

Joseph Goldstein and Michael Brown Demoting Egos, Promoting Success

Ruth Williams

A friend is one soul that lives in two bodies
—Aristotle (384-322 BC)

“He who finds a friend finds a treasure.” This adage is undoubtedly one of the absolute truisms of life, which is why it appears in so many cultures and languages throughout history, dating back to the Greek playwright Menander (c. 342-291 BC) and the Roman playwright Plautus (c. 254-184 BC). The lifelong friendship between Michael Brown and Joseph Goldstein is a beautiful illustration of the veracity of this adage. As they tell us in this interview, not only their personal lives but also their scientific work have been enormously enriched by their friendship. So deep is their bond that it is practically impossible to separate one from the other, personally and scientifically (and so, we had no choice but to set up a joint interview). This reminds me of the famous answer that Aristotle (384-322 BC) gave when asked the question, “What is a friend?” “One soul that lives in two bodies,” he said.

Among many other lessons, this profile of Brown and Goldstein should make us reflect on the incalculable dividends that can accrue from a true friendship. On a personal level, friendship is one of the greatest consolations that we have in this world. It illuminates and warms our life. It transforms everything. As Francis Bacon (1561–1626) put it, “Friendship doubles joys and halves grief.” The great minds of classical antiquity felt even more strongly. For example, Cicero (106-43 BC) went as far as stating that “without friendship, life is nothing,” echoing Aristotle’s earlier assertion that “without friends, no one would choose to live, even if he had everything else.”

In today’s increasingly impersonal society, the need for friendship is acute, perhaps even more so than in the past. And certainly, this is the case in science. The world of biomedical research is a highly competitive ecosystem, replete with unbridled selfishness and populated by morbidly hypertrophic egos. In this difficult environment, friendship offers a much-needed respite that helps us find the fortitude necessary to deal equanimously with the many strange personalities that we encounter in

our daily work. Unfortunately, partnerships such as the one between Brown and Goldstein are exceedingly rare in science, and is it not possible—as the two Nobel laureates point out below—to teach young investigators to develop this type of relationship. It must arise spontaneously from the right chemistry. Lucky are those who find it!

—Roberto Bolli

When Joseph Goldstein and Michael Brown decided to merge their two laboratories at the University of Texas Southwestern in Dallas, in 1972, it was the start of what is probably one of the longest running and most successful partnerships in science. It was also the start of groundbreaking research into the regulation of cholesterol metabolism, work that earned both of them the Nobel Prize in Physiology or Medicine in 1985.

The pair had first met 6 years earlier as fresh-faced interns at the Massachusetts General Hospital (MGH) in Boston. It was immediately apparent that they shared a great passion for research. After their internships, they took research positions at the National Institutes of Health (NIH) in Bethesda, Maryland. Brown studied enzymology with Earl Stadtman, while Goldstein studied molecular genetics with Nobel laureate, Marshall Nirenberg. In addition to their research, the young MDs also had clinical commitments. Goldstein’s was at the National Heart Institute (now the National Heart, Lung, and Blood Institute), and it was here that he first came across patients with familial hypercholesterolemia (FH). The disorder captured Goldstein’s attention, and he discussed it at great length with Brown. These discussions sowed the seeds of Goldstein and Brown’s future collaboration.

Soon after its formation, the Brown and Goldstein laboratory reported the discovery of a cell surface receptor that binds cholesterol-carrying low-density lipoproteins (LDLs)—the cholesterol transporters of the blood. The laboratory also reported the mechanism by which this LDL receptor regulates feedback control of cholesterol synthesis.^{1,2} Their work showed how blood cholesterol is controlled and provided strong genetic evidence that elevated LDL levels are sufficient, in themselves, to cause heart attacks.^{3,4} Their discoveries formed the basis for future clinical trials into cholesterol-lowering drugs, such as statins. As binding of LDL to its receptor triggers LDL entry into the cell, the work also elucidated the mechanisms of receptor-mediated endocytosis.^{5,6} After receiving the Nobel Prize for this body of work, Brown and Goldstein promptly returned to the laboratory where they continue to study cholesterol metabolism pathways to this day.^{7–9}

Goldstein grew up in a small town in South Carolina, Brown in New York and Philadelphia. But despite their disparate origins, the pair could not be more scientifically

The opinions expressed in this Profile in Cardiovascular Science are not necessarily those of the editors or of the American Heart Association. E-mail ruth.williams@absw.org.uk
(*Circ Res.* 2010;106:1006-1010.)

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Circulation Research is available at <http://circres.ahajournals.org>
DOI: 10.1161/RES.0b013e3181dcab4d



Figure 1. Joseph Goldstein.



Figure 2. Michael Brown.

compatible. After 44 years together, they are not only the leading authorities on cholesterol metabolism, but also on how to maintain a long and happy working relationship. They told *Circulation Research* all about the perks of partnership.

The Meeting of Minds

Both of Your Families Were in the Clothing Business. Where did the Idea to Study Medicine Come From?

Brown: They were in the clothing business, but on different sides: Joe's father ran a clothing store and my father sold textiles to clothing manufacturers.

Goldstein: My father used to go on a clothes-buying trip every year to New York. Come to think of it, he probably bought from the people Mike's father sold to.

Brown: Even though he wasn't a scientist or doctor himself, it was my father that planted the medicine seed in me. He was a hard-working salesman all of his life. It was a difficult life, and he saw medicine as a field in which you didn't have a boss. Doctors were the only people he knew who seemed to be independent, so that's what he wanted for me. It was always assumed I was going to be a doctor. I'm not sure where that idea truly originated. My father just used to say that I wanted to be a doctor from the time I could talk.

Goldstein: There was actually some family influence on my side too. I had a cousin who was a doctor, and I visited him often. That sparked an interest in medicine for me.

Besides Family, What Else Sparked Your Interest for Science?

Goldstein: I went to high school in a small town in South Carolina. But despite its size, we had wonderful teachers. My chemistry teacher was especially wonderful, and that's what really got me interested in science.

Brown: My interest in science was less to do with school and more to do with my interest in amateur radio operating. When I was 13, I got my radio-operating license and I used to build transmitters and receivers. I didn't design them or anything. I just built them from kits. But there is a lot of trouble shooting that one has to do when putting together a complicated piece of electronic equipment, and that's what fascinated me. I would build it, it wouldn't work, and I would have to figure out what had gone wrong. Basically, that's 97% of the job in science.

You Met After Medical School When you Were Both Interns at Massachusetts General Hospital. Tell me About That.

Brown: I went to the University of Pennsylvania medical school, which is the nation's oldest medical school, and Joe went to UT Southwestern medical school, which was at that time one of the youngest medical schools in the country. Frankly, I had never heard of that school, and I was surprised that the Massachusetts General Hospital would accept somebody from such an unknown school. I really had very low expectations of Joe. Within a day or two of our residency, however, it was clear that Joe knew more about medicine than any of the other residents, in fact, probably more than half of the faculty.

We immediately struck a bond. After our long days on the wards were finished and the patients were sleeping, we would sit around and talk about the underlying pathology of their diseases. We would discuss the basic biology. We shared an interest in trying to get a deeper understanding of what we were dealing with. Most of our fellow residents weren't interested.

Goldstein: My memory of meeting Mike is that, of the 14 interns, Mike was by far the youngest-looking one. He looked like a baby. [Laughs] That was my first impression. We certainly developed a natural affinity for each other, talking about these cases and so on.

Brown: Also, we both liked to play Duplicate Bridge. So, in the few evenings that we would have off, we would play. We weren't too good, but it certainly established our friendship.

Goldstein: Yeah, you have to learn a lot of trust and teamwork when you're playing Duplicate Bridge.

Building the Bond

Then you Both Went to the NIH?

Brown: Yes, but that was really by chance. We had both applied independently when we were in medical school before we even knew each other. At that time, the National Institutes of Health was probably the leading place for young people to get started in biomedical research, and since both of us were interested in that, we applied and were accepted. We were in separate labs but we maintained our friendship.

You Both Ended up in Dallas, But Joe you First Went to Seattle. Why?

Goldstein: When I was a medical student at Dallas, the Chairman Donald Seldin, offered me a job to start a medical genetics department if I went to get training. In the late 1960s, there were only a few places in the US that had a medical genetics program, one was at Johns Hopkins Medical School and another was at the University of Washington in Seattle. I opted for Washington and trained for 2 years with Arno Motulsky.

So, It was Always Your Intention to Return to Dallas. But Mike, Why did you Decide to go?

Brown: Joe kept telling me what a great place it was for young people who had the kind of interests that we had—bridging between science and medicine. There were a couple of professors from Dallas that visited the MGH when we were residents, and they were very impressive people. I realized that the quality of work going on in Dallas at that time was very high. I came for a visit, and it only confirmed my expectations.

The serious problem was my wife, Alice. Dallas did not have a great reputation. It was only a few years after the assassination of John Kennedy. In fact, Joe was a medical student when Kennedy was shot, and UT Southwestern runs the hospital Kennedy was brought to.

Alice and I grew up in the northeast, and we considered Dallas to be the deep south—ultraconservative and closed society—not the sort of place that we would want to live in, but the medical school was the complete opposite. It was full of people who were open and inquisitive and really trying to think deeply about disease.

I give Alice great credit for her willingness to move with me to Dallas. Our other opportunity was in San Francisco, and I know she would have preferred that. But, she came to Dallas nonetheless knowing it was best for my career.

How did you Make the Decision to Join Your Labs?

Brown: I actually came to Dallas and started my laboratory a year before Joe. That was important because Joe was already extremely well-known here. He was known as the brightest medical student that they had ever seen and will ever see again.

Goldstein: Oh, I don't know about that. [Laughs]

Brown: When Joe was a medical student, the other students went to the Dean and said they had to have a separate curve for grading Goldstein.

At any rate, he was already very well known, and his return to Dallas was very much anticipated. Because I arrived a year before, it gave me the chance to build up a reputation, as well. So, when the two of us started working together, we were considered as equals. I think that was very important for the partnership.

Goldstein: To begin with, our labs were geographically separate, but I would say within a year or so of my arriving in Dallas we had joined.

Brown: We had talked about working together to solve the problem of familial hypercholesterolemia when we were at the NIH. In Dallas, it started out as a side project for both of us that we collaborated on. But when we began to make interesting discoveries, we dropped our independent projects and started working on it full time.

Inspirations and Ethos

Who are Your Scientific Inspirations?

Goldstein: I was strongly influenced by Donald Seldin, the Chairman of Medicine here. He's arguably the best Chairman of Medicine of the last 50 years. He started the medical school here. He is a maestro of the biomedical enterprise. He is highly intelligent, inquisitive, energetic, peppy. He has a broad knowledge of medicine and knows how to integrate it into science, and he's also a phenomenal teacher. He was a great inspiration.

Also, at the NIH, I worked in Marshall Nirenberg's lab. In fact, I was there the year he won the Nobel Prize. He was just 31 when he figured out the genetic code and changed the world of science, so that was an incredible inspiration for a young person.

Brown: I would echo what Joe said about Donald Seldin. He built a department where science was at the core of patient care, and he was very demanding, challenging, and passionate about science and medicine. He was a tremendous inspiration for a whole generation of students. Also, my mentor at the NIH, Earl Stadtman, was a great enzymologist. He triggered my lifelong interest in enzyme regulation.

Goldstein: I should also add Arno Motulsky to my list of inspiring mentors. Not only did I learn a great deal about genetics from those 2 years with him, but he also taught me the importance of thinking about and focusing on the big problems of medicine and science.

Brown: It is interesting that Joe and I have both mentioned the people we worked with at the NIH. These two were both fundamental scientists. They never thought about disease. They were only interested in unraveling mechanisms of biology. It was that juxtaposition of having trained with fundamental scientists and then being exposed to people who wanted to apply science to medicine that was a motivational force for Joe and me. When we started working together, the first thing we did was to reduce the complex cholesterol problem down to a simple system where we could answer questions precisely and get data every day.

I think that exposing medical students to basic scientists who know how to do reductionist thinking is tremendously important for training the next generation of physician scientists.

How Hard do you Work?

Goldstein: In the old days, before the Nobel, for the first 10 or 15 years of our research, we were really very hard workers. We were in the lab 7 days a week. But in the last 20 years, we haven't really done lab work ourselves. It's done through the students and postdocs. We're now just involved in designing their experiments and teaching them how to write papers and so on.

Brown: In those early years we didn't have students or postdocs. For about the first 6 years, we just had a couple of technicians. Actually, I think this might be a valuable thing for young budding physician scientists to know: during those first few years when our science was at its most intense, we were fully active in a clinical department. We made ward rounds. Joe ran a genetic diseases clinic, and we were both active in teaching.

How Important do you Think Hard Work is to be Successful?

Goldstein: Well, in those days, it didn't really seem like work. It seemed like fun. It was so exciting.

Brown: When my first daughter, Elizabeth, was born, in 1973, she arrived late in the evening, and at about one or two in the morning, I left my wife and baby sleeping, and I went over in the pouring rain to Joe's apartment so that we could start planning experiments for the next day.

Practicalities of Partnership

How Does Your Working Relationship Manifest?

Goldstein: There's a constant dialogue where ideas are batted back and forth, most of which are bad, but somehow the good ones filter through. That's one of the advantages of having a partner whom you've worked with for many years, because we know each other's style and know how to criticize each other without hurting feelings.

Brown: One of the unique things about our partnership is that we supervise all of our students and postdocs together. So, they all have two mentors.

Our offices are adjacent to each other, and there's a door between and the door is always open. So, if one of the students comes in to talk to Joe and I think they are having an interesting conversation, then I'll just pop my head in. It is an unusual experience for the students. They have to adjust. For example, if there's a problem with an experiment, Joe might suggest one way to solve it and I might suggest another way. The smart ones do both.

Goldstein: And the ones that try to play one of us off against the other learn pretty fast that that doesn't work.

What about When It Comes to Writing Papers. How Does That Work?

Goldstein: In the early days, we wrote them all together. Now, we have evolved a style where I work with the students and postdocs on the legends and the methods and then Mike takes over with the results and discussion. Then, of course,

there are about 25 draft versions before we are happy with the final product.

Brown: The students now are amazed at how hard it is to write a paper with us. We go over every single detail multiple times and send the students back to the lab to do more experiments and answer other questions—it's laborious.

In the old days before computers, we still went through multiple drafts of papers. In those days, one of us would literally pick up a pencil and we'd dictate to each other.

Culturing Collaborations

Why do you Think There are Not More Collaborations Like Yours in Science?

Goldstein: Well, actually, if you look at the Nobel Prize in Medicine, there are a high proportion of partnerships, even if some of those were short lived. There's Watson and Crick, Jacob and Monod, Hubel and Wiesel, Bishop and Varmus, and others. There must be something about the meeting of the minds that enhances creativity.

Brown: But the partnerships normally dissolve at some point. I don't know why. Maybe people outgrow them. It's also not necessarily easy to start them. In our case, for example, Joe and I are both fairly competitive people. We both finished at the top of our medical school class, and we were both destined for success individually. So, to have to demote our egos for this partnership required lots of discussion. We used to have long talks about how we would handle different things. For example, we would rotate authorship with each paper. We also made the formal acknowledgement that if I said something brilliant on a Thursday, it was probably because Joe had said something equally brilliant on the Tuesday and had planted the idea. We decided that since everything is a give and take, it is impossible to credit ideas to either one of us. We said, okay, we're not going to do that. Whatever comes out of the lab is Goldstein and Brown, Brown and Goldstein.

Part of what has allowed our successful partnership, has been the environment, the leaders here. They allowed our careers to develop in parallel, so whenever one of us was promoted up the academic ladder, the other was always promoted at the same time. Nobody tried to make a distinction. I don't think we could have done this at a lot of other universities, because in order to get tenure, the committees want to know what did you actually do, and we can't say who did what. Here, they were willing to recognize the partnership and that helped a huge amount.

Would you Advise Young Scientists to Pair up?

Brown: We've done so many times, but they don't seem to take it.

Goldstein and Brown in synchrony: You have to find exactly the right person.

Goldstein: I think. . .

Brown: Hang on. I'll just say this. A partnership like this requires that one of the partners, and only one, is a saint. If neither of them are saints, then they are going to be fighting constantly. If both of them are saints, they'll be too nice to each other and nothing will get done. So, if it can't be two

saints and it can't be no saints, the only other possibility is one saint. And I'm not a saint.

Goldstein: Now, you see, I had a great thought there, and you just interrupted me.

Brown: That's the thing about getting older. If one of us interrupts the other, the thought is gone forever.

But you can also Finish Each Other's Sentences. So, it Balances out. Do you Ever Row?

Goldstein: We're on a committee right now trying to choose a head of a department, and we disagree on who it should be.

Brown: Of course we disagree on lots of small things, but we work them out. What makes it so fantastic is that when Joe disagrees with me, I may react violently to begin with. But, I realize that he is a smart fellow, he has a good track record, and he must have a reason for his opinion. And that happens vice versa. So, in the end, we always come together. We respect the opinions of the other.

Goldstein: I've remembered what I was thinking about before I was so rudely interrupted. I think the reason our partnership is so strong, and maybe why it is not more common for these partnerships to exist is that we met and started our scientific journey together before either of us really knew what serious science was about. Today it's not like that for students.

Brown: Another thing we tell students about the fun of a partnership is the shared joy of a result. In the old days, when we were doing experiments, a result would come in, and we would both be standing there, and we would look at each other and both share the moment. We didn't have to brag to anybody else about how exciting it was. We knew. It's an electric feeling that goes between the two of you. I really don't know what it would be like to make a totally independent discovery.

Most Nobel laureates go on to do something else. But we discussed it, and asked ourselves, what do we really enjoy the most? The answer was, making new discoveries and solving scientific problems, so we stayed where we were.

Have you Ever Been Through Tough Times? Does Having a Partner Make them Easier?

Goldstein: Most of our work since receiving the Nobel prize has been on this SREBP pathway, but there was a period of 4 or 5 years where we could not purify the SREBP transcription factor. Eventually we did, but it was a very difficult time. If the two of us had not been together during that period, we may have given it up.

Brown: I agree. When one of us has been feeling down, when things just aren't going well, almost invariably the other will pick them up. Having two people really does help to propel you over the rough spots. There's no question about that.

Key Advice

What are the Key Requirements to be Successful in Science?

Goldstein: Curiosity. If you are not born with curiosity, you are lost in science. There is no cure for curiosity. It is probably the single best quality to have. It is necessary. However, it is not sufficient.

Brown: Agreed. Curiosity is the engine that drives it, but you also need a steering wheel, and I think that comes from the training. I can't emphasize to students enough how important it is to find a good mentor, one who sees the frontier, knows their own field, not so much for learning techniques, but to learn how to be critical, and how to reach for the unknown. It's hard to discover that way of thinking by yourself.

What One Piece of Advice Would you Give to Young Researchers Starting Out?

Goldstein: I would say choose the right problem. In all likelihood the right problem is not the one that you've already been working on, because if you've done something interesting as a student or postdoc, then you'll be working on details thereafter. Young researchers who really do well in science are generally the ones who pick fresh problems when they start out on their own.

Brown: When we started out, it seemed like our fellow scientists were only interested in three areas: neuroscience, development, and cancer. So, we chose cholesterol. None of our superstar contemporaries showed any interest in cholesterol. They used to ask us why we worked on it—it's just an amorphous piece of glob, they would say. But that attitude was terrific for us because we didn't have to worry about a lot of competition!

As for my advice, I would say choose the right spouse. I happen to be very lucky that my wife Alice has been incredibly supportive and understanding. There were times when I wasn't at home much. We raised two daughters, we had a wonderful family life, but it might not have been what a lot of women would have demanded. So, I tell the young students to choose a spouse who really appreciates what they're doing and understands the level of commitment that they're going to have to make. I've seen so many bright young students immobilized because of the demands of their spouse (either gender). So, I thank my lucky stars for Alice. We met when she was 14 and I was 16, and we just had our 45th wedding anniversary and our first grandchild.

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Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Joseph Goldstein and Michael Brown: Demoting Egos, Promoting Success Ruth Williams

Circ Res. 2010;106:1006-1010

doi: 10.1161/RES.0b013e3181dcab4d

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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World Wide Web at:

<http://circres.ahajournals.org/content/106/6/1006>

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