

Joseph L. Goldstein

Let me begin by thanking Dan Foster and Jean Wilson for their wonderful and lively presentations. I assume that you all know that Dan and Jean are both native-born Texans, which means that they are terrific tellers of tall tales. So don't believe a word you've heard!

It is truly a great honor to join the distinguished company of previous Kober medalists. And it's also a great honor to share this award with my long-term partner in crime, Michael Brown, about whom I'll have more to say in a moment.

Growing up in a small town in the Old South, I was relatively insulated from the world of ideas and intellectuals. Kingstree High School was a far cry from the Bronx High School of Science. But nonetheless, I aspired to an individuality, yearned for achievement, and longed to succeed in some realm of otherness that I could not define at the time.

I did not discover that mysterious otherness until I became a medical student at UT Southwestern in 1962 and experienced the thrill of medical research. As you have just heard, at Southwestern I fell under the spell of Donald Seldin, a man of towering intellect, immense erudition, keen zest for life, irrepressible curiosity, and deep respect for clinical scholarship. As a teacher, Dr. Seldin was a true maestro in the way he taught clinical medicine to third-year medical students. His discussions of pathophysiology were enriched and enlivened with stories of the virtuoso performances of famous clinical investigators. Seldin was the Toscanini of the student CPC. If a patient with pernicious anemia were presented to Dr. Seldin, he would tell the remarkable story of how William Castle discovered intrinsic factor. If the patient was a young woman with amenorrhea and hirsutism, we learned about the adrenogenital syndrome and how Fuller Albright, in a tour de force of clinical reasoning, figured out its pathophysiology and predicted its treatment with suppressive cortisone.

If the patient had hemophilia, Dr. Seldin told us how Oscar Ratnoff was unraveling the complexities of the clotting cascade by studying the blood of his famous patient Mr. Hageman.

What a wonderful way for a student to be introduced to the beauty and excitement of clinical research. Given recent changes in medical education, I would be pleasantly surprised if any medical students have ever heard of Castle, Albright, or Ratnoff. It saddens me to realize that the future leaders of clinical medicine will have no appreciation of their rich academic heritage.

To paraphrase the Seldin dictum of the 1960s and put it into a contemporary context, each sick patient has a sick molecule and the route to medical progress is to investigate sick patients and their sick molecules. Seldin's tutorials made me a true believer in the church of biomedical research.

In 1966 I left Dallas and moved to Boston to begin a medical internship at the MGH. About three months into the internship, I was on duty in the emergency room with a fellow intern, Mike Brown, when a patient with partial lipodystrophy presented with acute meningococcal meningitis. This fascinating patient triggered a lively discussion between Mike and me on what might be the metabolic defect in

lipodystrophy. Little did we realize that the two of us would produce a mouse model of lipodystrophy 33 years later. It was clear from this first discussion that Mike and I shared an enthusiasm for sick patients and sick molecules, a subject on which we have had innumerable and interminable discussions during the last 36 years.

And let me remind you that 36 years is a really long time. It is seven years longer than the entire time it took Mozart to compose 41 symphonies, 27 piano concertos, 25 string quartets, 17 operas, and 516 other pieces of music. This is a sobering fact when you consider that Mozart accomplished all of this by himself — he didn't need the likes of a Brown-Goldstein collaboration.

But not all musicians are as clever as Mozart, and some of the most original and popular music of the 20th century resulted from legendary partnerships, such as those of Rodgers and Hammerstein, who worked together for 19 years, and Lerner and Loewe, who worked together for 17 years and wrote the most popular Broadway musical of all time, *My Fair Lady*.

The secret to the success of Rodgers and Hammerstein and Lerner and Loewe is the same that has worked for Brown and Goldstein. The secret is to have lots of ideas, whether they are



Figure 1

Le Mouvement perpétuel (Perpetual Motion) by René Magritte. 1935. Reprinted with permission of the Artists Rights Society.

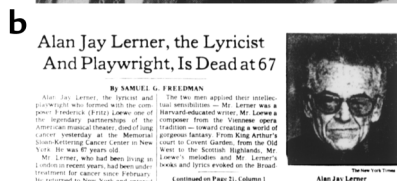


Figure 2
The Deathblow to a long-term partnership. (a) Alan Jay Lerner, left, and Frederick Loewe, right, the legendary partnership of 17 years that produced *My Fair Lady* and many other hit musicals on Broadway. (b) Obituary of Alan Lerner published on the front page of *The New York Times* on June 15, 1986. (c) Obituary of Frederick Loewe published on the front page of *The New York Times* on February 15, 1988.

the embarrassment of sharing each other's lunacy. Once two collaborators become accustomed to thinking aloud, the constant dialogue creates a remarkable energy and synergy of the minds, often propelling the research into unforeseen directions. The type of perpetual motion that can be generated from the meeting of two minds is illustrated in the painting in Figure 1 by the surrealist artist René Magritte. I will leave it to each of you to decide whether it's Brown or Goldstein who pulls his weight!

Long-term collaborations of the type that Mike and I have enjoyed are rare in both the musical world and the scientific world. But, remarkably, 11 of the last 20 Nobel Prizes in physiology or medicine have been awarded to two scientists who did their prize-winning work together in the same laboratory. Mike and I hold the record for the longest collaboration among these 11 pairs, having worked together for 30 years. Gertrude Ellion and George Hitching worked together for 23 years, David Hubel and Torsten Wiesel for 20 years, and Mike Bishop and Harold Varmus for 19 years. The only scientific partnerships longer than ours is that of Cori and Cori, who worked together for 33 years on glycogen metabolism, for which they received the Nobel Prize in 1947.

Although successful partnerships have many advantages, Francis Crick complains of one annoying problem — people are always getting him mixed up with Jim Watson. Mike and I have the same problem. People are always calling me Joe [sic].

This turns out to be a trivial problem compared to what *The New York Times* did to Lerner and Loewe, the legendary partnership that produced *My Fair Lady*. Figure 2a shows a picture of Alan Jay Lerner (left) and Frederick Loewe (right). When Alan Lerner died in 1986, *The New York Times* featured his obituary on the front

page together with a picture of him wearing his characteristic dark glasses (Figure 2b). Two years later Frederick Loewe died, and he too received a front page obituary in *The New York Times*. But *The Times* got Lerner and Loewe mixed up and published Lerner's picture alongside Loewe's obituary (Figure 2c). My only hope for obituary fame is to make sure that Mike lives forever.

The take-home lesson from the long-term partnerships of Broadway and Dallas is clear: Don't be afraid to enter into a long-term collaboration, provided the chemistry is right and you choose a partner who is smarter than you.

Michael S. Brown

I want to thank Dan Foster and Jean Wilson for doing so much homework. Three years ago I helped Joe write the Kober Medal Presentation for Jean, and I know how much work it is. For us it was a labor of love, and I hope that Dan and Jean feel the same way.

Joe's presentation to Jean featured several Magritte paintings, and you've seen more today. There's a Magritte for every purpose. Some of you may remember Jean's response — another Magritte — shown in Figure 3. It shows how a Kober medallist feels. This year, it's different (Figure 4). This proves that two swelled heads are bigger than one. Now we've started a new tradition — dueling Magrittes.

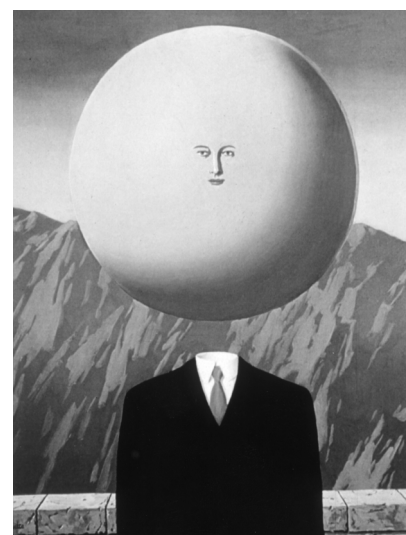


Figure 3
L'art de vivre (The Art of Living) by René Magritte. 1967. Reprinted with permission from the Artists Rights Society.

good or bad. In order to be creative, you have to have lots of bad ideas because it is only by sorting through the bad ideas that you hit upon the rare good idea. And this is where a good partner comes in. In the beginning of any new adventure, whether it be conceiving the personalities of Eliza Doolittle and Professor Higgins or conceiving the idea of an LDL receptor, the landscape is always blurry, and there are multiple possibilities for advancing different theories and taking different directions.

Choosing among the multitude of theories and directions for experiments is greatly facilitated by the constant dialogue that ensues between two different minds that are accustomed to batting ideas back and forth and that are comfortable with criticizing each other's way of looking at the world. It's also much more fun to play with ideas and theories and test them in the laboratory when you are working closely with someone who understands all the subtleties of the problem. The constant dialogue between two close partners allows you to get rid of the bad ideas rapidly so that you can discover the good ones.

The biggest challenge to establishing a long-term collaboration is to get into the habit of thinking aloud. When you think alone, you have the luxury of coming up with lousy ideas and secretly rejecting them. But with a collaborator, you have to overcome

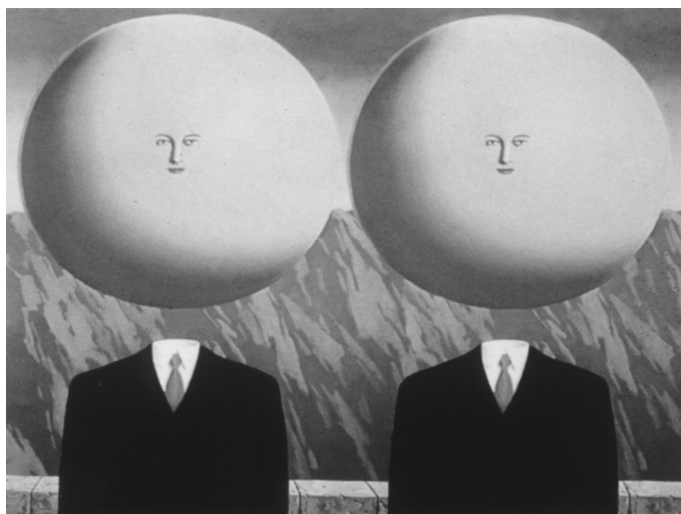


Figure 4
Updated version of *L'art de vivre* by René Magritte — adapted for two Kober medal recipients.

The four of us — Dan, Jean, Joe, and I — have something in common. We are all sons of Donald Seldin. But I differ from the other three. They are legitimate. They were created by Seldin and born into medicine. I was adopted later in life. Joe, Jean, and Dan were raised in small Southern towns: Kingstree, South Carolina; Wellington, Texas; and El Paso. They went to Southern colleges. Donald Seldin was the first Eastern intellectual that they ever knew. They met him when they entered medical school fresh out of college. I was born in Brooklyn and got my education at Penn, the oldest American university. I didn't meet Donald Seldin until after my residency when I came to Dallas as a GI fellow.

What bait did Seldin use to seduce four bright young men and scores of others like us? I can tell you what it was for me. As you have heard, I had done my residency at the Massachusetts General Hospital which was then, and may still be, the most famous and successful clinical training program in the world. Every year the top student at Penn applied to the MGH, and every year that student was rejected. The last Penn student accepted at the MGH was John Potts, and that was thirteen years earlier. For some reason, I was accepted. Of course I was thrilled —

until they sent the list of my fellow interns. There was Joseph Goldstein from Southwestern Medical School in Dallas, Texas. The year was 1966, only three years after the Kennedy assassination. Dallas didn't have a very good image, and I had never heard of Southwestern Medical School. I thought it was a Bible College. Why would the MGH accept Joseph Goldstein? Maybe no one had applied that year, and so they were desperate. That would explain my acceptance as well. These doubts were dispelled on the first day of internship when I met Joe and realized that somehow he seemed to know more than anybody else. He thought deeply about his patients, and he was interested in the mechanism of their diseases. He didn't want to know only what the patient had, but he wanted to know why the patient had it and how it came about. These were the questions that turned me on as well. This common interest in mechanisms ignited our friendship.

But where had Joe acquired this mechanistic curiosity? I was determined to find out, and so I visited Dallas, and there I found a dozen Joe Goldsteins running around Seldin's Department. The whole department focused on disease mechanisms. Everyone had a laboratory. You could

have called it the Department of Applied Physiology except that they took very good care of the patients at Parkland Hospital.

I quickly decided to move to Dallas, but my hardest job was convincing Alice. She was a New Yorker like me, and Dallas was the Deep South. But Alice put aside her doubts, and she made a wonderful life for herself and our daughters in Dallas. If I didn't have a wife like Alice, Joe would have had to look much harder for a partner — so he and I both owe everything to Alice.

When I arrived in Dallas, I was thrilled by the departmental conferences that Seldin dominated like a great oracle. These conferences were peppered with fiery arguments and salted by Seldin's demand for evidence to support every assertion. There are two kinds of evidence that one can use to win arguments in medicine. The first is inductive and observational. You go to the library, find the largest series of patients, and list their symptoms. The other evidence is deductive. You can reason from physiologic principles. At MGH you won arguments by induction. The person with the biggest series or the longest clinical experience won. This is natural. Clinical observations are the alpha and omega of medicine. All of our knowledge begins and ends with clinical observation. But for me, personally, this was not enough. I wanted to know the mechanisms of disease. I wanted to do science and medicine. MGH had great scientists, including Alex Leaf, the Chief of Medicine, but they were generally not the people who ran the wards. At Southwestern, scientists ran the place. You won arguments by deduction. Clinical observations were essential, of course, but they weren't complete unless you could explain the observation by a rational mechanism.

Now Seldin's children have grown, and we all have scientific children and grandchildren. I fervently hope that these young scientists have the same opportunity for mechanistic understanding that we had in the last third of the twentieth century in Dallas, Texas.