as the gateway to the glucose metabolic pathway through glucose 6-phosphate.

Phosphorus is primarily an intracellular ion. In addition to its critical intracellular roles, phosphate has a key extracellular role. The anion pairs with calcium in the hydroxyapatite crystal lattice that provides structural integrity to the skeleton (discussed earlier). As with calcium, phosphate is critical to skeletal strength, and disorders of phosphorus homeostasis, such as hypophosphatemic rickets, lead to pathologic skeletal fractures. The skeleton also serves as a major storage site for phosphate that is accessed in times of severe phosphate deficiency.

The broad intracellular roles for phosphate have two corollaries. First, clinically significant intracellular phosphate deficiency may exist without marked hypophosphatemia. Second, life-threatening phosphate deficiency is often unrecognized because its manifestations (i.e., reduced levels of consciousness, hypotension, respirator dependence, and muscular weakness) are nonspecific but common in intensive care unit settings. Astute clinicians learn to recognize general debility as a potential sign of phosphorus deficiency. Phosphate repletion in this setting may produce dramatic results.

In contrast to regulation of the serum calcium concentration, which is very tight, the regulation of serum phosphate concentrations is relatively lax. The serum phosphorus level is maintained in a broad range between about 3.0 and 4.5 mg/dL. In contrast to extracellular calcium concentrations, extracellular phosphate concentrations are not critically important. Because phosphate is abundant in most diets, a tight systemic regulatory mechanism for serum phosphate is unnecessary.

A physiologic black box can be developed for phosphate metabolism (Fig. 72-8). The box represents the ECF, and as with calcium, it has interfaces with the GI tract, kidney, and skeleton. Because most phosphate is contained within cells, the phosphate black box has a quantitatively significant interface with the intracellular compartment.

Intestinal Phosphate Absorption

A normal diet contains about 1200 to 1600 mg of phosphorus, and about two thirds of this amount, or 800 to 1200 mg, is absorbed each day. This fixed fractional absorption of about 67% occurs in the duodenum and jejunum. In the normal world of phosphate abundance, this intake is more than ample. Under conditions of dietary phosphorus deficiency, as occurs in chronic alcoholism, intensive care units, intestinal malabsorption, or phosphate-binding antacid use, failure of adequate phosphorus absorption presents a physiologic challenge for which no physiologic remedy exists.

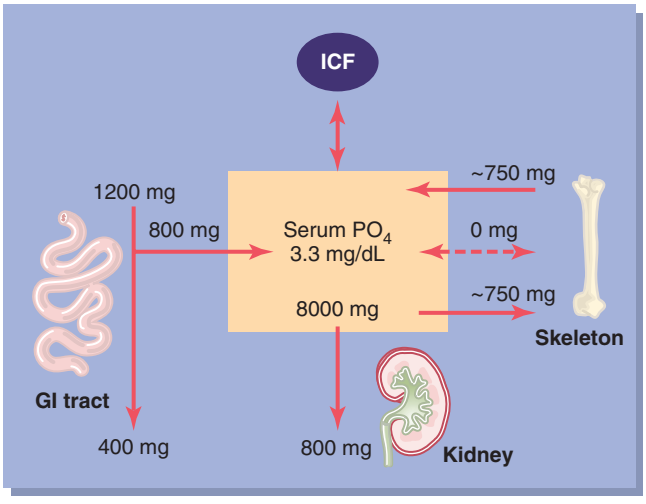

FIGURE 72-8 The phosphate physiologic black box. See Figure 72-1 for nomenclature and the text for details. GI, Gastrointestinal; ICF, intracellular fluid.

Skeletal Phosphate Fluxes

As with calcium, osteoclastic bone resorption and osteoblastic new bone formation (see Figs. 72-1 and 72-3) lead to skeletal phosphate exit or entry, respectively. Although the skeleton can be used as a source of phosphorus, phosphorus can be viewed as a passive passenger with calcium in the calcium regulatory process. Under pathophysiologic conditions, skeletal calcium fluxes may become important. For example, skeletal destruction in multiple myeloma or severe immobilization syndromes leads to hypercalcemia and hyperphosphatemia, which with the concomitant hypercalcemia leads to nephrocalcinosis and renal failure. Conversely, osteoblastic metastases in prostate and breast cancers and the hungry bone syndrome after parathyroidectomy lead to clinically significant hypophosphatemia.

Intracellular-Extracellular Phosphate Fluxes

Phosphate shuttles from extracellular to intracellular compartments. This issue becomes important in certain clinical settings. For example, in the setting of metabolic acidosis, phosphate leaves the intracellular compartment and may lead to hyperphosphatemia, whereas under conditions of alkalosis, serum phosphate concentrations decline, and hypophosphatemia develops as phosphate enters the intracellular compartment.

The intracellular phosphate level has important clinical implications, in part, in the settings of crush injury (i.e., rhabdomyolysis) and tumor lysis syndrome. In both conditions, large intracellular loads of phosphate are delivered into the ECF and result in hypocalcemia, seizures, nephrocalcinosis, and renal failure. Conversely, glucose shifts phosphate into cells as glucose 6-phosphate, and overzealous intravenous or oral caloric restitution in the undernourished patient can result in severe hypophosphatemia and sudden death.

Renal Phosphate Handling

The most important mechanism for maintaining a normal serum phosphorus concentration is renal phosphorus regulation. As with calcium, phosphate is filtered by the glomerulus, and 90% is reabsorbed (i.e., tubular reabsorption of filtered phosphate [TRP]). The remaining 10% is excreted (i.e., fractional excretion of phosphorus [FE_{Pi}]). The FE_{Pi} can be calculated in a spot urine sample as follows:

$$FE_{Pi} = (\text{urine Pi}[\text{mg/dL}]/\text{urine creatinine}[\text{mg/dL}])$$
$$(\text{serum creatinine}[\text{mg/dL}]/\text{serum phosphorus}[\text{mg/dL}])$$

The TRP is simple to calculate:

$$TRP = 1 - FE_{Pi}$$

The renal handling of phosphorus is best considered as a tubular maximum (Tm)–regulated process. The TmP is normally