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Acceptance of the 2003 John Howland Award: A Journey in Clinical Research

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Thank you, Fred, for that fulsome description of my efforts to meet the standards of Charles A Janeway, a Howland awardee, whom we both served with such admiration and respect. Of course, no one knows more than you about the leadership of Children's Hospital in Boston. You have been the right arm of no less than five chiefs of our Department. You have been best described by Gary Fleisher, our present chief, of what you, Bill Berenberg, Fred Rosen, and I have always called Dr. Janeway's department. Gary's first act as chair was to reappoint you as vice-chair of the department. Shortly thereafter, Gary called me to tell me that he had made a discovery. "For all these years," he said, " I thought you were an incredible chair. Now I realize it's all Fred Lovejoy."

Fred, you are the very soul of our department and a model of decency and loyalty to excellence for every student, house officer, and faculty member who knows you. Of course, I am deeply honored to receive the John Howland Award. It is the highest honor in academic pediatrics, but to receive it because you have nominated me is even more gratifying, and how this moment would please Charles A Janeway. We are both convinced that somehow, someway, he knows about our relationship and this heart-warming event.

It is customary for Howland awardees to reminisce about their careers with the hope, however vain, that somewhere in this vast room there is someone other than my dear and devoted wife, Jean, who will remain awake long enough to learn anything from such maundering. That touching faith and the convenient contraction of the memory of the elderly forces me into the accepted format.

My father wanted to be a physician. In fact, he was admitted to the Harvard Medical School in 1920, but my grandfather would have none of it. "No son of mine," he intoned, "is going to be a useless doctor. They come to your house to drink your coffee and they don't do a damned thing for you. My son will be an honest business man." Being a dutiful son, my father entered the business world, but he didn't give up his dream. It was transferred to me. Paul Starr writes of my grandfather's viewpoint in his insightful book, *The Social Transformation of American Medicine* (1). My grandfather's opinion of physicians was very representative of his times. In the preantibiotic era, doctors sat at the bedside watching the patient, drinking their coffee, and doing very little. All that changed with the discovery of sulfanilamide and penicillin. By the end of World War II, the biomedical revolution had begun and my grandfather's view of medicine was on its way to obsolescence. Academic medicine was to become a bastion of biomedical science. This change is important to us today at this celebration because John Howland was part of the Osler tradition. William Osler had no interest in laboratory-based or high-tech medical research. He believed that physicians should make an academic contribution by careful annotation of even more careful patient observations. Osler's view notwithstanding, Vannevar Bush's 1945 white paper entitled "Science the Endless Frontier" (2) formalized the changed future of academic medicine. Bush, commissioned by Harry Truman, recommended a sustained investment by the federal government in basic research in universities. He thought that applied research (and clinical research is certainly a form of applied research) should be performed in government laboratories like Los Alamos or Brookhaven and in pharmaceutical companies, and so the sleepy campus of the National Institutes of Health on the Wilson estate in Bethesda began to stir; but Congress did not entirely accept Bush's advice. The members agreed to fund basic science in universities, but they had constituents who wanted their chronic diseases cured. The advocacy groups that we know so well today represented the patient/constituents. They demanded disease-oriented clinical research. Now there are 20 different National Institutes of Health—Institutes that offer hope to patients with particular disorders. The National Institute of Child Health was created in 1962 in response to such advocacy. A huge and ever-increasing flow of extramural grants to universities to support both basic and clinical research began (Fig. 1). In 1960, the entire extramural budget of National Institutes of Health directed to US medical schools was about $250 million. Today, the total budget it is rapidly approaching $20 billion—an 80-fold increase in the absolute dollar investment and a 10-fold increase in constant dollars. The enormous growth of the fraction apportioned to US medical schools is shown here. The third bar of each cluster of three shows the logarithmic increase in the expense budgets of our medical schools. The middle bars in the clusters of three represent the growth of research grant income to the schools, and the left-hand bars represent the contributions from National Institutes of Health. A third of those National Institutes of Health–derived dollars supports clinical research (3). Note the massive growth of the medical school expense budgets, but also observe that in 1960, fully half of the relatively tiny expense budget of all of our US medical schools was met by National Institutes of Health grants. That ratio has progres-

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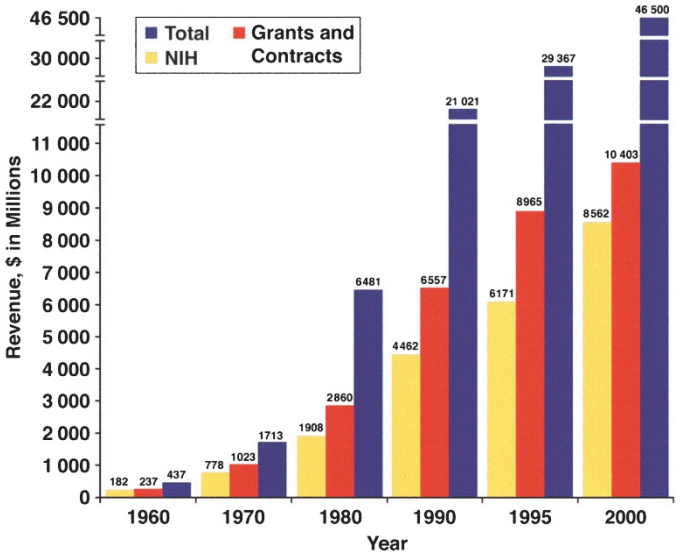

Figure 1. The growth of revenues of US medical schools from 1960 to 2000. The data do not include the revenues of independent teaching hospitals. Note that total grants and contract revenue has progressively fallen as a percentage of the vastly increased total revenue.

sively fallen. The uncertain income derived from health insurance has uneasily made up the difference.

Medical research investigators of my era were the direct beneficiaries of this incredible if unstable rate of growth. I was a particularly fortunate legatee. During my era, Children's built one new research building, and then, with the help of the Howard Hughes Research Institute, nearly doubled its size. Dana Farber Cancer Institute, our close ally, built three new buildings, and today Children's is building another. Indeed, the national bird of academic medicine is the crane. Everywhere around us, labs and new hospitals are going up. We are borrowing billions to pay for all this. My grandfather, who distrusted us so much, would be horrified because we are counting on philanthropy and a stock market recovery to help us pay the debt. Will donors and Wall Street be there for us in the future?

I graduated from Harvard Medical School in 1955, when the growth explosion was just beginning. The Korean War was winding down, but the doctor draft was very much alive. I had 1 year of internship in internal medicine in a particularly Dickensian Harvard teaching hospital, the Peter Bent Brigham (Fig. 2), a structure rivaled only by its neighboring Children's Hospital (Fig. 3) for outmoded research and clinical facilities. At the Brigham, I was influenced by Samuel A Levine, the great clinical cardiologist of his era, who taught me to worry about my patients all of the time. "If you worry," he urged, "a good idea will come to you." I have been worrying about them ever since.

Following internship, I chose so-called military service at National Institutes of Health in Bethesda, where I started my real clinical research training in the brand new 510-bed General Clinical Research Center then called Building 10 (Fig. 4). I couldn't believe my eyes. In this magnificent building were modern research beds and gleaming labs filled with every possible piece of clinical and scientific equipment and staffed by physicians and basic scientists who knew how to use them. I received ultramodern training and was actually ordered into hematology by my section chief, who told me that I would be a hematologist because he had four stripes on his sleeve and I had two. I remained a National Institutes of Health hematologist for 2 years and there began my career-long interest in disorders of the blood.

Equipped with primitive notions about how to obtain informed consent of patients for clinical research—none of which would be acceptable today—I returned to Boston, completed a year of senior residency in medicine, and plunged immediately into my field.

As I began to work in hematology at the Brigham, where I remained mercifully unfettered for nearly 7 years, the proxim-

Figure 2. The Peter Bent Brigham Hospital in the early 1950s. Used by permission from Brigham and Women's Hospital, Boston, MA.

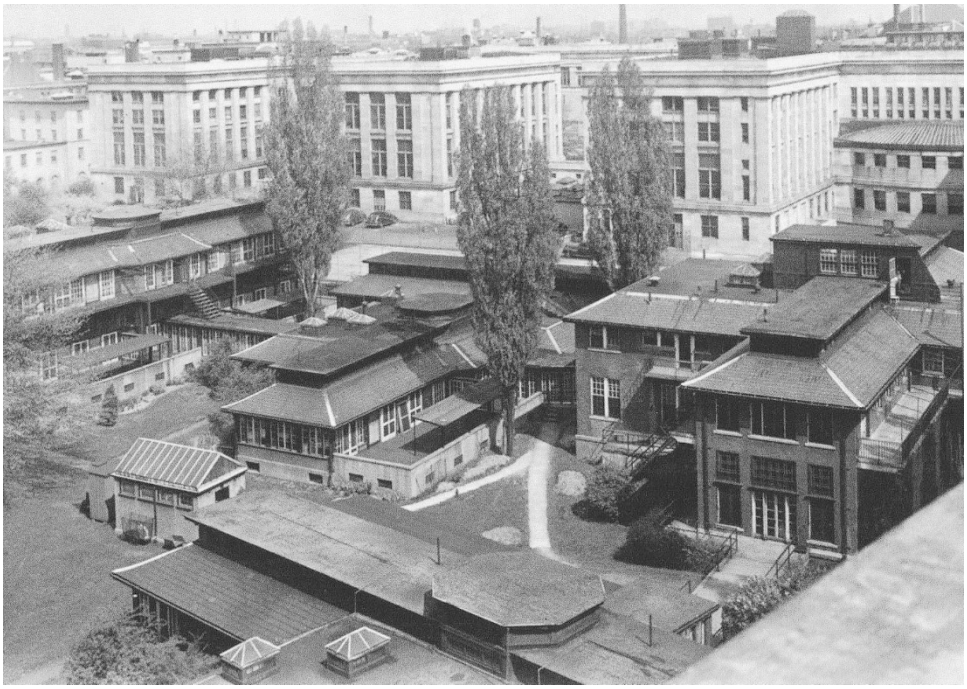

Figure 3. The Children's Hospital wards in the early 1950s. Used by permission from Children's Hospital Archives, Boston, MA.

Figure 4. Building Ten (The Clinical Center) of the National Institutes of Health in the 1950s.

ity of Children's Hospital began to reshape my life. The grandmaster of pediatric hematology and Howland awardee, Louis K. Diamond, was beginning to doubt the safety of splenectomy for hemolytic anemia in children (4). He was gathering evidence that splenectomized children might be very susceptible to death from overwhelming sepsis. As usual, he proved to be correct. Dr. Diamond decided to send me patients who might be eligible for splenectomy so that I could perform a red cell survival and splenic scan to be sure that the operation would be useful. Nuclear medicine departments were unknown at the time. Howard Pearson, the Howland Awardee of 2002, had left Children's for greener pastures (and there were few pastures that were not greener than Children's, at least with respect to salary), so Dr. Diamond's agent for many of these consultations became Frank Oski. Frank introduced me to one puzzling and fascinating case after another (5–10), cases that led me to a better understanding of the role of cation balance in the lifespan of the human red cell (11–14). We struck up an enduring friendship and collaboration that culminated in our textbook entitled *The Hematology of Infancy and Childhood* (15), now going into its sixth edition. I miss Frank so very much. He would have been a Howland Awardee, I am sure. To

him I owe my commitment to pediatric hematology and to general pediatrics.

Dr. Diamond was also interested in thalassemia because he was fundamentally interested in genetics. His very bright fellow, Park Gerald, began to send me adult patients with thalassemia intermedia, and they began to capture my full attention. In fact, Robert Gunn, a Harvard medical student and now the chair of physiology at Emory, and I made what I thought was a unique discovery on one of Dr. Diamond's patients. We showed that the red cells of splenectomized patients with β thalassemia had precipitates of what we were sure were α globin chains in their red cells (16). The huge deposits that damage the cells and cause their instant destruction are shown in Fig. 5. Suddenly we had an insight. Thalassemia is not simply a failure to make Hb; it is a disease characterized by unbalanced protein synthesis. The production of unstable, unmatched α globin, not just the failure of β globin synthesis, actually puts the quietus to the thalassemic red cell. Before that observation, Tom Gabuzda and I had observed the puzzling phenomenon that the life span of Hb F in the circulation of an untransfused patient with thalassemia intermedia is much longer than the life span of Hb A, or A_2, as shown by the blue lines overlying the inclusion-bearing red cells (17–19). The inclusions solved the puzzle. Hb F is variably distributed in the red cells of patients with thalassemia. Cells rich in Hb F survive longer because γ globin chains combine with free α chains to form $\alpha 2/\gamma 2$ or Hb F (20). From these studies and others, thalassemia investigators came to understand that a pathway to improved therapy could be found by investigating ways to prevent the fetal switch from γ to β chains. Induction of increased γ-chain production would prevent toxic α-chain precipitation. One product of that research is hydroxyurea for sickle cell anemia (21,22).

We now appreciate that protein precipitation causes many serious diseases from sickle cell disease to multiple myeloma to Alzheimer's disease and mad cow disease. Thalassemia began that appreciation.

In 1966, while much of this work was in progress, Dr. Diamond and his wife, Flo, decided to move to California to join their children. Charles A Janeway, urged on by Fred Rosen, himself a master clinical investigator, invited me to join the hematology division with the idea that I would become the division chief when Dr. Diamond left. In my first meeting with Dr. Janeway, he tried to assure me that I could make the transition to pediatrics from internal medicine because he had done so. I was not impressed—Dr. Janeway was amazingly intelligent. It was not clear to me that I would have the ability to learn a new clinical discipline as complex and exacting. After all, I am a clinical investigator. Patients inspire my research, and one cannot usefully study patients without excellent clinical skills. Furthermore, nearly all of my colleagues except Fred Rosen said it would be a career-threatening move. I would, they said, never learn enough pediatrics to be effective. So like everyone at Harvard who needed sound advice, I went to talk it over with Dr. William B. Castle. Castle listened to my angst. Finally he asked one penetrating question.

"Tell me," he asked in that marvelous nasal New England voice, "Does the idea of going to Children's Hospital make you happy?"

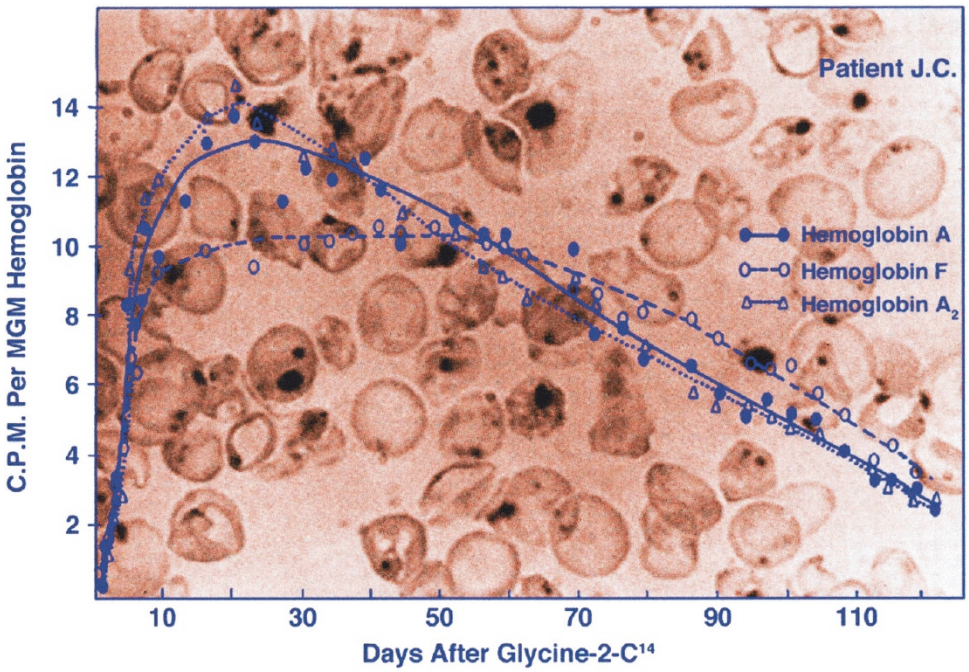

Figure 5. The red cells of a splenectomized patient with thalassemia intermedia stained with crystal violet. Note multiple inclusions of precipitated α chains. The morphology is overlain by the specific activity of the patient's hemoglobins after injection of glycine-2-C14.

"Oh yes," I responded, "that's the problem. It makes me very happy, but my friends all tell me its crazy."

"Well," he drawled, "most of the people who come to see me are unhappy. If I were you, I'd go to Children's."

Twenty-two years later, I interviewed Dr. Castle about his life in medicine. He told me that when he went to see Dr. Walter B. Cannon to tell Cannon that he, Castle, wanted to transfer from physiology to the then-new Thorndike Laboratory at the Boston City Hospital, Cannon's response was, "Ah, another brand for the burning." I think I fared much better than Castle in my quest for advice.

So my real life began. Three new fellows were there to greet me—Bill Mentzer (23), Eli Schwartz (24,25), and Bob Baehner (26–30)—among the last fellows recruited by Dr. Diamond. All three went on to distinguished careers of their own. Eli and Bob became department chairs, and there were so many more who followed them, their careers made possible by the growth of resources at Children's Hospital and, later, the joining of forces with the Dana Farber Cancer Institute, a great research and treatment facility with a focused commitment to pediatric hematology and oncology.

These excellent institutions helped us to recruit and train many remarkable young people between 1966 and 1985, when I left the leadership of the Division to become Chair of the Department of Pediatrics at Children's. Limits of time permit me to mention just a few. I present them proudly because I believe they represent the real legacy of what we tried to do. Some of our papers proved important, but most are evanescent and are replaced by the work of others. The careers of our trainees and their trainees represent the firm future of pediatrics and pediatric hematology.

Many of the early members of the training program were internists, and many had training at The National Institutes of Health. I emphasize only a few of them here. Ed Benz succeeded me as president of Dana Farber. Steve Burakoff led the Department of Pediatric Oncology at the Dana Farber for many years and recently became the Director of the NYU Cancer Center. Ed Benz, Frank Bunn (31–33), Y.W. Kan (25,34–41), Art Nienhuis (42,43), and Tom Stossel (44) became presidents of the American Society of Hematology. Nienhuis is the director of St. Jude Hospital. I am very pleased that George Buchanan, one of our most outstanding pediatric trainees, became president of the American Society of Pediatric Hematology an Oncology.

Space permits me to emphasize the contributions of just a few of the pediatricians who came to the program. Herb Abelson, Harvey Cohen, Alan Ezekowitz (45), and Alan Schwartz joined Eli Schwartz and Bob Baehner to become pediatrics department chairs. Blanche Alter (46–50) and Y.W. Kan were prime movers in the prenatal diagnosis of hemoglobinopathies. Alter transferred the technology to Dimitris Loukopoulos, whose work greatly reduced the incidence of new cases of thalassemia in Greece (51). Alter went on to make important contributions to our understanding of the fetal switch (52–54). Nancy Andrews has unfolded many of the important pathways of iron metabolism, and Alan D'Andrea has revealed many of the secrets of Fanconis anemia. Larry Boxer and Mary Dinauer studied granulocyte dysfunction with distinction and went on to their fine careers in Michigan and Indiana, while Eva Guinan (55–58), Robbie Parkman (59–63), and Bruce Camitta (64–69) made important contributions to our understanding of the pathophysiology and treatment of marrow failure. Bert Lubin (70,71), Steve Feig (72–76), Bert Glader (12–14), Bill Mentzer (23,77), Orah Platt (78), and George Segal (73,75) did valuable work on disorders of red cells. Barbara Miller (79–83) dissected genetic programs that are responsible for increased fetal Hb in certain sickle cell syndromes. Orah Platt (22) was the first to use hydroxyurea to raise fetal Hb in patients with sickle cell disease and explored a fascinating case of exercise induced xerocytosis (78). Nancy Olivieri (84,85) became one of the world's leading clinical investigators in thalassemia. Steve Sallan (86–89), our first fellow from Puerto Rico, Luis Clavell (89), and several other trainees made enormous contributions to the treatment of childhood leukemia; Susan Shurin (90) and Richard Propper (90–92) developed effective deferoxamine therapy to prevent iron overload. Colin Sieff (93–99) and Jeffrey Lipton (100–103) began our effort to understand the complexities of hematopoiesis, and David Williams (104), the first to insert a gene into the hematopoietic stem cells of a mammal, became the leader of hematology and oncology in Cincinnati.

Fortune truly smiled when Sam Lux and Stuart Orkin (48,105–108) joined our division over 25 years ago. They have each made major contributions of their own and have received many prizes for their work. Both have won the Mead Johnson award, as have Larry Boxer, Alan Schwartz, David Williams, Alan D'Andrea, and Nancy Andrews (109). Sam and Stuart are committed to the traditions that Janeway and Diamond established for us. When I moved from the leadership of the division 18 years ago to become chair of pediatrics and subsequently president of Dana Farber, I left the leadership of Children's and DFCI hematology and oncology in their totally competent hands. Now they share responsibility for a research program of 55,000 square feet of space and an annual research budget of more than $26 million per year. To my great satisfaction, Sam is now the Robert A Stranahan Professor of Pediatrics, my former chair, and Stuart is the David G. Nathan Professor of Pediatrics and Chief of Pediatric Oncology at Dana Farber. I could not have left my precious field in better hands.

My own inspiration has continued to come from patients like the one shown in the faded photograph taken 34 years ago and shown in Fig. 6. Khaled has severe β thalassemia and was 6 years old when this photograph was taken. When he first saw me, he had a Hb of 1.5 and had broken nearly every bone in his body because the enormous rate of ineffective erythropoiesis expands the medullary cavity and so weakens the bones. During the past 34 years, our division has devoted a vast amount of attention to him and children like him, and other centers have made critically important contributions to our understanding of the disease. Chelation therapy with deferoxamine has kept him alive while we try to find better solutions through clinical research. Ten years ago, he celebrated his 30th birthday at his brother's wedding. To greet that milestone, I wrote a book about him and his disease called *Genes, Blood and Courage* (110). Last year we celebrated his 40th. Now we are working on a new oral iron chelator for Khaled and the

Figure 6. Khaled when he was 6 years old and arrived with a Hb of 1.5 g/100 mL. Used by permission.

others who have waited for so long. ICL670 (Fig. 7) is a Novartis product and is in its developmental phase (111), but it looks very promising. A single dose of 20 mg · kg^{-1} · d^{-1} removes body iron and remains detectable in the blood for 24 h, where it chelates free iron and probably protects the heart. If its toxicity is reasonable, it will prove to be a much better drug than deferoxamine. Although I worked hard on deferoxamine, I will be very glad to see it go. Meanwhile, others are working on stem cell transplantation and even gene therapy. Clinical research is an ever exciting challenge.

Dr. Diamond told me that the joy of pediatrics is the care of kids like Khaled—watching them grow and giving them the chance to make it on their own. Truer words were never said.

The Howland Award is a great honor for any pediatrician. To receive it is to wonder how it all happened. I know why this has happened to me. First of all, I have had wonderful fellows. They have been committed to children and our field and have done great work, and they have had the benefit of the astounding growth of financial commitment to the field by federal and private sources. Second, I have had the assistance of Sam and Stuart, two of the finest hematologists in the world. Third, I have recognized that clinical research demands multidisciplinary collaboration. I have had enormous help from colleagues in the basic sciences at Harvard and at MIT. I am particularly grateful to Drs. David Baltimore, David Housman (112), Harvey Lodish (38,113–115), and Philip Sharp of MIT, who recognized the important potential of molecular biology in pediatric research and devoted as much energy as possible to the training of my fellows and junior faculty so that we could, together, move the field. I have also enjoyed a multidecade collaboration with David Weatherall and his great colleagues at Oxford (80,106,107,116–118). They have been important contributors to my research efforts and to my recent focus on the management of clinical research.

Clinical research is said to be in a troubled period, and I have worked to help it so that others can enjoy the field as I have enjoyed it. No one can know enough to do important clinical research alone. One needs a committed academic health center; a devoted department of pediatrics; and the commitment of the National Institutes of Health, private foundations, and industry. And the field needs colleagues of all disciplines who share the vision. I have had all of that, and I have shared responsibility for the supervision of houseofficers and junior faculty with physician-teachers of the quality of Fred Lovejoy. Above all, I have had role models like Charles Janeway, Louis Diamond, and William Castle. They are gone now, but they live on in us. I have tried to grasp the torch from them and hand it on to others. I hope John Howland, who started this tradition, is pleased. We have all been traveling the path that he created. Today we remember him and honor his memory. That I have been selected to be part of that honor means more to me than I can fully express.

I deeply thank the American Pediatric Society for welcoming another apostate internist and then bestowing this, its highest award, on me. I salute you and all of my colleagues in pediatric research. Thank you.

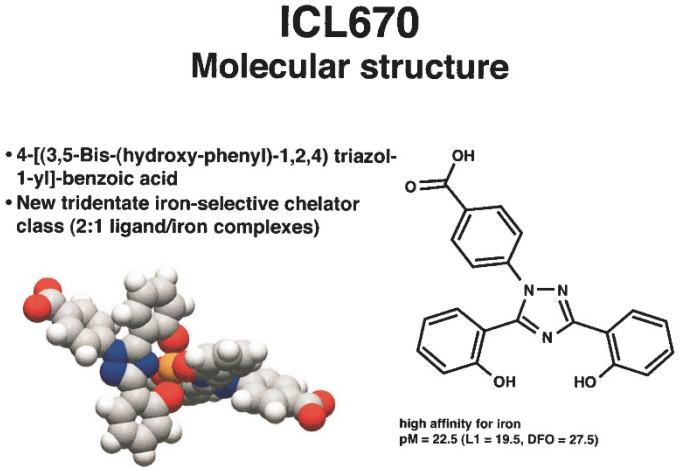

Figure 7. The molecular structure of ICL670 (courtesy of Dr. Daniele Alberti and Novartis SA). Used by permission.

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