audience and the molecular genetics of aneurysm disease.

The greatest cardiac surgeon of all time, Dr. Denton Cooley, who developed all essentially all cardiac surgical techniques in the 1950s and 1960s, tells a funny

story. Early in his career, he was sitting in the audience of a small scientific meeting, waiting to deliver his own talk. As he looked around, he saw the audience growing smaller and smaller as the lectures went on. Finally, he was called on to give his talk. There was one doctor left still sitting in the front row. “Thank you, Sir,” Dr. Cooley said to the gentleman in the front row, “for staying to hear my talk. I really appreciate that.” “Well,” said the gentleman in the front row, “you can thank me if you wish, but I am the next speaker!”.

We have probably all given lectures to small audiences. This happened to me about 20 years ago in Washington, DC. The audience was indeed very small, but that did not bother me. I gave my aneurysm-related talk, and a woman among the few remaining audience members ran up to the podium and said, with no introduction, “I want to work with you!”. This was no ordinary person who had run up with her invitation. This was 2001, and the human genome had just been sequenced, by the dramatically inventive and productive company Celera Genomics. This sequencing of the human genome stands as a great milestone in human history. Which human being was the first in history to be sequenced? Well, it was their visionary, iconoclastic, and, reputedly, self-centered leader, Craig Venter. He was the first human being in history to have his genome sequenced—at an estimated cost of 3 billion dollars. The lady who had rushed up to the podium to express her desire to work with me was a key scientific leader, Dr. Olga Iakoubova, from the Celera team. Of course, I was beyond thrilled to work with Dr. Iakoubova, who had come up to speak with me after my lecture.

We went on to conduct multiple studies together on the detailed molecular genetics of thoracic aortic aneurysms, all made possible by my having talked at a small, unimposing meeting in Washington, DC. This allowed our later extensive

investigations on aneurysm genetics, culminating last year in our discovery of three completely new aneurysm genes—all stemming from the random encounter I have described.

To the young investigators in attendance today, I say to you, please keep in mind: You never know who may be sitting in your audience, be it large or small.

In conclusion, what can we say? I have revisited with you some key turning points in my career—in which life offered me major scientific opportunities. I am certain the Parma faculty have encountered and benefited from similar turning points in their careers. By some good fortune, I was able to recognize these opportunities in the moment and to capitalize on them. Was this chance or serendipity at work at these critical junctures in my life? Was this fate? How did I have the good fortune to recognize these opportunities that might easily have been overlooked?

I do not know the answers to these philosophical questions. What I do hope is that, by recounting to you these seemingly random career-defining episodes in my life, I may encourage young trainees here in Parma to be vigilant, so as to recognize and pursue the many opportunities that Fortune will present to them in their young lives.

I do believe that Professor Pasteur highlighted a real truth about life: That “Fortune does favor the prepared mind”.

Thank you for the opportunity to be with you today and for the overwhelming privilege to receive this Honorary Degree from the historic University of Parma.