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AAP Kober Medal

I first met Bill Kelley in 1970 when I applied for a fellowship in his laboratory at Duke. I had the feeling in this first meeting that this was a man who could have a significant impact on my life. Thinking back 35 years now, I know that he did and I suspect that he had a similar influence on many in the Association of American Physicians. Bill has been a remarkable visionary leader, always knowing where he wanted to go and how to get there. He has transformed every place at which he worked by bringing in new people and ideas, developing creative programs, and constructing modern facilities. People remain at the heart of all that Bill has accomplished. He identified the best people, recruited them, provided them the resources to succeed, guided them in their careers, and watched with great pride from near or far as they made important contributions to American medicine and science. I am indebted to Martin Van Der Weyden, one of Bill's former fellows at Duke and now Editor of The Medical Journal of Australia, for calling up an ancient Chinese proverb that suggested the title for this presentation – Of Rice and Men: “For next year plant rice; for the next generation, train men.” Annually and day by day, Bill sowed rice everywhere [...]

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2005 Association of American Physicians Kober Medal

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Edward W. Holmes, M.D.

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Annually and day by day, Bill sowed rice everywhere he worked and ideas, programs, and facilities sprouted, as a generation of physician-scientists grew to maturity under Bill's watchful gaze.

Bill Kelley was born in Atlanta, Georgia, on June 23, 1939. It was an ominous year for world geopolitics, but a great year for movies. Atlanta received much attention that year in the movies because of the world premiere of *Gone With the Wind* — while Captain Rhett Butler became a movie legend, another commander who would come to be a major leader in the real world of American medicine was developing unnoticed in Atlanta.



William N. Kelley, M.D., received the Association of American Physicians' Kober Medal at the Association's annual meeting, April 17, 2005. Edward W. Holmes, M.D., presented the Kober Medal to Dr. Kelley.

Bill's fascination with the military was soon replaced with an interest in medicine based on his frequent excursions with his father on house calls and hospital rounds.

In 1956, he graduated from High School in West Palm Beach, Florida (Figure 1). Then it was on to Emory University where



Figure 1
Dr. Kelley as a young man.

he majored in math. Bill's fascination with data would influence the rest of his career, but he could not give up his first love — medicine — and he entered the Emory University School of Medicine in the fall of 1959. And he returned to his other first, and lasting, love, marrying Lois Faville, whom he had known since kindergarten (Figure 2). As his medical career began, so did his family, and Lois and Bill welcomed their first children — Paige in October 1960 and Ginger in January 1962.

Following medical school, Bill pursued internship and residency training in internal medicine at the University of Texas Southwestern Medical Center. Dan Foster, who had just taken a faculty position at Southwestern after returning from the NIH, remembers that Bill “was a dazzling resident.” Don Seldin, then Chairman of Internal Medicine at Southwestern, and a mentor to Bill throughout his career, encouraged Bill to pursue his interest in biomedical research and he arranged for Bill to pursue the next phase of his training at the NIH.

Before leaving Dallas, Lois and Bill added Lori, their third child, to the family.

Bill became a Clinical Associate in the Section on Human Biochemical Genetics at NIH. It was here — in the laboratory of Jay Seegmiller — that scientific inquiry first captured Bill's imagination.

Bill became intrigued by a young boy



Figure 2
Dr. Kelley's marriage to Lois.

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with self-destructive behavior and excessive urinary uric acid excretion. Bill quickly realized that understanding the molecular pathogenesis of an inherited defect such as this was the future of human genetics and modern clinical research.

The paper he published from his observations, Bill's first real experience with laboratory medicine, proved to be a landmark discovery reporting the deficiency of HGPRT enzyme activity as the molecular basis of the Lesch-Nyhan Syndrome. This report opened a new field of investigation; it launched Bill's career in human genetics and established a lifelong love affair with molecular medicine.

Shortly after the discovery of complete HGPRT deficiency in patients with the Lesch-Nyhan Syndrome, during the Christmas "break" — a prolonged and uninterrupted stretch in the lab including several all-nighters — Bill found that a partial deficiency of this same enzyme, HGPRT, was associated with uric acid overproduction and early onset gout but with mild or no neurological findings, sometimes referred to as the Kelley-Seegmiller syndrome. Bill went on to write 8 scientific papers on the control of purine metabolism with Seegmiller and colleagues in the laboratory.

After NIH, Bill took another year of clinical training at Massachusetts General Hospital. Alexander Leaf, then Chairman of Medicine at MGH, remembers Bill as a rising star in biomedical research and tried to persuade him to stay on the Harvard faculty in clinical pharmacology. But as Dr. Leaf said, "Bill had gotten a bit cocky as his research was receiving national recognition and he let me know that he had his eyes set on bigger things. Not surprisingly, he succeeded."

Bill turned to his mentor Don Seldin for advice on what he should do next. Seldin had offered Bill a faculty position at Southwestern but Bill was also entertaining an offer from Duke. Dr. Seldin advised Bill to do whatever he felt would be best for his career, and Bill accepted the offer at Duke. Dr. Seldin says this was the only fellow he ever lost.

At age 29, after only one year at Duke, Department Chair Jim Wyngaarden appointed Bill to be Chief of the Division of Rheumatic and Genetic Diseases. Jim recalls that Bill had relatively little experience in clinical rheumatology when he "volunteered" for the Chief position and he challenged Bill to become the best clinical rheumatologist at Duke. And Wyngaarden notes, "He became

Figure 3

Organizers of the 4th Winter Rheumatology Symposium, Snowmass, 1980. From left to right: Edward W. Holmes, M.D., William N. Kelley, M.D., and William Arnold, M.D.



a world leader in the field, going on to write one of the major textbooks in the field." Bill rose from assistant professor of medicine to professor in only 6 years at Duke, and he was also appointed associate professor of biochemistry.

Bill transformed the Rheumatic and Genetic Diseases Division into one of the nation's top 5 programs in the discipline, building a wide and deep research program.

Bill's research career flourished at Duke. He established what would become one of the premier laboratories in the world for the study of purine metabolism.

In a series of some 75 original publications during this 7-year span, Bill's laboratory laid the foundation for much of what is now accepted as the gospel in standard textbooks on the control of purine metabolism and the renal handling of uric acid. Many of us who trained in the Kelley laboratory during this time went on to establish successful careers working on just one of the enzymes or metabolic systems pioneered in the Kelley lab.

William Arnold, Irving Fox, and I were three of the first people in Bill's lab, like the advance group of a recruiting vanguard (Figure 3). Bill identified people he thought had some potential to succeed, assessed the raw material each of us presented, measured us, tested us continuously, and trained us to be physicians and scientists. It was a process to be repeated over the years.

At Duke, Bill's family continued to grow, as did the Division, and in October 1969, Lois and Bill's fourth child Mark was born.

Bill's curiosity and desire to know more led him to apply for and receive a Macy Faculty Scholar Award to study at Oxford University. There he worked at the Sir William Dunn School of Pathology doing cell biol-

ogy and cell hybridization studies, adding to his research skills and preparing himself for the next step. Bill's courage to adopt new technologies to answer scientific questions would be one of the hallmarks of his research career.

In 1975, Bill was recruited to the University of Michigan School of Medicine to be the Chairman of the Department of Internal Medicine. At age 36, he was the youngest chair of medicine in the country.

It was a challenge from day one. Upon his arrival, Bill was questioned about three unexpected deaths at the Ann Arbor Veterans Administration Medical Center occurring over the previous days — a strange coincidence in the minds of some law-enforcement officers. He faced a unionized housestaff threatening a job action that included a strike, was named in a lawsuit that involved a dissatisfied faculty member who had been removed by his predecessor, confronted a situation where planning for a new university surgical hospital excluded beds for medicine, and was told that eight promised positions could not be filled because of the institution's financial situation.

Needless to say, these and other impediments were no match for Bill. He resolved all of the initial issues and proceeded to build the Department of Medicine into one of the premier programs in the country. During his 14 years as chair, Bill led the Department from 42nd to 4th nationally in its level of NIH research funding.

He brought the Howard Hughes Medical Institute to Michigan, critical for the development of basic science and clinical investigation in the Department and the entire institution. He deftly used this resource to attract some of the best and brightest young people in the country to Michigan — all have gone on to major research accomplishments and hold national lead-



ership positions. These individuals laid the foundation for building an extraordinary research faculty across the department.

While building Michigan into one of the premier departments of medicine in the country, Bill continued to run a highly productive research laboratory. In the early 1980s before molecular biology was in vogue, Bill recruited a graduate student, Jim Wilson, to his lab and they published the complete amino-acid sequence of HGRT — a *tour de force* in that day. Bill's lab went on to sequence mutant forms of HGRT in several patients, closing the loop on studies he had begun at the NIH 15 years earlier.

Bill never lost sight of why he was in this field: to improve the health of patients. He was one of the first to appreciate the potential of gene therapy, and in two seminal papers published with Tom Palella, Bill's group demonstrated the successful transduction of human HGPRT into neuronal cells in culture and in intact animals.

Based on this pioneering work, the patent, submitted in December 1987 while at the University of Michigan, was issued on September 30, 1997 (Figure 4). This patent was one of the first and broadest to be issued covering the technique of in vivo gene therapy and recognized Bill's seminal contributions to this field from its inception.

At Michigan, Bill was also the leading institutional force behind the construction of the clinical and research buildings that today comprise Michigan's medical complex. One department chair, John Voorhees, says, "the cluster of buildings we call the Medical Center was for all intents and purposes built by Bill."

As recruiter and mentor, Bill has few

"KING OF THE KOBE(R)"

(Sung to the tune of "King of the Road")

Started out at Emory, Dallas made a memory
Then for a research start he figured out HGPRT
Then off to Boston, Mass, where all but Alex noted his class
He was marked for something special, King of the Kobe(r)!

Then Duke and then Go Blue, and he rounded up quite a crew
A recruiter without peer (I'm just a little bit partial here)
And then after those 14 years, it was time for Bill to change his gears
He made Penn the med-ultimate, King of the Kobe(r)!

Bridge:
When Bill Kelley went on student rounds
Not a dry seat could be found
He was telling them that "knowledge heals"
But they called it "clubbing the baby seals"

He just meant to teach them right, he was a role model day and night
In the lab, on the ward, at home — was that all Bill or does he have a clone?
So a lot of us that are here today learned from Bill to find our way
He was skating where the puck was gonna be, King of the Kobe(r)!

We know Bill gets his spark from Paige, Ginger, Lori, Mark
And Lois, we're all her fans, superwoman for a superman
So let us all now agree that a medical giant is he
He's our Man of the Year — that's Bill — King of the Kobe(r)!

Performed by Francis S. Collins for the presentation of the 2005 Association of American Physicians Kober Medal.

peers in academic medicine. In every place he's been, attracting top-flight faculty was Bill's highest priority. Tachi Yamada was recruited to Michigan as Chief of Gastroenterology and succeeded Bill as chair in 1989. Tachi says that "there is no one in academic medicine who has had a better eye for young talent than Bill."

Peter Ward, Chairman of Pathology, says that Bill "demonstrated his genius in identifying young faculty members who would, over time, become stars in the field of biomedical research."

Bill also had a unique ability in mentoring young faculty. Francis Collins notes that "Bill was a very supportive chairman in those scary early days. I was working on a very technically difficult method called chromosome jumping, and it was three years after my arrival before I had accumulated enough data to publish a paper in a reputable journal. I was sure I was failing, but Bill continued to provide reassurance that truly difficult projects take time."

As we all know, Francis did not fail and Bill's eye for talent was proven yet again. Francis' talents are not limited to the laboratory, however, and he has generously agreed to join me in recognizing Bill with a song [see "King of the Kobe(r)"].

Bill recruited to Michigan one of the great junior faculties in American medicine of that era — or any era. He recruited over 90 percent of the faculty and all but two of

United States Patent	5,672,344
Kelley, et al.	September 30, 1997
Viral-mediated gene transfer system	
1. A vector for direct delivery of a gene to a mammalian host comprising a recombinant viral vector which targets and expresses a mammalian gene in a selected cell in the mammalian host, the recombinant vector further comprising:	
a) at least a portion of the genome of a DNA virus which exhibits tropicity for the selected host cell, which portion is operatively arranged to infect the host cell, wherein the portion of the genome is modified to have a level of virulence less than the level of virulence present in a virulent wild type viral strain from which the recombinant viral vector is derived; and	
b) a mammalian gene operatively linked to the portion, wherein the operatively-linked gene is expressed in the host cell after infection of the cell.	

Figure 4
Broadest Claim of Patent #5,672,344, issued September 30, 1997.



Figure 5
Dr. Kelley with family members at the presentation of the Kober Medal.

the Division Chiefs who were there when he left. His recruiting record at Michigan was nothing short of remarkable, perhaps never to be matched again in academic medicine.

The Michigan years were family years as well, filled with innumerable family outings and milestones. In 1987, Ginger married Chris and Paige married Arvind. In the next three years, Caddie and Jamie were born to Paige, Lois and Bill's first grandchildren.

Michigan was spectacular, personally and professionally, but Bill had his sights set higher. Bill, the quintessential recruiter, was often recruited himself. No opportunity seemed just right until the University of Pennsylvania beckoned. In 1989, Bill left Michigan to become CEO of the University of Pennsylvania Medical Center and Health System and Dean of the School of Medicine. During the next eleven years, Bill was to effect another great institutional transformation.

Sheldon Hackney, then President of the University of Pennsylvania, brought Bill to Penn. He recalls that Bill provided strong, courageous, and imaginative leadership in a difficult environment. "I remember that he told me as he was getting started that he wanted to be a 'three-crane' dean" (the number of cranes on campus at one time to handle construction projects). Bill turned out not to be a three-crane dean – he went on to become a five-crane dean.

As at Michigan and Duke, the list of accomplishments across the research, education, and clinical enterprises is long and deep. In just over a decade at Penn, Bill moved the institution from 10th place to 2nd in NIH funding. By 1999, 14 of Penn's academic departments were ranked in the top 5 in their respective disciplines. Total research awards topped \$355 million. Overall, the School of Medicine's national rank-

ing, as measured by the annual *U.S. News & World Report* survey, improved from 10th to 3rd.

Bill launched and implemented a new medical curriculum – Curriculum 2000. He significantly expanded the M.D./Ph.D. program. He established 12 major multidisciplinary research centers and institutes at the medical-school level.

Bill recognized that access to patients was critical to achieve the medical school's academic missions. He conceived of and built the University of Pennsylvania Health System, the nation's first fully integrated academic health-care system. By 2000, the Health System included the School of Medicine, 4 owned and 12 affiliated hospitals, an 850-physician multi-specialty faculty practice plan, a 270-physician primary care regional network, and 2 off-site multi-specialty satellites. Today, five years after Bill left his CEO position at Penn, the Health System structure remains intact.

By the late 1990s, and for the first time, the Hospital of the University of Pennsylvania moved onto the honor roll of the nation's top hospitals in the *U.S. News & World Report* survey, ranking 10th by the year 2000.

And Bill built buildings, including two major research buildings, he renovated 658,000 gross square feet of research space, he built a new bed tower in the university hospital, and he renovated 1 million gross square feet of clinical space.

As at Michigan, identifying and recruiting the best people was the key to transforming the institution and elevating performance. Bill brought in an outstanding leadership group of department chairs and center and institute directors and management team.

Thirty-two chairs were recruited over a ten-year period, twenty from the outside,

including the first two women to receive permanent appointments as department chairs in the medical school's 240-year history.

The Kelley family grew during the Penn years. Mark married Hester in 1996 and Lori married Mark William in 2004. And an additional five grandchildren joined the Kelley clan – Hailey, Duncan, and Miranda to Ginger; Noah to Mark; and Rowan to Paige (Figure 5).

The Penn years were challenging as they were for all of academic medicine, but Bill's commitment to academic excellence never wavered. Roy Vagelos, retired Chairman and CEO of Merck and former Chairman of the Penn Board of Trustees, sums up Bill's tenure as CEO/Dean at Penn as follows: "Bill Kelley was the most effective leader of an academic medical center in several decades. His major accomplishments include the recruitment of a great faculty with a terrific leadership team. He largely rebuilt much of the medical center physical plant and added numerous new facilities and laboratories. He improved the care of patients. He totally overhauled and improved the education program. He raised the quality and quantity of research activity so that the University of Pennsylvania Health System was close to the top."

How then to sum up a life's work, a lifetime of accomplishment? Bill has been and continues to be someone who is committed to the greater good of academic medicine. He gives generously to organizations beyond the institutions where he has worked. He has founded and edited two major textbooks, served on 14 editorial boards, and has been a valued consultant to academia, government, and industry.

Bill's contributions have been widely recognized by election to the most prestigious academic societies and through receipt of numerous awards, of which only a few can be cited here (Table 1). He was President of the American Federation for Clinical Research and the ASCI; he has served on the council of the Institute of Medicine. He is the recipient of numerous prestigious awards for academic achievement, service to government, and the Emory Medal from his alma mater.

Bill's greatest gift to American medicine and science lives on in the men and women whose potential he discovered at an early age, whom he trained and whose careers he nurtured, and whose contributions to medicine, science, and society continue to this day and will extend far beyond.



We have gone on to positions of national prominence in academia, clinical medicine, industry, and government – to chair 14 academic departments, to become Deans of 7 medical schools and senior executives of 9 academic health systems and universities, to assume very senior positions in industry at 4 international corporations, and to take on 4 very senior posts in the federal government. Twenty of Bill's recruits have been elected to the Institute of Medicine, 2 to the National Academy of Sciences (including 1 new member this year), and 48 to the AAP (including 3 new members this year). And this accounting misses the many who have gone on to other splendid and productive careers in each of these domains.

For over three decades in positions of leadership and trust, Bill always planted next year's crop of rice, never forgetting that the real task was to grow the next generation. Many in our profession are in

Table 1

Selected honors for William N. Kelley, M.D.

- President, American Federation for Clinical Research
- President, American Society for Clinical Investigation
- President, American College of Rheumatology
- Chairman, American Board of Internal Medicine

- Elected to IOM; served on its Council
- Elected to American Academy of Arts and Sciences
- Elected to American Philosophical Society

- Robert H. Williams Award, APM
- David E. Rogers Award, AAMC
- John Phillips Memorial Award and Medal, ACP
- National Medical Research Award, National Health Council
- Emory Medal, Emory University
- Gold Medal, American College of Rheumatology

his debt, and we all thank him for what he passed on to us.

It is my great honor, on behalf of the

Association of American Physicians, to present the George M. Kober Medal to Dr. William N. Kelley.

2005 Association of American Physicians Kober Medal

Acceptance of the 2005 Kober Medal

William N. Kelley, M.D.

Thank you, Ed, for those wonderful comments and thank you, Francis, for your very special homegrown entertainment. Clearly, it has been people like the two of you who have contributed so much to make my professional career so immensely enjoyable.

Thanks also to the officers and councilors of the AAP for selecting me to receive the Kober Medal this year, certainly a signal event in my professional life. I have been sitting in the audience for virtually all of the Kober Medal presentations since 1966, nearly 40 years ago. I have enjoyed learning more about so many of my professional heroes, mentors, and colleagues through these many years. To have my name added to that list of legends of American medicine today is truly an unbelievable experience. Again, my deepest appreciation.

Before I go further, I would like to recognize my family. One takes great pride in one's

professional accomplishments and successes, and I certainly do. However, one's feelings, love, and devotion to family go far beyond one's life's work. So, I am especially pleased that most can be here today, including my wife of 45 years and best friend, Lois, 3 of our 4 adult children with their spouses, 2 wonderful foster parents, and 8 of our 9 grandchildren, along with 1 additional grandson here in utero. Would all of you please stand? We dearly miss our oldest daughter, Paige, who is institutionalized because of her severe mental illness and our oldest grandson, Jamie, who is severely retarded, mentally and physically, due to cytomegalovirus contracted in utero. Most families must deal with personal tragedy and sadness in their lives and ours is no exception. We are using this weekend to enjoy each other, and my warmest thanks to each of them for being here.

There are others I would like to thank in the time I have available. Perhaps first and foremost, I want to thank the many with whom I have worked closely over the years. Many are professional colleagues with whom I have interacted in innumerable settings throughout the world. Some are individuals that I have had an opportunity to recruit as faculty in one of the three great institutions where I have had an opportunity to serve. A few, who

are in some ways most meaningful to me, are those with whom I have had a chance to work in the laboratory. So much of the learning and mentoring I have received, as well as the enjoyment and pride I have felt, comes from the rich experience of working with so many truly outstanding people at every level. We learn from them, they help us mature in our thinking, and they provide incredible personal and professional satisfaction as they succeed in their careers. One evolves from the joy of discovery and getting one's work published in *Science*, the *JCI*, or *NEJM*, to even greater excitement and pride when one of your mentorees makes an important discovery, achieves important recognition, or assumes a major leadership position.

I would like very much to be specific about dozens of these very special colleagues in my life, many of whom are in the audience today. Given the practical constraints of this presentation, however, I will narrow the list to 5 senior physicians at the very top of that long list, who I would like to recognize and thank.

The first on the list is my late father, Dr. Oscar Lee Kelley. In the mid- to late 1940s, following his return from overseas duty with the Air Corps in World War II, he re-established his practice of cardiology in Palm

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