2006 Association of American Physicians George M. Kober Medal

Introduction of David G. Nathan, MD

Edward J. Benz Jr., MD

President Olefsky, members and guests of the association: It is both a privilege and a pleasure to present Dr. David Gordon Nathan, the 2006 awardee of the George M. Kober medal of the Association of American Physicians, to this distinguished gathering of colleagues, friends, and family. Dr. Nathan is an exceptional awardee. Like the distinguished individuals who have preceded him in receiving this honor, he has made outstanding contributions as an investigator, caregiver, educator, and leader. However, there is another dimension to David that makes his receipt of this honor add special luster to the Kober Medal. Nathan has also used his talents and his stature to launch and nurture the careers of an incredibly large number of extraordinary scholars and leaders whose own contributions directly amplify David's. They, in turn, have produced and are even now producing leaders. David Nathan's extraordinary impact and positive influence on the field are, and will be, reverberating for generations. At a time when we fear the demise of the physician-scientist and physician-scholar, he is personally keeping the pipeline flowing.

I have known David Nathan for more than 30 years. My first encounter was typical of so many whose lives he enhanced. Having done a successful undergraduate thesis in the nascent field of molecular genetics while at Princeton in the mid-1960s, I arrived at Harvard Medical School eager to apply these new approaches to human disease. I was rebuffed. The methods of molecular genetics would never be usable in humans; that was what several eminent professors told me. Then, I got lucky. David gave a brilliant set of lectures on the hemoglobinopathies to our class. Those inherited conditions struck me as possible candidates for study at the DNA and RNA level. Even more attractive was Nathan's enthusiasm and openness. It emboldened me to go to him and ask if I might work with him.

Graciously, David invited me to lunch to discuss opportunities in his laboratory that might be of interest to me. He also asked whether I would pay for my own meal and his as well! He claimed that he had forgotten to put any money in his wallet. I learned later, when I asked David for supplies for my research, that his wallet was again bereft of currency. All of us have learned that spending money is not his favorite activity. In fact his close friend and colleague, Sam Lux, took over David's division of hematology largely to prevent him from serving American cheese, popcorn, spaghetti, and diet Pepsi at lab meetings and reunion dinners. David taught me two great things that day. First, always take students seriously. Second, there is truly no such thing as a free lunch. Needless to say, David took me into his labs and my career was launched. Since then I have hosted, and been a guest at, many working meals. That first one with DGN, as we know him, remains the best investment of meal money I have ever made.

The Kober Medal is awarded every year to members of the association who have had uniquely distinguished leadership careers in academic medicine. David has certainly had an illustrious career. In fact he is one of three physicians (the others were Helen Taussig and James Gamble) to receive both the George M. Kober Medal and the John Howland Award of the American Pediatric Society. But the only medal that David keeps on his office wall is one he received in the sixth grade at the John D. Runkle School in Brookline, Massachusetts, a suburb of Boston. Shown here in all its glory is the Good Citizenship Award, which his mother framed, and David has kept in her honor (Figure 1). I note this seeming idiosyncrasy because it is telling. David Nathan never forgets where his roots are and he always remembers that he is a citizen of our community of scholars.

It is traditional at this presentation to begin the awardee's story at the very beginning. In David's case there are certain facts in those origins that tell us a lot about the man, facts that help us appreciate how he became so special. He was born in Boston and has lived in its environs ever since except for what he calls "two years off for good behavior" at the National Cancer Institute in Bethesda, Maryland. At Harvard, we have a term that describes someone who is an undergraduate and a medical student at Harvard, does a Harvard residency and a fellowship, and lives his or her entire faculty career at Harvard: such individuals are called "Preparation H." David is one of those, but he is hardly inbred or thrombosed! His outlook has always been worldwide, as has his impact.

Figure 1
The Good Citizenship Badge awarded to David Gordon Nathan in the sixth grade of the John D. Runkle School in Brookline, Massachusetts, on June 26, 1941.

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Figure 2
The Nathan family in the fall of 2005.

David's great-grandfather immigrated to Boston from Hungary at the onset of the Civil War to begin a family textile soap factory. His grandfather, Jacob Nathan, became a widower and lived with David and his father, Geoffrey, his mother, Ruth, and sister for many years. Jacob, Geoffrey, and Ruth had a profound influence on David's value system. David Baltimore once said, "David Nathan makes decisions with his father on one shoulder and grandfather on the other."

As a youngster, he was drawn to the sea; he is an accomplished boatsman and cherishes the times he has been spending on Nantucket since early childhood. It is his favorite place of respite with family. Indeed, he got much more out of Nantucket than a mere affection for boats and the sea. He captured the love of his life, Jean Friedman Nathan. They were married when David started medical school at Harvard in 1951. Now, nearly 55 years later, their children, Deborah, Linda, and Geof, their sons-in law, Michael Charness and Steven Cohen, and their six grandchildren, shown here in a recent family picture (Figure 2), are all living within the Boston community and enjoying each other's company. Three of them are here with us today. David promises to release his formula for keeping grandchildren within one's grasp for a small sum.

David first experienced clinical research as a second-year student at Harvard Medical School. Though he intended to start a group practice in Cambridge, he became fascinated by hepatic coma and its potential linkage to disordered ammonia metabolism and devised a method for measurement of blood ammonia (1). The mystery of hepatic coma and the small but important (to him) success in the laboratory committed David to a clinical research career.

David did his residency in internal medicine at the then Peter Bent Brigham Hospital. Like many great academic hospitals at the time, it was seemingly a Dickensian institution characterized by terrible facilities, but it was an extraordinary place for clinical care and research. It was the Brigham that caused him to be hooked for life on applying science to patients. Nathan then found his way to the National Cancer Institute where he was overwhelmed by the magnificence of the then brand-new, 500-bed clinical center. There he met his first research mentor, Nathaniel I. Berlin. Berlin encouraged him to pursue clinical research in hematology. If he had any thoughts of demurring, those thoughts were pre-empted by Berlin's quiet reminders that he (Berlin) was a government officer of higher rank. In fact David may be one of a very few hematologists who were literally ordered into the field simply because Berlin had four stripes on his sleeve and he had only two.

After two years at NCI, David returned to the Brigham, where he completed a senior residency in medicine and joined the junior faculty as a hematologist under the watchful eye of Frank H. Gardner. There he found himself exposed to patients with fascinating anemias and explored their bases with the then-novel use of radioisotopes. Renal transplantation was in full spate at the Brigham, and David's first important paper was devoted to a much-cited study of erythropoiesis in anephric man (2). This study clearly demonstrated that there must be extrarenal sources of erythropoietin in humans.

In the 1960s David's ability to dissect the basis of anemias came to the attention of Louis K. Diamond at the Children's Hospital, who created a close collaboration between David and his colleague, the late Frank Oski. Together David and Frank described the red cell abnormalities observed in pyruvate kinase deficiency (3–6) and the rare but fascinating defects that follow excessive monovalent cation permeability (7–10). During that period David also became fascinated by the thalassemia problem (11, 12) and with a then Harvard Medical student, the late Robert Gunn, wrote a classic paper that brought attention to the role of unbalanced hemoglobin synthesis in the pathogenesis of the anemia (13). David and I picked up on this theme in a paper noting that the genetic defect in the production of a single globin peptide produced a clinical syndrome of hyperproliferation (14). At its worst, beta thalassemia resembled a neoplastic disease far more than an anemia due to an intrinsic red cell defect. He thus was among the first to provide both insight and offer a concrete prototypical example of the important role of clinical pathophysiology in relating a genetic deficit to the often nonintuitive observed symptomatology.

By the mid-1960s, David had developed doubts about remaining in internal medicine. His interest was moving steadily toward inherited disorders of the blood cells. Frank Gardner did his best to expand his space and give him an office and a place for the liquid scintillation counter (Figure 3). Here a trailer is being lifted into place to serve as extra space while the then Division of Hematology at the Brigham waits expectantly. Those who have been disappointed at David's opinion about how much space they need should copy and frame this photograph. Great work can happen in cramped quarters.

Note the background of this picture. The shadow of the trailer is on the Children's Hospital. The image foretold David's real future as a world leader in pediatrics. Louis K. Diamond urged David to take up the

specialty in which the patients with congenital anemia were to be found. The late Fred Rosen and particularly Charles A. Janeway were also persuasive recruiters. David and Fred Rosen became lifelong friends, and David was particularly impressed by Janeway's brilliance and honesty. He remains devoted to their memories.

To settle the issue of internal medicine or pediatrics, David visited with William B. Castle, the Kober medalist of 1962. Castle asked David whether the thought of moving to the Children's Hospital made him happy. David replied that it made him very happy but that his internal medicine friends wondered how he as a non-pediatrician could be a successful clinical investigator in a field in which he had no clinical experience. Castle replied that most of the people who come to see him are unhappy. Being happy was more important than classical training. He advised David to make the move. David did, and pediatrics became the beneficiary of his devotion and brilliance.

That Castle was right has been proven by experience. During the three decades beginning in 1966 in which David led the Division of Hematology at Children's and then the combined Division of Pediatric Hematology and Oncology of the Children's Hospital and Dana-Farber Cancer Institute, the division rose to world-class stature. Nine of the trainees, including David, became members of the National Academies, eight joined the Howard Hughes Medical Institute, four became fellows of the American Academy of Arts and Sciences, two, including David, became members of the American Philosophical Society, thirty were elected to the Association of American Physicians, fifty-two were elected to the American Society for Clinical Investigation, and sixty-two were elected to the Society for Pediatric Research. Five presidents of ASCI and four presidents of ASH trained in his program. Though I have not reviewed the output of all training programs in pediatric and internal medicine specialties, I doubt very much that any of them could claim such a record. Meanwhile, David has published more than 350 papers, almost a third of which are found nearly equally distributed between the *New England Journal of Medicine* and the *Journal of Clinical Investigation*. His edited book, the *Hematology of Infancy and Childhood*, is the world's leading textbook of pediatric hematology and oncology (15). It is now entering its seventh edition. David is also among the most literate of our colleagues. He has written two popular books, *Genes, Blood, and Courage*, published in 1995 (16), and *The Cancer Treatment Revolution*, to be published in 2007 (17).

During this intensely productive period from 1966 to 1995 David continued to be stimulated by patients with congenital disorders of blood cells. Though scores of his papers dealt effectively with the pathophysiology of red cells, four critically important therapeutic and preventive contributions stand out.

Nathan and his colleagues demonstrated that continuous subcutaneous administration of deferoxamine could markedly prolong cardiac disease free survival in thalassemia (18–21). The observation has stood the test of time and the treatment has been the standard approach to chelation therapy for transfusion-induced iron overload for the past 30 years. Hopefully it will soon be replaced by orally active iron chelators, a subject to which David has also devoted considerable effort (22).

David and his colleague, Y.W. Kan, introduced clinically practical approaches to prenatal diagnosis of the hemoglobinopathies (23, 24). Then David, along with Blanche Alter, Henry Chang, John Hobbins of Yale, and Stuart Orkin, first utilized fetoscopy to make the prenatal detection of sickle hemoglobin (25–27) and demonstrated the first successful application of Southern blot based prenatal detection of thalassemia (28). Their efforts and, independently, those of Y.W. Kan have led to a marked reduction in new cases of thalassemia in the Mediterranean world. Indeed, the origins of DNA-based antenatal genetic testing lie in these studies. The impact these approaches have had on the social fabric and health care economics of societies like those in Sardinia, mainland Italy, Cyprus, and Greece cannot be overstated. The incidence of new cases of thalassemia, a disease once causing a huge social and economic burden, has been at or near zero in these areas since the adoption of these methods.

David and his colleagues were also the first to show that hydroxyurea can stimulate fetal hemoglobin synthesis in sickle cell anemia (29, 30). Large trials conducted by others, particularly George Dover and Samuel Charache (31), have since demonstrated that the treatment is clinically beneficial in at least half of the cases. I should note that this body of work has produced the first and, to date, only treatment that ameliorates the morbidity of sickle cell disease and enhances survival.

David also explored the biochemical basis of chronic granulomatous disease

Figure 3
The Division of Hematology of the Department of Medicine of the Peter Bent Brigham Hospital in 1964. The trailer, lifted by a crane, was to become David Nathan's office and a home for a liquid scintillation counter.

and showed that it is due to a deficiency of enzymes that produce toxic oxygen species (32, 33). Almost two decades later, David's student and then colleague, Stuart Orkin, cloned the gene for one of those enzymes (34).

All of this activity took place in a setting of a very busy clinical service and a rapidly growing laboratory establishment with strong ties to basic science laboratories at Harvard Medical School and at MIT. David's approach to clinical research is based on teamwork. No one can be expected to do it all or know it all. Solutions to tough medical problems require, in his view, intense collaboration among investigators with different skills.

The ways in which Nathan used his connections at MIT and Harvard University illustrate what makes his contributions even greater than his traditional body of work. He had absolutely perfect pitch when it came to matching up young trainees and faculty with major labs in these basic science programs. For example, he connected Bernie Forget and me with David Housman, David Baltimore, and Inder Verma. Bernie and I were enabled by this connection. We could never have identified the RNA defect in thalassemia without the resources and ingenuity of these scientists. Many other leaders can point to their own examples of how David's matchmaking accelerated their development.

After 20 years as a division chief, David was tapped to head pediatrics at Children's and Harvard. From 1985 to 1995, he served as Physician-in-Chief of the Children's Hospital—the job that Charles A. Janeway had held when David was first recruited to that hospital. His laboratory remained very active, and his influence on the hematology training program grew even more intense in that period, but most of his energy was devoted to strengthening the Children's Hospital. The results were remarkable. Among his most significant accomplishments was the establishment of a Howard Hughes Medical Institute program at Children's, the first HHMI unit devoted to pediatrics.

In 1995, David was asked to assume the leadership of the Dana-Farber Cancer Institute at a time of crisis. He transformed Dana-Farber from a highly regarded but somewhat insular cancer center to the hub of what became known as the Dana-Farber/Harvard Cancer Center. A survey of the Harvard medical community, including all of its affiliated hospitals, revealed 800 faculty members with an interest in cancer. All were invited to join the new center and most became members, thereby creating one of the best, and arguably the very best, cancer centers in the United States. In fact that is what brought me back to Boston to succeed David (though some have said that I took the job in order to have enough money to pay for my own lunch and his).

Despite the enormous pressures of the job at Dana-Farber, David took the time to work hard as the chair of Harold Varmus's NIH Panel on Clinical Research. In my view that panel came up with a very important menu of grants to support clinical researchers, both novices and established investigators. And the panel, urged on by one of its key members, Jean Wilson, the Kober awardee of 1999, strongly endorsed debt relief for clinical investigators — a program of great importance. David has written several key papers on clinical research policy that further established him as an experienced contributor to the national medical scene (35–40). Perhaps the most interesting is his recent paper in the *Journal of Clinical Investigation* in which he tries to give direct advice to young people entering the field (41).

Not surprisingly, David has received many honors and career awards including the National Medal of Science in 1990, the Stratton Medal of the American Society of Hematology, of which he was president, membership in the Institute of Medicine, an honorary degree from the University of Athens, and membership in the American Philosophical Society. But I know that the most meaningful awards to him are the recognitions from his clinical colleagues in pediatrics and internal medicine in the form of the Howland Award from the American Pediatric Society in 2003 and now the Kober Medal.

But it is time to let you hear from David himself. I am thoroughly delighted to present my teacher and friend, and now my employee, David G. Nathan, MD, as the 2006 recipient of the of the George M. Kober Medal of the Association of American Physicians.

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2006 Association of American Physicians George B. Kober Medal

Acceptance of the 2006 Kober Medal

David G. Nathan, MD

Thank you so much Ed. You have successfully appropriated my Good Citizenship Award. In all fairness, you and this tolerant assemblage should know that I lost the election for that award by a vote of twenty-two to two. My best friend voted for me and I voted for myself. The class was outraged when the teacher decided to "give it to the boy who came in second." This was their first exposure to a fixed election (Florida in 2000 was their second). I can only hope that the proceedings that led to the Kober Medal were more wholesome.

But thank you Ed. It is true that I forced you to pay for my lunch as well as your own when I first met you. You were so innocent then. It was impossible to avoid taking advantage of you. But despite my desperate desire to save a nickel, you emerged from an impecunious cocoon to be a fine clinical investigator and a true master of academic medicine. And now the tables are turned. The quality and I am afraid the quantity of my lunch now depend entirely on you. This is not a time in my life to irritate you. But I wouldn't anyway because I am desperately proud of your accomplishments in the lab, in the clinic, and now in the office. To be introduced by you as a peer of this distinguished audience is an honor that I will never forget.

President Olefsky, members of the council who have chosen me for this great honor, and fellow members of the Association of American Physicians: I find it difficult to summon the words that I need to thank you for the Kober medal, and I dedicate this wonderful occasion to the memory of Stanley Korsmeyer who would have eagerly shared this thrilling moment with me.

I have been coming to this meeting for 50 years. Decades ago I sat in the tobacco smoke–filled Steel Pier Theatre (which later burst into spontaneous combustion) listening to the plenary papers delivered at the annual meeting of the ASCI and AAP and noticing from the far back rows of that miserably uncomfortable gathering place the roped-off area in the front center where the lions of academic medicine were loosely caged. I remember as though it were yesterday when I was elected to membership in the ASCI. I saw my name on the blackboard and ran out to Haddon Hall to find a phone and tell my dear wife, Jean, that my career in academic medicine had actually amounted to something. Her response was memorable: "Don't forget the Steiff animals for the children." Jean has always been my practical lodestone.

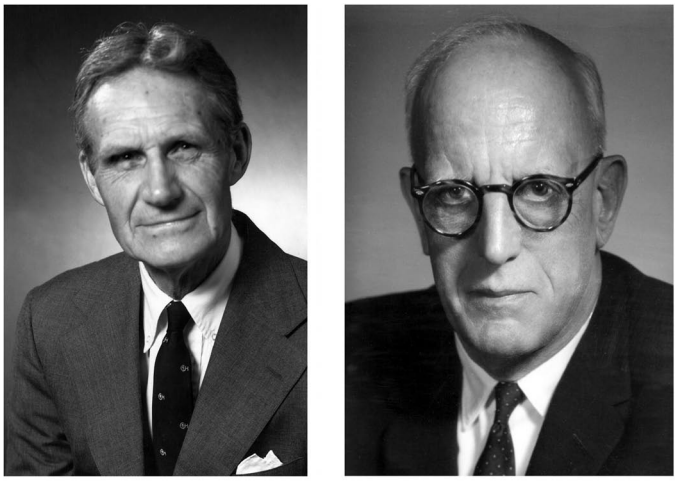

Figure 1
Charles A. Janeway and William B. Castle.

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