Practical Management of Haemoglobinopathies
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EDITED BY

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Haemoglobinopathies are the most prevalent inherited diseases that afflict mankind, and constitute a major health problem in many countries. There is a perceived need among practising health professionals and students for a book on sickle cell disease and thalassaemia designed to fill the gap between the major reference texts and the smaller ‘handbooks’ on the subjects. Such a book is expected to meet the day-to-day requirements of a growing number of trainees and health-care professionals working in the field. The need for a medium-sized textbook that deals with practical aspects of the laboratory, clinical and community care of people affected by haemoglobinopathies has increased as population screening programmes have been instituted in various countries, and general improvements in medical care have led to longer life expectancy of persons born with the disorders.

In this book, a multidisciplinary group of professionals who work on various aspects of haemoglobinopathy have attempted to share their experiences with colleagues in the field. It begins with an overview of the holistic care required by affected persons, proceeding to practical details of laboratory diagnosis, clinical management, community care, psychosocial support and counselling. The final chapter deals with the challenges faced by health-care professionals who attend to people who have sickle cell disease and thalassaemia, and offers suggestions on how to meet them. It is the profound hope of the contributors that this concise text will go a considerable way towards enabling health-workers to provide optimal care for people with sickle cell disease and thalassaemia.

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IE Okpala
Guy’s & St Thomas’ NHS Trust is proud of its annual week-long international conference on sickle cell disease and thalassaemia. The haematologists at the Trust, with the support of the whole organization, are leading the provision of services in Lambeth, Lewisham and Southwark for our many residents who experience these conditions.

We all know that sickle and thalassaemia are among the commonest of mankind’s inherited problems, with millions of sufferers across the world. The UK has the highest number of people with sickle cell disease in Europe, and within the UK one of the largest cohorts of patients is in our area of Central London. We estimate that over a quarter of the residents in our three boroughs are at risk of inheriting the sickle cell gene, and numbers are bound to rise. Therefore, we have an immediate and pressing need to ensure that our own local people receive the best possible care and treatment. Those affected by sickle cell disease and thalassaemia include of course the patients and their families and friends who themselves need support and advice. We at Guy’s and St Thomas’ therefore have not only direct responsibility for a significant group of people but also the opportunity as a famous teaching institution to lead research, to promote better understanding of both the causes and treatment of disease, and to share good practice. Mutual learning between patients, clinicians, researchers and voluntary sector workers can only be beneficial, and I know that all participants at our conferences leave encouraged by the example and commitment of others.

This book has contributions from many authors and has been compiled in response to requests from those who attended the course in previous years. It will, I hope, reach a wide audience so that many people who did not attend will also benefit from the ideas and discussions generated during the conference. The book demonstrates the co-operative efforts of the multidisciplinary team of health professionals and others who, at various times, have generated ideas during the course. I recommend its contents to everyone who provides services for those who suffer from sickle cell disease and thalassaemia, as it is only through real joint working that comprehensive care can be delivered. This wide-ranging and forward-looking approach, which seeks to understand all the needs of patients, is an approach that this Trust is proud to communicate to others. The example set by the team leading the conference is well demonstrated by this publication, and I am grateful to Dr Okpala and others for their work both in organizing the event and bringing this book together.

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**Definition of sickle cell disease**

Sickle cell disease (SCD) is a general name for a group of inherited conditions that have two characteristics in common: the presence of sickle- or crescent-shaped red cells in the blood, and development of illness (disease) as a result of having sickle cells. Simply put, sickle cell disease means disease caused by sickle cells. Clinical illness as a result of the presence of sickle red blood cells occurs in various inherited conditions that are types of SCD. These genetic disorders include homozygous (HbSS) sickle cell disease or sickle cell anaemia and compound heterozygous states such as sickle cell haemoglobin C (HbSC) disease, sickle cell thalassaemia (HbSthal), HbS/HbD Punjab (Los Angeles), HbS/HbO-Arab, HbS/HbE, and HbS/Hb Lepore Boston [1]. The carrier state, sickle cell trait (HbAS), is not considered as SCD because it does not cause clinical illness.

**What is comprehensive care of SCD?**

This is the multidisciplinary, holistic care of people affected by SCD. In addition to individuals who have SCD, the affected persons include relatives, friends and others whose lives are significantly affected by the patient’s illness. A mother who is absent from work to take her child to the hospital, the brother or sister who suffers maternal deprivation as a result, as well as the patient whose daily schedule could be suddenly interrupted by a sickle cell crisis without forewarning; all these individuals might need psychological support and counselling. The provision of facilities to enhance in-house mobility, and the construction of a ramp to ease access to the house, are non-medical services that improve the quality of life of a person with SCD complicated by stroke.

The medical care of individuals who have SCD is best provided by a team of different specialists because it is a multi-system disease that affects virtually every organ of the body. Although SCD is primarily a blood disorder, its clinical management should not be the sole responsibility of haematologists because, as blood flows to all parts of the body, the fundamental pathological process in SCD – blood vessel occlusion with reduced supply of oxygen and nutrients – can occur in any tissue, resulting in damage and diminished function of affected organs. Thus, effective management of stroke in SCD requires joint treatment by neurologists and haematologists; people with avascular necrosis of the hip joint benefit from a combined orthopaedic and haematology clinic; while expectant mothers who have SCD are best seen by a team of obstetricians, specialist nurses/midwives and haematologists.

The co-operation of people affected by SCD is indispensable for effective provision of the above medical and non-medical services. Without such partnership, comprehensive care cannot be delivered. The affected person is at the apex of the triangle of holistic management of SCD (Fig. 1.1). However efficacious or well-meaning the care plan for an individual is, if it is not presented in an acceptable, culturally appropriate manner that wins the patient’s or parent’s co-operation, very little may be achieved.
Components of comprehensive care of SCD

A comprehensive sickle cell service is dynamic, its composition evolves in response to changing situations. The component services discussed below are not meant to be exhaustive. Certain services are so crucial that no comprehensive care system could function without them. Others could be obtained by referral to relevant specialist units. It may not be feasible to provide all the component services within a single comprehensive care system, and appropriate referral should be made when necessary.

Haematology services

As appropriate for a primary genetic abnormality of the blood, the diagnosis and core clinical management of SCD has been the traditional role of haematologists who co-ordinate overall care of affected individuals, and liaise with providers of other component services in comprehensive care. The effectiveness of comprehensive care is critically dependent on efficient co-ordination of the various components to ensure that they work as a whole and provide a seamless service. Close collaboration between the children’s and adults’ haemoglobinopathy services is crucial. This facilitates accurate planning for the provision of the adult service in the future. A clinic held jointly by the paediatric and adult haematologists for young adults aged 16–18 years fosters this co-operation. Such a transition clinic provides opportunities for children to familiarize themselves with the adult team and their services before they are completely transferred to adult care. The haematologist is in a vantage position to provide initial explanation of the diagnosis and the nature of SCD to affected individuals. This should be supplemented by further information from sickle cell centres and counsellors.

Information about SCD

Various means of communication in non-technical language are used to share relevant information on SCD with affected individuals. Individual and group discussion, portable cards showing the person’s haemoglobin genotype, leaflets, booklets, video or audio cassettes, and posters are effective means of conveying information about the haemoglobinopathy. On a larger scale, public sickle cell awareness events could be held to increase the level of information about the condition in the community. As much as possible, communication should be in lay language, to facilitate understanding. Following the usually unpleasant effect of being told one has SCD, it is helpful to consolidate and further clarify this at a later date when the affected persons would have had time to think about it, and probably have questions about the practical implications of the diagnosis. While this could be carried out by specially trained counsellors or other healthcare professionals, it is crucial that the information provided is consistent, and that this important interaction takes place in a less formal and time-constrained atmosphere than that usually experienced in a busy clinic or ward round. The non-clinical setting of a Sickle Cell and Thalassaemia Centre enables this communication to be informal, and if practicable, a home visit to the affected person is ideal. If the above options are not feasible, consolidation of initial information could be carried out during a follow-up clinic visit.

Subsequent reinforcement and expansion of the initial information should be carried out when appropriate, such as when the child is about to start schooling, during adolescence, before transfer from the childhood to adult comprehensive care, and before starting a family. Genetic counselling, including information about pre-implantation genetic and prenatal diagnoses, is beneficial for couples whose haemoglobin genotypes are such that their offspring could have a clinically significant haemoglobinopathy [2, 3]. For such at-risk couples,
genetic counselling is best done pre-conceptually. Failing that, it needs to be done early enough to allow fetal tissue sampling by 11–12 weeks of gestation and possible termination of pregnancy thereafter. Genetic counselling is inextricably linked with antenatal screening. Close co-operation between the haematology laboratory and maternity services ensures that at-risk couples are referred to the medical geneticist at an early stage for assessment, and discussion of the intrinsic risks and error rate of prenatal diagnosis. The consultation is non-directive; it is ultimately the woman’s decision whether or not to carry on with an affected pregnancy. When health-care professionals invest time and effort in providing relevant information about SCD to affected individuals, it is very rewarding subsequently. It facilitates bridge-building between both parties, makes a sometimes-uneasy relationship cordial, and helps to win the patient/parent confidence and co-operation that is indispensable in the delivery of comprehensive care.

**Prevention of infections**

People who have SCD are prone to infection because of reduced splenic function, defective activation of the alternative pathway of complement and impaired ability of neutrophils to kill microbes [4–9]. The infection precipitates a sickle cell crisis, which may be life-threatening or may cause excruciating pain. Therefore, prevention of infection is an essential cornerstone of comprehensive care in SCD. Specific measures include prophylactic antibiotic or antimalarial therapy, and immunization against pneumococcus, meningococcus, *Haemophilus influenzae* type B, and hepatitis B and influenza viruses. A vaccine against parvovirus B19, which causes aplastic crisis, is available in some countries. Commencement of prophylactic penicillin at around the age of 3 months has been shown to reduce mortality from pneumococcal septicaemia [10].

**Social services**

The clinical manifestation of sickle cell disease is influenced by the social and economic circumstances of affected persons. The nature of a patient’s or parent’s occupation, level of general education and specific information about SCD, the suitability or spaciousness of the residential accommodation; all these have an impact on the patient’s health. Appropriate heating of the house in which an affected person lives helps to prevent chest infections that can predispose the individual to sickle cell crisis. This reduces the need for hospital attendance or admission, and frees up health-care staff and hospital beds, ultimately saving resources for the health service. Some issues that affected persons have to contend with are not medical. Social workers have very important roles in the comprehensive care of patients with haemoglobinopathies. It is their responsibility to assess the specific social needs of affected persons and ensure that services are provided to meet identified needs. Social services needed by individuals may include registration as disabled, practical help at home, and adaptations to the home such as constructing a ramp or installing a lift to facilitate mobility for people with SCD complicated by stroke or hip damage.

In some countries, currently available regulations for provision of social services are not adequate for the specific needs of people affected by haemoglobinopathies, and need to be reviewed. Some children with SCD fall within the group regarded as being in need. These are children who are disabled, or who require provision of social services to achieve a reasonable standard of health or development, or to prevent impairment of health or development. The Social Services Department has the responsibility to provide the right level of intervention and support that will enable people with haemoglobinopathies to achieve their potential in life.

**Psychological support**

An immense psychological burden is associated with a chronic illness manifesting as painful episodes that may be life-threatening and occur without forewarning [11, 12]. It is a credit to their resilience that most affected persons cope well with SCD despite this psychological stress. Unvoiced fears about sudden illness or even death, feelings of
carrying their burden alone or being depressed as a result, and anxiety about the uncertainty of their future are psychological issues for people who have SCD. These can increase the feeling of pain experienced during crisis or other physical illness [13], and make medical management difficult. As a result, some affected individuals may ask for inappropriate medical intervention such as opiate therapy when this is not really needed. Psychological disturbances could lead to withdrawal from family and friends, communication problems, poor performance at school or work, unemployment, poverty, dependence at an inappropriate age and low self-esteem. Recurrent priapism or prolonged penile erection is a source of anxiety in males who may not volunteer this information or may not even be aware that it is caused by SCD [14]. This can lead to suboptimal sexual function and can affect relationships. Psychological support for persons affected by SCD is needed for chronic pain, challenging behaviour, learning or attention difficulty, transition from paediatric to adult care, depression or anxiety states, and relationship problems. Psychological support may be provided for groups of affected persons, rather than individuals. Such Sickle Cell Support Groups enable people to learn from the experiences of others who have experienced challenges similar to theirs, and to appreciate that they are not alone. An important component of psychological evaluation is to assess the person’s quality of life. Cognitive behaviour therapy, a type of psychotherapy, helps affected people to cope with the chronic pain and psychological problems associated with SCD [15].

Drug dependency services

A very small minority of people with SCD become dependent on opiates or other addictive drugs. In most cases this results from use of these drugs in the treatment of SCD. Therefore, the situation calls for understanding, compassion and supportive management. The large amount of health service resources used up by the affected individuals is very much out of proportion to their small number. Health-care personnel have a duty to ensure effective analgesia for people with SCD. However, it is important to recognize when requests for opiates and other addictive drugs, such as temazepam, exceed the medical needs of the affected individual. The problem might not be obvious, or it may manifest as an apparently unconnected issue such as poor performance at school or work, difficult relationships with family, friends and health-care staff, or unusually frequent sickle cell crises. Affected individuals may use different names and personal details such as date of birth and address, and register with more than one hospital or general practice to enable them to receive prescriptions from different doctors without each one knowing of the other. Whereas differences in (the subjective) impression of the level of pain between doctors and patients are to be expected, a patient’s incessant objections to reduction in the dose of opiates considered medically appropriate after clinical review, habitual arguments about the starting dose, frequent requests for increasing the dose (especially if made to doctors-on-call after normal working hours), insistence on directing the dose and frequency of opiates prescribed by doctors without caring as much about antibiotics or other medications; all these should make one consider drug dependence. Opiate addiction is very rare among people with SCD [16, 17]. Addicts may acquire drugs unlawfully, and may commit crimes such as forging and altering prescriptions in attempts to obtain drugs or materials for injecting them. People who misuse drugs may be neither dependent nor addicted, yet they strive to obtain more than their medical needs and dispose of the rest. As opiates and other addictive drugs such as temazepam have street values, SCD might be used as a reason to obtain drugs that are completely disposed of, and it may be that none are taken personally.

The affected person should be referred to the Drug Dependency Unit for expert assessment if drug dependence or addiction is a differential diagnosis. Support from the family and the psychologist is important in management. Treatment requires the co-operation of affected individuals, some of who may not accept that there is an issue because of embarrassment, reluctance to go through treatment, or loss of any personal benefits from disposal of drugs. Only medically required doses of drugs should be prescribed at all times, so that inappropriate use is not encouraged.
The concept of comprehensive care of sickle cell disease

Specialty medical care

Although it is primarily a blood disorder, SCD affects virtually every part of the body through vaso-occlusion, ischaemia and infarction. As a result, SCD is a multi-organ disease that requires the co-operation of different medical specialties for optimal management. These include nephrologists for sickle nephropathy, neurologists for stroke, cardiologists for pulmonary hypertension, chest physicians for acute chest syndrome and chronic sickle lung disease, and gastroenterologists for peptic ulcer and liver impairment.

The life expectancy of people with SCD has increased continually with improvements in their medical and non-medical care. As a result an increasing number are surviving long enough to develop long-term complications of SCD such as nephropathy and pulmonary hypertension. The renal manifestations of SCD lead to considerable illness and loss of lives [18–21]. Therefore, proactive management of kidney disease is an essential component of comprehensive care for people with the haemoglobinopathy. Joint clinics run by haematologists and nephrologists facilitate co-operation between the specialties, formulation and implementation of joint treatment protocols, and ultimately, better care of people who have sickle nephropathy. Similar arrangements for joint management could be made with other medical specialties as necessary.

Orthopaedic and other types of surgery

The skeleton is the commonest site of infarction in SCD. The tissue necrosis involves bone and bone marrow, and predisposes to osteomyelitis because dead tissue is less able to resist infection than living cells. Other skeletal manifestations of the haemoglobinopathy include the pathognomonic hand-foot syndrome, bone pain crisis, septic arthritis and avascular necrosis of joints. The hip, shoulder and spine are commonly affected by avascular necrosis; the ankle and knee less frequently. The prevalence of avascular necrosis of joints increases with age; the hip alone is affected in about 41% of adults, although symptomatic in 3–5% [22–26]. Orthopaedic treatment is needed in cases of acute osteomyelitis with subperiosteal fluid collection, chronic osteomyelitis requiring sequestrectomy, avascular necrosis with chronic pain uncontrolled by medications, and other situations advised by the surgeon. Co-operation between haematologists and orthopaedic surgeons is essential for management of such cases, and joint consultation in a comprehensive clinic facilitates delivery of such care.

General surgery input in SCD is required for patients with symptomatic gall bladder stones or acute surgical abdomen. The latter may mimic vaso-occlusive crisis affecting abdominal organs, and may cause difficulty in differential diagnosis [26]. The management of major priapism unresponsive to medical therapy, or erectile dysfunction resulting from this manifestation of SCD, fall into the province of urosurgery [14]. Vaso-occlusive infarction may occur in the mandible or maxilla, predisposing to infection and loosening of the teeth. Dental assessment is beneficial in such cases, and tooth extraction may be necessary. Special measures to reduce the risk of hypoxaemia and red cell sickling are essential during anaesthesia and peri-operative management of people with SCD.

Obstetric care

The clinical severity of sickle cell disease may be increased during pregnancy, and the prevalence of complications of pregnancy is higher in people with SCD compared with HbAA individuals [27–31]. Therefore, pregnancy in SCD is considered high risk and appropriate for specialist obstetric care; preferably by health-care professionals with experience in attending to people who have this blood disorder. The multidisciplinary team of professionals may include obstetricians, genetic counsellors, midwives, specialist sickle cell nurses and haematologists. Monthly reviews in haematology clinics are recommended during pregnancy, and regular exchange blood transfusion for individuals with multiple pregnancy, poor obstetric history and frequent sickle cell crisis. Considering the risks associated with pregnancy in SCD, with a perinatal mortality as high as 15%, it is advisable to refer the expectant mother to a centre with considerable expertise if this is not available locally.
Specialist sickle cell nursing in the hospital and community

In both clinical and community settings, specialist sickle cell nursing has made increasing contributions to comprehensive care. The role of the clinical sickle cell nurse specialist includes initial assessment of patients in haematology clinics, exchange blood transfusion, desferrioxamine therapy in conjunction with pharmacists, data collection and management for the sickle cell register and database, and general nursing duties as and when necessary. The community sickle cell nurse specialist provides a link between the patient’s home, the hospital and community-based services. These include social workers, voluntary agencies, adult disability teams, rehabilitation centres, community occupational therapists and physiotherapists, housing officers, visual impairment teams, council staff who provide help at home, and general practitioners.

Developing and monitoring a comprehensive sickle cell service

A fundamental requirement of a comprehensive haemoglobinopathy service is the multidisciplinary team to deliver it. The team’s skill-mix should be appropriate to enable them to provide the various components of comprehensive care outlined above. While it may not be feasible in some circumstances to have the full complement of required professionals, every effort should be made to involve as many as possible. Once assembled, the team’s effectiveness and success depend critically on co-operation among its members. This is enhanced by leadership that actively promotes interaction and cohesion within the team, while supporting and encouraging individual roles. Co-ordination between hospital and community-based services is crucial. These two arms, by and large, deliver the bulk of comprehensive care; and it is important that each hand knows what the other is doing. To this end, regular briefing and planning meetings of the team are very useful. The comprehensive care team achieves better results by working in partnership with management staff of the hospital or the community-based services, the local health authority, and non-governmental agencies with similar goals such as the Sickle Cell Society and the Organisation for Sickle Cell Anaemia Research.

A service development that has had a great impact on the provision of holistic care to people affected by SCD is the establishment of a Comprehensive Sickle Clinic. This omnibus clinic provides the opportunity for affected persons to see various professionals in one place during a single hospital visit. Currently, the components of the Comprehensive Sickle Clinic in our centre are the Transition/Adolescent, Antenatal, Orthopaedic, Iron Overload and Renal Clinics. More components could be added in the future as the service evolves. The psychologist, sickle cell nurse specialist, counsellors and haematologist attend to affected persons with the appropriate medical or surgical specialist, depending on the clinic. The presence of a physiotherapist increases the quality of care delivered in the Sickle Orthopaedic Clinic, and a pharmacist dedicated to iron chelation therapy attends the Iron Overload Clinic. The comprehensive sickle clinic makes it possible to provide a wide range of services on an outpatient basis.

A comprehensive sickle cell service can be monitored effectively by regular audit of established practices, management protocols and treatment guidelines. Monitoring is greatly facilitated by having a patients register or a computer database that can, with appropriate controls, talk to regional, national or international networks. The service should be assessed continually, and improvements made to reflect findings from audit, research and suggestions from team members or users of the service.

A multidisciplinary team providing holistic care for people affected by haemoglobinopathies is a rich resource for continuing professional development (CPD) and for raising public awareness of globin gene disorders. Unique opportunities for training and education are available within a comprehensive haemoglobinopathy care system. Resources and protected time should be set aside for lectures and seminars to enhance the professional skills and knowledge of team members and staff of other units or organizations.
Advantages of comprehensive care over episodic treatment of SCD

Holistic care enhances the quality of life for people affected by SCD. A better overall result is achieved by interaction of a co-operative patient with the team of various professionals and organizations working in partnership. Comprehensive care reduces the number of hospital admissions for people with SCD, and shortens the length of hospital stay (Fig. 1.2a,b). These translate to considerable savings in the cost of health care. Complications of SCD such as renal impairment and avascular joint necrosis are detected and treated earlier; so reducing disease-related morbidity and mortality. The immense psychological burden for affected persons is ameliorated, enabling them to live a fuller life. The holistic approach provides opportunities for health promotion, community-based care and improved communication between various disciplines. When people affected by SCD experience the benefits of holistic care, they are more compliant with medical treatment and co-operate more willingly with professionals providing the non-medical aspects of the care. The advantages of comprehensive care over episodic treatment of SCD have been observed in various centres in different parts of the world, and include the benefits of proactive blood

![Hospital Admissions for Adults with Sickle Cell Disease](image)

**Fig. 1.2** (a) Hospital admissions for adults with sickle cell disease (SCD). Note the fall in admissions following the establishment of a Comprehensive Sickle Clinic in 1999. (b) Average length of hospital admissions for adults with SCD.
transfusion therapy for primary prevention of the devastation brought to the lives of affected persons by stroke [32, 33], a smoother transition from children’s to adult care [34], striking reduction in childhood mortality from splenic sequestration crisis achieved by parent education [35] and enhanced ability to secure employment as a result of psychosocial services [36]; all of which are achieved at lower cost to the health service [37].

These positive effects of comprehensive care make it the preferred mode of service delivery to people affected by sickle cell disease.

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Introduction

The normal adult red blood cell contains three types of haemoglobin, approximately 95% haemoglobin A (HbA) with haemoglobin A2 (HbA2) and F (HbF) forming minor fractions. Globin chains of amino acids linked to form a tetramer are an integral part of the haemoglobin molecule. HbA comprises two alpha and two beta chains (α₂β₂), HbA2 has two alpha and two delta chains (α₂δ₂) and HbF has two alpha and two gamma chains (α₂γ₂). Variations from normal can be classified into three major categories: structural variants, thalassaemias and hereditary persistence of fetal haemoglobin (HPFH).

Structural haemoglobin variants result from mutations that give rise to the formation of globin with an abnormal structure; the majority are point mutations. HbS is one of the best known of these and results from the substitution of the amino acid valine for glutamic acid at position six of the beta chain [1]. Other documented causes of structural variants include double point mutations, mutations resulting in shortened or lengthened chains and gene fusion [2–8].

Thalassaemias result from mutations that cause a defect in the synthesis of one or more globin chains disturbing the ratio of alpha to non-alpha chains. Beta thalassaemia results from deletional, frameshift and point mutations and can be divided into two types: beta zero in which no beta chains are produced and beta plus in which there is reduced chain production. Alpha thalassaemia is primarily caused by gene deletions. Again the nomenclature of alpha plus and alpha zero is used. This relates to the number of genes which are non-functional and therefore to the amount of alpha chains produced and thus clinical severity. HPFH refers to a benign group of conditions in which the synthesis of fetal haemoglobin remains raised throughout life.

Haemoglobinopathies have arisen in areas where malaria has been endemic and different mutations occur within the same ethnic group. Therefore, an important point to consider when diagnosing haemoglobinopathies is that it is possible for more than one type of abnormality to be co-inherited. It is clear that homozygosity for these abnormalities can lead to clinical disease such as sickle cell disease (SCD) or thalassaemia major. However, it is also possible for different types of beta chain variants, such as HbS and HbC, and for beta and alpha chain variants to be co-inherited. Globin chain variants may also be co-inherited with thalassaemia and/or HPFH. Similarly, alpha and beta thalassaemia may be seen in the same individual.

The purpose of this chapter is to provide an overview of the first-line laboratory tests for the diagnosis of haemoglobinopathies and interpretation of data obtained from these procedures. It is not intended to be comprehensive. If the results of routine laboratory tests do not provide enough information for definitive diagnosis, it may be necessary to determine the haemoglobin genotype by mass spectrometry or DNA analysis.

Blood counts

The full blood count (FBC) and blood film are important primary screening tests in haemoglo-
binopathy diagnosis. Neonatal screening is the exception, as dried blood spots are frequently used, precluding FBC analysis. If the FBC is available it should be noted that normal ranges are age-dependent. Of particular interest are the red cell indices: red count (RBC), haemoglobin (Hb), mean cell volume (MCV) and mean cell haemoglobin (MCH). These are essential in thalassaemia diagnosis. Classically the picture in thalassaemia trait is described as one with a mildly raised RBC, normal Hb and reduced MCV and MCH; these are referred to as thalassaemic red cell indices. However, this may not always be the case because other conditions, such as concomitant iron deficiency and co-inheritance of alpha and beta thalassaemia trait, will influence the results. Iron deficiency has the effect of lowering the red cell indices and has also been reported to lower the HbA2 value [9, 10]. Co-inheritance of alpha and beta thalassaemia may cause the red cell indices to normalize, as excess alpha chains are partly responsible for the pathology in beta thalassaemia.

Red cell indices are also useful in the differential diagnosis of delta beta thalassaemia trait and HPFH, as those with delta beta thalassaemia will have classically thalassaemic indices while those with HPFH will be normal.

A blood film can provide valuable information in the diagnosis of haemoglobinopathies. There are characteristic red cell features, such as sickle-shaped cells, basophilic stippling and target cells which may point to the haemoglobin variant present. Figure 2.1 shows a blood film with the characteristic sickle- or crescent-shaped cells seen in sickle cell disease, target cells can also be seen. Nucleated red cells are seen in some states including thalassaemia intermedia and major and SCD. The reticulocyte count should also be performed: with unstable haemoglobin variants and other chronic haemolytic processes, reticulocytes are elevated and the level can relate to the severity of haemolysis [11].

Tests used in haemoglobin analysis

High-performance liquid chromatography (HPLC)

HPLC systems are today the primary haemoglobinopathy screening mechanism in many laboratories. Usually automated, these systems comprise a reservoir for the mobile or liquid phase, pump, injector, chromatographic column, detector and a system for recording and processing data. In common with most other separation systems, HPLC uses the fact that most mutations cause a change in the charge of the molecule. For the analysis of haemoglobin variants, weak cation exchange columns are used. The column is negatively charged and the positively charged globin molecules bind with varying degrees of affinity according to the charge present on the molecule. Buffer of increasing cation concentration is passed through the column.
causing competition with bound globin molecules and elution of the globin at a time relative to the positive charge. Within each system the time of elution or as it is more commonly known, the retention time, is characteristic for each normal or variant analysed. The haemoglobins eluted are represented graphically and quantified optically as they pass through the detector. This allows accurate quantification of Hb variants and HbA2 and HbF, a major advantage over screening systems that utilize electrophoresis, as these require secondary methods for quantification of haemoglobins.

HPLC system manufacturers identify variants, which separate from HbA, in different ways. The more common haemoglobin variants, e.g. HbS and HbC, have well characterized retention times. In some systems, the instrument software will identify variants as the haemoglobin into which retention time window they have eluted. Haemoglobins eluting outside of these defined times will be labelled as unknown. Care must be taken when interpreting HPLC plots even when the variant has fallen into a known retention time window. It is possible for variants to overlap and for more than one haemoglobin to elute within a given window. Examples are Hb Lepore and HbE, which elute in the same window as HbA2. Thus all variants should have further confirmatory tests. Despite these limitations it is possible to provisionally identify a greater number of haemoglobin variants than by conventional electrophoresis screening methods. Figure 2.2(a–c) illustrates typical Biorad Variant HPLC

![Fig. 2.2 Typical Biorad Variant HPLC elution patterns (Biorad Laboratories, Hercules, CA, USA). (a) Normal. (b) Haemoglobin SS (HbSS). (c) Haemoglobin SC (HbSC). (d) Sickle cell trait (haemoglobin AS, HbAS). (e) Haemoglobin G (HbG) Philadelphia trait. (f) Haemoglobin S/G (HbS/G) Philadelphia compound heterozygote.](image-url)