

A seven-step plan for becoming a moderately rich and famous biochemist

DOI 10.1074/jbc.X118.006184

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Edited by Herbert Tabor and the Reflections Committee

Omega-6 polyunsaturated fatty acids were identified as essential nutrients in 1930. Their essentiality is largely due to their function as prostaglandin (PG) precursors. I spent most of my career in biochemistry determining how PG biosynthesis is regulated. PGs are lipid mediators formed in response to certain circulating hormones and cytokines. PGs act near their sites of synthesis to signal neighboring cells to coordinate their responses (e.g. when platelets interact with blood vessels). The committed step in PG synthesis is the conversion of a 20-carbon omega-6 fatty acid called arachidonic acid to prostaglandin endoperoxide H₂ (PGH₂). Depending on the tissue and the hormone or cytokine stimulus, this reaction is catalyzed by either cyclooxygenase-1 or cyclooxygenase-2 (COX-1 or COX-2). Once formed, PGH₂ is converted, again depending on the context, to one of several downstream PG subtypes that act via specific G protein-coupled receptors. Nonsteroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen, and naproxen) block PG synthesis by inhibiting COX-1 and COX-2. COX-2 is also inhibited by COX-2-selective inhibitors. Inhibition of COX-1 by low-dose aspirin prevents thrombosis. COX-2 inhibition reduces inflammation and pain. Investigating the mysteries of COXs anchored my scientific career. I attribute my successes to the great good fortune of having been surrounded by people who helped me make the most of my talents. I have written this reflection in a light-hearted fashion as a self-help essay, while highlighting the people and factors that most impacted me during my upbringing and then during my maturation and evolution as a biochemist.

Fig. 1 provides a timeline for my life and career. Much of my research career has been spent studying aspects of prostaglandin (PG)² biosynthesis and particularly the enzymes involved (Fig. 2). Ref. 1 provides a recent review of the cyclooxygenases

The author declares that he has no conflicts of interest with the contents of this article. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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² The abbreviations used are: PG, prostaglandin; PGHS, prostaglandin endoperoxide H synthase; AA, arachidonic acid; COX, cyclooxygenase; FA, fatty acid; NSAID, nonsteroidal anti-inflammatory drug; ER, endoplasmic reticulum; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; hu, human.

(COXs) that catalyze the committed step in PG formation. But more on these scientific topics later.

My wife and I winter near Tucson now, where I work to improve my golf game. Unfortunately, I am achieving the same scores I did when I was twelve. Some of this is bad luck. Last winter I hit a seemingly perfect drive that careened off a sprinkler head in the center of a fairway into a pond. In addition to a penalty stroke, this shot cost me an expensive golf ball sporting a “WE LOVE OUR GRANDDAD BILL” logo. There was a poor outcome to this near flawless shot. However, I confess to hitting even more numerous misdirected shots that have ricocheted off trees and rolled close to the hole. My life has been like this—an outsized abundance of unwarranted good fortune. Obviously, much of what happens is not anything we control. I think it likely that all that happens is attributable to fate. However, having put forth so many erroneous scientific hypotheses over the years, I grant that some outcomes can be ascribed to free will and involve good decision-making and hard work. With that in mind and based on limited experience, I proffer the following guidance.

I often joked with my trainees that if such and such an experiment “worked,” we would all be rich and famous (R&F). This was such a long-standing story in the laboratory that I thought it would be an appropriate framework with which to reflect on my career. I contend that there are seven requirements for becoming a moderately rich and famous (R&F) biochemist: (1) be lucky and have good timing; (2) have only one spouse; (3) get excellent training; (4) surround yourself with clever people; (5) work 60,000 hours; (6) be frugal, and (7) study an interesting and important topic—a science topic is best. There are some provisos. For example, scientists with combative personalities will need to work at least 120,000 hours, and living near an ocean can help in surrounding oneself with capable people. I provide more instruction on each of these requirements below.

1. Be lucky and have good timing

I was, in baseball vernacular, born on third base—an eldest boy arriving in a nurturing, enlightened American family as the U.S. was developing into the richest nation on the planet. And I have continued to be lucky. Seemingly by accident, life has gotten even better. By my early 30s, I had a wonderful, reasonably well-paying job at Michigan State University from which I could only be fired for serious legal offenses.

I calculate that I was conceived the evening of Saturday, January 27, 1945 in New London, Connecticut when my father was on leave from his role as a submarine commander in the Pacific

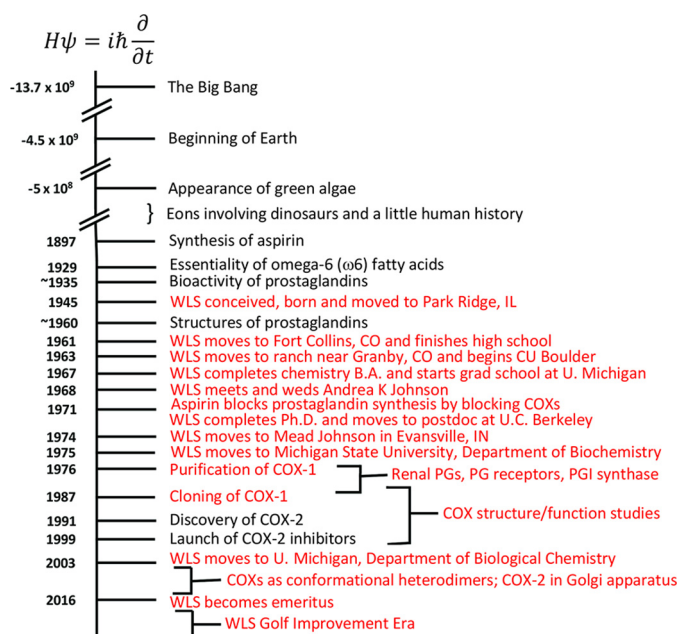


Figure 1. The life and times of William L. Smith (WLS), beginning with the appearance of the Hamiltonian operator.

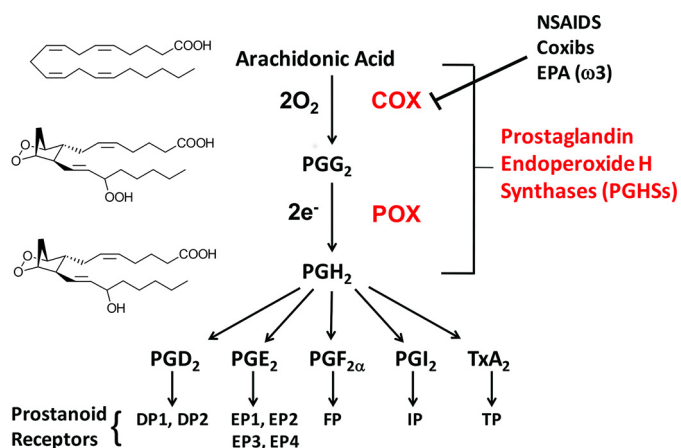


Figure 2. COX and peroxidase (POX) reactions catalyzed by prostaglandin endoperoxide H synthases (PGHSs). There are two PGHS isoforms that are commonly known as COX-1 and COX-2. Downstream PG products are formed from PGH₂ via different synthases. COX-1 and COX-2 activities are inhibited by nonspecific NSAIDs such as aspirin, ibuprofen, and naproxen. COX-2 is inhibited by COX-2-selective inhibitors called coxibs such as celecoxib and rofecoxib. Omega-3 fish oil FAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) preferentially inhibit COX-1. Various PG and thromboxane A₂ (TxA₂) products are formed from PGH₂ by various synthases. The latter biologically active prostanoids target specific G protein-linked receptors to mediate changes in second messenger levels. This figure and the legend are modified from Ref. 1. This research was originally published in the Journal of Biological Chemistry. W. L. Smith and M. G. Malkowski. Interactions of fatty acids, nonsteroidal anti-inflammatory drugs and coxibs with the catalytic and allosteric subunits of cyclooxygenases. J. Biol. Chem. 2019; 294:1697–1705. © Smith and Malkowski.

Ocean. I was delivered at St. John’s Hospital in Tulsa later in 1945. Both my parents were from Oklahoma. My mother was Martha Jean (Vandervoort) Smith (Fig. 3). She was a pretty, svelte, brunette, a homemaker and doting mother. I inherited her dark hair and reasonable disposition (my opinion). My father was William Lee Smith, Sr. He was a “self-made” man. He had a highly combative personality. I inherited his physique. I learned only when I was in my 30s that he had been awarded

two Navy Silver Stars for his WWII service. A Silver Star recognizes “combat valor.” It is a rarity to be awarded one Silver Star.

After WWII my parents nested in the Chicago area and purchased a house in suburban Park Ridge. I attended Eugene Field Elementary School along with Hillary Rodham who was two years behind me in my sister Donna’s class and in my mother’s Brownie Scout troop. I attended public school in Park Ridge until I was 15, and then completed the last two years of high school in Fort Collins, Colorado. The move to Fort Collins was precipitated by my father’s early retirement at age 44. By that time he had become a wealthy businessman but had tired of his work and wanted to do something he considered more enjoyable, as I will describe shortly.

I dreaded the move from Park Ridge to Fort Collins in the middle of high school, but it was one of the best things that ever happened to me. It was a fresh start. I count the time in Fort Collins as two of the happiest years of my life. I owe this to friends Jay French and Jim Guard who took me under their wings.

After selling his business and migrating to Colorado, my father bought the 1500-acre Walden Hollow Ranch abutting Lake Granby in the spring of 1963. At 6 a.m. the morning following my high school graduation, I boarded a bus to Granby, Colorado via Denver for a different education—ranching.

My father bought the ranch as a working ranch and operated it as a break-even proposition. He worked there year-round for about 10 years and then, after a second wife and family arrived, summered there for another 30 years but wintered in Boulder City, Nevada, where his second set of children went to school and he enjoyed tax advantages.

My father worked hard at ranching. He did it for the joy of controlling his own schedule, being outdoors in a beautiful mountain setting, and seeing the fruits of his physical labor. Beginning when the ground thawed in mid-May he would rise about 4 a.m. to slosh in discarded tennis shoes and old clothes through the miles of muddy irrigation ditches that watered the wild grasses that later would be cut and bailed as hay. Haying, which was a full-time job, began in late July and lasted a month (which seemed to me like a lifetime). However, he loved to fish and hunt and during other periods of the year spent plenty of time on these avocations. My father was fearless, well-educated, and street-smart with a wry sense of humor. For example, in his later years, he encouraged a neighbor rancher, who wanted to discuss some contentious irrigation rights, to send an E-mail to arrange a time—my father never owned nor operated a computer.

My mother was unenthused about transitioning from suburban Chicago to a mountain ranch on a county road 10 miles from Granby (pop. 1500). Our 350 cows and their calves and 25 bulls grazed upwind of an airy frame house of about 1200 square feet situated at 8500-foot elevation where annually there averaged 14 frost-free days. During the summers my two younger sisters Donna and Caroline and I would start work by 7 a.m. and work 12 hours. We viewed my father as Simon Legree, which at the time seemed to me to be a generous assessment. Years later a nephew dubbed the ranch the “dark farm” on account of the often tense and unpleasant environment. Among other things the elevation exacerbated my mother’s



Figure 3. The Smiths at Starved Rock Park, Illinois about 1953. From left to right, Donna Jean Smith, Martha Jean Smith, Caroline Sue Smith, William L. Smith, Sr., and William L. Smith, Jr.

congenital heart problem. She moved to Denver after two winters at the ranch. She and my father divorced when I was 25. Neither prospered to the same degree afterward—one reason for my “one spouse” recommendation.

Like many oldest children, I had intense relationships with both parents. With my mother, it was an unconditionally supportive, loving relationship. She died at age 63. My most significant regret is that I was not as good to her as I could have been (*i.e.* unrelated to but much more important than becoming moderately R&F is to be good to your mother). I had a conditional, contentious, occasionally tempestuous relationship with my father. Accordingly, as a youngster, I played elsewhere until required to be home for dinner to consume, either then or at breakfast, all of even the most undesirable victuals on my plate. Even so, I was never without. Being nurtured by a loving, sympathetic mother while being harried by a demanding, unsympathetic father were gifts that I later viewed as excellent preparation for life.

A favorite of my now nine former and current brothers-in-law is Patrick Schaetzle. Patrick did me an enormous service when my father was about 85 years old. He asked Patrick what this “Google stuff” was about. Patrick booted his laptop computer and had my dad type “William L. Smith” in the search bar. I came up as the first entry—the University of Michigan (UM) Biological Chemistry web site. My father was reportedly stunned. I heard that he bragged that I was gainfully employed and doing well. In the end, we were close, for which I am grateful.

Scientists whose careers spanned the 1965–2005 golden age of financing for scientific research would agree that we were lucky and had remarkably good timing. It was an era when scientific efforts were widely supported and appreciated. Unfortunately, I think that my generation of scientists has done a poor job of educating our citizenry about science. I first grasped the extent of this shortcoming when I read a few years ago that fewer than 60% of the U.S. citizenry believe in secular evolution.

2. Have only one spouse

I believe that choosing a mate is the single most important decision one makes. If you watch the *YouTube* versions of Ray Price’s “You’re the Best Thing That Ever Happened to Me” song or Spencer Tracy’s “Guess Who’s Coming to Dinner” soliloquy, you will get the flavor of what occurred in my case.

Andrea Kay Johnson and I met in mid-March of 1968 in Ann Arbor shortly before her graduation from the University of Michigan. We were married on December 21, 1968—the winter solstice (Fig. 4A). Make sure you marry a person who (*a*) is better than you and has high expectations for you; (*b*) believes that you need to hear the unvarnished truth—like it or not; but (*c*) realizes that while you have to spend 60,000 hours working, you also need to hit golf balls frequently.

Early in our married life I apparently was a trial to live with. At first I wondered whether I were becoming deified. Andrea would frequently say things like “God Bill, I cannot believe you said that” or “God Bill, I cannot believe you did that.” As she became more accustomed to the shocking situations to which I was exposing her, she would use only my given name but expand it to two syllables—pronounced ‘*Ba-ill!*’. As an example, shortly after our cloning of cyclooxygenase-1 (COX-1), E. J. Corey invited me to give a talk in the Harvard Chemistry Department. Naturally, I was flattered. Andrea accompanied me on this trip so that we could visit friends the following weekend. After the seminar visit, she and I enjoyed a dinner at a local boutique restaurant with Professor Corey and his wife. It was a pleasant spring evening, and they walked us back to our hotel along the Charles River. As we took the elevator up to the room, I commented to Andrea about what a nice evening it had been. She replied “*Ba-ill!*, you ate Dr. Corey’s salad.”

When you marry, it is unlikely that you will comprehend that you are marrying an entire family (in my case this was a plus). If you are a man, you will learn that at your house you are priority “*n+1*” where “*n*” is the sum of the number of children and pets; exceptions are hamsters, turtles, and hermit crabs. Related to this, Andrea and I have had the enormous good fortune of hav-

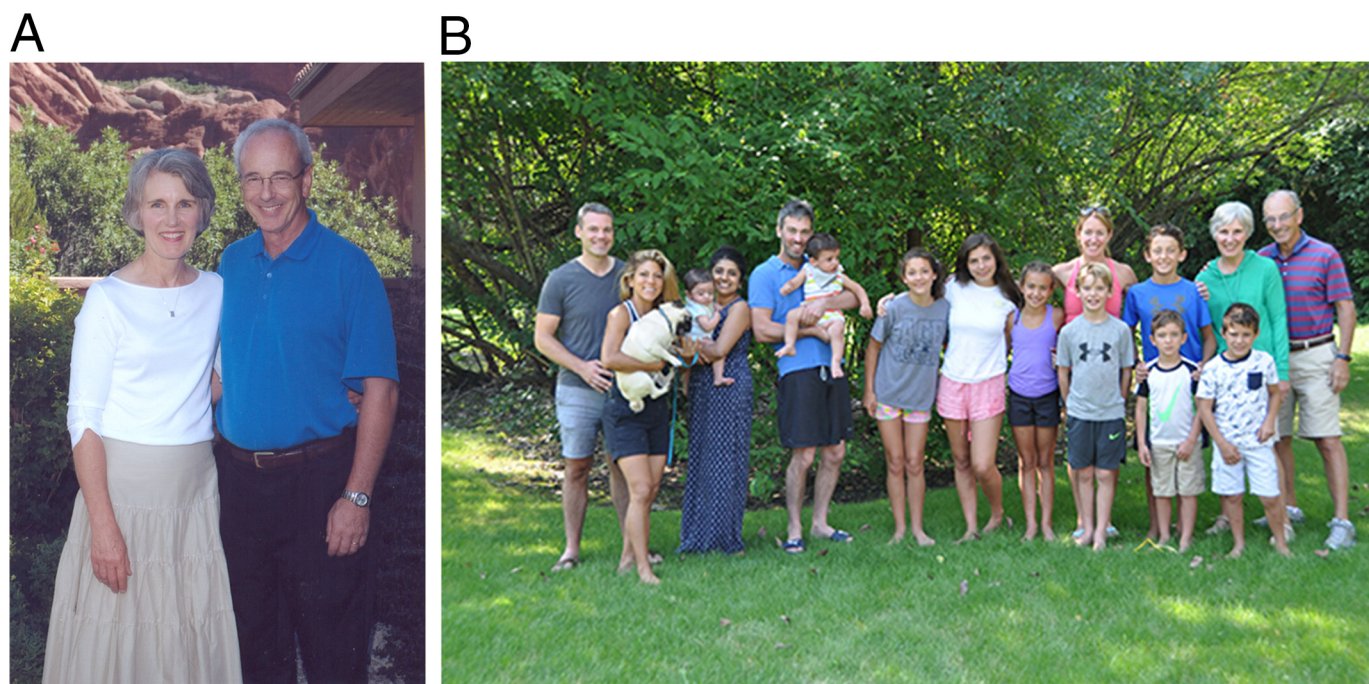


Figure 4. A, Andrea and Bill Smith about 2005 near Roxborough Park, Colorado. B, Smith Family in July, 2018 in Lake Forest, Illinois. From left: Tyler Smith, Rosy Smith, Rajai Smith, Niru Narayan, Zach Smith, Niam Smith, Daisy Smith, Faith Smith, Elyse McGinnis, Shannon McGinnis with Jake McGinnis in front, Scout McGinnis with David Smith in front, Andrea Smith with Will Smith in front, and Bill Smith. Missing and at work was Gray McGinnis.

ing three healthy children and now nine grandchildren (Fig. 4B). Daughter Shannon was born in 1973, and sons Tyler and Zachary were born in 1975 and 1979. Our family lifestyle was from the 1950s—Andrea focusing on childrearing and Bill on breadwinning. However, it was a priority for me to be home before 5 p.m. for a family dinner and play and reading. I returned to work as necessary after the children were in bed. We take great pride in each of our children having taken the initiative to acquire advanced degrees in their fields and becoming self-sufficient, responsible adults and now parents. While I participated in the childrearing, the outcome is a tribute to Andrea. She is the best thing that ever happened to me (and our children). I have been very lucky. If she left, I would be done for, plus I would need to locate a licensed barber.

3. Get excellent training

Early years

As noted above I did my kindergarten through high school education in Park Ridge, Illinois and Fort Collins, Colorado. The teachers I had and the pro-education environment of the Sputnik era provided me with terrific K-12 schooling.

My ranch experience consumed four summers and school “vacations” after high school and during college. I count this as a unique and valuable part of my education. I learned about hard physical labor: delivering calves in snowy pastures; driving and repairing tractors and bull dozers; building fences; herding and branding cattle; haying; irrigating; and using dynamite. Departing the ranch in September, 1963 for college, I felt liberated. The local equipment supplier delivered my replacement as I drove off—a motorized auger for digging fencepost holes.

College

It is important to go to the “right” schools for one’s professional training. I went to the University of Colorado-Boulder because it was the best in-state school. There was no discussion about Stanford or Harvard, etc. I do not recall that they were of interest to me—which is a good thing because I would not have made their wait lists. However, Boulder had, and still has, a stellar chemistry department (*i.e.* another example of my good fortune).

Going to college in 1963 in the U.S. is what children from my background did. I did not know what I wanted to do for a living, but I knew that I needed to become self-supporting by graduation time. To the question “what are you going to do when you grow up?” I answered with “I want to be a doctor” but had no idea what “being a doctor” entailed. What I was most enthused about were baseball and figuring out the meaning of life from literature, history, and extramural activities. None of that worked out. My baseball illusions vaporized my first year in college. And Robert Louis Stevenson’s simple adage: “To be what we are, and to become what we are capable of becoming” is as close to what makes sense to me as anything. My favorite bumper sticker is “Maybe the Hokey Pokey Is What It’s All About.”

I was not “scientifically inclined” as a youngster. I never asked for a chemistry set as a gift, and TV programs like *Mr. Wizard* were uninteresting to me. During my first two years at Boulder, however, I realized that I had two traits that would lead me to a career in biochemical research. First, I had a knack for chemistry. I cannot explain this—I think it involves a sixth sense of equilibria, mass balance, and kinetics coupled with an aptitude for spatial visualization. I assume it must be like having musical

talent, although I have none. Second, I realized that many in the pre-med group were not my type. I was less aggressive and more reflective than reactive.

Freshman chemistry was taught by Dr. Theodore Gilman. The course had a qualitative analysis component to it. Dr. Charles DePuy taught organic chemistry in my sophomore year. This was an era prior to undergraduate research programs, so I knew Drs. Gilman and DePuy only from a distance as lecturers and behavioral models. I admired them as organized, thoughtful academics with high standards. Coming from what I viewed as a threatening home environment, these behaviors were appealing. Additionally, I was excited to learn about melting points, solubility constants, sp^3 bonding, and stereochemistry. I could have done without the cookbook organic chemistry laboratory. I unfortunately learned about the rapid formation of HBr as a byproduct of the reaction of Br_2 with cyclohexene firsthand: In a hurry, I added 10 times more bromine solution than required and was instantly enveloped in a noxious brown cloud.

The third instructor at Boulder who greatly influenced my career was Dr. Alfred Hassner. I was the only undergraduate in his graduate qualitative organic class in the fall of 1966. I enjoyed my first hands-on exposure to IR, UV, proton NMR, and simple separation techniques. One day I discussed graduate school with Dr. Hassner, indicating that I was interested in physical organic chemistry. He said that physical organic chemistry was not a wise choice because the last time Boulder had hired someone in the area, there had been 200 applicants. He suggested biochemistry as an emerging field. I knew nothing about biochemistry, but his suggestion seemed reasonable. So, without further thought, I applied to graduate biochemistry departments. By the time I finished my training there were over 200 applicants for each academic position in biochemistry. No matter; Dr. Hassner provided me with much needed guidance, and importantly, with encouragement—another stroke of good fortune.

I got a minor in history while in Boulder. The quote on the entrance to the Norlin Library reads “Who knows only his own generation remains always a child.” It is an important quote. We see its absence in daily politics. In literature classes, I learned about the existence of and interrelationships among free will, fate, and faith. As noted above I have come to believe that most of what happens is fated. Finally, I performed the usual undergraduate experiments to determine whom not to date and what not to drink (in excess). With ranching during summer and holiday vacations, studying science, history, and literature on weekdays, and skiing and socializing on weekends, my college years were highly educational.

Graduate school

In the fall of 1967 I joined the Ph.D. program in the Department of Biological Chemistry in the University of Michigan Medical School. I was recruited to Ann Arbor by Minor Jessor (Jud) Coon, with whom I spoke when he was visiting family in Colorado in the spring of 1967. Unbeknownst to me Jud was a childhood friend of Julius Johnson, who was to become my father-in-law. I only learned of this on my wedding day.



Figure 5. William E. M. Lands as copied from a Christmas card in the early 1990s.

The Vietnam war was near full throttle in 1967. There was much protesting by the politically active. I did not recall that this was at the forefront of my concerns until a military draft was instigated. I know that neither I nor anyone else I knew was interested in joining the fray. I felt somewhat guilty about this until my father, who was both quite conservative and pro-military, shocked me by saying that he thought that the U.S. had absolutely no business being involved in that war. In 1968, I was classified “1A” by my draft board in Hot Sulfur Springs, Colorado but was then given an occupational deferment because of my studies on prostaglandins.

I received superb training at UM. In our first term of graduate school, all 15 students were enrolled in a graduate laboratory course where we were expected to spend most of our time. Two faculty members, Jules Shafer and Bill Jourdian, and two students, Dan Burleigh and Gordon Faust, shepherded this class. My laboratory sub-group included Niels Schonbeck and Steve Dungan. We were assigned to purify gluconate-6-phosphate dehydrogenase from yeast based on a paper from Horecker and co-workers (2). This required learning how to grind yeast cooled with dry ice and establishing an appropriate enzyme assay. I was overwhelmed. I had never heard of TPNH (now known as NADPH), ammonium sulfate precipitations, or enzyme kinetics. To me, enzymes were amorphous molecular clouds, and teasing out the chemistry underlying catalysis seemed impossible. I preferred the organization of physical organic chemistry to the seeming voodoo of enzymology.

I chose William Lands as my thesis advisor in early 1968 (Fig. 5). I had realized by then that I work best in situations where there is a combination of structure and pressure. I viewed him as a “tough love” advisor with the same high expectations as my father, albeit communicated in a less intimidating manner. I also had become interested in PGs based on a triad of papers published by Hamberg and Samuelsson in November, 1967 (3–5). One of these described an isotope enrichment experiment that I found intriguing. And Bill Lands had just returned from a sabbatical leave in the Samuelsson laboratory.

Bill Lands’ trainees spoke of him good-naturedly using the noun “WEML”—his full name is William Edward Mitchell Lands. He is particularly well-known for discovering the phos-



Figure 6. Lun Ballou and Clinton E. Ballou in Berkeley, California in 1984.

pholipid “retailoring” or “Lands” pathway (6) and connecting the biochemistry of essential polyunsaturated fatty acids (FAs) with their biologic effects. There were eight postdoctoral trainees but no graduate students in the lab when I started because of Lands’ reputation for being demanding and having a Socratic teaching style. Postdoctoral fellows Ed Hill, Hans Eibl, Ron Rietz, Harumi Okuyama, and others all viewed Bill with considerable respect. I wanted to yell “uncle” several times during my training with Bill, but I had been raised not to cry. About a year into my work in his laboratory, I was showing him some PG product data that I had been too lazy to interpret. He listened briefly, gave me a disdainful look, and then walked away without saying anything. He was actually “saying” that it was time for me to grow up and take charge of my project—and I did. He also taught me the scientific method—build a model based on all available information and test the model (and rebuild). This may be the most important aspect of becoming a scientist that one learns in graduate school.

Bill Lands took seriously his role as an educator. I heard him speak of it as acting as an athletic coach as opposed to a playground supervisor. I still depend on him to provide me with objective views on science and the world. I could not have made a better choice for a mentor. My advice for choosing a thesis adviser is to pick someone who will displace you from your comfort zone. It will make you better.

Postdoctoral training

I finished my Ph.D. in 1971 and went to University of California, Berkeley (UC Berkeley) for postdoctoral training with Clinton E. Ballou for two and a half years (Fig. 6). Andrea and I immensely enjoyed living in the Berkeley area. Clint is a reserved gentleman and, like Bill Lands, a careful thinker. I liked studying carbohydrate chemistry and working on their FA modifications of a lipopolysaccharide from *Mycobacterium phlei* and on yeast cell wall mannans. I learned how to work on bacteria and yeast and about yeast genetics, carbohydrates, and immunochemistry. However, the most significant lesson was

about the importance of working with purified material. This latter point should be highlighted. During my stay in Berkeley, I realized that I was more interested in working on PGs than on carbohydrates. This was because the biological and medical importance of PGs was more obvious to me.

Mead Johnson Company and Michigan State University

Impatient to get on with my career and not confident about competing for academic positions, I left Berkeley for a senior scientist position at Mead Johnson Co. in Evansville, Indiana to work on PGs in platelets with Norman Marquis. My father-in-law Julius Johnson was a Ph.D. biochemist who had trained at Boulder and with William C. Rose at the University of Illinois. Julius graduated during World War II and moved to the Dow Chemical Co. During the last 10 years of his career he served as Director of Research and on the Dow Board of Directors. In the context of Julius’ career, the move to Evansville seemed logical. Additionally, good facilities were available, and the people were supportive. While my choice was logical, it was not a job that truly excited me.

One evening two months after moving to Evansville, Andrea and I were lying in bed in our rickety, two-bedroom rental house under stormy yellow skies. Amid the intense springtime lightning and thunder, she asked one of those wifely rhetorical questions: “Are you really planning to stay here?” This led me to contact Clint Ballou and to attend the 1974 FASEB meeting. At a reception at Finn Wold’s house in Minneapolis (thanks to an invitation from Clint Ballou), I met Robert Barker who was moving to Michigan State University as Chair of Biochemistry. I need not provide details, but by mid-January, 1975, Andrea, daughter Shannon, and I were in East Lansing arranging housing. The lesson I learned from my Mead Johnson experience and one mantra I have repeated to trainees is: Only take a job or any other significant assignment if, in addition to logical reasons, you are truly excited about it.



Figure 7. Michigan State University Biochemistry Department Chairs during the period from 1975–2003 (ca. 1995). From left to right are John Wilson, Bill Smith, Jack Preiss, Bob Barker, and Chuck Sweeley.

4. Surround yourself with clever people

Trainees

I have had about 20 graduate and 30 postdoctoral trainees, and a half dozen faculty spent sabbatical leaves in my laboratory. There were also technicians and numerous undergraduates. Most people were productive in generating new information that led to publications. Since I cannot review my entire scientific path, I mention only some of them when I discuss details of my independent research career in the last major section of this Reflection.

I admired Bill Lands for his dedication to education, but I took a more hands-off approach with my laboratory. My assumption was that trainees could and should be resourceful and learn to resolve problems largely on their own, and that this would occur if they were provided an environment where funding and consultation were available. After I became unable to operate anything other than the on/off switches on my laboratory equipment, I modified my thinking. I found that having a weekly, one-hour-long private meeting with each trainee in addition to a weekly group meeting was a good way to operate.

I determined during the first third of my career that I could not keep track of what was happening in my laboratory if there were more than six trainees. I also recognized that at any one time there might be only one person who was generating most of the publishable data while other projects were in various gestational stages. Finally, I came to realize that I was reasonably good at getting trainees started on projects and was particularly effective with the last 5–10%—pushing projects to completion and publication. I was not so helpful in the middle of projects where I would often have a hard time seeing the finish line.

Trainees are like your children. Each trainee trained me more than I trained them, and each was a favorite in some way

although I had more facile interactions with some than others. While everyone is different, my supposition has been that virtually all the people that I have encountered in science were making a good faith effort to be productive—some just had fewer or different talents.

Michigan State University (MSU)

I was on the faculty at MSU for 28 years. MSU was an excellent fit for me personally and professionally. The Biochemistry Department faculty members were (and remain) of high quality and provided a nurturing, interactive environment. During my last eight years there, I served as Department Chair.

After becoming the Chair in 1994, there were problems with managing departmental finances using newly developed accounting programs. I called a friend Bob Tanis, the administrator of the Harvard Genetics Department, for advice. He reminded me that all that matters is that people trust you to make things right—excellent advice. I already knew to never even appear to enrich my laboratory or myself from university funds.

During my time as Chair at MSU I declared that the department needed to hire faculty and develop in three areas: structural enzymology, signaling, and plant biochemistry. I found this simple mantra to be an understandable and effective sales pitch for working with the deans—there were four who oversaw the MSU department. Because I had grown up at MSU, I was able to work well within that system. And it was very beneficial that the Biochemistry Department was one of the top three departments at MSU.

Among the MSU faculty who had a big impact on my career was Bob Barker—the Chairperson who hired me (Fig. 7). He was a careful, productive scientist and an even more remarkable administrative talent who left MSU in 1980 for Cornell Univer-



Figure 8. Herb Tabor and Colleagues at JBC AE Meeting in San Francisco, February 10, 2010. Back (left to right): Vince Hascall, Jerry Lingrel, Jim Stull, Ken Neet, David Russell, Chuck Samuel, Fred Guengerich, Jim Siedow, John Exton, Bob Lehman, Bob Simoni, and George Carman. Front (left to right): Norma Allewell, Bill Smith, Linda Spremulli, Tom Vanaman, Herb Tabor, Dale Benos, Judy Bond, Joel Gottesfeld, Martha Fedor, and Xiao-Fan Wang.

sity, where he later became provost. He was an administrative role model in terms of interacting impartially but positively with people and in structuring departmental guidelines so that faculty understood how decisions were made. Among the other MSU Biochemistry faculty who were my age or more senior and had a positive impact on my career were Shelagh Ferguson-Miller, Loran Bieber, John Wilson, Chuck Sweeley, Bill Wells, Dave McConnell, John Wang, Jack Preiss, and Pam Fraker. There were also many others who came later, several of whom I was responsible for hiring.

University of Michigan (UM)

I left MSU in early 2003 to become Chair of Biological Chemistry at the UM. I served in that position for over 10 years and formally retired at the end of 2015 to “active” emeritus status. The last person departed my laboratory in September, 2017. I joke that I left MSU because I was too happy there and had reached a point where I was sleeping through the night. There is considerable truth to this. It was time for a change. I never regretted making the move. It pushed me into a different, demanding environment, forced me to spend more time on my science, and definitely interfered with my sleep.

Conversations with faculty and others at UM and elsewhere had alerted me that rebuilding the department at UM would be a “daunting” task. My time at UM was administratively chal-

lenging and scientifically productive. The intellectual environment throughout the University of Michigan is superb. And my colleagues in the basic science and clinical departments in the medical school interacted frequently and collegially. More senior mainstays in the Biological Chemistry Department were individuals like Irwin Goldstein, Dave Engelke, Bob Fuller, Rowena Matthews, Charles Williams, Dave Ballou, Jud Coon, Jerry Menon, and Bernie Agranoff. There were also many others including those I was involved in hiring like Steve Ragsdale, Ruma Banerjee, Janet Smith, Ray Triebel and Pat O’Brien to name a few. The staff was also terrific and supportive. The excellent reputation of the University of Michigan rests with its truly superb faculty.

American Society of Biochemistry and Molecular Biology (ASBMB)

On January 1, 2000, I began serving as an Associate Editor (AE) for the *Journal of Biological Chemistry* (JBC). I was an AE for 15 years (Fig. 8). During the last year of my JBC tenure I became an AE at the *Journal of Lipid Research* (JLR) and transitioned to co-Editor-in-Chief with Ed Dennis at the beginning of 2016. At the JBC, who can ever forget the understated stars like Herb Tabor (“...and I’m sure you’ll all agree...”), Bob Simoni (who often did not), Bob Hill, Dick Hanson, Ken Neet, John Exton, Jim Stull, David Russell, Fred Guengerich, Chuck

Samuel, and George Carman and the excellent staff including Barbara Gordon, Chuck Hancock, and Nancy Rodnan. JLR has a similar roster of first-rate, civic-minded scientists. Joe Witzum, whom I replaced, coached me for six months about distributing manuscripts to other AEs. The JBC and JLR AEs are wonderful, erudite groups. I learned many things and got terrific advice—scientific and otherwise—from each of them. One example: At a formal JBC dinner one evening in Bethesda I told Dick Hanson, who by this time was in his late 70s, how nice he looked, which he did. He said: “Bill, as you get older you do not look good anymore. It is important to dress yourself up as best you can.”

5. Work 60,000 hours

Being a scientist takes time and dedication. One somehow accumulates knowledge by scientific osmosis in being around laboratories all day (and at night), talking with people, hearing snippets of conversations, and thinking about biochemistry (e.g. PGs and COXs and FAs) all day and throughout the night. Woody Allen’s remark is accurate: “80% of life is simply showing up.”

I had a mini-epiphany one pleasant summer evening when I was in my early 50s. It was near dusk, and I was gazing out at the courtyard from the window of my 5th floor office in the MSU Biochemistry Building. There was no one else in the laboratory or probably the building. I was crafting sentences for a JBC manuscript. I suddenly realized that what I was doing was what gave me very considerable personal satisfaction and that that was okay. I was not raised as an academic, but as someone who derives satisfaction from seeing the concrete outcomes of my labors. I mark this as the time when I came to understand that an occupation devoted to contributing information to the scientific edifice is truly valuable.

On another occasion I was attending a dinner at MSU with five or six accomplished scientists who came to a joint, but unsettling conclusion. As long as work was going well in the laboratory, we were each at peace, and it did not matter whether things were going that smoothly at home. We agreed that the converse was also true. While perhaps perverse, I suspect many dedicated scientists would concur.

6. Be frugal

When I started graduate school I lived in a sparse one-bedroom apartment. Having minimal interest in fine dining, I would buy frozen pot pies at the local grocery for twenty cents apiece. This was before microwave ovens, and so each evening I would wait hungrily for 45 minutes while two pot pies baked. I would eat one and a half for dinner and the other half for breakfast. The menu greatly improved after Andrea and I married. She taught elementary school in Ann Arbor, and we could afford hamburgers, peas, tomatoes, and potatoes—and a beer (or two) for Bill.

Andrea and I benefitted from our parents who, for example, contributed money to education accounts we had endowed for our children. We have done the same for our grandchildren. We have invested and saved carefully both for large purchases and for retirement. Our children think that we are overly cautious. It is hard to break ingrained habits. Plus, we have already

purchased everything we want. I even hit expensive monogrammed golf balls.

7. Study an important and interesting topic

From a career perspective this may have been my greatest stroke of good luck. My career, which I date from the beginning of graduate school in 1967, has revolved around PG biochemistry (Figs. 1 and 2). Now 50 years later, interest in PGs remains, although it is focused on topics such as identifying the basis for adverse cardiovascular effects of nonsteroidal anti-inflammatory drugs (NSAIDs), developing specific PG receptor ligands, and delineating nutritional advantages of omega-3 and omega-6 FAs. My accomplished friend Chuck Rock at St. Jude’s teases me about building an entire career on the hydroxyl group of a single serine residue—Ser-530 of COXs—the site of aspirin acetylation. Well, Chuck is just jealous.

Graduate school (1967–1971)

During my Ph.D. training, I worked with two related enzyme systems. One was relatively pure soybean lipoxygenase-1, which catalyzes the abstraction of the ω 8 pro-S hydrogen from 8,11,14-eicosatrienoic acid (dihomo- γ -linolenic acid) and related omega-3 and omega-6 FAs.

Lipoxygenase-1 products all contain a *cis/trans*-conjugated diene ($\epsilon_{234} \sim 35$ liters/cm⁻¹ mm⁻¹), so the enzyme can easily be assayed spectrophotometrically. Moreover, soybean lipoxygenase is a soluble protein and readily available commercially.

The second system was a crude acetone powder extract of microsomes prepared from ovine seminal vesicles, the tissue having the highest level of COX-1 activity. COXs catalyze a hydrogen abstraction reaction closely resembling that of lipoxygenase-1 (3, 5). The COX assay of 1968 was cumbersome and time-consuming. It involved using radioactive arachidonic acid (AA) or dihomogamma-linolenic acid, quenching the reaction with acidified chloroform/methanol, and multiple other steps that took two days of work. We also had—for the sake of WEML’s economy—to wash the glass scintillation vials and pour new TLC plates onto the original glass backing. We did take precautions such as not smoking when rinsing scintillation vials with organic solvents.

A publication on a FA oxygenase activity in bovine seminal vesicles in 1970 (7) and a subsequent hallway conversation with a fellow student Marcia Flashner (now Steinberg) from Vince Massey’s group alerted me to the Yellow Springs Instrument Company Model 53 oxygen electrode. We purchased this electrode. Its use transformed COX studies. I could now continuously monitor COX activity by measuring O₂ consumption even with crude enzyme preparations. Very quickly we noted a kinetic lag phase, its relationship to hydroperoxide activation of the enzyme, and what we called “burning out” or “suicide inactivation.” The latter was a phenomenon whereby, after the initial burst of oxygenase activity, the activity was quickly lost and could not be restored (8). Soybean lipoxygenase-1 shares similar kinetic features (9), although we now know that lipoxygenases are structurally unique and employ a nonheme iron-based mechanism for hydrogen abstraction (10).

It was at this time that John Vane and his colleagues published three landmark papers in the June 23, 1971 issue of

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Nature New Biology showing that aspirin and indomethacin inhibited PG biosynthesis (11–13). Their measurements of PG formation were all performed using bioassays for PGE₂ or PGF_{2α}, so it was unclear where in the conversion of AA to PGs the inhibition occurred. On August 23, 1971, we submitted a manuscript to the JBC showing that it is the oxygenase step in PG formation that is blocked by aspirin and indomethacin (14). We also reported that the effects of both aspirin and indomethacin were time-dependent, suggesting that the enzyme was undergoing a chemical modification. Roth *et al.* (15) were the first to provide evidence for acetylation of COX-1 by [³H]acetylsalicylate with a crude platelet enzyme preparation. We ultimately established this with purified ovine COX-1 (16). Later Kulmacz and Lands (17) and then Marnett and co-workers (18) and Percival *et al.* (19) showed that the time-dependent inhibition by indomethacin and many other COX inhibitors results not from covalent modification but from slowly reversible structural changes elicited by inhibitor binding.

MSU assistant professor (1975–1979)

Shortly after completing the aspirin/indomethacin work, I took leave of PGs and joined the Ballou laboratory. It was three and a half years later in February, 1975, when I arrived at MSU. It became obvious to me that if I wanted to become moderately R&F, I needed to purify COX-1. It seemed like a formidable task, but it was clearly the most important work that needed to be done in PG biochemistry. I collaborated with Bill Lands in these studies. Early steps in the COX purification work were done by Martin Hemler, then a student with Bill but now of tetraspanin fame and at the Dana-Farber institute. I worked out the final steps in East Lansing developing a Flurbiprofen–Sephacryl affinity chromatography column and employing the then new technique of isoelectric focusing. I'm proud to say that I performed the experiment establishing that the homogeneous ~70,000-kDa ovine COX-1 subunit was radiolabeled by [acetyl-³H]aspirin. Our purification and characterization of ovine COX-1 were big accomplishments (16), only slightly diminished by having Osamu Hayaishi's lab describe a purification of the bovine enzyme (20) a few months before our paper was published (but fortunately not before our paper was submitted).

I did not immediately follow up on examining COX enzymology after the purification of COX-1. Both Lands' and Hayaishi's groups were obviously interested in the topic, and by this time I had become more intrigued about cell biological aspects of PG biosynthesis. Specifically, I had become interested in applying immunochemical techniques learned in Clint Ballou's laboratory to determine the subcellular location of COX-1.

Using purified COX-1, I prepared and characterized a rabbit antibody to the enzyme. I used the antibody to stain sections of kidney with the help of Graham Wilkin, an English postdoctoral fellow in John Wilson's laboratory at MSU, and Tom Bell, a pathologist in the MSU veterinary school. We chose the kidney for our studies because it was known to have relatively high PG biosynthetic activity. A complete novice in histology, I quickly learned to prepare and stain tissue sections and even became adept at identifying different renal cell types. Intense COX-1 staining occurred in the renal collecting tubules,



Figure 9. My group at MSU in 1981 including Frank Grenier, Arlyn García-Pérez, David DeWitt, and Bill Smith.

whereas most other renal cells were devoid of immunostaining (21). Consequently, I became interested in the role of PGs in controlling water flux in the renal collecting tubule.

Excellent trainees joined my laboratory at that time including my first Ph.D. student Frank Grenier (Fig. 9) and an M.S. student Tom Rollins. With no sense of how to work with cultured mammalian cells, a technique just then coming into vogue, I asked Frank to isolate renal collecting tubule cells from rabbits. One day he mistakenly used a very hypotonic solution in his preparation and discovered that only a few cells in the crude renal medullary cell dispersion remained. The medullary collecting tubule cells had survived the osmotic stress, whereas all other renal medullary cell types had burst. *In vivo* these tubular cells are exposed to very different osmolarities on their luminal and basolateral surfaces. I still marvel that Frank deduced what had occurred with his seemingly failed cell purification protocol (22). Not surprisingly, he went on to a successful career at Abbott Laboratories.

Tom Rollins performed immunoelectron microscopy showing that COX-1 was primarily associated with the ER and nuclear envelope and not the plasma membrane as had been predicted (23). Again, I had no idea of how to perform immunoelectron microscopy or analyze the results. Fortunately, Dr. Karen Klomparens guided us. After receiving his M.S., Tom moved to Merck and has since become truly R&F. He was important in developing Sepracor and later became involved in numerous other businesses.

Rick Huslig was also in the laboratory then and studied COX-1 expression during the ovine estrous cycle (24). Our bioassay for day 1 of the cycle was performed by a vasectomized ram with MSU green grease painted on his underside. Rick left MSU to enter the University of Miami MD/PhD program and has gone on to be a successful oncologist.

MSU associate professor (1979–1983)

During the early 1980s, immunologists began “panning” for subpopulations of blood cells using monoclonal antibodies. Dave DeWitt (Fig. 9) had already developed monoclonal technology in our laboratory as an analytical tool for quantifying COX-1 and for purifying prostacyclin synthase (25). Arlyn García-Pérez (Fig. 9) joined the laboratory at about that time and developed monoclonal antibodies that she used to isolate different types of renal cells by a process we dubbed “immuno-dissection” (26). Arlyn is a wonderful, intelligent, hardworking, and fun person, including being an excellent piña colada bartender. She continues her very successful scientific and administrative career at the NIH.

MSU professor (1983–2003)

In parallel with the COX work in the mid-1980s, I spent a productive six month sabbatical leave with Lutz Birnbaumer at Baylor learning about G protein-linked receptors. During the mid-1980s Tsuyoshi Watanabe, Keizo Umegaki, and Akihito Nakao, all superb senior postdoctoral “trainees” from Japan, and Bill Sonnenberg, an exceptional graduate student, devoted considerable efforts to understanding renal PG receptors. Their work on the EP3 receptor and the regulation of cAMP levels in renal collecting tubules provided the groundwork for understanding PG receptor signaling in general and for cloning the receptors. Unfortunately, our cloning efforts ended abruptly, when Shuh Narumiya’s group reported the cloning of the EP3 receptor in 1992 (27). It was obvious that my laboratory could no longer compete in this area so we then focused 100% of our efforts on COX studies—a necessary but unpopular decision.

I owe my research successes primarily to my trainees. The trainee who contributed the most to my career was certainly David L. DeWitt (Fig. 9). He is now a well-respected dean at MSU. Dave joined my laboratory in the late 1970s and received his Ph.D. in 1984. He returned to his home state of California for a short-lived postdoc. In 1986 I recruited him back to East Lansing to clone COX-1. Dave was fearless at trying new techniques. Among the many tools he brought to my group was DNA technology. At the time I had not grasped what molecular biology could do for us, but I saw the biochemistry world heading in that direction and recognized that my laboratory had better head than tail as well. Dave did the COX-1 cloning work from scratch by himself with little more than moral support from me. He succeeded in isolating and sequencing a COX-1 cDNA, and we published the first report of the COX-1 sequence (28). Based on some peptide sequence data in the literature (29) and now the new cDNA sequence, it was clear that Ser-530 was the aspirin acetylation site. Most importantly, we had available the clone necessary to perform much exciting biochemistry. We soon determined that a S530A COX-1 mutant was catalytically active but refractory to aspirin (30). Thus, we proposed that aspirin acetylation of Ser-530 introduces a bulky group into the active site of COX-1 that interferes with AA binding. Crystal structures affirmed this (31).

One of our most important contributions to COX catalysis was done by postdoctoral fellow Teruhiko Shimokawa in a collaboration with Rich Kulmacz and Ah-Lim Tsai at the Univer-

sity of Texas Houston Health Science Center. We used a combination of site-directed mutagenesis, tyrosine specific labeling and epr studies with ^2H -labeled tyrosine to determine that Tyr-385 was the likely location of the active site tyrosyl radical (32, 33). Linda Hsi extended these studies to COX-2 (34).

Rich and Ah-Lim have contributed immensely to our understanding of COX catalysis (35). In my opinion, their work has been the most underappreciated of all COX studies. I have viewed them concurrently as competitors and friends. Similarly, another accomplished COX contributor is Larry Marnett at Vanderbilt, who has also been a friend for years and an occasional and more than worthy golf partner.

It had been known since 1979 from work by Hayaishi and co-workers (36) that COX-1 had both oxygenase and hydroperoxidase activities along with a heme prosthetic group. Using site-directed mutagenesis, Teruhiko identified the essential histidines of COX-1 as likely heme ligands. We were then able to deduce the approximate arrangement of key residues in the COX-1 active site including Ser-530, Tyr-385, and one of the two proximal histidines (37), even prior to Mike Garavito’s groundbreaking COX-1 crystal structure (38).

Phil Needleman’s and Tadashi Tanabe’s groups each published COX-1 sequences in 1988 shortly after we did (39, 40). COX-1 sequence information was the basis for the discovery of COX-2. There remain arguments about who was the real discoverer of COX-2. Harvey Herschman’s, Daniel Simmons’, and Donald Young’s groups all isolated inducible poly(A) transcripts with COX-1-related sequences. However, Herschman’s group showed that the protein expressed from his TIS-10 sequence had COX activity (41). So Harvey gets my vote. Dave DeWitt and Elizabeth Meade, an excellent student he was mentoring, and I authored the first publication establishing that there were pharmacological differences between COX-1 and COX-2 (42).

The discovery of COX-2 and the recognition of differences between the isoforms initiated a rush to identify and market a COX-2 inhibitor that had analgesic and anti-inflammatory activities but no adverse gastrointestinal effects, which were thought to be due to COX-1 inhibition. This led to the launch of rofecoxib (Vioxx[®]) and celecoxib (Celebrex[®]) as COX-2 inhibitors in 1999 (Fig. 1). Merck made what turned out to be a tactical mistake in one trial by comparing rofecoxib with naproxen, a mixed COX-1/COX-2 inhibitor that has among the worst gastrointestinal profiles of all COX inhibitors. Unexpectedly, naproxen caused significantly fewer adverse cardiovascular events than rofecoxib. This ultimately led to the withdrawal of rofecoxib. Naproxen also appears to have a better cardiovascular profile than other common COX inhibitors (43, 44), probably because of differences in its interactions with COX-1 *versus* COX-2 as discussed below (45).

In the early 1990s, it became clear we were overmatched in investigating COX biochemical pharmacology because of the numbers of investigators at pharmaceutical companies. I reasoned that we could make contributions only by persisting with curiosity-driven as opposed to cure-driven COX studies. Our COX work continued to involve structure/function studies performed proficiently by Linda Hsi, Inseok Song, Marc Lecomte, and Odette Laneuville. This group was great fun. Without pro-

viding the sordid details, I will mention that they collaborated to win the department's annual Halloween "Dress Your Pumpkin as a Faculty Member" contest.

During this period, we were continuing to investigate the subcellular localization and membrane-binding properties of the COXs. Jim Otto and later Andrew Spencer were graduate students who determined that both COX isoforms were anchored to the luminal surface of the ER and inner membrane of the nuclear envelope. Their work established what had been hypothesized by Garavito and colleagues from their X-ray crystallographic studies (38). In short, COXs are not transmembrane proteins but rather are anchored via four amphipathic helices to one surface of the membrane (46, 47). Jim Otto was a brilliant student, who was also an avid basketball player and fisherman. He currently works at Duke University. Andy now lives in Ann Arbor and is continuing his very successful career in the biotech industry.

It was also during this time that graduate student Martha Regier and Dr. Ikuo Morita, who was on a sabbatical leave, compared aspects of COX-1 and COX-2 subcellular localization and noted subtle differences in their patterns of immunofluorescence staining (48). The basis for this finding was resolved by innovative studies conducted after our move to UM by my most persistent and resilient graduate student Uri Mbonye in 2008 (49) and postdoctoral associates Masa Wada in 2009 (50) and Chong Yuan in 2015 (51). Collectively, they established that the 18-amino acid cassette unique to COX-2 and near its C terminus is involved in trafficking COX-2 to the Golgi apparatus. A polysaccharide *N*-linked to Asn-594 and found only in COX-2 is processed within the Golgi apparatus in advance of COX-2 degradation via the ER-associated degradation system. Whereas COX-1 only functions in the ER and associated outer layer of the nuclear envelope, COX-2 operates as part of a distinct Golgi PGE₂ biosynthetic system. In retrospect, it is clear that the relatively more intense perinuclear staining of COX-2 seen by Morita and Regier had been due to COX-2 in the Golgi apparatus. I am indebted to Dennis Voelker who, as JBC Associate Editor, contributed much through his careful editing and suggestions to the quality of Dr. Yuan's landmark 2015 JBC paper on COX-2 in the Golgi (51).

Our COX structure/function studies during the mid- to late 1990s and early 2000s involved a highly productive collaboration between my and Michael Garavito's laboratories. Our group performed the site-directed mutagenesis and enzymology studies while Mike's group performed X-ray crystallography of COX-1. We used various FA substrates and native and mutant COX-1 forms in which Co³⁺-heme was used to replace the Fe³⁺-heme of native COX-1 to catalytically neuter the enzymes. Mike Malkowski, Beth Thuresson, Karen Lakkides, Jill Rieke, Dipak Bhattacharyya, Christine Harman, and Jiayan Liu were the major contributors during this era. We mapped, for example, the contribution of each COX-1 active site residue to AA binding and catalysis (52).

Starting about 1995, several trainees become enamored with the regulation of COX-1 and COX-2 gene expression. Despite my not being enthusiastic about these types of studies, we made some useful contributions thanks to the insights and efforts of Cynthia DeLong, Yeon-Joo Kang, and Byron Wingerd (53). I



Figure 10. Gilad Rimon at MSU about 1989.

still consider Dr. DeLong's paper to be the best publication on COX-1 expression (54). Toshiya Arakawa was a superb postdoctoral fellow during this time and provided the intellectual and technical background for these efforts as well as isolating the EP4 receptor gene (55). He left my laboratory to resume his career at Hokkaido University.

At the University of Michigan (2003–2016)

While our cell and molecular biology studies continued, a major focus remained on COX enzymology, biochemical pharmacology, and omega-3 FAs (56). This period included an enjoyable and productive sabbatical leave with Robert Murphy and his group at the University of Colorado medical campus in Aurora (57).

What I believe to be the most creative contributions of my career were instigated by reports from Gilad Rimon and his co-workers (58) (Fig. 10). Gilad came from Ben-Gurion University of the Negev, Israel to spend several sabbatical leaves in my laboratory both at MSU and UM, in part to examine, using purified COXs, a pharmacologic enigma that he had observed with cultured cells and microsomal preparations of COX-1. Briefly, he had found that some COX-2 inhibitors interfered with COX-1 inhibition by some common NSAIDs but without affecting COX-1 catalytic activity toward AA (59). This was perplexing in the context of what was then believed about COX catalysis.

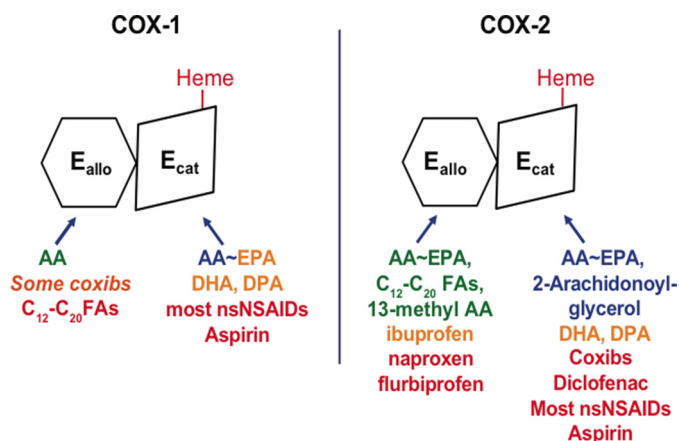


Figure 11. Isoform specific interactions of COX substrates, nonsubstrate FAs, and COX inhibitors with huCOX-1 and huCOX-2. Each COX isoform functions as a conformational heterodimer composed of an allosteric (E_{allo}) and a catalytic (E_{cat}) subunit. The individual subunits of human COXs differ both in their affinities for different ligands and in their responses to binding of the ligands. Efficient COX substrates are shown *blue* in approximate order of their catalytic efficiencies. FAs that are inefficient COX substrates can interfere with prostaglandin formation, typically by competing with AA for the E_{cat}; these are shown in *orange* (e.g. EPA, DHA, and docosapentaenoic acid (DPA)). Ligands shown in *green* allosterically stimulate COX activity. Ligands shown in *red* interfere with COX activity either allosterically by binding E_{allo} or competitively by binding E_{cat}. Ligands that bind E_{allo} can also affect responses to COX inhibitors. For example, nonsubstrate FAs bound to E_{allo} of huCOX-1 increase the rate of aspirin acetylation, whereas celecoxib (shown in *orange*) bound to E_{allo} of huCOX-1 can interfere with aspirin action. This figure and the legend are modified from Ref. 1. This research was originally published in the *Journal of Biological Chemistry*. W. L. Smith and M. G. Malkowski. Interactions of fatty acids, nonsteroidal anti-inflammatory drugs and coxibs with the catalytic and allosteric subunits of cyclooxygenases. *J. Biol. Chem.* 2019; 294:1697–1705. © Smith and Malkowski.

It had been known since 1977 that COX-1 was a homodimer (60), and for reasons documented elsewhere (1), it was widely believed that the monomers operated independently. Over the course of about 15 years through the work of Gilad Rimon, Chong Yuan, Masa Wada, Liang Dong, Narayan Sharma, Rana Sidhu, Hechang Zou, and a collaboration with Mike Malkowski at the University of Buffalo, we determined that despite being sequence homodimers, COXs function in solution as conformational heterodimers (45, 61–67). Complementary studies by Marnett and co-workers (68–70) using an alternative substrate 2-*O*-arachidonoylglycerol and various NSAIDs support this concept.

In solution, both COX isoforms exhibit half-site heme and inhibitor binding as first observed in the mid-1980s with COX-1 by Kulmacz and Lands (17, 71). Both isoforms are composed of a catalytic subunit (E_{cat}) with heme bound and an allosteric subunit (E_{allo}) lacking heme (Fig. 11). Different COX inhibitors and FAs bind with various different affinities to E_{allo} and E_{cat} to cause a variety of different effects on enzyme activity; moreover, the affinities differ between the subunits of the two isoforms as diagrammed in Fig. 11.

For example, aspirin acetylates only E_{cat}. Celecoxib, a COX-2-selective inhibitor, binds very tightly to E_{allo} of COX-1, preventing aspirin acetylation of E_{cat}; however, celecoxib binding to E_{allo} of COX-1 does not interfere with the oxygenation of AA by the E_{cat} subunit (62).

Another remarkable finding concerns naproxen (Aleve®). Naproxen inhibits COX-1 competitively by binding E_{cat} but

inhibits COX-2 allosterically by binding to E_{allo}. While naproxen can cause 100% inhibition of COX-1, it causes a maximum of 70% inhibition of COX-2. The differential effects of naproxen on COX-1 *versus* COX-2 may underlie the relatively modest adverse cardiovascular effects of naproxen (44).

Finally, we found that omega-3 fish oil FAs and particularly eicosapentaenoic acid effectively inhibit the oxygenation of AA by binding E_{cat} of COX-1 but that eicosapentaenoic acid binds E_{allo} of COX-2 and has little effect on AA oxygenation by E_{cat} of COX-2 (56). As my scientific career comes to its conclusion, I feel very fortunate to have been involved in the discovery that COXs function as conformational heterodimers (1).

Conclusion

I trust I've convinced you that these seven rules will help you become a moderately R&F biochemist, and that my instructions provide all the information you might need to follow the rules. Remember also and always that there is always hope—the key ingredient of the universe—until there isn't. I even shot an 81 recently on a difficult golf course.

Acknowledgments—My research was generously and continuously supported over the years primarily by the U.S. Public Health Service through National Institutes of Health Grants HD10013, DK22042, HL29685, DK20945, GM40713, GM57323, GM68848, CA130810, and HL117798.

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J. Biol. Chem. 2019, 294:1779-1793.
doi: 10.1074/jbc.X118.006184

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