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# 2012 Association of American Physicians George M. Kober Medal
# Introduction of Arthur H. Rubenstein

Kenneth S. Polonsky

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**AAP Kober Medal**

It is an honor to introduce my mentor, friend, and colleague, Arthur Rubenstein, as the 2012 recipient of the Kober Medal, the most prestigious award of the Association of American Physicians. Over the course of his career, Arthur has distinguished himself as a scientist, a mentor, and a major leader in three institutions and has been a wonderful colleague and friend to so many of us. Arthur graduated from medical school at the University of Witwatersrand in Johannesburg, South Africa. He is one of the most distinguished graduates in the history of the school and after residency began his endocrinology training with Russell Fraser at the postgraduate medical school and Hammersmith Hospital in London. He came to the University of Chicago in 1967, soon after Donald Steiner made the landmark discovery that insulin was formed in the body from a large single-chain precursor called proinsulin. Arthur's first job in Chicago was actually as a cardiology fellow, and we endocrinologists have often pondered how much diabetes research would have been lost if Steiner had not rescued him from the cardiac catheterization laboratory. Fortunately, Arthur found the lure of diabetes research irresistible. He worked as a cardiology fellow during the day and retreated to the endocrine laboratories at night and on weekends, but he soon joined the endocrinology program full-time to do […]



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Fortunately, Arthur found the lure of diabetes research irresistible. He worked as a cardiology fellow during the day and retreated to the endocrine laboratories at night and on weekends, but he soon joined the endocrinology program full-time to do diabetes research.

The core faculty members in the diabetes program at the University of Chicago at the time are shown in Figure 1. Arthur is on the left, next to Don Steiner. The late Howard Tager, a world-class biochemist who made very major contributions to our research, is in the middle, with myself and Graeme Bell on the right.

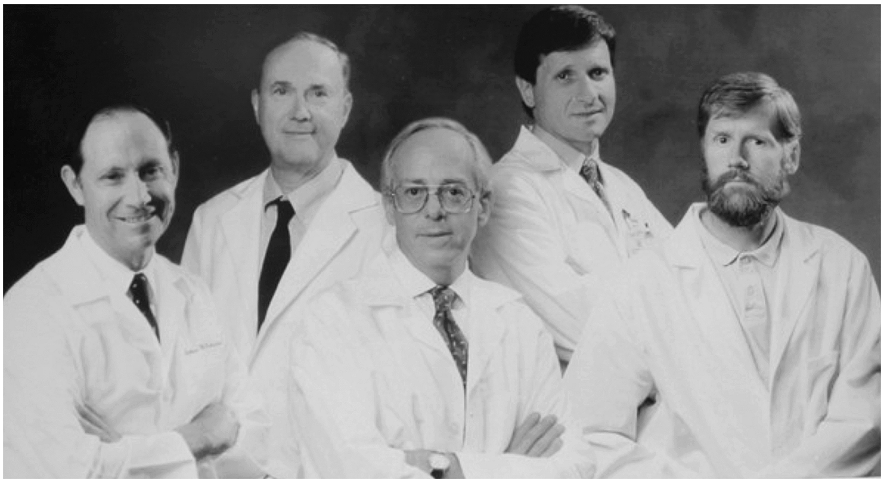

**Figure 1**
Scientific colleagues in diabetes research at the University of Chicago. Left to right: Arthur Rubenstein, Donald Steiner, Howard Tager (deceased), Kenneth Polonsky, and Graeme Bell.

Don and Arthur started our program and together performed a series of beautiful studies on proinsulin, C-peptide, and insulin secretion. Under their guidance, a truly interdisciplinary research program that went from bench to bedside and bedside to bench developed and flourished for over 30 years, beginning in the mid-1960s. The term "translational research" was not in common use at that time, but in retrospect this is what we were doing, and the work reflected the synergy between cell biology, biochemistry, genetics, physiology, and clinical investigation.

Figure 2 depicts the pathways of insulin biosynthesis and processing. Don Steiner showed that the product of insulin gene transcription is a large molecular precursor called preproinsulin, which is rapidly converted to proinsulin, and then after further processing, proinsulin is converted to insulin and C-peptide, which are then co-secreted in equimolar concentration. The research resulted in major advances in our understanding of this pathway.

The clinical implications of this work and Arthur's contributions are summarized in Table 1. His studies focused on using C-peptides to measure insulin secretion and in the differential diagnosis of hypoglycemia. He documented the importance of proinsulin as a marker of the pre-diabetic state and in the diagnosis of insulinoma and then identified and characterized patients with mutations in both insulin and proinsulin. Figure 3 summarizes why C-peptide is so useful and important in the measurement of insulin secretion. Proinsulin is converted into one molecule of insulin comprising

**Table 1**
Arthur H. Rubenstein: highlights of scientific contributions

| |
|---|
| **C-peptide** |
| Marker of insulin secretion |
| Natural history of diabetes |
| Differential diagnosis of hypoglycemic states |
| **Proinsulin** |
| Elevated in prediabetes and insulinoma |
| **Genetic mutations in insulin/proinsulin** |
| Familial hyperproinsulinemia |
| Mutant insulin syndrome |

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**Address correspondence to:** Kenneth S. Polonsky, University of Chicago, 5841 Maryland Avenue, MC 1000, Chicago, Illinois 60637-1447, USA. Phone: 773.702.3004; Fax: 773.702.1897; E-mail: polonsky@bsd.uchicago.edu.

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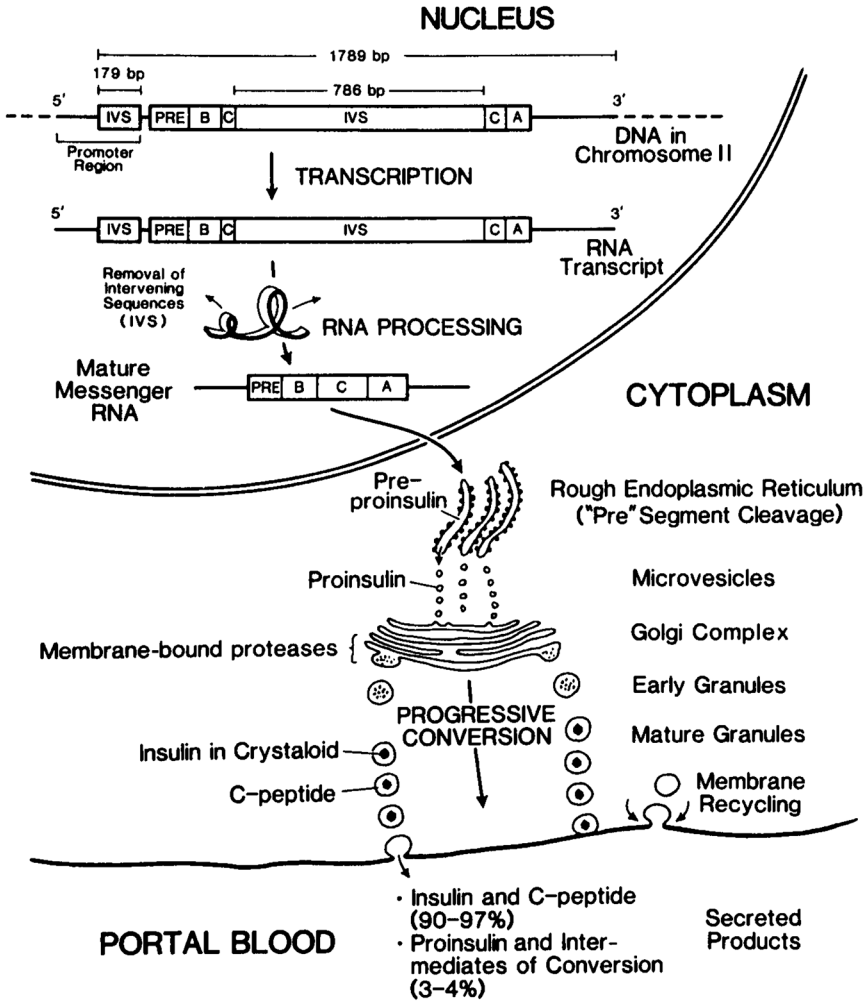


**Figure 2**
The biosynthesis of insulin in the pancreatic β cell. IVS, intervening segment or intron: PRE, prepeptide segment or "signal" peptide; B,C, and A, peptide segments of proinsulin (1). Reproduced with permission from the *New England Journal of Medicine* (1); adapted from an article by Steiner and Rubenstein (2).

A and the B chains and one molecule of C-peptide. About 40% of insulin is extracted by the liver on the first pass, and the amount extracted varies under different physiological and pathological conditions. As a result, peripheral insulin measurements more accurately reflect its posthepatic insulin delivery than its secretion. Since C-peptide and insulin are co-secreted in equimolar concentration, measuring C-peptide secretion provides an accurate understanding of insulin secretion, a major advance in research methodology and an approach initially proposed by Arthur and Don. The precise role of insulin secretion is a critical issue in diabetes research. Thousands of studies have based estimates of insulin secretion on peripheral C-peptide concentrations, and this has advanced our understanding of the role of insulin secretion in states of disordered carbohydrate metabolism.

An early study done by Marshall Block, one of Arthur's fellows, tracks the C-peptide concentrations over a three-year period in a patient with diabetes (Figure 4). Initially when the patient is able to secrete C-peptide, diet is sufficient to control the diabetes. As C-peptide concentrations fall, indicative of reduced endogenous insulin secretion and β cell function, exogenous insulin injections become necessary to control the glucose levels. This study, published in 1973, was one of the early studies to clearly document the role of insulin secretion in the natural history of diabetes.

When I first arrived in the laboratory in 1978 as an endocrine fellow, Arthur suggested that we develop a quantitative model to derive rates of C-peptide production from peripheral C-peptide concentrations, which could be readily measured. Initial validation work began in dogs, and when biosynthetic human C-peptide became available for use in humans, we were able to show that the exogenous infusion rate of C-peptide could be accurately estimated from peripheral concentrations by mathematical deconvolution using a two-compartment model and C-peptide metabolic clearance parameters. Figure 5 depicts experiments in which we infused exogenous C-peptide while simultaneously measuring peripheral C-peptide concentrations. We then determined how accurately we could estimate the infusion rate of C-peptide using the mathematical model that we had previously developed in dogs. The close concordance between the actual infusion rate and the model-derived infusion rate indicated it would be possible to measure C-peptide and therefore insulin secretion from peripheral C-peptide concentrations in humans.

This approach was used to define the characteristic patterns of insulin secretion in type 2 diabetes (Figure 6). Insulin secretory responses to meals are delayed and blunted in the diabetic subjects. These results formed the basis of additional studies on the impact of therapeutic interventions on insulin secretion in type 2 diabetes.

An important clinical application of the measurement of proinsulin concentrations is in the diagnosis of insulinoma. In this condition proinsulin concentrations are selectively increased compared with insulin, and this constitutes an important diagnostic criterion, as is demonstrated in the profiles from five patients with insulinoma (Figure 7). Increased proinsulin is now broadly accepted as a diagnostic test for insulinoma, and this flows directly from the work that Arthur and Don did on proinsulin.

The development of sophisticated techniques to characterize the circulating forms of insulin immunoreactivity and study its physiology led to the identification of interesting and unusual genetic forms of diabetes due to mutations in either insulin or proinsulin. The interdisciplinary nature of the program that Arthur and Don had developed allowed

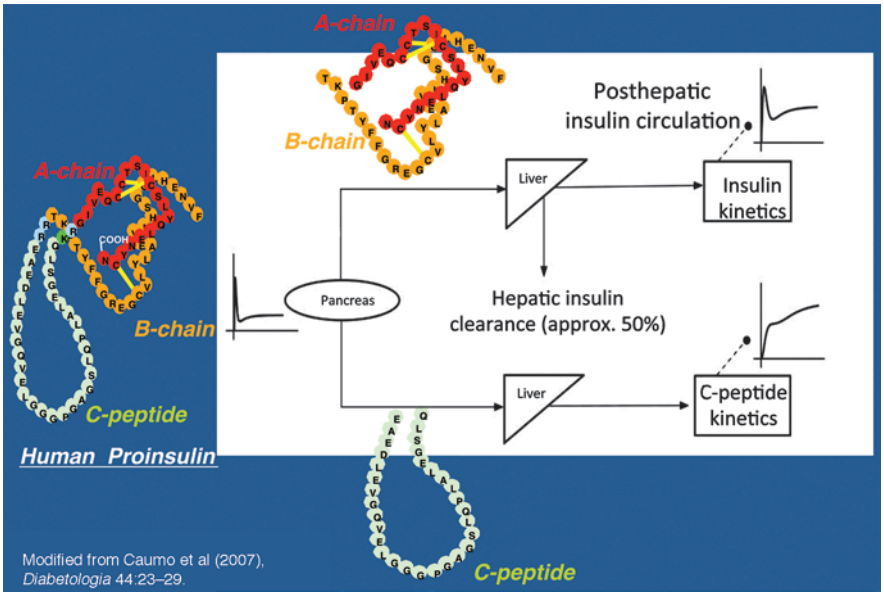


**Figure 3**
Summary of proinsulin, insulin, and C-peptide processing and secretion. Human proinsulin is converted into one molecule of insulin and one molecule of C-peptide in the insulin secretory granule of the pancreatic β cell. Approximately 50% of the secreted insulin is extracted by the liver on the first pass, and the fraction undergoing hepatic extraction varies under different physiological and pathophysiological conditions. Thus, peripheral insulin concentrations reflect posthepatic insulin delivery rather than insulin secretion. C-peptide is not metabolized by the liver, and its peripheral concentration more accurately reflects it secretion rate and therefore that of insulin, since they are co-secreted.

these patients to be studied clinically and biochemically and the underlying genetic abnormalities to be defined.

A family that secretes serine B24 insulin provides one example of this research (Figure 8). The mutant form of insulin can be differentiated from normal human insulin following HPLC separation of insulin immunoreactivity. These are heterozygous mutations, and so each affected family member secretes normal and mutant insulin, which are both present in the circulation. Interestingly, in this family the father was an insulin-requiring diabetic, and the bovine and porcine insulin present in the exogenous insulin injections were detectable in his serum.

What was it like to work in Arthur's laboratory? The environment was very exciting. Interesting postdoctoral fellows from many parts of the world regularly joined the lab, and there were constantly new and interesting projects. Arthur taught us to love science and the joy of pursuing new knowledge. We learned how to think critically and how to write and present the results of our experiments. I still remember giving what I thought was a near-perfect draft of my first paper to Arthur for his comments. In those days, comments were handwritten by Arthur using a red pen. After Arthur was done with my draft, there was almost only red ink on the paper. Of course the suggestions were all excellent, and after going through this drill on a couple of occasions, my writing skills improved dramatically. We were taught to work hard, to take nothing for granted, and to never to give up until we had succeeded.

Arthur was immersed in the science to the point that the details of day-to-day life sometimes passed him by. One example of this relates to our weekly endocrine clinical conference called Endorama, which in those days took place on a Saturday morning, something almost unimaginable in today's environment. Since Arthur and his wife Denise lived very near the hospital, he usually walked to attend this conference. One Saturday morning, he decided to take the car. When the conference was over, he followed his usual habit and walked home. That evening, when it came time for Arthur and Denise to leave for the opera, the car was nowhere to be found. Arthur just assumed that it had been stolen. He called the Chicago police to report the theft, and he and Denise took a cab. About an hour later, the police found the Rubensteins' vehicle parked outside the hospital, in the exact spot where Arthur had left it that morning. The next week Arthur emerged from rounds, determined not to repeat his mistake of the previous week, and spent an hour looking for the car. Of course he never found it, because he had resumed his usual habit and walked to work.

We also learned that you don't take it personally if Arthur dozes off while you are talking to him. This has happened to all of us, and although you may find it a little disconcerting at first, you get used to it. One has to realize that even if Arthur appears to be asleep, you cannot assume that he isn't listening to every word you

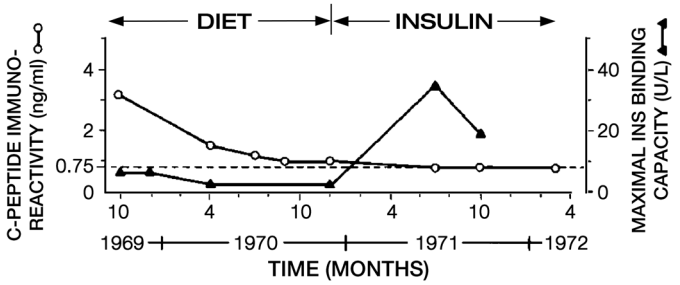


**Figure 4**
Measurement of C-peptide to define the natural history of changes in insulin secretion in a patient with diabetes. In 1969, significant C-peptide immunoreactivity is detectable in this patient's plasma, indicating that endogenous insulin secretion is present. As a result, diet therapy is effective. Over time, C-peptide concentrations fall and become undetectable, and this loss of endogenous insulin secretion corresponds with the need to use exogenous insulin injections to control blood glucose. Reproduced with permission from the *New England Journal of Medicine* (3).

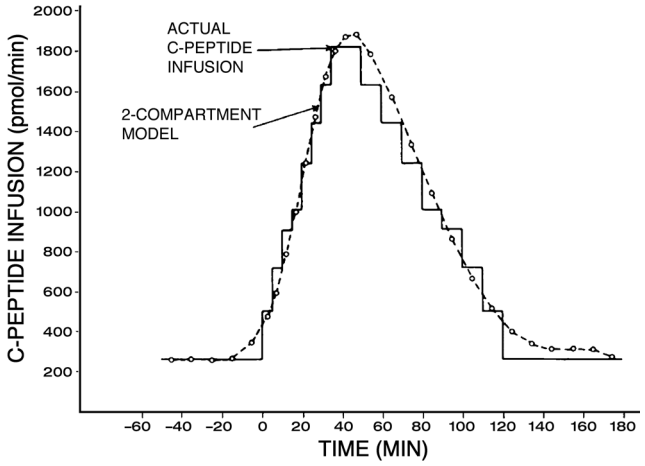


**Figure 5**
Estimation of C-peptide infusion rates from C-peptide concentrations. In these experiments, exogenous biosynthetic human C-peptide was infused at varying rates (solid line). C-peptide concentrations were simultaneously measured in peripheral plasma. The infusion rates of C-peptide were then estimated by deconvolution of the C-peptide concentrations using a two-compartment model of C-peptide kinetics (dashed line). The close approximation of actual and model-derived estimates of C-peptide infusion rates indicates that this approach can be used to derive secretion rates of C-peptide and therefore insulin. Reproduced from ref. 4.

have to say. One of the many legends surrounding him at the University of Chicago was his reputation for appearing to sleep through grand rounds, only to ask the most penetrating questions when the presentation was over.

Arthur had such obvious leadership skills that it was clear that he was going to be asked to take on important leadership roles. Within a few years of my joining the lab, he became the Chairman of the Department of Medicine at the University of Chicago. And as we all know, in time he became the Dean of Mount Sinai School of Medicine and the Dean and Executive Vice President of the Health System at the University of Pennsylvania. He also played leadership roles in a number of important organizations (listed in Table 2), most notably President of the Association of American Physicians.

Arthur received many recognitions and awards for his accomplishments. He received the two most prestigious scientific awards from the American Diabetes Association, the Outstanding Scientific Achievement Award (or the Lilly Award) for young investigators, and the Banting Medal for career contributions to diabetes research. The Association of American Medical Colleges recently recognized him with the Abraham Flexner Award for distinguished service to medical education, and he received the Robert H. Williams Distinguished Chair of Medicine Award from the Association of Professors of Medicine. He was elected to membership in the American Society for Clinical Investigation, the AAP, the Institute of Medicine, and the American Academy of Arts and Sciences.

Arthur is a wonderful leader. Wherever he has worked, he earned the trust and support of the faculty and staff and other institutional leaders. Even when he turned down requests for support, you did not feel embarrassed or humiliated. As head of Endocrinology at the University of Chicago, I was often in a position of asking Arthur for support, and he usually came through. On some occasions, I would come to his office with a list of requests, determined to negotiate with him very hard. He would disarm me by welcoming me into the office, telling me how pleased he was to see me, asking numerous questions about the family, the children, and how I was doing personally. By the end of the meeting, I'd completely forgotten why I was there and left the office in a really good mood, until I realized I'd come away completely empty-handed.

Arthur has made transformational improvements to the organizations that he has led. He recruited outstanding faculty and grew important programs. Education has always been a major focus, and he has paid particular attention to the students and house staff. Most notably, after long tenures at the University of Chicago and at Penn, people were very sorry to see him go. This is most exceptional in the current environment.

Over the last 10 years, Arthur has been the Dean and Executive Vice President of the Health System at the University of Pennsylvania. Arthur has loved his time at Penn Medicine and is justifiably proud of the spectacular progress made by the school during his tenure. He used an approach that he has termed "distributed leadership," or "distributed management," in which the department chairs and faculty share the responsibility of running the institution with the dean and the senior leadership in the hospital and health system. This has resulted in a dramatic improvement in the financial position of Penn Medicine that will only be strengthened by the recent gift from the Perelman family to endow the School of Medicine. Two new state-of-the-art facilities, the Ruth and Raymond Perel-

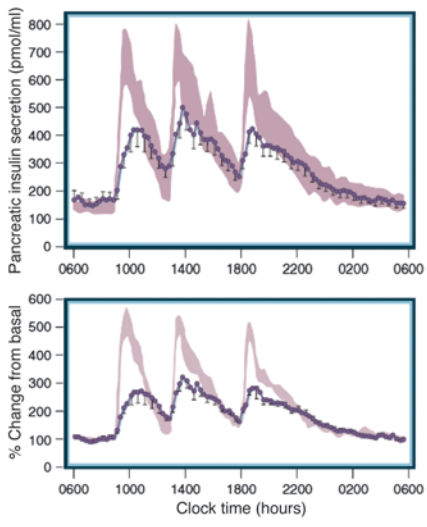


**Figure 6**
Insulin secretion in type 2 diabetes. Top panel: Insulin secretion rates were measured in subjects with type 2 diabetes (solid lines) and matched non-diabetic controls (shaded lines) over a 24-hour period that included 3 meals (breakfast, lunch, and dinner). Bottom panel: The insulin secretion rates are expressed as a percent changes from basal. In subjects with type 2 diabetes, the insulin secretory responses to meals are delayed and blunted. Reproduced with permission from the *New England Journal of Medicine* (5).

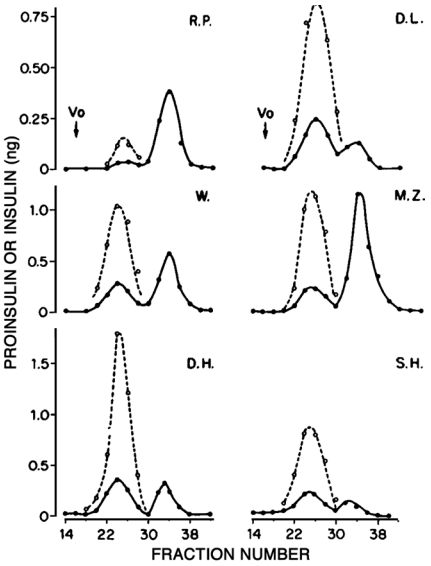


**Figure 7**
Elevated proinsulin in the diagnosis of insulinoma. Gel filtration chromatography of serum from a normal volunteer (top left) and 5 patients with insulinoma (other panels). After gel filtration, insulin immunoreactivity is found in positions corresponding to proteins of 9,000 and 6,000 daltons; immunoreactivity in the 9,000-dalton position is expressed on the basis of both insulin (solid line) and proinsulin (dashed line) standards. The larger protein, appearing nearest the void volume (Vo), contains proinsulin and intermediates of proinsulin conversion. Insulin is indicated by the second peak of immunoreactivity. Proinsulin-like material contributes less than 20%–30% of total immunoreactivity in normal subjects, whereas it is relatively increased in the majority of patients with insulinoma, regardless of total serum insulin concentration (1).

man Center for Advanced Medicine and the Translational Research Center, have been built. Particular efforts have been made to improve faculty morale and engagement, with fairly innovative solutions such as the Association of Senior and Emeritus Faculty, focused on retaining the engagement of this group in the institution. World-leading research centers have been established, including the Institute for Translational Medicine and Therapeutics, the Institute for Diabetes, Obesity and Metabolism, the Cardiovascular Center, and the Institute for Regenerative Medicine. It is really wonderful that Arthur's career accomplishments have continued on such an upward trajectory.

My friend and colleague, Holly Humphrey, the Dean for Medical Education at the University of Chicago, has summarized the lessons that she learned from Arthur in a paper she wrote for the American College of Physicians: Care for the residents, confront the uncomfortable, correct misbehavior promptly and decisively, don't take credit for other people's work, motivate followers and create a team, and show respect and kindness for all. Choose your words carefully, manage the coming and going of faculty, and remember the primacy of family. Arthur has been blessed with a wonderful, supportive family. His wife Denise, his sons Errol and Jeffrey, Jeffrey's wife Michaela, and their four children have served as Arthur's inspiration. I truly

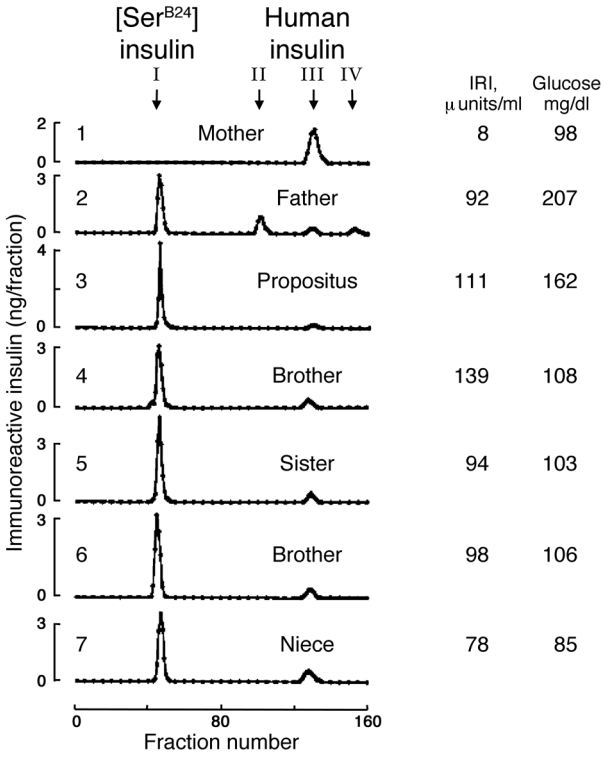


**Figure 8**
HPLC analysis of serum insulin from a subject with mutant insulin and six members of her family. Serum insulin was purified by immunoaffinity chromatography and was then subjected to HPLC, and immunoreactive insulin was measured in all the fractions eluting from the HPLC column. The amount of immunoreactive insulin is plotted against HPLC fraction number in each of the profiles. Arabic numerals identify the individual with respect to subsequent experiments; subject 3 is the propositus. Roman numerals I–IV identify the elution positions of human [Ser$^{B24}$]-insulin, bovine insulin, normal human insulin, and porcine insulin, respectively. Columns to the right of the figure list the fasting serum levels of immunoreactive insulin and glucose determined for each of the seven subjects.

**Table 2**
Arthur H. Rubenstein: leadership roles

| |
|---|
| Chairman of Medicine, University of Chicago, 1981–1997 |
| Dean, Mount Sinai School of Medicine, 1997–2001 |
| Dean/Executive Vice President of the Health System, University of Pennsylvania, 2001–2011 |
| President, Association of American Physicians |
| Chairman, American Board of Internal Medicine |
| President, Association of Professors of Medicine |
| Chair, Association of Academic Health Centers |
| President, Central Society for Clinical Research |

believe that much of his success is rooted in his close-knit family bonds. In closing, I would like to thank the AAP for providing me the opportunity to tell you about my mentor, friend, and colleague, Arthur Rubenstein. I can think of no one more deserving of this prestigious award and congratulate the AAP on their wise selection. Thank you.


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### Acceptance of the 2012 Association of American Physicians George M. Kober Medal

# A fortunate life in academic medicine

**Arthur H. Rubenstein**

Good morning everybody. And thank you, David, for this great honor, and to the councilors and leadership of the Association of American Physicians, and, of course, to all of you for coming here today. I do wish to express my deepest appreciation to the AAP for honoring me with the Kober Medal, which has been awarded to me today. This is a great honor that I feel very humble to receive. I particularly wish to thank my close friend and colleague, Dr. Kenneth Polonsky, for his beautiful presentation today and for his continuous support for more than 30 years. He and his wife, Lydia, and his family have been like an extended family to Denise and me, and to our children as well, since he became my fellow in the late 1970s. Now that Dr. Larry Jameson has succeeded me, I actually had the luxury of time to think, and I've considered the factors that have influenced my career and brought me to this very special day. I think there are three main factors (Table 1). The first is family, as Kenneth has so rightly pointed out. The second is mentors and a network of colleagues. And thirdly, is being in the right place, at the right time, and with the right people. Of course, all of that had nothing to do with me, so you have to have good luck and fortune in your life, and I've been abundantly showered with that.

Let me begin with my family (Figure 1). My father was a refugee from Poland after the First World War and became a pharmacist, as he did not have the money or resources to become a physician, which was his first love. When I decided to become an accountant after graduating from high school, he took me aside and said quietly, "I think it would be better, Arthur, if you became a physician." And because of my enormous respect for him, I said, "That's a good idea, Dad," and then I enrolled in medical school. My mother was a remarkable role model; a generous, kind, warm-hearted woman who always did the right thing. Both my father and mother's influence on my sister, brother, and myself, and many other family members, was indelible. Denise, my wife of nearly 50 years (Figure 2), was actually my resident at the University of Witwatersrand Hospital. I was her intern and, after trying and failing to best her in terms of clinical acumen and basic knowledge on ward rounds, I decided that I better just ask her to marry me.

**Table 1**
Key elements in shaping the author's career

| |
|---|
| Family |
| Mentors and network of colleagues |
| Good fortune: |
| Right place |
| Right time |
| Right people |

**Figure 1**
The author's mother and father.

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**Address correspondence to:** Arthur H. Rubenstein, University of Pennsylvania Perelman School of Medicine, TRC 12th Floor, Room 12-122, 3400 Civic Center Boulevard, Building 421, Philadelphia, Pennsylvania 19104-5160, USA. Phone: 215.746.8587; Fax: 215.573.9138. E-mail: ahrdean@mail.med.upenn.edu.

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