CHAPTER

62 Sickle Cell Disease

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Although reports suggestive of the disease that would come to be known as sickle cell anemia were published in the 1800s,[1,2] Dr. James B. Herrick is credited with the first modern description in 1910. Herrick and his intern Ernest E. Irons described the case of Walter Clement Noel, a male dental student from Grenada (West Indies), who originally sought care for a cough and fever and whose blood film revealed what Irons described as "peculiar elongated and sickle-shaped red blood corpuscles."[3,4] In this first report, Herrick went on to describe isosthenuria, now recognized as one of the most common manifestations of sickle nephropathy.

Current understanding of sickle cell disease reveals it to be a genetic disorder that follows a pattern of Mendelian autosomal co-dominant inheritance[5,6] and affects numerous organ systems. Molecular studies have demonstrated the defect to be with the hemoglobin molecule,[7] specifically, the result of a substitution of the amino acid valine for glutamic acid at position 6 of the β chain.[8–10] A high prevalence of sickle cell disease and heterozygous sickle hemoglobin exists in areas with a high burden of malaria, including sub-Saharan Africa, the Arabian peninsula, and parts of the Indian subcontinent. The presence of hemoglobin S (HbS) has long been postulated to confer a protective benefit to infection by Plasmodium falciparum, making carriers less susceptible to malarial morbidity and mortality. This characteristic offers possible explanation for the global distribution and persistence of the mutation.

This chapter focuses on renal abnormalities caused by the presence of sickle hemoglobin. Since Herrick's initial description of isosthenuria, a greater understanding of the clinical effects of sickle hemoglobin on kidney morbidity has been gained. The chapter also includes a discussion of the rare but lethal cancers seen among individuals with sickle cell disease. In addition, the chapter describes the potential role of heterozygote inheritance of hemoglobin S in renal disease.

GENETICS

Several decades following Herrick's description, Linus Pauling noted differing electrophoretic properties of hemoglobin taken from individuals with sickle cell anemia in 1949.[7] With this discovery, it became known as the first "molecular disease." Shortly thereafter, Vernon Ingram and James Hunt identified the exact nature of the molecular alteration—the substitution of valine for glutamic acid at the sixth residue of the β chain of hemoglobin.[9–11]

The genetic mutation responsible for the single amino acid substitution occurs on the short arm of chromosome 11, and asserts as an autosomal recessive pattern of inheritance. The mutation itself results from a single nucleotide substitution from a GAG to GTG codon mutation. Because of incomplete recessive inheritance, those with a single mutation (i.e., carriers with sickle cell trait), produce a measurable quantity of hemoglobin S.

The hemoglobin S mutation seems to have arisen in at least two separate occurrences, one in Africa and the other in Asia. In fact, there are four African specific β-globin gene haplotypes—the Benin, Cameroon, Senegal, and Central African Republic (CAR) haplotypes—and one specific to Asia–the Arab-Indian haplotype.[12,13] These several variations in the β-globin gene mutation do seem to confer variance in the observed phenotype. Those individuals with the Senegal haplotype seem to have the least severe disease course, whereas those with the CAR haplotype have the worst disease manifestations.[13] Worldwide, sickle cell disease is estimated to affect over 275,000 live births annually, and over 300 million individuals are carriers of the gene for sickle hemoglobin. In North America and Europe, 2,600 and 1,300 individuals, respectively, are born yearly with these disorders, whereas in southeast Asian regions and Africa these numbers reach 26,000 and 230,000, respectively.[14] These disease frequencies closely parallel the distribution of malaria, prior to the interventions to control its spread.[12]

PATHOPHYSIOLOGY

Normal adult hemoglobin (HbA) is a 68 kilodalton molecule composed of two pairs of α and β polypeptide chains folded around an iron-containing heme ring. Fetal hemoglobin (HbF), consisting of α and γ chains, predominates during in utero development. The β chain synthesis overtakes γ chain

production shortly after birth and the hemoglobin tetramer takes on adult form.

The result of the point mutation in the β chain is a modest change in the three-dimensional spatial configuration but a profound change in the solubility of hemoglobin. Glutamic acid is a charged amino acid and as a polar molecule, highly soluble in water. Valine is uncharged, making it poorly soluble in water. The entire sickle hemoglobin molecule takes on the property of the valine amino acid, becoming nonpolar and poorly soluble in water. The loss of charge, incidentally, explains the altered migration of sickle cell hemoglobin during electrophoresis.

The clinical sequelae of sickle cell disease, including kidney manifestations, arise from the properties of the hemoglobin resulting from the glutamine to valine amino acid substitution of the β subunit. The key steps that lead to organ injury include (1) polymerization of the sickle hemoglobin; (2) adhesion of affected red blood cells; and (3) ischemic/oxidative injury to the vasculature. The degree of injury to any organ system, including the kidney, depends on a number of factors that promote or inhibit these key steps.

Left unimpeded, the uncharged, poorly soluble valine residues allow the hemoglobin molecules to adhere to one another. Polymerization of the hemoglobin S results from the continued aggregation the insoluble molecules. Classically, seven pairs of sickle hemoglobin chains aggregate to form large, insoluble polymers.[15] The rate of sickle hemoglobin polymerization has been proposed to determine the ultimate morphology of the red blood cell[16]; slow polymerization results in long sickle hemoglobin fibers with classic sickle shape whereas rapid polymerization leads to shorter, more granular fibers. Once polymerized, sickle hemoglobin forms a highly viscous, semisolid "gel"[16] with a solubility much less than hemoglobin A and forms elongated structures that distort the red cells into their characteristic sickle and other abnormal shapes (Fig. 62.1).

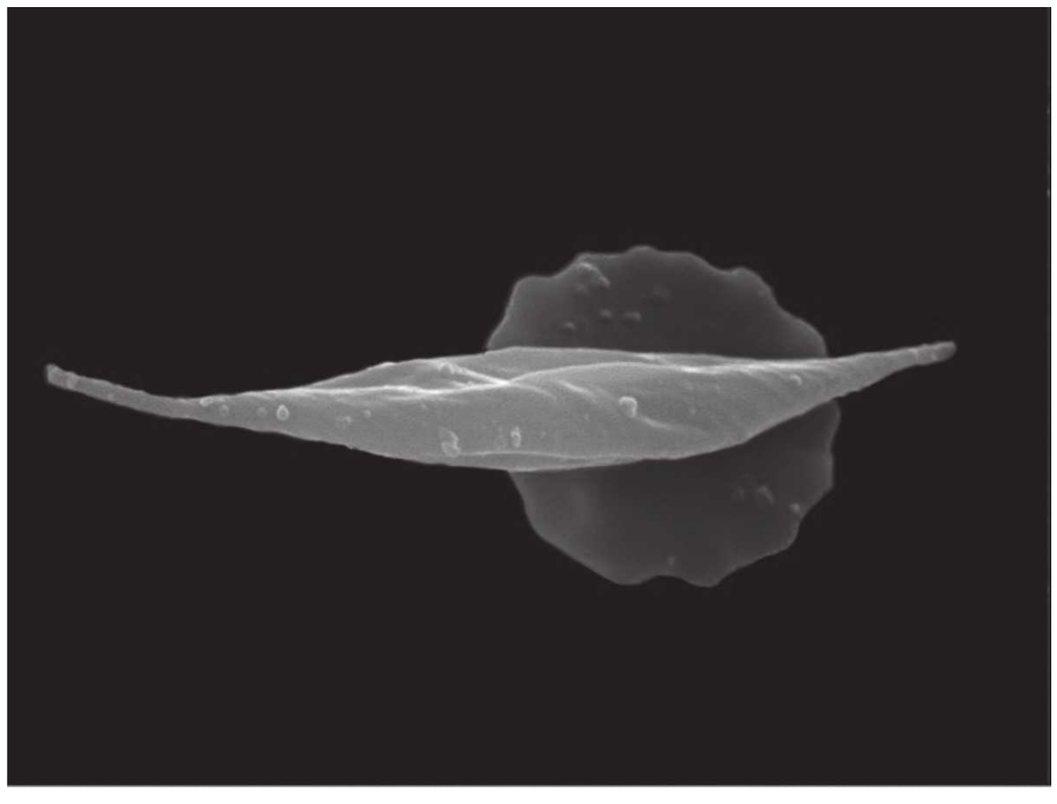

FIGURE 62.1 Normal red blood cell (*background*) and red blood cell affected by sickle-cell anaemia (*foreground*). Wellcome Library, London, "Sickle Cell Anemia" under Creative Commons by-nc-nd 2.0 UK: England & Wales, with permission from the Wellcome Trust. (See Color Plate.)

The polymerization of sickle hemoglobin leads to mechanical deformation of the red blood cell. Acquired red blood cell membrane abnormalities result, including a loss of phospholipids, asymmetry, increased fragility, and abnormal integrin–protein interactions.[17] This injury, in addition to the retention of adhesion molecules, promotes sickle red blood cell adhesion to vascular endothelium.[18,19] Furthermore, the presence of hemoglobin S accentuates red cell endothelial adhesion,[20,21] potentially producing stasis and occlusion in slow-flowing renal vessels under even mild physiologic stress. Clinical disease severity has been correlated with red blood cell adhesivity.[22]

Oxidative injury related to free heme exposure is a notable feature of the pathology of renal injury. Heme oxygenase (HO), the rate-limiting enzyme in heme degradation, serves as a measure of oxidative stress. Studies in transgenic murine models and in humans have demonstrated renal induction of heme-oxygenase-1 (HO-1), the isozyme induced by oxidative stress (Fig. 62.2). Inhibition of glutathione synthesis in the same transgenic murine model to produce acute oxidative stress precipitated acute vaso-occlusive episodes in the kidney, further demonstrating the role of oxidative stress to renal pathology.[23]

Physiologic, metabolic, and genetic conditions promote and mitigate the polymerization process and may help to explain the variability of clinical disease. In vitro studies have demonstrated that decreased oxygen concentration, increased hydrogen ion concentration, rapid deoxygenation, low temperature, advanced red blood cell age, high osmolality, and high intracellular HbS concentration promote the formation of the sickle polymers.[24–29]

Two well-established genetic modifiers of phenotypic severity are fetal hemoglobin concentrations and coinheritance of α-thalassemia. Fetal hemoglobin concentration may range between 1% and 30% and is determined by at least three different genetic loci.[12] With higher levels of fetal hemoglobin, the concentration of hemoglobin S in the erythrocyte is reduced. Nearly 30% to 50% of patients with sickle cell disease have coexistent α-thalassemia trait, which leads to an overall reduction in the concentration of total erythrocyte hemoglobin and reduced hemoglobin S polymerization.[12] Both of these modifying genetic factors have been shown to modulate the severity of clinical manifestations.[12]

Normal physiologic functions of the kidney include excretion of acid and solute. Gradients of acid and solute occur as a result of counter-current transport, and render the medulla with especially high concentrations of both. Furthermore, the renal medulla has a very low partial pressure of oxygen (10–20 mm Hg),[30] sufficient to induce sickling.[31] In aggregate, the conditions of the renal medulla—relative hypoxia, hyperosmolarity, acidity, and sluggish blood flow (Fig. 62.3)—represent an environment primed for sickling of red blood cells containing hemoglobin S. Angiographic studies have demonstrated significant renal vascular disruption and vessel dropout in individuals with HbSS and HbAS compared to individuals with normal hemoglobin

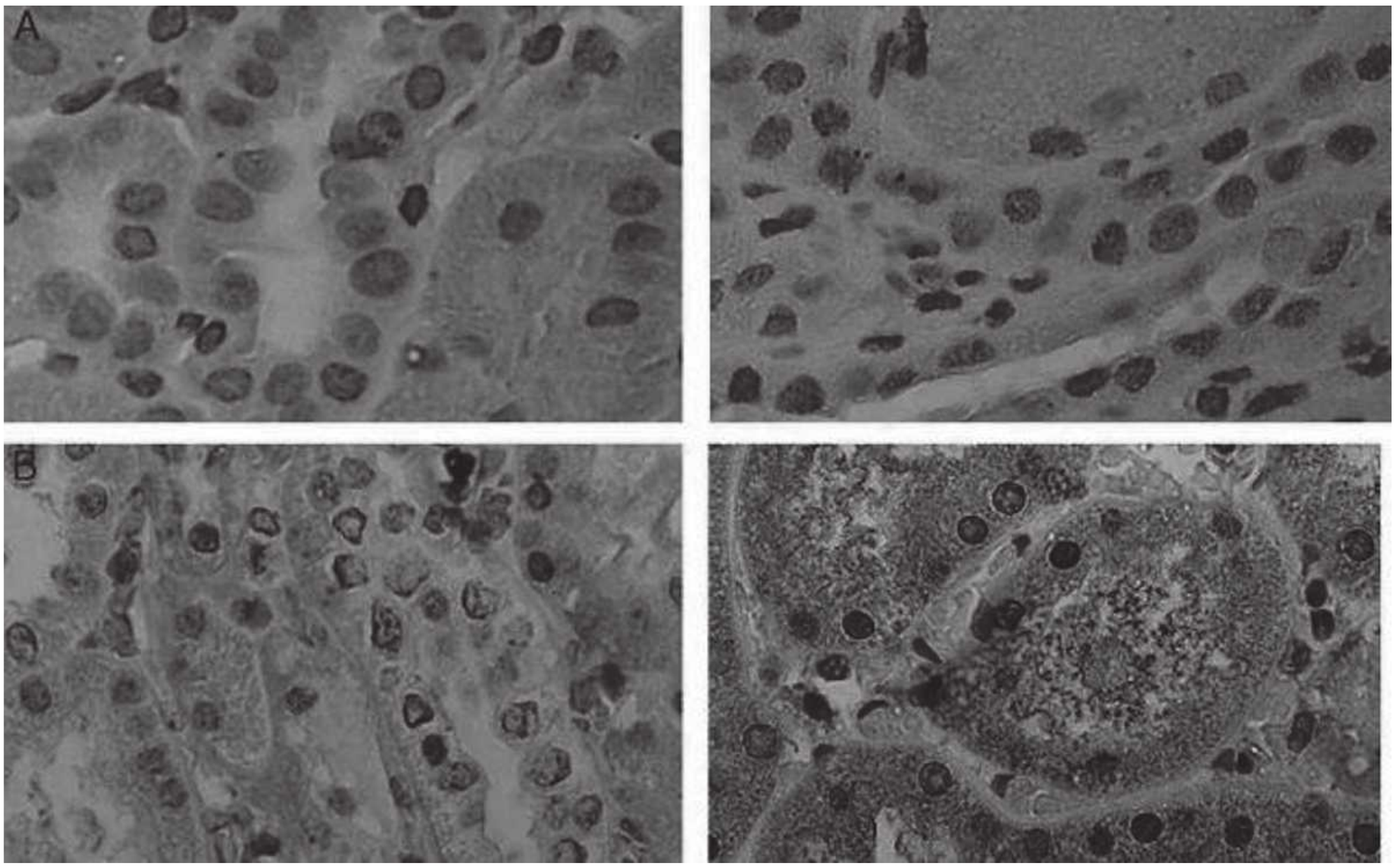

FIGURE 62.2 Immunoperoxidase staining for HO-1 in normal human kidney **(A)** and in the kidney of a patient with sickle cell disease **(B)**. In **A** and **B**, immunoperoxidase studies were undertaken in the absence (*left*) and presence (*right*) of HO-1 antibody. **B:** Positive staining with the HO-1 antibody in renal proximal tubules in the kidney of the patient with sickle cell disease (*right*). Original magnification, ×400. (From Nath KA, Grande JP, Haggard JJ, et al. Oxidative stress and induction of heme oxygenase-1 in the kidney in sickle cell disease. *Am J Pathol.* 2001;158:893–903, with permission from Elsevier at the courtesy of the editors.)

(HbAA)—likely the result of repeated episodes of red blood cell sickling with resultant ischemia (Fig. 62.4).[32] Experimental mouse models of sickle cell anemia have demonstrated an exquisite sensitivity to ischemic injury.[33,34] Chronic hypoxia may mediate the development of focal segmental glomerular scarring and subsequent proteinuria notable in sickle cell disease.

Recent investigations into the pathophysiology have also demonstrated a role for endothelial dysfunction. Patients with sickle cell disease demonstrate high levels of soluble fms-lke tyrosine kinase-1 (sFlt-1), which is a member of the vascular endothelial growth factor (VEGF) receptor family. High levels of sFlt-1 are felt to promote endothelial dysfunction by binding to the receptor-binding domains of circulating VEGF and preventing the normal interaction with endothelial cell receptors. A recent cohort study of 73 patients with sickle cell disease demonstrated statistically higher values of sFLT-1 among those patients with albuminuria, suggesting it may induce glomerular endothelial dysfunction.[35]

Additional investigations into the pathophysiology of chronic kidney disease (CKD) have gone beyond previous understanding of genetic modifiers as mentioned previously and have focused on the role of coinherited gene polymorphisms in the development of kidney disease.[36] Specifically, investigators have focused on the transforming growth factor beta and bone morphogenetic protein (TGF-β/BMP) pathway, implicated in the development of diabetic nephropathy and also associated with other organ involvement in sickle cell anemia.[37–42] In a longitudinal analysis of over 1,000 individuals with sickle cell anemia, the authors found that

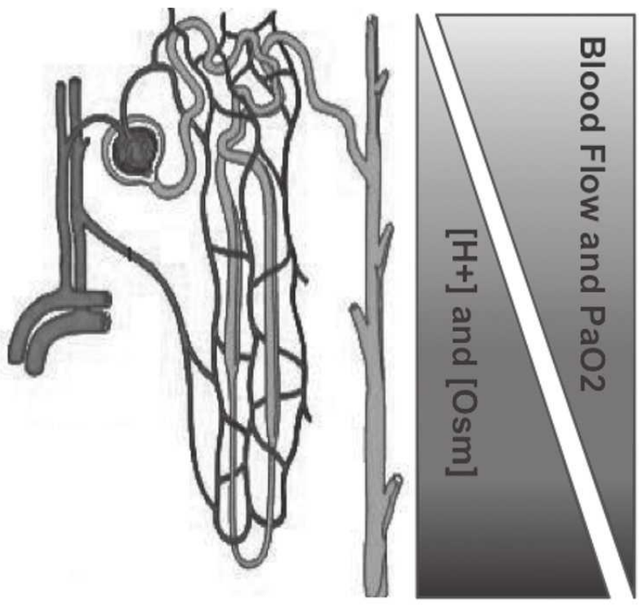

FIGURE 62.3 The renal medulla produces an environment in which red blood cells containing hemoglobin S are more likely to undergo sickling. As red blood cells traverse the renal vasculature into the medulla, they enter an area of increasing acidity and osmolarity and decreasing oxygen content and blood flow.

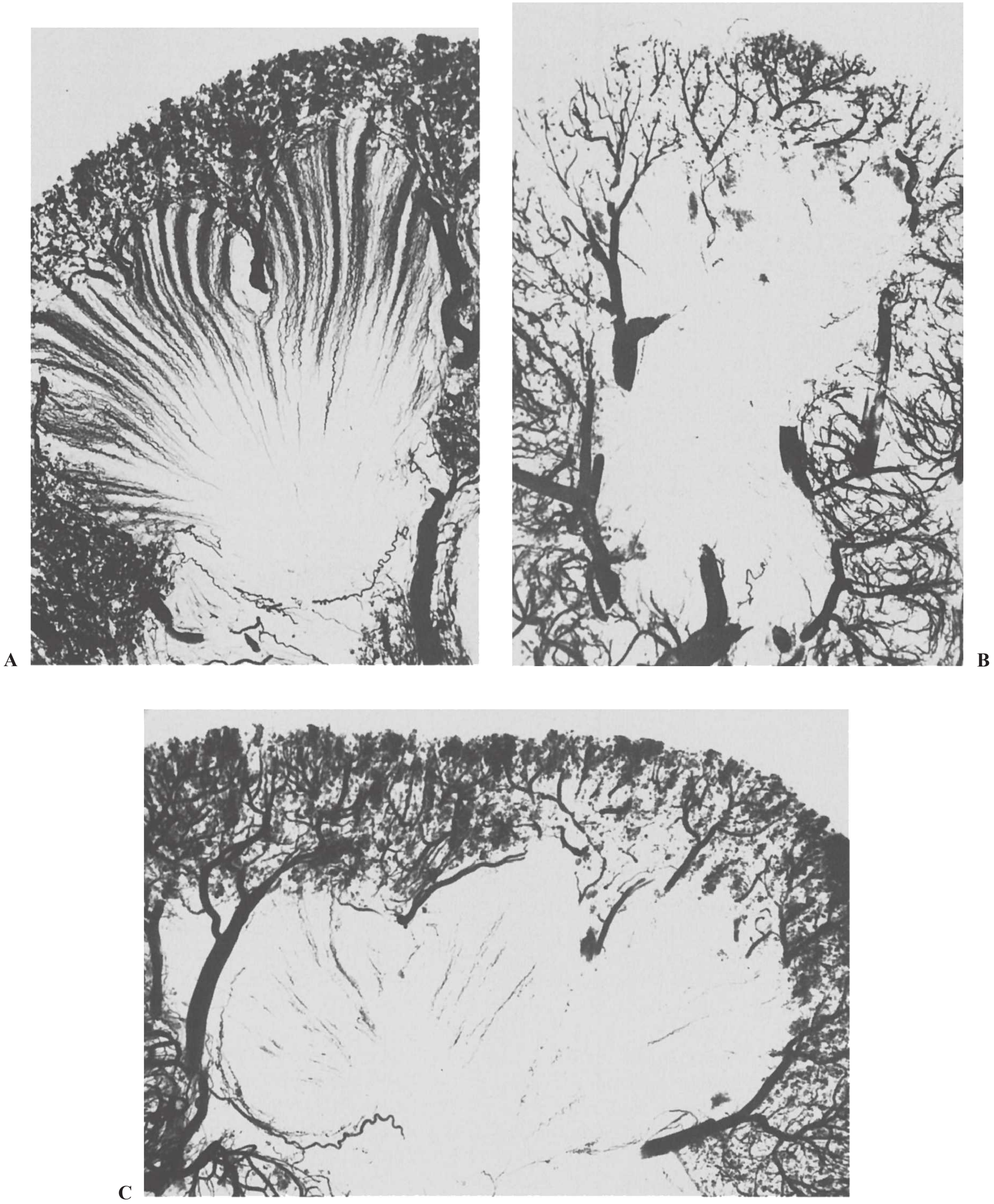

FIGURE 62.4 Injection microradioangiographs of kidneys from a subject without hemoglobinopathy **(A)**, a patient with sickle cell disease **(B)**, and a patient with sickle cell–hemoglobin C disease **(C)**. In the normal kidney **(A)**, vasa recta are visible radiating into the renal papilla; in sickle cell anemia **(B)**, vasa recta are virtually absent. Those vessels that are present are abnormal, are dilated, form spirals, and end bluntly, and many appear to be obliterated. The patient with Hb-SC **(C)** shows changes intermediately between the Hb-SS patients and the normal subjects. (Reprinted from Statius van Eps LW, et al. Nature of concentrating defect in sickle cell nephropathy, microradioangiographic studies. *Lancet*. 1970;1:450, with permission from Elsevier at the courtesy of the editors.)

four distinct single nucleotide polymorphisms (SNPs) in the BMPR1B, a receptor gene, were significantly associated with GFR. Utilization of genomewide association studies (GWAS) has identified further SNPs that may be important to explaining the phenotypic heterogeneity of sickle cell disease.[43] Additional analyses are needed to confirm promising exploratory studies that demonstrate modulation of renal morbidity among individuals with sickle cell anemia.

RENAL MANIFESTATIONS

StructuralChanges

Renal Size

The kidneys of patients with sickle cell disease typically vary in size with age. Infants and young children have kidneys of near-normal size.[44] The kidneys increase in length and weight in older children and young adults—on average the kidneys growing by 5 to 8 mm per year by ultrasound imaging in patients with Hb-SC and Hb-SS disease as compared with age-matched controls.[45] After age 40 years, the size decreases.[46]

Other structural changes are commonly seen on radiographic imaging. These findings increase with advancing age and likely reflect the cumulative effect of repeated episodes of "sickling." Cortical scarring is seen on intravenous pyelography among 8% of individuals aged 16 to 25 years, and rising to 45% among those over 35 years.[47] Calyceal abnormalities such as blunting, cysts, and clubbing are seen among 28% of youths and among 57% of individuals over 35 years.[47] Papillary necrosis among adults is seen at high frequency, ranging from 15% to 65%.[48–50] B-mode ultrasound imaging can reveal increased echogenicity of the kidneys in up to 25% of individuals with sickle cell anemia.[51,52]

Kidneys removed due to severe hematuria may demonstrate submucosal hemorrhages in the pelvis, medulla, and cortex.[53] Radiographic changes suggesting papillary necrosis, medullary cavitations, ring shadows, and calcifications in the pyramids have also been observed.[54,55] Occasionally, minimal papillary necrosis is apparent only on microscopic examination. Renal vein thrombosis is also an occasional finding in Hb-SS disease. Finally, the macroscopic appearance of kidneys of affected individuals may show irregularity and granularity of the surface.

Vasculature

Microradioangiographic studies (Fig. 62.4) have been performed on kidneys removed at autopsy from patients with normal hemoglobin, patients with Hb-SS disease, and patients with Hb-AS and Hb-SC disease.[32] A significantly reduced number of vasa recta are seen in kidneys from Hb-SS patients. The vessels that remain are abnormal as they are dilated, show spiral formation, and end bluntly. Patients with Hb-AS and Hb-SC disease show changes intermediate between those of the Hb-SS patients and normal subjects. In patients with Hb-AS, sparse bundles of vasa recta are surrounded by a chaotic pattern of dilated capillaries, with loss of the original bundle architecture. The changes presumptively result from occlusion of vasa recta and represent the structural basis for the development of functional changes. The loss of the highly specialized structure of parallel running loops of Henle and vasa recta disrupts the normal countercurrent multiplication and exchange.

Histology

Glomerular

Enlargement of the glomeruli is a common finding in patients with sickle cell disease. The glomeruli may be visible by the naked eye and have been described as red "pinheads."[27,56] Individuals with homozygous sickle hemoglobin have both an increase in glomerular diameter and size compared to normal controls.[57,58] Glomerular enlargement and congestion are more common in children beyond the age of 2 years and are most marked in juxtamedullary glomeruli.[57,59] When the size of juxtamedullary glomeruli is systemically measured, there is a distinct difference between those of children with sickle cell disease and normal children. In older patients, this glomerular enlargement and congestion may lead to progressive ischemia and fibrosis with obliteration of glomeruli.[46,60]

Histology of the enlarged glomeruli is notable for the marked hypercellularity and lobulation of the glomerular tuft. Other changes include replication of the basement membrane and mesangial proliferation.[57,61,62] Aggregates of sickled red blood cells may pack and distend the glomerular capillaries and the afferent and efferent arterioles. Electron microscopy of glomeruli may reveal foot process effacement and local thickening of the basement membrane,[61] although an exact prevalence is difficult to ascertain.

Clinical syndromes resulting from glomerular pathology, including glomerulonephritis, have been described among individuals with sickle cell disease. These conditions are discussed later in the chapter.

Medullary

The major components of the medulla are the vasa recta and renal tubules. As noted earlier, physiologic factors favoring sickling are routinely found in the medulla and, as such, medullary lesions are among the earliest and most prominent renal abnormalities. Initial changes consist of edema, focal scarring, and interstitial fibrosis. Progressive scarring leads to tubular atrophy and infiltration of mononuclear cells. Iron deposition has been observed in proximal tubules and pigmented casts may be seen.[55,57,61] Defective iron metabolism, as suggested by decreased renal cortical spin echo with magnetic resonance imaging (MRI), may contribute to the nephrotic syndrome.[63] All these changes could be the result of the observed obliteration or attenuation of the medullary circulation.[32]

Functional Changes

Renal Hemodynamics and Function

Renal hemodynamics are thought to be either normal or supernormal in homozygous (Hb-SS) patients younger than 30 years of age.[64–66] In Hb-SS infants, increased values have been observed for both GFR and effective renal blood flow (ERBF), as well as for the tubular transport maximum of para-aminohippurate (Tm_{PAH}). A recent study of a cohort of infants with sickle cell disease has demonstrated similar findings of increased GFR.[67,68] ERBF has been reported to be normal or elevated, although less elevated than effective renal plasma flow (ERPF) because of the typically very low hematocrit, while the extraction ratio of para-aminohippurate (E_{PAH}) was decreased. Filtration fraction (GFR/ERPF) has been found to be decreased (mean 14% to 18%; normal 19% to 22%).[64,65,69] Selective damage of the juxtamedullary glomeruli might result in a lower filtration fraction because these nephrons have the highest filtration fractions.[70,71] Microradioangiographic studies lend support to this suggestion.[32]

In sickle cell trait, Hb-SC disease, Hb-CC disease, hemoglobin C trait, and Hb-Sβ^+thalassemia, GFR, and ERPF have been reported to be within the range of normal.[72] As compared to patients with Hb-SS, studies in individuals with sickle cell trait do not appear to demonstrate significant age-related increases in GFR or microalbuminuria.[73]

Several mechanisms have been postulated for the increase in renal hemodynamics in patients with sickle cell disease. With severe anemia, peripheral vascular resistance decreases and cardiac output increases, possibly causing blood to be preferentially shunted to the renal circulation. However, in studies with short follow-up, correction of the anemia does not alter the GFR or ERBF.[64,74] Multiple transfusions with Hb-AA blood to patients with Hb-SS result in significant, although temporary, increases in hemoglobin concentration, with gradual and almost complete replacement of Hb-S by Hb-A. Because this procedure does not reduce the supernormal GFR and ERPF,[64] the cause of the supernormal renal clearances in sickle cell nephropathy cannot be explained by the anemia per se or by the presence of the abnormal hemoglobin. Altered nitric oxide production and renin secretion as seen in transgenic sickle cell mouse models may play a role in hyperfiltration.[75,76] (See section entitled "Pathophysiology.") The ischemic damage to the medulla could also be a stimulus for increased prostaglandin synthesis that may drive hyperfiltration.[66,69,77] Administration of indomethacin, an inhibitor of prostaglandin synthesis, to individuals with sickle cell anemia results in a significant fall in GFR, ERPF, creatinine clearance, and urea clearance supporting this contention.[69]

A number of possible mechanisms may be responsible for the decline in renal hemodynamics with aging, sometimes ending in renal failure with shrunken end-stage kidneys at necropsy. Although advancing age has an effect on renal hemodynamics and overall kidney function in all individuals, these effects may be heightened in individuals with sickle cell anemia because of the disruption of the medullary vasa recta. Support for the idea of a reduction in medullary blood flow in sickle cell disease can be found in the microradioangiographic examination of Hb-SS kidneys (Fig. 62.4).[32] In these studies of kidneys obtained at autopsy, perfusion of the vasa recta by contrast medium is virtually absent, suggesting an almost complete absence of vasa recta in Hb-SS. Supernormal hemodynamics and hyperfiltration have been proposed as causative mechanisms of glomerulosclerosis,[78] which may lead to the chronic renal failure seen in sickle cell disease. Increased apoptosis, stimulated by ischemic and/or oxidative injury, may also contribute to progressive renal dysfunction.[79–81] Over a number of years, continued loss of medullary circulation, interstitial fibrosis, and possibly superimposed pyelonephritis may lead to a progressive decline in GFR and advanced renal insufficiency in the patient with Hb-SS disease. Thus, there is a progressive decline in ERBF, ERPF, and GFR,[65,82] although there are rare individuals with apparently normal kidney function.

Clinically, the progressive loss of GFR is used to stage CKD. Stages 1 and 2 capture a GFR range above 60 mL/min/1.73 m^2 with proteinuria whereas stages 3 to 5 include a GFR range less than 60 mL/min/1.73 m^2 and stage 6 denotes those receiving renal replacement therapy or dialysis. Although advanced renal failure—that which requires renal replacement therapy, or that which is ascribed as a cause of death—is well documented,[83–86] estimates of earlier stages of renal failure vary widely[87,88] and should be interpreted with caution. Death from nonrenal causes (infection, pulmonary disease, etc.) may be a competing risk, limiting detection of CKD or end-stage renal disease (ESRD). Determining CKD prevalence is further complicated by the fact that serum creatinine, derived from muscle tissue and routinely used to estimate GFR in a variety of formulas,[89–91] may actually overestimate GFR determined by gold standard radionucleotide excretion studies in individuals with sickle cell anemia.[92,93]

Generation of Negative Solute-Free Water

The capacity to generate negative solute-free water (Tc_{H2O}) has been studied in patients with sickle cell disease using different protocols of mannitol loading with conflicting results. Although Whitten and Younes found normal Tc_{H2O} in Hb-SS children,[94] Levitt et al. describe two patients with a Tc_{H2O} of 3.2 mL/min/100 mL glomerular filtrate.[95] Hatch et al. similarly noted a mean Tc_{H2O} of 4.2 ± 0.9 SD mL/min/100 mL glomerular filtrate in 11 Hb-SS patients compared to a mean Tc_{H2O} of 5.7 ± 1.2 SD mL/min/100 mL glomerular filtrate in 7 control subjects.[96] These results suggest that Tc_{H2O} after mannitol loading is impaired in sickle cell anemia.

Studies following the response to saline infusion[96,97] demonstrate impaired Tc_{H2O} in Hb-SS patients. From these studies, sickle cell anemia patients were concluded to have a defect in the water impermeable medullary loops of Henle that transports solute. The normal solute-free water clearance under standard conditions argues against such

impairment in sodium chloride reabsorption from the ascending limb of the loop of Henle. However, in comparison to normal solute-free water clearance, a normal Tc_{H2O} depends on adequate function of the portion of the loop of Henle that is localized in the inner medulla. Sickle cell anemia patients are able to increase urinary osmolality generally to 450 mOsm per kg H_2O or higher, to the level that can be generated in the outer medulla. As shown in Figure 62.4, the capillary plexus surrounding short loops of Henle in the outer zone does not necessarily penetrate into the inner medullary zone.

Urinary Diluting Capacity

Patients with sickle cell anemia are capable of diluting their urine normally.[74,96,98] Under conditions of water diuresis, the fall in urinary osmolality and percentage of filtered water excreted (C_{H2O}/GFR) has been found to be the same in Hb-SS patients when compared to[99,100] controls. Therefore, the capacity to reabsorb solute in the thick portion of the medullary ascending limb of the loop of Henle apparently is intact in sickle cell anemia.

This combination of a defect in renal concentrating capacity with a normal diluting capacity is quite characteristic for sickle cell anemia. However, unlike control subjects, the normal diluting capacity of sickle cell patients may be particularly dependent on prostaglandins. In one series, administration of indomethacin, an inhibitor of prostaglandins, led to a greater fall in C_{H2O}/GFR in sickle cell subjects and a rise in urinary osmolality from 42 to 125 mOsm per kg H_2O (Fig. 62.5).[99,100] These results suggest that impairment of renal prostaglandins may hamper the normal diluting capacity in sickle cell anemia.

Urinary Acidification

Although systemic acidosis is generally not a feature of sickle cell disease in the absence of advanced renal failure, patients with Hb-SS or Hb-SC may demonstrate an incomplete form of renal tubular acidosis.[101–104] In response to a short-duration acid load, between 29% and 100% of patients with Hb-SS [101–104] are unable to decrease urine pH below 5.3, whereas normal subjects can achieve a urinary pH of 5.0 or lower. Titratable acid and total hydrogen ion excretion are lower in patients with Hb-SS and Hb-SC, but ammonia excretion is appropriate for the coexisting urine pH in most cases. The increased ammonia excretion induced by acid loading is also impaired by indomethacin,[101] suggesting the assumed enhanced prostaglandin synthesis in sickle cell disease[105] may also be important to maintaining normal ammoniagenesis in sickle cell disease. When a maximal acidifying stimulus is employed, such as infusion of sodium sulfate, patients with Hb-SS may lower urine pH and increase net acid excretion to the same degree as normal subjects. Thus, the distal tubule of Hb-SS patients apparently requires a greater-than-normal stimulus to generate a normal urine-to-blood hydrogen ion gradient. In contrast, renal acidification has been found to be normal in patients with sickle cell trait.[106]

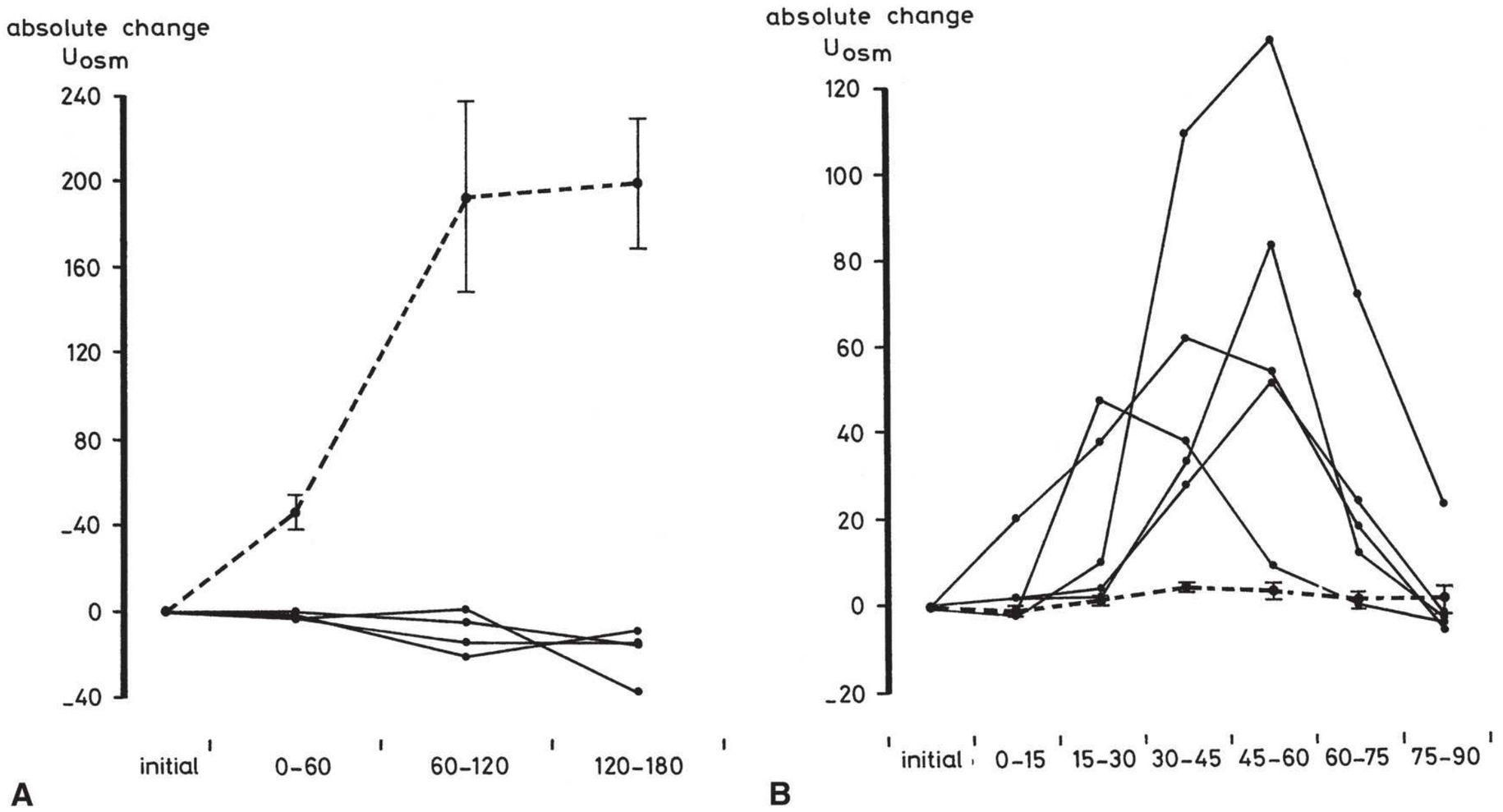

FIGURE 62.5 The effect of indomethacin (75 mg as a suppository) in the water-depleted state **(A)** and the effect of indomethacin (0.25 mg/kg body weight intravenously) in the water-loaded state **(B)**. The *broken lines* represent the mean ± standard error of the mean in control subjects, and the *continuous lines* represent the individual data in patients with sickle cell anemia. (Reproduced with permission from De Jong PE, et al. The influence of indomethacin on renal concentrating and diluting capacity in sickle cell nephropathy. *Clin Sci.* 1982;63:53, © the Biochemical Society.)

The acidification defect has been classified as distal rather than proximal[103] and is characterized by failure to achieve a normal minimal urinary pH with acid loading but is not associated with bicarbonate wasting. Because patients studied not were acidemic or hyperchloremic before acid loading and no generalized proximal tubular reabsorptive defect was observed, the acidification defect was consistent with an incomplete distal renal tubular acidosis.[106] Speculatively, alterations in microcirculation of the renal papillae may impair maintenance of the normally steep hydrogen ion gradients in the collecting ducts. This very subtle defect in renal acidification generally does not cause a systemic metabolic acidosis, which could increase sickling. Several studies globally[102,104,107,108] have been unable to demonstrate evidence of metabolic acidosis in the absence of a sickle cell crisis, but do exhibit changes consistent with a mild chronic respiratory alkalosis.

Potassium Metabolism

In addition to the defect in hydrogen ion excretion, potassium excretion may also be impaired in sickle cell patients.[109–111] Following potassium chloride, sodium sulfate, or furosemide administration, potassium excretion was found to be subnormal in patients with sickle cell disease. Hypoaldosteronism does not appear to explain these findings as both plasma renin activity and plasma aldosterone concentration were normal, both during normovolemia and after volume contraction. Additionally, despite impaired renal potassium excretion, hyperkalemia did not develop in these patients during acute potassium chloride loading. Although administration of angiotensin-converting enzyme (ACE) inhibitors and other agents may elevate plasma potassium concentration,[112] significant alterations in plasma potassium concentration has not been seen with ACE inhibitor therapy for proteinuria in sickle cell disease.[113]

As with the defect in water and hydrogen ion excretion, the disturbance in potassium excretion could be due to an abnormality resulting from ischemic injury to the collecting duct; potassium excretion is known to reflect primarily secretion in the distal nephron. Potassium excretion in sickle cell trait appears to be normal.[114]

A hyperkalemic, hyperchloremic metabolic acidosis in sickle cell nephropathy has been reported.[109] Among six patients—three with Hb-SS, two with Hb-AS, and one with Hb-SC—all had impaired renal potassium excretion. Five of these patients had a moderate-to-severe decrease of GFR and all patients had spontaneous metabolic acidosis. Selective aldosterone deficiency was found in three patients, two with normal and one with low plasma renin activity.

Other reports describe hyporeninemic hypoaldosteronism in patients with sickle cell disease.[110,114] Diminished renin secretion may result in impaired function of the adrenal glomerulosa cells, reduced aldosterone secretion, and subsequently impaired ability to excrete potassium loads. In these cases, the hyperkalemia responded favorably to treatment with mineralocorticosteroids.

Proximal Tubular Secretion

Although severe disturbances in medullary transport occur in patients with sickle cell anemia, proximal tubular activity, both secretory and reabsorptive, appears to be supernormal. The tubular transport maximum of para-aminohippurate is elevated in sickle cell anemia, particularly in children.[66] Other evidence of an increased proximal tubular secretory capacity has been obtained from studies regarding uric acid excretion. Despite the increased red cell turnover and consequent uric acid overproduction, most patients with sickle cell anemia are normouricemic due to augmented urate clearance[62,115] from increased pyrazinamide-suppressible urate.[115,116] Hyperuricemia in Hb-SS patients may occur with decreased urate clearance, but these patients often have some decrement in renal function or proteinuria.[62,117,118] Urate clearance decreases with age and the incidence of hyperuricemia increases as renal function deteriorates.[62] Attacks of gout can occur[118–120] and sometimes be clinically difficult to differentiate from vasoocclusive crises or sickle cell arthropathy.[121]

As previously mentioned, the tubular secretion of creatinine can be elevated, with a 20% to 29% rise in fractional creatinine excretion in Hb-SS patients compared to controls.[69,77] However, one study demonstrated that following an intravenous load of creatinine to adults with sickle cell disease, most without proteinuria, creatinine clearance did not increase as expected. Compared to controls, GFR remained the same.[122] The investigators suggested that reduced tubular secretion of creatinine in response to a creatinine load may be an early indicator of renal dysfunction. Importantly, this abnormal tubular function may adversely impact the utility of creatinine clearance measurements to estimate GFR in sickle cell disease.

Proximal Tubular Reabsorption

Relative tubular reabsorption of phosphate is also increased in sickle cell anemia. Consequent to this higher phosphate reabsorption, serum phosphate can be elevated in some subjects.[123,124] High phosphate reabsorption may reflect increased reabsorptive activity of the proximal tubule.[123] In contrast, children with sickle cell anemia have lower serum phosphate levels than normal children[125] that is associated with significantly lower renal tubular resorption of phosphate. This contrast may be due to increased parathyroid levels reported in children with sickle cell disease[126] or may simply indicate the absence of sickle cell renal injury early in life.

Sodium reabsorption in the proximal tubule parallels phosphate reabsorption and may also be enhanced in HbSS patients. Indeed some studies report increased plasma volume in the steady-state Hb-SS patients.[96,127,128] Conversely, increased proximal tubular sodium reabsorption may be a secondary mechanism to correct for defects in salt reabsorption in the more distal nephron. One might expect patients to develop volume depletion as a consequence of defects in medullary

water and sodium conservation. However, such distal compensatory mechanisms would not increase plasma volume.

Increased tubular uptake of β_2 microglobulin has also been described in sickle cell anemia.[129] Resorption of β_2 microglobulin positively correlates with the reabsorption of phosphate, providing further evidence of increased proximal tubule activity. However, estimates of GFR are comparable among ^{51}Cr-EDTA, creatinine clearance, and β_2 microglobulin determinations in sickle cell patients older than 40 years of age.[130] Zinc excretion has also been found to be abnormal in Hb-SS patients, exceeding the filtered load as compared to controls whose excretion is lower than the filtered load.[131]

Therefore, Hb-SS patients have a defect in renal medullary functions with a tendency to lose water and sodium, whereas ERPF, GFR, and proximal tubular activity are increased. In general, under typical conditions of health, the ultimate result of this compensation is normal homeostasis of fluid and electrolytes.

Renal Hormones

Erythropoietin

Data on plasma erythropoietin (EPO) levels in sickle cell anemia are conflicting. EPO levels strongly correlate with red cell mass in sickle cell disease patients.[132] Increased values have been reported during infectious episodes and in asymptomatic patients.[133] However, when comparing plasma EPO concentrations in sickle cell anemia to other causes of anemia, Hb-SS patients have been shown to have similar or decreased values.[134] EPO titers in patients with pure red cell aplasia, for instance, may be 10-fold higher than those in Hb-SS patients.

Other observations have shown patients with sickle cell anemia produce less EPO at a given hemoglobin concentration than do patients with non–sickle cell anemias.[135,136] Notably, pediatric patients with sickle cell anemia have significantly higher EPO levels than do adults.[136]

In a study of patients older than 40 years, a fall in the Hb concentration was observed that correlated with declining renal function. The investigators postulated that lower Hb concentrations may be due to reduced EPO production. In sickle cell disease patients with renal failure, supplementation with erythropoietin using doses of 100 to 150 U per kg three times a week,[137–139] up to 30,000 U per week,[140] result in increased reticulocyte counts, but may not increase the absolute hemoglobin value.

Renal transplantation may correct the erythropoietin-resistant anemia in Hb-SS patients with ESRD.[140,141] This improvement may reflect decreased uremic and other toxins or reduced inflammation that may suppress erythropoiesis or even enhance hemolysis.[141] Hydroxyurea therapy in some patients with sickle cell disease may increase erythropoietin levels 5 to 10 days after starting therapy[142] but this increase is not necessarily sustained.

Potential mechanisms for the low EPO levels observed in sickle cell disease include interference with the renal synthesis of EPO, as a result of renal damage by the sickling process, and the displacement to the right of the oxygen equilibrium curve. Circulating red blood cell progenitors from patients with sickle cell disease have increased expression of erythropoietin receptors, which correlated with increased stimulated and autocrine erythroid colony development.[143] This may be a compensatory mechanism, in the absence of renal disease, for relatively lower erythropoietin levels in sickle cell disease.

Renin–Angiotensin–Aldosterone System

Plasma renin activity and aldosterone concentration are generally normal in patients with Hb-SS disease during steady-state conditions[69,111] despite lower mean arterial pressure than controls.[144] After volume depletion, normal or increased values may occur,[145] and both supine and upright plasma renin activities for different sodium intakes always were higher in Hb-SS patients than in control subjects.[146] Upregulation of renin has been demonstrated in the kidneys of transgenic sickle cell mice exposed to hypoxia.[75] As mentioned previously, some patients may exhibit hyporeninemic hypoaldosteronism and hyperkalemia.[110,114] Interestingly, high plasma renin activity has been described in a patient with intermittent hypertension occurring during a painful crisis. When the crisis had subsided, blood pressure normalized again.[147] Typically, though, hypertension seldom occurs in Hb-SS patients, even during crisis.

Renal Prostaglandins

Prostaglandin production occurs in renal interstitial medullary cells and collecting duct cells[148] and is promoted by various vasoconstrictor stimuli.[149] The interstitial cells of the medulla in patients with sickle cell anemia contain aggregates of granular electron-dense material,[61] likely representative of prostaglandin production. Speculatively, ischemic and/or oxidative insult to the inner medulla in sickle cell anemia may induce synthesis of vasodilator prostaglandins. The role of renal prostaglandins in sickle cell anemia has been studied in several ways: indirectly using indomethacin as a prostaglandin synthesis inhibitor, directly measuring urinary prostaglandin E_2 and $F_{2\alpha}$ (PGE_2 and $PGF_{2\alpha}$) excretion, and via assessment of gene regulation in the transgenic sickle cell mouse model.

As already discussed, indomethacin administration does not change GFR and ERPF in controls, but a significant fall in both were found after indomethacin administration to Hb-SS patients.[69,76] These findings suggest prostaglandins maintain the supernormal or normal GFR and ERPF in sickle cell anemia and may play a role in hyperfiltration and subsequent rise in GFR seen in young sickle cell patients. The rise in renal blood flow and glomerular filtration may also explain the increased proximal tubular activity in these patients.

In normal subjects, indomethacin causes sodium and water retention and a rise in body weight. In Hb-SS patients,

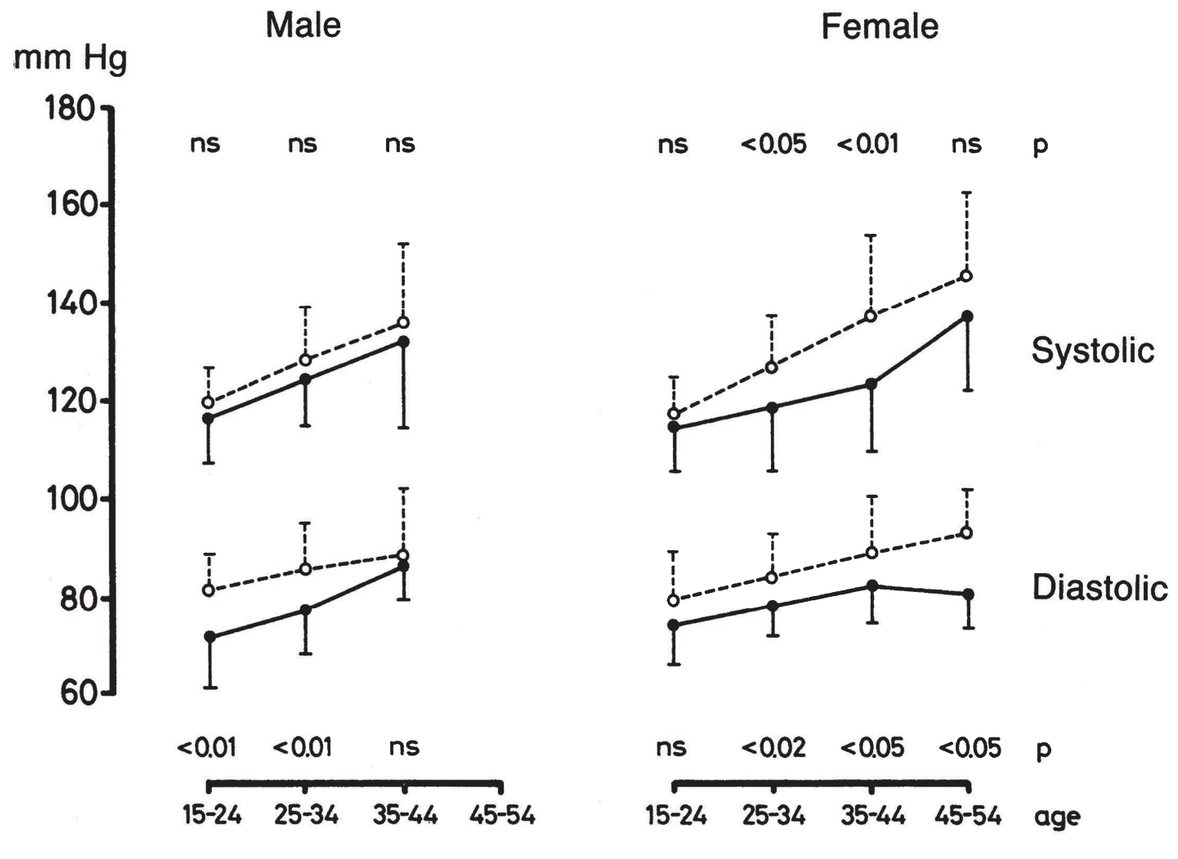

FIGURE 62.6 Mean ± standard deviation of systolic and diastolic blood pressure in control subjects (*dotted lines*) and patients with sickle cell anemia (*closed lines*) who are age- and sex-matched. (From De Jong PE, et al. Blood pressure in sickle cell disease. *Arch Intern Med.* 1982;142:1239; and reprinted by permission from Macmillan Publishers Ltd. De Jong PE, Statius van Eps LW. Sickle cell nephropathy. New insights into its pathophysiology. [Editorial review]. *Kidney Int.* 1985;27:711, through courtesy of the editors.)

similar sodium retention occurs after indomethacin administration, but without water retention or an increase in weight. Rather, serum osmolality increased in these patients.[66]

Indomethacin administration to water-deprived normal subjects leads to a rise in urinary osmolality of 836 to 1,027 mOsm per kg H_2O, whereas the defect in urinary concentration in sickle cell anemia does not improve after indomethacin[100] (Fig. 62.5). This result supports a diminished solute gradient in the inner medulla of patients with Hb-SS that is not modulated by prostaglandins. During a water load, however, a rise in urinary osmolality in sickle cell subjects occurs after indomethacin administration, but not in controls. Normal diluting capacity in sickle cell patients therefore appears to be dependent on adequate renal prostaglandin synthesis.[77,100]

Both in the dehydrated and in the water-loaded state, PGE_2 excretion is normal in patients with sickle cell disease. $PGF_{2\alpha}$ excretion, however, is decreased; therefore, the $PGE_2/PGF_{2\alpha}$ ratio is higher than in healthy persons.[105] Because PGE_2 and $PGF_{2\alpha}$ have different and sometimes opposite effects on renal hemodynamics, renin release, and sodium and water excretion,[150,151] an abnormal balance between these two prostaglandins may contribute to some characteristics of sickle cell nephropathy. For example, the relative excess of vasodilating PGE_2 could explain the rise in renal blood flow and GFR, particularly in juxtamedullary nephrons.

In the transgenic sickle cell mouse, cytochrome P450 4a14 is upregulated in renal tissue.[75] This enzyme catalyzes arachidonic acid to 20-hydroxyeicosatetraenoic acid (20–HETE), which regulates renal vascular tone, tubular resorption, arterial pressure, and natriuresis.[75]

Atrial Natriuretic Peptide

In normal subjects, atrial natriuretic peptide (ANP) exerts its effects in several nephron segments dependent on prevailing ANP levels. Infusion of a low-dose ANP induces natriuresis in normal individuals but not in matched patients with sickle cell disease.[152] This observation suggests that low-dose ANP inhibits sodium reabsorption in the long loops of Henle, possibly by increasing medullary blood flow and renal interstitial pressure. Natriuresis under supraphysiologic plasma levels of ANP appears to be multifactorial, by an increase in GFR and a decrease in both proximal and distal tubular sodium reabsorption. Infusion of high-dose ANP in patients with sickle cell disease and normal subjects induces a similar degree of natriuresis.[152]

Hypertension and Sickle Cell Disease

The incidence of hypertension in the adult black population in the United States is 32%, contrasting sharply with its incidence in sickle cell disease. Reports from both the Caribbean,[153,154] the United States,[146,155] and Europe[144] demonstrate hypertension in only 2% to 6% of Hb-SS patients overall (Fig. 62.6) and in 15% of patients older than 55 years of age. The explanation for these findings remains unclear. Renal salt losing has been suggested as an etiology,[114] but these data are not convincing. Hb-SS patients are able to conserve sodium adequately on a severely restricted sodium diet.[145,146] Moreover, the demonstration of an increased, rather than lowered, plasma volume[127,128,146] does not support the hypothesis that these lower blood pressures are related to volume loss. Altered systemic vasoreactivity also has been postulated, but with limited study. One study demonstrating decreased forearm vascular resistance that does not increase with cold-induced, sympathetic-mediated stimulation or angiotensin II suggests altered vascular reactivity protects patients from hypertension.[146]

CLINICAL MANIFESTATIONS

Hematuria

In 1948, Abel and Brown were the first to discover a relationship between sickle cell disease and hematuria.[156] They described a young black soldier who underwent nephrectomy

because of severe and persistent unilateral hematuria. A renal neoplasm was suspected, but histopathology of the excised kidney demonstrated only sickled red blood cells in medullary vessels.

Hematuria is a very dramatic manifestation of sickle cell nephropathy. Gross hematuria in affected patients can occur at any age, including young children, and may be more common in males than in females.

The pathologic abnormalities causing hematuria have not yet been elucidated. Kimmelsteil[157] describes the changes as temporary capillary stasis after spasm. As a consequence, plugging of capillaries by sickled cells results in vessel wall injury and, rarely, in true capillary thrombi with ischemia and necrosis. In a study of 21 kidneys from Hb-SS patients removed due to massive blood loss and possible renal neoplasm,[53] the absence of significant gross alterations emphasize that these lesions are inconspicuous and may be easily missed. The most striking change noted was severe stasis in peritubular capillaries in the cortex and most markedly in the medulla. Extravasation of blood, mainly into the collecting tubules, was also observed. Hb-SS erythrocytes traversing the hyperosmotic inner renal medulla have been shown to undergo instant sickling resulting from an increase in intracellular hemoglobin concentration.[158] Moreover, the acidic and hypoxic environment of the renal medulla promotes sickling and red cell adhesion in the vasa recta. Vasoocclusion and increased blood viscosity may result in microthrombi, ischemia, oxidative/reperfusion injury, and/or necrosis, which could cause structural changes leading to hematuria.

Hematuria is generally unilateral in 90% of cases, and interestingly involves the left kidney four times more often than the right kidney. Increased pressure in the left renal vein due to its length and course between the aorta and superior mesenteric artery[159] may explain this observation.

In almost half of all such patients with gross hematuria, blood clots produce filling defects by intravenous urography in the renal pelvis that may be confused with neoplasm, calculus, or hemangioma. Such findings have led to unnecessary nephrectomy in the past. Computed tomography (CT) can generally exclude the presence of a renal neoplasm.[160]Although hematuria can be massive and life threatening, the treatments of choice are conservative measures including bed rest, urinary alkalinization, and maintenance of high urine flow rates. Intravenous triglycyl vasopressin has been successful in two cases of persistent hematuria.[157,161] Epsilon aminocaproic acid (EACA) may have a therapeutic effect in the control of hematuria associated with hemoglobinopathies.[162] Complete inhibition of fibrinolytic activity normally occurs with 8 g of EACA daily. Urinary levels of EACA reach 50 to 100 times those of plasma. With repeated oral dosage, gradual sustained renal excretion occurs so that adequate urinary levels are maintained. The reported results of EACA for hematuria of sickle cell nephropathy have been successful, although therapeutic regimens have varied in dose and frequency.[162–165] Thrombotic complications may occur in patients receiving large doses of EACA, usually in excess of 12 g per day. Control of hemorrhage often can be obtained with doses as low as 2 or 3 g per day.[165] Therefore, EACA should be administered on a short-term basis at the lowest dosage required to inhibit urinary fibrinolytic activity. Surgical intervention (i.e., nephrectomy) should be considered in the presence of life-threatening hemorrhage that does not improve with conservative therapy. If bleeding can be localized to a distinct part of the kidney, one should consider embolization. Other causes of hematuria should also be considered, including mild bleeding disorders (e.g., von Willebrand disease), other forms of kidney disease such as polycystic kidney disease, and renal medullary carcinoma.

Urinary Tract Infections

In a review of 321 children with sickle cell disease, 7% have had urinary tract infections, 60% of which were associated with a febrile illness.[166] The incidence of asymptomatic bacteriuria during pregnancy and the puerperium appears to be twofold higher in women with sickle cell disease or sickle cell trait than in nonpregnant women or women without sickle cell disease or trait.[167] The rate of pyelonephritis is approximately 1%, similar to that in non–sickle cell pregnant populations.[168] An increased incidence of "pyelonephritis" found at autopsy in Hb-AS patients[169] may reflect the pathologic changes due to Hb-S nephropathy (medullary ischemia and fibrosis). Pyelonephritis or urosepsis, like other infections, may precipitate a crisis. Most episodes of gram-negative sepsis in sickle cell patients are due to urinary tract infections.[170] Patients with painful crises should be evaluated for infection, including the urinary tract.

Papillary Necrosis and Caliectasis

Renal papillary necrosis and caliectasis are frequent occurrences in sickle cell disease, in both homozygotes and heterozygotes. Renal papillary necrosis in sickle cell nephropathy has an incidence ranging from 15% to 36%.[55] As in sickle cell nephropathy, the distinctive abnormalities of the renal medulla and papillae are obliteration of the vasa recta and medullary necrosis and fibrosis; papillary necrosis is a logical consequence of these processes.[54]

Gross, painless hematuria[171] is a common symptom reported. Renal colic from passage of blood clots or ruptured particles of necrotic papillae is less frequent. Intravenous pyelography is the method of choice to diagnose papillary necrosis.[54,171] Most commonly a medullary type of partial papillary necrosis is found, appearing as cavitation within one or more of renal papillae (SS). Multiphasic helical CT may permit early detection of medullary and papillary necrosis and allows visualization of the entire kidney, facilitating the identification of other conditions.[160] Treatment is supportive and similar to the management of hematuria. Ureteral obstruction by thrombus or necrotic material should be relieved by stenting if required.[171] Renal papillary necrosis has not been associated with an increased risk of renal failure.[87]

Microalbuminuria, Proteinuria, and the Nephrotic Syndrome

As in other disease states, microalbuminuria may indicate early glomerular injury and renal dysfunction. Although most often attributed to hyperfiltration, early permselectivity pore defects may occur in glomerular capillaries.[172,173] As assessed by urine albumin/creatinine ratio (U Alb/Cr), the prevalence of microalbuminuria increases with age and is uncommon before age 7, but is present in up to 20% to 40% of children between ages 10 and 18.[174,175] The presence and amount of albuminuria correlates with age and hemoglobin levels, but not consistently with other clinical manifestations of sickle cell disease, such as pain or other acute sickling events,[175] although one recent study demonstrated a correlation with pulmonary hypertension.[35] The prevalence of microalbuminuria in adolescents and young adults with sickle cell disease ranges from 9% to 40%, depending on the type of sickle cell disease.[176,177] In one study of 72 adult sickle cell disease patients estimates of urinary albumin excretion found using a spot U Alb/Cr to be highly variable and inconsistently correlated with 12-hour urine samples to quantitate albumin excretion.[178] Furthermore, the spot U Alb/Cr did not demonstrate the reduction in albumin excretion achieved by ACE inhibitor therapy, which was detected using 12-hour collections.[178]

Reduction in microalbuminuria with ACE inhibitor therapy has been demonstrated. In eight adult sickle cell patients treated with enalapril over 120 days, albuminuria normalized or was markedly reduced without changes in sodium, potassium, or lithium excretion or in mean arterial blood pressure.[179] Two years after stopping enalapril, four of six patients still had normal albumin excretion. A placebo-controlled randomized trial of captopril in 22 adult sickle cell patients demonstrated a mean 37% reduction in albumin excretion with captopril over placebo after 6 months of therapy,[180] and was associated with a 5 mm Hg drop in diastolic blood pressure in the treatment group. To date, no long-term trial data exist to demonstrate whether ACE inhibitor therapy reduces prevalence or progression of chronic renal disease in sickle cell patients.

Overt proteinuria is a frequent finding in sickle cell disease, occurring in about 30% of patients when observed over a prolonged period. Nephrotic range proteinuria has been reported in children and adults with sickle cell disease,[181,182] although its prevalence is not well studied. From a review of 386 patients with sickle cell anemia,[183] 78 patients (20.4%) had proteinuria and 17 (4.6%) had renal insufficiency. Both renal insufficiency and proteinuria increased with age, reaching rates of 33% and 56%, respectively, in patients 40 years and older. In some series, proteinuria occurs in 40% of patients with sickle nephropathy[184] and is associated with progression to chronic renal failure and early mortality.[87,113,184,185]

Falk et al. investigated 381 patients with sickle cell disease for proteinuria and renal insufficiency.[113] Twenty-six (7%) had serum creatinine concentrations above the normal range and 101 (26%) had proteinuria of at least 1+ by urinalysis. Among 44 patients with a complete 24-hour urine collection, protein excretion ranged from 28 mg per 24 hours to 10.8 g per 24 hours, with a mean of 1.7 g per 24 hours and SD of ±2.4 g. Twelve patients excreted more than 2.5 g of protein per 24 hours, associated with other features of the nephrotic syndrome. In 10 biopsied patients with proteinuria, administration of enalapril decreased 24-hour urinary protein excretion by 57% (range 23% to 79%), which then increased to 25% below baseline after discontinuation of enalapril. No significant change in GFR, ERPF, filtration fraction, or decrease in arterial pressure occurred. Other causes of proteinuria and nephrotic syndrome should be considered including primary and secondary renal diseases before one assumes sickle cell nephropathy is present.

Postinfectious and membranoproliferative glomerulonephritis[61,186–190] are among the more common case reports. Whether a mechanism specific to sickle cell anemia is responsible for the glomerular diseases or whether these result from the increased susceptibility to encapsulated bacterial organisms remains unclear.

Nephrotic syndrome, rather than just proteinuria, has been described among individuals with sickle cell disease. The causes of nephrotic syndrome have been varied, and include focal segmental glomerular sclerosis,[113,177,191] and mesangioproliferative glomerulonephritis (and is usually associated with albuminuria). Mechanistic theories for these lesions include iron deposition,[192] mesangial phagocytosis of fragmented and sickled red cells,[58,185] hyperfiltration,[191] or infection with parvovirus B19.[193,194]

Acute Renal Failure

Despite the underlying functional and structural changes in the kidney, reports of acute renal failure in sickle cell disease are rare. Some reports describe reversible acute oliguric renal failure in the setting of sickle cell crisis.[195,196] In both studies rhabdomyolysis was suggested to be the cause of acute renal failure. In another study of 12 sickle cell patients with acute renal failure, volume depletion in the setting of crisis was the most common cause.[183] Of the 12 patients, 10 survived and had recovery of renal function.

A syndrome of acute multiorgan failure has been described in 14 sickle cell patients (10 Hb-SS, 4 Hb-SC) occurring during an unusually severe sickle cell crisis event.[197] At least two of three organs (lung, liver, or kidney) demonstrated acute injury. Acute renal insufficiency developed in 13 episodes, with a rapid, reversible elevation of serum creatinine concentration above 2.0 mg per dL over 24 to 36 hours. Acute liver abnormalities and pulmonary infiltrates were observed. All but one patient recovered after treatment with multiple blood transfusions.

RENAL MEDULLARY CARCINOMA

Renal medullary carcinoma is a rare tumor that occurs among individuals with sickle hemoglobinopathy. The vast majority of individuals with the tumor have been shown

to have sickle trait rather than homozygous sickle hemoglobin. To date, there are about 137 cases reported in the literature.[198,199]

The pathogenesis of renal medullary carcinoma is not known. Like much of the morbidity associated with sickle disease, the pathogenesis is felt to be medullary ischemia. One study with a small number of patients demonstrated an amplification of the known oncogene, ABL.[200] Structurally, the tumors are believed to arise in the renal medulla, possibly from the renal papillae.[198] They grow rapidly in an infiltrative pattern into the renal sinus. Histologically, renal medullary carcinoma has glandular and squamoid features along with inflammatory and desmoplastic elements, findings that suggest origination from transitional epithelium.

The typical age of presentation is among individuals less than 40 years of age. Diagnosis of the tumor is difficult as it is rapidly growing and has a nonspecific presentation. Renal medullary carcinoma is often found unexpectedly during evaluation of hematuria. The tumor often has grown extensively in the kidney, and has produced local nodal metastases. Diagnosis is made by biopsy and histologic examination. Treatment options such as chemotherapy or surgery are limited because of the advanced stage of presentation.

TREATMENT

General treatment of sickle cell anemia has focused on the use of antibiotic prophylaxis in childhood and support of management of acute vasoocclusive crises. Hydroxyurea has been used as well in patients to induce hemoglobin F (fetal hemoglobin) and reduce the overall percentage of hemoglobin S and subsequently sickling episodes. Bone marrow transplantation in severe cases may provide more definitive therapy. Specific therapies related to renal manifestations of sickle cell disease are discussed in the following text.

Chronic Kidney Disease

Intervention for proteinuria has been the most well-studied intervention for CKD associated with sickle cell disease. The previously described series by Falk et al. demonstrated a reduction in proteinuria by approximately 60% with the use of ACE inhibitors.[113] Subsequent data have reiterated this effect of ACE inhibitors. Present management of renal disease in sickle cell disease primarily involves screening for the development of macroalbuminuria ($\geq$300 mg per day of urinary albumin excretion) as the earliest manifestation of chronic kidney disease. Once detected blockade of the renin-angiotensin-aldosterone systems (RAAS) via ACE inhibitors or angiotensin receptor blockers (ARBs) should be initiated. Hydroxyurea, used commonly for other manifestations of sickle cell disease as above, may also play a role in the management of proteinuria. A small case series of pediatric patients had demonstrated that the addition of hydroxyurea to patients with proteinuria already on ACE inhibitor therapy led to further reductions in proteinuria.[12,201] Another small study involving nine patients with microalbuminuria who were treated with hydroxyurea for other indications demonstrated resolution in four patients. Furthermore those without microalbuminuria who were treated with hydroxyurea failed to develop proteinuria in follow-up.[202,203] A recent report from the BABY HUG cohort,[204] a study of infants with sickle cell disease evaluating use of hydroxyurea in infancy, failed to demonstrate a difference in the increase in GFR between the treatment and placebo groups.[68,203] However, the very young age of the group at enrollment (9 to 19 months) with only 2 years of follow-up may have precluded the investigators' ability to predict longer term effects of hydroxyurea on eGFR. However, the optimal use of this agent in management of sickle cell renal disease remains to be determined.

Concomitant hypertension is predictive of progressive loss of renal function, and is therefore a target for intervention. With management of hypertension, further progression of disease may be allayed.[205] Apart from the use of RAAS blockade for proteinuria, no other specific antihypertensive therapy has been indicated. Some have advocated for the avoidance of diuretics as they may exacerbate the tendency for dehydration.[205]

End-Stage Renal Disease

As a whole, patients with sickle cell disease represent less than 1% of the total ESRD population in the United States.[86] Either peritoneal or hemodialysis present viable options although these patients are more likely to choose hemodialysis.[184] Management of these patients while receiving dialysis is similar to that of others with the exception of the use of erythropoietin-stimulating agents (ESAs). These agents should be reserved only for those with profound anemia, and sickle cell disease patients should not be assigned to the same hemoglobin targets as other ESRD patients. Unfortunately, little data and no consensus exist to further guide ESA dosing although many suggest hemoglobin goals should not exceed 10 mg per dL. Sickle cell disease patients receiving dialysis in early reports were suggested to have a 2-year mortality of 60% although a more recent series has suggested mortality up to 40% in the first year alone.[86] Additionally, McClellan et al. also demonstrated that sickle cell disease patients were more likely to have disparities in care when entering dialysis. More sickle cell disease patients are likely to have had prior stroke and heart failure at the time of dialysis initiation. Importantly, a trend to less arteriovenous fistula use and less pre-dialysis nephrology care was seen.[86] These disparities in entry care may represent later than needed nephrology referral and may be a point of intervention to improve care.

Renal Transplantation

Renal transplant is also a viable option of renal replacement therapy for those with sickle cell disease. Unique complications at the time of transplantation do exist including allograft vein thrombosis and recurrent sickle cell crises.[206]

The use of hydroxyurea and exchange transfusion has been explored at the time of transplantation to prevent these complications. Sickle cell disease transplant patients do not fare as well as African Americans in the general transplant population, with 67% surviving for 7 years following transplantation (compared to 83%). However, allograft transplantation is still preferable, with 56% surviving at 10 years compared to only 14% on dialysis.[206] Recurrence of sickle cell nephropathy has been reported as early as 3.5 years following transplantation.[206,207] Simultaneous bone marrow transplantation may be explored in the future as an included measure to "cure" sickle cell disease.[206]

SICKLE CELL TRAIT

Although sickle cell trait (SCT; i.e., heterozygous inheritance of the HbS mutation) has generally been regarded as a benign carrier state, renal abnormalities are perhaps the best-acknowledged complications of SCT. The renal medulla presents an ideal environment to promote dehydration and sickling of erythrocytes containing hemoglobin S. As a result, some of the same features seen in sickle cell disease present among carriers of the disease, although perhaps as less severe manifestations.

Hematuria is thought to be the most common manifestation of SCT, having first been reported more than 50 years ago.[208] From a large Veterans Administration series, hematuria was the reason for hospitalization in 4% of African American patients with SCT, nearly twice the rate of those with normal hemoglobin phenotypes.[209] The true prevalence of hematuria among the general population of those with sickle cell trait remains undetermined. Bleeding, typically painless, may present as either microscopic or gross hematuria and can occur with or without frank renal papillary necrosis. The left kidney is involved more commonly due to its slightly larger size and its higher venous pressure due to compression of the left renal vein by the aorta and superior mesenteric vein.[210,211] As with sickle cell disease, bedrest and aggressive hydration is usually all that is needed to manage urinary bleeding. In cases that remain refractory to conservative management, use of desmopressin or epsilon aminocaproic acid (EACA), and even invasive intervention via ureteroscopy and angiography, have been advocated.

Impaired urinary concentration is also a common occurring characteristic of those with SCT and likely results from the same vascular abnormalities that cause hematuria via ischemia and microinfarction. Microradiographs performed at autopsy in those with SCT demonstrate reduction in the number of vasa recta and disruption of the remaining medullary vascular architecture.[32] While these changes are not as severe as those seen in sickle cell disease, they likely account in part for the observed impairment of urinary concentration in patients with SCT.[32] Furthermore, this loss of maximal concentration capacity is thought to predispose these patients to dehydration, which is thought to play a role in the higher rates of rhabdomyolysis and sudden death related to extreme exercise observed in SCT.[212–215]

Urinary concentration has also been found to be variable among subjects with SCT, and relates to the percentage of hemoglobin S expressed as determined by the coinheritance of the α-globin gene deletion(s).[216] In one series of SCT individuals, maximal achievable concentration of urine following administration of intranasal desmopressin acetate ranged between 530 and 845 mOsm. The range observed correlated inversely with the number of α-globin gene deletions.[98] With two α-globin gene deletions, HbS concentration averaged 29% of total hemoglobin expressed and urine concentration was only moderately reduced. In those with no α-globin gene deletions, mean HbS concentration was 42% and impairment of urinary concentration was highest.

With the various structural and functional abnormalities noted to occur in the kidney, some have posited that SCT may represent a risk factor for CKD.[217–219] Microalbuminuria, thought to be a marker of early renal injury, has been reported by some to be more common in those with SCT, particularly among diabetic men.[73,220] Other studies in diabetics, however, have shown no association.[221,222] In the ESRD population, SCT has been reported more commonly among African American patients with polycystic kidney disease (PCKD), and those with SCT and PCKD appear to progress more quickly to ESRD and perhaps have more frequent bleeding episodes.[223–225] A recent study utilizing systematic screening of African American ESRD patients demonstrated a twofold prevalence of SCT, as identified by hemoglobin phenotyping, compared to that of the background population.[217] In contradistinction, analysis of genotyping results of African American ESRD patients recruited into a large genetic cohort study with both diabetic and nondiabetic nephropathy failed to demonstrate a similar association.[226] Yet the data remain preliminary in nature and the potential role of sickle trait in CKD needs further investigation. These studies, furthermore, have not addressed the potential contribution of SCT to progression of established CKD.

The presence of sickle trait may also affect the comorbidity associated with ESRD. One study has demonstrated SCT patients on hemodialysis may be more likely to receive higher doses of ESAs, although again, the data for this is relatively preliminary.[227] Additionally, other potential morbidities associated with SCT, such as venous thromboembolism,[228,229] may have particular importance in the ESRD population.

Presently the association between SCT and CKD remains speculative, albeit biologically plausible, and warrants further evaluation via larger, prospective studies. Furthermore, no data exist as to whether detection of SCT in early CKD would allow meaningful intervention to modify disease progression (i.e., RAAS blockade). Although the effect size at an individual level may be modest or only contributory to renal disease, due to its relative commonality (7%–9% among African Americans in the United States), the population effect could be relatively large.

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