Clinical Reports

Anaesthesia for renal transplantation in sickle cell disease

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Sickle cell disease (SCD) is associated with many pathological and functional abnormalities affecting all organ systems. Renal manifestations of SCD may result in end-stage renal disease (ESRD), which can be treated by chronic haemodialysis or renal transplantation. Renal transplantation was successfully performed in a 25-yr-old male with sickle cell beta-thalassaemia and nephrotic syndrome. We present a case report of this patient, a discussion of the renal complications associated with SCD and the perioperative management of a patient with SCD undergoing renal transplantation.

L'anémie falciforme peut entrainer une myriade d'anomalies fonctionnelles et pathologiques impliquant tous les systèmes avec entre autres, de l'insuffisance rénale chronique sévère. Nous vous présentons un cas de transplantation rénale réussie chez un homme de 25 ans atteint d'un syndrome néphrotique avec une hémoglobinopathie de type Sβ-thal. Nous discutons de l'impact de l'anémie falciforme sur la fonction rénale et des considérations péri-opératoires propres à la transplantation rénale chez ce type de patient.

Sickle cell disease (SCD) is a haematological disorder of the human red blood cell, caused by the inheritance of the sickling gene alone or in combination with another abnormal haemoglobin gene. The commonest genotypes are homozygous sickle cell disease (SS), sickle cell haemoglobin C disease (SC) and sickle cell beta-thalassaemia (Sβthal). The disease is found most commonly in people of black African origin but it also occurs in other pigmented races. It is common in tropical Africa, the Caribbean, USA and to a less extent, in the Middle East, Greece, Turkey and India.

Key words
ANAESTHESIA: transplantation;
BLOOD: anaemia, sickle cell disease;
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The molecular abnormality of sickle haemoglobin is an amino acid substitution (valine for glutamic acid) in the beta chain of the haemoglobin molecule. Under conditions of reduced oxygen tension, sickle haemoglobin undergoes gelation, causing a reduced deformability of the erythrocyte which assumes the elongated "sickled" shape. In the microcirculation, this leads to stasis, increased blood viscosity, thrombo-embolic phenomena and haemolysis. Sickling-induced stasis may lead to occlusion of the microcirculation, local hypoxia and further sickling.

The clinical course of SCD tends to be most severe in the SS genotype but there is a wide spectrum of presentation and the clinical course of sickle cell haemoglobin C disease and sickle cell beta-thalassaemia may be indistinguishable from homozygous sickle cell disease. Many complications of SCD have been reported and these affect all organ systems in the body. For a review of the aetiology, clinical features, complications and general management of SCD, the reader is referred to Serjeant,[1] Weatherall,[2] and Abdalla.[3] The anaesthetic problems associated with sickle cell states have been reviewed recently by Esseltine *et al.*[4]

Renal manifestations of SCD include hyposthenuria, polyuria, haematuria, proteinuria, glomerulonephritis, pyelonephritis and the nephrotic syndrome.[5-12] End-stage renal disease (ESRD) is common in adult patients with SCD and some of the complications of renal failure, especially acidosis, cardiac failure, fluid and electrolyte disorders, can encourage sickling. End-stage renal disease in patients with SCD may be due to other causes[13] unrelated to the sickling process, and in some cases a definite diagnosis is not possible. Irrespective of aetiology, the clinical presentation and management of ESRD remain the same; it may be treated by haemodialysis or renal transplantation.

Following a survey by Chartterjee,[14] renal transplantation was recommended for patients with SCD and ESRD.

Anaesthesia for renal transplantation is complicated by the effects of grossly abnormal renal function in a patient undergoing major surgery and patients with SCD present a greater anaesthetic risk[15,16] because of the effects of chronic anaemia and vaso-occlusive crises in the perioperative period. However, there are no reports of the anaesthetic management of patients with SCD undergoing renal transplantation. We present a case of renal transplantation in a patient with SCD and a discussion of the problems of anaesthetic management.

Case report

The patient was a 25-yr-old Omani, a black male of East African origin with sickle cell beta-thalassaemia diagnosed 14 yr earlier. He had been admitted to hospital about ten times within this period for management of crises. He presented at this hospital with a history of progressive generalised swelling, loss of appetite, fullness in the abdomen, low back pain and non-productive cough. Two younger siblings had sickle cell disease and three had sickle cell trait. He looked pale and had generalised oedema. The BP was 130/90 mmHg, with signs of high output cardiac failure. He had a haemic murmur and a left pleural effusion. The abdomen was distended and the liver was palpable just below the right costal margin. The ECG showed sinus rhythm with left ventricular hypertrophy.

Investigations showed hypoalbuminaemia, gross proteinuria, no glycosuria, normal blood sugar and normal liver function. The BUN was 8 $mM \cdot L^{-1}$ and creatinine 271 $mM \cdot L^{-1}$. He had a microcytic, hypochromic anaemia with a haemoglobin concentration of 4.5 $g \cdot dl^{-1}$. Renal biopsy showed a mesangiocapillary glomerulonephritis. There was no history of renal disease in the family. The clinical features were consistent with the nephrotic syndrome and treatment was started with blood, albumin and diuretics. Later, dipyridamole, hydralazine and captopril were added to control hypertension. However, his renal condition continued to worsen. He was considered unsuitable for chronic renal dialysis because of unfavourable social conditions and about nine months after presentation, arrangements were made for renal transplantation. His 45-yr-old mother was found to be the most suitable donor. She had a mild anaemia which had been present all her life. Haematological investigations showed no sickling but they were suggestive of beta-thalassaemia trait.

Preoperatively, he weighed 44 kg and had marked ascites. The heart was enlarged but the lung fields were clear. He was anaemic, with a haemoglobin of 3.0 $g \cdot dl^{-1}$. He was transfused with three units of packed cells and one unit of whole blood over several days to raise his haemoglobin concentration to 11.8 $g \cdot dl^{-1}$. Estimation of HbS was not done because the necessary reagents were not available. Biochemical investigations on the morning of surgery were: sodium 136 $mM \cdot L^{-1}$, potassium 5.6 $mM \cdot L^{-1}$, BUN 28.5 $mM \cdot L^{-1}$, creatinine 824 $mM \cdot L^{-1}$, total protein 57 $g \cdot L^{-1}$ and albumin 29 $g \cdot L^{-1}$. He was given pre-medication with 3 mg lorazepam orally one and a half hours preoperatively. He also received preoperative immunosuppression with azathioprine and cyclosporin and antibiotics. He was not receiving any anti-hypertensives at the time of surgery.

In the operating room, an intravenous infusion was started with 0.9 per cent saline through a 14G cannula. Electrocardiographic electrodes and a blood pressure cuff were applied and baseline readings taken. Skin electrodes were applied over the wrist for peripheral nerve stimulation. Neuromuscular block was monitored by the observation of thumb adduction to supramaximal nerve stimulation from a peripheral nerve stimulator (Bard) using train-of-four (TOF) stimuli repeated every 12 sec. A warming blanket with water pre-heated at 37° C was used and all intravenous fluids and blood were warmed to 37° C.

After pre-oxygenation for three minutes, anaesthesia was induced with fentanyl 100 μg and thiopentone 100 mg intravenously and the trachea was intubated with a cuffed tube following atracurium, 25 mg. Anaesthesia was maintained with nitrous oxide 50 per cent in oxygen and isoflurane 0.5–2 per cent. Additional doses of fentanyl (total 400 μg) were given as required. Neuromuscular block was maintained with an infusion of 0.1 per cent atracurium in 0.9 per cent saline given by a syringe pump, starting with a dose of 0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ and adjusted to maintain visibly, the first twitch of TOF stimulation. The lungs were ventilated mechanically to maintain normocapnia. The right subclavian vein was cannulated with a 16G cannula for central venous pressure monitoring and a 20G cannula was inserted into the left radial artery for monitoring of blood pressure and blood gases. The ECG, BP, oxygen saturation and temperature were monitored by a Hewlett-Packard 78354A monitor. Inspired O_2 and end–tidal CO_2 were monitored by an Accucap (Datascope) monitor.

The donor kidney was transplanted by anastomosis of the renal artery to the internal iliac artery, the renal vein to the external iliac vein and the ureter to the bladder. Dopamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started and continued into the early postoperative period. The graft was well perfused and urine was produced promptly following the administration of mannitol 20 g and frusemide 40 mg.

The cardiovascular system was stable throughout surgery. Nasopharyngeal temperature remained at 35° C. Initial blood gas analysis showed severe metabolic acidosis with a pH of 7.14 and this was partially corrected to 7.30 with 150 mM of sodium bicarbonate. The total

duration of surgery was approximately six hours. The estimated blood loss was 1.4 L and 2 L of ascitic fluid was aspirated from the abdomen. A total of 4 L crystalloids, 1 L colloids, and 1.5 L fresh blood were transfused.

On completion of surgery, nitrous oxide, isoflurane and atracurium were discontinued. The total dose of atracurium used was 125 mg. Residual neuromuscular block was reversed with 1.2 mg of atropine and 2.5 mg of neostigmine. Recovery was rapid and the trachea was extubated after full return of neuromuscular function and respiration was deemed to be adequate.

Cardiovascular and respiratory monitoring continued into the postoperative period. Morphine was given intravenously for pain relief when required. He maintained a massive diuresis with a rapid decrease of plasma creatinine level to normal within 48 hr. Immunosuppression was continued with prednisolone, azathioprine and cyclosporin. On the fourth postoperative day, he had three convulsions lasting for a few seconds to two minutes and he was treated with diazepam and magnesium because of a low serum magnesium of 0.55 $mM \cdot L^{-1}$ (normal 0.75–1.25 $mM \cdot L^{-1}$).

He was discharged from the hospital on the tenth postoperative day. Mild hypertension was treated with nifedipine. Two months after surgery, he continued to show progressive gain in weight without evidence of oedema. In the fourth postoperative month, he was readmitted with sickle cell pain crises which were treated with analgesics, hydration and antibiotics. Following that, he was admitted to hospital almost weekly with painful crises. Two months later, two units of blood were transfused because of a sudden decrease of haemoglobin concentration to 5.8 $g \cdot dl^{-1}$. He has been free of pain since then and nine months after transplantation he remains healthy at home, on regular treatment with prednisolone, cyclosporin, folic acid, chloroquine and benzathine penicillin prophylaxis. The haemoglobin levels remain relatively high (above 9 $g \cdot dl^{-1}$) and renal function is excellent with all biochemical indices within normal limits.

Discussion

The pathological changes of SCD affect all organ systems in the body and many renal abnormalities have been described. Beginning from childhood[5,6] decline in renal function occurs in severe SCD and renal impairment is common in adults with SCD.[17] Sickle cell related renal disease is commoner in adults and is an important cause of death after the age of 20 years.[18]

Renal manifestations of SCD are: inability to concentrate urine, polyuria, polydipsia, enuresis, nocturia, proteinuria, haematuria, impaired potassium secretion, impaired acidification of urine, pyelonephritis, glomerulonephritis and the nephrotic syndrome.[5–12,17–23] These abnormalities may be due to the changes in renal structure and function as a result of the haemodynamic effects of a chronic anaemia and vaso-occlusion of the renal vessels, especially within the medulla. Obliteration of the vasa recta results in reduction of renal blood flow. The combination of hypoxia, acidosis and hyperosmolarity in the renal medulla leads to sickling, vaso-occlusion, medullary and papillary necrosis. Morphologic changes include renal fibrosis, atrophy, scarring of the medulla, obliteration of the vasa recta, glomerular hypertrophy and iron deposits in tubular epithelial cells. Other possible causes of renal changes in SCD are infection, drugs,[22] autoimmune nephritis[23] and hyperperfusion of renal cortical vessels.[10] Sickle cell disease and ESRD frequently co-exist but sickle cell-induced renal disease may not be distinguishable from renal disease due to other causes.

The nephrotic syndrome (oedema, albuminuria and hypoalbuminaemia) may be caused by other factors[13] but the clinical presentation and histological findings of the nephrotic syndrome caused by SCD[7] may be indistinguishable from those of different aetiology. The nephrotic syndrome may be considered as the extreme form of glomerular dysfunction in SCD.[7] The prognosis of the nephrotic syndrome in association with SCD is poor, with a higher mortality rate compared with other patients with SCD.[24]

Renal disease may have adverse effects on the clinical course of SCD. Patients with SCD and ESRD have severe anaemia and problems associated with multiple blood transfusions, angina pectoris, cardiomegaly, hyperkalaemia and metabolic acidosis.[22] Hyposthenuria leads to dehydration which can promote further sickling.[5] When on renal dialysis, these patients may have problems associated with cardiovascular instability, infections[22] and decreased ability to excrete potassium[19,20] from the remaining functioning nephrons.

Our patient presented with many of the clinical features of SCD and ESRD. Some of these, chronic anaemia, acidosis, fluid and electrolyte imbalance and cardiac failure are common to the two disease entities.

The anaemia of SCD is caused by excessive haemolysis and decreased red cell lifespan but hypochromic anaemia has been described,[25] especially where there is added malnutrition or excessive bleeding. The anaemia of ESRD is probably caused by impaired erythropoiesis, decreased red cell life span, increased haemolysis and bleeding. The degree of anaemia in patients with SCD and ESRD is more severe than that in other patients with renal disease of comparable severity.[22]

Acidosis in SCD may be due to circulatory stasis and impaired acidification of urine. The sickling process is enhanced by acidosis and the routine correction of

acidosis with alkali[16,26] has been recommended but does not seem to offer any long-term benefits. Excessive alkalinisation may also decrease oxygen delivery to the tissues as a result of the shift of the oxygen dissociation curve to the left. Acidosis in renal disease is due to the inability of the kidney to excrete the acid load of metabolism; acidification of urine is regained with a functioning graft.

Renal transplantation is considered the best long-term treatment for patients with ESRD but' relatively few patients with SCD and ESRD have received transplants. This may be due to the increased perioperative morbidity and mortality in patients with SCD[15,16,26] and lack of essential medical facilities in countries where SCD is most prevalent.[27] There is also the possibility that sickle cell nephropathy may recur in a transplanted kidney.[28] The number of renal transplants in patients with SCD is not known but following a survey in 1987 Chatterjee recommended maintenance dialysis and renal transplantation for patients with SCD and ESRD.[14]

However, there have been other reports of postoperative complications following renal transplantation in patients with SCD. Barber *et al.*[29] found that allograft survival for patients with SCD was less than half the rate for black recipients without SCD, one year following cadaveric renal transplantation. They concluded that transplantation may not offer better renal replacement therapy than dialysis for adults with SCD. Spector *et al.*[30] reported the case of a 34-yr-old female with homozygous SCD, two years after renal transplantation. The patient developed severe painful crises postoperatively, which were managed successfully with partial exchange transfusions. It was inferred that the crises were caused by the increased haematocrit following renal transplantation. A patient of Gonzalez-Carrillo *et al.*[31] with SCD and ESRD required repeated exchange transfusions for high HbS levels following renal transplantation. One patient developed recurrent sickle cell nephropathy in a transplanted kidney.[28] Donnelly *et al.*[32] reported a case of sickling in the renal microvasculature six days after renal transplantation. Therefore, the role of renal transplantation in patients with SCD and ESRD remains uncertain.

The major problems of anaesthesia in renal transplantation are: fluid and electrolyte imbalance, chronic anaemia, disorders of acid/base state, hypertension, cardiac dysrrythmias, cardiac failure, pericardial and pleural effusion, diminished respiratory function, coagulation disorders and the effects of abnormal renal function on drug pharmacokinetics and metabolism.[33] In addition these patients require other drugs as maintenance therapy and the possibility of adverse drug reactions during anaesthesia is increased.

In order to reduce the problems associated with anaesthesia, there have been many recommendations for the anaesthetic management of patients with SCD. Elective surgery should be performed when the patient is not having a crisis and is free from infection.[16,27] Oduro and Searle[15] suggested a safe and simple anaesthetic technique, with adequate oxygenation, ventilation and maintenance of circulating volume and good postoperative care. Attempts to abolish the sickling process by alkalinisation[16,26] or other drug regimens[34–36] have proved ineffective in the long term or have been associated with many undesirable side-effects. Piracetam[37] and citiedil[38] prevent sickling *in vitro* and *in vivo* but their effects are yet to be proven in a large series of cases. In the absence of any effective and safe therapeutic means of suppressing the sickling process, the recommendations for safe anaesthesia remain valid and factors known to promote sickling must be avoided.

Preoperative blood transfusion was considered necessary because of the need to increase the arterial oxygen carrying capacity in a patient with a haemoglobin of 3 $g \cdot dl^{-1}$ about to undergo major surgery. The amount of blood transfused would be sufficient to decrease the concentration of HbS to less than 40 per cent and reduce the risk of further sickling. Vaso-occlusion is less likely to occur in a patient who has been transfused preoperatively.[4] Preoperative transfusion also causes bone marrow depression,[26] resulting in the production of fewer erythrocytes with HbS. Preoperative exchange transfusion has been recommended for patients with SCD[16,26] but the advantages must be considered against the disadvantages of multiple blood transfusions. Esseltine *et al.*[4] have published guidelines for preoperative transfusion in patients with SCD. Blood transfusion is associated with improved graft survival in renal transplants.[39]

Preoperative medication must aim to attenuate anxiety in a patient with chronic debilitating disease undergoing a major operation which is likely to lead to a marked change in lifestyle. A preoperative visit is mandatory in addition to the prescription of the appropriate premedicants, which should produce anxiolysis without undue cardiovascular or respiratory depression. Oral pre-medication is recommended because of the dangers of bleeding in uraemic patients following intramuscular injections.[33] The benzodiazepines seem to satisfy these criteria. It is also necessary to continue maintenance therapy for the treatment of hypertension, prophylatic antibiotics, steroids and immunosuppressive therapy into the perioperative period.

Hypoxia is the commonest cause of sickling and a high inspired concentration of oxygen is required during anaesthesia in patients with SCD. This is usually achieved by pre-induction oxygenation and maintenance with 50 per cent oxygen in nitrous oxide.[4,15,16,26,27] This practice

will also be advantageous in patients with ESRD where anaemia is present. The use of a pulse oximeter offers a simple, accurate and safe method of continuous assessment of arterial oxygenation.[40]

In spite of its depressant action on the cardiovascular and respiratory systems, thiopentone in minimal doses[41,42] is satisfactory as the induction agent in patients with SCD and ESRD. Other induction agents, methohexitone and propofol have been used with satisfactory results in anaesthesia for both disease states.

The inhalational agents are useful supplements for the maintenance of general anaesthesia and have the advantage of non-renal elimination. Isoflurane seems to be the agent of choice because of the cardiovascular stability it provides and lack of nephrotoxicity even in large doses.[43] However, other inhalational agents have been used successfully in patients with SCD and ESRD. The shorter acting opioids, fentanyl, alfentanil and sufentanil offer advantages over the longer-acting drugs morphine and pethidine for intraoperative analgesia.[44]

None of the neuromuscular blocking drugs (NMBD) seems to offer any special advantages in patients with SCD. However, the choice of a NMBD has important implications in anaesthesia for patients with ESRD. When rapid tracheal intubation is desirable, succinylcholine is the relaxant of choice; otherwise its use is avoided because of its unwanted effects on serum potassium and cardiac rhythm.[45]

The older, longer-acting non-depolarising NMBD, d-tubocurarine[46] and pancuronium[47] have been used extensively in patients with ESRD since they are eliminated from the body via renal and non-renal routes. Gallamine[48] and metocurine[49] are excreted predominantly by the kidney and are therefore contraindicated in renal failure.

The newer non-depolarising NMBDs vecuronium and atracurium offer greater advantages because of their shorter duration of action, easy reversibility and lower incidence of cardiovascular side effects.[50] Vecuronium is eliminated by renal and extra-renal factors and whilst some reports indicate that its duration of action is little affected by renal dysfunction,[50,51] others suggest the possibility of accumulation with large doses.[52–54]

Atracurium would seem to be the relaxant of choice because its metabolism is independent of the kidney or the liver and the duration of action is the same in patients with or without renal disease.[55,56] The use of a continuous infusion provides a constant level of neuromuscular block for prolonged periods which is easily reversed at the end of surgery.[57] Clearance of laudanosine, a metabolite of atracurium with cerebral irritant effects, is not affected by renal failure.[56,58] The neuromuscular junction must be monitored whenever vecuronium or atracurium is used.

Cyclosporin A is an immunosupressant drug frequently used to prevent rejection of the transplanted kidney. The use of cyclosporin and its solvent cremophor may be associated with prolonged neuromuscular block in cats[59] and humans[60,61] and this effect is greater with pancuronium and vecuronium than with atracurium.[59,62] There was no evidence of prolongation of neuromuscular block in this patient.

A stable cardiovascular system is desirable in patients with SCD undergoing renal transplantation in order to avoid sickling and enhance perfusion of the renal allograft. Close monitoring of ECG, blood pressure and central venous pressure is required. Non-invasive blood pressure monitoring is usually adequate but we chose to monitor direct intra-arterial pressure in this patient because of the added advantage of monitoring the changes in acid/base state. Fluid and blood loss must be replaced promptly because of the dangers of dehydration and hypotension.

Early recovery with a full return of cardiovascular and respiratory responses is essential. The use of drugs with non-renal routes of elimination and short duration of action offers the advantages of early recovery even in the absence of normal renal function. Neuromuscular drugs must be fully reversed to ensure that the patient is able to maintain satisfactory ventilation postoperatively.

The same attention that is taken intraoperatively must be extended into the postoperative period. The patient must be nursed in a high-dependency nursing ward where cardiovascular and respiratory monitoring and oxygen therapy can be continued as required for patients with SCD and ESRD who have undergone major surgery. Arterial hypoxaemia is most common in the immediate postoperative period[63,64] and must be avoided in a patient with SCD. Postoperative analgesia must be given without causing undue cardiorespiratory depression: small doses of opiates intravenously are adequate.

The cause of postoperative convulsions may have been hypomagnesaemia or SCD. Hypomagnesaemia can be caused by excessive diuresis and may lead to muscle twitching, tetany, tremors, mental irritability, hallucinations and convulsions.[65] There may be an association between the neurotoxic effects of cyclosporin and hypomagnesaemia.[66] The neurological complications of sickle cell disease are convulsions, hemiplegia, intracranial haemorrhage, vertigo and coma.[1] The absence of any neurological disorder in the preoperative period and the rapid response to magnesium replacement therapy make it unlikely that SCD was the cause of convulsions in this patient.

Conclusion

Until further evidence is available, the role of renal transplantation in SCD and ESRD remains uncertain. However, the variable clinical course of SCD, from almost benign to very severe, makes controlled studies on the benefits of renal transplantation difficult to evaluate. Improved medical care means that more people with SCD are living long enough to develop ESRD and it is likely that the need for renal transplantation in SCD will increase. An understanding of the two disease entities by the anaesthetist is essential for successful outcome in patients with SCD undergoing renal transplantation.

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References

1 *Serjeant GR*. Sickle Cell Disease, 1st ed. New York: Oxford University Press, 1985.
2 *Weatherall DJ*. Disorders of the synthesis and function of haemoglobin. *In*: Weatherall DJ, Ledingham JGG, Warell DA (Eds.). Oxford Textbook of Medicine, 2nd ed. Oxford: Oxford University Press, 1987; 19: 108–30.
3 *Abdalla SH, Weatherall DJ*. Haematological problems. *In*: Manson-Bahr PEC, Bell DR (Eds.). Manson's Tropical Diseases. 19th ed. London: Balliere, Tyndall 1987: 942–86.
4 *Esseltine DW, Baxter MRN, Bevan JC*. Sickle cell states and the anaesthetist. Can J Anaesth 1988;35: 385–403.
5 *Kunz HW, Mellin GW, Cheung MW, Pratt EL*. Impairment of urinary concentration in sickle cell anaemia. Am J Dis Child 1953; 86: 512.
6 *McCrory WW, Goren N, Gornfield D*. Demonstration of impairment of urinary concentration ability or "Pitressin Resistance" in children with sickle-cell anaemia. Am J Dis Child 1953; 86: 512–3.
7 *McCoy RC*. Ultrastructural alterations in the kidney of patients with sickle cell disease and the nephrotic syndrome. Lab Invest 1969; 21: 85–95.
8 *Buckalew VM, Someren A*. Renal manifestations of sickle cell disease. Arch Int Med 1974; 133: 660–9.
9 *Alleyne GAO, Statius van Eps LW, Addae SK, Nicholson GD, Schouten H*. The kidney in sickle cell anaemia. Kidney Int 1975; 7: 371–9.
10 *De Jong PE, Statius van Eps LW*. Sickle cell nephropathy: new insights into its pathophysiology. Kidney Int 1985; 27: 711–7.
11 *Strauss J, Zilleruelo G, Abitbol C*. The kidney and haemoglobin S. Nephron 1986; 43: 241–5.
12 *Pearson HA*. The kidney, hepatobiliary system and spleen in sickle cell anaemia. Ann N Y Acad Sci 1989; 565: 120–5.
13 *Houston JC, Joiner CL, Trounce JR*. Diseases of the kidney. *In*: A Short Textbook of Medicine, 7th ed. London: Hodder and Stoughton, 1982; 448–97.
14 *Chartterjee SN*. National study in natural history of renal allografts in sickle cell disease or trait: a second report. Transplant Proc 1987; 19: 33–5.
15 *Oduro KA, Searle JF*. Anaesthesia in sickle cell states: a plea for simplicity. Br Med J 1972; 2: 596-8.
16 *Gilbertson AA*. Anaesthesia in West African patients with sickle anaemia, haemoglobin SC disease and sickle cell trait. Br J Anaesth 1965; 37: 614–21.
17 *Morgan AG, Serjeant GR*. Renal function in patients over 40 with sickle cell anaemia. Br Med J 1981; 282: 1181–3.
18 *Thomas AN, Pattison C, Serjeant GR*. Causes of death in sickle cell disease in Jamaica. Br Med J 1982; 285: 633–5.
19 *De Fronzo RA, Taufield PA, Black H, McPhedran P, Cooke CR*. Impaired renal tubular potassium secretion in sickle cell disease. Ann Int Med 1979; 90: 310–6.
20 *Battle D, Itsarayoungyuen K, Arruda JAL, Kurtzman NA*. Hyperkalaemic hyperchloraemic metabolic acidosis in sickle cell haemoglobinopathies. Am J Med 1982; 72: 188–92.
21 *Thomas R, Holdbrook T*. Sickle cell disease: ways to reduce morbidity and mortality. Postgrad Med 1987; 81: 265–80.
22 *Cruz IA, Hosten AO, Dillard MG, Castro OL*. Advanced renal failure in patients with sickle cell anaemia: clinical course and prognosis. J Natl Med Ass 1982; 74: 1103–9.
23 *Pardo V, Strauss J, Kramer H, Ozawa T, McIntosh RM*. Nephropathy associated with sickle cell anaemia. An autologous immune complex nephritis. II. Clinicopathological study of seven patients. Am J Med 1975; 59: 650–9.
24 *Bakir AA, Hathiwala SC, Ainis H et al*. Prognosis of the nephrotic syndrome in sickle glomerulopathy. Am J Nephrol 1987; 7: 110–5.
25 *Davies S, Henthorn J, Brozovic M*. Iron deficiency in sickle cell anaemia. J Clin Pathol 1983; 36: 1012–5.
26 *Gilbertson AA*. The management of anaesthesia in sickle cell states. Proc R Soc Med 1967; 60: 631–5.
27 *Oduro KA*. Anaesthesia in Ghana: a review with particular reference to indigenous medical conditions. Anaesthesia 1969; 3: 307–16.
28 *Miner DJ, Jorkasky DK, Perloff LJ, Grossman RA,*

Tomaszewski JE. Recurrent sickle cell nephropathy in a transplanted kidney. Am J Kidney Dis 1987; 10: 306–13.

29 *Barber WH, Deierhoi MH, Julian BA et al.* Renal transplantation in sickle cell anaemia and sickle cell disease. Clinical Transplantation 1987; 1: 169–75.

30 *Spector D, Zachary JB, Steriof S, Millan J.* Painful crises following renal transplantation in sickle cell anemia. Am J Med 1978; 64: 835–9.

31 *Gonzalez-Carrillo M, Rudje CJ, Parsons V, Bewick M, White JM.* Renal transplantation in sickle cell disease. Clin Nephrol 1982; 18: 209–10.

32 *Donnelly PK, Edmunds ME, O'Reilly K.* Renal transplantation in sickle cell disease. (Letter) Lancet 1988; 2: 229.

33 *Sear JW.* Anaesthesia in renal transplantation. *In*: Morris P (Ed.). Kidney Transplantation, Principles and Practice, 3rd ed. Philadelphia: Saunders, 1988: 235–61.

34 *Dean JD, Schechter AN.* Sickle cell anaemia: molecular and cellular bases of therapeutic approaches. N Eng J Med 1978; 299: 863–70.

35 *Cho YW, Aviado DM.* Clinical pharmacology for pediatricians. II. Antisickling agents, with special reference to new vasoerythroactive drugs. J Clin Pharmacol 1982; 22: 1–13.

36 *Ueno H, Bai Y, Manning J.* Covalent chemical modifiers of sickle cell haemoglobin. Ann N Y Acad Sci 1989; 565: 239–46.

37 *Gini EK, Sonnet J.* Use of piracetam improves sickle cell deformability in vitro and in vivo. J Clin Pathol 1987; 40: 99–102.

38 *Benjamin LJ.* Membrane modifiers in sickle cell disease. Ann N Y Acad Sci 1989; 247–61.

39 Editorial: Blood transfusion and allograft survival. Lancet 1984; 1; 830–1.

40 *Taylor MB, Whitwam JG.* The current status of pulse oximetry: clinical value of continuous noninvasive oxygen saturation monitoring. Anaesthesia 1986; 41: 943–9.

41 *Dundee JW, Hassard TH.* The influence of haemoglobin and urea levels on the induction dose of thiopentone. Anaesthesia 1983; 38: 26–8.

42 *Christensen JH, Andreasen F, Jansen J.* Pharmacokinetics and pharmacodynamics of thiopental in patients undergoing renal transplantation. Acta Anaesthesiol Scand 1983; 27: 513–8.

43 *Eger II EI.* The pharmacology of isoflurane. Br J Anaesth 1984; 56: 71S–99S.

44 *Bailey PL, Stanley TH.* Pharmacology of intravenous narcotic anaesthetics. *In*: Miller RD (Ed.) Anesthesia 2nd ed., New York: Churchill Livingstone, 1986: 745–97.

45 *Durant NN, Katz RL.* Suxamethonium. Br J Anaesth 1982; 54: 195-208.

46 *Miller RD, Matteo RS, Benet LZ, Sohn YJ.* The pharmacokinetics of d-tubocurarine in man with and without renal failure. J Pharmacol Exp Ther 1977; 202: 1–6.

47 *Somogyi AA, Shanks CA, Triggs EJ.* The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 1977; 12: 23–9.

48 *Ramzan MI, Shanks CA, Triggs EJ.* Gallamine disposition in surgical with chronic renal failure. Br J Pharmacol 1981; 12: 141–7.

49 *Brotherton WP, Matteo RS.* Pharmacokinetics and pharmacodynamics of metocurine in humans with and without renal failure. Anesthesiology 1981; 55: 273-6.

50 *Hunter JM, Jones RS, Utting JE.* Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. Br J Anaesth 1984; 56: 941–51.

51 *Fahey MR, Morris RB, Miller RD, Nguyen T-L, Upton RA.* Pharmacokinetics of Org NC45 (Norcuron) in patients with and without renal failure. Br J Anaesth 1981; 1049–53.

52 *Bevan DR, Donati F, Gyasi H, Williams A.* Vecuronium in renal failure. Can Anaesth Soc J 1984; 31: 491-6.

53 *Starsnic MA, Goldberg ME, Ritter DE, Marr AT, Sosis M, Larijani GE.* Does vecuronium accumulate in the renal transplant patient? Can J Anaesth 1989; 36: 35–9.

54 *Pollard BJ, Doran BRH.* Should vecuronium be used in renal failure? (Letter) Can J Anaesth 1989; 36: 602–3.

55 *Hunter JM, Jones RS, Utting JE.* Use of atracurium in patients with no renal function. Br J Anaesth 1982; 54: 1251–8.

56 *Ward S, Beheimer N, Weatherly BC, Simmonds RJ, Dopson TA.* Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients with renal failure. Br J Anaesth 1987; 59: 697–706.

57 *Flynn PJ, Hughes R, Walton B, Jothilingham S.* Use of atracurium infusions for general surgical procedures including cardiac surgery with induced hypothermia. Br J Anaesth 1983; 55: 135–8S.

58 *Parker CJR, Jones JE, Hunter JM.* Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. Br J Anaesth 1988; 61: 531–40.

59 *Gramstad L, Gjerlow JA, Hysing ES, Rugstad HE.* Interaction of cyclosporin and its solvent cremophor, with atracurium and vecuronium. Studies in the cat. Br J Anaesth 1986; 58: 1149–55.

60 *Crosby E, Robblee JA.* Cyclosporin-pancuronium interaction in a patient with a renal allograft. Can J Anaesth 1988; 35: 300–2.

61 *Wood GG*. Cyclosporine-vecuronium interaction (Letter). Can J Anaesth 1989; 36: 358–66.
62 *Viby-Mogensen J*. Interaction of other drugs with muscle relaxants. Seminars in Anaesthesia 1985; 6: 52.
63 *Nunn JF, Payne JP*. Hypoxaemia after general anaesthesia. Lancet 1962; 2: 631–2.
64 *Canet J, Montserrat R, Vidal F*. Early post-operative arterial oxygen desaturation: determining factors and response to oxygen therapy. Anaesth Analg 1989; 69: 207–12.
65 *Wierner K*. Calcium, magnesium and phosphate. *In*: Gowen-Lock AH (Ed.). Varley's Practical Clinical Biochemistry, 6th ed. London: Heinemann 1988; 601–21.
66 *Thompson CB, June CH, Sullivan KM, Thomas ED*. Association between cyclosporin neurotoxicity and hypomagnesaemia. Lancet 1984; 2: 1116–20.