Herrick [1] was the first to discover sickle cell hemoglobin (α2β2) with sickle-shaped erythrocytes. In 1910, he described the case of a young black student from the West Indies with severe anemia characterized by “peculiar elongated and sickle-shaped red blood corpuscles.” Herrick also noted a slightly increased volume of urine of low specific gravity and thus observed the most frequent feature of sickle cell nephropathy: inability of the kidney to concentrate urine normally.
Sickle Cell Nephropathy

The term sickle cell nephropathy encompasses all the structural and functional abnormalities of the kidneys seen in sickle cell disease. These renal defects are most pronounced in homozygous sickle cell anemia (Hb SS), double heterozygous sickle cell hemoglobin C disease (Hb SC), sickle cell hemoglobin D disease, sickle cell hemoglobin E disease (SE) disease, and sickle cell β-thalassemia. Identification of this familial autosomal codominant disorder as an abnormality of the hemoglobin molecule was made in 1949 by Pauling and coworkers [2].

Sickle Cell Anemia

In 1959, Ingram [3] discovered the exact nature of the defect: substitution of valine for glutamic acid at the sixth residue of the β chain, establishing sickle cell anemia as a disease of molecular structure, “a molecular disease” based on one point mutation. It is most fascinating that one substitution in the gene encoding, with the resulting replacement of β6 glutamic acid by valine, leads to the protean and devastating clinical manifestations of sickle cell disease. The structural and functional abnormalities in the kidneys of patients with sickle cell disease, all resulting from that one point mutation, are described and discussed.

When sickle hemoglobin (Hb S) is deoxygenated the replacement of β6 glutamic acid with valine has as a consequence a hydrophobic interaction with another hemoglobin molecule (reproduced schematically in Fig. 4-3). One of the two β subunits forms a hydrophobic contact with an acceptor site on a β subunit of a neighboring β chain. An aggregation into large polymers is triggered. The twisted ropelike structure to the right is a polymer composed of 14 strands.

In a concentrated solution of deoxygenated Hb S, large polymers and free tetramers are demonstrated readily. However, species of intermediate size cannot be detected. This means polymerization of Hb S occurs easily and can be regarded as a simple crystal solution equilibrium [4].

As a rule, renal hemodynamics are either normal or supernormal in patients with Hb SS and who are less than 30 years of age. The filtration fraction (glomerular filtration rate/effective renal plasma flow) has been found to be decreased (mean, 14% to 18%; normal, 19% to 22%). It has been suggested that selective damage of the juxtamedullary glomeruli might result in a lower filtration fraction because these nephrons appear to have the highest filtration fractions. Microradioangiographic studies lend support to this suggestion [5].

Speculation exists as to the possible mechanisms responsible for the decline in renal hemodynamics with age, sometimes ending in renal failure with shrunken end-stage kidneys. This decline could be the result of the loss of medullary circulation, as suggested by the microradioangiographic studies. Another possible mechanism is the relationship between supernormal hemodynamics, hyperfiltration, and glomerulosclerosis [6].

An inability to achieve maximally concentrated urine has been the most consistent feature of sickle cell nephropathy.
Molecular Pathogenic Mechanisms and Sickling

FIGURE 4-1
Three-dimensional drawing of a hemoglobin molecule. Shown are the interrelationship of the two α and two β chains, localization of the helices, amino acids in the chains, and iron molecules in the porphyrin structure. Of the α1 and β1 chains the helical and nonhelical segments can be identified easily. The individual amino acids are marked as circles and connected to each other. The dark rectangles represent the heme group, and within their center is the iron molecule. These heme groups are localized between the E and F helices. The helices in a hemoglobin molecule are designated by letters from A to H, starting from the amino end. The whole molecule has a spherical form with a three-dimensional measurement of 64 by 55 by 50 Å. (Adapted from Dickerson and Geis [7]; with permission.)

Respiratory Movement of the Hemoglobin Molecule

FIGURE 4-2
Respiratory movement of a hemoglobin molecule. From a functional point of view the so-called respiratory movement of the hemoglobin molecule is of great importance. When the four oxygen atoms bind to oxyhemoglobin, the firmly bound α1-β1 and α1-β2 move away from each other slightly. After full oxygenation the heme groups of the β chains are 7 Å closer to each other (R configuration). After deoxygenation the opposite occurs (T configuration). This "respiratory movement" (R indicates the relaxed and T the tense configurations) is of great importance in our understanding of the pathogenesis of sickling: polymerization occurs when the T configuration takes place. (Adapted from Dickerson and Geis [7]; with permission.)
4.4 Systemic Diseases and the Kidney

**FIGURE 4-3**
Schematic representation of the interactions of sickle red cells. Sickle red cells (dark circles) traverse the microcirculation, releasing oxygen from oxyhemoglobin, and change into deoxyhemoglobin (light circles). Deoxygenation of hemoglobin S induces a change in conformation in which the β sub-units move away from each other. The hydrophobic patch at the site of the β where the valine replacement has occurred (shown as a projection) can bind to a complementary hydrophobic site of the β valine replacement (shown as an indentation). This mechanism is important for the formation of a polymer (see Fig. 4-4). The diagram to the right shows the assembly of deoxyhemoglobin S into a helical 14-strand fiber: a polymer is formed (see Fig. 4-5). As the deoxyhemoglobin S polymerizes and fibers align, the erythrocyte is transformed into a “sickle” shape, observed at the bottom by scanning electron micrography. (Adapted from Bunn [4]; with permission).

**FIGURE 4-4**
Polymerization of sickle cell hemoglobin. This polymerization occurs in three stages: 1) nucleation, 2) fiber growth, and 3) fiber alignment. The end stage is a complicated structure for a helical fiber: four inner fibers surrounded by 10 outer filaments. Sickling, the process of polymerization, occurs under three different circumstances: 1) deoxygenation, 2) acidosis, and 3) extracellular hyperosmolality. These circumstances produce shrinking of the erythrocytes that causes elevation of the intracellular hemoglobin concentration. This mechanism occurs in the inner medulla of the kidney and renal papillae as a result of countercurrent multiplication. Extracellular osmolality increases with the results previously mentioned [8].
Electron Microscopy and Three-Dimensional Reconstruction of a Polymerized Fiber of Hemoglobin

FIGURE 4-5
Structures of polymerized fibers. A, Electron microscopy of a polymerized fiber of hemoglobin S. B–D, Structures of a three-dimensional reconstruction of such a fiber. Each small sphere represents a Hb S tetramer. B, A complete fiber, consisting of 14 grouped filaments in helical structure. C, The inner core of four filaments. D, A combination of inner and outer filaments. (From Edelstein [9]; with permission.)

Polymerization of Hemoglobin S

FIGURE 4-6
Polymerization of hemoglobin S. Polymerization of deoxygenated hemoglobin S is the primary event in the molecular pathogenesis of sickle cell disease, resulting in a distortion of the shape of the erythrocyte and a marked decrease in its deformability. These rigid cells are responsible for the vaso-occlusive phenomena that are the hallmark of the disease [4]. Interesting shapes of variable forms result depending on the localization of the polymers in the cell. A collection of electron microscopy scans of sickle cells undergoing intracellular polymerization is shown here. The slides were created in different laboratories. A, Characteristic peripheral blood smear from a patient with sickle cell anemia. Extreme sickled forms and target cells are seen. B, Electron microscopy scan of normal erythrocytes.

(Continued on next page)
FIGURE 4-6 (Continued)

C, Electron microscopy scan of a normal erythrocyte and a sickle cell. D–L, This series of sickle cells show many possible formations of sickled erythrocytes. The variety of shapes results from the intracellular localization of the polymers. In banana- or sickle-shaped cells the polymers have formed bundles of fibers oriented along the long axis of the cell. In cells with a holly-leaf shape (panel E), the hemoglobin fibers point in different directions.
Types of Sickle Cells and Released Membrane Structures

Franck and coworkers [10] reported that the normal membrane phospholipid organization is altered in sickled erythrocytes. These authors presented evidence of enhanced trans-bilayer movement of phosphatidylcholine in deoxygenated reversibly sickled cells and put forward the hypothesis that these abnormalities in phospholipid organization are confined to the characteristic protrusions of these cells. Scanning electron micrographs of various types of sickle cells and released membrane structures are shown. 

- **A**, Deoxygenated despicular red sickle cells (RSC). 
- **B**, Deoxygenated native RSC. 
- **C**, Oxygenated irreversibly sickled cell. 
- **D**, Spicules. 
- **E**, Purified microvesicles. 

The free spicules released from RSC by repeated sickling and unsickling as well as the remnant despicular cells were studied by following the fate of $^{14}$C-labeled phosphatidylcholine. The results are shown in Figure 4-8. The free spicules have the same lipid composition as do the native cell but are deficient in spectrin. These spicules markedly enhance the rate of thrombin and prothrombin formation, explaining the prethrombotic state of the patient with sickle cell disease and the tendency toward the occurrence of crises. The prethrombotic state, also present in the renal circulation, stimulates sickle cell formation occurring in the inner renal medulla and papillae where hyperosmosis also contributes to sickling and microthrombi formation in the vasa recta. (From Franck and coworkers. [10]; with permission.)
Penetration and Deconstruction of the Erythrocyte Membrane

Penetration and destruction of the erythrocyte membrane. A, The membrane is penetrated and destroyed by the intracellular formation of polymers, resulting in spicule formation. B, Interruption of the binding between the membrane and protein skeleton results in a massive exchange of lipids between the inside and outside of the cell. This process is called flip-flop. An abnormal membrane skeleton causes an increased flip-flop. The result in the spicule is a change in the chemical structure, increasing the tendency toward coagulation of sickle cell blood (prethrombotic state). C, The relationship between the protein skeleton of the erythrocyte and lipid membrane is shown. (Adapted from Franck [11]; with permission.)
FIGURE 4-9

Macroscopy and microradioangiographs of sickle cell kidneys. The kidneys of patients with sickle cell disease usually are of near normal size, and most kidneys show no significant gross alterations. Abnormalities can be expected in the renal medulla as erythrocytes form sickles more readily in the relatively hypoxic and hyperosmotic renal medulla than in other capillary circulations. Formation of microthrombi causes further impairment of the vasa recta circulation. A and B, Injection microradioangiographs of the kidney in a person without hemoglobinopathy are shown: the entire kidney (panel A) and a detailed view (panel B). C and D, Injection microradioangiographs of the kidney in a patient with sickle cell disease are shown: the entire kidney (panel C) and a detailed view (panel D). E, Injection microradioangiograph of a kidney in a patient with sickle cell hemoglobin C disease. In the normal kidney (panel A), vasa recta are visible radiating into the renal papilla. In sickle cell anemia (panel D), vasa recta are virtually absent. Those vessels that are present show abnormalities: they are dilated, form spirals, end bluntly, and many appear to be obliterated. In the patient with hemoglobin SC (panel E) changes are seen intermediately between patients with hemoglobin SC and normal persons. (From van Eps et al. [5]; with permission.)
FIGURE 4-10
A–H, Models to demonstrate the principle of countercurrent multiplier in creating high urine concentration. The first panel illustrates the relation between urine osmolality and arginine vasopressin excretion. The long loops of Henle and their accompanying vasa recta reaching the papillae comprise only 15% of the total nephron population but are necessary for producing concentrated urine [12]. As seen, the mechanisms of countercurrent multiplication and countercurrent exchange create an increase in osmolality in the kidney from 280 mOsm at the cortex to about 1200 mOsm/kg H₂O in the inner medulla and papillae. Reabsorption in the collecting ducts results in production of highly concentrated urine.

(Continued on next page)
Urine concentration and dilution: countercurrent multiplier

Descending limb
- Na\(^+\), Cl\(^-\), Urea, H\(_2\)O

Loop of Henle
- Na\(^+\), Cl\(^-\), Urea, H\(_2\)O

Ascending limb
- Na\(^+\), Cl\(^-\), Urea, H\(_2\)O

Collecting duct
- Na\(^+\), Cl\(^-\), Urea, H\(_2\)O

Urine
Systemic Diseases and the Kidney

Figure 4-10 (Continued)

Urine concentration and dilution: countercurrent diffusion (exchange)

Loop of Henle (countercurrent multiplier system)

Vasa recta (countercurrent exchange system)
Urine concentration and dilution: concentrating kidney

**FIGURE 4-10 (Continued)**
4.15 Sickle Cell Disease

**Relationship Between Maximal Urinary Osmolality and Age**

![Graph showing relationship between maximal urinary osmolality and age in normal subjects and in patients with hemoglobinopathies. Results of an investigation into a large group of normal persons and those with homozygous hemoglobin disease (Hb SS), heterozygous hemoglobin disease (Hb AS), sickle cell hemoglobin C disease (SC), hemoglobin C trait (AC), and hemoglobin C disease (Hb CC). Normal persons have a mean maximal urinary osmolality of 1058 ± 128 mOsm/kg H₂O. The most marked impairment in concentrating capacity occurs in Hb SS disease. Maximal urinary osmolality decreases significantly in the first decade of life and stabilizes in patients over 10 years of age at a mean of 434 ± 131 mOsm/kg H₂O. The measurement has been designated the fixed maximum of sickle cell nephropathy. In patients with Hb AS and Hb SC, a progressive decrease in maximal urinary osmolality can be observed with age. C hemoglobin alone (AC or CC) does not impair the concentrating ability of the kidneys. The renal concentrating capacity of the heterozygote (Hb AS) also is affected, but only later in life. (Adapted from van Eps et al. [13]; with permission.)

**Figure 4-11**

**Relationship Between Nephron with Long Loops and Those with Short Loops of Henle**

![Diagram showing relationship between nephron with long loops and those with short loops of Henle. In the normal human kidney, approximately 85% of the nephrons have short loops of Henle restricted to the outer medullary zone. These nephrons may be largely responsible for achieving the interstitial osmolality of about 450 mOsm/kg H₂O that exists at the transition of the outer and inner medulla. The remaining 15% of human nephrons are juxtamedullary nephrons with long loops of Henle, extending into the inner medullary zone and renal papillae. Together with the parallel hairpin vasa recta, these units are responsible for further increasing interstitial osmolality during antidiuresis to about 1200 mOsm/kg H₂O at the tip of the papillae. In experiments with rats, selectively removing the papillae destroys only nephrons originating in the juxtamedullary cortex. In such animal preparations, a severe loss of concentrating capacity during fluid deprivation has been observed. Thus, juxtamedullary nephrons are necessary for achieving a maximal urine osmolality. These pathophysiologic mechanisms help clarify the abnormal findings in sickle cell nephropathy. On the basis of these mechanisms, the concentrating defect in sickle cell disease can be explained as a consequence of the sickling process per se and the resultant ischemic changes in the medullary microcirculation [5]. It has been demonstrated that Hb SS erythrocytes form sickle erythrocytes within seconds when placed in surroundings as hyperosmotic as is the renal medulla during hypotension [8]. Sicking of renal blood cells causes a significant increase in blood viscosity that could interfere with the normal circulation through the vasa recta, preventing both active and passive accumulation of solute in the papillae necessary to achieve maximally concentrated urine. Increased viscosity of blood and intravascular aggregations of Hb SS erythrocytes could also produce local hypoxia and eventually infarction of the renal papillae.

**Figure 4-12**

Relationship between nephron with long loops and those with short loops of Henle. In the normal human kidney, approximately 85% of the nephrons have short loops of Henle restricted to the outer medullary zone. These nephrons may be largely responsible for achieving the interstitial osmolality of about 450 mOsm/kg H₂O that exists at the transition of the outer and inner medulla. The remaining 15% of human nephrons are juxtamedullary nephrons with long loops of Henle, extending into the inner medullary zone and renal papillae. Together with the parallel hairpin vasa recta, these units are responsible for further increasing interstitial osmolality during antidiuresis to about 1200 mOsm/kg H₂O at the tip of the papillae. In experiments with rats, selectively removing the papillae destroys only nephrons originating in the juxtamedullary cortex. In such animal preparations, a severe loss of concentrating capacity during fluid deprivation has been observed. Thus, juxtamedullary nephrons are necessary for achieving a maximal urine osmolality. These pathophysiologic mechanisms help clarify the abnormal findings in sickle cell nephropathy. On the basis of these mechanisms, the concentrating defect in sickle cell disease can be explained as a consequence of the sickling process per se and the resultant ischemic changes in the medullary microcirculation [5]. It has been demonstrated that Hb SS erythrocytes form sickle erythrocytes within seconds when placed in surroundings as hyperosmotic as is the renal medulla during hypotension [8]. Sicking of renal blood cells causes a significant increase in blood viscosity that could interfere with the normal circulation through the vasa recta, preventing both active and passive accumulation of solute in the papillae necessary to achieve maximally concentrated urine. Increased viscosity of blood and intravascular aggregations of Hb SS erythrocytes could also produce local hypoxia and eventually infarction of the renal papillae.
A–E. Relationship between concentrating capacity and patient age. Over a prolonged period, we investigated the effect of multiple transfusions of hemoglobin A erythrocytes into children and adults with sickle cell anemia (4, 7, 11, 15, and 40 years). In the first panel, the effects of multiple transfusions of normal blood given to a 4-year-old boy with homozygotic sickle cell anemia. A significant improvement in concentrating capacity can be observed. This diminishes in older patients.

(Continued on next page)
FIGURE 4-13 (Continued)
FIGURE 4-13 (Continued)
Relationship Between Age and Ability to Reverse the Defect in Urinary Concentration by Blood Transfusions

**FIGURE 4-14**

Relationship between age and ability to reverse the defect in urinary concentration by blood transfusions in patients with sickle cell disease. **A**, The maximal urinary osmolality achieved before transfusion (lower point of each vertical line) and after multiple transfusions with normal blood (upper point of each vertical line) in 14 patients with sickle cell disease, ranging in age from 2 to 40 years. **B**, The percentage of increase in maximal urinary osmolality resulting from transfusion. Maximal urinary osmolality before transfusion is depressed at all ages; significant improvement after transfusion occurs only in children and adolescents. (From van Eps et al. [13]; with permission.)

Length of the Loops of Henle in Animals Correlated with Kidney Concentrating Capacity

**FIGURE 4-15**

Length of the loops of Henle in animals correlated with kidney concentrating capacity. **A**, Investigations of animal species [14] with different lengths of the loops of Henle and correlation with the concentrating capacity of their kidneys reveal their relationship. **B**, Desert animals with very long loops of Henle can produce highly concentrated urine; in contrast, beavers living in water-rich surroundings have only short loops of Henle and cannot produce urine concentrate over 450 mOsm.

(Continued on next page)
In sickle cell disease the long loop of Henle has been obliterated and the concentrating capacity of the kidney is not higher than 400 mosm, much as in beavers. An overview has been reproduced. (From van Eps and De Jong [15]; with permission.)

**Urinary Acidification**

**FIGURE 4-16**

A, Urinary acidification. Patients with hemoglobin SS or SC demonstrate an incomplete form of renal tubular acidosis. In response to a short-duration acid load, all of the patients studied by Goossens and coworkers [16] with otherwise normal renal function were unable to decrease urine pH below 5.3, whereas normal persons achieve a urinary pH of 5.0 or lower. Titratable acid (TA) and total hydrogen ion excretion are lower in patients with Hb SS or Hb SC; however, in most cases, ammonia excretion is appropriate for the coexisting urine pH. The acidification defect has been classified as distal rather than proximal, because no associated wasting of bicarbonate occurs, and the acidification defect is characterized by failure to achieve a normal minimal urinary pH during acid loading. Investigators from several centers have found no evidence of metabolic acidosis in the absence of a sickle cell crisis; however, they have found changes consistent with mild chronic respiratory alkalosis [15].

(Continued on next page)
Sickle Cell Disease

4.21

FIGURE 4-16 (Continued)

B. Relationship between renal concentrating and acidifying capacity in Hb AS, SC, and SS and in normal persons [16].

Tubular Reabsorption of Phosphate in Sickle Cell Nephropathy

FIGURE 4-17

Relationship between $C_p$/glomerular filtration rate and serum phosphate. Closed circles represent values for patients who had fasted from food and drink; open circles are values obtained when $U_{pV}$ was 0.032 mmol/min. The continuous line shows the mean of the values in patients with sickle cell anemia, and the hatched area indicates the range for normal persons. $C_p$—clearance of phosphate; $T_{mP}/GFR$—tubular maximum reabsorption of phosphate/glomerular filtration rate. (Adapted from De Jong and coworkers [17]; with permission.)
4.22 Systemic Diseases and the Kidney

Blood Pressure in Sickle Cell Disease

![Blood pressure and sickle cell anemia](image)

FIGURE 4-18

Blood pressure and sickle cell anemia. Mean standard deviation of systolic and diastolic blood pressure in control subjects (dotted lines) and patients with sickle cell anemia (closed lines) who are matched for age and gender. (From De Jong and van Eps [20].)

References