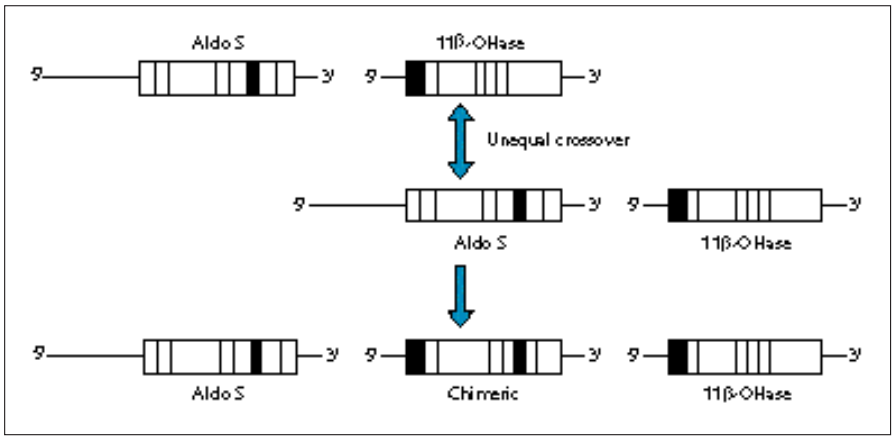

FIGURE 3-17

Genetics of glucocorticoid-remediable aldosteronism (GRA): schematic representation of unequal crossover in GRA. The genes for aldosterone synthase (Aldo S) and 11 β-hydroxylase (11 β-OHase) are normally expressed in separate zones of the adrenal cortex. Aldosterone is produced in the zona glomerulosa and cortisol, in the zona fasciculata. These enzymes have identical intron-extron structures and are closely linked on chromosome 8. If unequal crossover occurs, a new hybrid gene is produced that includes the 5' segment of the 11 β-OHase gene (ACTH-response element and the 11 β-OHase segment) plus the 3' segment of the Aldo S gene (aldosterone synthase segment). The chimeric gene is now under the contol of ACTH, and aldosterone secretion is enhanced, thus causing hypokalemia and hypertension. By inhibiting pituitary release of ACTH, glucocorticoid administration leads to a fall in aldosterone levels and correction of the clinical and biochemical abnormalities of GRA. The presence of Aldo S activity in the zona fasciculata gives rise to characteristic elevations in 18-oxidation products of cortisol (18-hydroxycortisol and 18-oxocortisol), which are diagnostic for GRA [8].

Hypokalemia: Clinical Manifestations

CLINICAL MANIFESTATIONS OF HYPOKALEMIA

- Cardiovascular
  - Abnormal electrocardiogram
  - Predisposition for digitalis toxicity
  - Atrial ventricular arrhythmias
  - Hypertension
- Neuromuscular
  - Smooth muscle
    - Constipation/ileus
    - Bladder dysfunction
  - Skeletal muscle
    - Weakness/cramps
    - Tetany
    - Paralysis
    - Myalgias/rhabdomyolysis
- Renal/electrolyte
  - Functional alterations
    - Decreased glomerular filtration rate
    - Decreased renal blood flow
    - Renal concentrating defect
    - Increased renal ammonia production
    - Chloride wasting
    - Metabolic alkalosis
    - Hypercalciuria
    - Phosphaturia
  - Structural alterations
    - Dilation and vacuolization of proximal tubules
    - Medullary cyst formation
    - Interstitial nephritis
- Endocrine/metabolic
  - Decreased insulin secretion
  - Carbohydrate intolerance
  - Increased renin
  - Decreased aldosterone
  - Altered prostaglandin synthesis
  - Growth retardation

FIGURE 3-18

Clinical manifestations of hypokalemia.

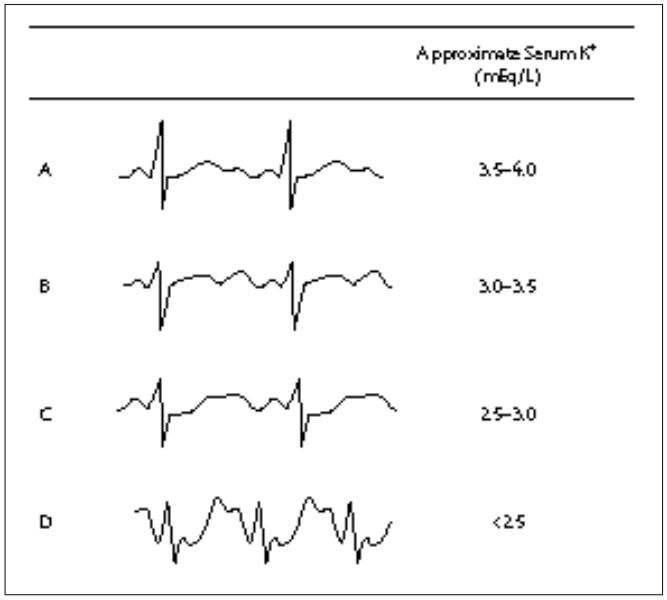

FIGURE 3-19

Electrocardiographic changes associated with hypokalemia. **A**, The U wave may be a normal finding and is not specific for hypokalemia. **B**, When the amplitude of the U wave exceeds that of the T wave, hypokalemia may be present. The QT interval may appear to be prolonged; however, this is often due to mistaking the QU interval for the QT interval, as the latter does not change in duration with hypokalemia. **C**, Sagging of the ST segment, flattening of the T wave, and a prominent U wave are seen with progressive hypokalemia. **D**, The QRS complex may widen slightly, and the PR interval is often prolonged with severe hypokalemia. Hypokalemia promotes the appearance of supraventricular and ventricular ectopic rhythms, especially in patients taking digitalis [16].

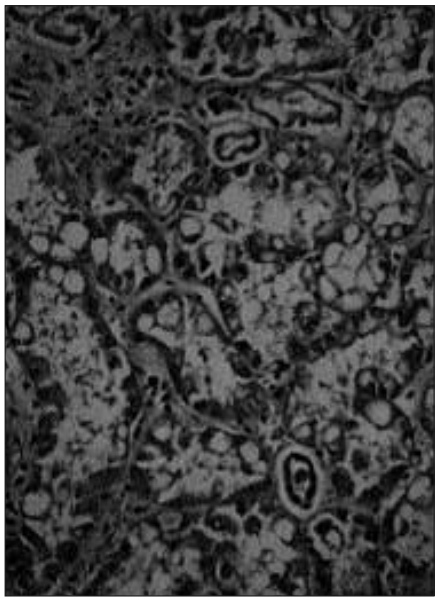

FIGURE 3-20

Renal lesions associated with hypokalemia. The predominant pathologic finding accompanying potassium depletion in humans is vacuolization of the epithelium of the proximal convoluted tubules. The vacoules are large and coarse, and staining for lipids is usually negative. The tubular vacuolation is reversible with sustained correction of the hypokalemia; however, in patients with long-standing hypokalemia, lymphocytic infiltration, interstitial scarring, and tubule atrophy have been described. Increased renal ammonia production may promote complement activation via the alternate pathway and can contribute to the interstitial nephritis [17,18].

Hypokalemia: Treatment

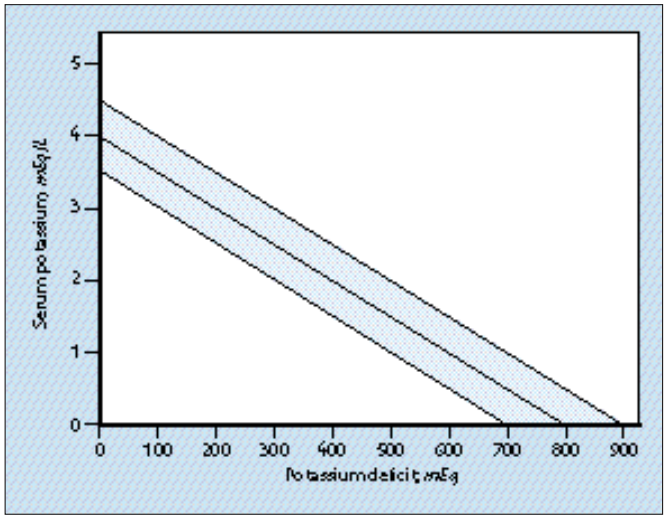

FIGURE 3-21

Treatment of hypokalemia: estimation of potassium deficit. In the absence of stimuli that alter intracellular-extracellular potassium distribution, a decrease in the serum potassium concentration from 3.5 to 3.0 mEq/L corresponds to a 5% reduction (~175 mEq) in total body potassium stores. A decline from 3.0 to 2.0 mEq/L signifies an additional 200 to 400-mEq deficit. Factors such as the rapidity of the fall in serum potassium and the presence or absence of symptoms dictate the aggressiveness of replacement therapy. In general, hypokalemia due to intracellular shifts can be managed by treating the underlying condition (hyperinsulinemia, theophylline intoxication). Hypokalemic periodic paralysis and hypokalemia associated with myocardial infarction (secondary to endogenous β-adrenergic agonist release) are best managed by potassium supplementation [19].

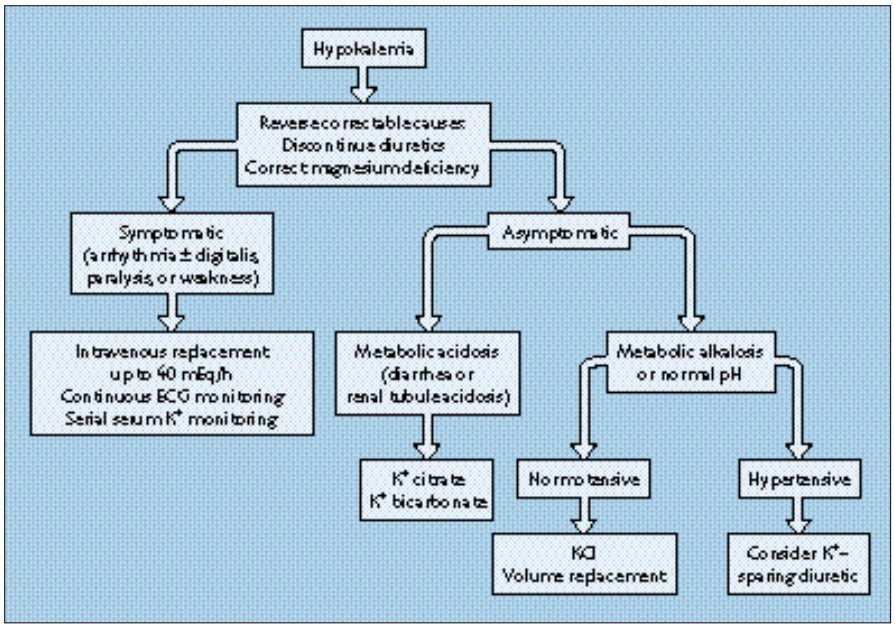

FIGURE 3-22
Treatment of hypokalemia.

Hyperkalemia: Diagnostic Approach

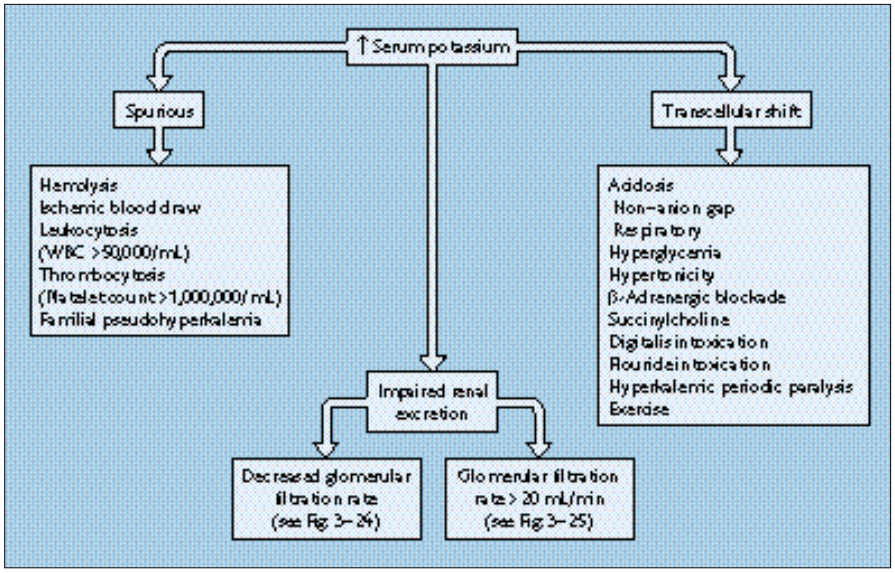

FIGURE 3-23
Approach to hyperkalemia: hyperkalemia without total body potassium excess. Spurious hyperkalemia is suggested by the absence of electrocardiographic (ECG) findings in patients with elevated serum potassium. The most common cause of spurious hyperkalemia is hemolysis, which may be apparent on visual inspection of serum. For patients with extreme leukocytosis or thrombocytosis, potassium levels should be measured in plasma samples that have been promptly separated from the cellular components since extreme elevations in either leukocytes or platelets results in leakage of potassium from these cells. Familial pseudohyperkalemia is a rare condition of increased potassium efflux from red blood cells in vitro. Ischemia due to tight or prolonged tourniquet application or fist clenching increases serum potassium concentrations by as much as 1.0 to 1.6 mEq/L. Hyperkalemia can also result from decreases in K movement into cells or increases in potassium movement from cells. Hyperchloremic metabolic acidosis (in contrast to organic acid, anion-gap metabolic acidosis) causes potassium ions to flow out of cells. Hypertonic states induced by mannitol, hypertonic saline, or poor blood sugar control promote movement of water and potassium out of cells. Depolarizing muscle relaxants such as succinylcholine increase permeability of muscle cells and should be avoided by hyperkalemic patients. The mechanism of hyperkalemia with β-adrenergic blockade is illustrated in Figure 3-3. Digitalis impairs function of the Na^+-K^+-ATPase pumps and blocks entry of potassium into cells. Acute fluoride intoxication can be treated with cation-exchange resins or dialysis, as attempts at shifting potassium back into cells may not be successful.