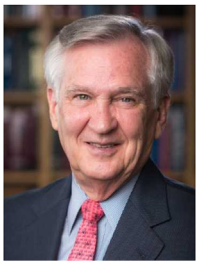
Preface
Thalassemia



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The thalassemia syndromes are inherited disorders of hemoglobin synthesis associated with heterogeneous clinical manifestations ranging from barely detectable microcytosis to profound transfusion-dependent anemia associated with severe stigmata of hemolysis and ineffective erythropoiesis. Taken as a group, the thalassemias are likely the single most common inherited disorders in the world. Indeed, in some populous Southeastern Asian regions, gene frequencies for certain thalassemia alleles can range as high as 30% to 40%, comparable to the frequency of blood group A+ in the United States. In these and several other areas of the world, the serious forms of thalassemia thus represent significant public health issues and, importantly, are a major cause of human suffering.

The vast majority of individuals heterozygous for thalassemia ("thalassemia trait" or "thalassemia minor") exhibit only mild hematologic laboratory abnormalities and no or minimal symptoms. In areas of the world where malaria is endemic, they appear to have a selective advantage by being at least partially protected from its most severe manifestations. Individuals homozygous for thalassemia alleles, or compound heterozygous for a thalassemia allele and an allele for another hemoglobinopathy, such as hemoglobin E or sickle hemoglobin, exhibit varying degrees of hemolytic anemia and deficient production of mature red cells due to ineffective erythropoiesis. The genetic, molecular, and pathophysiologic basis for these hematologic abnormalities and clinical manifestations has been characterized in considerably greater detail, perhaps, than for almost any other human illnesses. After many years during which red cell transfusions and the use of iron-chelating agents to mitigate consequent hemosiderosis were the only therapeutic options available to these more severely afflicted patients, a number of exciting new disease-modifying and even curative options are either available or on the horizon. Thus, for hematologists and oncologists, it is mandatory to develop a thorough understanding of the thalassemias, their clinical variability, and the standard and emerging therapeutic strategies available to individual patients.

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In addition to their clinical and public health importance, the thalassemias are also extraordinarily important as "molecular medicine's index case." As outlined in the article entitled, "Introduction to the Thalassemias, Molecular Medicine's Index Case" in this issue, these disorders were the first to be delineated as arising from deficient *biosynthesis* of the specific protein products of specific genes, namely the genes encoding the individual globin subunits of hemoglobin. Delineation of their molecular pathophysiology constituted the first demonstration of the clinical consequences not only of deficient production of a specific protein but also of the imbalanced accumulation of the components of multimeric proteins. Studies of the molecular genetics of the thalassemias led to the first demonstration of messenger RNA defects and specific gene deletions responsible for human disease, the first isolation of an individual messenger RNA product of a human gene, the first cloning of human cDNAs and genomic loci, the first DNA-based techniques for antenatal diagnosis of inherited disorders, and numerous other initial breakthroughs that inspired the incursion of molecular biology into the study of clinical medicine. The study of these syndromes set the paradigm for investigating and illuminating the pathway that connected specific mutations with their consequences on the expression of the affected gene, and the cellular, organismic, and homeostatic consequences of altered expression of the affected gene or genes. This approach has been adopted to the study of many inherited and acquired disorders. More recently, these disorders have been targeted for the first application of CRISPR/Cas9 genome editing in the clinic. Some familiarity with the molecular pathology and pathophysiology of the thalassemia syndromes thus remains important for students of hematology, oncology, and, indeed, most medical specialties.

The editors and authors of this issue dedicate it to the memory of Sir David Weatherall. He more than any other single individual codified the thalassemia syndromes as specific disorders impairing the expression of specific genes that are needed to produce an essential life-sustaining protein, namely, hemoglobin. His contributions over the span of his career can quite literally be credited with opening the doors of medicine to the transformative strategies and techniques that we now call precision molecular medicine. The article in this issue entitled, "Remembering the Contributions of David Weatherall," provides a remembrance and appreciation for the positive impact he made on this field, on hematology, and on global health.

We, the guest editors, attempted to organize this issue in a manner that offers an interrelated array of articles covering the distinct and most important features of the thalassemias, both clinically and scientifically. We hope that they will provide the reader a richer level of understanding and insight into the complex yet elegantly defined pathophysiology and clinical features of these numerous but interrelated syndromes. We also feel that this update is timely. Earlier this year, the Food and Drug Administration approved the first gene replacement therapy for the treatment of transfusion-dependent forms of these illnesses. In addition, the past two to three years have witnessed the introduction and expanded use of disease-modifying drugs that, in properly selected patients, ameliorate many of the more severe manifestations of the disease. These agents are based on emerging insights into the complex derangements of the bone marrow microenvironment, hematopoietic stem cell function, and inflammation that occur as the result of defects in globin gene expression. We thus hope that the material included in this issue will be useful to the reader, both as a practical clinical update about the prevention, diagnosis, and treatment of patients with these conditions and as an important heuristic lesson for understanding the flood of

information emerging daily about the molecular genetic abnormalities associated with myriad disorders, particularly hematologic neoplasms.

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