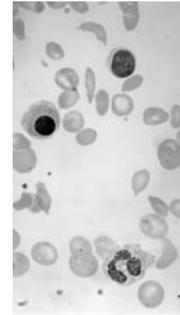Chapter **34**

Inherited Disorders of Hemoglobin

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As a result of carrier protection against malaria, the inherited hemoglobin disorders are the commonest diseases attributable to single defective genes. Approximately 7 percent of the world's population is a carrier, and 300,000 to 500,000 babies with severe forms of such disorders are born each year (WHO 1989). Although these disorders are most frequent in tropical regions, they are now encountered in most countries because of migrations of populations.

INTRODUCTION

If untreated, many of the inherited hemoglobin disorders result in death during the first few years of life. Their effect on the burden of disease has only recently been recognized, following an epidemiological transition caused by improvements in hygiene, nutrition, and control of infection that has reduced childhood mortality. Babies with severe hemoglobin disorders are now able to survive long enough to present for diagnosis and treatment. The impact of these diseases is being felt throughout the Indian subcontinent and much of Asia. Although the situation will worsen in Sub-Saharan Africa as it undergoes a similar transition, such diseases are already responsible for a major health burden. International health agencies and the governments of affected countries need to understand the future extent of the problem and to develop programs to control and manage these diseases.

Normal Hemoglobin

Hemoglobin (Hb), the pigment in the red blood cells that transfers oxygen to the tissues, changes structure during human development. In adults two components exist: a major hemoglobin, Hb A, and a minor hemoglobin, Hb A_2. The bulk of the hemoglobin during later fetal life is Hb F. These hemoglobins each consist of two pairs of unlike globin chains. The adult hemoglobins and fetal hemoglobin have α chains combined with β (Hb A, $\alpha_2\beta_2$), δ (Hb A_2, $\alpha_2\delta_2$), or γ chains (Hb F, $\alpha_2\gamma_2$). Each of the different globin chains is controlled by distinct genes; two genes exist for the α and γ chains and one for each of the other chains. Their structure and the regions of the genes that control the production of the different globin chains have been determined (Steinberg and others 2001; Weatherall and Clegg 2001b).

Spectrum of Inherited Hemoglobin Disorders

Inherited hemoglobin disorders fall into two main groups: the structural hemoglobin variants and the thalassemias, which are caused by defective globin production. They all follow a recessive form of inheritance. Those with a single defective globin gene—carriers or heterozygotes—are symptomless. If two carriers marry, a one in four chance exists that each child they produce will receive defective genes from each parent—that is, they are homozygous for the particular disorder.

The structural variants result mostly from single amino acid substitutions in the α or β chains. Often these are innocuous, but in some cases they may alter the stability or functional properties of the hemoglobin and lead to a clinical disorder. They are designated by letters of the alphabet or by the place names where the condition was first discovered. Even though researchers have identified more than 700 structural hemoglobin variants, only three (Hb S, Hb C, and Hb E) are widespread.

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The homozygous state for the sickle cell gene results in sickle cell anemia, whereas the compound heterozygous state for the sickle cell and Hb C genes results in Hb SC disease. Hb SC disease, although milder, also has important public health implications. Hb E, the commonest variant globally, is innocuous in its heterozygous and homozygous states, but because it is synthesized less effectively than Hb A, it interacts with β thalassemia to produce an extremely common condition called Hb E β thalassemia, which is becoming an increasingly important health burden in many parts of Asia.

The thalassemias are classified according to the ineffectively synthesized globin chains. From a public health viewpoint, only the α and β thalassemias are sufficiently common to be important.

Clinical Features

The inherited hemoglobin disorders are characterized by an extremely diverse series of clinical syndromes of varying severity.

Sickle Cell Anemia and Related Disorders. The clinical features of sickle cell disorders reflect the red blood cells' propensity to assume a sickle shape in deoxygenated blood, leading to shortened red cell survival and a tendency to block small blood vessels (Bunn 1997; Serjeant 1992). Even though patients may adapt to their anemia, their illness is interspersed with acute episodes, including: attacks of bone pain; sequestration of blood into the lungs, liver, or spleen; or thrombosis of cerebral vessels, which may cause a stroke. They are extremely prone to infection, particularly during early childhood, and to a wide range of chronic complications. For reasons not yet understood, the severity of the disease varies extensively. Even in populations in eastern Saudi Arabia and parts of India, which have a high frequency of α thalassemia and an unusual ability to produce Hb F in adult life, both of which, when inherited with sickle cell disease, result in a milder form of the illness, morbidity is still high.

Although little is known about mortality from "sickling" disorders in developing countries, in Sub-Saharan Africa many children die early because of these conditions (Akinyanju 2001; Fleming and others 1979). Fleming and others, working in rural Nigeria, found that even though more than 2 percent of all newborns had sickle cell anemia, it was absent in the adolescent and adult populations. At the same time, they found that urban centers in Nigeria, where medical care was available, had an increasing number of affected adults, and by the late 1970s, a significant improvement in survival had clearly followed the introduction of antimalarial measures (Molineaux and others 1979). Both in Jamaica and in the United States, death appears to peak between one and three years of age, usually from infection. Recent U.S. data suggest that the median age of adult death is 42 for men and 48 for women (Dover and

Platt 1998). Even though Hb SC disease is milder than sickle cell anemia, it is associated with many complications, including a higher frequency of proliferative retinopathy.

Thalassemias. The homozygous or compound heterozygous states for β thalassemia also run a variable course, although without transfusion, death usually occurs in the first few years (Weatherall and Clegg 2001b). With adequate transfusions and the administration of drugs to remove iron, children may develop well and survive to adulthood. However, these drugs are expensive, and even when they are available in poorer countries, many children receive inadequate dosages and die in childhood or adolescence from iron overload. The situation is further complicated because the common β thalassemias of intermediate severity—notably Hb E β thalassemia—exhibit a clinical spectrum ranging from transfusion-dependent disease to a condition compatible with normal survival and growth into adult life without treatment.

The α thalassemias are equally heterogeneous. The extremely common milder forms (termed $α^+$ thalassemias because some α chains are produced) produce only a mild hypochromic anemia in homozygotes. In contrast, the $α^o$ thalassemias, so called because of the absence of α chain synthesis, result in stillbirth in their homozygous states following pregnancies with toxemic and postpartum complications. The compound heterozygous states for $α^+$ and $α^o$ thalassemias result in Hb H disease, which varies in severity and may be transfusion dependent.

The thalassemias are extremely heterogeneous at the molecular level: more than 200 different mutations of the β globin genes have been found, and the α thalassemias are almost as varied. Every severely affected population in the world has a few common mutations unique to a particular region, together with varying numbers of rare ones.

Population Genetics and Dynamics

The high gene frequencies for the hemoglobin disorders are attributable to the effects of natural selection. Although severely affected homozygotes would, in the absence of medical interventions, have died early in life, asymptomatic heterozygotes for Hb S, Hb C, and probably β thalassemia and Hb E, as well as those with mild forms of α thalassemia, are more resistant to severe malarial infection than normal persons. Hence, in environments in which malaria was common, carriers were protected and survived to have more children, and the gene frequencies rose until they were balanced by loss of severely affected homozygotes from the population. Although some decline in frequency among immigrant populations may occur because of lack of exposure to malaria and outbreeding, this decline will occur over many generations, and even if malaria were completely eradicated, an equally long time would pass before any significant fall occurred in the global frequency.
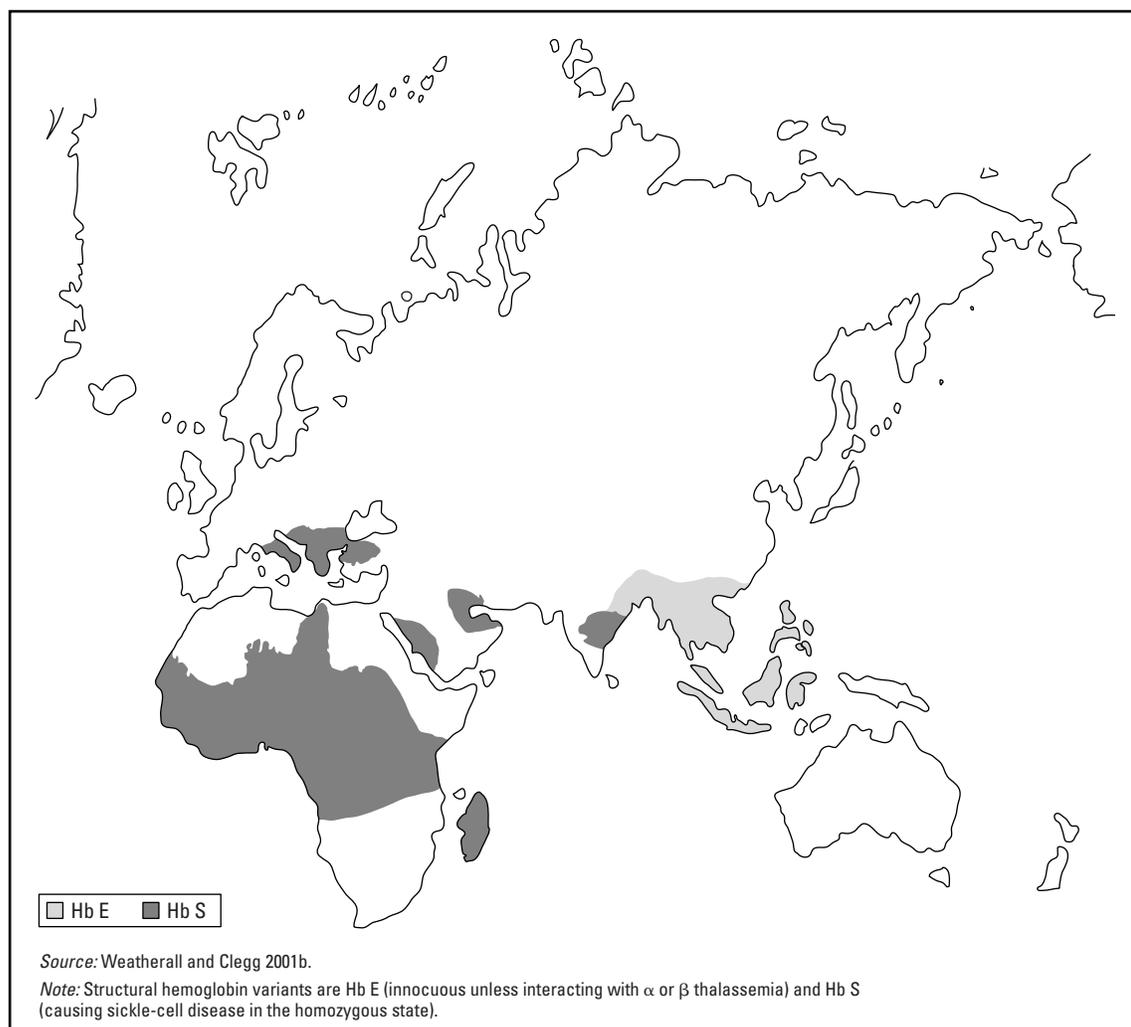
Changes resulting from variation in selection or in population dynamics will, however, be small compared with the effect of the demographic and epidemiological transitions that many countries have recently undergone. For example, thalassemia was not identified in Cyprus until 1944, when major improvements in public health revealed that the disease was common. By the early 1970s, estimates indicated that, in the absence of steps to control the disease, in about 40 years approximately 78,000 units of blood would be required each year to treat all the severely affected children, 40 percent of the population would be carriers, and the cost to the health system would equal or exceed the island's health budget (Weatherall and Clegg 2001b).

Global Distribution and Frequency of the Hemoglobinopathies

Figures 34.1a and 34.1b show the global distributions of the hemoglobinopathies. Table 34.1 shows approximate carrier frequencies by region.

The gene for Hb S is distributed throughout Sub-Saharan Africa, the Indian subcontinent, and the Middle East, where carrier frequencies range from 5 to 40 percent or more. Hb E is found in the eastern half of the Indian subcontinent and throughout Southeast Asia, where carrier rates may exceed 60 percent. Thalassemia is frequent in a broad band from the Mediterranean basin and parts of Africa, throughout the Middle East, the Indian subcontinent, Southeast Asia, and Melanesia and into the Pacific islands. The α^+ thalassemias occur right across the tropical zone, reaching extremely high frequencies in some populations, whereas the α^o thalassemias are restricted to parts of Southeast Asia and the Mediterranean basin (table 34.1).

Several World Health Organization (WHO) workshops have attempted to estimate the global burden of the thalassemias and important structural hemoglobin variants (Angastiniotis and Modell 1998; Weatherall and Clegg 2001b; WHO 1989, 1994). There are perhaps 270 million carriers and 300,000 to 500,000 annual births of infants with sickle cell

□ Hb E   ■ Hb S

Source: Weatherall and Clegg 2001b.

Note: Structural hemoglobin variants are Hb E (innocuous unless interacting with α or β thalassemia) and Hb S (causing sickle-cell disease in the homozygous state).

Figure 34.1a Global Distribution of Hemoglobinopathies Hb E and Hb S

Figure 34.1b Global Distribution of Hemoglobinopathies α and β Thalassemias

Table 34.1 Carrier Frequencies for Common Hemoglobin Disorders, by World Health Organization Region, 2001
*(percent)*

Region	Hb S	Hb C	Hb E	β thalassemia	α⁰ thalassemia	α⁺ thalassemia
Americas	1–20	0–10	0–20	0–3	0–5	0–40
Eastern Mediterranean	0–60	0–3	0–2	2–18	0–2	1–60
Europe	0–30	0–5	0–20	0–19	1–2	0–12
Southeast Asia	0–40	0	0–70	0–11	1–30	3–40
Sub-Saharan Africa	1–38	0–21	0	0–12	0	10–50
Western Pacific	0	0	0	0–13	0	2–60

Sources: Livingstone 1985; Weatherall and Clegg 2001a, 2001b.
Note: Many of these data are derived from small population samples.

anemia or serious forms of thalassemia. Southeast Asia, where the thalassemias and Hb E predominate, is most severely affected. Sub-Saharan Africa has the second-highest burden, reflecting the high incidence of Hb S. Weatherall and Clegg (2001b)

summarize information about the different thalassemia mutations in those regions.

These data only approximate the problems for health care services that the hemoglobin disorders will pose in the future.
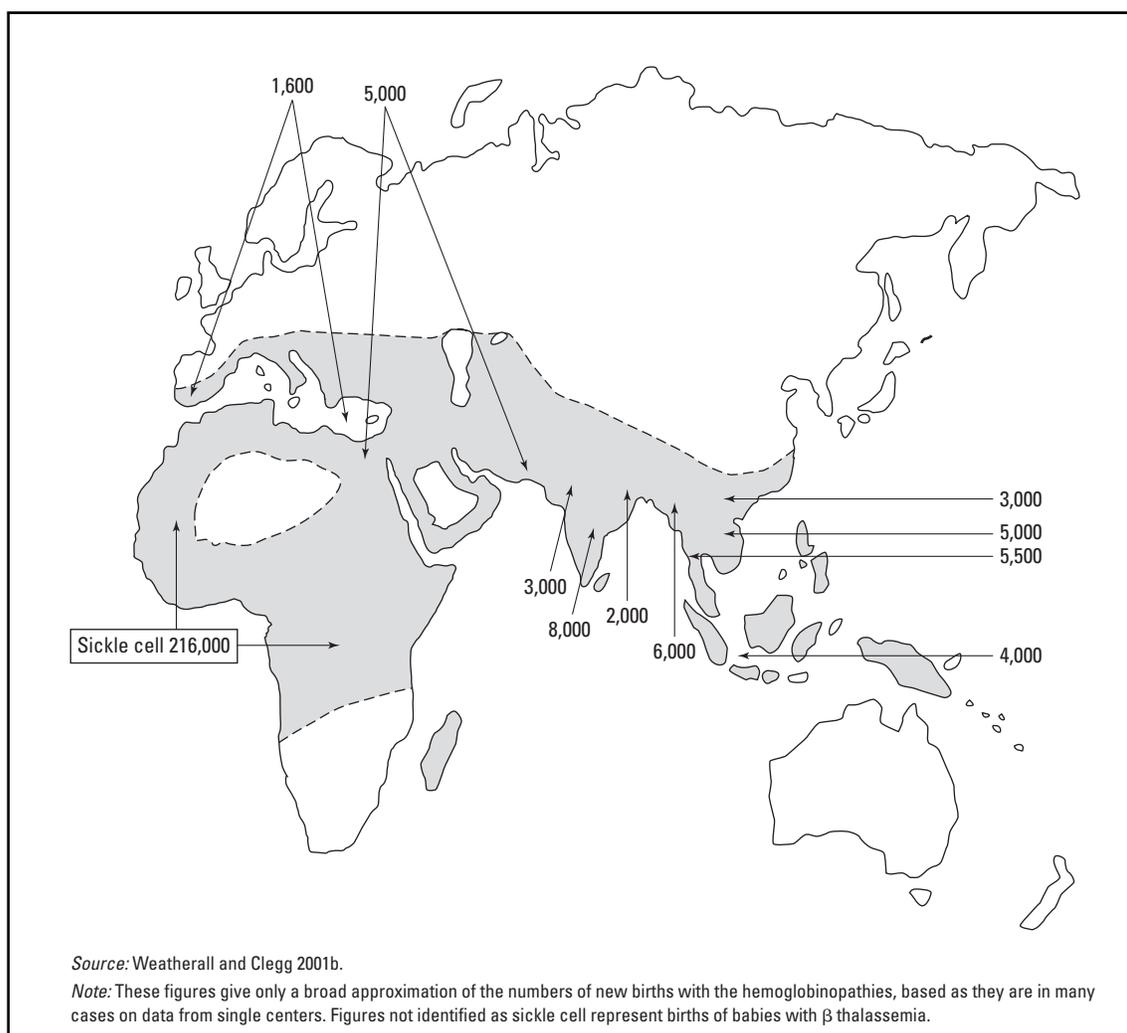
Figure 34.2 Approximate Annual Births of Babies with Sickle Cell Anemia and β Thalassemia

Unfortunately, few of the data are based on micromapping of incidence in different populations. Weatherall and Clegg's (2001b) review of studies in Indonesia, Sri Lanka, and Thailand reveals the extent of variability of incidence within relatively short geographic distances, suggesting that the number of annual births of babies with β thalassemia major or Hb E β thalassemia may be underestimated. Similarly, published data for the annual births of babies with sickle cell anemia in India and the Middle East are almost certainly too low, because estimates based on gene frequency suggest that the figure may be close to 100,000. The data in table 34.1 and figure 34.2, therefore, represent a minimal estimate of the future likely health burden resulting from inherited hemoglobin disorders. Furthermore, in many cases, the data are not based on projected increases in birth rates.

Because of these uncertainties, including how long countries will take to pass through the epidemiological transition, assessing the burden that the disorders will impose on health services is difficult. As more babies survive and present for treatment, the population on long-term therapy will steadily expand; the more effective the treatment, the greater the burden will be on health services. For example, from 2005 to 2025, an estimated 100,000 cases of Hb E β thalassemia will be added to the Thai population, and 20,000 β thalassemia homozygotes will be born each year in southern China (Weatherall and Clegg 2001b). If these children all survive to adulthood, they will account for a large proportion of health service expenditure.

BURDEN OF DISEASE

WHO disease burden estimates do not include the incidence or prevalence of the hemoglobin disorders, nor the deaths or disability-adjusted life year (DALY) losses from sickle cell disease

or thalassemia. Neither do they treat these disorders as risk factors for anemia, infection, stroke, and other conditions or estimate the prevalence (frequency) of the underlying genetic factors. Thus, the estimates provided here are necessarily incomplete and speculative.

For severe β thalassemia, figure 34.2 suggests 43,100 births per year, nearly all in low- and middle-income countries, where affected babies are likely to die before reaching two years of age. At least 41,500 deaths probably occur each year, or 0.3 percent of all deaths of children under five. This estimate may be too low, because it does not include the estimated 20,000 births per year in China. Thus, the severe β thalassemias probably account for 50,000 to 100,000 deaths per year, or 0.5 to 0.9 percent of all deaths of children under five in low- and middle-income countries. Each death accounts for 29.2 DALYs if it occurs before the child reaches the age of one. Taken together, all the deaths contribute 1.46 million to 2.92 million DALYs to the world burden.

Treated β thalassemia victims who survive to age 40 or older contribute much less to the disease burden because they are fewer and their residual disability weight is only 0.02 to 0.10 (chapter 15 provides an explanation of disability weights). Living with poorly treated thalassemia has a weight equal to or greater than 0.1. No global estimates of the number of treated survivors are available, but estimates indicate that 500,000 may exist in Thailand alone, of which perhaps 55,000 are transfusion dependent with severe disabilities. Their total DALY loss, including disability for those with milder Hb H disease, would be only some 15,000 per year, trivial relative to the DALYs resulting from premature mortality. Deaths by age 10 from homozygous β thalassemia or by age 30 from Hb E β thalassemia would add 53,600 DALYs in Thailand.

α^o thalassemia contributes to the burden of disease primarily through stillbirths or deaths shortly following birth and secondarily through mothers' disability during pregnancy. WHO does not count stillbirths, and no data on affected births are available except for an estimate of 1,250 per year in Thailand, which adds 37,242 DALYs. Assuming that mothers suffer a disability weight of 0.3 during the last trimester would add only 100 DALYs. Every 1,000 homozygous α^o thalassemia pregnancies contribute about 30,000 DALYs, but insufficient information is available on incidence elsewhere to use the Thai estimate to project global or regional levels.

For sickle cell disease, the burden is harder to estimate because of the higher survival rate and the disability during crises. Figure 34.2 shows an estimated 216,000 births per year in Africa alone, but reliable data on survival are not available. Early studies suggested a mortality rate greater than 80 percent by age five, but more recent estimates indicate that the figure is probably greater than 50 percent, with the improvement resulting from treatment and from control of the infections that cause most early sickle cell deaths. Mortality of 50 to 80 percent at ages one to five implies at least 21,600 to 34,500 deaths

per year and possibly as many as 173,000. These translate into 0.5 million to 4.5 million DALYs, accounting for less than 1 percent, but perhaps as much as 2 percent, of the burden for children under five. Life expectancies and the extent of disabilities among survivors in Africa are unknown, so the low DALY number is no doubt underestimated.

Outside Africa, Weatherall and Clegg (2001b) estimate 60,000 sickle cell births per year concentrated in India and the Middle East and among descendants of Africans in the Americas. The actual figure may be as high as 100,000. Without treatment, deaths peak in the first 2 years of life, and half of all deaths occur in the first 20 years. If 25 percent of sufferers die at age 1 and 25 percent at age 10, those deaths would contribute almost 14,000 DALYs for every 1,000 births in a low- or middle-income country. Including deaths after age 20 and disability might double the estimate.

Survival elsewhere is greater than in Africa, because of lower risks of infection and greater access to treatment. The United Kingdom has about 10,000 survivors (Davies and others 2000), and the United States has some 50,000 (Ashley-Koch, Yang, and Olney 2000). No good estimates are available of the numbers or age distribution of survivors in most of the rest of the world, but Hambleton's (2004b) cohort study in Jamaica shows how treatment increased survival: 70 percent of those enrolled starting in 1973 survived to age 20, as did 80 percent of those enrolled three to six years later.

Of 1,000 babies born with sickle cell disease, Jamaican clinic records and follow-up show how many would die at each age in each year, allowing an estimate of the burden from premature mortality (Hambleton 2004a). Table 34.2 presents those results: 560 deaths per year represent almost 14,000 DALYs. Deaths after age 50 contribute less because they are fewer, and life expectancy and DALYs per death decline with age. Thus, 18,000 to 22,000 DALYs per year for deaths at all ages is a reasonable estimate of the mortality burden from 1,000 sickle cell births per year at Jamaican levels of treatment coverage and effectiveness. Applied to the estimated 60,000 to 100,000 births per year outside Africa, this figure implies at least 1.08 to 2.20 million DALYs, or 0.1 percent of the total burden in low- and middle-income countries.

Three sources of disability also contribute to the burden: anemia without painful crises or other complications; disability from mild or severely painful crises; and other clinical events, both acute and chronic (for example, leg ulcers and retinopathy).

For the first source, the disability weight is assumed to average 0.04. This source adds a constant 0.04 DALYs for every year a sickle cell patient survives. The loss per year per 1,000 births in Jamaica is multiplied by 2.5 for deaths during each five-year interval (because deaths are assumed to occur at the midpoint of the interval) and by 5.0 for survivors, who suffer disability for the entire five years. This loss adds about 10 percent to the loss from premature mortality.

Table 34.2 Burden of Sickle Cell Disease by Age Group, Assuming 1,000 Births per Year and Survival to Various Ages, Jamaica, Starting in 1973

Category	Age group (years)										Total or average
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Number of survivors	876	834	807	777	727	680	627	564	491	440	682.3
Number of deaths	124	42	27	30	50	47	53	63	73	51	560
Death rate (percent/year)	2.61	0.98	0.66	0.75	1.32	1.33	1.61	2.10	2.73	2.17	1.63
Number of DALYs lost/death	28.90	28.59	27.77	26.84	25.82	24.69	23.43	22.00	20.39	18.58	24.70
Total DALY losses from deaths	3,584	1,201	750	805	1,291	1,161	1,242	1,386	1,488	948	13,856
Number of DALYs lost from background (chronic) anemia	188	171	164	158	150	141	130	119	106	93	1,420
Total DALYs lost from deaths and chronic anemia	3,772	1,372	914	963	1,441	1,302	1,372	1,505	1,594	1,041	15,276
Number of pain crises/year	242.7	381.0	383.8	584.4	866.7	600.5	523.6	473.4	309.6	182.2	4,548
Number of other acute clinical events	77.5	22.2		182.2							281.9
Number of other chronic clinical events	49.8	14.8	12.8	10.9							88.3

Source: Authors' calculations based on Hambleton 2004a, 2004b.

Note: The number of DALYs lost per death is calculated assuming all deaths occur at the midpoint of the age interval. Life expectancies by age are those for all low- and middle-income countries together. The number of pain crises is the total during one year for all the individuals in an age group. Those who die during the interval are assumed to die in equal numbers at the midpoint of each of the five years and, therefore, to suffer half as much disability from chronic anemia and half as many pain crises in that year as those of the same age who survive the year. Blanks in the table indicate that clinical events are rare in the corresponding age groups and their numbers are not well recorded. The totals of acute and chronic clinical events are therefore probably slight under-estimates.

For the second source of disability, even mild crises should be weighted considerably worse than background anemia, and severe crises requiring hospitalization should be weighted worse still: values of 0.2 and 0.5, respectively, are assumed. The number of crises and the share that are severe vary with age, with peak severity at ages 21 to 45 for a mean disability weight of 0.35. Because each crisis lasts only 7 to 10 days, or about 0.023 year, the loss per 1,000 births in each five-year age group never exceeds 10 DALYs and makes no difference to the total burden.

The third source of disability may carry disability weights of 0.135 for a leg ulcer, 0.276 for stroke survivors, 0.279 for acute chest syndrome, and 0.567 for retinopathy, but disability weights for a number of other conditions are unknown. Even if acute conditions last one month with an average disability weight of 0.5, they add less than 10 DALYs in any five-year interval. These conditions occur much less frequently than painful crises, but chronic ones may last much longer, contributing more or less to the burden than pain crises but adding little to mortality losses. Table 34.2 therefore includes only the estimated losses from background anemia and the frequencies, but not the DALY losses, of painful crises and other events that add negligibly to the burden.

CONTROL AND TREATMENT

With the exception of the few patients who can obtain a bone marrow transplant, no cure exists for the inherited disorders of hemoglobin. Even though research directed at their correction by means of somatic cell gene therapy is ongoing, this technology will probably not be generally applicable for some time, and when it is developed, it may be extremely expensive. Thus, for the moment, the major approaches to the control and management of these diseases are population screening, genetic counseling and prenatal diagnosis, and management of symptoms.

Prevention

Programs to reduce the number of seriously affected individuals follow two approaches. First, population screening and counseling programs can be established to educate populations about the risks of having children with similarly affected partners. Data about the effectiveness of this approach are extremely limited. In an early study in Greece, people's knowledge of their genetic makeup had no effect on marriage patterns (Stamatoyannopoulos 1973); however, a recent study in the Islamic Republic of Iran found that about 50 percent of affected couples decided to separate, and births with severe β thalassemia fell to about 30 percent of those expected (Samavat and Modell 2004). The reasons for this remarkable discrepancy require further investigation.

The second preventive approach also involves population screening or screening in prenatal clinics. If women are found to be carriers, their partners are screened, and following counseling they are offered a prenatal diagnosis and termination of

affected fetuses. This method has been used widely in the Mediterranean region and elsewhere, resulting in a major reduction in newborns with serious forms of thalassemia (Cao, Galanello, and Rosatelli 1998; Weatherall and Clegg 2001b). Prenatal diagnosis programs are available in China, India, the Islamic Republic of Iran, Lebanon, Pakistan, Singapore, Thailand, the United Arab Emirates, the United States, and many European countries; several other countries are establishing similar programs.

Because severe thalassemia is incompatible with survival without regular blood transfusions, prenatal diagnosis is a logical approach where acceptable until more definitive treatments become available. The situation with sickle cell anemia is different. First, it is not uniformly fatal in early life, and morbidity and mortality during this period can be controlled. Second, the clinical course of the condition is unpredictable: some patients' symptoms are relatively mild, whereas others develop life-threatening complications. Hence, even though some countries are practicing prenatal diagnosis, in others neither communities nor doctors consider that it should be applied widely. This complex issue would be clarified if the reasons for the phenotypic variability of the sickling disorders were better defined.

Whether or not screening programs are backed up with an offer of prenatal diagnosis, they require an intense period of education of the population about the nature of inherited hemoglobin disorders. This education requires input from many sectors of society, including the media, public health workers, local volunteer societies, and the medical community. Programs of this type require careful planning as well as availability of facilities for screening and counseling when the program is initiated. Their development also requires prior discussion between the government, health care workers, and members of the community—including religious leaders.

Treatment

The treatment of the hemoglobinopathies varies widely depending on the disease. The severe forms of β thalassemia require lifelong blood transfusions. The family of β thalassemia intermediate diseases ranges from transfusion-dependent forms to symptomless carrier traits. Hb E β thalassemia, the commonest hemoglobinopathy in Asia, varies in severity from forms that require regular or intermittent transfusions to milder anemia that does not require lifelong transfusions unless complications arise, particularly hypersplenism. Weatherall and Clegg's (2001b) review of studies in Asia indicates that the medical community does not always appreciate these subtleties and that many patients who receive regular transfusions might well have survived without transfusions had their early management been more effective.

Thus, those managing patients with severe forms of β thalassemia must make absolutely sure in infancy that regular transfusions are required. If so, babies and children require transfusion at monthly intervals using washed red cells rather than whole blood. In addition, blood must be screened for hepatitis B and C, for HIV, and—in some countries—for malaria. Because patients accumulate iron from transfusions, they also require lifelong treatment with a chelating agent, the most effective being desferrioxamine delivered subcutaneously overnight using a pump. Oral chelating agents, which would undoubtedly improve compliance, are available, but their efficacy and safety have yet to be verified. Some children with the major form of β thalassemia—and many with the intermediate varieties—will at some point require splenectomy, to be preceded by appropriate vaccinations and followed by prophylactic penicillin. They also require regular assessments of their iron status by measurements of serum ferritin or, better, by hepatic iron concentrations. Various complications occur, particularly for those not adequately transfused, including endocrine deficiencies, bone disease, and infection. Bloodborne infections, particularly hepatitis C and HIV/AIDS, are an increasing hazard. Most children with β thalassemia also require regular folate supplementation and vitamin C with their chelation therapy.

The serious forms of α thalassemia, α^o thalassemia, cause stillbirth late in pregnancy and several maternal complications. Although some infants have been given exchange transfusion or transfusion in the immediate neonatal period and survived, they have gone on to a transfusion-dependent life. Because of the increased risk of congenital malformations as a result of the disease—and particularly because of maternal complications—this course of action is not recommended, and this disease is an important indication for prenatal diagnosis. Those who inherit α^o thalassemia from one parent and α^+ thalassemia from the other have a moderately severe form called Hb H disease that is usually compatible with a life independent of transfusions except for periods of stress, such as infection. The α^+ thalassemias cause no clinical problems, either in their homozygous or heterozygous states.

Patients with sickle cell anemia are at high risk from infection early in life; therefore, diagnosis as early as possible is vital. Excellent evidence, at least in developed countries, indicates that prophylactic penicillin significantly reduces early morbidity and mortality.

Even though many children adapt well to their anemia, many eventually develop sickle cell crises (Ballas 1998). The most common form, the so-called painful crisis, is characterized by severe bone pain that often requires hospital admission and treatment with analgesics, oxygen, and infection control. More life-threatening crises, including stroke, marrow aplasia associated with viral illness, and pulmonary crises with severe hypoxia, require urgent hospital treatment. Regular Doppler testing of the cerebral blood flow can anticipate neurological complications that can be prevented by regular transfusions (Adams and others 1998), which can be continued indefinitely.

Because most aplastic crises result from human parvovirus infection, the development of a vaccine would be a great advantage. The other acute complication, splenic sequestration causing rapid enlargement of the spleen, is associated with profound anemia. It necessitates urgent hospital admission and blood transfusion, plus sometimes splenectomy. A variety of other complications require hospital treatment, including priapism, aseptic necrosis of the femoral or humoral heads, renal failure, and recurrent hematuria. At every age patients with sickling disorders seem to be more prone to infection that often requires hospital admission. In most sickling disorders, crises are more frequent and anemia worsens during pregnancy. A review of extensive clinical trials in the United States shows that the long-term administration of hydroxyurea reduces the frequency of crises and prolongs life in adult sufferers (Weatherall 2003).

Although milder, Hb SC disease is clinically important, particularly because of the relatively high incidence of ocular complications.

Requirements

Screening and diagnosis for the hemoglobin disorders requires relatively simple laboratory techniques combined with a well-organized program for their application in the community.

Screening and Carrier Detection. Unlike many genetic diseases, carrier screening for the main hemoglobin disorders is well established, accurate, and inexpensive. The initial screening for thalassemia usually measures the mean cell volume and the mean cell hemoglobin. Thresholds below which the likelihood of some form of thalassemia is great are well established. The diagnosis of β thalassemia is confirmed by finding a raised level of Hb A_2 using high-performance liquid chromatography (HPLC) or cheaper forms of chromatography or quantitative hemoglobin electrophoresis. Ideally, the initial blood count should use an electronic cell counter, and the Hb A_2 should be measured using HPLC. However, the equipment for HPLC analysis is expensive, and the cost per sample is approximately US\$2. For this reason, several more economical approaches have been developed (Fucharoen and others 2004). The initial screening can be done using a single-tube osmotic fragility test, which, even though it may result in a relatively high number of false positive results, usually gives fewer false negatives. Commercial kits for osmotic fragility testing have recently been produced, and at least one variety has been validated in Thailand. Further validation of this approach is required before it can be recommended. Various cheaper methods for measuring the Hb A_2 level are available.

When the red cell indices suggest thalassemia or an osmotic fragility test is positive but the Hb A_2 level is normal, it is vital to distinguish between iron deficiency and α thalassemia.

Several simple, cheap tests are available for diagnosing iron deficiency, but α thalassemia presents more of a problem. Screening tests will identify those heterozygous for α^o thalassemia or homozygous for α^+ thalassemia but will miss most cases of heterozygosity for α^+ thalassemia. However, given the restricted distribution of α^o thalassemia, these distinctions are clinically important only in areas where α^o thalassemia is common. Further diagnosis of the α thalassemias requires DNA analysis.

Several simple and cheap screening tests are available for sickling disorders, but all of them require confirmation of the genotype by hemoglobin electrophoresis. Neonatal screening requires electrophoresis because the solubility test, which is used widely for adult screening, is unreliable in the first months of life.

Throughout Asia, screening for Hb E is also necessary, either with a one-tube dye test or by hemoglobin electrophoresis. The Hb E trait is missed by measuring cell size or osmotic fragility.

Initial Diagnosis of More Severe Hemoglobinopathies. The initial diagnosis of β thalassemia is usually clinical. It can be confirmed by finding typical thalassemic changes of the peripheral blood, together with an elevated level of Hb F. A variety of cheap tests for measuring Hb F levels are available, or HPLC analysis can be used. Hemoglobin electrophoresis or HPLC is used to diagnose α^o thalassemia homozygotes and children with Hb H disease.

Sickle cell anemia, Hb SC disease, or combinations of the sickle cell gene with forms of β thalassemia can all be identified by hemoglobin electrophoresis and can be confirmed by a family study.

Further Analysis. More detailed confirmatory analysis, including identification of the underlying mutation, is required for the β thalassemias as a prerequisite for prenatal diagnosis. A variety of approaches to mutation analysis based on the polymerase chain reaction, which amplifies particular regions of DNA, are available, but because every population has a number of less common mutations, a central reference laboratory in each country must be able to sequence the β globin genes. Rapid DNA-based techniques for identifying the different deletion and nondeletion forms of α thalassemia are also available (Weatherall and Clegg 2001b).

Facilities and Organization. To provide an adequate laboratory service, each country with a high incidence of β thalassemia or sickle cell anemia (a carrier rate equal to or greater than 1 to 2 percent) requires at least one central reference laboratory to carry out accurate hemoglobin and DNA analyses. Peripheral hospital laboratories with expertise in screening tests and their quality control are also required.

General pediatricians, pediatricians with a special interest in blood diseases, or pediatricians or other clinicians who devote their entire time to the management of such diseases may care

for children with severe hemoglobin disorders. A problem arises for older patients, who must often change their doctors during adolescence. There is a serious dearth of physicians trained to care for older patients. Ideally, every country with a high incidence of inherited hemoglobin disorders should have centers specially designated for treating patients of all ages. Such centers require outpatient transfusion facilities, space for parents to wait while their children are being transfused, inpatient facilities, and access to basic laboratory diagnostic services. Centers involved in prenatal diagnosis require access to appropriate obstetric services. The advantage of specialist centers is continuity of care. Patients with chronic disease must have confidence in their medical advisers. Such confidence can be achieved only if they see the same staff over the entire course of their illness.

As concerns personnel, a WHO working group has recommended one doctor, three nurses, one laboratory technician, one counselor, and one administrative assistant for every 50 to 100 patients (WHO 1994). Overall, the workload is higher in centers for thalassemia than for sickle cell anemia, largely because of the lesser need for regular blood transfusions for those with the latter condition. However, sickle cell anemia is associated with more acute inpatient episodes per year.

The other major role of centers of this type is education, including training other clinicians, medical students, counselors, nurses, and others needed to provide information to local communities.

A number of publications describe treatment protocols to use in managing patients (Weatherall and Clegg 2001b; WHO 1985, 1987, 1989, 1994). Treatments include the following:

- *Blood transfusion.* Although regular transfusion is required most frequently for managing the thalassemias, it is increasingly being applied for the prophylaxis of serious complications of sickle cell anemia. Treatment centers need to cooperate closely with national blood transfusion programs. Washed or otherwise leukocyte-depleted blood should always be used. Blood has to be screened for hepatitis B, hepatitis C, HIV, and—in some populations—malarial parasites. Blood requirements for patients with thalassemia range from 500 to 1,500 liters per 100 patients per year, depending on their age distribution.
- *Iron chelation.* Transfusion-dependent thalassemic patients and patients with sickle cell anemia maintained on transfusion for prophylactic purposes require 30 to 50 milligrams per kilogram per day of desferrioxamine infused subcutaneously by pump. One pump is required per patient. Regular assessment of body iron and assessment for complications are essential.
- *Immunization and other prophylactic measures.* Every child with sickle cell anemia should receive oral prophylactic penicillin from the time of diagnosis. Some centers now

routinely immunize patients with polyvalent pneumococcal, meningococcal, and *Haemophilus influenzae* vaccines. However, the effectiveness of regimens of this type has not been clearly established even for splenectomized patients.
- *Splenectomy.* Each year, 2 to 3 percent of patients with severe β thalassemia require splenectomy. When patients who have received suboptimal treatment first receive standard treatment, the proportion needing splenectomy can be much higher—up to 30 percent in the first one or two years (WHO 1994). Because of the spleen's natural tendency to atrophy, splenectomy is required only in patients with sickle cell anemia who are having repeated splenic sequestration episodes or who develop hypersplenism.
- *Bone marrow transplantation.* Given the continuing improvement in results, bone marrow transplantation is now a realistic option for patients with severe forms of β thalassemia and sickle cell anemia who have histocompatible related donors and, in particular, are relatively free of complications, particularly chronic hepatitis and severe iron loading (Giardini 1997). Marrow transplantation requires specialized facilities and a trained staff, and the initial capital expenditure is high, but it should be considered wherever the serious hemoglobinopathies are a major problem if the alternative is lifetime treatment.
- *Prenatal diagnosis programs.* If prenatal diagnosis programs are part of an existing genetic and diagnosis service, fetal sampling will involve only marginal costs. If they must be set up from scratch, they require at least two obstetricians trained in fetal medicine, access to ultrasound, and a specialist nurse. Disposable or reusable sampling equipment is also required, together with suitable sterile facilities for amniocentesis, facilities for termination of pregnancy in the first or second trimesters, and access to experienced bereavement counselors. Access to a laboratory able to carry out mutation analysis is also required.
- *Other treatments.* Patients with hemoglobinopathies require folate supplements. Those infected with hepatitis C require treatment with antiviral agents. Those with endocrine damage caused by iron loading may require hormone replacement therapy.

In addition, centers for hemoglobin disorders require a trained counselor or clinical psychologist to handle both genetic and social issues. They should interact with local public health organizations to disseminate information about inherited hemoglobin diseases to schools and to the community at large. Many countries have parent support groups. The Thalassemia International Federation, an international body run largely by parents and lay members, provides advice and support for national parent associations and hemoglobinopathy programs.

COSTS AND EFFECTIVENESS OF DIAGNOSIS AND MANAGEMENT

Defining the full costs of treating patients with inherited disorders of hemoglobin is difficult, and comparing them between countries is even harder. The variables that confound such estimates include different health care systems, varying methods of obtaining donated blood, widely varying practices in screening blood for pathogens, and differing costs of drugs and equipment. WHO working parties and others have produced approximate data (Alwan and Modell 1997; WHO 1985, 1987, 1989, 1994).

Thalassemias

Information about the economic aspects of the thalassemias is sparse, including the costs and effectiveness of different interventions, three of which are discussed here: screening and counseling, treatment using transfusions and chelation, and cure by means of bone marrow transplant.

Screening and Counseling. Screening and counseling are cost-effective to the extent that they avert an affected birth or ensure early and adequate treatment of an affected child. Several studies, beginning with community screening programs in Montreal (Scriver and others 1984), have provided strong evidence that screening and prenatal diagnosis are highly effective in relation to control of the thalassemias. Alwan and Modell (1997), Davies and others (2000), and Modell and Kuliev (1991, 1993) provide detailed discussions of the issues involved, together with estimates of the costs of screening and counseling programs compared with the treatment of established disease, and even though the estimates are based mainly on studies in developed countries, the findings are probably more generally applicable.

The effectiveness of prenatal diagnosis programs can be quite high if more than 2 percent of the population is a carrier and the public education programs that precede their establishment are well designed. In Europe, 80 to 90 percent of counseled at-risk couples now request prenatal diagnosis, and a rapid reduction in affected births has been observed. The thalassemia birth rate fell almost 100 percent between the late 1970s and the late 1980s in Cyprus and Sardinia and about 80 percent in mainland Greece and Italy (Modell and Kuliev 1991). Between 1974 and 1986, such births fell by 40 percent in the United Kingdom (Modell and Kuliev 1991).

In terms of cost-effectiveness, terminating a pregnancy cannot be compared with improving the health of a child carried to term, but it is clearly cost saving compared with treatment. Modell and Kuliev (1991) estimate the cost of replacement (when a couple terminates an affected pregnancy and subsequently has a normal child) at only 30 percent of the annual cost of treatment, or 2 percent of the discounted lifetime cost. Similarly, Scriver and others (1984) estimate the costs of preventing an affected birth in Canada as less than annual treatment costs and about 4 percent of lifetime costs.

Treatment. Investigators have made several estimates of the costs of treating the β thalassemias. Approximate annual costs of care in Thailand in 2003 were as follows (authors' estimates updated from unpublished Thai sources):

- homozygous β thalassemia: US$19.84 million for patients in their first year of treatment and US$17.7 million per year for patients in subsequent years of treatment
- Hb E β thalassemia: US$100.3 million for patients in the first year of treatment and US$92.4 million for patients in subsequent years of treatment
- homozygous α^o thalassemia: US$727,000
- Hb H disease: US$7.49 million.

The life expectancy of a child in Thailand homozygous for β thalassemia is only 10 years, reflecting an inability to provide the bulk of patients with expensive chelating drugs. These costs are therefore not fully comparable to those from more developed countries, where better care means that children live longer. Han, Han, and Myint (1992) provide data for Myanmar that are comparable to those for Thailand.

Table 34.3 shows the annual costs for a program in Toronto that offers a high level of symptomatic care, and table 34.4 presents treatment costs for the eastern Mediterranean, taking into account the increasing expenditure required as children grow and require higher doses of maintenance drugs and more units of blood each year. Despite the difficulties of making comparisons, tables 34.3 and 34.4 indicate that the costs for managing β thalassemia in the eastern Mediterranean are roughly similar to those in Toronto, exclusive of transfusion, and are therefore probably reasonable estimates of the costs of managing thalassemias in developed countries.

Transfusion is required to keep a child with severe thalassemia alive beyond age one or two, but by itself prolongs life only to age 10 to 15. The gain is the added 9 to 14 years lived with disability weights of 0.1 to 0.5, implying 0.50 DALY gained for the last years and 0.75 to 0.90 per year earlier. Table 34.4 shows the costs of transfusion at ages 7 to 11, and figures in parentheses in the table show the costs at age 2 and for adults. Costs and health gains run parallel, so it makes little difference whether they are discounted when summed over an interval. Table 34.5 shows discounted total costs and DALYs gained for death at age 10 or 15 and using disability values of 0.1 and 0.25. For both ages, the cost per DALY is about US$2,000 for low disability and about US$3,000 for high disability for transfusion only.

Table 34.3 Annual Costs of Hemoglobinopathy per Outpatient, Excluding Transfusion, Toronto
(2001 US$)

Category	Thalassemia		Sickle cell disease	
	Chelated	**Nonchelated**	**Chelated**	**Nonchelated**
Clinic staff salaries	1,011.95	183.68	1,011.95	252.99
Clinic supplies	930.19	25.15	930.19	34.65
Medical and surgical outpatient unit	2,069.57	n.a.	2,069.57	n.a.
Consultations	92.58	88.39	92.58	11.94
Diagnostic tests	742.58	281.44	905.89	210.99
Laboratory costs	413.96	31.04	414.01	42.74
Laboratory costs (medical dayunit visits)	665.81	n.a.	665.81	n.a.
Total	5,926.64	609.70	6,090.00	553.31

Source: Estimated costs provided by Nancy Oliveri of the University of Toronto.
Note: n.a. = not applicable.

Table 34.4 Costs of Treatment of Thalassemia for One Patient Age 7 to 11, Eastern Mediterranean
(2001 US$)

Category	Minimum treatment		Full treatment	
Costs other than iron chelation				
Day transfusion: hotel and nursing	375		375	
12 transfusions/year	1,088	(600–1,575)	2,250	(1,390–3,150)
Investigations	135	(135–435)	278	(278–870)
Occasional costs (such as operations)	150		645	
Staff salaries	300		620	
Total if no desferrioxamine therapy	2,048	(1,560–2,835)	n.a.	n.a.
Desferrioxamine therapy (iron chelation)	3,080	(1,440–4,725)	6,165	(2,880–9,450)
Total with desferrioxamine therapy	5,128	(3,000–7,560)	10,333	(6,190–15,110)

Source: Alwan and Modell 1997.
Note: n.a. = not applicable. The figures in parentheses show the range of costs for a two-year-old and an adult; where no range is shown, the cost is independent of age. Both minimum and full treatment include transfusion and chelation. *Full treatment* means more frequent transfusion and consultations, more laboratory work, and more surgery.

A thalassemic patient can be kept alive beyond adolescence, possibly for a normal life span, if also chelated. This treatment means added annual costs of about US$3,000, or about US$6,000 (table 34.4) for full treatment, plus higher costs of transfusion and other components. Besides prolonging life, full treatment is assumed to reduce disability from 0.10 to 0.02 and from 0.25 to 0.10. Table 34.5 also shows discounted incremental costs, DALY gains, and cost per DALY of full treatment compared with those of minimal treatment. The incremental cost per DALY is high up to age 15 because of the modest gain compared with prolonging life with greater disability. From age 15, the cost drops because the child would otherwise die. If a life expectancy of 80 years is assumed, lifetime costs are some US$9,000 to US$11,000 per DALY at a disability weight of 0.1 and roughly US$10,000 to US$12,000 at a disability weight of 0.25.

Comparing full treatment to none, annual costs rise with age from US$6,190 to US$15,110 (table 34.4). As table 34.5 shows, up to age 15, 10.8 to 11.8 discounted DALYs are gained at a total cost of US$121,284 and a cost per DALY of approximately US$10,300 to US $11,200, comparable to lifetime incremental costs. Beyond age 15, the cost per DALY is some US$16,000 to US$17,000, and over the lifetime it is between US$13,000 and US$15,000. Because costs and gains run parallel—and also because of discounting—the lifetime cost per DALY is not sensitive to age at death of 45 or older, so differences in regional life expectancies do not matter.

These cost estimates come from the eastern Mediterranean. In Thailand, the first-year costs are much higher than the costs shown in table 34.5 and include the costs of delivering the child and protecting it from infection. Thereafter, the cost per year of treating the 6,250 survivors of each birth cohort

Table 34.5 Cost-Effectiveness of Treatment for Homozygous β and Transfusion-Dependent Hb E β Thalassemia

Category	Cost/patient (US$)	DALYs gained/patient		Cost/DALY (US$)	
		Disability weight = 0.1	Disability weight = 0.25	Disability weight = 0.1	Disability weight = 0.25
Minimal treatment, transfusion only					
Until death at age 10	17,368	6.96–7.60	6.00–6.39	2,285–2,495	2,718–2,896
Until death at age 15	23,840	10.25–10.81	7.52–7.87	2,206–2,325	3,029–3,170
Full treatment with chelation: incremental compared with minimal treatment					
Until age 15	60,467	1.03–3.80	0.55–2.03	15,912–58,706	29,787–109,940
Beyond age 15 to maximum age 80	132,901	17.25	16.35	7,704	8,129
Total lifetime	193,368	18.28–21.05	16.90–18.38	9,186–10,578	10,520–11,442
Full treatment with chelation: total compared with no treatment					
Until age 15	121,284	11.81	10.84	10,273	11,186
Beyond age 15 to maximum age 80	274,662	17.25	16.35	15,922	16,799
Total lifetime	395,946	29.06	27.19	13,625	14,578

Source: Authors' calculations. All costs and DALYs gained are discounted at 3 percent annually, starting at birth.
Note: Differences in DALYs gained for a given age range and disability weight depend on how rapidly health is assumed to deteriorate in the years immediately preceding death.

with transfusion alone (assuming they live only 10 years) drops, implying a cost per DALY of US$3,146 to US$3,776. Half the 97,500 people with Hb E β thalassemia are assumed to require treatment, leading to a cost per DALY of US$2,100 to US$2,500, consistent with costs in the eastern Mediterranean. For chelated patients in Toronto, the estimate of US$5,927 per year (table 34.3) implies a cost per DALY of US$6,600 to US$8,000, considerably less than in the eastern Mediterranean, but the costs do not include transfusion. Thus, data from three different regions on the cost-effectiveness of full therapy for victims of the common treatable forms of thalassemia are roughly comparable.

De Silva and others' (2000) study provides approximate costs for treating thalassemia in Sri Lanka. If we assume that a prevention program will probably not be developed in the near future, the data suggest that management of the disease will consume approximately 5 to 8 percent of the country's health budget based on 1999 figures. Those estimates have not been used to derive cost-effectiveness results.

Bone Marrow Transplantation. Angelucci and Lucarelli (2001) discuss the economic aspects of bone marrow transplantation. The 1991 cost was US$73,250, excluding follow-up but including the expense of setting up a program. This amount is almost certainly cost saving compared with lifelong transfusion and chelation, and it is also more cost-effective, given the reduction in disability from curing the disease.

Sickle Cell Disease

Extensive data on the costs of sickle cell anemia come from Davis, Moore, and Gergen's (1997) analysis in the United States. An estimated 75,000 hospitalizations of both children and adults occurred each year from 1989 through 1993. The average cost of hospitalization in 1996 was estimated at US$6,300, resulting in a total direct cost of US$575 million per year. In this and subsequent studies, the bulk of hospitalizations was confined to a subset of about 10 percent of the total patient population.

In the United States, specialized treatment centers provide a cost-saving approach to the care of sickle cell anemia. Patients enrolled in these centers used emergency rooms and inpatient units significantly less frequently than those cared for in the general hospital community, resulting in significantly lower health care costs (Nietert, Silverstein, and Abboud 2002; Yang and others 1995). Currently, only a small proportion of patients are treated in centers of this kind, even in developed countries. A pilot study in Benin found that the development of a comprehensive clinical care program reduced the frequency and severity of acute complications related to sickle cell anemia (Rahimy and others 2003). The annual cost per family using the program was US$40, and the annual cost for each hospitalization was US$100.

Neonatal Screening and Prophylaxis. Extensive controlled trials in several developed countries have demonstrated the

Table 34.6 Cost-Effectiveness of Penicillin Prophylaxis for Sickle Cell Disease Detected by Newborn Screening, Jamaica

Category	Monthly injection	Daily oral dose	Total/1,000 children
Monthly cost of penicillin (J$)	22	250	26,560
Nurse's time, 10 minutes/month (J$)	90	n.a.	88,200
Clinician's time, 20 minutes 4–6 times/year (J$)	152.67–229.00	152.67–229.00	152,670–229,000
Total year 1, 8 treatments (J$)	2,117–2,728	3,221–3,832	2,140,000–2,750,000
Total, each of years 2–4, 12 treatments (J$)	3,176–4,092	4,832–5,748	3,210,000–4,130,000
Discounted total (discount rate of 3 percent), first 4 years	11,101–14,303	16,889–20,091	11,220,000–14,420,000
Equivalent in U.S. dollars[a]			
US$1 = J$49.8	223–287	339–407	220,000–290,000
US$1 = J$59.8	186–239	282–336	190,000–240,000
Number of deaths averted by prophylaxis	0.024/child	0.024/child	24 deaths
Costs per death averted (US$)	7,750–11,958	11,750–16,958	7,830–12,058
Costs per DALY gained (US$)	267–412	405–585	270–416

Source: Authors' calculations based on data from Hambleton 2004a, 2004b.

Note: n.a. = not applicable. The results are based on a cohort study of 315 cases.

a. Two exchange rates are shown because the exchange rate changed during the course of the study.

life-saving effect of giving prophylactic penicillin from birth. A randomized trial suggested that this approach would save significantly more lives than starting prophylactic penicillin when an infant presents with symptoms of the disease. Without treatment, pneumococcal infection is the leading cause of death before age five. Penicillin by monthly injection or daily oral dose from about age four months to four years reduces bacteremia by 83 to 86 percent (D. Bonds, personal communication, September 28, 2004; Gill and others 1989, 1995; Panepinto and others 2000). Prophylaxis also reduces the case-fatality rate from infection from 27 to 18 percent.

Data from the United States show that neonatal screening for sickle cell disease followed by the use of appropriate prophylactic treatment prevents deaths (Tsevat and others 1991). With 16 percent of the U.S. population being African American, without screening and treatment 13 deaths would occur per million infants. Six of these deaths could be prevented by targeting only African Americans, and two more could be prevented by universal screening. Ignoring disability and discounting at 3 percent, we find that targeted screening costs US$6,709 per life year saved, or somewhat more per DALY. At more than US$30,000 per life year saved, universal screening would not be cost-effective compared with targeted testing (Panepinto and others 2000).

Data from a Jamaican cohort of 315 children with sickle cell disease allow for a similar cost-effectiveness analysis in a middle-income country (Hambleton 2004a, 2004b). They suggest that treatment averts seven to eight deaths, or that a newly diagnosed child's chances of dying before age four are reduced by 2.4 percentage points. Because bacteremia becomes less frequent with age, few cases occur—and little is known about the mortality risk—after childhood.

In the Jamaican cohort, up to 2 percent of children take prophylactic penicillin orally; the rest receive monthly injections requiring 10 minutes of a nurse's time. A clinician sees each child for 20 minutes four to six times a year. Table 34.6 shows the costs of personnel and penicillin. Other recurrent costs, such as those for syringes, will be low in comparison. No allowance is made for capital costs. The marginal cost of detecting sickle cell disease in newborns who have already been screened for other conditions such as phenylketonuria is only about US$3.30 (D. Bonds, personal communication, September 28, 2004). The cost of screening children who do not have sickle cell disease depends on prevalence and is not included in the estimates. It becomes unimportant as more of the population is at risk.

On average, preventing a death costs about US$8,000 to US$12,000 by means of injection and about US$5,000 more when oral penicillin is used. Because death would typically occur between one and two years of age, each death averted saves 29 DALYs and costs about US$270 to US$400 per DALY. Penicillin prophylaxis is probably more cost-effective than any other intervention. It is standard practice in Jamaica and the United States and can be recommended for middle-income countries where the prevalence is high enough—in the general population or in those of African origin—to justify screening.

Application to Other Countries. The limited data available indicate that specialized treatment centers and neonatal screening programs are effective approaches toward the control of sickle cell anemia. Although these conclusions should be valid for developing countries, many uncertainties remain. In particular, data on the causes of infection in infants with sickle cell disease in Africa are sparse. Because the spectrum of infection

may be different, the value of penicillin prophylaxis in Africa is unknown.

Laboratory diagnosis is well defined, is cheap, and does not differ depending on the level of available technology. The major uncertainty is whether the increasing indications for prophylactic transfusion in developed countries will be mirrored in other populations.

Other Treatments. As indicated in the discussion of the burden of disease, sickle cell patients suffer various clinical events for which treatment may be life saving, such as transfusion for aplastic crises. For painful crises, intervention (analgesics and possibly hospitalization) is only palliative. Because of the lack of information on costs and of consensus on the associated disabilities with and without treatment, we have not assessed the cost-effectiveness of any of these treatments.

OPTIONS FOR CONTROL AND MANAGEMENT OF INHERITED HEMOGLOBIN DISORDERS

Even though much more work is needed on both the scientific and the economic aspects of the hemoglobinopathies, certain issues are now clear. Until more definitive ways of treating them are available, reliable knowledge exists on how they can best be managed symptomatically. Furthermore, compelling evidence suggests that population screening programs combined with prenatal diagnosis can reduce the financial burden these increasingly common diseases impose on health services. Defining several options for their control and management is therefore possible. These are based, with some modifications, on Alwan and Modell (1997).

Severe β Thalassemias

This list provides most of the possible options for the control and management of β thalassemia in developing countries.

- *Option one:* best possible patient care, together with retrospective genetic counseling after the first affected child is diagnosed
- *Option two:* best possible patient care, together with retrospective genetic counseling and the option of prenatal diagnosis for subsequent pregnancies
- *Option three:* best possible patient care, together with retrospective genetic counseling and prospective (premarital) carrier screening and counseling, but no prenatal diagnosis
- *Option four:* best possible patient care with premarital, family-based, and population-based prospective carrier screening and genetic counseling, but no prenatal diagnosis
- *Option five:* best possible patient care, premarital and prenatal prospective carrier screening and genetic counseling, and the option of prenatal diagnosis

- *Option six:* based on option four or five but includes the availability of a bone marrow transplant program.

Options one and two, though still commonly practiced in many countries, offer little prospect of reducing the frequency of serious forms of thalassemia. Overall, that reduction is best achieved by option five, which combines maximum possibilities for reducing the frequency of severe disease with the best possible care for affected children. Although thalassemia births have fallen sharply in some developed countries, the effect of prenatal screening is likely to be lower for the large mainland populations of Asia if this policy is implemented, which is why this option includes best-practice treatment. Limited studies also suggest that families that undergo prenatal diagnosis tend to settle at the population norm for the number of children that they subsequently have and that their views on their ability to have unaffected children are extremely positive. For those countries or groups in which termination of pregnancy is unacceptable for religious or cultural reasons, option four is recommended. Option six, which is possible only in countries where bone marrow transplantation is available, should be exploited by any country with a high frequency of the disease, because it offers a potentially cost-effective approach to managing some proportion of affected children.

For the extremely heterogeneous intermediate forms of β thalassemia, notably Hb E β thalassemia, options three and four would probably be best, at least until a better understanding has been gained of the clinical heterogeneity of these thalassemias.

α Thalassemias

Few options are available for the α^o thalassemias. Homozygous babies with this condition are stillborn. However, because of the serious maternal complications of carrying these babies, this condition should be screened for prenatally, and affected babies should be identified by prenatal diagnosis with a view to terminating the pregnancy.

Hb H disease, the compound heterozygous state between α^+ and α^o thalassemia, is generally a relatively mild disorder that simply requires careful follow-up and treatment of complications. Although some have suggested that screening and prenatal diagnosis may be relevant for the more severe forms, more data are required to reach a conclusion.

Sickle Cell Disorders

These options for the management of the sickle cell disorders are directed particularly at the populations of developing countries, although, overall, they are relevant to most countries:

- *Option one:* best possible patient care with the use of prophylactic penicillin following diagnosis, together with retrospective genetic counseling

- *Option two:* best possible patient care, together with a neonatal screening program and the use of penicillin for all homozygous babies, together with retrospective screening and counseling
- *Option three:* best possible patient care, together with neonatal screening and the use of prophylactic penicillin from birth for homozygotes, together with population screening and prospective genetic counseling
- *Option four:* as for option three, plus the availability of prenatal diagnosis, bone marrow transplantation, or both.

Option three would be required to combine best management with the possibility of reducing the frequency of the disease, although whether this option would have any effect by altering the pattern of marriage is not clear. Whether prenatal screening of mothers would be valuable is also not clear: it would reduce the number of neonates who require screening, but because the cost of screening for sickle cell trait is so small, the issue is probably not important. Prenatal diagnosis can be developed (option four), but this option does not seem to be a high priority for sickling disorders in many developed countries, at least until more is known about the reasons for their phenotypic heterogeneity. By contrast, demand is greater in developing countries with limited facilities for the care of these patients. Some developed countries are beginning to immunize children with sickling disorders against infections with pneumococcus, *H. influenzae,* and meningococcus, but in developing countries, this treatment would add enormously to the burden of management programs. Clinical trials to test the efficacy of prophylactic penicillin with or without these vaccine regimens are urgently needed. Similarly, more information about the pathogens that cause early deaths in developing countries is required before the widespread use of prophylactic penicillin can be recommended.

Bone Marrow Transplantation

Experience in developed countries indicates that bone marrow transplantation may offer a cost-effective approach to managing a subset of patients with inherited disorders of hemoglobin (Borgna-Pignatti 1985). In developing countries, if this service is available at all, it is usually confined to the private sector or to those who can pay the fees teaching hospitals require. Given this context, defining the role of bone marrow transplantation in the global control of these diseases is difficult.

International and National Support Groups

Largely through the efforts of parents with affected children and clinicians who have taken an interest in the hemoglobin disorders, many countries have developed national thalassemia or sickle cell anemia societies that provide support for parents, workshops for doctors, and a variety of other important inputs.

In the case of thalassemia, the Thalassemia International Federation acts as an international coordinating body that helps countries develop workshops for training in diagnosis and treatment and organizes international meetings at which experts from different countries share their research and clinical experiences. In 1996, a group of doctors formed the Fédération des Associations de Lutte contre la Drépanocytose en Afrique (Federation of Associations to Control Sickle Cell Anemia in Africa). The membership has grown to 13 Sub-Saharan countries. The federation represents a major initiative in relation to regional training in both the diagnosis and the treatment of sickle cell disease in Sub-Saharan Africa. Unfortunately, it has been unable to raise sufficient funds to equip and run even a modest secretariat. Considering the success of the Thalassemia International Federation, particularly in countries with limited facilities for managing the hemoglobin disorders, the lack of support for this initiative in Africa is a clear indication of the importance of educating nongovernmental organizations and similar bodies about the increasing public health problems resulting from the inherited hemoglobin disorders.

Ethical and Social Issues

The various options for controlling and managing the hemoglobin disorders raise many ethical and social issues (see Weatherall and Clegg 2001b for more details). These issues arise most often in developing countries, where the level of education is often low and understanding of genetic diseases is limited. Serious genetic diseases such as thalassemia are associated with social problems such as patient stigmatization and broken marriages because one partner blames the other for the birth of an affected child. In countries where arranged marriages are still common, screening programs for heterozygotes may make it difficult for female carriers to find husbands. In addition, cultural and religious objections about interfering with nature arise when pregnancies are terminated because children have serious genetic diseases. At the same time, if governments perceive prenatal diagnosis and termination of pregnancy to be a highly cost-effective way of controlling these diseases, which they are, the danger arises that governments will pressure women to undergo these procedures. Therefore, before any programs are established, extensive discussions between governments, the medical profession, and the community about how to control these diseases are vital.

FURTHER RESEARCH

Despite the progress made toward understanding the molecular pathology, pathophysiology, and management of the inherited hemoglobin disorders, many gaps persist:

- First, much better data are required about their frequency and distribution in many developing countries.

- Second, more information is required about the reasons, both genetic and environmental, for the remarkable clinical heterogeneity of these conditions.
- Third, much better criteria are required for the management of the intermediate forms of thalassemia and of sickle cell anemia.
- Fourth, much more work is required on the role of the environment, a topic that has been badly neglected compared with research on the genetics of these conditions.
- Finally, further studies are required on better methods for their symptomatic management or a definitive cure.

One important approach toward progress in controlling these diseases is further development of North-South partnerships (WHO 2002). Arrangements of this kind have been extremely successful for thalassemia but have not evolved for sickle cell anemia research. In both cases such partnerships should evolve and lead to local South-South networks allowing individual countries to share their expertise about these increasingly important conditions.

Finally, a great deal more work needs to be carried out, particularly in developing countries, to investigate the economic aspects of these diseases, in terms of both their overall health burden and their control and management.

CONCLUSIONS

The inherited hemoglobin disorders are posing an increasing global health problem, killing thousands of children because of the inadequacy or unavailability of treatment. With appropriate therapy, many children can survive and have an excellent quality of life, despite requiring lifelong treatment. Even though the full economic burden of managing these disorders is currently unknown, in the case of thalassemia, screening and prenatal diagnosis are cost-effective means of prevention. Penicillin prophylaxis provides cost-effective protection from infection for babies with sickle cell disease and should be standard practice wherever it is affordable.

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REFERENCES

Adams, R. J., V. C. McKie, L. Hsu, B. Files, E. Vichinsky, C. Pegelow, and others. 1998. "Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on Transcranial Doppler Ultrasonography." *New England Journal of Medicine* 339 (1): 5–11.

Akinyanju, O. 2001. "Issues in the Management and Control of Sickle Cell Disorder." *Archives of Ibadan Medicine* 2 (2): 37–41.

Alwan, A., and B. Modell. 1997. *Community Control of Genetic and Congenital Disorders.* Eastern Mediterranean Region Office Technical Publication Series 24. Alexandria, VA: World Health Organization.

Angastiniotis, M., and B. Modell. 1998. "Global Epidemiology of Hemoglobin Disorders." *Annals of the New York Academy of Sciences* 850: 251–69.

Angelucci, E., and G. Lucarelli. 2001. "Bone Marrow Transplantation in Thalassemia." In *Disorders of Hemoglobin,* ed. M. H. Steinberg, B. G. Forget, D. R. Higgs, and R. L. Nagel, 1052–72. New York: Cambridge University Press.

Ashley-Koch, A., Q. Yang, and R. S. Olney. 2000. "Sickle Hemoglobin (HbS) Allele and Sickle Cell Disease: A HuGE Review." *American Journal of Epidemiology* 151 (9): 839–45.

Ballas, S. K. 1998. "Sickle Cell Disease: Clinical Management." *Clinical Haematology* 11 (1): 185–214.

Borgna-Pignatti, C. 1985. "Marrow Transplantation for Thalassemia." *Annual Review of Medicine* 36: 329–36.

Bunn, H. F. 1997. "Pathogenesis and Treatment of Sickle Cell Disease." *New England Journal of Medicine* 337 (11): 762–69.

Cao, A., R. Galanello, and M. C. Rosatelli. 1998. "Prenatal Diagnosis and Screening of the Haemoglobinopathies." *Clinical Haematology* 11 (1): 215–38.

Davies, S. C., E. Cronin, M. Gill, P. Greengross, M. Hickman, and C. Normand. 2000. "Screening for Sickle Cell Disease and Thalassaemia: A Systematic Review with Supplementary Research." *Health Technology Assessment* 4 (3): i–99.

Davis, H., R. M. Moore Jr., and P. J. Gergen. 1997. "Cost of Hospitalizations Associated with Sickle Cell Disease in the United States." *Public Health Report* 112 (1): 40–43.

De Silva, S., C. A. Fisher, A. Premawardhena, S. P. Lamabadusuriya, T. E. A. Peto, G. Perera, and others (Sri Lanka Thalassaemia Study Group). 2000. "Thalassaemia in Sri Lanka: Implications for the Future Health Burden of Asian Populations." *Lancet* 355 (9206): 786–91.

Dover, G. J., and O. S. Platt. 1998. "Sickle Cell Disease." In *Hematology in Infancy and Childhood,* ed. D. G. Nathan and S. H. Orkin, 762–801. Philadelphia: W. B. Saunders.

Fleming, A. F., J. Storey, L. Molineaux, E. A. Iroko, and E. D. Attai. 1979. "Abnormal Haemoglobins in the Sudan Savanna of Nigeria: I. Prevalence of Haemoglobins and Relationships between Sickle Cell Trait, Malaria, and Survival." *Annals of Tropical Medicine and Parasitology* 73 (2): 161–72.

Fucharoen, G., K. Sanchaisuriya, N. Sae-Ung, S. Dangwibul, and S. Fucharoen. 2004. "A Simplified Screening Strategy for Thalassaemia and Haemoglobin E in Rural Communities in South-East Asia." *Bulletin of the World Health Organization* 82 (5): 364–72.

Giardini, C. 1997. "Treatment of B-Thalassemia." *Current Opinion in Hematology* 4: 79–87.

Gill, F., A. Brown, D. Gallagher, S. Diamond, E. Goins, R. Grover, and others. 1989. "Newborn Experience in the Cooperative Study of Sickle Cell Disease." *Pediatrics* 83 (5, pt. 2): 827–29.

Gill, F., L. Sleeper, S. Weiner, A. Brown, R. Bellevue, R. Grover, and others. 1995. "Clinical Events in the First Decade in a Cohort of Infants with Sickle Cell Disease." *Blood* 86 (11): 776–83.

Hambleton, I. 2004a. "Lifetime Survival Estimates for People with SS Disease in Jamaica." Note prepared for the Disease Control Priorities Project, University of the West Indies, Mona, Jamaica.

———. 2004b. "Mortality among People with Homozygous Sickle Cell Disease in Jamaica." Note prepared for the Disease Control Priorities Project, University of the West Indies, Mona, Jamaica.

Han, A. M., K. E. Han, and T. T. Myint. 1992. "Thalassemia in the Outpatient Department of the Yangon Children's Hospital in Myanmar: Cost Analysis of the Day-Care-Room Services for Thalassemia." *Southeast Asian Journal of Tropical Medicine and Public Health* 23 (2): 273–77.

Livingstone, F. B. 1985. *Frequencies of Hemoglobin Variants: Thalassemia, the Glucose-6-Phosphate Dehydrogenase Variants, and Ovalocytosis in Human Populations.* Oxford, U.K.: Oxford University Press.

Modell, B., and A. M. Kuliev. 1991. "Services for Thalassaemia as a Model for Cost-Benefit Analysis of Genetics Services." *Journal of Inherited Metabolic Disorders* 14 (4): 640–51.

———. 1993. "A Scientific Basis for Cost-Benefit Analysis of Genetics Services." *Trends in Genetics* 9 (2): 46–52.

Molineaux, L., A. F. Fleming, R. Cornille-Brogger, I. Kagan, and J. Storey. 1979. "Abnormal Haemoglobins in the Sudan Savanna of Nigeria: III. Malaria, Immunoglobulins, and Antimalarial Antibodies in Sickle Cell Disease." *Annals of Tropical Medicine and Parasitology* 73 (4): 301–10.

Nietert, P. J., M. D. Silverstein, and M. R. Abboud. 2002. "Sickle Cell Anaemia: Epidemiology and Cost of Illness." *Pharmacoeconomics* 20 (12): 357–66.

Panepinto, J. A., D. Magid, M. J. Rewers, and P. A. Lane. 2000. "Universal versus Targeted Screening of Infants for Sickle Cell Disease: A Cost-Effectiveness Analysis." *Journal of Pediatrics* 136 (2): 201–8.

Rahimy, M. C., A. Gangbo, G. Ahouignan, R. Adjou, C. Deguenon, S. Goussanou, and E. Alihonou. 2003 "Effect of a Comprehensive Clinical Care Program on Disease Course in Severely Ill Children with Sickle Cell Anemia in a Sub-Saharan African Setting." *Blood* 102 (3): 834–38.

Samavat, A., and B. Modell. 2004. "Iranian National Thalassaemia Screening Programme." *British Medical Journal* 329 (7475): 1134–37.

Scriver, C. R., M. Bardanis, L. Cartier, C. L. Clow, G. A. Lancaster, and J. T. Ostrowsky. 1984. "Beta-Thalassemia Disease Prevention: Genetic Medicine Applied." *American Journal of Human Genetics* 36 (5): 1024–38.

Serjeant, G. R. 1992. *Sickle Cell Disease.* Oxford, U.K.: Oxford University Press.

Stamatoyannopoulos, G. 1973. "Problems of Screening and Counseling in the Hemoglobinopathies." In *Fourth International Congress on Birth Defects,* ed. A. G. Motulsky and W. Lenz, 268–76. Amsterdam: Excerpta Medica.

Steinberg, M. H., B. G. Forget, D. R. Higgs, and R. L. Nagel, eds. 2001. *Disorders of Hemoglobin.* New York: Cambridge University Press.

Tsevat, J., J. B. Wong, S. G. Pauker, and M. H. Steinberg. 1991. "Neonatal Screening for Sickle Cell Disease: A Cost-Effectiveness Analysis." *Journal of Pediatrics* 118 (4, pt. 1): 546–54.

Weatherall, D. J. 2003. "Pharmacological Treatment of Monogenic Disease." *Pharmacogenomics Journal* 3 (5): 264–66.

Weatherall, D. J., and J. B. Clegg. 2001a. "Inherited Haemoglobin Disorders: An Increasing Global Health Problem." *Bulletin of the World Health Organization* 79 (8): 704–12.

———. 2001b. *The Thalassaemia Syndromes.* 4th ed. Oxford, U.K.: Blackwell Science.

WHO (World Health Organization). 1985. *Report of the Third and Fourth Annual Meeting of the WHO Working Group for the Community Control of Hereditary Anaemias.* HMG/WG/85.8. Geneva: WHO.

———. 1987. *Report of the Fifth WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes, Heraklion, Crete, 24–25 October 1987.* WHO/HDP/WG/HA/89.2. Geneva: WHO.

———. 1989. *Report of the Fifth WHO Working Group on the Feasibility Study on Hereditary Disease Community Control Programmes (Hereditary Anaemias) Cagliari, Sardinia.* WHO/HDP/WG/HA/89.2. Geneva: WHO.

———. 1994. *Guidelines for the Control of Haemoglobin Disorders. Report of the Sixth Annual Meeting of the WHO Working Group on Haemoglobinopathies, Cagliari, Sardinia, 8–9 April 1989.* Geneva: WHO.

———. 2002. *Genomics and World Health.* Geneva: Advisory Committee on Health Research, WHO.

Yang, Y. M., A. K. Shah, M. Watson, and V. N. Mankad. 1995. "Comparison of Costs to the Health Sector of Comprehensive and Episodic Health Care for Sickle Cell Disease Patients." *Public Health Report* 110 (1): 80–86.