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Acceptance of the 2006 Kober Medal: *2006 Association of American Physicians George B. Kober Medal*

David G. Nathan

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AAP Kober Medal Acceptance

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 […]

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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.

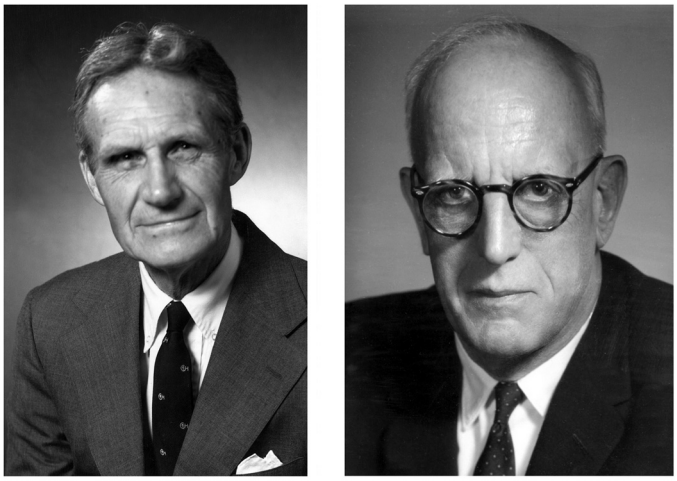

Figure 1
Charles A. Janeway and William B. Castle.

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Charles A. Janeway (Figure 1) later nominated me for membership in the AAP and I know that he received the strong support of William B. Castle and Carl Moore in that effort. It was Castle who taught me about being a clinical investigator. He also established a standard for probity and honesty about one's strengths and weaknesses, while Janeway taught me something else. He tried to impress on me that a great division in a department of medicine or pediatrics depends on teamwork. "Don't," he said, "focus on people's weaknesses. Focus, instead, on their strengths and put a team together that as a team can play all the positions."

Castle emphasized honesty about one's own strengths. I had to argue with him to support my sabbaticals at MIT and in the basic science departments at Harvard Medical School. One of his favorite phrases was, "Don't get into the ring with Joe Louis — he will beat you up." He was referring then to remarkable biologists like Harvey Lodish and David Baltimore at MIT. "You are a clinical investigator and not a basic scientist. Your strength is your patients. Do not leave them for a mouse or a dish of separated cells."

Castle (Figure 1) made that point very clear in his acceptance of the Kober Medal in 1962, four years before I was elected to membership in the Young Turks. Let me quote from that acceptance speech. "Indeed, we should then regard the study of the patient including all aspects of his disease and of its relation to his physical and cultural environment as the basic research area appropriate for the physician" (1).

I have taken that advice very seriously and have followed the precepts of Alexander Pope upon which they are based. "The proper study of mankind is Man." Surely one of the best living exemplars of that precept is Victor McKusick, who has never lost his focus on patients with inherited disease and after Garrod is the modern founder of human genetics.

I do not mention McKusick because I dream that I am somehow close to that level of accomplishment. I mention him because Castle was correct. It is possible to make large contributions to the fundamental medical sciences by focusing entirely on patients. Barry Marshall, the discoverer of *H. pylori*, is another example, and there are many more.

But I must admit that during the recent past, there has been a declining morale in patient-oriented research circles. Joe Goldstein and Mike Brown, in a masterful paper published in the *JCI* in 1997 (2), drew the important distinction between patient-oriented and disease-oriented physician-scientists. The latter function as basic scientists with a medical bent. The former focus on patients. They participate in the care of those patients as well as in the studies that illuminate their pathophysiology and treatment. It is that latter group of what I call POTCIs (3), patient-oriented translational clinical investigators, together with investigators who focus on clinical trials epidemiology, outcomes, and behavioral research who have found themselves in particularly straitened circumstances in the past two or more decades.

With the guidance of distinguished members of the AAP including Harold Varmus, Judy Swain, Jean Wilson, and Lee Rosenberg, among others, I have tried to define improvements that might enhance the lot of these vital members of the biomedical research community (4). And I am satisfied that the relatively new K30, K23, and K24 awards that our 1995 NIH Director's Panel on Clinical Research formulated, together with the debt relief programs that the entire academic clinical research enterprise fostered, have made a substantial difference (5). But in the past three years, the commitment of NIH to clinical research is again slipping. The ratio of clinical to total awards and budget is in decline (6). I have not formally gathered these data, but senior NIH staff have given me discomforting information.

Today the upper tiers of NIH management have constructed another layer of support that is meant to bolster the national GCRC effort. The present doyens of building 1 seem to hold that our panel's K awards and debt relief constitute a mere Band-Aid and a failed holding action. They have constructed a procrustean grant program that my father would surely have described in his favorite portrait of overkill as "resplendent, redundant, and rococo". The application process itself is totally exhausting. In fact, those who are struggling with it bear a close resemblance to statues of Laocoan and his children. And at the end of the tortuous process, most of them will look like Goya's wounded mason.

Paul Nurse, in a recent outstanding perspective published in *Cell* (7), has decried the tendency of NIH to wrap money in enormous bundles of paper or trillions of bytes of electronic transmission. He begs for simplicity of grant application design,

Figure 2
My patient, "Immortal Sword," at age 6.

but the NIH is on a different course. Our desperate efforts to save the POTCIs may be swallowed up in labyrinthine process.

The short answer to our present difficulty is budget relief (8). And that must mean private as well as federal relief. Foundations that support clinical research like the Doris Duke and Burroughs Welcome and powerful organizations that have put a toe into clinical research such as Howard Hughes need to resolve to support the effort. And those of us who care must ceaselessly jawbone those in charge in an effort to salvage as much as we can of the single discipline that will bring the fruits of biomedical research to the bedside and to the clinic.

And without overtrumpeting our accomplishments, we have much to say. In my own career, I have seen supportive therapy for congenital diseases improve incredibly. Enzyme therapy for Gaucher's disease and starch diet for glycogen storage disease are just examples.

Figure 2 is a photo of a six-year-old boy distorted and shrunken by thalassemia. An authority no less than Fanconi had informed his parents that he would be dead at fifteen. I have devoted much of my career to him and those like him. In fact, I wrote a book about him when he reached

his thirtieth birthday (9). Here he is at his brother's wedding (Figure 3) at age 33. He is now in his mid-40s, sustained by the first orally active iron chelator to be approved by the FDA (10). He is alive and productive because of POTCI-type clinical research, huge advances in basic research, and a close and unconflicted relationship with pharmaceutical companies.

I have seen the prognosis of childhood leukemia change from universally fatal when I went to NIH in the 50s to 85 percent curable today. Even infant leukemia, incurable five years ago, is coming around. And smart drugs that hit the very enzymes and signaling systems that drive cancer are coming into practice at a remarkable rate.

We are in a therapeutic revolution. Mortality from heart disease has plummeted because we have learned how to reduce cholesterol and blood pressure. Cancer mortality is beginning to turn the corner, but we cannot reduce its incidence because cancer is time dependent. The more we age, the more it will occur. Despite our inability to reduce its incidence, we are dissecting the very basis of the cancer cell's success. Only five years ago Gleevec, the first smart drug in a pill form, was used to treat patients with CML, a leukemia driven by mutant abl kinase. Today we have a list of genes and proteins that are known to cause cancer and we have drugs that inhibit many of them. Armed with DNA array technologies and rapid sequencing, we will soon make a molecular diagnosis instead of an organ diagnosis of cancer and we will use imaging to determine the correct set of drugs for an individual patient.

I want to conclude by telling you how deeply grateful I am for this recognition by my colleagues in internal medicine. That I was similarly recognized by my coworkers in pediatrics brings me enormous pride. But I know that this would not have happened had I not been lucky enough to choose trainees who would make me look much better than I am. As examples I offer Sam Lux and Stuart Orkin (Figure 4), who picked up the leadership of my precious division of hematology and oncology and brought it to true greatness. To them, to my mentors, Castle and Janeway, to all of you, and particularly to my wonderfully supportive family, I offer my heartfelt thanks on this splendid day.

Figure 3
My patient (far right) at age 33.

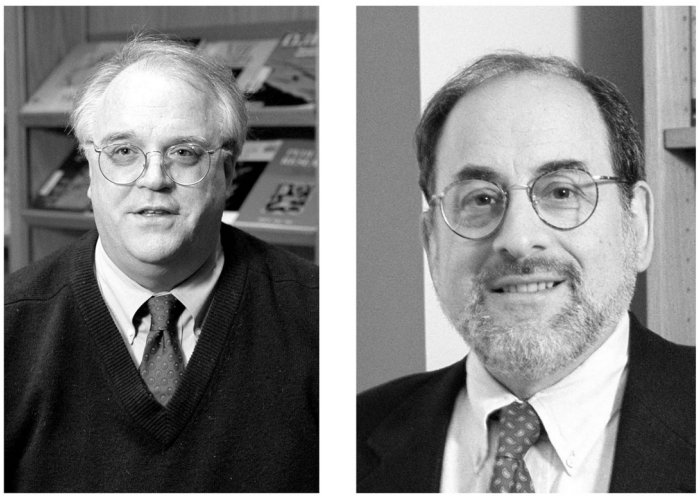

Figure 4
Samuel E. Lux and Stuart H. Orkin.

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