the number of Na^+ channels in the apical membrane of the collecting duct. In CKD, the excretion of the dietary load of potassium occurs at the expense of an elevation in serum potassium concentrations.

SODIUM As renal function is reduced with CKD, there is a reduced ability to excrete sodium. Thus, patients with advanced kidney disease are often fluid overloaded. In early disease, however, there are functional adaptations that the kidney assumes to help to maintain the *milieu intérieur*. With loss of functional nephrons, the remaining nephrons are hyperperfused and are hyperfiltering in a manner that can be influenced by dietary protein intake. Although protein restriction can decrease this compensatory hyperperfusion, there is generally more sodium and water filtered and delivered to the remaining nephrons. There is some preservation of glomerulotubular balance with increased proximal tubule sodium and water reabsorption associated with increased levels of the Na/H exchanger in apical membranes of the tubule. The tubuloglomerular feedback (TGF) of the remaining nephrons is sensitive to sodium intake. With high sodium intake in normal renal function, a negative feedback process occurs by which increased distal delivery results in reduced GFR and hence filtration of sodium. In CKD, the TGF becomes a positive feedback process by which increased distal delivery results in increased filtration so that the need to excrete an increased amount of sodium per nephron is achieved. This conversion from a negative feedback process to a positive feedback process may be due to conversion of an adenosine-dominated vasoconstrictive feedback on the afferent arteriole of the glomerulus to a NO-dominated vasodilatory feedback. Like so many of these adaptive responses, this one may turn maladaptive, resulting in higher intraglomerular hydrostatic pressures with increased mechanical strain on the glomerular capillary wall and podocytes and increased glomerulosclerosis as a consequence.

ACID-BASE HOMEOSTASIS The kidneys excrete approximately 1 mEq/kg per day of dietary acid load under normal dietary conditions. With decreased kidney functional mass, there is an adaptive response to increase H^+ excretion by the remaining functional nephrons. This takes the form of enhanced nephron ammoniagenesis and increased distal nephron H^+ ion secretion, which is mediated by the renin-angiotensin system and endothelin-1. NH_3 is produced by deamidization of glutamine in the proximal tubule. NH_3 is converted to NH_4^+ in the collecting duct, where it buffers the secreted H^+. It has been argued, however, that these mechanistic attempts to enhance H^+ secretion can be maladaptive in that they can contribute to kidney inflammation and fibrosis and hence facilitate the progression of CKD.

MINERAL METABOLISM In CKD, there is a decrease in the ability of the kidney to excrete phosphate and produce 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$]. There is a resultant increase in serum phosphate and reduction in serum calcium (Fig. 333e-2). In response, the body adapts by increasing production of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) in an attempt to increase phosphaturia. The elevated levels of PTH act on bone to increase bone resorption and on osteocytes to increase FGF-23 expression. Elevated levels of PTH increase FGF-23 expression by activating protein kinase A and wnt signaling in osteoblast-like cells. There are a number of other factors that increase bone FGF-23 production in CKD including systemic acidosis, altered hydroxyapatite metabolism, changes in bone matrix, and release of low-molecular-weight FGFs. Although the production of PTH and FGF-23 initially are adaptive attempts to maintain body phosphate levels by enhancing excretion by the kidney, they become maladaptive due to systemic effects on the cardiovascular system and bone, as renal function continues to deteriorate. PTH and FGF-23 decrease the kidney's ability to reabsorb phosphate by decreasing the levels of the sodium-phosphate cotransporters NaPi2a and NaPi2c on the apical and basolateral membranes of the renal tubule. FGF-23 also reduces the ability of the kidney to generate $1,25(OH)_2D_3$. In the parathyroid gland, the FGF-23 receptor, the klotho-fibroblast growth factor 1 complex, is downregulated with a consequent loss of the normal action of FGF-23 to downregulate PTH production. PTH and FGF-23 have been implicated in the cardiovascular disease that is so characteristic of patients with CKD. With CKD, there is less klotho expression in the kidney and the parathyroid glands. Klotho deficiency contributes to soft tissue calcifications in CKD. FGF-23 has been associated with increased mortality in CKD and has been reported to be involved causally in the development of left ventricular hypertrophy. PTH also has been reported to directly affect rat myocardial cells, increasing calcium entry into the cells and contributing to death of the cells.

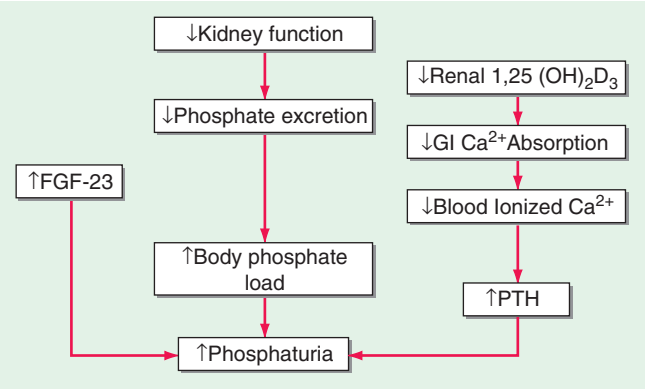

FIGURE 333e-2 Modification of the trade-off hypothesis of Slatopolsky and Bricker as it relates to the adaptation of the body to decreased functional renal mass in an attempt to maintain calcium and phosphate stores and serum levels. $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; FGF-23, fibroblast growth factor-23; GI, gastrointestinal; PTH, parathyroid hormone.

THE EFFECTS OF ACUTE KIDNEY INJURY ON SUSCEPTIBILITY TO SUBSEQUENT INJURY (PRECONDITIONING)

Preconditioning represents activation by the organism of intrinsic defense mechanisms to cope with pathologic conditions. Ischemic preconditioning is the phenomenon whereby a prior ischemic insult renders the organ resistant to a subsequent ischemic insult. Renal protection afforded by prior renal injury was described approximately 100 years ago, in 1912, by Suzuki, who noted that the kidney became resistant to uranium nephrotoxicity if the animal had previously been exposed to a sublethal dose of uranium. This resistance of the renal epithelium to recurrent toxic injury was proposed to be a defense mechanism of the kidney. There have been a number of studies over the years demonstrating that preconditioning with a number of renal toxicants leads to protection against injury associated with a second exposure to the same toxicant or to another nephrotoxicant. It is not, however, a universal finding that toxins confer resistance to subsequent insults.

Kidney ischemic preconditioning is the conveyance of protection against ischemia due to prior exposure of the kidney to sublethal episodes of ischemia. In some experiments in rodents, these prior exposures were short (e.g., 5 min) and repeated or longer. Subsequent protection was generally found at 1–2 h or up to 48 h, but there has been a report of protection in the mouse for up to 12 weeks after the preconditioning exposures. Unilateral ischemia, with the contralateral kidney left alone, was also protective against a subsequent ischemic insult to the postischemic kidney, revealing that systemic uremia was not necessary for protection.

Remote Ischemic Preconditioning Remote ischemic preconditioning is a therapeutic strategy by which protection can be afforded in one vascular bed by ischemia to another vascular bed in the same organ or a different organ. A large number of studies have demonstrated that ischemia to one organ protects against ischemia to another. There are very few mechanistic studies of remote preconditioning in the kidney. In one study, naloxone blocked preconditioning in the kidney, implicating opiates as effectors. Remote preconditioning induced by ischemia to the muscle of the arm induced by a blood pressure cuff can result in protection of the kidney against a subsequent insult, such as one related to contrast agents in humans. Some of the cellular processes and signaling mechanisms proposed to explain preconditioning in the kidney and other organs are listed in Table 333e-3. These protective