

The inherited diseases of hemoglobin are an emerging global health burden

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It is estimated that in excess of 300 000 children are born each year with a severe inherited disorder of hemoglobin and that approximately 80% of these births occur in low- or middle-income countries. As these countries go through an epidemiologic transition, with a reduction in childhood and infant mortality due to improved public health measures, babies who would have previously died of these diseases before they were recog-

nized are now surviving to present for diagnosis and treatment. Hence, they are presenting an increasing global health burden. Because of their uneven distribution in high-frequency populations, reflecting their complex population genetics, the true magnitude of this burden is still unknown. In many poor countries there are virtually no facilities for the diagnosis and management of these conditions, and even in richer countries there

are limited data about their frequency, clinical course, or mortality. Without this information, it will be impossible to persuade governments about the increasing importance of these diseases. The situation will only be improved by concerted action on the part of the hematology community of the richer countries together with input from the major international health organizations and funding agencies. (*Blood*. 2010;115(22):4331-4336)

Introduction

It has been estimated that more than 7 000 000 babies are born each year with either a congenital abnormality or a genetic disease, and that up to 90% of the births occur in low- or middle-income countries.¹ Of these births, approximately 25% consist of only 5 disorders, 2 of which, the inherited disorders of hemoglobin and glucose-6-phosphate dehydrogenase deficiency, are monogenic diseases. A minimum estimate suggests that in excess of 300 000 children are born each year with either sickle cell anemia or one of its variants or a form of thalassemia.² In the case of the sickle cell disorders similar data have been obtained recently by the MalariaMap program.³

One of the problems with these estimates is that they are based mainly on studies that were carried out before 1980.^{4,5} Since then there have been relatively few population analyses of the gene frequencies of the different hemoglobin disorders. Rather, work of this kind has focused on the underlying mutations that are involved. Similarly, there is a serious lack of information about the clinical course, complications, and mortality rates of these conditions in most of the poorer countries. Even in many richer countries, data of this kind are scarce. Hence, it is extremely difficult at present to provide an estimate of the health burden that will be encountered, particularly by the poorer countries of the world, as the hemoglobin disorders become even more frequent in the future.

Recent surveys have also indicated that many of the developing countries have next to no facilities for the diagnosis, control, and management of the common hemoglobin disorders.⁶ In short, the global situation regarding the control and management of these conditions is extremely unsatisfactory and cannot continue to be ignored by the international hematology community and health agencies.

Estimations of the global burden of the major hemoglobin disorders

A breakdown of the estimated annual births of the major hemoglobin disorders is shown in Table 1. Sickle cell anemia is by far the commonest; a further analysis of the data suggests that close to

180 000 babies are born each year in sub-Saharan Africa with this condition,² a figure that has been confirmed in a more recent analysis of published surveys.³ Surprisingly, the serious forms of β thalassemia are equally divided between β thalassemia major and hemoglobin E (HbE) β thalassemia. The latter occurs at a high frequency in parts of the Indian subcontinent, Bangladesh, Myanmar, and throughout Southeast Asia.⁵ The high frequency of the severe forms of α thalassemia is also restricted mainly to Southeast Asia.

There are several reasons why these data must be interpreted with caution. First, they are based on surveys that in many cases reflect information obtained from a limited number of centers in each of the countries analyzed. Recent micromapping studies, which are analyses of samples taken from many different centers in a particular country or region, have disclosed a remarkable heterogeneity in the distribution of the hemoglobin disorders, often within short geographical distances. For example, even in a relatively small island population such as Sri Lanka, there is a remarkable variation in the frequency of β thalassemia and HbE.⁷ Similarly, recent data obtained from 2 states in northwest India also show a remarkable variation in the frequency of β thalassemia over short distances,⁸ suggesting that earlier figures for the frequency of β thalassemia in the Indian subcontinent may have been underestimated. And, from such data as are available, it is probable that the published figures for the births of babies with sickle cell anemia in India, approximately 25 000, may also be an underestimate of the true rate. Preliminary data from my laboratory indicate an equal degree of geographic heterogeneity of the important hemoglobin disorders in Indonesia and Vietnam.

Clearly, therefore, our current figures for the annual births of babies with important hemoglobin disorders may be inaccurate; a better estimate of the global burden of these disorders will require further micromapping studies, particularly in countries in which they occur at a high frequency.

Table 1. Breakdown of the annual number of births with the different hemoglobin disorders from data available²

Major hemoglobin disorder	No. of annual births
β thalassemia major	22 989
HbE β thalassemia	19 128
HbH disease	9 568
Hb Bart hydrops (α^0/α^0)	5 183
SS disease	217 331
S β thalassemia	11 074
SC disease	54 736

SS indicates sickle cell anemia; SC, sickle cell; and Hb, hemoglobin.

Population genetics and dynamics

There are several reasons for the extremely high frequency and patchy distribution of the genes for the different hemoglobin disorders. By far the most important is natural selection, although consanguineous marriage, which is practised widely in many countries in which the hemoglobin disorders are common,⁹ also plays a significant role in their high frequency. Other factors include gene drift and founder effects.

Extensive evidence now shows that the main reason for the high frequency of the hemoglobin disorders is heterozygote, and in the case of α^+ thalassemia and HbC, homozygote protection against *Plasmodium falciparum* malaria. Evidence in favor of this mechanism, and the cellular and immune processes through which it may be mediated, have been reviewed.^{10,11}

The different distribution of particular varieties of the hemoglobin disorders among the world populations almost certainly reflects the occurrence of de novo mutations that expanded rapidly under the pressure of natural selection. Just like the hemoglobin disorders, the distribution of malaria within different populations is quite heterogeneous.³ For example, the regions of Sri Lanka with the highest frequency of β thalassemia or HbE coincide quite remarkably with those of high transmission of malaria before the early eradication programs.^{7,12} Hence, it can be expected that in most populations in which these diseases reach a high frequency their geographic distribution is likely to be extremely heterogeneous.

Recently, a further mechanism has been described that contributes toward the heterogeneous distribution of these diseases. Strong evidence now shows that there are important epistatic interactions between different hemoglobin variants with respect to malaria protection. For example, the sickle cell trait offers a high level of protection against the severe complications of malaria, as do the heterozygous and homozygous states for α thalassemia, yet those who are heterozygous for both the sickle cell trait and α thalassemia are no more resistant to malaria than healthy controls.¹³ By modeling 2 epistatic interactions of this type, sickle cell trait and α thalassemia and the ameliorating effect of α thalassemia on β thalassemia, it has been possible to provide a convincing basis for why the sickle cell trait predominates in Africa, whereas α and β thalassemia are the common hemoglobin disorders in the Mediterranean region, even though it is known that the sickle cell trait was imported into the Mediterranean in at least one period during human evolution.¹⁴

These issues are of considerable practical significance. Even if malaria is largely eradicated in the future, it will take many generations before any significant effect on the gene frequency of the hemoglobin disorders will occur and, hence, on the reduction of the numbers of homozygotes or compound heterozygotes born with these conditions.⁵ It seems likely that most high-frequency popula-

tions that have come under strong selection by exposure to malaria will have an extremely patchy distribution of genes for these diseases; hence, the critical importance of micromapping to determine their probable health burden in any particular population. Furthermore, we cannot continue to completely ignore the environment when considering the control of the common genetic disorders of hemoglobin. Although it is now clear that *P falciparum* malaria has been an important factor in maintaining their high gene frequencies, recent evidence suggests that at least some forms of thalassemia are more susceptible to the malarial parasite *Plasmodium vivax*, which affects thousands of people in parts of Asia and South America.^{15,16} These observations may have important implications for hemoglobinopathy control programs in these regions.

Effects of epidemiologic and demographic transitions

When, as the result of improvements in hygiene, nutrition, and public health, poor countries pass through a transitional phase of reduced levels of infant and childhood mortality, infants with diseases such as thalassemia that would previously not have been recognized survive to present for diagnosis and treatment. Changes of this kind were graphically illustrated in Cyprus, a country that underwent this kind of transition shortly after World War II. Although thalassemia was not identified in Cyprus until 1944, by the early 1970s it was estimated that, if no steps were taken to control the disease, in approximately 40 years' time, the blood required to treat thalassaemic children would amount to 78 000 units per annum, 40% of the population would need to be donors, and the total cost to the health services would equal or exceed the island's health budget.⁵

The same phenomenon is being observed in many poor countries that are going through this transition, and in many cases they are those with the highest frequency of the inherited disorders of hemoglobin. Furthermore, in many cases they are the countries with the highest rate of increase of their population.¹⁷ Despite uncertain census data, it is currently estimated, for example, that the population of Africa has risen to approximately 1 billion and could reach close to 2 billion by 2050. Although growth has slowed down in India and China, their populations also will increase. Hence, although the rate of progression of the epidemiologic and demographic transitions may be slower in countries with a rapidly increasing population, there is no doubt that, given the world distribution of the hemoglobin disorders, these transitions combined with increased population growth will lead to a major increase in the numbers of babies born with one or other hemoglobin disorder over the next half-century.

Current position in the developing countries

Although considerable progress has been made toward the control and management of the sickle cell disorders and thalassemias in rich countries, the current position for many of the poorer countries where these diseases are so common is completely unsatisfactory. With the exception of Jamaica, where carefully controlled long-term cohort studies have provided invaluable information about the natural history of sickle cell disease and are leading to improvements in its control and management,¹⁸ the position in other parts of the world is extremely worrying. Very little is known about the natural history of sickle cell disease in Africa, where it is assumed

Table 2. Current services available for the control and management of thalassemia in Asian countries

Country	Transfusion	Iron chelation			BMT	PND	National program
		DFO	L1	Exjade			
Bangladesh	(+)	(+)	–	–	–	–	–
Cambodia	(+)	(+)	–	–	–	–	–
China							
Guangxi	+	(+)	(+)	–	(+)	+	–
Hong Kong	+	+	+	(+)	+	+	+
Taiwan	+	+	+	(+)	+	+	+
India	(+)	(+)	(+)	–	(+)	(+)	–
Indonesia	(+)	(+)	(+)	–	–	(+)	–
Laos	(+)	(+)	–	–	–	–	–
Malaysia	+	+	+	(+)	+	+	+
Maldives	+	+	+	–	(+)	–	+
Myanmar	(+)	(+)	–	–	–	–	–
Philippines	+	(+)	–	(+)	–	–	–
Singapore	+	+	+	(+)	+	+	+
Sri Lanka	+	+	+	–	–	–	+
Thailand	+	+	+	(+)	+	+	+
Vietnam	(+)	(+)	(+)	–	(+)	–	–

Data collected and updated with the help of Dr Suthat Fucharoen and the Asian Thalassaemia Network.²³

BMT indicates bone marrow transplantation; PND, prenatal diagnosis; DFO, desferrioxamine; L1, deferiprone; +, services available; (+), services available only to those who can afford them; and –, complete lack of availability.

that most babies die of infection within the first few years of life. Recent studies in Kenya have shown that the common infective organisms that are responsible are similar to those in the richer countries, suggesting that neonatal screening and appropriate prophylaxis would have a similar beneficial effect in Africa as it does in the United States and Europe.¹⁹ But there have been no long-term studies of the natural history of the disease in Africa, and apart from a few centers management is virtually nonexistent. Because the sickle cell gene arose independently in a different genetic background in India,²⁰ sickle cell anemia in Indian populations tends to be milder than in Africa,²¹ although, again, there have been no long-term cohort studies. Virtually nothing is known about mortality and about the pattern of complications compared with children in Africa. There is a similar lack of data from the Middle East, where the situation is particularly complex because the sickle cell genes have been introduced from both Africa and India.²²

Over the past few years a thalassemia network has been established in Asia at which meetings of representatives from many countries have attended. The first objective was to determine the current position for the control and management of thalassemia in Asian countries. The present situation is summarized in Table 2. It is clear that, although some countries have developed services for prenatal diagnosis and for adequate management of thalassemia, in many cases virtually no services of this kind exist. These problems are compounded because the common form of severe β thalassemia in Asia is HbE β thalassemia, a disease which has a remarkably variable phenotype, ranging from a transfusion-dependent disorder to a condition that is compatible with reasonable growth and development without treatment.²⁴⁻²⁶ Much remains to be learned about the reasons for this heterogeneity and about the ideal way to manage this complex condition. The collation of these data by the Network has emphasized the serious neglect of patients with thalassemia in many Asian countries.

It has been argued that the poorer countries of the tropical belt are still dealing with the ravages of malnutrition, communicable disease, and the effects of natural disaster and war. In addition, as their diets and lifestyles are becoming westernized, they are also having to deal with a rapid increase in disorders such as coronary artery disease and diabetes. Therefore, genetic diseases such as the

hemoglobin disorders remain a low priority for their health care programs. However, as these countries go through the epidemiologic transition and their populations increase in size, the hemoglobin disorders will pose an increasing financial burden on these limited services. A crude estimate carried out in 2001 suggested that, if all the patients born with thalassemia were to be treated, in Sri Lanka the annual cost would amount to some 10% of the country's total expenditure on health.⁷ An equally approximate estimate of the disability-adjusted life years, the most commonly used measurement of health burden, suggested that at least in Asia the thalassems would be responsible for several disability-adjusted life years comparable with those for malaria.⁶

Clearly, therefore, although there are huge gaps in our knowledge about the actual health burden posed by the hemoglobin disorders, enough is known to indicate that action is urgently required.

What is required?

Clearly, the first priority must be to establish centers in countries where limited knowledge of the hemoglobin disorders exists at which doctors, nurses, and social workers can be trained in the basic diagnosis and management of the hemoglobin disorders. One of the first actions required of such centers will be to carry out micromapping studies of their populations to determine the true burden of these diseases. Because of the remarkable genetic and clinical variability of both the sickle cell disorders and the thalassems, it will be equally important for these centers to establish natural history programs of the pattern of disease in their particular environment.

In view of the scale of the problem, priority will have to be given to the avoidance of these conditions, a more appropriate term than "prevention" because mutations cannot be prevented. Unfortunately, there is little evidence that the development of premarital screening and counseling programs have had much effect on the numbers of babies born with severe hemoglobin disorders. The complex organizational, social, and religious reasons for the failure of this approach are discussed in detail elsewhere.^{5,27,28} Recent

work in Kenya has shown that the organisms responsible for severe infection and death of young children with sickle cell disease is similar to that in the United States and Europe; malaria is not a major cause of early mortality as has been previously thought. Hence, the introduction of neonatal screening and prophylactic antibiotics has the potential to save thousands of lives. In the case of the severe β thalassemias, in those countries in which there are no ethical or religious objections, prenatal diagnosis programs should be established. This will require at least 1 or 2 centers in each country with expertise in DNA diagnostics. Although this approach has reduced the birth rate of babies with β thalassemia in many countries,⁵ it has been applied less widely for the control of sickle cell anemia. This may be because of its remarkable clinical heterogeneity, which makes it impossible to provide individual parents with a clear prognosis; the same problem is also relevant to HbE β thalassemia and HbH disease. This important question requires careful counseling and debate, both within individual families and different populations, supported by further research directed at understanding the basis for the clinical diversity of these conditions.

A long-term goal of course would be to try to introduce modern approaches for the management of the hemoglobinopathies into the poorer countries, a process that will undoubtedly require the help of international health agencies and the pharmaceutical industry. In the case of β thalassemia in Asia, which is largely HbE β thalassemia, new approaches to management are absolutely critical, not in the least to find out what happens to the older patients with this condition who have grown and developed reasonably well at relatively low hemoglobin levels. Increasing evidence suggests that patients with this condition can adapt better to anemia than those with other forms of thalassemia intermedia,²⁶ although it is not yet clear whether this leads to cardiac, bone, or other complications later in life. If this is not the case, it is quite possible that many patients with HbE β thalassemia in Asia are receiving unnecessary transfusions and, hence, wasting valuable resources.

In the case of the thalassemias broader public health issues may have to be considered when developing control programs. As mentioned earlier, it has been found that HbE β thalassemia and some forms of α thalassemia appear to render patients more susceptible to malaria due to *P vivax*.^{15,16} Although until recently this form of malaria was thought to be less severe and life threatening than that due to *P falciparum*, there is growing evidence that it has an extremely high morbidity and an increasing mortality in many Asian countries.²⁹ These recent observations will have to be explored further and serious consideration given to the use of prophylaxis for *P vivax* infection as part of the management of the more severe forms of β thalassemia in Asia.

What can be done to improve the current situation?

Clearly, something has to be done for the families and patients with severe hemoglobin disorders in the developing countries. One thing seems certain; we cannot rely on the major international health agencies or granting bodies to take the appropriate action. The World Health Organization (WHO) has produced numerous reports and manuals for the prevention and management of these disease, but little action has followed. Similarly, the major international funding bodies are committed almost entirely to the prevention and management of communicable disease and are showing little interest in noncommunicable disease as a whole and genetic

disease in particular. Although they are doing excellent work, we cannot expect international parent organizations such as Thalassaemia International Federation to solve these problems. Is there, therefore, a role for the hematologic community in the richer countries?

Over many years there have been a few prolonged partnerships between centers with expertise in sickle cell anemia, and rather more thalassemia, and centers in poorer countries where there is limited knowledge of these diseases. In many cases these so-called North/South partnerships have led to the development of considerable expertise in the control and management of these diseases in the poorer countries involved. They have usually been supported by research agencies in the rich countries and, in addition to training appropriate staff and other forms of capacity building, they have involved a considerable amount of basic and clinical research. Hence, provided they are genuine partnerships, they have also offered the opportunity for training young doctors in the poorer countries in research methods and how to write research papers, an outcome that is reflected in a considerable number of papers in leading journals. Of course, given the political instability, poverty, and the numerous other problems of countries in the developing world, these partnerships have not always been successful. However, based on patient long-term sustainability and strong leadership, their successes have undoubtedly exceeded their failures. Because of the tighter financial control that is possible with partnerships of this type compared with undirected government aid from the richer countries, they have been a much more cost-effective approach to developing national programs for improving the control and management of the hemoglobin disorders.

As is clear from Table 2, there are several countries in Asia that already have genuine expertise in the control and management of thalassemia. This has led to the concept of the development of South/South partnerships between these countries and those where no such knowledge exists. The main objectives of such partnerships include capacity building through training clinicians, nurses, and counselors and developing national centers with expertise in the control and management of the hemoglobin disorders. They should also include several simple research objectives, including micromapping of the frequency of the hemoglobin disorders, work directed at a better understanding of the phenotypic diversity of these conditions, and studies of the pharmacogenetics of the oral chelating agents that are becoming available for the management of iron loading, both in thalassemia and in patients with sickle cell anemia who receive transfusions. Recent work also suggests that it will also be important to study the interaction of both common forms of malaria with the more severe homozygous or compound heterozygous forms of the sickle cell disorders and the thalassemias.

In 2002 the WHO published a report titled *Genomics and World Health* that recommended North/South and South/South partnerships as an approach to the control and management of common genetic diseases such as the hemoglobin disorders as well as a way of introducing DNA diagnostics for communicable disease into the developing countries.³⁰ These recommendations were later confirmed by the WHO Executive Board, and at the 59th World Health Assembly resolutions were passed to urge member states to develop programs for the prevention and management of the hemoglobin disorders. Later, a meeting was held under the auspices of the WHO and Thalassaemia International Federation that published further recommendations for the development of international partnerships of this kind for the control of the hemoglobin disorders.³¹ Since then there has been no action, and it was never clear whether the WHO would play any role in supporting these

developments. There will undoubtedly be problems in obtaining adequate funding for these partnerships. Those who control both governmental and charitable research sources may feel that they are more directed at capacity building than research per se, but, given the track record of many of the North/South partnerships that they have supported, somehow the message must be transmitted to them that this is an extremely cost-effective approach for the better control and management of an increasingly common group of diseases of the poor countries.

Conclusions

Despite extremely limited data on the birth rates, survival, and clinical course and complications of the hemoglobin disorders, there is sufficient evidence that these diseases will pose an increasingly severe global health burden for the foreseeable future. Because of their distribution, much of this burden will fall on poorer countries.

Richer countries are facing severe problems posed by the increasing cost of health care, particularly for their aged populations, and it is becoming clear that the only possible way forward is by improvements in preventative medicine. In the context of the hemoglobin disorders, although there is little evidence that population screening and premarital advice per se has had much effect on their birth frequency, in the case of the β thalassemias the application of screening and prenatal diagnosis has resulted in a major reduction in the number of births of affected babies in many countries.⁵ However, because of their remarkable clinical heterogeneity and our current inability to predict the clinical course in any particular case, the value of this approach for the control of sickle cell anemia and HbE β thalassemia, which, globally, accounts for one-half of all cases of severe β thalassemia, requires further study. Clearly, one of the main goals for the partnerships that have been considered must be to set the scene for screening, counseling, and, where applicable and acceptable, prenatal diagnosis.

It will be argued of course that the development of partnerships of the kind described earlier may be a waste of time in countries in which governments cannot afford to take on the costs of running hemoglobinopathy programs. However, our limited experience suggests that this is not the case. Once sufficient local expertise is developed for screening and counseling for these conditions and for establishing limited gene frequency studies in the population and, hence, providing some indication of the burden of disease that the hemoglobin disorders will pose compared with other health priorities, it is possible to make slow progress. Although the adequate management of established cases of sickle cell anemia or thalassemia presents formidable problems for these countries, transfusion services are improving, and there are signs, albeit

limited, that the pharmaceutical industry is starting to take a more realistic approach to the problems of developing countries.

For these reasons it is essential that the hematologic community of the richer countries starts to take a greater interest in the problems of the poorer countries. However, it is not enough to simply invite a few doctors and nurses from these countries for training. This help must entail sustainable partnerships over a reasonably long period. At the same time, we must continue to try and educate the international health agencies and funding bodies, together with our governments and those of the developing countries, about the increasing burden of disease that will be produced by the hemoglobin disorders for the foreseeable future.

For the first time the hemoglobin disorders are to be included in the revised version of the *Global Burden of Disease* program.³² Those involved in compiling these data have become aware of the serious deficiencies in our knowledge of their frequency, mortality, and natural history, even in the richer countries. It has been estimated recently that if the survival rate of children with sickle cell anemia in Africa increases to only one-half the African norm, more than 6 million Africans will be living with sickle cell anemia.² Although the numbers are smaller, the same principles apply to sickle cell anemia and thalassemia in Asia. We are, in effect, sitting on a genetically determined time bomb. It is time for action. At least as a start, the major hematology societies of the richer countries might convene a group to decide whether the general approaches to the problem outlined here are an appropriate way forward. If so, and if helped by their journals, they might have sufficient influence to persuade international health agencies, governments, and major funding bodies that they cannot continue to ignore the global importance of these increasingly common genetic diseases.

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