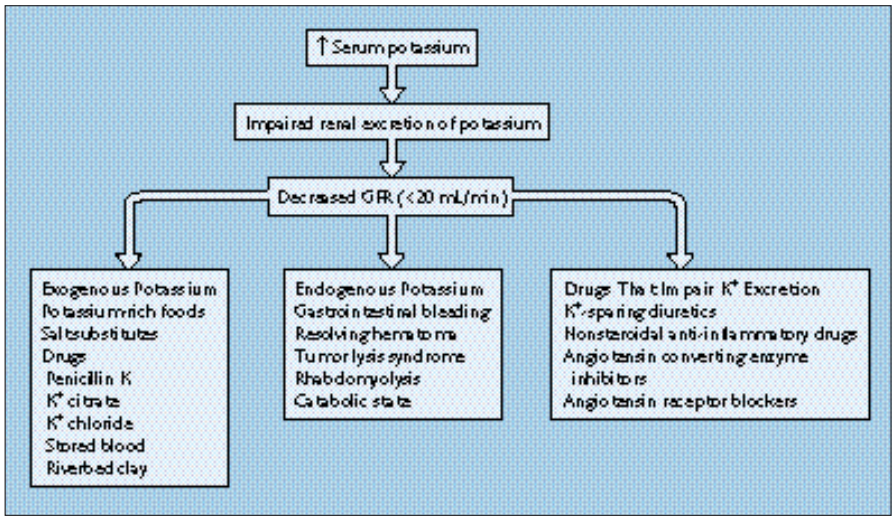

FIGURE 3-24

Approach to hyperkalemia: hyperkalemia with reduced glomerular filtration rate (GFR). Normokalemia can be maintained in patients who consume normal quantities of potassium until GFR decreases to less than 10 mL/min; however, diminished GFR predisposes patients to hyperkalemia from excessive exogenous or endogenous potassium loads. Hidden sources of endogenous and exogenous potassium—and drugs that predispose to hyperkalemia—are listed.

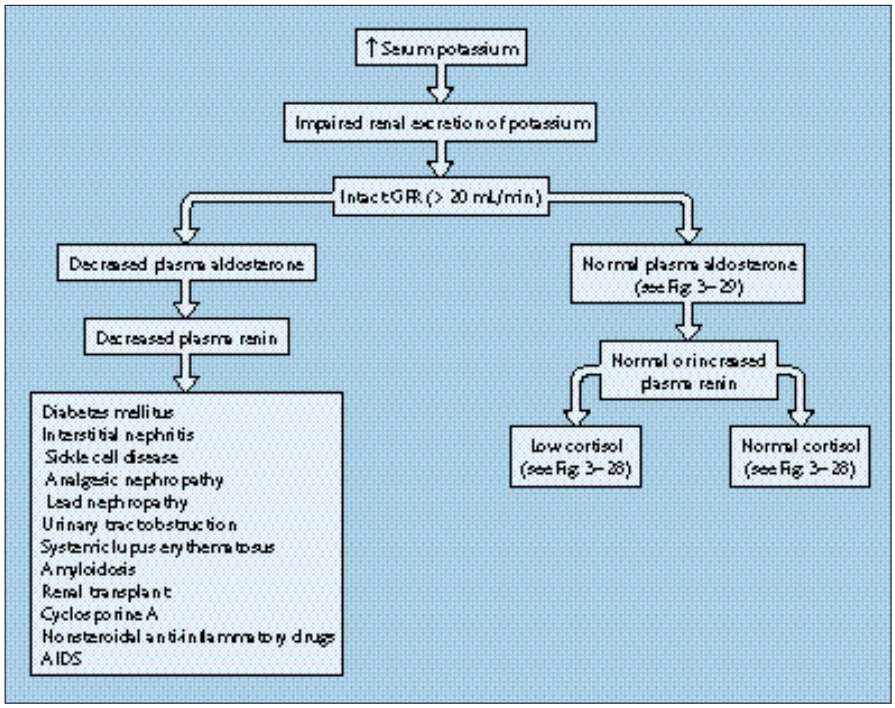

FIGURE 3-25

Approach to hyperkalemia: hyporeninemic hypoaldosteronism. Hyporeninemic hypoaldosteronism accounts for the majority of cases of unexplained hyperkalemia in patients with reduced glomerular filtration rate (GFR) whose level of renal insufficiency is not what would be expected to cause hyperkalemia. Interstitial renal disease is a feature of most of the diseases listed. The transtubular potassium gradient (*see* Fig. 3-26) can be used to distinguish between primary tubule defects and hyporeninemic hypoaldosteronism. Although the transtubular potassium gradient should be low in both disorders, exogenous mineralocorticoid would normalize transtubular potassium gradient in hyporeninemic hypoaldosteronism.

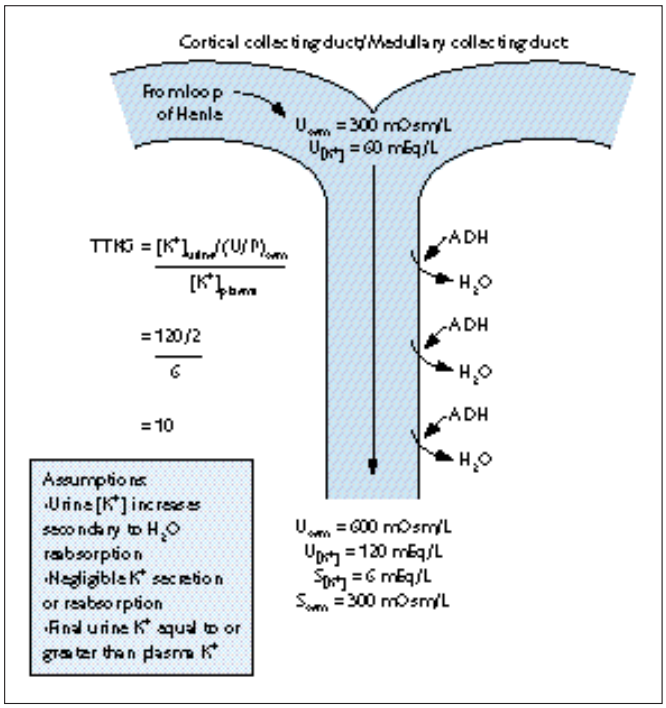

FIGURE 3-26

Physiologic basis of the transtubular potassium concentration gradient (TTKG). Secretion of potassium in the cortical collecting duct and outer medullary collecting duct accounts for the vast majority of potassium excreted in the urine. Potassium secretion in these segments is influenced mainly by aldosterone, plasma potassium concentrations, and the anion composition of the fluid in the lumen. Use of the TTKG assumes that negligible amounts of potassium are secreted or reabsorbed distal to these sites. The final urinary potassium concentration then depends on water reabsorption in the medullary collecting ducts, which results in a rise in the final urinary potassium concentration without addition of significant amounts of potassium to the urine. The TTKG is calculated as follows:

$$TTKG = ([K^+]urine/(U/P)osm)/[K^+]plasma$$

The ratio of $(U/P)_{osm}$ allows for "correction" of the final urinary potassium concentration for the amount of water reabsorbed in the medullary collecting duct. In effect, the TTKG is an index of the gradient of potassium achieved at potassium secretory sites, independent of urine flow rate. The urine must at least be iso-osmolal with respect to serum if the TTKG is to be meaningful [20].

CAUSES FOR HYPERKALEMIA WITH AN INAPPROPRIATELY LOW TTKG THAT IS UNRESPONSIVE TO MINERALOCORTICOID CHALLENGE

- Potassium-sparing diuretics
  - Amiloride
  - Triamterene
  - Spironolactone
- Tubular resistance to aldosterone
  - Interstitial nephritis
  - Sickle cell disease
  - Urinary tract obstruction
  - Pseudohypoaldosteronism type I
- Drugs
  - Trimethoprim
  - Pentamidine
- Increased distal nephron potassium reabsorption
  - Pseudohypoaldosteronism type II
  - Urinary tract obstruction

FIGURE 3-27

Clinical application of the transtubular potassium gradient (TTKG). The TTKG in normal persons varies much but is genarally within the the range of 6 to 12. Hypokalemia from extrarenal causes results in renal potassium conservation and a TTKG less than 2. A higher value suggests renal potassium losses, as through hyperaldosteronism. The expected TTKG during hyperkalemia is greater than 10. An inappropriately low TTKG in a hyperkalemic patient suggests hypoaldosteronism or a renal tubule defect. Administration of the mineralocorticoid 9 α-fludrocortisone (0.05 mg) should cause TTKG to rise above 7 in cases of hypoaldosteronism. Circumstances are listed in which the TTKG would not increase after mineralocorticoid challenge, because of tubular resistance to aldosterone [21].

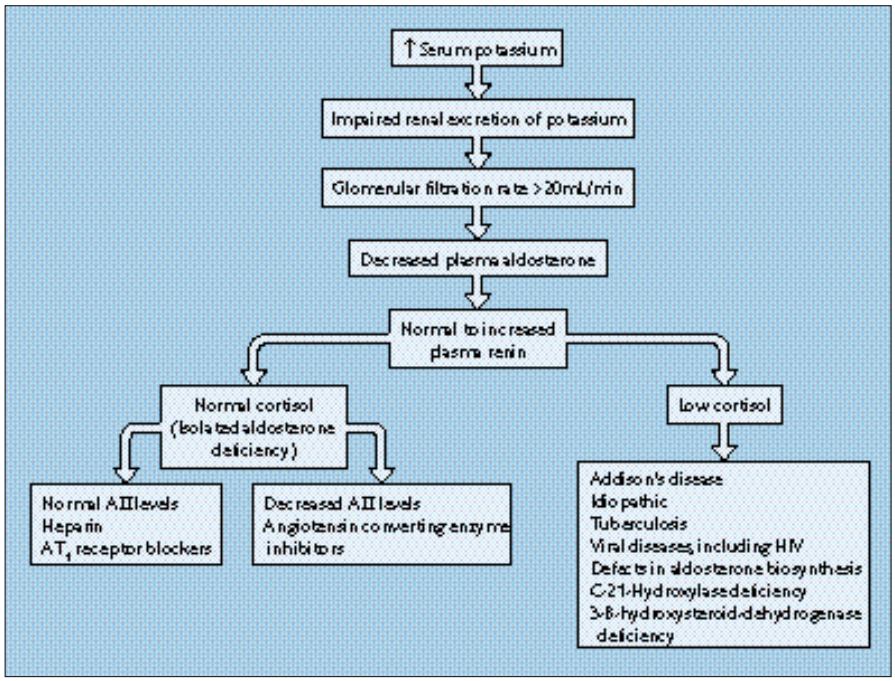

FIGURE 3-28

Approach to hyperkalemia: low aldosterone with normal to increased plasma renin. Heparin impairs aldosterone synthesis by inhibiting the enzyme 18-hydroxylase. Despite its frequent use, heparin is rarely associated with overt hyperkalemia; this suggests that other mechanisms (*eg*, reduced renal potassium secretion) must be present simultaneously for hyperkalemia to manifest itself. Both angiotensin-converting enzyme inhibitors and the angiotensin type 1 receptor blockers (AT_1) receptor blockers interfere with adrenal aldosterone synthesis. Generalized impairment of adrenal cortical function manifested by combined glucocorticoid and mineralocorticoid deficiencies are seen in Addison's disease and in defects of aldosterone biosynthesis.

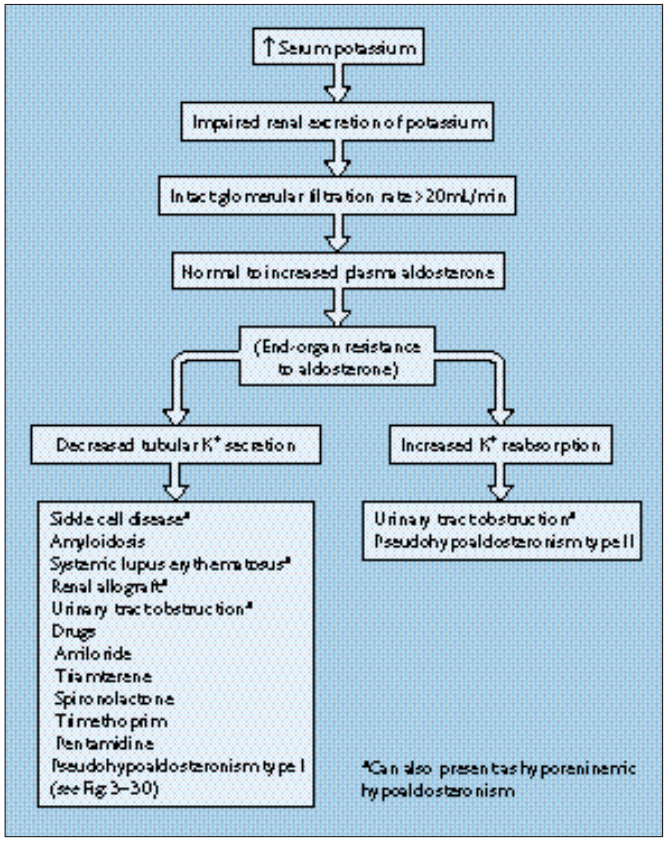

FIGURE 3-29

Approach to hyperkalemia: pseudohypoaldosteronism. The mechanism of decreased potassium excretion is caused either by failure to secrete potassium in the cortical collecting tubule or enhanced reabsorption of potassium in the medullary or papillary collecting tubules. Decreased secretion of potassium in the cortical and medullary collecting duct results from decreases in either apical sodium or potassium channel function or diminished basolateral Na^+-K^+-ATPase activity. Alternatively, potassium may be secreted normally but hyperkalemia can develop because potassium reabsorption is enhanced in the intercalated cells of the medullary collecting duct (*see* Fig. 3-4). The transtubule potassium gradient (TTKG) in both situations is inappropriately low and fails to normalize in response to mineralocorticoid replacement.