Anaesthesia for peculiar cells—a century of sickle cell disease

P. G. Firth*

Nuffield Department of Anaesthetics, The John Radcliffe, Headley Way, Headington, Oxford OX3 9DU, UK
*E-mail: pgfirth@doctors.org.uk

Sickle cell disease is a congenital haemoglobinopathy characterized by deformed red blood cells, acute episodic attacks of pain and pulmonary compromise, widespread organ damage, and early death. The central pathological event has traditionally been assumed to be an increase in sickling or deformation of erythrocytes, as a result of the insolubility of the deoxygenated mutant sickle haemoglobin, haemoglobin S. While acute pain and pulmonary complications often have no clearly identifiable triggers in the community setting, the perioperative period is a well-recognized and predictable time of disease exacerbations. As these problems occur in an environment of close patient management and observation, the perioperative period can offer a unique insight into the origins of acute and chronic complications of sickle cell disease (SCD). An examination of the assumptions and consequences of anaesthetic practice aimed at the prevention and treatment of these complications similarly can provide a useful distillation of management principles. This historical review examines the origin and development of anaesthetic management concepts, sketches the emergence of a wider understanding of the disease pathophysiology, and suggests a fresh anaesthetic view of these peculiar cells.

A peculiar anomaly

In March 1904, a letter appeared in the journal Science, recording a ‘peculiar anomaly in human red blood corpuscles … Examination disclosed the fact that the colored corpuscles … were elliptical and not circular’.15 This article by Melvin Dresbach was the first publication to identify human sickle cells, the pathognomically deformed erythrocytes of SCD. Following the initial report of these elliptical erythrocytes discovered in an apparently healthy medical student, an article the next year reported that the person with these peculiar cells had died abruptly from ‘cardiac failure subsequent to an attack of acute inflammatory rheumatism … preceded by tonsilitis’.16 The clinical features of acute complications of SCD, including associated infection, fever, bone pain, cardiac murmurs, and respiratory distress, closely mimic fulminant acute rheumatic fever.51 Although not identified at the time, this was very probably a description of a characteristic acute sequential course of SCD: an infective trigger, a bone pain crisis, subsequent pulmonary complications of acute chest syndrome (ACS), and sudden death.

Although Dresbach’s brace of letters provided the first probable account of SCD in the scientific literature,15 16 it was James Herrick’s classic clinical description of the disease symptoms in 191042 that brought it to the wider attention of the modern Western medical community. Herrick’s case report of a dental student detailed the key features of the disease—jaundice, shortness of breath, lymphadenopathy, dark urine, leg ulcers, epigastric pain, and anaemia associated with ‘peculiar elongated and sickle-shaped red blood corpuscles’. Numerous clinical accounts that followed soon afterwards confirmed Herrick’s clinical description, and recognized further symptoms of intermittent bone pain, stroke, and splenic infarction.51 11 30 46 54 59 85 86 92 The first surgical procedure for a patient with SCD, a cholecystectomy, was reported in 1911,92 and a case report of an appendicectomy for acute abdominal pain was published in 1914.7 Further reports of splenectomy,54 85 cholecystectomy,52 and exploration of suspected osteomyelitis,17 were
published in the 1920s. Numerous other laparotomies for splenectomy and acute abdominal pain were recorded in the following years,\textsuperscript{54,60} prompting a review of the differential diagnosis of SCD vs surgical causes of abdominal and bone pain in 1935.\textsuperscript{11} ‘Pneumonia’ was noted as a postoperative complication in 1927;\textsuperscript{5} this was probably the first published case of postoperative ACS. Perioperative deaths\textsuperscript{3,4,11,60,94} were also reported during the following decades, but specific SCD complications after surgery were not identified by an early extensive review of surgical management published in 1950.\textsuperscript{94}

\textbf{What is in a name?}

The striking deformity of the red blood cells led to the disease being termed ‘sickle cell anemia’ in 1922\textsuperscript{59} and ‘sickle cell disease’ in 1940,\textsuperscript{3} names that reflected the subsequent acceptance that erythrocyte distortion was central to the development of symptoms. In 1917, Emmel noted that the degree of erythrocyte deformation varied with time,\textsuperscript{20} and in 1927, Hahn and Gillespie demonstrated that this eponymous\textsuperscript{59} change was induced by deoxygenation.\textsuperscript{30} Boston physicians Ham and Castle published the first clear-cut hypothesis of the relationship between sickling and symptoms in 1940.\textsuperscript{31} They suggested that any condition that caused a ‘primary increase in the plasma viscosity’ would delay passage of the erythrocytes through the capillaries, producing an increase in sickling and a ‘vicious cycle’ of venous stasis, further sickling, capillary congestion, and infarction.

Another significant publication appeared in 1949.\textsuperscript{68} Using haemoglobin electrophoresis, Pauling and his colleagues demonstrated that the haemoglobin of SCD carried a different electric charge to normal haemoglobin. They hypothesized that a single molecular flaw was responsible for the haemoglobin abnormality and ultimately all subsequent symptoms. Pauling termed the disease a ‘molecular disease’, the first to be identified as a consequence of an isolated molecular abnormality. (Pauling was not, however, the first to identify a disease as a result of a specific congenital defect. That plaudit goes to Garrod, who recognized alkaptonuria as an ‘inborn error in metabolism’ in 1902. Symptoms of darkened urine were later discovered to be caused by a congenital absence of the enzyme homogentisic acid oxidase, leading to a build-up of homogentisic acid in the body.) Family pedigree studies, published around the same time, demonstrated an autosomal recessive mode of transmission,\textsuperscript{4,65} confirming Dresbach’s original 1904 suggestion of a hereditary cause of the erythrocyte abnormality.\textsuperscript{15} These discoveries came against an exciting background of advances in genetic science: the DNA molecule had been established as the carrier of genetic information in 1944, while the double helix structure was decoded in 1953. Although beaten to the 1962 Nobel Prize for Medicine in the race to describe the structure of DNA, Pauling’s work on what he dubbed Haemoglobin S\textsuperscript{68} was part of a series of papers on the fundamental structure of proteins for which he was awarded his first Nobel, the 1954 Prize for Chemistry.

\textbf{Anaesthetic concepts—the next 50 yr}

The first substantial anaesthetic review\textsuperscript{80} in 1955 followed on a number of fundamental concepts about SCD established in the half century following the discovery of this ‘peculiar anomaly’.\textsuperscript{15} ‘Sickle cell anemia’\textsuperscript{59} was a genetically encoded ‘molecular disease’\textsuperscript{68} of haemoglobin that caused red cell deformation on deoxygenation,\textsuperscript{30} which in certain circumstances would lead to a ‘vicious cycle’ of further sickling, vaso-occlusion, ischaemia, infarction, and pain.\textsuperscript{31} While the surgical literature of the previous three decades had focused largely on the surgical problems produced by the disease, the anaesthetic review by Shapiro and Poe\textsuperscript{80} pointed out that surgical procedures in turn triggered or exacerbated SCD complications. In a series of 15 patients, they noted a high incidence of postoperative complications, and suggested that avoidance of hypoxia and sickling was central to preventing complications. The ‘vicious cycle’ hypothesis was subtly modified in that sickling was suggested as the precipitant of ischaemia and infarction, rather than vaso-occlusion occurring consequent on the ‘primary increase in the plasma viscosity’.\textsuperscript{31} The dangers of increasing sickling by ‘over heavy pre-medication, hypotension, . . . blood stagnation with high spinal analgesia, localized stasis from positioning of the patient, (and) respiratory depression’, were emphasized. The theoretical concept that avoidance of sickling is essential to management has dominated much of the anaesthetic literature to the present day.

The following decades saw extensive research into the biochemical aberrations of the disease.\textsuperscript{18} Ingram outlined the abnormalities of haemoglobin S in publications in 1956 and 1957,\textsuperscript{49,50} and identified the substitution of valine for glutamic acid as the critical peptide abnormality. During the 1950s and 1960s, polymerization of haemoglobin and subsequent precipitation from solution were identified as the mechanisms producing the characteristic erythrocyte sickling. The 1927 findings of Hahn and Gillespie\textsuperscript{30} on the impact of hypoxia and acidosis on sickling were confirmed, while cellular dehydration was also recognized to hasten gelation of haemoglobin.\textsuperscript{18} As an extrapolation of this latter finding, intravascular dehydration was consequently suggested as another potential perioperative trigger.

Clinical accounts from areas other than the perioperative period also influenced anaesthetic thinking. A report of SCD complications induced by aircraft travel was cited as evidence of the dangers of hypoxia and sickling.\textsuperscript{25,64,78} Hypothermia was also identified as a potential perioperative danger,\textsuperscript{25} based on an anecdotal account of cold weather triggering pain crises.\textsuperscript{77} Although a left shift of the oxygen dissociation curve would limit deoxygenation and inhibit sickling, hypothermia-induced vasoconstriction was suggested to slow peripheral transit time and increase sickling.
Biochemical advances and an improved grasp of the clinical sequelae of the disease coincided with numerous anaesthetic case reports, reviews, and studies of SCD. Despite this fairly extensive perioperative literature, there remained considerable uncertainty over the extent and nature of postoperative complications. Major causes of this arose from the difficulties in distinguishing unique SCD complications from other non-specific perioperative complications, and in precisely defining these complications. The diverse symptoms of the disease closely mimic other disease presentations. This was largely the reason why SCD was only clearly identified as a distinctive disease in the early 1920s; previously the symptoms of SCD had been attributed to other diseases prevalent in the American South, the Caribbean, Africa, and Asia that produced similar clinical signs. Similarly, Melvin Dresbach’s original reports of the ‘peculiar anomaly’ of blood cells did not distinguish acute rheumatic fever from a new clinical entity. ACS was only defined as a specific complication of SCD, separate from pneumonia, severe atelectasis, or other acute pulmonary processes, in 1979. At present there is still no generally accepted definition of a pain crisis, making evaluation of the incidence and severity of this complication difficult. The small size and differing circumstances of many of the surgical populations examined weakened the conclusions of many early reports, while the anecdotal nature and inherent reporting bias of case reports also contributed to the confusion. A landmark observational study of 1079 surgical cases, published in 1995, helped to delineate perioperative epidemiology. Sickle cell complications occurred at a rate ranging from 0 to 19%, depending on the surgical procedure. Perioperative mortality was low at 1.1%. A contemporary publication of a series of 604 cases noted a rate of acute SCD exacerbations of approximately 15%, with a mortality rate of 0.3%. While there was controversy over the type and frequency of complications, the basic assumption of 40 yr earlier remained largely unchallenged over the decades: ‘these problems may arise from perioperative hypoxia, hypoperfusion, and acidosis, which cause erythrocytes to sickle, thus precipitating vaso-occlusion and organ dysfunction’ (Fig. 1).

**Empirical evidence**

Largely because of the clinical complexities of SCD and the consequent shortage of definitive perioperative studies, anaesthetic management has historically been based on extrapolation from the pathophysiological model of the disease. The presence of supportive data can suggest a hypothesis is true within the limits of set confidence intervals. An absence of confirmatory evidence does not necessarily disprove a theory, but certainly means that a hypothesis must be viewed as unproven. In contrast, contradictory or inconsistent facts mean that the concept must be at least revised, if not rejected. A review of the facts pertinent to the ‘vicious cycle’ hypothesis produces some interesting information.

A study published by Klinefelter in 1942 noted the effects of hypoxaemia in people with SCD. The author noted that a number of his patients had a chronic baseline hypoxaemia, and reasoned that hypoxia per se was not a cause of acute complications. Four subjects with chronic symptoms of SCD were exposed to 10 min of inspired oxygen 10% in order to assess oxygen delivery. There were no significant adverse effects or acute SCD symptoms. Detailed data from one subject were reported, noting arterial haemoglobin oxygen saturation dropping from 89.3% on room air to 51.2% on inspired oxygen 10%.

Another study published in 1946 examined the effect of hypobaric hypoxia on African-American airplane pilots. The 332nd Fighter Squadron was a famous African-American fighter unit in the segregated US Air Force of

![Fig 1](https://academic.oup.com/bja/article-abstract/95/3/287/258427)
World War Two. A number of these ‘Tuskegee airmen’ had sickle cell trait, the heterozygous carrier state of the mutant sickle gene. In attempting to assess the effect of hypobaric hypoxia on pilots who had already spent many hours flying at high altitude without apparent impairment, an experiment was carried out in which trait subjects were studied in decompression chambers. As the pilots tolerated decompression without apparent ill effect, a civilian volunteer with clinical signs of haemoglobin SCD was also subjected to prolonged decompression to barometric pressures as low as 54.91 kPa (412 mm Hg). Despite a resultant arterial haemoglobin oxygen saturation of 74%, he did not develop SCD complications, but rather ‘withstood the lowered oxygen tension even better than did individuals with (sickle trait) or the control subjects’.40

Given that the ‘vicious cycle’ hypothesis of hypoxia-induced sickling and subsequent capillary blockage had been published in 1940, the ethics of this experiment on a SCD subject might be questioned. However, investigators did not understand the difference between SCD and sickle cell trait at the time. Although a genetic basis for the disease was long suspected,15 16 confusion between the heterogeneous trait and homozygous disease state led to the misconception that SCD was an autosomal dominant condition,46 with the sickle cell trait as simply a milder and less expressed version of the same disease. The researchers therefore assumed that they were simply dealing with a variant of the same pathological process, and proceeded cautiously with close observation for any incipient problems. Pauling’s electrophoresis study68 demonstrated the presence of two versions of haemoglobin, while family studies also confirmed autosomal recessive inheritance of the disease—these were only published in the English language literature in 1949.165

The pathophysiology of SCD remained unclear, despite the ‘vicious cycle’ hypothesis31 and the demonstrable link to haemoglobin S.68 Other contemporaneous studies noted chronic arterial hypoxaemia in small series of subjects with SCD.56 73 These reports40 56 73 provided the ethical basis for a further study, published in 1958, examining the physiology of oxygen transport in SCD.51 Sixteen subjects, with sickle haemoglobinopathy proven by electrophoresis, were exposed to 30 min inhalation of hypoxic gas mixes ranging from 8.9 to 16% inspired fraction of oxygen. This produced arterial oxygen tensions ranging from 6.13 kPa to as low as 3.73 kPa (46–28 mm Hg). Despite a mean (sd) arterial hypoxaemia of 4.41 (0.92) kPa [33.1 (6.9) mm Hg] and haemoglobin oxygen saturation of 62.4 (3.5)% during one experimental series, there was ‘no discernible acute or chronic symptomatology’ in any subject.81 As Ingram was characterizing the molecular abnormality of haemoglobin S49 50 predicted by Pauling and colleagues,68 Sproule and colleagues81 were demonstrating in vivo that the widely recognized consequence of this abnormality—hypoxia-induced sickling—did not necessarily produce acute symptoms. While the biochemical brilliance of Ingram and Pauling received widespread attention, the more prosaic practicalities of Sproule’s demonstrations passed largely unnoticed—despite the clear and striking clinical implications.

Further evidence pointing to the ability of people with SCD to tolerate hypoxaemia and apparent extensive sickling, comes from a variety of clinical observations. People with end-stage sickle cell lung disease survive with chronic baseline hypoxaemia during the last phases of life,57 71 while at the other end of the age spectrum, there are reports of SCD patients surviving past infancy with congenital cyanotic heart disease such as Tetralogy of Fallot and double outlet ventricle.33 47 67 74 87 Adult haemoglobin supersedes fetal haemoglobin as the predominant variant at 3–6 months of extra-uterine life. While both Tetralogy of Fallot and SCD may vary widely in severity, it is difficult to reconcile the co-existence of even mild variants of these congenital abnormalities with the concept of a circulation teetering on the knife-edge of sickling-induced catastrophe. More recently, three retrospective observational series of orthopaedic surgical patients described the use of occlusive arterial orthopaedic tourniquets on 37 occasions without causing SCD complications.166 82 Inadvertent and uneventful transfusion of deoxygenated autologous haemoglobin-SC blood, without the potentially confounding effect of concurrent homologous transfusion, has also been documented.55

There is therefore clinical evidence from varied and independent sources that strongly contradicts the anaesthetic ‘vicious cycle’ theory. In contrast, there is a lack of definitive data to prove or support the hypothesis underpinning the previous 50 yr of anaesthetic management. This suggests that increased perioperative sickling is not the cause of sickle cell complications.

An alternative model
The remarkably variable sites and precipitants of acute SCD complications confound attempts to outline a single common pathophysiology. However, certain broad themes may be common to many acute problems. In more recent decades, the convergence of the greater awareness of the fluid and changeable nature of vascular endothelial function, contemporary evidence of SCD endothelial dysfunction,39 70 and decades of anatomical evidence of vascular damage in SCD,8 48 57 71 84 86 96 points to the endothelium as the immediate origin of symptoms in many acute episodes.

If evidence countering the ‘vicious cycle’ theory has long existed, so too have observations in favour of an ‘inflammatory vascular damage’ hypothesis. In 1923, Sydenstricker had reported thickened and tortuous splenic arterioles, but had attributed this vascular pathology as secondary to splenic infarctions and fibrosis.30 Pathological vascular changes were noted in the pulmonary circulation in 1937, but were again attributed to end-stage organ damage and subsequent arterial hypertension.96 In 1939, Bridgers noted similar
long-standing changes in the cerebral arterial vessels, but without sufficient pre-existing end-organ pathology to account for the changes. He accordingly suggested that arterial damage was a primary rather than secondary feature of SCD. This insightful observation was largely ignored until the publication in 1972 of a series of cerebral angiograms, demonstrating widespread cerebral vasculopathy. Sickle cell neurological pathology, such as haemorrhagic or infarctive stroke, therefore arises from cerebral arterial damage, rather than venous sickling. Similarly, it was only in 1988 that Powars and colleagues published a seminal paper, following longitudinal changes in pulmonary function in these patients. This study demonstrated that progressive pulmonary vascular damage preceded, rather than followed, episodes of ACS and pulmonary infarction. As in the brain, severe insidious vasculopathy preceded end-organ damage and infarction.

The key point of Pauling’s ‘molecular disease’ concept was that unique features of the mutant haemoglobin molecule must ultimately explain all symptoms—that is haemoglobin S is the sine qua non of SCD pathology. In 1974, an additional specific characteristic of haemoglobin S was published—the oxygenated form had a highly unstable structure. Other researchers confirmed this finding afterwards. These observations occurred in an academic milieu of an evolving understanding of the nature and significance of haemoglobin structure and function. Haem is contained in a hydrophobic globin pocket that both limits the reaction of iron with oxygen and shields the cell from free radicals produced by the highly reactive iron compounds. With this model in mind, the consequences of haemoglobin S instability became clear to biochemists during the 1980s. Impaired stability of the globin leads to accelerated breakdown of the molecule, releasing large quantities of toxic iron and haem compounds into the cell. In addition, pathologically accelerated auto-oxidation of haemoglobin to met-haemoglobin produces increased amounts of hemichromes. These mechanisms produce widespread oxygen damage to the cell membrane, disruption of the phospholipid bilayer and protein distribution, and impairment of normal membrane functioning. Disrupted cell membrane structure and function lead to increased adhesion of iron-laden, oxidizing erythrocytes to the vascular endothelium, inducing endothelial damage and dysfunction. This little appreciated feature of haemoglobin S—instability, rather than insolubility—helped to explain the link between the unique characteristics of the mutant haemoglobin and the clinical observations of extensive vascular damage.

The concept of a disease of ‘sticky cells’ rather than ‘sickle cells’ directed attention from the red cells to the vascular endothelium. The significance of vascular wall integrity to haemostasis has been appreciated since Virchow outlined his triad in 1845, while the application of Ohm’s law to the fluid dynamics of the circulation highlighted the key role of vascular tone in the control of blood flow. The identification of nitric oxide as a key endothelium-derived relaxing factor in 1987 fuelled an explosion of research into the diverse and dynamic role of the vascular endothelium in haemostasis, vasmotor regulation, and vascular modelling. This led to a perception of the endothelium not as a passive anatomical interface between blood and vessel wall, but rather as the master regulator of vascular homeostasis. The discovery of diverse biochemical markers of endothelial inflammation in SCD subjects during the 1990s led to the concept of SCD as a chronic inflammatory vascular disease. This coincided with growing evidence of prothrombotic anomalies in SCD, manifested by markers of platelet activation, increased thrombin generation, and lowered anticoagulant protein S. The identification of deranged nitric oxide physiology in SCD, and the suggestion soon afterwards that inhaled nitric oxide may have a therapeutic effect, stimulated a flurry of research into SCD-related disturbances of nitric oxide signalling. The excess extracellular free haem compounds released by the accelerated breakdown of unstable haemoglobin S bind avidly to free nitric oxide. Pathological scavenging of bio-available nitric oxide may play an additional role in disruption of endothelial signalling and vascular homeostasis.

Given the discovery of widespread abnormalities attributable largely to the instability and accelerated breakdown of haemoglobin S, it might be asked whether haemoglobin polymerization and erythrocyte sickling is in fact a clinically significant feature of SCD. The publications on the effects of hypoxia cited earlier in this review might be interpreted as suggesting that acute sickling is irrelevant to the development of clinical complications. Another perioperative study, for example, compared the effects of dilution of haemoglobin S by simple transfusion of haemoglobin A blood with that of an exchange transfusion designed to reduce haemoglobin S to 30% of total haemoglobin. This study demonstrated no dose effect to the examined levels of haemoglobin S dilution, and that acute complications occurred at high rates in both groups—despite removal of 70% of the sickle cells in the exchange transfusion group. Other clinical evidence points towards the importance of sickling, however. The thalassemias are a group of congenital haemoglobinopathies caused by partial or complete deficiency of α- or β-globin chain synthesis. They share with the sickle haemoglobinopathies accelerated haemoglobin denaturation and degradation, excess free iron release, heightened oxidative stress, a hypercoagulable state, and widespread vascular damage. Common clinical features include chronic haemolytic anaemia, pulmonary damage and hypoxaemia, progressive neurological damage, intracranial haemorrhage, thrombotic stroke, deep vein thrombosis, arterial occlusion, leg ulcers, and shortened life expectancy. Other hereditary chronic haemolytic anaemias, such as hereditary spherocytosis and paroxysmal nocturnal haemoglobinuria, also develop haemolysis-associated vascular damage and similar clinical complications. In contrast, the classic features of SCD—pain crisis and some types of ACS—are pathognomonic complications. This suggests that a unique characteristic
of haemoglobin S—presumably deoxygenation-induced polymerization, with subsequent gelation and cell sickling—is essential to the development of these distinctive clinical syndromes.

Biochemical knowledge of the pathological derangements of haemostasis and vasomotor regulation has therefore expanded considerably. Although the sequence of events leading to ischaemia and vaso-occlusion remains unclear, endothelial activation—the expression of adhesogenic and thrombogenic molecules on the endothelial cell membrane—is probably a key mechanism (Fig. 2). Surgical stress, infection, and possibly microvascular ischaemia–reperfusion injury, are triggers of endothelial activation. Endothelial changes may be mediated via humoral signalling factors or inflammatory cytokines such as tumour necrosis factor, interleukins, interferon γ, thrombin, vascular endothelial growth factor, and histamine. Acute impairment of the peripheral delivery of bioavailable nitric oxide, with its vasodilatory, anti-thrombogenic properties, is another possible triggering pathway. Binding of activated white cells to the endothelium, or increased attachment of sickle erythrocytes mediated by plasma fibronectin or by

---

**Fig 2** The ‘vascular inflammation’ hypothesis suggests that vaso-occlusion is triggered and propagated largely by alterations in the chronically disrupted cellular, plasma, and vascular components of haemostasis, rather than by fluctuations in sickling. Sickle cell disease causes chronic vascular inflammation, and triggers such as surgical stress produce pathological haemostatic responses. Abbreviations: A = adenine, G = guanine, T = thymine, IL-1, IL-6 = interleukin 1 and 6, TNF = tumour necrosis factor.
thrombospondin released from activated platelets, may further stimulate inflammatory changes.\textsuperscript{10,37,39} These various pathways lead to increased endothelial expression of cell adhesion molecules such as vascular cell adhesion molecule-1 and CD-36.\textsuperscript{10,39} These molecules increase endothelial–erythrocyte binding, which may impede blood flow and impair tissue oxygenation. Fibrin and platelet deposition together with white blood cell adhesion may further exacerbate endothelial perturbation. The endothelial regulatory balance between vasodilatation/constriction and pro- and anticoagulation is therefore disturbed, leading to ischaemia, vaso-occlusion, and pain. Vaso-occlusion is probably triggered not by acute fluctuations in sickling \textit{per se}, but rather by changes in the chronically disturbed cellular, plasma, and vascular components of haemostasis and vasomotor regulation. Sickling is a secondary, exacerbating event, rather than the trigger of vaso-occlusion.

A cautionary codicil must be appended to the ‘vaso-occlusive’ model of pain crisis, in that the strikingly symmetrical distribution of bony pain present during some pain crises\textsuperscript{79} cannot be explained on the basis of vaso-occlusion alone. Conceivably, autoimmune dysfunction may play a role in the development of symmetrical symptoms. Although immunological abnormalities are well recognized in SCD, the role of autoimmune disturbance in the development of acute and chronic pain has received relatively little attention to date. Similarly, potential changes in pain neuronal function have not been well investigated. The notion of chronic vascular inflammation is therefore an incomplete model that may serve as a framework for investigating more specific pathophysiological details of the varied features of the disease.

**Prophylactic anaesthetic measures**

A new pathophysiological model has a number of implications for present and future anaesthetic management. The sickling-orientated anaesthetic approach, based largely on extrapolation from in vitro studies, must be critically evaluated for efficacy and side-effects. Commonly recommended perioperative management includes pre-emptive erythrocyte transfusion, aggressive hydration, and avoidance of hypoxia, hypothermia and acidosis.\textsuperscript{83,88}

**Avoidance of sickling**

Avoidance of hypoxia is the key goal in sickling-based management. Pre-medication and opioid analgesia have traditionally been used with extreme caution in SCD because of concern about respiratory depression, hypoxia, and sickling.\textsuperscript{88} However, the SCD population has high levels of psychological distress as a result of the effects of a chronic, incurable, incompletely understood, and ultimately lethal disease.\textsuperscript{91} Avoiding anxiolytic pre-medication may be inappropriate if otherwise indicated for an anxious and frightened patient. Similarly, there is a high level of analgesic tolerance in a population with recurrent episodes of severe pain. While regional analgesia such as epidurals may be a highly effective choice for surgical anaesthesia or pain control during a pain crisis, large doses of opioids are often the mainstay of analgesia.\textsuperscript{91} Withholding adequate doses of potent analgesia because of excessive concern about the potential risks of increased sickling may produce excessive and unnecessary suffering. Orthopaedic complications are common in SCD,\textsuperscript{91} but occlusive arterial orthopaedic tourniquets have traditionally been considered to be contra-indicated because of resultant local hypoxia, acidosis, and venous stasis. However, clinical reports to confirm this theoretical danger are lacking, while a small series totalling 37 patients reported tourniquet use without SCD complications.\textsuperscript{166,82} There was one episode of bony pain,\textsuperscript{66} but as this occurred 7 days after the tourniquet use, it was not clear that the tourniquet was the precipitating cause. While there are inadequate published clinical data to definitively assess the safety of tourniquets, these studies indicate that SCD is not an absolute contra-indication to regional arterial occlusion. A misplaced focus on the significance of sickling may therefore result in the unwarranted avoidance of useful and necessary treatment.

While the effects of acute perioperative sickling may historically have been overestimated, the clinician nevertheless cannot afford to be sanguine about hypoxia. Many patients with SCD have impairment to oxygen delivery secondary to pulmonary damage, widespread macro- and microvasculopathy, increased blood viscosity, anaemia, impaired vascular regulation, and disturbed nitric oxide signalling.\textsuperscript{51,53,57,71,81} They therefore may have limited reserve to cope with further reduction in oxygen delivery. In addition, acute hypoxia may induce endothelial activation or a heightened pro-inflammatory response, possibly a triggering event in the development of acute SCD complications.\textsuperscript{70} Parenthetically, this model might explain some part of the paradoxical clinical response of SCD subjects on exposure to sub-acute moderate hypoxia during rapid ascent to high altitude or prolonged airplane flights, in comparison with the lack of complications in response to acute short-term or chronic hypoxia.\textsuperscript{22} High altitude journeys and extended flights are known triggers of pain crises and ACS. Ascent to altitude places an adaptive stress on the vascular endothelium which, as a regulator of blood flow and oxygen delivery, is a key link in the chain of oxygen delivery. An impaired adaptive ability to a prolonged hypoxic stress may plausibly play a role in the development of symptoms.\textsuperscript{22} While the precise effects of hypoxia in SCD remain unclear, the avoidance of hypoxia is the foundation of anaesthetic management of any patient. The anaesthetist should therefore supplement oxygenation as needed to maintain tissue oxygenation at or near preoperative baseline as a basic standard of care.

**Avoiding of sickling exacerbations**

The postulated danger of acidosis is based on in vitro work demonstrating increased sickling with decreasing pH, rather
Intracellular haemoglobin dilution

Intravascular dehydration has been suggested as a precipitant of SCD complications, based on the fact that intracellular dehydration increases haemoglobin concentration, and consequently the rate of sickling. There is a paucity of definitive clinical observations to support this assumption, and no published study to evaluate the effect of aggressive hydration in reducing the incidence of postoperative SCD complications. Sickle cell dehydration and consequent in vivo sickling is the result of pathological cell membrane changes, rather than passive osmotic gradients. Prolonged hospitalization for preoperative or postoperative hydration is therefore an inconvenience and expense of little or no benefit, while central venous monitoring has little role beyond that indicated by the surgical procedure or degree of renal impairment.

Dilution of sickle cells

The use of perioperative prophylactic red blood cell transfusion remains a controversial topic. If erythrocyte sickling is a central pathophysiological event with acute symptoms, dilution of sickle cells by transfusion with normal haemoglobin A erythrocytes should reduce complications. If SCD complications are an exacerbation of chronic inflammatory vascular damage, the rationale for acute erythrocyte dilution is less compelling.

The use of prophylactic erythrocyte transfusion to prevent SCD complications was first suggested in case reports published in 1958 and 1963. A more aggressive practice involved exchange transfusion, removing the patient’s sickle erythrocytes while transfusing normal red cells. The use of prophylactic transfusion for most operations became widespread during the 1970s and 1980s in North America, despite the absence of controlled studies to demonstrate efficacy. A large prospective randomized trial published in 1995 compared an aggressive transfusion strategy, involving the use of exchange transfusion to reduce the proportion of haemoglobin S to 30%, with a conservative transfusion strategy, using simple transfusion to achieve a target haematocrit of 30%. The surgical procedures were predominantly low risk, such as hernia repair or distal extremity surgery, or intermediate risk, such as laparotomy or more major orthopaedic procedures; high-risk procedures such as cardiopulmonary bypass or craniotomy were not evaluated extensively. The study found no benefit to more aggressive transfusion, but found a higher incidence of transfusion complications with the aggressive transfusion strategy. Sickle complications occurred at statistically identical rates in both comparison groups. The study therefore failed to show a dose effect to the treatment intervention, but did find a higher iatrogenic complication rate. The study did not have a non-transfusion arm, as the authors felt the risk of not transfusing patients was too great. The authors recommended aiming for a haematocrit of 30% as a transfusion goal.

Others have questioned the assumption of the universal need for transfusion. For minor surgical procedures and for patients at lower risk—younger patients, or patients with milder symptoms of SCD—the risk of postoperative sickle complications is low. In these situations, the costs and risks of transfusion may outweigh any potential benefits. In patients undergoing more invasive procedures, the efficacy of transfusion remains unclear. Some studies have suggested a benefit, while others failed to detect a useful effect. However, these studies have been limited variously by small study size, retrospective nature, non-randomization, confusion over the definition of SCD complications, non-uniformity of surgical procedures and patient population, and changing surgical and anaesthetic practice. There is no published randomized, prospective trial comparing the effectiveness of sickle cell dilution by transfusion with that of a non-transfusion strategy. While transfusion for minor procedures is not indicated, a definitive assessment of the efficacy of transfusions for more invasive operations is difficult to make.

Although the first report of craniotomy, for resection of an intra-cerebral aneurysm, did not note the use of exchange transfusion in 1965, aggressive dilution of sickle cells was subsequently used during the 1970s and this technique became widespread for neurosurgical procedures for the following 30 yr. The logic of prophylactic dilution of sickle cells to prevent venous sickling during craniotomy was questioned in 2000 when it was pointed out that the primary cerebrovascular pathology induced by haemoglobin S is one of arterial damage, not venous occlusion. Similarly, the rationale for routine exchange transfusion during cardiac surgery originated from the early case reports in the mid-1960s, describing the use of exchange transfusion to overcome the hypothetical danger of sickling in the cardiopulmonary bypass circuit. Ironically, in many cases these artificial circuits were being employed for procedures to repair congenital cyanotic circulations such as Tetralogy of Fallot that allow right–left communication and extensive in vivo sickling. In 1998, a report from Ghana described two cases of cardiopulmonary bypass without preoperative or intra-operative transfusion—bypassing three decades of the theoretical assumptions of cardiac anaesthetic SCD management. Both cardiac and neurosurgical operations can therefore be performed with minimal or no transfusion. However, there are no adequate published control data to assess the role of transfusion in preventing sickle complications following these high-risk procedures. The clinical
impact of prophylactic transfusion therefore remains unclear in these surgical populations.

**Alloimmunization**
The dangers of blood transfusion reactions in SCD have been recognized since the 1940s, yet the extent of alloimmunization and transfusion problems in the perioperative period only became widely appreciated in the mid 1990s. Alloimmunization, the development of antibodies to non-ABO blood groups, has a high incidence in the SCD population. The reasons remain unclear but may relate to immune dysregulation produced by alterations in sickle erythrocyte membrane protein distribution, splenic dysfunction, or disruption to the vascular endothelium. Alloantibodies may complicate future cross-matching for potentially life-saving transfusion. Transfusion reactions have been associated with stroke, pain crises, and acute respiratory failure. The incidence of alloimmunization can be decreased by extended phenotype matching for the Rhesus, Kell, and Lewis antigen groups, the commonest source of antigen immunization. Extended cross-matching for these antigens should therefore be routine for SCD patients. Avoidance of transfusion for unclear or unproven indications when possible is, however, the most effective way of preventing transfusion complications.

**Hypontrahnia**
Hypontrahnia has been suggested as a perioperative trigger of SCD complications, but this is based on extrapolation from a relatively small number of observations from non-hospital settings. There is no publication to demonstrate a direct link between perioperative hypontrahnia and sickle complications. The mechanisms of the apparent hypontrahnia-induced crisis are unknown, although aberrant vasoconstriction has been suggested as a contributing factor. Iatrogenic hypontrahnia may be indicated during cardiac and neurosurgical procedures, and there is no direct clinical evidence to demonstrate that this should be avoided in SCD patients. If vasoconstriction is indeed a key factor, the vasodilation accompanying the deep anaesthesia induced during these procedures might be expected to be protective. In general, however, maintenance of norntrahmia is a basic standard of anaesthetic care and should be a goal for the SCD patient, as in the general surgical population.

**Management of complications**
The anaesthetist, with specialized skills in pain management, ventilation, and critical care may play a role in treating complications of SCD such as pain crisis and ACS.

**Pain crisis**
Acute recurrent episodes of pain, typically in the long bones, ribs, vertebrae or abdomen, are the hallmark of SCD. Bone pain is thought to arise from ischaemia and infarction of the marrow or cortex, while abdominal pain can be caused by bowel dysfunction, organ infarction, or referred from the ribs. Management of pain is based on the site and severity of the discomfort, and should be guided by pain analogue scoring scales. Oral analgesics may be adequate for minor attacks, while opioids such as morphine, hydromorphone, pethidine, or fentanyl are appropriate for control of severe pain. Patient-controlled i.v. analgesia, with baseline analgesia provided if required by background infusion or supplemental fentanyl transdermal patch, is the most effective means of delivery. Caution should be exercised about the accumulation of the epileptogenic breakdown product norpethidine, particularly with patients with impaired renal function, lowered seizure thresholds secondary to cerebrovascular disease, or opioid tolerance as a result of recurrent analgesic requirement.

Opioid tolerance can be a significant problem in some patients who have needed high doses in the past. Ancillary analgesics such as acetaminophen or non-steroidal anti-inflammatory analgesics have an opioid-sparing effect and should be used in conjunction with narcotics to improve analgesia and decrease side effects. High dose methylprednisolone can reduce opioid requirements, presumably by decreasing marrow oedema and pressure on the bone cortex; however, a higher pain relapse rate on withdrawal of steroids has been noted. Regional anaesthesia, such as peripheral nerve block or epidural analgesia, is a highly effective alternative or complementary method of pain control.

Although aggressive hydration and supplemental oxygenation are often prescribed, it is unclear if these are of benefit in uncomplicated pain crises. Red blood cell transfusion is not indicated in the absence of complications. ACS, precipitated by fat embolism from infarcted marrow, is a dangerous consequence of a bone pain crisis. Respiratory splinting from abdominal or rib pain may also potentially cause or predispose to pulmonary complications. Effective pain control, early mobilization, incentive spirometry and close and regular pulmonary examination and monitoring may be effective in the prevention and detection of respiratory problems during a pain crisis.

**Acute chest syndrome (ACS)**
ACS is defined as the onset of a new lobar infiltration on chest x-ray, excluding atelectasis, accompanied by fever greater than 38.5°C, respiratory distress, or chest pain. A heterogeneous group of precipitants can trigger this syndrome of sickle-related acute lung injury in the non-hospital setting, and the precise prophylaxis and management of postoperative ACS have not been established definitively. The incidence following more invasive surgical procedures such as intra-abdominal operations or joint replacement is approximately 10–15%. ACS is typically detected 2–3 days postoperatively. Pulmonary vascular damage, evidenced by an abnormal lung field on chest x-ray or
pulmonary hypertension (diagnosed by Doppler echocardiography) is associated with a markedly increased incidence of ACS and sudden death in the community. Similarly, vascular damage is probably a risk factor for the development of postoperative ACS. Postoperative splinting and atelectasis are associated with ACS, and routine aggressive pulmonary toilet may decrease its incidence. As in an established sickle pain crisis, mobilization, good control of surgical pain, incentive spirometry, physiotherapy, and attention to pulmonary function may be important in the prevention of postoperative sickle cell lung complications.

Treatment of ACS involves supplemental oxygenation and ventilatory support as indicated by the severity of respiratory compromise and extent of pulmonary involvement. Reactive airway disease is present in up to half of patients with SCD, and bronchodilators should be used if bronchospasm is suspected. I.V. dexamethasone has been noted to decrease the severity of ACS in children, and may be of potential benefit in postoperative ACS. Pneumonia can trigger and complicate ACS, and broad-spectrum antibiotics such as a cephalosporin and erythromycin in combination are indicated if infection supervenes. Correction of anaemia by transfusion improves arterial oxygenation when ACS produces hypoxaemia; this may improve outcome although this impression has not been subject to rigorous study. Patients who may particularly benefit include those with severe anaemia, thrombocytopaenia, or multilobar involvement. The value of erythrocyte exchange transfusion remains ill-defined, and this intervention should be reserved for severe cases if initiated. Continuous positive airway pressure or mechanical ventilation as indicated should be initiated if respiratory failure develops.

Caution in practice
A sickle-orientated approach therefore has adverse implications without confirmed benefit. The philosophical starting point of medical practice is encapsulated in the maxim *primum non nocere*—first do no harm. The clinician should therefore concentrate on the basic standards of generally accepted anaesthetic practice, rather than adopting potentially harmful but unproven strategies. Instead of viewing the problem as that of random acute exacerbations of sickling, the anaesthetist should approach the disease as one of progressive, chronic vascular damage. This gestalt provides for a better understanding of silent but insidious end-organ damage in the brain, kidneys, and lungs. This allows for more accurate preoperative assessment, with a better grasp of the potential for perioperative organ dysfunction in the individual patient. It also points to the development of potentially effective ways of preventing perioperative sickle cell complications.

Anaesthesia—the next 50 yr
An awareness of the broader abnormalities of SCD that extend beyond the immediate consequences to the red blood cell suggests potential for novel anaesthetic prophylactic or therapeutic interventions.

Steroids
An approach to SCD as a chronic inflammatory condition implies a place for pre-emptive anti-inflammatory agents. The concept of severe asthma as an inflammatory process rather than an isolated problem of airway reactivity, for example, has led to the effective pre-emptive use of steroids for severe cases in the perioperative period. Limited evidence suggests a role for steroids in the treatment of SCD complications, and this class of drugs could prove to be effective preventative treatment in the surgical patient. Nevertheless, a prophylactic role for steroids remains at present a speculative but interesting option.

Heparin
S.C. heparin is now accepted standard prophylaxis against postoperative venous thrombosis in the wider surgical population. Given the prothrombotic tendency of SCD patients, postoperative heparin may be a simple, inexpensive, and effective pre-emptive intervention against some SCD complications. A definitive controlled perioperative study of this hypothesis would be difficult to construct, however, as withholding a drug with known benefit against deep vein thrombosis would be unethical.

Nitric oxide
The role of inhaled nitric oxide for the treatment of pain crises and ACS is currently under investigation. Initial reports suggest inhaled nitric oxide may reduce analgesic requirements during pain crises, and can improve oxygenation during severe ACS.

Conclusions
SCD has often been cited as a classic example of a ‘molecular disease’—diverse and varied clinical effects arising from an isolated error of genetic information. The anaesthetic history of this disease may be seen as an analogous illustration of medical practice—widespread and potentially harmful alterations to practice based on an essential error in the mental construct of the disease. The ‘peculiar anomaly’ of human red blood cells and clinical consequences were first described some 100 yr previously, while the concept of sickling-centred management originated 50 yr ago. The accumulation of evidence since then has revealed SCD to be an illness defined by progressive inflammatory vascular damage, rather than simply by erythrocyte sickling. Organized scepticism, the methodical questioning and testing of beliefs and theories, is the bedrock of scientific professionalism. The lesson from the anaesthetic history of SCD in the previous century is one of the importance of objective evidence in confirming credible hypotheses. Although our current concept of SCD seems plausible, the impact of this on future anaesthetic methods must be guided by empirical
clinical outcome data. For the present, the basis of SCD management therefore must remain attention to the fundamentals of anaesthetic practice.

Acknowledgements
This work was supported by the Nuffield Department of Anaesthetics, Oxford. The author wishes to thank Todd L. Saititi PhD (East Carolina University School of Medicine, North Carolina, USA) for assistance in locating various early publications on SCD. In addition the author gratefully acknowledges the assistance and advice of the anonymous reviewers, and the former editor of the BJA Professor Jennifer Hunter (Professor of Anaesthesia, University of Liverpool).

References
4 Beet EA. The genetics of sickle-cell trait in a Bantu tribe. Ann Eugen 1949; 14: 279–84
5 Bell AJ, Kotse RH, Mitchell AG, Cooley TB, Lee P. Sickle cell anemia. Reports of two cases in young children in which splenectomy was performed. Am J Dis Child 1927; 34: 923–33
6 Bernini JC, Rogers ZR, Sandler ES, Reisch JS, Quinn CT, Buchanan GR. Beneficial effects of intravenous dexamethasone in children with mild to moderate acute chest syndrome complicating sickle cell disease. Blood 1998; 92: 3082–9
8 Bridgers WH. Cerebral vascular disease accompanying sickle cell anemia. Am J Pathol 1939; 15: 353–62
15 Dresbach M. Elliptical human red corpuscles. Science 1904; 19: 469–70
17 Dreyfoos M. Sickle cell anemia. Arch Pediatr 1926; 43: 436–47
22 Firth PG. Head CA. Sickle cell disease and anesthesia. Anesthesiology 2004; 101: 766–85
30 Hahn EV, Gillespie EB. Sickle cell anemia. Arch Intern Med 1927; 39: 234–54
31 Ham TH, Castle WB. Relationship of increased hypotonic fragility and of erythrocytosis to the mechanism of hemolysis in certain anemias. Trans Assoc Am Physicians 1940; 55: 127–32
32 Hamilton JF. A case of sickle cell anemia. US Veterans’ Bureau Med Bull 1926; 2: 497–500
33 Harris LC, Haggard ME, Travis LB. The co-existence of sickle cell disease and congenital heart disease; a report of three cases with repair under cardiopulmonary bypass in two. Pediatrics 1964; 33: 562–70
35 Hebbel RP. The sickle erythrocyte in double jeopardy: autooxidation and iron decompartmentalization. Semin Hematol 1990; 27: 51–69
38 Hebbel RP, Morgan WT, Eaton JW, Hedlund BE. Accelerated auto oxidation and heme loss due to instability of sickle hemoglobin. Proc Natl Acad Sci USA 1988; 85: 273–41
39 Hebbel RP, Vercellotti GM. The endothelial biology of sickle cell disease. J Lab Clin Med 1997; 129: 288–93
40 Henderson AB, Thornell HE. Observations on the effect of lowered oxygen tension on sicklema and sickle cell anemia among military flying personnel. J Lab Clin Med 1946; 31: 769–76
42 Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med 1910; 6: 517–21
91 Vijay V, Cavenagh JD, Yate P. The anaesthetist’s role in acute sickle cell crisis. Br J Anaesth 1998; 80: 820–8
95 Windsor T, Burch GE. Electrocardiogram and cardiac state in active sickle-cell anemia. Am Heart J 1945; 29: 685–96