In Memoriam: Burton E. Sobel
A Tribute from Family, Friends and Colleagues
October 21, 1937 – May 3, 2013

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Introduction

by David J. Schneider, MD

In this issue of the journal of the Society of Experimental Biology and Medicine (SEBM), **Experimental Biology and Medicine** (EBM), we pay tribute to a remarkable man who devoted his career to scientific investigation that was focused on improving the care of patients with cardiovascular disease. Burton E. Sobel was born on October 21, 1937 and he died on May 3, 2013. His distinguished career began with undergraduate training at Cornell University and he received his medical degree *magna cum laude* in 1962 from Harvard Medical School. He completed resident training in Internal Medicine at the Brigham Hospital in Boston and fellowship training in

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Cardiology and Pharmacology in the intramural program of the National Heart, Lung and Blood Institute. His first faculty position was in the Department of Medicine at the University of California, San Diego where he served as the Director of the Coronary Care Unit and the Myocardial Research Unit. In 1973 he became Director of the Cardiovascular Division at Washington University, St. Louis, and in 1985, he was named the Lewin Distinguished Professor in Cardiovascular Disease and Director of the Center for Cardiovascular Research at Washington University. From 1994 to 2005 he served as the Amidon Professor and Chair of the Department of Medicine at the University of Vermont. In 2002, Sobel launched the Cardiovascular Research Institute at the University of Vermont and directed the institute until his death in 2013. In 2009, Sobel was named a Distinguished Professor of the University of Vermont.

The scientific prowess of Burton Sobel was widely recognized. Among the many awards bestowed upon him were the Distinguished Achievement Award by the American Heart Association Scientific Councils in 1984 and the Distinguished Scientist Award by the American College of Cardiology in 1987. Sobel received the James B. Herrick Award from the American Heart Association in 1992. This award honors physicians whose scientific achievements have contributed profoundly to the advancement and practice of clinical cardiology. Later in his career, Sobel's contributions were recognized through awards named in his honor. The Cardiovascular Division at Washington University has awarded the Burton E. Sobel Award in Cardiovascular Research to the graduating fellow with the highest degree of achievement. The Society for Experimental Biology and Medicine has established the Burton E. Sobel Annual Young Investigator Award.

While a bright and inquisitive mind are essential ingredients for effective scientific research, Sobel brought additional characteristics that enabled his success. His energy and enthusiasm were boundless and contagious. Each twist and turn in a scientific investigation was viewed as an opportunity. Sobel had an uncanny ability to focus his investigative efforts on what would ultimately be identified as the core of the problem. His intuition regarding these decisions was remarkable.

Another point that distinguished Sobel was his willingness and ability to share his intuitive talents with other scientists. Burt helped focus the research efforts of individuals working in disciplines quite different from his own. Although his ability of identifying key elements for study was partially innate, Sobel enhanced it through his voracious desire to expand his knowledge base. An unassuming individual, rather than feign knowledge when encountering a new topic, he would freely admit his inexperience. In the 20 years that I knew him, I never saw him need to admit a lack of knowledge more than once. Burt believed in preparation and was always thoroughly prepared for new opportunities. Many a fellow and junior faculty was rescued by Sobel's dedication to preparation.

Scientific investigation was a passion for Sobel. His active mind appeared to work nonstop to solve the latest query. Those who were fortunate enough to have worked with Burt will likely recall telephone calls at odd hours of the day and night. Breakthroughs and the associated excitement were meant to be shared and the joy of that sharing required immediate gratification. I caught myself the other day reading a remarkable manuscript and immediately considering that I needed to share this with Burt when I see him next. The scientific world would have less attrition if every young investigator could benefit from the encouragement, the insight, and the work ethic of Burton Sobel.

One component of the focus that Sobel brought to research was his goal to translate scientific discovery into better patient care. Burt had a healthy respect for scientists who focused on more esoteric issues but he clearly kept to his self-proscribed agenda. An example of this approach was the progression from sizing of a myocardial infarction to his focus on thrombolytic therapy designed to reduce the size of infarcts. During the last 20 years of his investigative life an important research focus was the role of plasminogen activator inhibitor type 1 (PAI-1) in diabetes and macrovascular disease. Sobel recounted more than once the story of a young lady who suffered from the complications of diabetes. His passion to improve the care of patients through scientific investigation was a product of his scientific cornerstone.

Since his death, I have had the privilege of listening to stories that allowed me to see Burton Sobel through the eyes of other individuals. In the pages that follow you too will be given that opportunity. Burt was a brilliant scientist, a wise businessman, and a humanist who truly cared about other people. What better way to show the many sides of this great man than to allow those whose lives he touched to tell their stories? Burt saw every scientific investigation as a story that was unfolding and so we endeavor to honor him by recounting his story.

BURTON E. SOBEL: Becoming a Quadruple Threat (1964–1973)

By Eugene Braunwald, M.D.

I met Dr. Burton Sobel (Burt) in l964. The doctor draft was still in place, although the U.S. was at peace, militarily. However, the cold war with the Soviet Union was at its peak. Because of the Soviet's successful launch of its first space satellite, ''Sputnik'', in 1957, the federal government responded by providing vigorous support for strengthening the sciences. The biomedical science programs were led largely by the National Institutes of Health (NIH), which had a robust intramural program on its campus in Bethesda, Maryland. The NIH was able to attract the most promising young physicians into its program because of its excellent senior scientists as well as superb facilities and generous support for conducting research. Because the NIH was within the U.S. Public Health Service, assignment to the NIH was considered to be equivalent to military service. For those considering an academic career this was, of course, a ''plum'' assignment and the competition for the small number of openings was keen.

When Burt applied to the National Heart Institute (now the National Heart, Lung and Blood Institute) he was one of

the four young physicians, out of more than 250 well-qualified applicants, selected to serve as a Clinical Associate. In this position, he divided his time between the clinical care of research patients, much like a medical resident, and research in one of the institute's laboratories. Thus, by being accepted into the Clinical Associates program he was already considered to be one of the best and brightest aspiring academic physicians.

The 1960s, during which Burt matured as an academic physician, were the ''golden years'' for the intramural program of the NIH. The budget grew by about 20% each year and the laboratory and clinical facilities were adjacent to one another in the same large building, the Clinical Center. An important shift was occurring in academic medicine during this period. Clinical medicine was changing from an art based on careful observation of patients with most illnesses treated largely symptomatically, to an evidence-based discipline in which new technologies were brought to bear on the pathogenesis, diagnosis and treatment of disease. This drastic change in medicine was accompanied by the appearance of so-called ''triple threats'' who were in the vanguard of this change. This new generation of academic physicians prided themselves on balanced excellence in each of the three legs of the academic medical tripod – research, teaching, and clinical care. These were high aspirations and only a small number of young physicians became successful. At the time, the intramural program of the NIH was probably the best breeding ground in the world for the triple threats.

Burt was the prototype of this new group. We met in 1964, when as part of his clinical responsibilities as a Clinical Associate, he rotated for four months on the clinical cardiology service, which I then headed. I interacted with him daily on ward rounds. My first memories of Burt were that he was a superb young physician, who was kind and empathetic and who, in addition to being knowledgeable beyond his years, possessed the intuition to use that knowledge on his patients' behalf. He was articulate and self confident, but never cocky and was not embarrassed to ask for help in the rare circumstances when he needed it. He was liked by his patients and related especially well to their families. Clearly, he was ''on track'' to be an excellent clinician. He asked many questions about the scientific evidence on which our clinical decisions were based and was not satisfied with the sketchy answers.

Although Burt could have joined the Cardiology Branch for his research training, he selected the Experimental Therapeutics Section of the institute. He worked closely with a young biochemist, Walter Lovenberg, and his very first paper, co-authored with Lovenberg, was published in the prestigious Proceedings of the National Academy of Sciences (1). This paper was approved by and communicated by Academy member Christian B. Anfinsen, who would win a Nobel Prize in Chemistry in 1972. Not a bad launching pad for a future triple threat!

Burt then began research on the effects of adrenalin on the function of cardiac mitochondria, a paper that had several ''firsts''. It was the first of what would prove to be hundreds of important papers by Burt and his colleagues that used biochemical techniques to study cardiac function and dysfunction, the first paper on which Burt was the first author, the first that he published in Circulation Research, which was the first journal devoted entirely to cardiovascular research. This work brought him closer to what we were doing in the Cardiology Branch and proved to be a turning point for him. After returning to the Brigham where he completed his senior medical residency, I invited him to join the Cardiology Branch. At the time, our group was studying the physiology of experimental chronic heart failure and Burt showed that the abnormal function of cardiac muscle in this condition was not caused by an abnormality of mitochondrial function (3), an important finding that has stood the test of time.

In 1968, I accepted the chairmanship of the Department of Medicine at the new medical school of the University of California, San Diego (UCSD). I invited Burt to join me in developing the department. Not surprisingly, Burt had an attractive offer to return to Harvard and the Brigham to join the faculty in cardiology. To my surprise and delight, he was caught up by the spirit of adventure and played a major role in setting up a strong academic program, literally in the desert. His first faculty position was as Assistant Professor of Medicine at UCSD and Director of the Coronary Care Unit at the University Hospital. In the latter capacity, Burt accepted not only major clinical responsibilities but equally important duties in teaching residents, cardiology fellows and medical students. He proved to be an inspiring teacher because he had the intuitive ability to put himself into the shoes of his trainees and engage them in discussions rather than lecturing to them. He also helped to design and teach the course in Physiology given to first year medical students. So, by 1969 and at the age of 32 Burt had become a bona fide triple threat academic physician.

Burt's research took an interesting turn at UCSD. Despite many advances in coronary care, acute myocardial infarction was still the most common cause of death in industrialized nations. The major problem was that large infarctions caused failure of the cardiac pump and therefore there was intense interest in reducing infarct size and thereby cardiac mortality. Burt worked closely with and mentored his first research fellow, John Kjekshus, a young Norwegian physician, and they developed a technique for measuring creatine phosphokinase (CPK), an enzyme in heart muscle. They showed that the concentration of CPK was reduced in the hearts of rabbits and rats with experimental myocardial infarction. Their paper ended with a prescient statement: ''... since depression of CPK activity in groups of hearts subjected to coronary artery occlusion appears to correlate with myocardial damage, its measurement has potential value in assessing the effect of therapeutic and prophylactic measures on the extent of myocardial necrosis following experimental coronary occlusion...'' (4). This paper laid the groundwork for a subsequent study in dogs in which Burt joined others in the Cardiology Division by measuring CPK in cardiac tissue to demonstrate that after coronary occlusion infarct size could, in fact, be altered by a variety of interventions (5). Working with his colleagues, he showed that reperfusion of the myocardium three hours after occlusion reduced infarct size, measured by both histology and by cardiac CPK measurements (6).

Burt was ''on a roll''. He was anxious to take the next step in his quest to reduce infarct size and thereby to reduce the mortality of patients with myocardial infarction. But first, he had to develop a method of measuring infarct size non-invasively in patients and he and his colleagues accomplished this by analyzing serial changes of CPK activity in the plasma in conscious dogs (7). He quickly moved to adapt this approach to his patients in the Coronary Care Unit and became the first investigator to determine the size of an infarct in intact patients, and he and his team then related this size to their patients' prognosis (8). The next step was to reduce infarct size in patients and he used vasodilation which reduced ventricular afterload and thereby the heart's needs for oxygen. He demonstrated the value of this intervention, first in conscious dogs and then in patients (9).

In 1971, at the age of 34, he was promoted to Associate Professor of Medicine at UCSD and in addition to directing the Coronary Care Unit was given the additional responsibility of directing the Myocardial Infarction Research Unit, one of the eight large NIH supported comprehensive research centers in the U.S., that conducted both basic and clinical research.

In 1973, Burt left UCSD to become Director of the Cardiovascular Division at Washington University and Barnes Hospital in St. Louis. He continued his work on infarct size reduction using novel fibrinolytic agents to achieve successful myocardial reperfusion. I was privileged to observe his enormous achievements mostly from a distance but on occasional visits. When he moved to St. Louis he took on major administrative responsibilities as he built one of the top academic programs in cardiology in the country, a program which balanced efforts in research, education and clinical care. On top of his continued personal excellence as a triple threat, Burt also became an inspiring, visionary academic leader. Thus, he advanced to that most elite and rarest class of academic physicians – a quadruple threat – which he remained for the rest of his life.

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Personal Remembrance of Burton Sobel, MD:

By James T. Willerson, MD

I first met Burt Sobel about 1974 when he walked into my laboratory at The University of Texas Southwestern Medical School in Dallas. He was visiting the medical school and told others there that he wanted to meet me. I was a young assistant professor, and he was the Chief of the Cardiovascular Division at Washington University Medical School and Barnes Hospital in St. Louis. At the time he walked in and introduced himself, I was trying to set up an external perfusion system for isolated rat hearts. He remained watching and talking with me as I set about this work. After about an hour, he left, wishing me good luck in all that I did.

I was very impressed by Dr. Sobel in this meeting. I knew of his work, but I did not know Burt Sobel. I was also impressed with his self-confidence, his friendliness, his wonderful sense of humor, often self-deprecating, and his courage.

From that meeting forward, we became great competitors and great friends—competitors as each of us worked to make our respective efforts in cardiovascular medicine the best they could be, and friends as we confided in one another, offering advice about everything in our professional and sometimes personal lives.

I respected Burt Sobel enormously. He was one of the real visionaries and leaders of cardiovascular medicine worldwide for more than two decades. He created and led an outstanding educational, research, and service effort in cardiovascular medicine at Washington University Medical School and Barnes Hospital, and later extended this excellence and leadership to the University of Vermont where he served as Chairman of Medicine. Every meeting with him was special. His creative and innovative vision, his passion, his integrity, and his fierce determination and optimism were evident all of the time. His faculty and students were ever supportive of him and were grateful for all that he did to help them and to create an environment in cardiovascular medicine that was admired world-wide. He was a role model for students everywhere. Both cardiovascular medicine and I have lost a very special friend.

IN MEMORIUM
Burton E. Sobel (1937–2013)

by Robert Roberts, M.D.

Dr. Burton E. Sobel (Burt) was a Distinguished University Professor at the University of Vermont and Director of the University of Vermont Cardiovascular Research Institute at the time of his death in Colchester, Vermont on May 3rd, 2013.

Burt completed his undergraduate training at Cornell University and received his medical degree magna cum laude in 1962 from Harvard Medical School. He did his residency at the Peter Bent Brigham Hospital followed by his Fellowship in Cardiology and Pharmacology at the National Heart, Lung and Blood Institute (NHLBI). Burt was recruited to the Department of Medicine, University of California in San Diego, California, where he became Director of the Cardiac Care Unit and the Myocardial Infarction Research Unit. In 1973, Burt assumed the position of Director of the Cardiovascular Division at Washington University School of Medicine and Barnes and Wohl Hospitals in St. Louis, Missouri, where he was named the Lewin Distinguished Professor in Cardiovascular Disease in 1985 as well as Director of the Center for Cardiovascular Research at Washington University. Burt later served at the University of Vermont as the E. L. Amidon Professor and Chair of the Department of Medicine from 1994 to 2005.

Burt was recognized as a giant in his field for his scientific contributions: quantification of myocardial infarction (MI); thrombolysis in the treatment of MI; elucidation of the molecular pathway whereby diabetes predisposes to myocardial infarction; and for his leadership role (Editor of Circulation, Editor of Coronary Artery Disease, Chief of Cardiology, Chief of Medicine) as well as his role as a spokesman and statesman for Cardiology. Burt received several prestigious national and international awards including: The Society for Experimental Biology and Medicine Distinguished Scientist Award; James B. Herrick Award of the American Heart Association; Robert J. and Claire Pasarow Foundation Award; American College of Cardiology Distinguished Scientist Award; and American Heart Association Scientific Councils Distinguished Achievement Award.

The field of cardiology moved forward because of Burt's many landmark scientific contributions and his leadership to pursue a more fundamental scientific basis for the practice of cardiology. I shall refer to some of his contributions, through my personal interactions, which I had the privilege to experience during 11 years with Burt as my mentor, colleague and personal friend.

Recruited by Dr. Eugene Braunwald to San Diego, Burt was reshaping cardiology for a bold new approach to MI, the number one killer. Burt formulated the concept that on serially measuring creatine kinase (CK) in the blood during infarction, one could estimate the total amount of CK released and from it calculate how much myocardial tissue had undergone damage to release that amount of CK in the blood. This was truly an original, exciting concept and Burt's formulation of quantifying MI and how it would change the future management of MI was truly enticing to the cardiovascular community. Burt showed that the extent of myocardial damage (infarct size) as estimated by plasma CK, correlated with the patients' short and long term prognosis including mortality. This provided scientific credence to the movement that limiting infarct size should favourably improve prognosis. Multiple clinical trials such as the NHLBI sponsored Myocardial Infarction Limitation Study (M.I.L.S.) would confirm that the infarct size was a major determinant of the patient's prognosis.

It was during this time I started my research career in Burt Sobel's laboratory, where my job was to develop a quantitative assay for MBCK isoenzyme. Assays were available to recognize MBCK, however, these were qualitative, and to measure infarct size required a precise quantitative assay. Over the next 6 to 8 months, I made many unsuccessful attempts to quantify the MBCK isoenzyme by fluorescent scanning of the acetate strips on which the CK isoenzymes MM and MB were separated by electrophoreses. Burt was supportive, encouraging and patient as I tried to find my way in biochemistry. Burt's style of mentorship is typified by the following incident. Burt suggested I consult with a physicist in Los Angeles, whom he thought might be able to help us with quantitative scanning of MBCK. During my visit with him in Los Angeles, he actually convinced me that scanning the MBCK on acetate would likely never be truly quantitative. Continuing to ponder the problem while driving back from Los Angeles, it occurred to me that NADPH (which provided the visualization of MM & MB on the acetate strip) is water soluble and if I simply cut the strip into parts with one containing MM and the other MB and insert them into separate containers of water, it would elute from the acetate into a homogeneous solution which could be measured accurately in a spectrometer. I called Burt. He was so excited, he said, ''we must get together tonight''. We met at midnight and Burt was immediately confident that it would work, he knew exactly what to do and we only had about 3 weeks to submit an abstract to the American College of Cardiology (ACC). From midnight to 3:00 AM, we had not only planned the experiments, but had also written most of the manuscript. That was the beginning of a series of exciting and stimulating events that I would experience over the next 10 years, first in San Diego and later in St. Louis. Susan, his wife, also a very intellectually driven individual, understood what it would take for Burt to build an academic program. As I observed their two children, Jonathan and Elizabeth, growing into childhood, Burt tutored me into academic maturity. Burt was a nighthawk with unlimited energy and Susan was very tolerant of Burt's long working hours, for which I will always be indebted to Susan as well as Burt for the many hours of tutelage. Burt taught the rigours of scientific investigation and was superb at teaching all of us how to write grant applications and deliver scientific presentations. Burt was so very bright, so very knowledgeable and above all incredibly focused with the ability to completely compartmentalize from one problem to the next. Burt always said, even a simple observation deserves a pensive moment.

Burt was a great motivator. Burt could in fact head up any marketing division: he was gifted in taking facts, arranging them, selecting the positive features to communicate the concept. Burt loved being a thinker, pulling apart the fundamental elements of a complex problem, or taking the fundamentals and build on them into something truly exciting and enticing. Burt had an appreciation for what it took to make life exciting and make it positive.

On moving to Washington University in 1972, as Chief of Cardiology, Burt needed to blaze a new trail in cardiology from a specialty dominated by hemodynamics, to one that would emphasize the fundamental molecular basis. Burt had no doubt that this was where cardiology should go, and under his leadership, would go. Burt established a cardiology program at Washington University that would be among the best in the world and its cardiology training program established new standards that would be emulated by others. Shortly after arriving at Washington University, Burt's research provided the world with a new approach to treating acute MI. Burt performed the first study in humans using recombinant tissue plasminogen activator (t-PA) for the lysis of coronary clots in patients with MI, assessing its effect on infarct size estimated by CK and C-11 positron imaging. Over the next few years, Burt would make many contributions to understanding the beneficial effects of thrombolysis along with the many pleiotropic effects of t-PA.

On assuming his role as Chief of Medicine at the University of Vermont, he continued his research on thrombolysis and the effect of diabetes. He observed that type 2 diabetes was associated with higher levels of plasminogen inhibitor which contributed to MI and less effective thrombolysis.

Burt was an outstanding spokesman for the cardiovascular community, always well prepared, explicit, motivating and usually challenging. He was as much at home at the patients' bedside as he was on a national or international podium. He articulated his message with great purpose and conviction, whether as Editor of Circulation, Editor of Coronary Artery Disease, or as an invited speaker at a local, national or international society. Together, his scientific contributions, his publications and oratory as an educator and statesman, touched cardiology world-wide.

Burt's tomorrow was always inspiring. He founded a movement that would see the next generation of cardiologists with greater appreciation of molecular cardiology. We are grateful and fortunate that a generation of cardiologists and physician scientists, transformed by Burt, will continue to transform and inspire the next generation. Burt has left the world many gifts and for me, many long lasting memories.

BURTON E. SOBEL, M.D.
The San Diego and St. Louis years

by Philip A. Ludbrook, M.D., F.A.C.C.

''Ain't Nature Wonderful''.
Edna Ferber

Perhaps the key to understanding Burt Sobel's genius lies in an appreciation not just of his commitment to doing science and doing it with elegance, but even more, of his love of the science itself. Burt was passionate about Biology and its application to medical practice, and his intense engagement with scientific research was prescient to the nascent field of translational research: ''From the laboratory to the bedside'' was his credo and his raison d'être for scientific investigation. His numerous contributions, many of which created new paradigms of medical care, were a testament to his rare gift for discerning the clinical application of basic science – particularly the biochemical sciences. Among the many ramifications for medical diagnosis and treatment were cardiac biomarkers, myocardial metabolism, positron emission tomography, myocardial infarct sizing and protection, ischemic arrhythmogenesis, coronary thrombolysis, and diabetic coronary and myocardial disease. These were just a few of his pressing interests that made sine-qua-non contributions to new strategies in the treatment of patients with cardiovascular disease.

The fundamental limitation of obituaries is that mere words, no matter how eloquent, cannot even begin to scratch the surface of the story of the individual whose life they are meant to portray. Burt had a rare gift for being if not all things to all people at least many things to many people, and to many diverse people at that! When Burt was appointed to establish a new Division of Cardiovascular Disease at Washington University School of Medicine, he recruited a small nucleus of widely differing colleagues: A biologically oriented clinical investigator, a cardiovascular physiologist, an experienced cardiovascular technologist, and an invasive cardiologist (in Burt's lexicon a ''hemodynamacist''. To him, the designation ''angiographer'' did not even come close to the role he foresaw). Within a short time other promising but equally diverse colleagues were added, but Burt knew and understood each individual and his scientific aspirations and clinical capabilities and goals intimately. The extent of his scientific talent and his ability to nurture each individual's intellectual career and development remains an inspiration. I marveled at the breadth of his interests and expertise in all of the biological sciences, especially biochemistry, physics, mathematics, information technology, scientific writing and journalism, not to mention disciplines as diverse as literature, English grammar, medical ethics, and music, being himself a gifted, Julliard-trained pianist with extraordinary talent for improvisation, who once considered a career as a professional jazz pianist, and actually led a professional jazz trio throughout his Cornell years. He was forever curious about acquisition of new knowledge, and the list of his interests was seemingly endless. Burt possessed an amazing ability to master, with enthusiasm, any and every field of his endeavor with characteristic excitement and commitment, untiring interest and passion, allowing him to relate closely with those around him of similar zeal. But I shall narrow my ongoing comments to my own personal encounter with Burt, and my own memories of his genius and leave it to others to share theirs.

The mountain-top experience of my own relationship with Burt was our tenure of the Editorial Board of Circulation in the 1980's. Though demanding of time and effort, this experience provided not only an opportunity for close interaction with Burt at his best, but also a crucible for the expansion of one's own scientific and clinical acumen and for the privilege of informing the entire cardiovascular community of new discoveries – truly a daunting challenge! It was at one such editorial meeting during the halcyon era of tissue plasminogen activator (t-PA) research, a field which so captured his attention that, fascinated by the exquisite feedback loop of vascular wall t-PA inhibitor, Burt whispered in awed tones ''ain't nature wonderful''

and he really meant it. For me, that inspired exclamation of respect and fascination for nature and for science epitomized his signature vibrant excitement, not just for the scientific endeavor per se but even more, for the biology itself and its promise for fruitful application in medical practice.

It was also during that Circulation Editorial Board era that Burt's appreciation for the art of good writing came to the fore. Reminiscent of novelist Gustave Flaubert, who when describing his writing style once remarked that he had remained literally stuck for two weeks capturing the right word, Burt was a stickler for the right word and the right phrase not just for scientific precision and clarity, but for the sheer beauty of good expression and harmonious syntax. Amongst our own faculty, Burt's blue pencil was a thing to be feared – we knew only too well the experience of our finely-honed penultimate manuscript drafts returning almost unrecognizable from Burt's late night editing, of course all the better for the radical transformation that he imbued. Precision and exactitude of expression were his keynotes! Scientific abstracts and presentations received similar attention: ''Say what you mean and say it concisely and clearly'' was his priority. Then came the rehearsals . . . and re-rehearsals. Even rehearsals of questions and answers from the floor. But the quality of the final product always spoke volumes for his invaluable, painstaking coaching.

Burt excelled at grantsmanship and for many of us, grant-writing was yet one more opportunity to profit from Burt's spirited mentorship. In numerous federally-funded programs, from the Myocardial Infarct Research Units (MIRU) to a succession of Specialized Centers Of Research (SCOR) in Ischemic Heart Disease, Cardiovascular Research Training grants, Thrombolysis In Myocardial Infarction (TIMI) awards, RO1s, and many other privately funded research awards as well as numerous unfunded projects, Burt's organizational talent was of key importance to our success. From conceptualization of the scientific question to planning, writing, editing, and submitting of grants, Burt's personal tutelage and organization were instrumental to our success. Not only that, the process nurtured our own skills in posing a relevant scientific question, conceiving methodologies for answering the question, and preparing competitive grant submissions. In this setting, as in so many others, Burt enthusiastically encouraged original thinking and creative innovation, and he thrived on the competitiveness so necessary for success.

Given his love of the right word and good expression, Burt was an articulate lecturer at the podium, an engaging discussant in the classroom, and an empathic communicator in one-on-one conversation or at the bedside. Convincing logic, clear explanation and mastery of the spoken word were all second nature to Burt. I well recall my awe at his ease in assembling an important lecture from a folder of 35 mm slides for presentation at a highly visible national meeting, just hours beforehand, while en-route in the air, and to deliver a masterful, eloquent, well-organized presentation a short time later. His unassuming poise and unassailable confidence at the podium were legendary, naturally engendered by his command of language, his intimate familiarity with his material, his crystal clear clarity of thought and his genuine respect for his audience. Burt encouraged the use of only minimal notes at the podium – no reading from a prepared manuscript, though he acknowledged that this could be a challenge for the less-gifted orator. Amongst his key tips for success were ''Be cautious about use of humor at the podium,'' and ''Never assume the listener's sense of humor.'' Importantly, he strongly encouraged sincere respect for the audience and its level of information. ''Finish on time'' and ''Don't argue with the questioner'' were his maxims. His diplomatic response, ''We can debate that if you wish'', politely silenced many an argumentative questioner.

Despite his undisputed genius as a scientist and researcher, Burt was an acknowledged Master Clinician. The extent of his knowledge of clinical cardiovascular medicine was extraordinary, whether at the bedside, on teaching rounds or at the podium. I gained immense respect for his exceptional diagnostic acumen when he and I once presented a CPC, discussing an unknown case of complex congenital heart disease for diagnosis. Being well-versed in adult congenital heart disease, I was awed though not surprised when Burt, by meticulously sifting through the Van Praagh classification of congenital heart disease, correctly diagnosed a single outlet variant of double outlet right ventricle with an atretic aortic valve!

Throughout his tenure at Washington University, Burt was a charismatic teacher: in the medical students' Introductory Pathophysiology courses, the cardiovascular fellows' core curricula, medical Grand Rounds, and at the bedside. Genuine respect for the individual patient was the hallmark of Burt's persona, nowhere more apparent than at the bedside. While empathic, sharing conversation with the patient was of primary importance, sitting on the foot of the bed in the manner of well-meaning clinicians of the era was verboten as condescending, and first-name familiarity was eschewed as presumptuous.

My recognition of Burt's high regard for the primacy of patient care was once amply confirmed by his encouraging affirmation when I congratulated him on his success in acquiring a major new grant: ''Every procedure you do in the cath lab is more important than all of those grants.'' Successful grantsmanship and scientific discovery were Burt's gifts, but his appreciation and respect for clinical attributes were of vast reassurance to me and many colleagues whose skills were focused on patient care and investigation.

From the personal perspective, Burt, well prepared with a degree in psychology, truly enjoyed people and was adept at successfully building and often smoothing interpersonal relationships. He was at all times and in all circumstances gracious, affable, and polite, though he eschewed ostentation and pomposity, and disdained arrogance and self-aggrandizement. Rather, his personal demeanor exemplified dignity and confidence, yet with a rather charming sense of modesty. He cared much about the extracurricular and personal lives of his colleagues and especially his closer friends, but was quite private about his own personal issues, though to those who knew him well, his own pressing concerns did sometimes become more apparent. Even then, however, he remained stoical, allowing empathy,

but rarely sympathy. To his colleagues, Burt was consistently respectful, highly complementary, fiercely loyal, and scrupulously honest. He could express his opinions openly and strongly, but patiently with appropriate explanation and always with the utmost diplomacy and never argumentatively – he respected others and their viewpoints too much to argue, and certainly not to exhibit anger openly. While his motivation and zeal for getting the job done could sometimes engender frustration, he always kept his irritation well masked, except perhaps, for an occasional subtle quiver of the lip – a tell-tale sign that prompted the sympathetic observer to back off!

To his close friends, Burt was a committed, loyal advocate and supporter, quite prepared to go out on a limb to support a friend under fire, sometimes even to his own disadvantage. ''That is what friends are for,'' he encouraged in one such encounter.

Burt was a charismatic teacher and an effective mentor; nurturing the professional and personal growth and accomplishments of colleagues at all levels was one of his deepest commitments, and seemingly one of his most fulfilling and enjoyable responsibilities. For decades, I eagerly looked forward to his regular Friday afternoon invitation to ''share a cup of tea'' in his office – in reality, a genial euphemism for a private, one-on-one discussion about research, a manuscript, a new scientific or clinical strategy, or even one's own personal issues. And Burt was quietly yet deeply devoted to his own family and loved ones, always so proud of their accomplishments, more comfortable sharing their successes than his own. It was once my privilege, and one of my greatest honors, to take care of his mother during her hospitalization for a serious illness, and was generously rewarded by Burt's heart-felt assurance: ''I can pay you no greater compliment than to ask you to take care of my own mother.'' Then, and now, I regarded myself as so privileged, honored and blessed to be counted amongst his friends and colleagues upon whom he relied and trusted, and most touching, enjoyed.

Burt was in every way the epitome of a gentleman and a scholar: a brilliant, gifted and accomplished scientist, a master clinician, an ardent teacher, an effective mentor, a charismatic leader and perhaps most importantly, a devoted husband, father and friend, as close to a brother as I ever had. Truly the qualities of a brilliant, extraordinarily talented man, who inspired generations of physicians and investigators, established new frontiers in scientific medicine and translational research, contributed meaningfully to the health of countless patients, and enthusiastically committed his many gifts to the betterment of science and society.

Fair Winds and Following Seas: A Tribute to Burton E. Sobel, M.D.

by Steven R. Bergmann, M.D., Ph.D.

While not completely an introvert, I generally warm up slowly to people when I first meet them. However, I knew within five minutes of meeting Burton E Sobel, M.D. (hereafter Burt), that I had to work with him. As luck would have it, Burt offered me a position to join him after he heard me present my Ph.D. thesis research at a national meeting. Burt's personality, enthusiasm for investigation, and zest for life, were infectious. And so, I decided to accept his offer for a fellowship at Washington University in St. Louis where he was the Chief of the Cardiology Division. There was one problem, however. I had already signed a contract to start work at another institution. It was then that I got my first demonstration of how Burt helped people solve problems. He picked up the phone, called my employer, and artfully got them to release me from my contract, as only Burt could. In fact, a key management strategy that I learned from Burt was to deal with complex problems head-on and immediately. One did not always like such meetings with Burt, but the outcome was unambiguous and conclusive. And so I moved to Washington University in St. Louis. My 16 years there working with Burt proved to be some of the best of my life. He started out as my boss, but the relationship blossomed into one of collaborative colleagues and life-long friends.

Burt had enormous vision and energy. He seemed to be in multiple places at the same time. Under his leadership, the Cardiology Division at Washington University was one of the most creative and productive research enterprises, continually funded by Specialized Center of Research (SCOR) awards (among many other grants) from the National Heart Lung and Blood Institute. Burt had recruited and established a first-rate clinical and research faculty at Washington University that ushered in wide-ranging advances in cardiology including the development of creatine kinase to measure infarct size (1); the development and use of positron emission tomography (PET) to quantify myocardial blood flow and metabolism noninvasively (2,3); the use of coronary thrombolysis and the development of tissue-type plasminogen activator (t-PA) (4-6); understanding the mechanisms underlying ischemic arrhythmogenesis (7); the development of ultrasound and use of the signal averaged EKG (8,9); approaches to diminish infarct size and insights into hemodynamics (10,11); the use of radiolabeled cells to follow cell trafficking (12); and the identification and understanding of the importance of plasminogen activator inhibitor-1 (PAI1) (13-14). I will never forget the excitement in the lab upon using the first batches of t-PA developed by Dr. Desire Collen from Belgium demonstrating clot-specific coronary thrombolysis, first in dogs (5), and then in humans (6). It was electrifying to stand with Burt in the control room of the Cardiac Catheterization Laboratory at Barnes Hospital watching the first use of t-PA in the United States to dissolve an intracoronary clot in a patient with an evolving myocardial infarction. Burt directed the Division like an expert conductor, making sure that each section of the orchestra did its part to produce the magnificent whole. We should all be thankful that Burt did not feel he could make a living as a jazz pianist and instead chose to attend medical school. All patients with coronary artery disease have benefitted from the pioneering work directed by Burt.

Burt's creative and physical energy, his organizational skills, and his ability to motivate people led to a huge family of basic scientists and clinical investigators infused with his intellectual DNA. Many have since gone on to

leadership careers in the world's premier institutions. Burt delighted in the success of his colleagues and it gave him a great sense of accomplishment and joy to see one of his fellows or associates publish or present a major paper, obtain a new grant or receive an academic appointment. In turn, his fellows and colleagues were fiercely loyal to Burt. All who had the joy of working with him are better for it.

Burt's academic contributions were prodigious. He published over 580 peer-reviewed papers, more than 350 editorials, chapters and reviews, and over 35 books. He was an editor or on the editorial board of the most elite journals in Cardiology. He was regularly honored by major academic institutions and professional organizations. Burt was especially touched to have a Young Investigator Award named for him by the Society of Experimental Biology and Medicine, since training the next generation of physicians and scientists was always one of Burt's core missions.

Burt could be tough on you. He expected much of his fellows and colleagues and could be a hard taskmaster. But this was only because he was a seeker of discovery and perfection in science, and the high standards that he set brought out the absolute best in people. I often recount to my fellows how Burt was a stickler for language and the presentation of ideas. I once wrote a paper (15) that went through at least ten re-writes before I gave it to Burt for review. The very next day, he handed it back to me, telling me what a marvelous job I had done. When I got back to my office, so pleased to receive such a compliment from him, I looked at the paper, and every single line was crossed out, in red, and re-written in Burt's chicken scratch that only people with a PhD in hieroglyphics (or his secretaries) could read.

Burt also played hard. The incisiveness and energy that he applied to his investigative and administrative career was also applied to family dinner discussions, tennis, skiing, playing piano and sailing. Winning was a big thing for Burt – in everything he did – although I think the joy of the struggle was an even bigger thing.

What would Burt say to us now? I think he would say: "There is time for mourning, but not for moping." As we carry on Burt's legacy, there are deadlines to meet; there are papers to be written that sing – and now have to be made to do so without Burt's editorial genius; there are patients to be served because they are sick and are worthy of our service; there are fellows to teach, and medicine to be practiced, because Burton Sobel taught us that the craft of teaching and research and the art of medicine can be a good and joyous thing.

When I first learned of Burt's illness several years ago, I gave him a favorite book of mine called Learning to Fall – the Blessings of an Imperfect Life by Philip Simmons (16). It is a book that talks about the approach to life and illness. Simmons says: ''Only by letting go our grip on all that we ordinarily find most precious – our achievements, our plans, our loved ones, our very selves, can we find ultimately the most profound freedom.''

So, we can honor Burt by living each day well and as Burt did – with vigor and spirit, con brio. Thanks to his beloved wife Susan, and his children, Jonathan and Elizabeth, for sharing him with us. We carry you in our hearts. Burt and I had plans to go sailing this season on his beloved Alerion sailboat, Encore. I regret we will not be able to do that.

Burt, fair winds and following seas.*

*Burt would have queried me on this quotation. It does not make complete sense. It has a long history as a traditional way of wishing a sailor safe passage, a nautical blessing. While the "fair winds" phrase is obvious, the phrase "following seas" is problematic. Following seas typically refer to waves that are breaking unto the back of the boat, which is usually not very comfortable, and at times, dangerous as it can lead to a broach. However, Bowditch's American Practical Navigator defines "following seas" as "a sea in which the waves move in the general direction of the heading" (17), which, of course would speed one to their destination. I hope Burt would be happy with that clarification.

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Burton E. Sobel M.D. Thank you for being you

By Allan Jaffe, M.D.

It is difficult writing about a close friend and mentor and finding just the right words to express how one feels. I know several things I will avoid. There will be no nouns used as adjectives and no split infinitives; BES hated both. My first paper (pre word processors) contained many such modifiers and after innumerable drafts and his final approval, BES told me to take them all out. My secretary nearly killed me when I asked her to retype the manuscript but I learned to never again use nouns as adjectives. By the way, I missed one that we only detected when the article came out in Circulation; it was in the title. BES was one of the brightest individuals I have ever met. He was blessed with insomnia yet despite being up all night, he still could write brilliantly and coherently and be concise and to the point. Not only was he bright and engaged but he was mentally facile. Many times I could answer the question posed but often he came to the proper answer before I did. This ability along with his gift of sophisticated gab made him a tremendously effective presenter, be it at national meetings or site visits. Even when he was wrong (not that he would admit it), his verbal abilities alone enabled him to win arguments, except perhaps against Susan.

BES had tremendous insights into science and was deeply committed to it. He respected clinical work and wanted there to be good care applied, but it was second to good science. He seemed to have all the right instincts about scientific endeavors almost all of the time. He knew a huge amount of basic biochemistry but he also had fantastic insights into how one might deploy the techniques he was developing far into the future. The first site visit I presented at was about using insulin clamp technology in a positron tomography project to study fatty acid metabolism in diabetics. It was 1978 and they slaughtered us at the site visit but those studies were then done in the 1990s by others, much after BES had first proposed the approach. He was always ahead of his time. One reason for that was his ability to listen and cut to the bottom line. In the early 1980s, the NIH called meeting in Bethesda to decide if we should do a randomized national trial of thrombolysis versus placebo for AMI. We all listened to a brilliant scientist named Desiree Collen who had developed a new plasminogen activator. Most of the audience focused on the issues at hand: a national trial. BES met with Desiree and the rest is history. He could see the benefits and he could see how those of us at Washington University could fit into the equation. He was visionary and he was right.

Part of that vision accrued I think because he was always open to learning. I remember when Elizabeth was learning calculus, BES relearned it so he could interact with her in a better way. He and my son who is an ancient Greek scholar often exchanged views on controversial topics. Their last argument was over the book ''Hitler's Willing Assassins.'' He was intrigued by everything he could learn. We loved baseball together and he was fascinated about how the shortstop and second baseman signaled to each other about who covered second base and how they signaled to the outfielders about the pitches and how Joaquin Andujar would be wild high when he did not bend his front leg adequately. BES was interested in everything. Curiosity was a fundamental aspect of his nature.

Not only did he have that sixth sense about science, but he had it also about people. He recruited the best and the brightest and often knew the difference. Once when choosing fellows, the faculty decided to override BES, which was a tough thing to do but we thought it essential to get someone we thought would be a superb fellow. Unfortunately, BES was right and we were wrong; the fellow was somewhere between mediocre and terrible.

Finally, BES was a great friend when the going was tough. He was always there and always helpful. If there were a war, being in his foxhole would have been the best strategy. That did not mean he was easy on you, but he was always supportive when the going got tough.

One could write story after story about BES and there would still be much more to say, but one has to stop somewhere. Perhaps I will end with 2 quotations. The first from Emerson goes: ''The purpose of life is not to be happy. It is to be useful, to be honorable, to be compassionate, to have it make some difference that you have lived and lived well.'' The second is from Maya Angelou who wrote ''I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel.'' BES made a difference to the science of cardiology that will live for years to come because of his vision. He also made a major difference to many of us who he helped nurture. We are all better for knowing him and he inspired us in so many ways. I will miss the person but will hope with my words and deeds to continue his legacy.

Dr. Burton E. Sobel and Coronary Thrombolysis with tissue-type plasminogen activator (t-PA)

By Désiré Collen, MD, PhD

The first time I met Dr. Burton (''Burt'') Sobel was at a NIH workshop organized towards the end of 1980 (or was it 1981?), to discuss the involvement of the National

Institutes of Health in thrombolytic therapy of acute myocardial infarction. I was invited to give an introductory lecture on the biochemistry of the fibrinolytic system and I presented data on tissue-type plasminogen activator (t-PA), including early results on its thrombolytic effect in rabbits with pulmonary embolism and dogs with femoral artery thrombosis. My lecture did not impress the distinguished audience of clinicians, who were focusing on the use of streptokinase to treat heart attacks and were putting the TIMI-1 trial on the rails. However, during the lunch break Dr. Sobel proposed to me to study the potential of t-PA for coronary thrombolysis in a dog model of copper-coil induced coronary artery thrombosis which was available in his laboratory and to compare the efficacy of t-PA to that of Streptokinase, not only on clot dissolution but also on myocardial function. This resulted in our joint publication in Science (Bergmann et al. Science 1983; **220**:1181-1183,). Soon thereafter, Burt secured FDA approval for the first use of melanoma-derived t-PA in heart attack patients in a joint pilot trial with F. Van de Werf in Belgium (N. Engl. J. Med. 1984; **310**:609-613). Burt's group also participated in the first ''three center'' study of recombinant t-PA (Activase) in coronary thrombolysis (Collen et al. Circulation 1984; **70**:1012-1017).

Many people, too many to give deserved credit in this limited space, contributed significantly to the development of recombinant t-PA for the treatment of heart attack and stroke, at different stages, but Burt's seminal contributions to the initial experimental animal and pilot patient studies were ground breaking and trendsetting. Since our first meeting in Bethesda at the NIH workshop we had become good friends. During our discussions on the occasion of my visits to his laboratories in St. Louis, MO and subsequently in Burlington, VT, I was always impressed by Burt's broad and clear views on medical problems and on strategies towards their resolution. No surprise to me that he was a graduate ''Magna cum laude'' from Harvard. I learned much of his approach to solving problems and of his superior writing and communication skills. On several occasions, I admitted with respect and admiration ''Burt, I wish I could say and write things half as well as you do''. Our professional paths diverged since the 1990's, but our friendship has endured.

Of course, coronary thrombolysis was by far not the only field in which Dr Sobel made seminal basic and clinical research contributions, but his many collaborators in these fields are better placed to provide adequate testimony on these achievements.

Dear Burt, you were a leader in the field, an important architect of the development of coronary thrombolysis and a true friend. I will miss you very much and will cherish your memory for as long as I live. Farewell my friend, wherever you are.

Recollections of Burt Sobel

By George P. Vlasuk, PhD

When I was asked to write my recollections and thoughts on my experiences in working with Burt over the years, it brought back fond memories of a man who I admire and have the deepest respect for as someone dedicated to the highest level of science. It also reminded me of the many contributions Burt has made in translating that knowledge of science into practical applications working with many companies to bring basic discoveries to patients. My experience in working with Burt in this capacity goes back to when I first met him back in the late 1980's when I was a young researcher at Merck. My group had published several papers on a new natural anticoagulant isolated from ticks that specifically inhibited the coagulation factor Xa(fXa) called TAP. I was quite surprised when Burt asked me to visit his group at Washington University (WUSTL) to discuss the work since Burt was a giant in the area of cardiovascular medicine and especially the use of thrombolytic agents to treat acute myocardial infarction. This was an area where we thought the use of a potent anticoagulant targeted to fXa might aid in enhancing thrombolytic reperfusion and preventing reocclusion. I must say I was quite nervous meeting Burt for the first time but as soon as we started talking science I knew this was someone that respected what we had accomplished and I could learn a great deal from. As a result of that visit, we struck up a collaboration with Burt's group and I continued to stay in touch with him as he made his move to Vermont. In 1990, not seeing a clinical interest in an injectable fXa anticoagulant at Merck I too moved on, to a new early stage biotechnology company in San Diego called Corvas to continue drug discovery on new anticoagulant strategies. In the early days our discovery efforts at Corvas were very productive in identifying a novel antagonist of factor VIIa/tissue factor (fVIIa/TF) isolated from hookworms (rNAPc2) as well as a natural antagonist of neutrophil activation (NIF) isolated from the same organism which was licensed to Pfizer. This, coupled with an active medicinal chemistry program pursuing a new oral anticoagulant to replace Coumadin, which was supported by Schering-Plough, made our efforts one of the most comprehensive in the industry at the time. When a new CEO came into Corvas, I suggested that Burt be added to the Board of Directors since we needed an independent science based view on the Board and Burt's experience in this capacity was already known. My subsequent elevation to the Board as Chief Scientific Officer offered me the opportunity to not only work with Burt on collaborative science programs which we continued but also see how he interacted with the other members of the Board and offered advice and counsel on important strategic issues facing the company. Over the years this advice was critical since being an early stage science driven company, many of the key issues were related to whether we were doing the right thing in terms of clinical trials, interactions with our partners and certainly spending priorities. Through it all Burt was objective, focused and dedicated to seeing the company succeed. Indeed, even though by this time I felt we had developed a close professional relationship, this did not enter into the discussions at the Board on the directions we were taking in discovery and subsequent clinical development with rNAPc2. Burt's advice and criticisms were key in keeping the efforts on track and informing the Board as an impartial member with his unique perspective. This approach as a

Board member was critical when the company faced a significant challenge resulting from the failure of NIF to demonstrate efficacy in a Phase 2 trial in stroke patients. This, coupled with the end of the Pfizer and Schering-Plough relationships, started a series of events that eventually led to the merger (in reality an acquisition) of Corvas with the cancer immunotherapy company Dendreon. I remember, through many tense Board meetings, the discussions on whether this was the best direction or not, and Burt's steady resolve to be objective and do the right thing for the investors. I think this is one of the great strengths of Burt in the role of Board member and businessman in terms of clear and focused decision making and helping people understand the often times complex issues facing science-driven companies.

It was Burt's role on the Board that reminds me of a particular story that highlights how Burt reacted to crisis. On September 11, 2001, we had a scheduled Board meeting being held at the Corvas offices. Driving to work that morning, I heard on the radio of a mysterious plane crashing into the World Trade Center building. In the office, the television was on with many employees gathered around and it was clear there was a serious crisis unfolding. As the morning progressed the Board members arrived and by that time it was clear what was happening and the decision had been made to shut down all airline travel in the US. One of our Board members at the time was Susan Bayh, a lawyer, business executive and wife of U.S. Senator Evan Bayh. As the morning wore on, bringing news of the Pentagon attack, Susan's concern grew, since her two children were in Washington D.C. and she could not initially contact Senator Bayh, who had been moved to a secure location. Susan obviously wanted to get back to D.C. ASAP but couldn't due to the air traffic shutdown. Thus, a decision was made to send her back by limousine. It was at that time Burt said he would accompany Susan back to keep her company and make sure she arrived in D.C. Now I never got a report from Burt on that 3-plus day trip but I am sure Susan was grateful for his company.

These are but a few of the fond recollections I have of knowing and working with Burt over the many years since our initial meeting at WUSTL. While we kept in touch and continued to collaborate after I left Corvas for Wyeth and subsequently Sirtris/GSK, our interactions had not been as frequent. Nevertheless, I will always consider Burt as someone I have a great deal of respect and admiration for as a scientist, businessman, mentor, and friend who I will greatly miss.

Remembering Burt Sobel

By RJ Kirk

I met Burt around fifteen years ago when I joined the board of directors of a California-based biotechnology company, Scios, Inc. He already had been serving on the board of this company, as one of two academics thereon (the other was the neuroscientist Solomon Snyder of Johns Hopkins). Although I initially knew little of his background at that time, I was struck almost immediately by the breadth and depth of Burt's knowledge on so many matters that pertained to this developer of B-type natriuretic peptide for both therapeutic and diagnostic uses in congestive heart failure. His understanding of and interpretive skills surrounding relevant science, preclinical and clinical data, regulatory affairs and clinical practice seemed always at least equal and often superior to anyone on staff at the company. I quickly learned that his was a voice well worth hearing.

But I had not been alone in this appreciation. Almost immediately apparent to me when I joined was the fact that he played a special role on that board, being on the one hand capable of interrogating scientific and medical staff so as to rapidly gain an understanding of a situation or issue but on the other being equally adept at explaining such matters to those of us on the board who were businesspeople. While often being 'the smartest guy in the room,' however, his manner always was modest and genteel. If he had been impressed by an idea or some work, he was prone to the use of superlatives, but if he had not been so favorably struck then his opinions would lose such complimentary features. ''Unimpressive,'' I believe, is the harshest epithet that I ever heard him utter.

He served on that board until the sale of Scios to Johnson & Johnson in 2002. Later, at my invitation, he also served on the boards of directors of New River Pharmaceuticals (the developer of Vyvanse^{TM}), of Clinical Data (developer of Viibryd^{TM}) and, until last year, of Intrexon Corporation, a synthetic biology company that I currently head. At each of these companies, he continued to occupy that rarified space between science, medicine and business, not for the purpose of imposing his own ideas or will but always in order to encourage the best thinking from others. To be so astonishingly conversant in so many fields could easily have led a lesser person to become arrogant or overly opinionated, even domineering, but this was never the case with Burt. His manner seemed forever that of the greatest teachers and in this regard his preferred method often seemed Socratic. This attribute, among others, made him a very fine director.

As I am sure other testimonials will attest, Burt was a gifted and ever-curious polymath with interests (and with the talents to match) in areas as varied as recreational mathematics, piano and sailing, not to mention the vast range of his scientific and medical interests and expertise. Yet despite his extraordinary professional and scholarly accomplishments, two attributes distinguished him among fellow geniuses. First, he always was gracious, kind and personable. He connected with people in a very humanitarian way and I think that this must have been because he genuinely liked others. The second characteristic was perhaps his defining one, however. If it ever could be fair to typify a complex man of such intense curiosity, varied interest and broad expertise in a word, it would be this: He was a teacher.

I know this to be true because it was the central feature of my relationship to Burt. He rewarded interest and encouraged inquiry, patiently explaining even the more rudimentary matters when necessary (as was unfortunately often the case for me),all in furtherance of the mental or programmatic process of the other. He seemed to take the same

delight in seeing another's intellectual advance as he did in advancing his own thinking, a mission that was to him as vital and regular as respiration. Yet as fundamental as these features were, he never lost sight (and frequently reminded others) of the reason and purpose of his chosen vocation: to help patients.

Indeed, he had reminded me of this again in our penultimate email exchange, on May 1 of this year, when Intrexon had a news item out about a new therapeutic program for a condition of high unmet need. My reply was ''Thanks, Burt. I hope you are well. I miss you!'' and his return was ''Mutual, Or to use an RJ phrase, I revert.'' And so the world will miss Burt Sobel for quite some time, I think, as he now has reverted.

But that last exchange also reminds me that we must supplement Burt's polymathic catalog to include logophilia.

Dr. Burton Sobel and BARI 2D We join in the celebration of the life of Dr. Burton Sobel.

By Dr. Robert Frye with contributions from Dr. Maria Brooks, Dr. Sheryl Kelsey, Dr. Saul Genuth, Dr. Trevor Orchard
On behalf of the BARI 2D Study

Dr. Sobel played a fundamental role in developing the scientific rationale for the design of BARI 2D, led in the trial implementation, and provided continued intellectual stimulus for fully exploring multiple issues of basic mechanisms and clinical realities of managing patients with Type 2 Diabetes Mellitus and Coronary Artery Disease.

Our collaboration with Burt evolved after the reporting of the results from the original BARI Trial. Indeed, the first person who appeared at the end of the session at the AHA meeting in Anaheim to offer congratulations was Burt. BARI was a controversial trial. It was a startling experience in that setting to have someone come forward with eyes literally brimming with enthusiasm about the results of the trial. We had all been aware of Burt's many contributions with particular interest in thrombolysis and more recently insulin resistance. His insights led to a prompt editorial in *Circulation*. We provide an excerpt as follows which so clearly describes the basis for his interest and the mental process so clear with Burt, i.e. an analysis of basic pathogenesis. The debate re PTCA vs. CABG was irrelevant to his passion. It was the experience of a clinical trial provoking consideration of basic mechanisms that engendered his enthusiasm. This is reflected in the following which was entitled ''Potentiation of Vasculopathy by Insulin: Implication from an NHLBI Clinical Alert.'' (Circulation 1996; 93:1613-1615).

''Clinical alerts (safety bulletins) emanating from data monitoring and policy boards of large-scale clinical trials are both hallmarks and progenitors of progress. A recent clinical alert from the National Heart, Lung, and Blood Institute based on experience in the Bypass Angioplasty Revascularization Investigation (BARI) multicenter, international, randomized patient assignment trial is a cogent example . . . the clinical alert was that for patients with type I or type II diabetes mellitus who were being treated with oral hypoglycemic agents or insulin, the 5-year mortality rate was 35% after initial revascularization with PTCA, significantly greater than the 19% mortality for patients treated with CABG, even though the angioplasties themselves were not unsuccessful or associated with undue complications. Mortality in both groups was considerably greater than the 9% mortality associated with PTCA and with CABG in nondiabetic patients and in diabetic patients not being treated with insulin or oral hypoglycemic agents . . . The implications are intriguing. The BARI observations imply that in patients with diabetes mellitus in whom exogenous insulin is being given or in whom endogenous insulin is high (in view of the insulin resistance associated with type II diabetes mellitus and the stimulation of pancreatic β-cells resulting from the use of oral hypoglycemic agents), progression of vascular disease after surgery or PTCA is accelerated compared with that in nondiabetic patients or in diabetic patients who are not being treated with drugs. Furthermore, deterioration after PTCA by far exceeds that after surgery. Thus, the response of an ''injured'' vessel (i.e., one subjected to angioplasty) appears to be particularly adverse.''

How fortunate we all were to have Burt's interest and commitment to BARI 2D. He brought his considerable intellectual prowess to the planning, conduct, and analytic phases of the trial. His core laboratory to study inflammatory markers and fibrinolysis has provided fascinating insight to understanding patients with type 2 Diabetes mellitus and coronary artery disease. His personal example of providing both leadership and collaboration has been a model for all. Always respectful of other opinions and wanting to know alternate points of view, but never dodging controversial issues or failing to make his own views clear, he exemplified the highest standards of integrity and commitment to the scientific method in research. His unique ability to bring his basic science prowess to the bedside, and vice versa, is legendary. We will miss him.

The Platonic ideal of Burt Sobel

By Peter Spector MD

There can be no doubt that Burt Sobel's contributions to the world were great and numerous.

Due to his successes in research and the myriad scientists and doctors he trained or inspired, his impact has been, and will be, felt by millions who may never have heard his name.

Burt had an enormous impact on my life; I knew his name.

Despite the titanic nature of his career (compared with anyone's, no less mine) Burt and I had a deeply personal connection. He was the intellectual's intellectual; profoundly curious, energetic and enthusiastic. He shared his brilliance and perhaps equally impactfully, he shared his infectious optimism. Burt seamlessly managed to be both a mentor and a friend. He had a tremendous influence on my trajectory through life.

I met Burt, like many I suspect, having already heard quite a bit about him. He was billed as a giant, not simply by virtue of his enormous contributions to cardiology research but more particularly because of his powerful personality. He was described as intimidating; this was never remotely my experience. The depth and speed of his intelligence, combined with the strength of his convictions were formidable. He was, however, open minded. He was happy for anyone to throw their hat in the arena and let the best ideas emerge. To be sure, it was unwise to enter ill prepared either factually or analytically; properly equipped it was thrilling, rewarding and fun to be in the arena with Burt.

Our first interaction was when he called me to ask that I come to work at the University of Vermont. He called, Burt-like, despite the fact that I had declined two prior job offers from others at UVM. He started the conversation by saying, ''Don't say no yet''. He proceeded to marinate me in grandiose, idealistic visions of what could be. Burt was nothing if not compelling. I didn't believe that a high caliber academic electrophysiology program could be built in a rural, sparsely populated state. Burt believed and he convinced me. He was a big thinker and a builder, who focused on goals rather than the paths to those goals. He was undeterred by obstacles. I'm not sure whether he would have loved Ayn Rand, but Ayn Rand would have loved him.

Burt was an unabashed supporter of academic medicine. He fostered creative thinking in those around him and fought for institutional support to nurture an inquisitive approach to medicine.

When he entered my life I was extremely enthusiastic and filled with ideas – gloriously disorganized and untamed ideas. Burt helped me to harness the engine of my thinking by focusing my thoughts. Despite the fact that he was in an entirely different field of cardiology, Burt consistently helped me to choose the ''right'' questions to ask or the ''right'' ways to answer them.

After he stepped down as Chair of Medicine he had much more time. I was, much to my everlasting benefit, a recipient of this time. For many of the last five years we met weekly in a small group of super-nerds. We had protracted, heated and unstructured conversations on a wide range of topics from the technical details of data analysis to the very nature of electric charge. These meditations led us to study vector calculus, Maxwell's equations, the speed of light, neural networks, genetic algorithms and non-linear dynamics.

Over the last several years of his life I watched Burt spend an enormous amount of time and energy learning math. He was fascinated by the manipulation of pure, abstract ideas. He was palpably enthused with each new revelation. What he sought to master was a deep understanding of the relationships between concepts rather than the details of a given formula. Shortly after Burt's death I thought about all that was lost that day. All of his other knowledge not withstanding I thought about his recent successes understanding math. At first I thought about what a waste it was to lose what he had worked so hard to gain. But shortly thereafter I focused not on what Burt took with him and not even all that he left behind for all of us, but rather on how wonderful it is that he was, right to the last moment, the Platonic ideal of Burt Sobel . . . and that he so thoroughly enjoyed and appreciated that in its full.

In Essence: Unquantifiable
A Tribute to our Father

By Elizabeth Sobel Avera
With contribution from Jonathan Sobel

Thank you for the opportunity to contribute to this in memoriam issue. Considering the Society's interdisciplinary nature, we can think of no better forum for reflecting on the multi-faceted, boundary-busting, perpetually-in-motion man we called ''Dad.''

No such thing as halfway

Whatever the challenge or activity, Dad pursued it with unrelenting zeal. He could dissect a hand of bridge (and play it out 3 different ways), improvise like Count Basie on piano, and maintain proper alkalinity levels for anemones in his saltwater aquarium. When he liked a Broadway show (A Chorus Line and Billy Elliott were two favorites), you heard the continuously looped soundtrack for weeks afterwards. Home repairs (and later, computer troubleshooting) were epically convoluted endeavors. And if you think he was intense about lab data, you should've seen him plotting our family's day on the ski slopes, strategically finishing at the very top of the mountain at 4:00 when the chairlifts stopped. On a more somber note, during 9/11, Dad's tenacity prompted a 72-hour, cross-country limo ride (2 drivers, alternating shifts) from San Diego, CA to Burlington, VT. He was determined to get safely home to his wife, and he found a way to do it.

A voracious and open mind

One look at the man's bookshelves – ranging from literature to geopolitics, sailing technique, music, and quantum physics– reveals what an incredibly agile and active mind he had. The only hitch: it never turned off. One time while driving, Dad noticed special road markings, theorized they were measures of distance, and started testing his hypothesis. A highway patrol officer pulled him over for erratic driving (but let him off with a warning, and probably a chuckle). Math, science, and science fiction held particular allure. The Hobbit and Lord of the Rings were our bedtime stories; Star Trek (the original), our home-sick-with-a-fever cure; watching planes take off from the San Diego airport, our Sunday recreation. In more recent times, Dad turned to Apollo 13 for solace. And before his sudden passing, he was in the midst of an MIT online course in differential equations. Let us also not forget his long-running romance with language and writing. Alliteration, obscure grammar rules, and arcane vocabulary (''perspicacious,'' ''lugubrious,'' ''irascible'') were his specialty.

Just as impressive as the breadth of his studies was Dad's talent for creative problem-solving. He was originally left-handed (hence the chicken scratch handwriting), and his equally dominant analytical and creative spheres equipped him to both a) define a problem, and b) come up with an

innovative solution. We were regularly tutored in this technique on Tuesday nights, when our mom worked late and Dad made dinner . . . arrangements. Over eggrolls and wonton soup at a Chinese restaurant, he would pose a logic problem. We'd spend the rest of the meal exercising deductive reasoning and lateral thinking to arrive at the answer.

Compassion, courage, and making a difference

Dad's curiosity extended beyond the theoretical. He was genuinely interested in – and concerned about – his fellow human being. With his quick wit and engaging personality, he could casually converse with anyone. (Restaurant wait-staffs, amazingly, never tired of his limited Mandarin.) His empathy showed every time he saw a disabled person going about their business normally. He admired their courage and resilience, as he admired others – from Nelson Mandela to Bud Powell – who fought prejudice and hardship. Dad's personal values, deep well of compassion, and scientific curiosity were prime movers of his work. What culminated in the BARI 2D trial started years ago, from a chance encounter with a young woman with diabetes. She had gone blind, and had also been told she was at risk for heart disease. Dad yearned to improve her odds: through his work, he did.

''What's the plan?''

In Burt Sobel World, one could never be too prepared. A master of contingencies, he had spare parts, instruction manuals, procedures, and plans for everything. This past spring, when major construction was to begin next door to CVRI, Dad procured an industrial-sized box of earplugs to counter the disruption. He came by his MO honestly, though, having grown up in the Sobel family's insurance business. Look at the data, assess the risk, do a worst-case scenario. Dad had an addendum, however: if it's something you really, truly believe in, then go after it. Both of us have embarked on entrepreneurial ventures in our careers, and no matter the outcome(s), we've learned tremendously from the experience. As our avowed Optimist in Chief would remind us, there are no failed experiments so long as you gain new knowledge in the process.

Loyalty, not lip service

Dad was never in the military. Organized sports were not his thing. Yet he defined his own teams, to which he was fiercely loyal. When one of us was being bullied at school, he confronted the kid's parents. When a certain academic institution sidelined a dedicated professor – purely because of his advanced age – Dad spoke up. When colleagues came wrongfully under fire, and the controversy hit the fan, no one defended them more vehemently than Dad. As his teams at UCSD, Washington University, UVM, and CVRI could attest, he really did take care of his own.

Show gratitude

They're referred to as ''the little things'' or ''small kindnesses,'' but to Dad, showing appreciation was no minor matter. He went out of his way to graciously acknowledge everyone – and we mean everyone – he came in contact with. A job well done by an electrician, plumber, or chimney-sweep merited a glowing email to the boss. A productive meeting with associates brought forth effusive praise. He even sent summary recaps and thank yous to the crew du jour after sailboat outings on the lake. Though he would cringe at us discussing his illness (Dad was very private), he wouldn't mind us mentioning his inspiring reaction to it. Rather than focus on symptoms, side effects or emotional anguish, Dad was grateful for the time he had, and used it to the fullest.

Now, it is our turn to show gratitude for all the values, the gifts, the lessons, and the love our father imparted. Investigative science is predicated on replicable, measurable results. But for us, and probably many of you, the Burton E. Sobel effect has been categorically unique and immeasurable.

''Memorial gifts to help endow a fund can be directed to the Burton Sobel Memorial Fund at the University of Vermont Foundation.'' (www.uvmfoundation.org)