RETROSPECTIVE

# Phil Majerus: Champion of low-dose aspirin therapy

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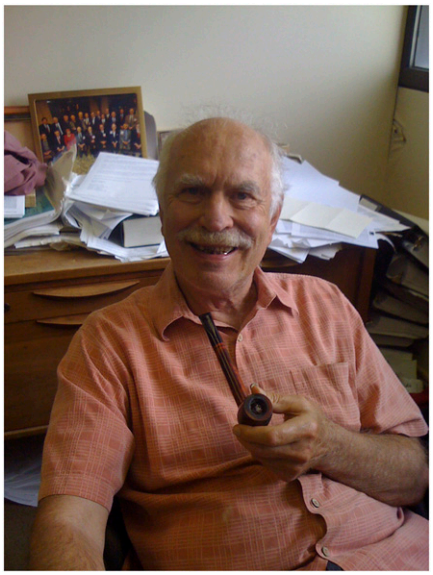
On June 8, 2016, the field of hematology lost one of its giants, Phil Majerus, who died after a long illness. Phil was truly one of a kind: a biochemist extraordinaire with a passion for life, a quick wit, and a colorful personality, whose discoveries changed the practice of medicine.

Phil was born on July 10, 1936 in Chicago and grew up in Quincy, Illinois, where his father owned a five-and-dime store. An outstanding athlete, Phil attended the University of Notre Dame on a tennis scholarship. Upon graduation in 1957 with a Bachelor of Science degree, Phil entered Washington University School of Medicine in St. Louis, Missouri, where he was immediately recognized as a brilliant student who was unafraid to challenge his professors when he disagreed with their opinions. Phil graduated at the top of his class and went to the Massachusetts General Hospital for residency training in internal medicine. He then secured a research associate position at the National Institutes of Health, which allowed him to work in any laboratory he selected. Phil chose to join the laboratory of P. Roy Vagelos, who was doing groundbreaking work on fatty acid biosynthesis. Although he had no background in laboratory research, within a year Phil published his first paper on the purification and properties of acyl carrier protein, the key intermediate in fatty acid biosynthesis (1). Over the next two years, Phil, working alongside Al Alberts in the Vagelos laboratory, produced a series of classic papers that defined the steps that occur during the synthesis of fatty acids. This training in biochemistry provided the foundation for his subsequent research.



Phil Majerus. Image courtesy of Elaine Majerus (photographer).

When his time at NIH was nearing its end, Phil entertained a number of job offers in basic science departments, but chose to accept the one offer from a clinical department. This offer was to join the Hematology Division at Washington University School of Medicine. The offer was extraordinary, as Phil had no formal training in hematology, but the chairman of the Department of Medicine, Carl V. Moore, said that Phil could learn on the job while establishing his independent laboratory. Interestingly, Carl Moore made a similar offer to me, and in July 1966 Phil and I joined the Hematology Division to begin our research careers and to learn clinical hematology. This could never happen today. At the same time, Roy Vagelos moved to St. Louis to assume the chairmanship of the Department of Biochemistry, following Nobel Laureate Carl Cori.

When we arrived in St. Louis it became clear why Dr. Moore was so accommodating with the job offers. A few months previously almost the entire faculty of the Hematology Division had moved to the University of Miami, leaving in place just two faculty members. So we were given accelerated training in clinical hematology and began to serve as attending hematologists within two years. Phil was a quick learner and soon developed into an outstanding clinical hematologist, with a knack for coming up with unexpected diagnoses. To cite one example, Phil was conducting a Clinical Pathologic Conference focused on a patient with liver cancer. In going through the nurses' notes in the patient's hospital chart, he noticed that the patient was said to be well tanned. He also recognized that the patient had diabetes. Putting this information together, Phil's diagnosis was hemochromatosis, an iron overload syndrome characterized by bronze skin color, diabetes, and liver cancer. The stunned pathologist in the case, as well as the clinicians caring for the patient, had never considered this diagnosis. Phil instructed the pathologist to do special stains on the patient's liver to evaluate this diagnostic possibility. Sure enough, the liver was loaded with excess iron, confirming Phil's diagnosis. It is rare for the clinician to outsmart the pathologist who has the great advantage in this situation, but Phil did so on a number of occasions.

Phil's exposure to clinical hematology had a major impact on the direction of his research. When he first

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started his laboratory at Washington University, he continued his studies of fatty acid synthesis, but he soon turned to the role of platelets in the clotting of blood. At the time it was felt that platelets form plugs at sites of vascular injury and then provide a nonspecific membrane surface for the activation of blood clotting factors. Phil showed that this concept was incorrect and that platelets have a surface binding site for clotting factors, Va and Xa, that greatly accelerates the process of clot formation compared with a nonspecific phospholipid surface. To establish the physiological relevance of these biochemical studies, Phil showed that the basis for a hereditary bleeding condition in a patient was the lack of the platelet surface binding site for clotting factor Va. This was one of many instances in which Phil combined his medical knowledge with his biochemical expertise to uncover the basis for a disease process. These studies focused attention on the role of cell surface receptors in regulating hemostatic reactions.

In a remarkable series of studies that continue to resonate to this day, Phil and his postdoctorate fellow, Gerald Roth, elucidated the mechanism by which aspirin inhibits platelet function. Aspirin was known to inhibit the ability of platelets to synthesize prostaglandins, but the mechanism was not understood. Phil discovered that aspirin specifically acetylates cyclooxygenase, the first enzyme in the prostaglandin biosynthetic pathway, thereby preventing it from binding its substrate arachidonic acid. The acetylation was shown to be irreversible, resulting in inactivation of the enzyme for the entire 10- to 14-day life span of the platelet. Phil further demonstrated that this acetylation occurred with low doses of oral aspirin and proposed that this pharmacology might allow low-dose aspirin to be used as an antithrombotic agent without the major bleeding side effect seen with higher doses. Phil, in collaboration with Herschel Harter, director of the renal dialysis unit, then conducted a clinical trial in patients undergoing hemodialysis that showed that aspirin reduced the thrombosis of arteriovenous shunts by over 50% compared with placebo-treated controls. This pioneering study was followed by many trials that have established the effectiveness of aspirin as an antithrombotic agent for a wide variety of vascular disorders, including myocardial infarction and stroke.

Phil's studies of platelet activation led him into yet another area, the enzymology of phosphoinositide metabolism, and much of our current knowledge of these important signaling molecules is attributable to his work. Phil isolated, characterized, and often cloned many of the enzymes of inositol lipid and inositol phosphate metabolism, and in a number of instances showed that defects in these enzymes give rise to serious disease states.

Phil's enthusiasm and energy were evident in everything he did, be it running the 10K path around Forest Park, skiing in Colorado, backpacking in Wyoming with his family, or leading the conversation at the Hematology Division Friday afternoon beer rounds. But nowhere were these more evident than in his laboratory, which for decades attracted top MD–PhD students, along with hematology fellows interested in careers as physician-scientists. In fact, the very first student to be accepted into the Washington University in St. Louis MD–PhD program (Richard Jacobs) selected the Majerus laboratory for his doctorate studies. Under Phil's close, honest, and imaginative guidance, many of his trainees went on to have extremely successful careers. Among his trainees are one dean of a medical school, two chairs of biochemistry, seven heads of hematology divisions, and one director of a medical research foundation. Phil was legendary for asking probing and insightful questions during clinical rounds and journal club sessions. This was quite intimidating to trainees at the time, but it made them think deeply about the work they were presenting. In fact, many of his former trainees have commented that Phil's grilling was the single most memorable and effective aspect of their educations!

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Phil's accomplishments have been recognized with numerous awards and honors, including serving as president of both the American Society of Hematology and the American Society for Clinical Investigation. He also served as editor of the *Journal of Clinical Investigation* and was a long-time member of the Editorial Board of PNAS. Phil was especially proud of receiving the Nature Medicine/University of California, San Diego Mentorship Award in recognition of his success in training leaders in hematology and oncology.

Phil Majerus made an indelible impression on all of us who knew and worked with him. He led an extraordinary life and has left a lasting legacy.

**1** Majerus PW, Alberts AW, Vagelos PR (1964) The acyl carrier protein of fatty acid synthesis: Purification, physical properties and substrate binding site. *Proc Natl Acad Sci USA* 51(6):1231–1238.