A tribute to Philip W. Majerus

Philip W. Majerus, a leading expert in clinical hematology and professor emeritus of medicine at Washington University School of Medicine in St. Louis, died at his home in St. Louis on June 8, 2016. Phil was a member of the National Academy of Sciences (Figure 1) and a member and former president of the American Society for Clinical Investigation, among other honors. Phil grew up in Quincy, Illinois, where, according to his family (Janet Majerus, personal communication), he was completely uninterested in school except for science. His chemistry teacher Mr. Watson recognized a special spark and challenged a young Majerus by organizing a laboratory where he could do hands-on chemistry — and Phil was hooked. He then raced through the University of Notre Dame, majoring in chemistry, not distracted by extracurricular activities, but gathering enough credits after only three years to enter Washington University School of Medicine. Along with speed at Notre Dame, he achieved the highest grade point average in the history of the university. He repeated that performance at medical school, where his love for science was stimulated by the great faculty who taught him, including Carl Cori in Biochemistry, Oliver Lowry in Pharmacology, and Carl Moore in Medicine. Phil did a medical residency at Massachusetts General Hospital (MGH), where he established his reputation as being brilliant but not patient with fellow mortals.

Phil had been deferred from military service because of his medical training and owed Uncle Sam two years of service time. He seized the option of going to the National Institutes of Health (NIH) as a research associate instead of going to Vietnam. Phil joined the NIH laboratory of Roy Vagelos in 1963 as Vagelos was returning from a sabbatical with Jacques Monod in Paris. After Phil had asked to join his laboratory, Vagelos contacted friends at MGH, where Phil was finishing a medical residency. The word came back: "Phil is very smart, and he gets things done — fast." That was a gross understatement.

Phil burst into the Vagelos laboratory with unbridled enthusiasm at the time when Vagelos and a close associate, Alfred W. Alberts, were studying the early steps in fatty acid biosynthesis, involving acetyl-coenzyme A (acetyl-CoA) and malonyl-CoA, in *Escherichia coli*. Previous experiments had indicated that this process required a heat-stable protein whose function was unknown. Specifically, Peter Goldman, a former postdoctoral fellow, had derived preliminary evidence that the intermediates in fatty acid biosynthesis might be covalently linked to this protein (1). Phil, working along with Al, purified large quantities of this protein, which was found to contain a prosthetic group, 4′-phosphopantetheine. This prosthetic group, which constitutes the active end of CoA, is involved in forming the high-energy thioesters of CoA that are active in the β-oxidation of fatty acids. It was immediately clear that this protein, through its 4′-phosphopantetheine, might form high-energy thioester intermediates in fatty acid biosynthesis. Such presumptive biosynthetic intermediates were synthesized chemically, and all the enzymes involved in the biosynthesis of long-chain fatty acids were identified and characterized. This centrally active protein was called acyl carrier protein (ACP) (2). The Vagelos laboratory was buzzing with excitement over all the new information, which was being published at an astonishing rate. Fatty acid biosynthesis was solved, and Phil Majerus was ready to move on.

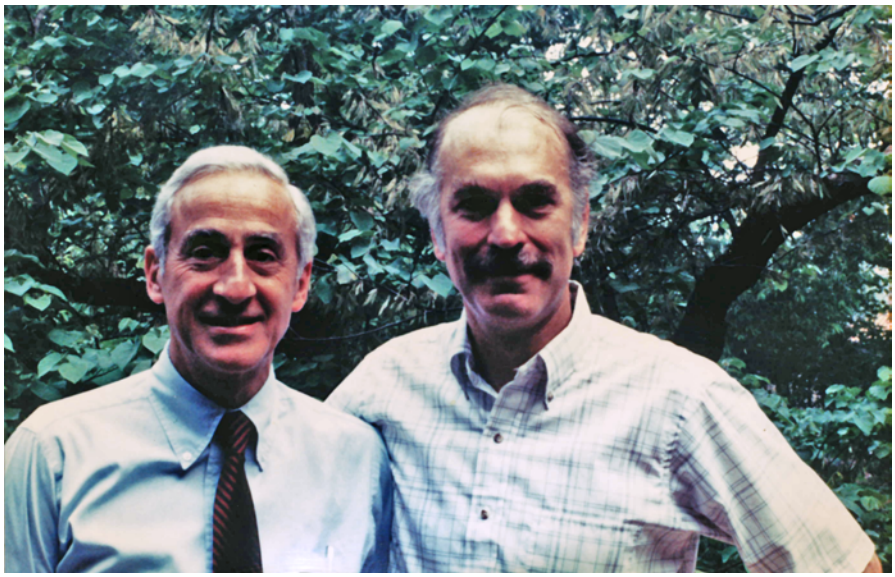

Figure 1. Phil Majerus (right) with his mentor Roy Vagelos in 1986, after Phil was informed that he had been elected to the National Academy of Sciences. Photo courtesy of Elaine Majerus.

During his time at the NIH, Phil's knowledge of biochemistry grew exponentially, and his dream for the future was a career in biomedical research. With seemingly ever-growing budgets from the NIH, this dream would soon become a reality. While he worked incredibly long hours, Phil always had time for his family and for fun, which often included the Vagelos family. Very close friendships developed and extended into the future. Laboratory parties were at the start, and eventually these were complemented with tennis matches, family Christmas parties, and ski holidays. Phil even dragged the Vagelos family on a ski adventure, although they had skied

Reference information: *J Clin Invest*. 2016;126(9):3161–3164. doi:10.1172/JCI89724.

Figure 2. Phil Majerus back packing at Ross Lake, Wind River Range, Wyoming, in July 2005. Photo courtesy of John York.

only once before. Phil's enthusiasm was infectious. When it was time for a move back into academia, Phil thought of only one place, Washington University (Wash U). When an invitation arrived from Carl Moore to join the university in the Hematology Division, Phil was ecstatic. Shortly after, Vagelos was invited to succeed Carl Cori as chairman of Biochemistry at Wash U. For Phil, this was a no-brainier: the two families must move to St. Louis. There was no other way; these were the best possible jobs in the world. Before moving to St. Louis, Roy arranged for Phil to have a faculty appointment in Biochemistry, along with his primary appointment in Medicine. The Majerus and Vagelos families moved to St. Louis together in 1966.

Phil arrived in the Hematology Division at Wash U with several objectives: become an expert in clinical hematology; build a major research program; and train the next generation of physician scientists and basic scientists. Once at Wash U, Phil quickly gained clinical expertise, following the example of Carl Moore, who had been head of the Division of Hematology prior to becoming chairman of Medicine at Wash U. Phil also greatly benefited from a tremendous relationship with Stuart Kornfeld, who arrived as an assistant professor at the same time and with whom he would ultimately co-lead the Division of Hematology for decades.

It took some time for Phil to reorient his research from fatty acid biosynthesis in *E. coli* to focus on work that could impact hematology. For several years, his research meandered among several projects that had some hematological interest but did not lead into a major new field. Then he hit upon a research subject that won immediate clinical notoriety. Aware that aspirin causes patients to bruise easily, he undertook studies of the effects of aspirin on the various components of blood involved in coagulation. He used radioactive aspirin labeled either in the acetyl group or the salicylate part of the molecule and discovered that aspirin chemically modified (by acetylation) and inactivated a specific protein in the membrane of platelets (3, 4). This protein, prostaglandin synthetase, is a critical factor in blood coagulation. Phil further demonstrated that the dose of aspirin required for this effect was far lower than that needed for the antiinflammatory and analgesic effects of aspirin. In a typical Majerus assault on a scientific target, he quickly carried out a clinical trial in patients undergoing hemodialysis who were at high risk of thrombosis that demonstrated the expected reduced rate of thrombosis in patients on aspirin (5). These exciting results, as well as others later demonstrating reductions in myocardial infarction and stroke rates, led to the acceptance of low-dose aspirin as the most used (and perhaps the least expensive) prophylactic drug in the world. What more could a physician-scientist wish for? Phil's studies have directly benefited the cardiovascular health of millions of people. These results were newsworthy and led to a number of well-deserved awards for Phil. Equally important, these studies led Phil and his colleagues to study the numerous factors involved in blood coagulation, ultimately leading to studies that constituted the phosphatidylinositol story and inositol-signaling reactions that opened up an important new field.

Phil's contributions to the second messenger signaling field centered around metabolism and enzyme regulation of the kinases, phosphatases, and lipases, which in turn regulate the production and destruction of arachidonate and a myriad of inositol lipid–derived messengers (6–8). In the early days, Phil's laboratory focused on the purification and characterization of many of these activities, notably concerning the diglyceride lipase phospholipase C, lipid phosphatases, and inositol phosphate kinases. As the molecular biology revolution hit the field, Phil maintained his position at the front edge and cloned numerous enzymes that ultimately served as prototypes that defined families of proteins for which there are many gene products. Phil's work often challenged the dogmatic views of the time and set many precedents that expanded our knowledge of the role of an array of lipids and soluble signaling pathways in a variety of metabolic processes. His discoveries contributed to identification of the first in-born errors of inositide metabolism in the pathophysiology of disease; understanding the role of lipids as messengers; metabolic and functional determination of inositol phosphate signals; and expansion of the field's scope to include activation of cellular membrane

receptors. Phil was passionate and fearless when it came to exploration of new molecules, and given his love of mountaineering (Figure 2), perhaps this represented his version of scientific reconnoitering.

Phil, along with his brilliant colleague and friend Stuart Kornfeld, had great institutional influence as co-director of the Division of Hematology at Wash U. A magnificent highlight of the leadership exhibited by Phil and Stuart was their early adoption of the newly formed Medical Scientist Training Program (MSTP). Vagelos, who also championed the MSTP, wrote one of the first MD PhD training grants nearly half a century ago. Vagelos recalls: "Phil and Stuart quickly agreed to take MSTP students into their labs, which established immediately the important role of the clinical departments in basic science training of the students at Wash U." Wash U's MSTP community rose to national prominence, and many of the country's leading physician-scientists trained in the Division of Hematology. The infamous Hematology journal club is another great example that represented Phil at his best — demanding, rigorous, intimidating, and insistent on folks bringing their "A" game. Many of us remember Phil sitting in the front of the room working the overhead projector. Pity those who did not impress Phil with their preparation, interpretation of experimental results, or pace of delivery — in the middle of a sentence, their overheads were whisked away, as if to say, move along, this is not worth my time. Such a testing ground served to sharpen, temper, and elevate everyone's steel.

Among Phil's greatest contributions to science is his legacy of trainees. Whether you studied in the Division of Hematology as a fellow, student, or faculty colleague, you felt his extended reach. Phil's passion and skill at developing the next generation of physicians, physician-scientists, and scientists was truly remarkable. For those privileged to train in Phil's laboratory, there is unity in the sense that Phil was appreciated for his encyclopedic memory, extreme intelligence, creative brilliance, and fierce desire to unravel the unknown. He taught his trainees that the convergence of data and ideas from distinct angles builds confidence, and Phil instilled a relentless desire to apply first principles of scientific methods and critical thinking to interesting biological problems. He trained by example, getting into the trenches and frequently helping lab members with his strong work ethic. While his persona espoused an unfiltered, brash, no-nonsense style, his agenda was pure as he sought to gain knowledge through discovery. Perhaps the reflections of President Truman are appropriate: "I never did give anybody hell, I just told the truth and they thought it was hell" (9), or George Bernard Shaw's definition of progress: "The reasonable man adapts himself to the world, the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man" (10). Phil's accomplishments define progress, and the world is forever better off.

Phil also possessed a tremendously warm, optimistic energy that served to motivate and enable those around him. Many times experiments would go awry, and Phil would recount stories of his own trials at the bench, a form of commiseration and humor through his amazing storytelling ability. Defining the unknown meant lots of hard work, nights, weekends, and sacrifice, but Phil understood that "all work and no play" wasn't good in the long run, and he therefore created Friday "beer rounds" gatherings, which met 52 weeks a year, started promptly at 5 pm, and somehow remained financially cost-neutral thanks to Phil's uncanny knowledge of current events that he used to challenge colleagues with a weekly one dollar "yes or no" bet. The rule for this bet was that you had to pay a dollar if you lost. Some would visit the Hematology Division years after leaving, and Phil would say, "I think you owe me a dollar," then find the page in the book, and sure enough, dues were paid. Saturday morning, of course, meant a run around Forest Park and afterwards watching Phil sit at someone's desk chair dripping with sweat while eating goodies from World's Fair Donuts. He would engage those interested with incredible stories, and you knew your training was approaching fulfillment when you had heard many of them before. Certainly among the favorites was his serendipitous run in Forest Park with soon-to-be President Bill Clinton as he campaigned in St. Louis. Then it was "get back to work." It has been said that if two or three of your trainees go into the professorship, then you have done your job well. Phil trained too many to count, and for this he will always stand as a giant in the profession.

John York first met Phil at Merck Research Laboratories in 1989, the same year the company was led by then CEO Vagelos and voted Fortune Magazine's "America's Most Admired Company" for the third straight year. York worked as a molecular biologist technician in the area of hematological anticoagulant and fibrinolytic natural products and was introduced to Phil by Tom Connolly, a group leader and former Majerus lab trainee. York was relocating to St. Louis to follow Sally York, who was entering Wash U's MSTP. Phil loved to reminisce that he was interviewing Sally for the MSTP and that he offered John a job on the spot as a means to bring molecular biology to his laboratory. Phil's tremendous gifts of picking fertile research trends kept his laboratory at the leading edge for a stunning half century and maintained continuous funding from the NIH during his entire career. York paid his dues in the lab for a year, entered the PhD program in the fall of 1990, and graduated in the fall of 1993. During this time, after countless triumphs and failures, a bond was forged that is rare in life. The best professional decision ever made by York had a return on investment that included education, mentorship, and nearly thirty years of friendship.

It is perfectly fitting and a bit ironic that the authors became connected through Phil Majerus and Merck Research Laboratories — a lineage that began with Vagelos training Majerus, Merck connecting York and Majerus, and Majerus introducing Vagelos and York. This is but one of many examples of the indelible influence of Philip W. Majerus, and for that we celebrate the tremendous life of a brilliant colleague and dear friend.

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