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Thalassemia at the dawn of the 21st century

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The progress in acquiring new knowledge and treatment of the thalassemia syndromes has truly been extraordinary during the latter half of the last century. The molecular pathology of the globin genes is now largely known. Treatment program with regular transfusions and iron chelation has extended the life span of many patients into the 4th decade and beyond. Stem cell transplantation provides the possibility of cure for many. Prenatal diagnosis is safe, accurate, and well accepted in many areas around the globe.

This pace of advancement is anticipated to increase in this new century. The approval and availability of oral chelators for clinical use (both singly and in combination) has generated much excitement for the prevention and treatment of iron overload. Ongoing clinical trials will be critical to determine the optimal treatment strategy with these compounds and others being developed. The procurement of sufficient and safe blood supply remains a challenge.

Criteria for patient selection and optimal time to undergo stem cell transplantation for patients with thalassemia major will need to be further refined. Several areas that will require additional investigation include transplantation with unrelated donor or cord blood cells, less intensive conditioning regimens prior to transplantation, and minimizing the effects of graft versus host disease. Gene therapy has the potential to alleviate the underlying abnormalities of thalassemia, but the road to the safe and successful implementation of this treatment has proven to be arduous. Yet despite these challenges, the dawn of this long awaited therapy appears to be very near.

It is well known that there can be significant dichotomy between the clinical phenotypes manifested by patients with identical globin gene mutations. For example, the presentations of Hb Bart hydrops fetalis fetuses vary quite considerably. Genotype/phenotype correlation is an area that deserves to be pursued in earnest. These studies will require meticulous longitudinal observations and record keeping by both clinicians and laboratory physicians. The possible role of environmental factors in disease phenotype has not been scrutinized extensively until recently. Pulmonary hypertension is only recently shown to be related to hemolysis as one of the underlying factors. The possible pathogenetic roles of coagulation and also oxidative injury in thalassemias have not yet been well deciphered. Research on these topics can lead to novel means of treatment.

There are still large gaps in knowledge regarding the mechanisms of regulation of globin gene expression and silencing of fetal globin genes in adults. The demonstration that genes unlinked to the globin gene clusters can affect globin gene expression illustrate that there are other genes or quantitative trait loci that will modulate globin

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gene expression. The identification of these might provide targets for future drug therapy.

In the post-genomic age, it is now possible to undertake extensive genetic association studies to look for thalassemia genetic modifiers throughout the whole genome. Well-characterized and large patient populations are required for these investigations. This truly multidisciplinary research demands close collaboration between clinicians and laboratory physicians, molecular biologists, experts in genetic epidemiology, bio-informatics, biostatistics and data management, and even mathematicians. Understandably, genomic research also requires large sums of funds. Taken together, this important research is best undertaken by inter-institutional, and even international collaboration. As never before, comprehensive genomic research can potentially allow us to look for genes and genetic loci throughout the genome that interact with globin genes. Their identification will add to our knowledge in the pathophysiology of the disease, be useful for prognosis, and also design for novel treatment targets.

In spite of the phenomenal explosion of new knowledge on globin gene biology and treatment strategies, health care for patients with thalassemia major and their families in many developing countries still lags far behind. The magnitude of the disease burden in each community can be better assessed if accurate carrier frequency is known, and patient registry is available. Community wide and school education is essential. New screening protocols to identify at risk couples have to be developed and tailored to local cultures and needs. Non-invasive prenatal diagnosis will be helpful. Centralized diagnostic laboratories have to be set up. Local and national governments as well as international health agencies need to be fully informed and persuaded to recognize the importance of thalassemia prevention and treatment as part of the integral public health programs.

This promises to be the century when the long sought after control and cure of thalassemia syndromes will come to pass. To accomplish this important goal, we need to encourage and foster young, bright, and enthusiastic physicians, scientists, health care workers, and lay leaders to be involved in advancing this exciting field of global health importance. Innovation and collaboration will be the key to making major contributions to the science and medicine of the thalassemia at the dawn of this 21st century.