22.6.3 Anaemia as a challenge to world health 5366

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section 22 Haematological disorders 5366 patient depends mainly on the severity of the anaemia and its cause. For example, a young patient with a haemoglobin level of 50 g/litre who is shown to have an active duodenal ulcer should probably be transfused because they would be at severe risk from a further brisk bleed from the ulcer. On the other hand, a patient of similar age with a similar haemoglobin level due to chronic nutritional iron defi- ciency might well be allowed to restore their haemoglobin level by oral iron therapy. Occasionally, patients present in gross congestive cardiac failure with profound anaemia. This picture is usually seen in elderly pa- tients with long-standing pernicious anaemia or iron deficiency. This type of condition still carries a high mortality and requires urgent treatment. Such profoundly anaemic patients require trans- fusing up to a safe level, that is, a haemoglobin value of 60 to 80 g/ litre. This can usually be achieved by the slow transfusion of one or maybe two units of packed red cells. A very careful check on the neck veins and lung bases should be made throughout the period of transfusion. Ideally, a central venous pressure line should be in- serted before the transfusion is started. FURTHER READING Koury MJ (2005). Erythropoietin: the story of hypoxia and a finely regulated hematopoietic hormone. Exp Hematol, 33, 1263–70. O’Donnell A, et al. (2007). Age-related changes in adaptation to severe anemia in childhood in developing countries. Proc Natl Acad Sci U S A, 104, 9440–4. Prchal JT (2010). Clinical manifestations and classification of erythro- cyte disorders. In: Kaushanasky K,

et al. (eds) Williams' hematology, 8th edition, pp. 455–62. McGraw-Hill Medical, New York. 22.6.3 Anaemia as a challenge to world health David J. Roberts and David J. Weatherall† ESSENTIALS Anaemia is a very common problem in low- and middle-income countries (LMICs): 27% of the world's population or 1.93 billion people are affected by anaemia (2013) and more than 90% of people with anaemia live in the developing world. Preschool children and women of reproductive age are particularly affected by anaemia and more 60% of anaemia is caused by iron deficiency. Causes of anaemia in LMICs—this is often multifactorial, with causes including (1) nutritional deficiencies—iron, folate, vitamin B12; (2) chronic infection—including malaria, tuberculosis, AIDS; (3) blood loss—hookworm, schistosomiasis; (4) protein–energy malnutrition; (5) malabsorption—for example, tropical sprue; (6) hereditary—for example, thalassaemias, haemoglobin variants, glucose-6-phosphate dehydrogenase deficiency. A series of vicious cycles exist in LMICs—maternal anaemia due to iron or folate deficiency and chronic malaria is associated with the birth of underweight infants who frequently have low iron stores, may also be folate deplete, and are usually anaemic from about 6 months of age. Such infants are prone to infection, particularly gastrointes- tinal, and may be further depleted of iron or folate by inappropriately prolonged breastfeeding or weaning onto an inadequate diet. They are exposed to hookworm infection as soon as they start to crawl, malaria becomes an important problem after 6 months, and in many populations the increasingly common haemoglobinopathies are a further cause of anaemia after the first few months of life. Introduction Despite improvements in nutrition and hygiene, which have re- duced childhood mortality in many low- and middle-income coun- tries (LMICs), anaemia continues to be an important problem in the health of the world's population. It is not, of course, a disease in its own right but simply a by-product of a wide variety of different dis- orders, most of which are described in detail elsewhere. However, because of its importance as a source of chronic ill health in many populations, the global aspects of the aetiology and manifestations of anaemia are summarized briefly in this chapter. Readers who wish to learn more of the complex literature on this important topic are referred to the extensive reviews cited at the end of the chapter. Definition and prevalence It has been very difficult to produce an adequate definition of anaemia. 'Normal' haematological values vary with age, between sexes, at dif- ferent altitudes, and, possibly, between races. On the other hand, it is helpful to have a standard set of haemoglobin levels at different ages below which 'anaemia' is defined. The World Health Organization (WHO) has attempted to set out criteria of these types, summarized in Table 22.6.3.1. Despite their many shortcomings, including meth- odological vagaries, they at least provide a way of obtaining an ap- proximate comparison of the distribution and frequency of anaemia among the different countries of the world and still remain valid. The global prevalence of anaemia was first estimated in the 1980s. A review of the epidemiological data available at this time sug- gested that about 1.3 billion people were affected by anaemia, par- ticularly in LMICs. Infants, young children, menstruating women, Table 22.6.3.1 Definition of haemoglobin levels below which anaemia is said to exist in populations at sea level (WHO 1968) Haemoglobin (g/litre) below Children, 6 months–6 years 110 Children, 6–14 years 120 Adult males 130 Adult females (nonpregnant) 120 Adult females (pregnant) 110 † It is with great regret that we report that David J. Weatherall died on 8 December, 2018.

22.6.3 Anaemia as a challenge to world health 5367 and, especially, pregnant women were the most severely affected groups (Table 22.6.3.2). More recent estimations suggest that al- though the prevalence of anaemia has declined, nearly 2 billion people worldwide are affected by anaemia. Using publicly available data, Kassenbaum and colleagues estimated mild, moderate, and severe

anaemia from 1990 to 2010 for over 180 countries, by sex and well-defined age groups and attributed the cause of anaemia using data from the Global Burden of Diseases, Injuries and Risk Factors (GBD) 2010 Study. Global anaemia prevalence in 2010 was 32.9%, causing 70 mil- lion years lived with disability (YLDs), which amounted to just under 10% of health loss for all conditions. The prevalence of an- aemia declined for both sexes from 1990 to 2010, particularly for males. Anaemia is most common in South Asia and sub-Saharan Africa, while the greatest reduction in the burden of anaemia over this period was in Asia. Iron deficiency anaemia was the top cause globally but over 15 diseases were considered to contribute to an- aemia and such a survey could not describe the multifactorial nature of anaemia in individuals. About one-fifth of perinatal mortality and one-tenth of maternal mortality in LMICs are attributable to iron deficiency. In total, 0.8 million deaths worldwide are now attribut- able to iron deficiency, that is, about 1.3% of all male deaths and 1.8% of all female deaths. These global surveys also highlight the more complex aetiology of anaemia in older age groups. Gynaecological causes, led by uterine fibroids, are important causes of anaemia in females from menarche to menopause in all settings. Chronic kidney disease and gastro- intestinal disorders increase sharply in older individuals to become the most important causes of anaemia in many areas. The complex and multiple aetiology of anaemia in low- and middle-income countries The main causes of anaemia in LMICs are summarized in Box 22.6.3.1. It is very difficult to determine their relative import- ance, particularly in LMICs. Most surveys have focused on one particular mechanism (e.g. iron or folate deficiency). To obtain a true picture of the cause of anaemia in a particular population it is essential to obtain consecutive data over a long period. For ex- ample, work in the Gambia has shown that the haemoglobin levels in children vary significantly at different times of the year; anaemia is much more common in the wet season when malaria transmis- sion is at its highest. To complicate matters, this is also the time when diarrhoea and malnutrition are most common. Heavy rains after many dry months have profound effects on the community; sanitation measures are disrupted and food stores are at the lowest level in the annual cycle (Fig. 22.6.3.1). These observations underline the multifactorial aetiology of an- aemia across the world. Nonetheless, it is clear that iron deficiency, which probably affects at least 15% of the world’s population, is the most important factor; the many other diseases that can exacer- bate anaemia are often operating on a background of low body iron stores. Table 22.6.3.2 Estimated prevalence of anaemia by region and sex Region Percentage anaemic Children Women 15–49 years Men 0–4 years 5–12 years Pregnant All 15–59 years LMICs 51 46 59 47 26 HICs 12 7 14 11 3 World 43 37 51 35 18 LMICs, low- and middle-income countries; HICs, high-income countries.

Data from DeMaeyer EM, Adiels-Tegman M (1985). The prevalence of anemia in the world. World Health Statist Quart, 38, 302–16. Box 22.6.3.1 Important causes of anaemia in LMICs Acquired • Nutritional:

— Iron, folate, vitamin B12 • Chronic infection:

— Malaria, leishmaniasis, schistosomiasis, tuberculosis, HIV • Blood loss:

— Hookworm

— Schistosomiasis • Protein–energy malnutrition • Malabsorption:

— Tropical sprue and related disorders Hereditary • Thalassaemias • Haemoglobin variants • Glucose-6-phosphate dehydrogenase deficiency • Ovalocytosis Number of cases 120 100 80 60 40 20 0 Rains Severe anaemia Malnutrition Gastroenteritis Jan Apr Jul Oct Rains Rains Jan Apr Jul Oct Jan Apr Jul Oct 1990 1989 1988 Fig. 22.6.3.1 Admissions to the children's ward in a hospital in the Gambia over dry and rainy seasons. Data from Brewster DR, Greenwood BM (1993). Season variation of paediatric disease in The Gambia, West Africa. Ann Trop Paediatr, 13, 133.

section 22 Haematological disorders 5368 Iron deficiency The causes of iron deficiency anaemia are extremely complex and vary widely among different populations (see Chapter 22.6.4). The absorption of nonhaem iron, except from breast milk, is compara- tively restricted, and the content of iron in breast milk is very low. Iron deficiency is particularly common in communities in which food is predominantly of vegetable origin. The three great staples in these populations are rice, wheat, and maize. Sorghum and millet are also important in parts of Africa and Asia. Soy and similar leg- umes are an important source of protein in many countries. The iron content of these diets is generally low, and, furthermore, absorption is inhibited by fibre, phytates, phosphates, and polyphenols, all of which occur in high levels in vegetarian diets. Populations who have remained as hunter-gatherers, and pastoralists who eat meat, appear to have a lower frequency of iron deficiency anaemia. The body's response to infection may also reduce iron stores and iron utilization. Hepcidin is regulated by proinflammatory medi- ators, such as tumour necrosis factor and interleukin-6, which are elevated in a wide variety of infections. High hepcidin levels stimu- lated by malaria infection or bacterial infections reduce absorption of iron from the gut and also reduce incorporation of iron into red cells. Iron may act as a growth factor for malaria parasites, and so raised hepcidin and reduction in available iron may form part of a protective innate response to malaria infection. However, this pro- tective response may contribute to functional iron deficiency and anaemia in endemic areas. Against this background of deficient or borderline dietary iron intake, there are several other factors which may exacerbate iron deficiency. Iron requirements are greatly increased during preg- nancy because of the expansion of the maternal red cell mass (c.500 mg), iron transport to the fetus (c.300 mg), and the consti- tution of the placenta (c.25 mg), together with any blood loss at birth. Although there is some compensation by the cessation of iron loss due to menstruation (c.200 mg), the total requirements for a single pregnancy are more than 1 g. Iron is also excreted in breast milk and although the concentration is low, this loss, par- ticularly with prolonged breastfeeding, places a further burden on maternal iron stores. In many tropical countries, there are important sources of patho- logical iron loss due to parasitic infection. Hookworm infestation affects millions of people worldwide. These parasites attach them- selves to the mucosa of the intestinal tract. With a worm load of 1000 eggs/g faeces, the intestinal blood loss averages about 2.5 ml/ day, representing 1 mg of iron. Although some of this is reabsorbed, perhaps up to 40%, hookworm infestation is an important source of iron imbalance. Infection with Schistosoma mansoni results in intes- tinal blood loss, while S. haematobium results in chronic haematuria. In Kenyan children, for example, mean iron losses in those infected with S. haematobium varied from 149 to 652 µg/day, according to the magnitude of the egg counts. Finally, it should be remembered that chronic ill health due to protein–calorie malnutrition or chronic infection may, by its effect on a patient's appetite, result in further depletion of iron intake. It must be emphasized that many surveys for assessing body iron stores have used methods which are confounded by associated in- flammatory disease or other disorders. These problems are particu- larly germane to surveys which have been based on serum iron or ferritin levels. More recently, screening methods based on estima- tion of transferrin receptor

levels and/or hepcidin have been devel- oped but their application to large populations is, as yet, limited. Folate deficiency Folate deficiency is thought to be the second most frequent cause of nutritional anaemia in the world's population. The mechanisms are complex and differ widely between different populations depending in the way in which food is prepared, in particular the temperature at which it is cooked. It is also clear that dietary folate deficiency is not the whole story. Research in Africa suggests that the continuous anorexia which accompanies recurrent infections such as malaria or tuberculosis is a major cause of folate deficiency in children. Postinfective malabsorption and the tropical sprue syndrome are also important causes of folate deficiency, particularly in the Indian subcontinent. Folate requirements may be increased in patients with erythroid hyperplasia secondary to chronic haemolytic anaemia (e.g. sickle cell anaemia, or chronic malarial infection). They also increase markedly during pregnancy. In women with low baseline folate stores, megaloblastic anaemia in pregnancy or the puerperium is particularly common. Vitamin B12 deficiency Nutritional vitamin B12 deficiency is uncommon, although it is observed in true vegans, particularly in the Indian subcontinent. Infants born of mothers with sprue or postinfective malabsorption who are fed on breast milk or goat's milk containing insufficient vitamin B12 may develop megaloblastic anaemia with locomotor complications during the early months of life. Infection Almost any chronic infection may produce anaemia. Globally, the most important are the parasitic disorders, malaria, visceral leishmaniasis (kala-azar), schistosomiasis, and some forms of trypanosomiasis. Malaria is still the most important parasitic illness of humans. Currently it is estimated that it has a global incidence of about 200 million cases per year, with over 450 000 deaths. Its trans- mission and clinical manifestations are considered in Chapter 8.8.2. Profound anaemia is a major cause of mortality and mor- bidity during acute attacks of Plasmodium falciparum malaria in nonimmune individuals, but, from the perspective of health in LMICs, chronic infection with this organism in childhood is an extremely common cause of anaemia. This is most com- monly seen in areas of high malarial transmission and is also a growing problem in regions of lower transmission because the rise in antimalarial drug resistance prolongs the average duration of infection. The anaemia of chronic malaria has a complex basis involving haemolysis, hypersplenism, and a suboptimal bone marrow response, often set against a background of iron or folate deficiency. In some populations, notably those of Africa, India, and parts of South-East Asia, chronic malarial infection may be complicated by the hyper-reactive malarial splenomegaly syn- drome, in which hypersplenism plays a major role in the gener- ation of chronic anaemia. The haematological manifestations of the other common parasitic illnesses in the tropics are considered elsewhere in this text.

22.6.3 Anaemia as a challenge to world health 5369 Malabsorption Many people in tropical climates, both indigenous populations and expatriates who have worked in rural areas, have abnormalities of the intestinal mucosa, often associated with impairment of absorp- tion. These structural and functional alterations of the gut have been called 'tropical enteropathies' (see Chapter 15.10.8). It is likely that they result from adaptation to life in the contaminated environment of the tropics, with frequent gastrointestinal infections and differ- ences of diet. More severe malabsorption syndromes, called sprue and postinfective malabsorption, are associated with chronic diarrhoea, wasting, and a variable degree of anaemia. The pathophysiology and world distribution of these syndromes are considered in Section 15. They are nearly all associated with anaemia, which has a com- plex aetiology including folate deficiency and, in some cases, iron deficiency. It should also be remembered that in a tropical setting malabsorp- tion can also result from colonization of the small bowel by specific parasites, including Giardia lamblia, Strongyloides

stercoralis, crypto- sporidium, and others. Abdominal tuberculosis with malabsorption is also common. In Africa, HIV infection is now an important cause of malabsorption and bone marrow suppression. Inherited anaemias The inherited haemoglobin disorders are becoming an increasingly common cause of anaemia, particularly in LMICs countries. They are described in detail in Chapter 22.6.7. Due to heterozygote advantage against P. falciparum malaria, the important inherited haemoglobin disorders, notably sickle cell anaemia and the thalassaemias, have a high frequency throughout tropical populations of Africa and Asia (Table 22.6.3.3). Sickle cell anaemia and its variants are particularly common in Africa, some Mediterranean populations, and throughout the Middle East and parts of India. They also occur at a high frequency in the Caribbean and in other regions with large African populations. The thalassaemias occur at a high frequency in parts of Africa, the Mediterranean, the Middle East, the Indian subcontinent, and throughout South-East Asia. There is now clear evidence that these conditions will produce a major public health problem in these countries in the future. Children with sickle cell anaemia are highly susceptible to systemic bacterial infection and without neonatal screening for this disease and delivery of vaccination, prophylaxis, and good medical care, up to half of children born with HbSS may die within the first 3 years of life. As poorer countries go through the demographic transition, resulting from better hygiene and con- trol of infectious illness, infants with these genetic anaemias are now surviving long enough to present for diagnosis and treatment. The relatively high frequency of consanguineous marriages in many LMICs also plays an important role in maintaining the frequency of these recessively inherited diseases. The effect that a high frequency of a disease such as thalassaemia can have on the health economy of an emerging country was shown graphically in the case of Cyprus after it passed through the demo- graphic transition in the 1950s. It was estimated that if every patient with this disease was treated with regular blood transfusion and ap- propriate medication, within 15 years the management of this one condition would consume up to 40% of the island's health budget. Recent studies in Indonesia indicate that, at a minimum estimate, approximately 1.25 million units of blood will be required each year to treat a proportion of the thalassaemic population in future years. In many populations, there are hundreds of thousands of car- riers for β-thalassaemia or the more common severe forms of α-thalassaemia. Although they are asymptomatic they have haemoglobin values which are, on average, 10 to 15 g/litre below normal. During pregnancy, they retain this difference so that in the midtrimester they have haemoglobin values of approximately 80 g/ litre or less. They have increased folate requirements and, in some populations, there appears to be an increased frequency of folate de- ficiency in pregnancy. It should be remembered that the inherited anaemias may be ex- acerbated by other illnesses which are widespread in tropical coun- tries. Folate requirements are increased in all these conditions and secondary folate deficiency is extremely common. They may also be exacerbated by malaria; children may develop malarial infec- tion from infected blood donors. There is also a high frequency of other blood-borne infections, particularly hepatitis C and, in some populations, HIV. Furthermore, there is clear evidence that sickle cell anaemia and thalassaemia can render children more prone to infection. In short, like all forms of anaemia in the tropical world, the inherited disorders of haemoglobin may present with a complex series of complications due to a background of nutritional deficiency and a wide variety of infections. These complex interactions have a dominant effect on the prog- nosis for the important inherited haemoglobin disorders. Early studies in Africa reported a marked paucity of patients with sickle cell anaemia despite a very high carrier frequency, indicating that very few patients with this disorder were surviving beyond early childhood. This may still be the case in parts of rural Africa. On the other hand, in more developed countries, and with a high quality of medical care, patients with this disease are regularly surviving

into adult life; the mean survival time in the United States of America is now approximately 42 years, with many patients surviving to old age. A similar situation exists for β-thalassaemia. In poorer coun- tries, supplies of blood may be limited, there may be difficulties in screening blood for agents such as hepatitis C and HIV, and the pro- hibitive cost of iron-chelating agents means that even children who Table 22.6.3.3 Annual births of severe disorders of haemoglobin Sickle cell anaemia Sub-Saharan Africa 240 900 Elsewhere 93 000 HbSC disease 54 700 Thalassaemia β-Thalassaemia major 23 300 HbE β-thalassaemia 20 600 HbH disease 14 500 HbS β-thalassaemia 12 300 Hb Bart's hydrops 5200 These data have to be viewed with caution because in many cases they are based on small surveys from a small number of centres in individual countries; there is evidence that the distribution of these conditions in different countries is extremely heterogeneous. The data are based on Modell and Darlinson (2008), Pielet et al. (2010), and Weatherall (2011), together with a variety of personal communications to the author.

section 22 Haematological disorders 5370 receive transfusion die from iron loading before they reach the age of 20 years. There are other inherited anaemias which are particularly common in tropical countries due to heterozygote advantage against malaria. Glucose-6-phosphate dehydrogenase deficiency is estimated to occur in some 100 million individuals worldwide. Its clinical and haematological manifestations are discussed in Chapter 22.6.11. They include haemolytic reactions to a wide variety of drugs, and, of particular public health significance, to certain foods (favism). There is a form of ovalocytosis, particularly common in Melanesia, which is associated with a mild and well-compensated haemolytic anaemia. Recent studies have shown that carriers of Melanesian ovalocytosis are protected against cerebral malaria. Consequences of anaemia The results of many studies directed at determining the functional consequences of anaemia are still controversial. It is often difficult to distinguish between the effects of anaemia per se and the conse- quences of iron or folate deficiency on other physiological functions. Whatever the mechanism, chronic anaemia is associated with di- minished function. Many studies have suggested that even mild anaemia may re- duce near-maximal work capacity. The WHO has recently stressed the increasing evidence that iron deficiency in children may reduce learning ability, intelligence, and, in extreme cases, may lead to intel- lectual disability. There is no doubt that anaemia increases maternal mortality and morbidity. There is a very large literature on the effect of iron deficiency on resistance to infection, as mediated through either immune function or the bacteriostatic and bactericidal roles of iron-containing proteins such as transferrin and lactoferrin. The complex relationship between iron status and susceptibility of infec- tion requires further work. It is clear that folate deficiency is asso- ciated with an increased prevalence of obstetric complications and fetal malformation, although its effect on intellectual and immune function is less clear. In short, because of the remarkable ability of otherwise healthy individuals to adapt to moderate anaemia it seems likely that many of the associated manifestations which have been observed result from the effects of different deficiency states on other physiological functions rather than the anaemia per se. On the other hand, chronic severe anaemia, particularly in childhood, results in a wide variety of complications including failure of growth and development and possibly susceptibility to infection. Prevention Anaemia was responsible for roughly 8% of all nonfatal health loss for all diseases in 2013, counting some 70 million YLDs. To put this in perspective, it is roughly the same as the health loss caused by depressive disorders (61.6 million YLDs) but is greater than dis- ability due to asthma, diabetes, and cardiovascular disease com- bined (61.3 million YLDs). However, a considerable proportion of the burden of disease from anaemia has the potential for remedy. It is beyond the scope of this brief review to discuss the pro- tean aspects of the prevention of anaemia, particularly in poorer countries. As outlined, the

prevalence of anaemia is a reflection of gross poverty, particularly as manifested by nutritional deficiency, infection, and malabsorption. Its control requires action on many different fronts, including improvements in diet, fortification of commonly eaten foods with iron, the use of modified milk formulae for infants, malaria and hookworm control, iron and folate supple- mentation in pregnancy, and all-round improvements in hygiene. Good antenatal care helps to prevent anaemia in childhood by re- ducing prematurity, increasing average birth weight, and improving the nutritional status of the newborn. Widespread and indiscriminate iron supplementation where malaria and bacterial infections are common is potentially harmful and certainly controversial. Current research is addressing when and how to give iron safely. Progress in reducing the prevalence of anaemia has been substantial where comprehensive, intersectoral ap- proaches to prevent anaemia have been implemented. For example, in Bangladesh, anaemia prevalence fell by more than 40% between 1990 and 2013. FURTHER READING Beales PF (1997). Anaemia in malaria control: a practical approach. Ann Trop Med Parasitol, 91, 713–8. DeMaeyer EM, Adiels-Tegman M (1985). The prevalence of anemia in the world. World Health Stat Q, 38, 302–16. DeMaeyer EM, et al. (1989). Preventing and controlling iron-deficiency anaemia through primary health care. World Health Organization, Geneva. Drakesmith H, Prentice AM (2012). Hepcidin and the iron-infection axis. Science, 338, 768–72. Gallacher PG, Ehrenkranz RA (1995). Nutritional anaemias in in- fancy. Clin Perinatol, 22, 671–92. Global Burden of Disease Study (2015). Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 385, 117–71. Hercberg S, Galan P (1992). Nutritional anaemias. Clin Haematol, 5, 143–68. Kassebaum NJ, et al. (2014). A systematic analysis of global anemia burden from 1990 to 2010. Blood, 123, 615–24. Khusun H, et al. (1999). World Health Organization hemoglobin cut- off points for the detection of anemia are valid for an Indonesian population. J Nutr, 129, 1669–74. Murray CF, et al. (2013). Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study. Lancet, 384, 1005–70. Modell B, Darlison M (2008). Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ, 86, 480–7. Piel FB, et al. (2010). Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun, 1, 104. Weatherall DJ, Kwiatkowski D, Roberts D (2009). Hematologic manifestations of systemic diseases in children of the developing world. In: Orkin SH, et al. (eds) Nathan and Oski’s hematology of infancy and childhood, 7th edition, pp. 1741–68. WB Saunders, Philadelphia. Weatherall DJ (2011). The challenge of haemoglobinopathies in resource-poor countries. Br J Haematol, 154, 736–44.

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