Dedication

Remembering the Contributions of Professor David J. Weatherall

We dedicate this issue of the *Hematology/Oncology Clinics of North America* to the memory of Professor Sir David J. Weatherall (**Fig. 1**). The field of thalassemia research has, for the past 75 years, been marked by seminal discoveries that laid the foundation for molecular medicine. It has been populated by many of the world's most outstanding scientists. Among these, David Weatherall stands out, universally acknowledged as the individual who contributed more than anyone. He provided foundational insights into the mechanisms underlying these severe inherited anemias and advanced an entire field through his laboratory and clinical research, his writings, and his advocacy. His leadership inspired generations of world-class investigators to make truly breakthrough discoveries in ways that have improved the outlook for many patients afflicted with these inherited disorders.

Sir David's career was embedded in his deep compassionate concern for the plight of the first patient with thalassemia that he encountered. Driven to understand the causes of her symptoms, he pursued decades of groundbreaking research that codified their nosology, genetics, ontogeny, hematology, biochemical and molecular pathology, and fundamental strategies for their diagnosis and therapy. This attracted many talented investigators to study the globin genes, causing them to be the first human genes characterized, isolated, and expressed in model systems. By so doing, Weatherall's contribution to science and medicine transcended even his profound impact on the thalassemia field. As discussed in the article in this issue by Edward J. Benz Jr entitled, "Introduction to the Thalassemias, Molecular Medicine's Index Case," these studies of hemoglobinopathies demonstrated the feasibility of applying the emerging techniques and strategies of molecular genetics to the study of human diseases. Indeed, the globin genes remain the best (though incompletely) understood in terms relating their structure and function to the development of complex phenotypes expressed in embryonic, fetal, and postnatal life.

Professor Sir David John Weatherall was born March 9, 1933, in Liverpool, United Kingdom, where he spent his childhood and youth, ultimately graduating in Medicine from Liverpool University in 1956. While serving his military duty he was assigned to a military hospital in Singapore. Having had no specialty training in Pediatrics, he encountered a young girl, named Jaspir Thapa, who, since the age of 3 months, had been severely anemic and kept alive only by repeated blood transfusions.[1] Exhibiting the relentless commitment to the care of his patients that marked his entire career, Weatherall did extensive research to try to find the cause of her anemia and, perhaps, a more effective treatment. This yielded no fruit until a chance meeting with a Maltese biochemist named Frank Vella, who was on the faculty at the University of Singapore. Hearing the description of Ms Thapa's anemia and transfusion dependency, he pointed Weatherall to a paper that had been published a few years earlier describing a patient with "Mediterranean anemia" (ie, thalassemia) in

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Fig. 1. Professor Sir David Weatherall (*center*) with Dr Nancy Olivieri (*left*) with whom he founded the nonprofit advocacy group, Hemaglobal, and pediatrician Dr Mahinda Arambepola (*right*), during a consulting visit a local clinic to Sri Lanka. (*Courtesy of* Dr Nancy Olivieri, see Ref. 3.)

Thailand. This paper pointed out that there were patients in southeast Asia whose clinical features strongly resembled thalassemia, a condition that at that time was thought to be common only in the Mediterranean region.

In the mid-1950s, techniques to characterize, separate, and quantitate human hemoglobins were just emerging. Lacking access to state-of-the-art scientific resources, Weatherall adapted a new method called starch gel electrophoresis to analyze Ms Thapa's blood. He improvised, using filter paper as his matrix and automobile batteries as his power source. He was able to confirm that Jaspir did indeed suffer from thalassemia. Weatherall and Bella published a paper in the *British Medical Journal* entitled "Thalassemia in a Gurkha family."[2] In his book, "Thalassemia: the Biography,"[1] Weatherall wryly noted that this was an inauspicious start to his career in academic hematology, because he was nearly court-martialed for publishing a paper without permission, and especially, for reporting that the family of elite Gurkha officers had "bad genes."[1] This vignette, well known to almost everyone who is a student of the thalassemia syndromes, marked the beginning of a career that would lead David to preeminence in advancing our understanding, diagnosis, and treatment of the thalassemias.

Upon completing his military service, Weatherall undertook a Fellowship in Hematology at Johns Hopkins, where he mastered the specialty under the tutelage of C. Lockhart Conley and began his lifelong study of hemoglobinopathies. He returned to Liverpool from 1965 until 1974, when he was recruited to Oxford University as the Nuffield Professor. He founded Oxford's Institute for Molecular Medicine in 1989 (renamed the Weatherall Institute for Molecular Medicine in 2000 by Oxford University in recognition of his profound influence on the founding the field of molecular medicine). In 1992, he was appointed Regius Professor, the most prestigious professorial appointment in the United Kingdom.[1,3,4]

Throughout his incredibly productive career, Sir David made many contributions to hematology, particularly the hemoglobinopathies. He contributed nearly 600 papers to the literature, many books and monographs, and communications for the lay press outlining the basic understanding of molecular biology and its relevance to clinical medicine. During those early years at Johns Hopkins and Liverpool, he made some of his most seminal contributions.

By the late 1950s and early 1960s, it was well established that the various hemoglobins consisted of tetramer of globin peptides, each bound to the heme group consisting of a protoporphyrin IX moiety within which was coordinated an ion of reduced iron

(Fe^{++}) (see the article in this issue by Edward J. Benz Jr entitled, "Introduction to the Thalassemias, Molecular Medicine's Index Case"). It was also clear that there were several forms of thalassemia. By far, the most common forms were the alpha-thalassemias, due to reduced or absent accumulation of alpha-globin chain and beta-thalassemia, reflecting deficient accumulation of the beta-globin chains. What was not clear was the mechanism by which these globin chains failed to accumulate. Most investigators believed that the underlying cause was defective biosynthesis; others believed that posttranslational instability was responsible. Unfortunately, there were no methods available for measuring the biosynthesis of the individual globin chains, until, in 1965, Weatherall and his colleagues made perhaps the most pivotal advance in our understanding of the cause of the thalassemias by demonstrating unequivocally that the reduced accumulation of globin chains was due to reduced biosynthesis.[5]

A major problem impeding the analysis of the individual globin chains is that they are both resistant to dissociation and highly insoluble in aqueous solutions. Solutions containing 8-molar urea dissociated the individual globins, but the chains aggregated, prohibiting further analysis. Weatherall and his colleagues J.B. Clegg and M.A. Naughton discovered that adding 2-mercaptoethanol alleviated the aggregation. They then demonstrated that the soluble disaggregated chains could be cleanly separated by ion exchange chromatography on columns comprising carboxy-methylcellulose resin. Exploiting the new availability of C-14–labeled amino acids, coupled with the observations of others that circulating reticulocytes retain the protein synthetic machinery, Weatherall and Clegg were able to compare the biosynthesis of alpha- and beta-chains by normal and thalassemic reticulocytes. These studies demonstrated definitively that the defect responsible for reduced globin *accumulation* in thalassemia was due to defects in the primary biosynthesis of the affected globin chain.[5]

As described in the article in this issue by Edward J. Benz Jr entitled, "Introduction to the Thalassemias, Molecular Medicine's Index Case," this development opened the doors to the studies by several groups of the underlying defects in the protein biosynthetic apparatus responsible for the defective production of the affected globin chains. Neinhuis and Anderson[6] and Benz and Forget[7] ultimately utilized "Clegg columns" to measure the synthesis of globin chains in cell-free systems primed with mRNA from nonthalassemic and thalassemic reticulocytes. Their results proved that the defects leading to reduced biosynthesis were due to defective amounts or translatability of globin mRNA. These breakthroughs demonstrated that the early methods of molecular biology could be used to study human diseases. They were possible only because of the availability of the Clegg columns and the Weatherall group's proof that thalassemias arose from defective biosynthesis of the affected globin.

Throughout his career, Weatherall had a genius for collaborations and for attracting distinguished investigators into the study of the thalassemias. Douglas Higgs, John B. Clegg, Bill Woods, John Pritchard, Swee Lay Thien, among numerous others, emerged as key contributors. Their work helped to advance the field. Sir David also collaborated with laboratory investigators around the world, and with clinicians in the regions most affected by the thalassemias (see the article in this issue by Aurelio Maggio entitled, "The Epidemiology of the Thalassemia Syndromes").

In 1965, Weatherall and Clegg[8] published a monograph entitled simply "The thalassemia syndromes." This monograph was equally pivotal in advancing the field. It synthesized massive amounts of loosely connected reports into a coherent picture of what was then known about the globin gene system, and their abnormalities in the thalassemias. To this day, his nosology of the thalassemias remains the guide for diagnosing these illnesses. This monograph, throughout several subsequent editions, continues to be universally regarded as the "Bible" for students of thalassemia. Each

succeeding edition elegantly incorporated disparate advances in the field into a coherent whole that guided further advances in their study.

Sir David's passion for studying the thalassemia syndromes was rooted in his concerns for patients around the world, many in the most socioeconomically deprived areas. He constantly pointed out to those of us in the field that thalassemia, while fascinating scientifically, is a massive public health concern in many areas of the world where access to the resources needed to provide the most advanced life-prolonging therapies is limited or nonexistent. He wrote and lectured extensively about these global health issues, pointing out that, as these economies began to emerge and develop the public health measures that prevent many of the childhood infectious diseases that previously carried these debilitated patients away, the need for basic infrastructure and resources, such as a blood supply, access to iron chelating medicines, and so forth, would present an enormous social, moral, and economic burden on the countries most affected. Subsequent events proved him right.

Sir David did not merely write and speak about these issues. He invested substantial amounts of his time throughout his career, even while holding the prestigious Regius Professorship and the Directorships of the Institute for Molecular Medicine at Oxford. He worked with collaborators in the field and at the bedside, fully engaged and enhancing patient care and onsite research. He advocated tirelessly for the provision of adequate support that could provide for the diagnostic and therapeutic resources needed for optimal care of these patients. He guided where feasible the development of clinical trials' infrastructure that made patients eligible to participate in studies of emerging therapies. His devotion to this cause was such that it eventually led to a life-altering injury. He suffered a fall in Sri Lanka that tore both of his quadriceps. The fall occurred in a temple, prompting Sir David, in keeping with his legendary wry British wit, to observe that he "should have known better than to go into a place of worship."[3]

Sir David was uncomfortable about having attention focused on him. Weatherall was so unassuming that it was sometimes possible to overlook how truly brilliant he was. At many meetings, we observed him sit quietly throughout heated debates about this or that scientific point, and then politely ask a question or make a comment that pulled all of the contending points together into a synthetic conclusion or hypothesis that was illuminating. Yet, it was inevitable that he would be repeatedly honored for his many contributions.[3,4] He was elected a Fellow of the Royal Society in 1977, knighted by the British Empire in 1987, was elected to the American Philosophical Society in 2005, and received the Lasker Award, the "American Nobel Prize," in 2010. Among many other prestigious awards and recognitions included selection as one of the few foreign members of the US National Academy of Sciences and appointment as Knight Grand Cross of the Order of the British Empire in 2017.

For those of us who knew him and were blessed to be numbered among his friends as well as colleagues, David will be most fondly remembered and missed for who he was even more than what he accomplished. He was an unassuming individual whose wit was often self-deprecatingly directed at himself, or, affectionately, at his long-time, very close friend, Professor David G. Nathan, of Harvard Medical School, Children's Hospital of Boston, and the Dana-Farber Cancer Institute. Indeed, the "two Davids" constantly exchanged affectionately barbed correspondence for decades. Nathan chided Sir David for his failure to obtain an invitation for Nathan to have tea with the Queen, while Weatherall would constantly grouse about the many times he had to cross the pond to attend fests for Nathan as he retired from one position after another. He was a wonderful house guest, being completely undemanding except for his need to "smoke me pipe." In fact, one of the few things he ever groused about in the United

States was the increasingly stringent limitation on where one could smoke at meetings, conferences, in hotels, and so forth. Indeed, the best way to have an informal chat with David during his later years was in an outdoor space near the auditorium or lecture hall, in any weather, at any temperature, where he could puff on his beloved pipe.

For his brilliant contributions as a scientist, his compassionate care and concern of many, many patients with hemoglobinopathies and other blood disorders, his uncanny ability to integrate the most advanced biological sciences, clinical medicine, epidemiology, public health, and clinical research into a coherent picture of one of the world's most common inherited disorders, for his authenticity, genuine warmth, and the integrity with which he carried out his professional and academic life, we are deeply honored as editors of this issue to dedicate it to Professor Sir David John Weatherall.

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