Metabolic

MEDICAL GRAND ROUNDS

MAY 12, 1983

HYPOPHOSPHATEMIA AND PHOSPHORUS DEFICIENCY

JAMES P. KNOCHEL, M.D.

The general topic of hypophosphatemia and phosphorus deficiency was reviewed at this Grand Rounds in 1975. Since then, a considerable amount of new information has become available that has served to clarify a number of previously unsettled issues and point out new and important complications. In addition, some useful studies have permitted assessment of phosphate treatment for diabetes ketoacidosis. These issues will be discussed. Finally, I would like to review once again the harm that may occur in patients with severe weight loss who are treated by total parenteral nutrition.

I. NORMAL PHOSPHORUS METABOLISM

Phosphorus content of a healthy 70 kg adult is approximately 23 mol (700 g). Eighty percent of this quantity is contained in bone, 9% in skeletal muscle and the remainder in viscera and extracellular fluid.

As potassium is the major intracellular cation, phosphate is the major intracellular anion, existing in a concentration of approximately 100 mEq/L. Most phosphorus in cell water is contained within organic compounds including intermediary carbohydrates, nucleic acids, nucleotides, phospholipids and some proteins. In the extracellular space, phosphate circulates as a free ion and is present as hydroxyapatite, a major component of bone. Each cell possesses enzymes capable of adding phosphate as ester or acid anhydride linkages to other molecules. Other enzymes are capable of removing phosphorus from its compounds.

Phosphorus absorption occurs by active transport in the mid-jejunum. Its absorption is regulated by 1,25-dihydroxycholecalciferol as discussed elsewhere in this text. The level of phosphate in serum regulates formation of 1,25-dihydroxycholecalciferol by the renal tubule. Thus, low serum phosphorus levels stimulate production of this hormone and high levels depress formation of the hormone.

Since the molecular weight of phosphorus is 30 Daltons, a concentration of 3 mg of inorganic phosphorus per dL is the equivalent of 1 mmol of phosphorus or phosphate per liter. About 12% of circulating phosphate ions in plasma are bound to plasma proteins. About 75% of orthophosphate ions in plasma exist as HPO_4^{-2} and $H_2PO_4^{-1}$. The ratio of the two moietes is governed by blood pH. Using a pK of 6.8, the ratio of HPO_4^{-2} and $H_2PO_4^{-1}$ at a plasma pH of 7.4 is 4:1. Since the molecular weight of the two species of orthophosphate differs, acceptable terms by which serum phosphorus concentration may be expressed include either elemental inorganic phosphorus/dL or as mmols, not mEq, of phosphate per liter. In children, serum phosphorus concentration varies between 4 and 7.1 mg/dL. In adults, it normally ranges between 2.7 and 4.5 mg/dL. During growth, the higher range of serum phosphorus is usually associated with higher activities of the enzyme alkaline phosphatase in serum.

Phosphate concentration in serum or plasma is the result of the quantity eaten in the diet, absorption by the intestine, its distribution between extracellular and intracellular fluids, and excretion into the urine and feces. A number of important factors may result in acute alterations of serum phosphorus concentration. These include blood pH, free insulin levels, concentration of parathyroid hormone, vitamin D and renal function. Inorganic phosphorus is easily measured in serum and other body fluids by a number of chemical procedures that are easily adapted to automated analytical instruments.

In order to prevent spurious elevation of phosphorus concentration, blood samples should be allowed to undergo normal clot retraction and the measurement performed on serum. In the event that phosphorus is measured in plasma, one should take care to avoid separating the red cells from the plasma in a refrigerated centrifuge or storage of the anticoagulated blood sample on ice since this permits loss of phosphorus from red cells (1). Thereby spurious hyperphosphatemia occurs apparently by means of hydrolysis of organic compounds inside the cells and diffusion of phosphate into the plasma.

Mannitol may interfere with measurement of phosphorus if the DuPont method is employed and result in spurious hypophosphatemia (2).

A healthy adult consuming a nutritious diet ingests approximately 1 gram of elemental phosphorus a day. This quantity varies widely and tends to be higher in those individuals who consume large quantities of meat or dairy products. Soluble dietary phosphates, such as those found in meat or milk, are essentially completely absorbed from the mid-jejunum of which approximately 90% will be excreted into the urine. In contrast, insoluble or undigestible phosphate, such as those existing in certain vegetable fibers, may not be absorbed. As a result, persons ingesting normal mixed diets may excrete from 60 - 90% of the ingested phosphorus in the urine.

Phosphate excretion by the kidney is regulated by glomerular filtration and tubular reabsorption. Besides regulating phosphate balance, excretion of phosphate into the urine is an important pathway of hydrogen ion excretion as titratable acid. Thus, phosphate plays a critical role in the regulation of acid-base balance. Studies on the distribution, exchange, and excretion of radioactive phosphorus have been published by Levenson and his associates (3).

Conventional and time proven methods to quantitate high energy phosphate compounds in living tissues require that the tissue either be frozen in situ, e.g., by means of precooled Wallenberg clamps or in lieu of this, removed by needle biopsy and immediately immersing the sample in ice cold perchloric acid. This is necessary because creatine phosphate, ATP, and other organic phosphates readily decompose into their respective metabolites and inorganic phosphate. Such procedures are not performed in clinical laboratories. However, when these techniques are performed carefully and correctly in research laboratories, the values obtained are essentially the same as those obtained by more modern procedures such as nuclear magnetic resonance spectroscopy (NMR). Indeed, in order to quantitate phosphate compounds by NMR, by one method standard values are first determined by the use of perchloric acid extracts and subsequent comparison of NMR signals to these values to establish a baseline. Employing reliable data, values of ATP expressed in terms of μM/g wet weight obtained by ^{31}P NMR averaged 5.09 + 0.1. Values obtained by standard tissue analysis techniques vary between 4.$\overline{8}$ and 5.4 μM/g wet weight. Thus, values obtained by both techniques are essentially identical. NMR derived values for creatine phosphate in rat heart average 5.85 + 0.1 μM/g wet weight. Those obtained employing standard techniques average 6.$\overline{19}$ + .37 μM/g wet weight, values that are essentially identical. However, the value of NMR resides in its ability to analyze tissue for its pH and content of creatine phosphate, ATP, inorganic phosphate, nicotinamide adenine dinucleotide (NAD), and sugar phosphates without the necessity of sampling the tissue. Perhaps of more importance, resolution of signals from ^{31}P is sufficiently rapid so that changes in the latter compounds can be ascertained under various metabolic conditions including exercise (4). Nevertheless, even with such modern techniques as NMR, one must be cautious about overinterpreting the precise meaning of any values obtained. For example, each muscle in man is composed of three types of skeletal muscle fibers. These include:

1. ATPase type 1; high oxidative, low glycolytic
2. ATPase type 2a; high oxidative, high glycolytic
3. ATPase type 2b; low oxidative, high glycoltic.

Each of these fibers has a different composition of monovalent ions, as well as organic phosphates. In patients with rhabdomyolysis due to phosphofructokinase deficiency (Tarui's disease or glycogenosis type 7), selective damage

occurs only in the ATPase type 2a muscle fibers (5). Since the other fibers remain intact, it is virtually impossible to assess the meaning of changing ratios of creatine phosphate, ATP and other related phosphate compounds in the whole muscle and assign these to type 2a fibers. Such discrepancies might account for the finding by Ross et al (6), in which they reported that a patient with myophosphorylase deficiency (McCardle's syndrome) showed decreased creatine phosphate levels during exercise but constant levels of ATP. Such findings by NMR spectroscopy are normal based upon serial biopsy of normal volunteers during exhaustive exercise (7). On the other hand, the heart is composed of but one fiber type and consequently, the potential of confusion derived from NMR techniques is much less in that tissue (8).

II. HYPOPHOSPHATEMIA AND PHOSPHORUS DEFICIENCY

The development of automated techniques to measure serum phosphorus concentration has revealed that hypophosphatemia is an exceptionally common laboratory finding in hospitalized patients. It is to be emphasized that hypophosphatemia *per se* does not always indicate the coexistence of phosphorus deficiency. Similarly, phosphorus deficiency may be associated with normal or even elevated levels of serum phosphorus.

TABLE I

Causes of Hypophosphatemia

A. Decreased dietary intake

B. Decreased intestinal absorption

1. Vitamin D deficiency
2. Malabsorption
3. Steatorrhea
4. Secretory diarrhea
5. Vomiting
6. PO_4-binding antacids

C. Shifts from serum into cells

1. Respiratory alkalosis
   a. sepsis
   b. heatstroke
   c. hepatic coma
   d. salicylate poisoning
   e. gout
2. Recovery from hypothermia
3. Hormonal effects
   a. insulin
   b. glucagon
   c. epinephrine
   d. androgens
4. Nutrient effects
   a. glucose
   b. fructose
   c. glycerol
   d. lactate
   e. amino acids
   f. xylitol

D. Increased excretion into the urine

1. Hyperparathyroidism
2. Renal tubular defects
   a. aldosteronism
   b. licorice
   c. saline infusion
   d. inappropriate secretion of ADH
   e. mineralocorticoid hormone administration
   f. diuretics
   g. corticosteroids

In broad terms, hypophosphatemia occurs as a result of either decreased dietary intake, decreased intestinal absorption, shifts from serum into cells, or decreased reabsorption in the renal tubule. There is no evidence available at this time indicating that intestinal secretion or renal tubular secretion of

phosphate can be responsible for hypophosphatemia or phosphorus deficiency. Starvation alone does not ordinarily lead to pronounced reductions of serum phosphate. Indeed, simple starvation associated with ketosis is most commonly associated with normal or elevated levels of phosphorus in blood. Hypophosphatemia tends to occur more often in patients who ingest a diet containing absorbable nutrients, such as carbohydrate, that is deficient in phosphorus. In animals, administration of a phosphorus deficient but otherwise normal diet results in only a modest depression of serum phosphorus concentration. It is not until phosphate binding antacids are added to the diet that severe hypophosphatemia occurs (see p 8). Metabolites of vitamin D play a major role in phosphate absorption in the jejunum. Hence, vitamin D deficiency may result either from lack of exposure to sunlight, deficiency of vitamin D in the diet, or steatorrhea resulting in malabsorption of vitamin D normally dumped into the gut by the enterohepatic circulation. Thereby, phosphate absorption by the jejunum may be reduced. In addition, even if vitamin D precursors are available, severe liver disease may interfere with production of 25(OH) cholecalciferol ($25(OH)D_3$). The most potent vitamin D metabolite promoting phosphate absorption by the gut is $1,25(OH)_2D_3$. Synthesis of this metabolite occurs in the kidney and depends upon an adequate supply of $25(OH)D_3$ from the liver (9). At least in experimental animals, normal production of insulin and the hydrogen ion concentration are important regulators of $1,25(OH_2)D_3$ metabolism. Reduction of insulin production by administration of alloxan has been shown to decrease production of the $1,25(OH)_2D_3$ metabolite to 1/8 of its normal value (10). Similarly, administration of ammonium chloride to produce metabolic acidosis also reduces production of $1,25\ (OH)_2D_3$ (11). It is has also been shown that hypophosphatemia stimulates and hyperphosphatemia reduces $1,25(OH)_2D_3$ production by the kidney. That $1,25(OH)_2D_3$ increases in response to hypophosphatemia probably explains why patients who have been hypophosphatemic for sufficient periods of time display an enhanced capacity to absorb phosphate by the gut (12).

The precise effect of steatorrhea on phosphate absorption is not by any means clear. We know that steatorrhea leads to formation of calcium and magnesium soaps and in addition, that malabsorption of fat reduces absorption of fat soluble vitamins. The decreased transit time through the intestinal lumen as a result of the irritant effects of fatty acids and divalent ion soaps might well reduce phosphate absorption. It also seems possible that pronounced secretory diarrhea might also reduce phosphate absorption. However, the losses of phosphate by this mechanism are thought to be modest at most. Diarrhea produced by colonic disease apparently does not increase phosphate loss.

Perhaps the most common cause of modest hypophosphatemia in hospitalized patients is respiratory alkalosis. Upon admission to hospitals, many patients are in pain, or may be frightened and as a result hyperventilate sufficiently to reduce arterial PCO_2 and elevate their arterial pH. Severe hyperventilation may occur with bacteremia and sepsis, heat stroke, hepatic coma, salicylate poisoning or painful attacks of gout. By such means, respiratory alkalosis and hypophosphatemia are exceptionally common findings in patients who are ill with a large variety of disorders. In many instances, modest hypokalemia occurs simultaneously.

Administration of glucagon may lead to hypophosphatemia and phosphaturia (13). Epinephrine administration may occasionally lead to hypophosphatemia, perhaps by induction of hyperglycemia (14). Androgens may cause hypophosphatemia if their administration is followed by an anabolic response. Androgens may also reduce phosphorus levels in acromegaly (15).

Serum phosphate concentration may be reduced in patients receiving large doses of glucocorticoids and also in patients with Cushing's syndrome. Moderate hypophosphatemia and phosphaturia that appear following renal transplantation are presumably related to decreased renal tubular reabsorption of phosphate (16).

Transient hypophosphatemia has been observed during recovery from hypothermia (17). Presumably, phosphate ions move into cells with potassium as monovalent ion transport is re-activated upon warming.

Administration of glucose may also cause moderate hypophosphatemia. Administration of insulin increases the cellular uptake of glucose and phosphorus. Most of this occurs in the liver and skeletal muscle. In normal individuals, the decline in serum phosphorus as a result of glucose or, independently, insulin administration, does not exceed 0.5 mg/dL. That its decline after glucose is less than normal in patients with stable diabetes mellitus was once proposed as an aid to identify this disease (18,19). In patients with diffuse disease of skeletal muscle such as muscular dystrophy, hypophosphatemia is appreciably less after administration of glucose or insulin than normal (20). However, when glucose is administered to a starving individual or patients with hepatic cirrhosis, the hypophosphatemic response may be much more pronounced (21-23). This occurs in those whose somatic cells are "hungry" and capable of a sharp antabolic response. As will be subsequently discussed, this is a common cause of severe hypophosphatemia.

In contrast to glucose, administration of fructose may be associated with a more pronounced reduction of serum phosphorus concentration, especially if administered intravenously. Although fructose administration was recommended at one time for the treatment of diabetic ketoacidosis because it can be taken up by liver cells without insulin, it is now well appreciated that its use intravenously is fraught with hazard. The mechanism of hypophosphatemia during administration of fructose is related to the unregulated uptake of fructose by the liver (24). Specific kinases in the liver catalyze phosphorylation of glucose (glucokinase) to glucose-6-phosphate and fructose (fructokinase) to fructose-1-phosphate. Increasing concentrations of glucose-6-phosphate inhibit the activity of glucokinase, thereby regulating uptake of both glucose and phosphorus during glucose infusion. In contrast, increasing concentrations of fructose-1-phosphate do not inhibit fructokinase. Thus, fructose phosphorylation is unregulated and in consequence hypophosphatemia is more pronounced after fructose than glucose. The mechanism whereby fructose may induce cellular injury when administered intravenously will be discussed subsequently.

Moderate hypophosphatemia as a result of increased urinary losses is common and has many explanations. Parathyroid hormone reduces phosphorus reabsorption by the renal tubule and thereby facilitates its excretion into the urine. Of interest, patients with primary hyperparathyroidism seldom show serum phosphorus concentrations below 2 mg/dL unless their intake of phosphorus is low or they simultaneously ingest phosphate binding antacids for gastrointestinal distress. Serum phosphate concentration may be normal or depressed in osteomalacia depending upon its cause. Similarly, serum calcium concentration may be normal but is usually modestly depressed in patients with osteomalacia. In many of these instances, not only is phosphate absorption impaired but phosphaturia occurs by means of excessive parathyroid hormone secretion as a result of hypocalcemia. Similar findings may prevail in patients with steatorhea and malabsorption. In such instances, infusion of calcium sufficient to induce hypercalcemia generally results in rapid suppression of parathyroid hormone

secretion so that phosphate excretion and phosphate clearance fall sharply, thus differentiating secondary from primary hyperparathyroidism. A number of hereditary abnormalities or toxic products such as heavy metals result in proximal renal tubular epithelial injury so that phosphate absorption is impaired. In many of these instances, other substances are cleared excessively into the urine that are normally reabsorbed in the proximal tubule. These substances may include glucose, uric acid, amino acids and bicarbonate. Their excretion in the presence of normal or reduced concentrations in serum constitutes strong evidence for proximal tubular dysfunction.

A disproportionate elevation of phosphate clearance to inulin clearance is seen in virtually all conditions associated with expansion of the extracellular fluid volume, provided the glomerular filtration rate remains normal. Typical of such instances are volume expansion produced by overproduction of aldosterone, ingestion of licorice, a high salt diet or saline infusions. The extracellular fluid volume expansion that prevails in patients with the syndrome of inappropriate secretion of antidiuretic hormone or in persons receiving mineralocorticoid hormones to produce retention of sodium chloride and water are additional examples.

Administration of diuretics may also be associated with reduction in serum phosphate concentration.

III. THE CAUSES OF SEVERE HYPOPHOSPHATEMIA

Severe hypophosphatemia, defined as a serum phosphorus concentration between 0.1 and 1.5 mg/dL occurs in a limited number of circumstances. These are listed in Table II.

Table II. Causes of Severe Hypophosphatemia

A. Chronic alcoholism and alcoholic withdrawal
B. Dietary deficiency and phosphate binding antacids
C. Severe thermal burns
D. Recovery from diabetic ketoacidosis
E. Hyperalimentation
F. Nutritional Recovery Syndrome
G. Respiratory Alkalosis
H. Renal Transplantation

A. Chronic Alcoholism and Alcohol Withdrawal

For those physicians who practice in hospitals dealing with large numbers of indigent persons, chronic alcoholism and alcoholic withdrawal are the major causes of severe hypophosphatemia. That hypophosphatemia occurs in as many as 50% of hospitalized alcoholics is widely appreciated (25-27). Although an association between hypophosphatemia and chronic alcoholism is unquestionable, the impact and common occurence of this event were not appreciated until serum phosphorus measurements became an integral part of routine automated laboratory procedures. Most chronic alcoholics who are not acutely ill show either a normal or slightly depressed serum phosphorus concentration. In many instances, such patients have been unable to eat for a period of days before admission to the hospital or alternatively, enter a state of alcoholic withdrawal shortly after admission to the hospital. Administration of intravenous fluids containing nutrients without phosphorus and in addition, the usual development of hyperventilation and respiratory alkalosis in withdrawing alcoholics, result in a rapid depression of serum phosphorus concentration to levels as low as 0.1 mg/dL. On the first day of hospitalization, before the decline of serum phosphorus, Miller and his associates (28) have observed that such patients may excrete as much as 1 gram or more of phosphorus into the urine per 24 hours. This may be looked upon as an inappropriately large quantity of phosphorus excretion for a person who has virtually no phosphorus intake in the diet. Phosphaturia in such instances has been ascribed to the associated ketoacidosis and/or lactic acidosis. The high rate of phosphorus excretion into the urine under conditions of metabolic acidosis will be discussed subsequently in the section on diabetic ketoacidosis. Nevertheless, upon administration of nutrients and the development of respiratory alkalosis as a manifestation of alcoholic withdrawal, serum phosphorus begins to decline and during this time phosphorus virtually disappears from the urine. Thus, the development of hypophosphatemia under these conditions is the consequence of a shift of phosphorus from extracellular to intracellular fluids.

Although the foregoing events would adequately explain the development of hypophosphatemia in the hospitalized alcoholic, the underlying causes are much more complicated. Measurement of muscle composition in severe chronic alcoholics discloses a complex derangement consisting of severe total phosphorus deficiency, a modest deficiency of magnesium, and abnormally high values of sodium, chloride and calcium (29,30). In some but certainly not all patients, potassium content of skeletal muscle is low. As indicated in Table III, while the average value for total phosphorus content in alcoholic patients was 20 mmol/dg fat-free dry solids compared to a normal value of 28 mmol/dg, some patients demonstrate values as low as 12 mmol/dg. If one assumes that muscle tissue is uniformly affected, and that skeletal muscle occupies 40% of the body mass, the total deficiency of phosphorus in skeletal muscle alone extrapolates to a value of 1,800 mmols in those patients with the lowest values. Although one can speculate that a poor phosphorus intake, and perhaps the associated use of phosphate binding antacids, vomiting or diarrhea might have caused such a deficit of phosphorus, we have shown that chronic administration of intoxicating quantities of ethanol to dogs causes equally severe phosphorus deficiency in skeletal muscle despite a generous intake of all essential nutrients, including phosphorus (31,32). The values we observed in dogs following administration of intoxicating doses of ethanol twice daily for two months are also shown in Table

III. Our observations suggest that alcohol per se, despite simultaneous ingestion of a nutritious diet, somehow exerts toxicity on the muscle cell and is responsible for disorganization of muscle composition. The precise cause whereby these effects occur is unknown. Since ethanol interferes with sodium transport, and since phosphate transport in nearly all tissues examined is dependent upon normal sodium transport, perhaps deranged sodium transport is responsible for loss of phosphate from muscle.

TABLE III MUSCLE CELL COMPOSITION*

	P	Mg	Ca	Na	Cl	K
NORMAL n=12	28.7	8.1	1.8	9.9	7.5	42.8
ALCOHOLICS n=23	20.4	6.0	6.2	25.1	12.0	35.8
ALCOHOLIC DOGS	21.3	7.8	3.1	24.5	10.8	31.1

* mmol (P) or mEq/dg Fat Free Dry Weight

B. Dietary Deficiency and Phosphate-Binding Antacids

Phosphorus is sufficently abundant in natural foods so that phosphorus deficiency resulting from an inadequate food intake in normal man is virtually impossible. To develop phosphorus deficiency as a result of poor dietary intake usually requires two factors. The first is consumption of a diet that is grossly inadequate in its phosphate content such as one composed of only carbohydrates that may eaten by a food fadist. In almost all instances, the second factor is the concomitant ingestion of phosphate binding antacids. Thus, in clinical situations, some of the most severe instances of phosphorus deficiency have occurred in patients with either an extremely low or negligible intake of phosphorus who consume phosphate binding antacids for dyspeptic disorders.

Classic studies in normal subjects and patients with hypoparathyroidism by Lotz and Bartter (33) have established that feeding a diet selectively deficient in phosphorus and ingestion of large quantitities of phosphate binding antacids, may in time lead to a rather distinct clinical syndrome. These subjects became anorectic, weak and complained of bone pain. The latter symptoms appeared only when serum phosphorus concentration fell below 1.0 mg/dL. Clinical improvement occurred rapidly when phosphorus was restored to the diet. Of interest, each subject developed hypercalciuria. Although its cause was not apparent, it was suspected that the excess urinary calcium was derived from bone as phosphorus was mobilized from that site in an attempt to maintain a normal concentration in serum. Although serum calcium tended to increase in patients with hypoparathyroidism, hypercalcemia did not occur. When serum phosphorus levels became depressed in these subjects and patients, phosphorus virtually disappeared from the urine.

Phosphorus deficiency in both experimental animals and men results in increased magnesium excretion into the urine. Muscle magnesium and potassium

contents fall moderately during phosphorus deficiency. In fact, whenever a diet is fed to an experimental animal that is deficient in one of three major intracellular ions, either phosphorus, magnesium or potassium, the remaining two ions eventually leave the cell. The mechanism underlying this apparent homeostatic attempt to maintain a normal internal composition of the cell has no known explanation (34). Perhaps this also explains why an animal or man depleted of one of the major intracellular ions becomes anorectic. Nitrogen stores in cells are mobilized and as they leave, it follows that the major intracellular ionic components would also leave the cell. Such adjustments would appear to correspond to the anatomic character of atrophy that would be associated with a modestly deranged but not irreversibly scrambled chemical composition of the cell.

C. Severe Thermal Burns

In patients with extensive third degree burns whose kidney function remains intact, serum phosphorus concentration usually begins to decline on the second to the 10th day. Hypophosphatemia may become very severe. According to most observers, as serum phosphorus declines, phosphorus excretion into the urine usually falls to very low levels. Most patients with burns at this particular time of their illness hyperventilate, thus accounting for the liklihood that respiratory alkalosis is responsible. On the other hand, it has been suggested that renal tubular injury, volume expansion as a result of fluid administration, mobilization of retained salt and water from injured tissue and the resulting diuresis could all be responsible for the declining phosphorus levels in serum.

Lennquist et al (35) studied 33 patients with severe thermal burns for a period of two weeks. The lowest values of serum phosphorus occurred in seven patients who died. Simultaneous reduction of urinary phosphate excretion indicated that the depletion of phosphorus was mainly prerenal. However studies of fractional excretion of phosphate showed that renal losses might have contributed to the hypophosphatemia. A finding not previously reported in hypophosphatemia in burns was a marked rise in serum calcitonin levels. These patients also showed marked increases in catacholamine levels.

Hypophosphatemia in burns has potentially important connotations since it has been implicated as a contributing factor in burn wound sepsis.

D. Diabetic Ketoacidosis

Severe hypophosphatemia is commonly observed in patients undergoing treatment for diabetic ketoacidosis (DKA). Untreated patients generally show hyperphosphatemia even though phosphorus deficiency may co-exist. Insulin deficiency and acidosis act in concert to reduce phosphorylation, cellular uptake of glucose and glycolysis so that net phosphorus balance by the cell is negative. Deficiency of insulin and excess of glucagon may also contribute to the marked catabolism in DKA.

The extent of phosphorus deficiency in DKA varies widely. Conscientious patients who become acidotic and seek medical care within a few days obviously have not had time to become severely phosphorus deficient. On the other hand, those who have had many days or weeks of polydipsia, polyuria, ketoacidosis and glycosuria may sustain very severe phosphorus deficiency. Such patients often present a history that vomiting has not been a serious problem thus permitting a sustained fluid intake. This, in turn, facilitates greater urine flow and

accordingly, a greater degree of phosphorus deficiency. The latter type of patient is rather unusual. In such a patient if initial measurements of serum phosphorus are normal or low despite severe ketoacidosis, deficiency of this element is very likely severe.

E. Hyperalimentation

Administration of nutrients in large quantities either intravenously or via the gut may cause severe hypophosphatemia. Its prerequisites include (a) an inadequate quantity of phosphorus in the diet in comparison to total calories and other nutrients and (b) a cellular mass that is shrunken but yet capable of an anabolic response. Most clinical instances of hyperalimentation-induced hypophosphatemia have occurred in patients with severe weight loss or those with gastrointestinal disorders who were unable to consume or absorb adequate nutrients. As will be pointed out subsequently, some of the most prominent cause and effect relationships between hypophosphatemia, erythrocyte dysfunction, and central nervous system dysfunction have been described in this setting.

F. Nutritional Recovery Syndrome

The nutritional recovery or refeeding syndrome represents a constellation of findings observed during treatment of patients with severe protein calorie malnutrition or starvation. In contrast to hyperalimentation, hypophosphatemia may occur during administration of calories in normally required quantities.

This syndrome can be reproduced in experimental animals and is commonly seen during overzealous feeding of patients who have lost marked quantities of weight as the result of food fadism or anorexia nervosa. Based on clinical description, such patients closely resemble the prisoners after World War II. In addition to hypophosphatemia provoked by nutrients, most of these patients show other serious disturbances such as hypokalemia, hypomagnesemia, and severe glucose intolerance. The observation that feeding with small quantities of skim milk rather than pure carbohydrates caused less morbidity is very likely ascribable to the reduced calories and the higher phosphorus and potassium contents of skim milk.

G. Respiratory Alkalosis

Profound hypophosphatemia may occur with severe and prolonged respiratory alkalosis. Mild hyperventilation induces a slight decline of phosphorus concentration (see pages 4 and 5). However, that prolonged, intense hyperventilation may lead to a decline of serum phosphorus to values in the vicinity of 0.5 mg/100 ml is well known. This could have a very important bearing on the appearance of severe hypophosphatemia in patients withdrawing from alcohol.

Using normal volunteers, Mostellar and Tuttle (37) compared the effects of respiratory alkalosis and metabolic alkalosis on serum phosphorus concentration and phosphorus excretion into the urine. Their results are shown in Fig. 1.

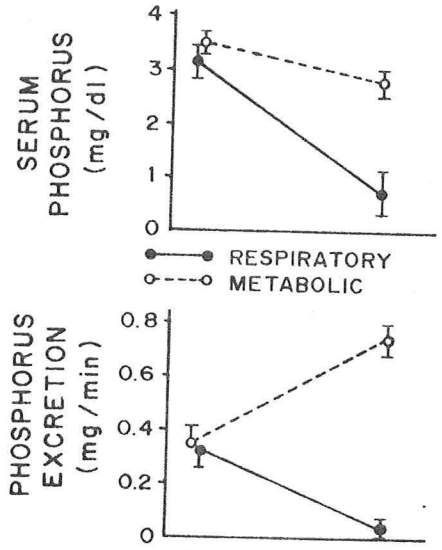


Fig 1.—Respiratory alkalosis may depress serum phosphorus concentration markedly in normal subjects and cause virtual disappearance of phosphorus from urine. Serum phosphorus only falls slightly with same degree of alkalosis produced by infusion of $NaHCO_3$ and is associated with an increase of phosphaturia. Prepared from data published by Mostellar and Tuttle (37).

Serum phosphorus concentration in respiratory alkalosis fell from a mean value of 3.1 to 0.8 mg/100 ml. Values as low as 0.3 mg/100 were observed. In contrast, infusion of sodium bicarbonate to elevate arterial blood pH to the same level produced by respiratory alkalosis was associated with a decline of serum phosphorus concentration from an average value of 3.5 mg/100 ml to only 3.0 mg/100 ml. During respiratory alkalosis, phosphorus virtually disappeared from the urine. In contrast, phosphorus excretion nearly doubled during infusion of sodium bicarbonate. Several mechanisms could account for these differences. In respiratory alkalosis there is a free movement of carbon dioxide from the intracellular space because of its rapid diffusibility. The increase of intracellular pH activates glycolysis so as to increase formation of phosphorylated carbohydrate compounds within the cell. The source of phosphorus for these compounds is the readily diffusible inorganic phosphate pool. Consequently, serum phosphorus concentration falls precipitously. Excretion of phosphorus into the urine falls because of hypophosphatemia. In contrast, infusion of bicarbonate is known to induce only slight or modest changes in intracellular pH since bicarbonate ions are poorly diffusible. As a result,

intracellular glycolysis is not accelerated as much as it is in acute respiratory alkalosis, and hypophosphatemia is much less. Furthermore, because of the associated volume expansion related to the quantity of sodium bicarbonate infused, the fractional excretion of phosphorus into the urine increases. Finally, expansion of plasma volume dilutes ionized calcium, PTH is released, and the fractional excretion of phosphorus increases.

H. Hypophosphatemia Following Renal Transplantation

Severe hypophosphatemia has also been noted in some patients who have had renal transplants. Such patients apparently have a renal tubular reabsorptive defect that permits excessive loss of phosphate into the urine. This has often occurred during corticosteriod therapy and administration of phosphate-binding antacids, both of which could contribute toward development of hypophosphatemia.

IV. THE EFFECT OF ACUTE HYPOPHOSPHATEMIA WITHOUT PHOSPHORUS DEFICIENCY IN NORMAL SUBJECTS

Modest hypophosphatemia per se does not appear to produce any detectable abnormality of cellular structure or function. Rather, it is more important as a laboratory marker that under appropriate circumstances, demands further evaluation of its cause. For example, it may indicate the presence of hyperparathyroidism.

Whether severe hypophosphatemia has any adverse effects when it occurs in a healthy person is an unsettled issue. Patients with neurotic hyperventilation may show serum phorphorus values less than 1.0 mg/dL when they experience paresthesias, tetany and lightheadness. Nonetheless, I am not aware of specific disorders related to hypophosphatemia in such patients. Similarly, there has been no indication that voluntary hyperventilation of sufficient magnitude to reduce serum phosphorus to such levels has caused any harmful effects. In studies (38) of underweight but normal dogs made hypophosphatemic by hyperalimentation (serum P < 1.0 mg/dL), we observed no chemical evidence of tissue injury. Studies by Brautbar and his associates (39) on dogs made hypophosphatemic by hyperventilation and glucose infusion, similarly showed no evidence of tissue injury.

Many investigators have found that a diet deficient in phosphorus results in immediate mobilization of bone apatite so as to provide a source of phosphorus to maintain serum levels within a normal range (v.i.). Our own studies (38) suggest that acute hypophosphatemia also rapidly mobilizes phosphorus from muscle.

Hill and his associates (40) studied phosphorus distribution in hyperalimentation induced hypophosphatemia. They studied rats that were fasted for a period of four days and then given a solution intravenously that was devoid of phosphorus. On the fourth day, serum labeled with 32 P was administered in a hyperalimentation solution. They found more radioactivity in skeletal muscle and bone than in control animals. These studies, in light of our findings that total bone and muscle phosphorus contents were less than normal, suggest an increased rate of phosphorus turnover in those tissues during hyperalimentation-induced hypophosphatemia. The increased uptake suggests that although phosphate uptake is accelerated, the simultaneous loss of phosphorus must exceed this value and resulted in a net loss of phosphorus from muscle tissue.

Derr and Zieve (41) examined distribution of phosphate in the underfed rat during total parenteral nutrition. As indicated by the same authors in another study using the same model and treatment (42), simultaneous values for blood glucose concentration were in excess of 1,000 mg/dL. Their studies during hypophosphatemia induced by hyperalimentation and hyperglycemia suggested that the bulk of administered radiophosphorus became incorporated into organic compounds in the cells of liver, muscle and bone. They did not measure adenine nucleotides or chemical phosphorus content of the tissues. The foregoing studies support our ongoing contention that hypophosphatemia of itself, and of short duration, apparently results in no harmful effects to the cell. This would explain why evidence of cellular injury is generally lacking in patients with simple hyperventilation induced respiratory alkalosis, and the large number of clinical conditions associated with modest degrees of hypophosphatemia in which phosphorus deficiency apparently does not coexist. In contrast, if cell injury caused by phosphorus deficiency (43), or clinical alcoholism (44) pre-exists, induction of acute hypophosphatemia by hyperalimentation may be associated with evidence of frank cellular destruction. Perhaps such evidence explains the notable rarity with which hypophosphatemia induced by glucose and insulin in patients recovering from diabetic ketoacidosis causes evidence of muscle cell injury. Frank rhabdomyolysis and myoglobinuria has been reported in only one instance (45) in a patient treated for diabetic ketoacidosis and has been observed at the VA Hospital in Dallas in one additional patient being treated for DKA who was also an alcoholic. As pointed out previously in this discussion, most diabetics with ketoacidosis have not had sufficient time to develop significant degrees of phosphorus depletion.

The only instance in which acute hypophosphatemia of short duration has been responsible for tissue injury is that associated with intravenous administration of fructose or xylitol to a normal person. As pointed out earlier, fructose phosphorylation by the liver and kidney is unregulated and therefore, fructose causes a sharp reduction in cytosolic phosphate, even though the decline in serum phosphate is only modest. The mechanisms by which fructose injures the liver and kidney are best understood by considering its effects on the phosphorylation potential (49).

The phosphorylation potential is useful to assess the overall energy state of the cell (38a). It is defined mathematically as follows:

$$\text{Phosphorylation Potential} = \frac{[ATP]}{[ADP] \times [P^i]}$$

Theoretically, any condition that causes severe hypophosphatemia could conceivably reduce influx of phosphate ions into the cell sufficiently so as to elevate the phosphorylation potential and in turn, reduce the respiratory rate of mitochondria. As mitochondrial respiration falls, ATP production falls.

A second major important effect of reducing cytoplasmic phosphate concentration is a reduction in the adenine nucleotide pool. A severe reduction of cytosolic phosphate levels activates the enzyme AMP-deaminase, converting AMP to inosine monophosphate (IMP). IMP is then irreversibly metabolized to urate.

If ATP concentration falls to low levels in the cell, the enzyme 5' nucleotidase is activated. This also serves to reduce the adenylic acid pool.

These reactions, marked by increased degradation of the overall adenine nucleotide pool, probably account for the appearance of hyperuricemia and hyperuricosuria when nutritional therapy is conducted too rapidly in a starved patient. That this might be useful as a clinical tool is discussed in a later section.

The classic experimental model to induce cellular injury by the foregoing mechanism is administration of fructose by the intravenous route. When fructose is consumed by mouth, it is phosphorylated by the intestinal epithelium at a sufficiently slow rate so that fructose per se does not appear in the blood in significant quantities. However, when given intravenously, its unregulated phosphorylation by the liver and the renal cortex can result in acute phosphate-trapping, elevation of the phosphorylation potential, reduction of mitochondrial respiration, reduction of ATP levels, and finally, a critical reducion in the size of the entire adenine nucleotide pool with increased uric acid production.

Demonstrable histologic injury has been reported in the liver in normal humans following small doses of intravenous fructose (38b). Experimentally, renal injury induced by fructose is potentiated by pre-existing phosphorus deficiency (126). Xylitol, utilized in some preparations for total parenteral nutrition, has been shown to be hepatotoxic in man and a very potent phosphate-trapping agent (38c).

In summary, the critical factor determining whether cellular injury occurs in the various models of acute hypophosphatemia is the level of inorganic phosphate in the cellular cytoplasm. In hypophosphatemia induced by respiratory alkalosis, glucose infusion or insulin administration, cytosolic phosphate concentrations are either normal or only slightly depressed. In contrast, infusion of substances that are phosphorylated at uncontrollable rates, such as fructose or xylitol, reduce phosphate concentrations to levels sufficiently low that cellular injury follows. On the other hand, in prolonged episodes of severe hypophosphatemia, specifically meaning levels of 0.1 - 0.3 mg/dL, it seems likely that cytosolic phosphate levels could fall sufficiently to induce damage.

V. PATHOLOGICAL EFFECTS OF HYPOPHOSPHATEMIA

A. SKELETAL MUSCLE INJURY AND RHABDOMYOLYSIS

1. Chronic Hypophosphatemic Myopathy

Abundant clinical evidence indicates that chronic phosphorus deficiency in man results in a proximal myopathy (46,47). In representative cases, proximal muscle atrophy and weakness may be striking. Osteomalacia usually accompanies this disorder. Laboratory findings characteristically show normal values for CPK and aldolase activities; phosphorus in serum is modestly depressed, calcium may be low or normal and alkaline phosphatase activity is usually sharply elevated.

In experimental studies, we have shown (48) that chronic, selective phosphorus deficiency causes a reversible injury to muscle cells of the dog. These changes include a depressed resting membrane potential, increased cellular content of Na, Cl and water, and decreased content of phosphorus. Chronic phosphorus deficiency apparently does not cause acute rhabdomyolysis.

2. Acute Hypophosphatemic Myopathy

Both clinical and experimental studies have suggested a relationship between phosphorus deficiency, the rapid development of acute hypophosphatemia and the occurrence of acute rhabdomyolysis (43,44).

Almost all such cases have occurred in alcoholics either during withdrawal or in those treated with nutrients devoid of phosphorus. It usually appears within the first few days in the hospital and is marked by a sudden elevation of CPK activity. Although clinical observations suggest that prevention of hypophosphatemia in such patients may prevent rhabdomyolysis, such an effect has not been rigorously proven. As discussed previously (p. 8), in our experience (29), each of these patients has been found to have phosphorus deficiency as determined by skeletal muscle analysis. Deficiency of phosphorus and additional derangements of muscle element composition can be reproduced in dogs by chronic administration of ethanol despite a nutritious diet containing normal quantities of phosphorus (31).

A limited number of studies have been published concerning the precise effect of acute hypophosphatemia on skeletal muscle. All observations indicate that rhabdomyolysis does not occur with acute hypophosphatemia in the absence of preexisting damage to muscle cells (38).

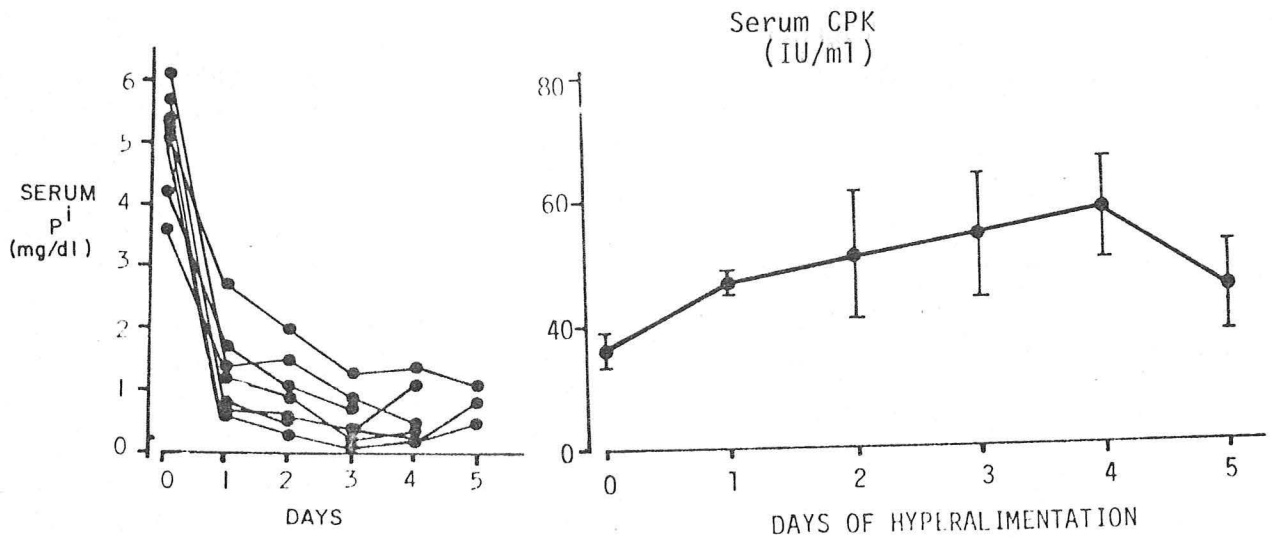
Brautbar and his associates (39) studied the biochemical effects of moderate hypophosphatemia (2.3 mg/dL) in dogs induced by hyperventilation and hyperventilation plus glucose infusion on muscle glycolysis. By their calculations, a rather astounding quantity of phosphorus accumulated in skeletal muscle during a three hour experiment (as much as 20% of total body phosphorus) in dogs infused with glucose during hyperventilation. They measured adenine nucleotides and inorganic phosphorus in muscle as a means to calculate the phosphorylation potential of skeletal muscle cells, [ATP] : ([ADP] X [P^i]) (49). Since muscle cell content of ATP, ADP and inorganic phosphorus increased almost hand in hand during glucose infusion and hyperventilation, the phosphorylation potential remained essentially the same. This is thought to be strong evidence that cellular injury did not occur by such a degree of hypophosphatemia. Unfortunately, it is possible that the levels of hypophosphatemia were neither sufficiently depressed nor of sufficient duration to assess its effects.

In studies from our own laboratory, the effects of acute hypophosphatemia on skeletal muscle cells have been examined under two sets of conditions. In the first (43), hypophosphatemia was imposed upon cells pre-injured by caloric deprivation and phosphorus deficiency. These results were compared to the effects of hyperalimentation with enough phosphorus to prevent hypophosphatemia. In the second model (38), hypophosphatemia was induced in animals that had lost weight as the result of simple caloric deprivation without phosphorus deficiency. In these studies, advantage was taken of the liklihood that any cell that is atrophic and not irreversibly injured would demonstrate a sharp anabolic response under conditions of hyperalimentation so that acute hypophosphatemia will occur very rapidly.

When the animals in the first study had lost 30% of their initial body weight, they were split into two groups. The first group received 140 calories/kg body weight contained in a liquid mixture which provided 1.87 grams of elemental phosphorus per day. The other group was also fed 140 calories/kg/day of the same mixture but without phosphorus. Serum phosphorus rapidly declined to values below 1.0 mg/dL. Those dogs hyperalimented without phosphorus became very ill, displaying marked weakness, inability to swallow their secretions, muscle fasciculations and in some, convulsions. They also showed a pronounced elevation of CPK activity in serum. Histologic examination of skeletal muscle showed frank rhabdomyolysis.

In the dogs hyperalimented in a similiar fashion but given the large phosphorus supplement, gavage feeding was not necessary since the animals willingly consumed their feedings. Serum phosphorus did not fall and CPK activity did not increase. After five to seven days, the animals were subjected to muscle biopsy. These samples appeared normal in every instance. Based upon the foregoing information, it appears that in the dog, frank rhabdomyolysis may be produced by severe hypophosphatemia if muscle cells are first injured by semi-starvation and phosphorus deprivation. In contrast, if hypophosphatemia were prevented under the same conditions, rhabdomyolysis did not occur.

A second study was conducted to define the biochemical effects of acute hypophosphatemia in an animal that had not been phosphorus depleted before hyperalimentation (38). To accomplish this, dogs were placed on a synthetic phosphorus deficient diet in a quantity calculated to provide recommended quantities of carbohydrate, fat, protein, minerals and vitamins in terms of their body weight. To this diet was added 1.87 grams of elemental phosphorus as sodium phosphate each day. After receiving this diet for a period of two weeks, blood and muscle samples were obtained and the dogs were then begun on one-half this quantity of diet until their weight had declined by 30% of its initial value. The dogs then received their full complement of diet as provided in the control study without phosphorus but containing additional carbohydrate to provide a total intake of 140 calories/kg/day. Serum phosphorus concentration was measured daily and when it reached 1.0 mg/dL or less, the dogs were studied. Under pentobarbital anesthesia, the dogs were placed on a Harvard respirator to maintain a normal blood pH. Organs were sampled to determine their total phosphorus content, and contents of sodium, potassium, chloride, magnesium and calcium. Skeletal muscle was sampled using Wallenberg clamps precooled in liquid nitrogen to permit analysis of tissue content of ATP, ADP, creatine phosphate and inorganic phosphorus. Although hypophosphatemia appeared very quickly and usually attained levels below 1 mg/dL by the second or third day of hyperalimentation, CPK levels did not become abnormally high (Fig. 2).



* It is noteworthy that the method employed in our studies, viz. hyperalimentation, cause an acute depletion of phosphorus from muscle, liver and bone. This stands in contrast to the effects of hyperalimentation and glucose infusion as utilized by Brautbar and his associates in which phosphorus rapidly accumulated in muscle and liver and became rapidly depleted from bone (39).

Measurement of total phosphorus content of various tissues showed a marked decline in skeletal muscle, liver and bone. In contrast, total phosphorus content of cerebral cortex, left ventricle, adrenal gland, pancreas, renal cortex, renal medulla, thyroid and spleen remained within normal limits.

TABLE IV

EFFECT OF HYPOPHOSPHATEMIA AND PHOSPHORUS DEFICIENCY ON ADENINE NUCLEOTIDES AND PHOSPHORYLATION POTENTIALS IN SKELETAL MUSCLE AND MYOCARDIUM

Model	Skeletal Muscle Acute Hyperalimentation		Skeletal Muscle Chronic Phosphorus Deficiency		Left Ventricle Chronic Phosphorus Deficiency	
	con	hypoP	con	P-def	con	P-def
n	8	8	6	5	6	5
P^i serum mmol/L	1.49	0.27**	1.60	0.41**	1.60	0.40**
ptot mmol/kg FFDW	28.9	21.5**	27.9	24.7*	31.2	30.9
ATP mmol/kg WW	6.83	6.03	4.3	2.2*	5.0	4.4
ADP mmol/kg WW	0.78	0.74	0.4	0.2	0.7	0.5
P^i mmol/kg WW	10.24	9.44	12.8	5.9*	10.8	6.9*
$\frac{[ATP]}{[ADP]\,[P^i]}$ =	855 M-1	863 M-1	839 M-1	1860 M-1	661 M-1	1280 M-1
CP	4.1	5.0	4.8	3.5	2.5	2.3

Table IV illustrates data on skeletal muscle under conditions of hypophosphatemia induced by acute hyperalimentation described in the 2nd study (p. 17), and in skeletal muscle and left ventricle of dogs with chronic hypophosphatemic myopathy. The data on the heart was kindly provided by Dr. Thomas Fuller of Gainesville, Florida. These dogs were fed a phosphorus deficient diet mixed with aluminum hydroxide gel for 28 days in a manner identical to that previously reported (48).

Despite sharp falls in total muscle phosphorus and inorganic phosphorus content in serum, ATP, ADP and P^i content of muscle tissue remained within normal limits in dogs with acute hypophosphatemia. Thus, the phosphorylation potential, which was 855 moles/L in control animals, remained essentially unchanged at a value of 863 moles/L in the hypophosphatemic animals. If we would have conducted studies in which hyperalimentation was induced with a phosphorus deficient, high calorie diet on animals that had already been deficient in phosphorus, in which rhabdomyolysis supervenes, ATP content would have

obviously fallen severely. In contrast, measurements obtained in these studies suggest that there must be a very potent phosphate transport system in skeletal muscle that maintains a normal inorganic phosphate concentration in sarcoplasm despite coexistent hypophosphatemia. In addition, the cytosolic concentration of P^i must be adequate to maintain normal levels of ATP so that the phosphorylation potential remains within normal limits.

In contrast to the acute hypophosphatemic model, chronic phosphorus deficiency caused a pronounced change in muscle content of high energy components. Although total phosphorus content fell only 3.2 mmols/kg, ATP, ADP and inorganic phosphate each fell by approximately 50%, thus seriously reducing the total adenylate pool. In addition, the increased value for the phosphorylation potential indicates a reduced rate of mitochondrial respiration, hence a reduced rate of ATP synthesis. The situation in the heart is grossly different from that in skeletal muscle. ATP and ADP were not reduced significantly. However, because inorganic phosphate was reduced, the phosphorylation potential was approximately double the control value.

A criticism of the acute studies such as that reported by Brautbar and his associates (38) and the one from this laboratory is that the duration of hypophosphatemia is obviously short, namely only a few days. It appears possible that serious cellular injury could occur in the absence of other abnormalities if severe hypophosphatemia itself were sustained for a prolonged period of time. In accordance with this possibility, Kreusser and his associates (50), studying the effects of phosphorus deficiency on adenine neucletide metabolism in the kidney, showed that ATP concentrations are maintained in the presence of low extracellular phosphate levels for a considerable period of time, but eventually they fall to low levels.

Our studies also indicate that not only bone but in addition, skeletal muscle is apparently a major reservoir for phosphorus so that in the event of acute hypophosphatemia, muscle phosphorus is mobilized so as to help provide normal quantities of phosphorus for vital organs. Although not examined in our study, if phosphorus is mobilized from bone at the quantities and rates we observed, eventually there must be a mobilization of other critical cellular components, such as potassium and magnesium. Thus, one could predict that prolonged phosphorus deficiency and hypophosphatemia would eventually either induce cellular injury or an orderly decline of all protoplasmic components of the cell, which would be representative of cellular atrophy. Although it has been contended that serum phosphorus and cytosolic phosphorus concentrations were in diffusion equilibrium, findings observed by us suggest that this is not the case. In the control state, the gradient between inorganic phosphorus in cytosol and serum was 6.9. Following weight loss, hyperalimentation and hypophosphatemia, the cytosol to serum ratio rose to 35 (see Table IV). In unreported studies by Fuller (51), dogs fed a phosphorus deficient but otherwise nutritious and calorically replete diet for a period 28 days developed the classical electro-chemical myopathy characterized by high values for sodium and chloride, low values for phosphorus, and a low resting membrane potential which was reversible upon repletion of phosphorus in the diet. When these animals were studied after four weeks of deficiency before repletion, they showed a 50% decline in the concentration of ATP and inorganic phosphorus in their muscle tissue. A low value for ATP implies that such a cell is in jeopardy. Thus, in the event of a superimposed insult, such as more pronounced hypophosphatemia or perhaps anoxia from a variety of influences in the phosphorus deficient state, ATP levels must necessary fall. A large amount of evidence suggest that when

ATP levels decline to critically low values, cellular death may supervene. Additional evidence indicates that if sodium transport is sufficiently impaired so that sodium ions accumulate in muscle cytoplasm, there is decreased activity of the sodium-calcium exchanger so that calcium may accumulate in the cell in sufficient quantities to activate lysosomal enzymes and lead to destruction of the cell (52).

Although hypoxia secondary to decreased red cell content of 2,3-DPG might be implicated in muscle injury in phosphorus deficiency, some evidence suggests this is not the case. Studies by Ross and Hlastala (53) showed that although the P_{50} of hemoglobin may be altered by chronic phosphorus deficiency, the ability of muscle cells to extract oxygen is unimpaired. The same capacity for oxygen extraction may well prevail in other tissues.

It seems apparent that an important species difference exists between rats, dogs and man in terms of their response to phosphorus depletion and hypophosphatemia (54). As pointed out previously, humans and dogs appear to respond to phosphorus depletion induced by dietary deprivation and administration of phosphate binding antacids in a virtually identical manner. In contrast, rats fed a phosphorus deficient diet (without added aluminum phosphate gel), as reported by Kretz and his associates, (55) showed no changes of sodium, potassium or water contents of skeletal muscle although serum phosphorus declined from 2.75 to 0.92 mmoles/L. Similarly, there occurred only a very slight change in phosphate content of muscle and no change in calcium. Measurements of ATP, ADP and AMP content of quadricep muscle of phosphorus depleted rats were normal. Resting skeletal muscle membrane potential values remained unchanged in diaphragm. Finally, preparations of sarcoplasmic reticulum vesicles showed no abnormality of calcium transport as a result of hypophosphatemia. In contrast to these findings in rats fed a phosphorus deficient diet, chronic phosphorus deficiency in the dog induced by feeding a low phosphorus diet in conjunction with phosphate binding antacids causes a substantial increase in salt and water content of muscle, a slight decline of potassium content, a decline of resting muscle membrane potential and a substantial loss of total phosphorus content. In chronic phosphorus deficient dogs, concentrations of ATP, ADP and inorganic phosphate all fall.

Although one might argue that most studies examining the effects of phosphorus deficiency on rat skeletal muscle have not established the severity of phosphorus deficiency as those studies employing dogs, the likelihood remains that rats are not good models to study experimental myopathy induced by deficiency of critical intracellular elements. In our own studies of myopathies induced by selective deficiencies of potassium or magnesium (56,57), adverse effects in the dog replicate those observed in man with similar deficiencies whereas such abnormalities in rats do not apparently occur. In contrast, rats may be an excellent model to study the effects of hypophosphatemia on the heart as discussed in that section.

B. THE RED CELL IN HYPOPHOSPHATEMIA AND PHOSPHORUS DEFICIENCY

The red cell is unique in that it is the only tissue in the body that produces 2,3-diphosphoglycerate. Many years ago, Guest and Rapoport (58) surmised that 2,3-DPG served as a sink or an appendage on the glycolytic pathway that served to store phosphorus in case it was needed for other processes within the cell, such as production of ATP. However, it was subsequently discovered that the most important physiological role of 2,3-DPG was promotion of oxygen

release from hemoglobin (59,60). ATP also has this effect but to a much lesser extent. The interaction of 2,3-DPG in oxyhemoglobin has been well characterized. Its functional status may be expressed quantitatively by the term P_{50}, which refers to the oxygen tension at which hemoglobin is 50% saturated. The normal value for P_{50} is about 27 $\pm$ 1.2 mm Hg. Studies by Lichtman showed that severe phosphorus deficiency might reduce P_{50} to the vicinity of 16 mm Hg. In studies in which red cells were depleted of ATP and 2, 3-DPG, it has been observed that either when phosphorus is restored to previously hypophosphatemic cells or when adenosine is added in the presence of phosphorus, the recovery rate of 2,3-DPG exceeds that of ATP (61,62).

1. The red cell in diabetic ketoacidosis

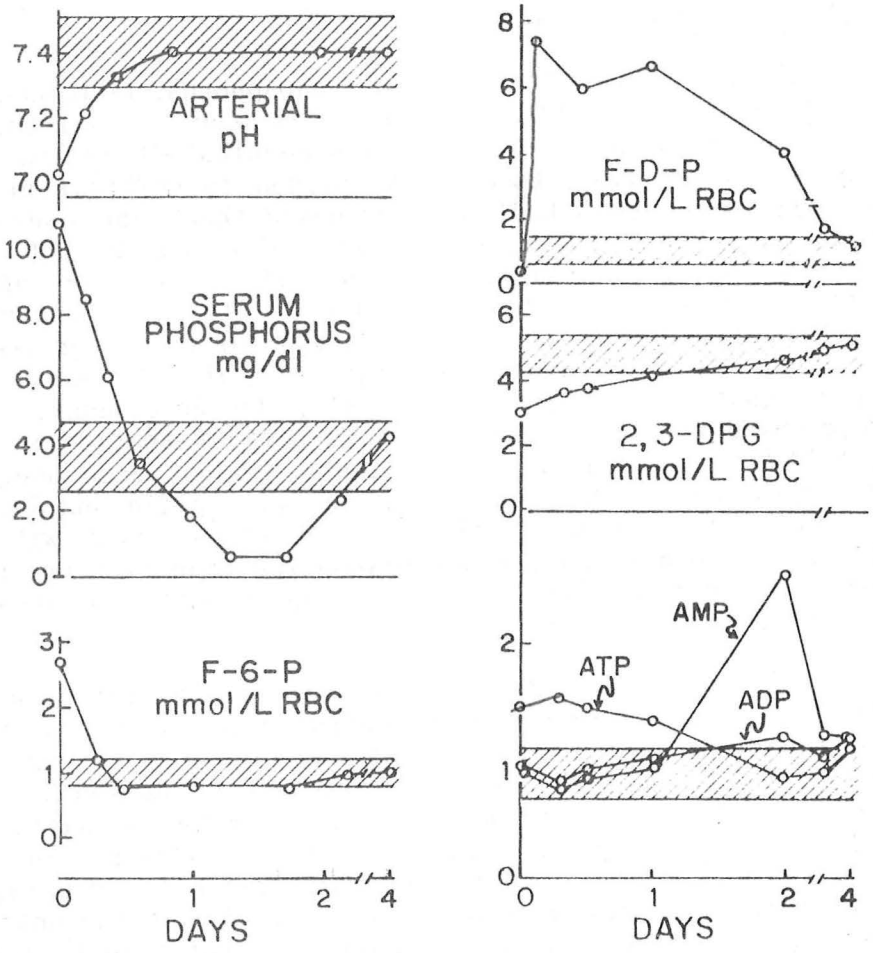
Both metabolic acidosis (63) or severe phosphorus deficiency may reduce concentrations of red cell 2,3-DPG. Ditzel suggested (64-66) that this could be implicated in the pathogenesis of coma in diabetics with ketoacidosis. Thus under such conditions, red cell delivery of oxygen to critical tissues such as the brain might be impaired. Ditzel also proposed that subtle abnormalities of oxygen release in peripheral tissues could be implicated in such complications as diabetic neuropathy, retinopathy, endothelial injury, or other vascular complications in long standing diabetes mellitus. Although studies on patients with diabetic ketoacidosis reported many years ago (67-69) suggested that severe phosphorus deficiency was the rule in all cases of diabetic ketoacidosis, more recent studies suggest that this may actually be an unusual complication. Clearly, the vast majority of patients with diabetic ketoacidosis develop this complication over just a few days so that there has not been adequate time to permit development of severe phosphorus deficiency. Seldin and Tarail reported phosphorus excretion rates from 28-110 mg/hour in patients with DKA before treatment (70). On the other hand, newly discovered diabetics who have been out of control for prolonged periods have more opportunity to develop serious phosphorus depletion.

Measurements of red cell 2,3-DPG content in patients with diabetic ketoacidosis are most often only slightly depressed and show a pattern of rapid recovery during treatment despite the almost invariable occurence of transient hypophosphatemia. Keller and Berger (71) compared 12 patients with diabetic ketoacidosis who were not treated with phosphate with 12 patients who were treated with phosphate. Red cell 2,3-DPG was depressed in both groups initially, and although the rate of recovery was slightly more rapid in those treated with phosphate, recovery also progressed rapidly in the untreated group. In practical terms, the difference was probably not sufficient to be important clinically. In addition, this study also indicates that 2,3-DPG levels in red cells can be restored despite ongoing hypophosphatemia.

Kono and his associates (72) examined red cell glycolytic compounds and adenine nucleotides in six patients with diabetic ketoacidosis. Although hypophosphatemia appeared in each patient during treatment with insulin and the usual replacement of salt, potassium chloride and fluids, red cell 2,3-DPG was reconstituted despite a progressive fall of serum phosphorus concentration. Data from a representative patient in this report is shown in Figure 3. This was a 45 year old man. His plasma glucose concentration was 583 mg/dL, his arterial pH on admission was 7.06, PCO_2 was 12.6 mm HG and bicarbonate concentration 3.3 mEq/L. Large concentrations of ketones were present in both

blood and urine. As arterial pH was corrected, his serum phosphorus values fell from > 10 to a value < 1 mg/dL. As serum phosphorus fell and pH was corrected,

DIABETIC KETOACIDOSIS*



45 y/o man-Glucose 583 mg/dl, pH 7.06,
pCO_2 12.6mmHg, HCO_3 3.3, Ketosis

* (Kono et al, DIABETES 30:346, 1981)

the value for fructose-6-phosphate, initially elevated, rapidly fell to a normal range. On the other hand, fructose diphosphate values were initially abnormally low but increased rapidly in response to correction of acidosis and remained elevated until treatment was underway for a period of two days. Of interest,

his value for 2,3-DPG was slightly depressed but rose to normal values within 24 hours with correction of pH and without treatment with phosphate. It is notable that his red cell content of ATP was slightly elevated.

This patient is probably representative of the great majority of diabetics with ketoacidosis as they are admitted to the hospital. Phosphorus deficiency has not become so severe as to result in gross distortions of red cell glycolyic products or adenine nucleotides. One of the most important regulators of phosphofructokinase activity is pH. The studies by Kono and his associates (72) suggest that the bulk of glycolytic abnormalities result from inhibiting PFK activity because of metabolic acidosis independently of hypophosphatemia or intracellular stores of phosphorus. Thus, simple correction of acidosis is usually sufficient to correct these abnormalities. Such findings seriously question Ditzl's hypothesis (64-66) that vascular disease or perhaps retinopathy could have resulted from repeated bouts of cellular hypoxia related to deficient 2,3-DPG in red cells in poorly controlled diabetics. Of importance, such informaion clearly indicates that the majority of patients with DKA do not require treatment with phosphorus.

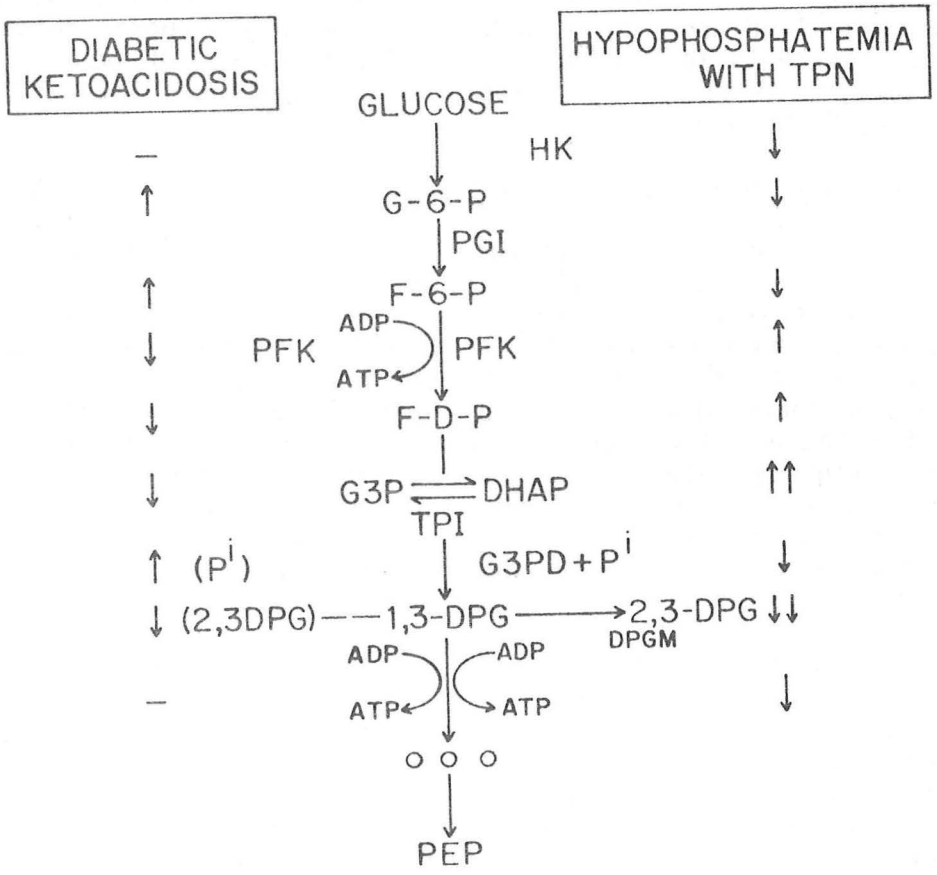
2. The red cell in hypophosphatemia produced by hyperalimentation

In a study of a 52 year old woman with steatorrhea (73), whose serum phosphorus concentration fell from 3.1 to 0.3 mg/dL during hyperalimentation, Lichtman demonstrated a decline of red cell ATP and 2,3-DPG content, decreased utilization of glucose by the red cell and impaired lactate production. Hemolysis did not occur in this patient. The same author also examined red cells from patients with uremia. In most of these, hyperphosphatemia was associated with increased contents of ATP in red cells although 2,3-DPG may be at normal or slightly below normal values because of metabolic acidosis. In the event that serum phosphorus becomes severely depressed as a result of consuming excessive quantities of phosphate binding antacids in conjunction with decreased dietary intake of phosphorus, both ATP and 2,3-DPG contents may fall. Yet, neither of these patients showed evidence of hemolysis.

Travis and her associates (74) measured intermediary glycolytic products in red cells of five patients whose serum phosphorus concentration fell to 1 mg/dL or less during the course of intravenous hyperalimentation. The sum of dihydroxyacetone phosphate and glyceraldahyde-3-phosphate (together referred to as "triose phosphates"), is about 8 mumoles/ml in normal red cells. In patients with hypophosphatemia, this value rises enormously to a range of 200 to 600 mumoles/ml. This piling up of "triose phosphates" in red cells occurs because inorganic phosphate is a cofactor necessary for activity of glyceraldehyde-3-phosphate dehydrogenase which facilitates conversion of triose phosphates to 1,3 diphosphoglycerate. As a consequence, erythrocyte glycolysis below this step in suppressed. Thereby, not only is formation of 2,3-DPG limited but also the formation of ATP.

According to Travis (74), the decline of ATP has two additional important effects. First, low ATP decreases red cell hexokinase activity and thus retards formation of glucose phosphate. Thereby, the supply of precursor for all glycolytic organic products in the cell is reduced. Second, low ATP increases the activity of phosphofructokinase. Thereby, conversion of fructose-6-phosphate to fructose-di-phosphate and in turn triose phosphates, increases. In a prospective study, Travis and her associates were able to show that administration of intravenous phosphate for two days was associated with a prompt recovery of 2,

3-DPG to normal despite a simultaneous decline of serum phosphorus from 0.9 to 0.6 mg/dL. The important studies by Travis (74) and Kono (72) points out clearly that red cell glycolytic products and adenine nucleotides depend not only on hypophosphatemia but of equal importance, on the pH status of the cell. The contrasting effects of these two clinical status are shown in Fig. 4. Once again, it is to be emphasized that gross hemolysis did not occur in any of the patients discussed thus far.



3. The red cell in alcoholic ketoacidosis

Jacob and Amsden (75) studied a 47 year old man, a severe alcoholic, who for one week had epigastric pain, diarrhea and profuse vomiting. When admitted to the hospital he was alert, jaundiced, displayed tachycardia and a respiratory rate of 28/min. He was weak and tremulous. Laboratory findings showed an elevated amylase, a blood pH ranging from 6.98 to 7.06, a bicarbonate concentration of 1, chloride 102, sodium 135, potassium 4.7 and an anion gap of 32. Ketones and lactate in plasma were elevated. Serum magnesium was 1.1 mEq/L. When given sodium bicarbonate intravenously, the patient developed convulsive seizures and remained disoriented thereafter. At this time, his serum phosphorus was found to be 0.1 mg/100 ml. During the first five hospital days, the patients hematocrit fell from 44 to 25%, bilirubin rose from 3 to 8 mg/dL and reticulocytosis appeared. His blood smear showed marked polychromasia and microspherocytosis. Red cell ATP during hypophosphatemia in this patient was 0.39 μmoles/gram hemoglobin, which is about 11% of normal. Such a low value corresponds to findings of others that once red cell ATP content falls to levels of 15% or less than normal, the risk of hemolysis increases (76). This case illustrates that even severe phosphorus deficiency apparently requires additional injurious factors to produce hemolysis. The alcoholic red cell is the victim not only of ketoacidosis and hypophosphatemia, but also plasma membrane injury, increased sodium permeability and decreased Na, K-ATPase activity in the presence of ethanol (77).

In experimental studies on dogs conducted by Yawata and his coworkers (78), red cell alterations induced by hypophosphatemia were characterized. In sequence, the cells became spheroidal, dehydrated, rigid and finally entrapped by the spleen. These changes were prevented or reversed if cellular ATP was maintained by providing phosphate supplements in vivo or by briefly incubating depleted cells with adenosine and phosphate in vitro.

While it is clear that severe hypophosphatemia and phosphorus deficiency may set the stage for hemolysis, continued studies and reports since that time indicate that these two factors alone do not cause hemolysis. In two reports of hemolysis associated with hypophosphatemia, superimposed events such as alcoholic ketoacidosis (79), or coincidential aspirin poisoning treated with hemodialysis (80) have been present.

To summarize the effects of hypophosphatemia on red cell structure and function, available evidence suggests that hemolysis occurs only rarely and then only when serum phosphorus concentration is less than 0.5 mg/dL and only if an additional influence such as severe acidosis or other causes of cellular injury coexist. Severe acidosis, quite independently of hypophosphatemia, may inhibit phosphofructokinase and in turn inhibit synthesis of ATP. If ATP falls to extremely low levels, namely, less than 15% of normal, hemolysis may supervene in rare instances. That the bulk of patients with diabetic ketoacidosis are not severely phosphorus deficient probably explains why frank hemolysis has never been reported in such patients. Simple correction of acidosis in most patients with diabetic ketoacidosis leads to correction of the metabolic abnormalities despite hypophosphatemia.

C. THE SKELETAL SYSTEM IN HYPOPHOSPHATEMIA

Decreased dietary intake of phosphorus, especially in conjunction with ingestion of phosphate binding antacids, may cause severe hypophosphatemia.

Consuming a diet deficient in phosphorus results in a almost immediate dissolution of apatite crystal in bone. Since this response occurs even before serum phosphorus concentration declines, it has been proposed that the bone mobilization is the effect of a humoral substance (81). That the humoral substance is apparently not parathyroid hormone is supported by two lines of evidence. First, the response occurs in parathyroidectomized animals (50). Second, in intact animals, levels of immunoreactive parathyroid hormone promptly decline as a result of phosphorus deprivation or hypophosphatemia (82). In children or growing animals, the osteolysis associated with phosphorus deprivation is sufficiently brisk so that hypercalcemia usually occurs (83). This is presumably the result of an increased basal rate of bone turnover. In contrast, phosphorus deprivation in healthy adults is seldom if ever associated with hypercalcemia, but regularly associated with hypercalcuria (81). In association with the hypercalcuria, there is an immediate decrease in the fractional excretion of phosphorus by the kidney. This probably results from diminished levels of parathyroid hormone. If the basal rate of bone turnover in an adult operates at a higher set point than normal, then phosphorus deprivation may result in hypercalcemia. Such a response may be seen in patients with metastatic cancer to bone, Paget's disease, or hyperparathyroidism. Indeed, before availability of definitive laboratory tests to identify primary hyperthyroidism, phosphorus deprivation was employed as a test to help identify primary hyperparathyroidism in those unusual patients in whom serum calcium levels were either normal or only slightly elevated (84).

In phosphorus depleted man, intestinal calcium absorption increases markedly. Furthermore, urinary calcium excretion increases in phosphorus depletion even in the presence of calcium deprivation. Based upon such evidence, and that published by Emmett and his associates (85) showing that colchicine interrupts the hypercalcuria of phosphorus deficiency by chemical blockade of bone mobilization, one can conclude that some factor is responsible for mobilization of bone in the presence of phosphorus deprivation in the diet that results in hypercalcuria. Raisz and his associates (86), employing in vitro studies, showed that bone resorption increased when the level of inorganic phosphate in the incubation medium was lowered. Studying hypophosphatemic thyroparathyroidectomized rats, Baylink (87) show a marked increase in endosteal bone absorption. Such studies indicate a direct effect of phosphorus depletion stimulating osteoclastic bone resorption that is independent of parathyroid hormone (88). It would appear that the teleological reason for this response is to maintain the critically important level of inorganic phosphorus in serum despite deficiency of this important mineral. Based upon our own studies, phosphorus is not only mobilized from bone but it is also mobilized from skeletal muscle. Thus, muscle appears to provide a very readily mobilized, major pool of phosphorus to supply phosphate ions to more vital tissues such as the heart, the liver or the brain. Our studies conducted in dogs, suggest that acute, transient dislocation of phosphorus from skeletal muscle apparently has no adverse effect on muscle cells provided that the muscle tissue was initially normal. Similar results were observed in rats that were infused with high caloric phosphorus deficient solutions following a period of starvation (89). Those investigators noted that animals receiving a higher phosphorus intake tended to preserve phosphorus content in skeletal muscle, as one would predict.

Most authorities support the view that severe and prolonged phosphorus deficiency in adults may cause typical osteomalacia. In contrast, one group (90) described studies on 19 patients with chronic hypophosphatemia related to idiopathic renal phosphate wasting. In these patients, serum phosphorus levels

were in the moderately depressed range (2.3 - 2.7 mg/dL), serum calcium was normal, urinary calcium excretion was abnormally elevated and immunoreactive PTH levels were low. Histomorphometric data showed decreased osteoblastic surfaces with normal resorption surfaces, normal osteoid volume and normal calcification front. Their findings suggested a form of osteopenia which they termed "nonosteomalacic osteopathy" and not osteomalacia. The usual definition of osteomalacia consists of defective mineralization of newly formed organic matrix of the skeleton.

Such findings have been described in phosphorus deficiency by Cooke (91). Osteomalacia in adults does not involve the epiphyseal growth plates. Involvement of those structures during growth constitutes the major difference between osteomalacia and rickets. In experimental animals, Harrison and associates (92) described disorganization of the epiphyseal plate with Vitamin D deficiency and changes in phosphorus deficient animals that resembled the effects of long term, excessive parathyroid hormone administration, although it is known that phosphorus deficiency reduces parathyroid hormone secretion.

Apparently, the rare disease oncogenic osteomalacia may result from the secretion by certain tumors of a substance that either interferes with the action of Vitamin D on the gut with resulting malabsorption of calcium and phosphorus or (93), as reported by Sweet et al (94), frankly depresses 1, 25-dihydroxy Vitamin D_3 levels by an unknown product of the tumor. Hypophosphatemia, weakness, bone pain and histologic findings of osteomalacia are usual findings in this unusual disease of bone. It may occur with a variety of benign fibrous or angiosclerotic tumors as well as certain malignancies. It may respond to removal of the tumor.

Osteomalacia secondary to phosphate depletion may also occur in patients treated for morbid obesity by jejuno-ileal bypass. Compston et al (95) identified osteomalacia in 10 of 21 patients so treated for obesity. In patients with bone disease compared to those without, plasma $25(OH)D_3$ and plasma phosphate concentrations were significantly lower and plasma PTH concentrations significantly higher. Levels of Vitamin D metabolites in blood did not correlate with bone histologic changes. They suggested that factors other than simple Vitamin D deficiency, such as phosphorus deficiency *per se* may contribute to development of osteomalacia under such conditions.

Antacids, Phosphorus Depletion and Increased Excretion of Calcium into the Urine

Two studies in 1941 (96,97) and another in 1943 (98) showed very clearly that ingestion of aluminum hydroxide gel in the presence of a modest calcium intake causes calcium wasting to the urine. Since these compounds bind phosphorus in the gut and sharply reduce urinary phosphorus excretion to levels that are barely measureable, aluminum hydroxide gel has been advocated as a treatment for patients who form kidney stones composed of calcium phosphate (99). If an adult does not habitually consume substantial quantities of milk or dairy products in his diet, his calcium intake is within the range that hypercalcuria will occur if he ingests aluminum hydroxide or other phosphate binding antacid compounds. Spencer (100,101) recently published evidence suggesting that such a situation may pose a common and potentially severe health hazard in this country. Thus, a number of adults do not ingest dairy products at all so that their dietary calcium intake is in the vicinity of 250 mg/day. Should such an individual consume phosphate binding antacids in a nominal dose of only 30 cc three times a day, not only may total calcium excretion into the urine exceed

the quantity of calcium ingested into the diet by 100 - 300 mg/day, but at the same time, their fecal loss of calcium also increases.

TABLE V ANTACIDS AND CALCIUM EXCRETION

(n=17 MALES , Ca INTAKE 250 mg/DAY)

		Ca excretion/day	
PREPARATION	n	CONTROL	TREATMENT
MAALOX	8	140	192
AMPHOJEL	7	100	142
GELUSIL	2	183	241
MYLANTA	1	174	251

SPENCER ET AL AM. J. CLIN. NUTR. 1982

Table V shows values for urinary excretion of calcium in to illustrate the effect of various preparations of phosphate binding antacids on calcium balance. Based upon such data, it is obvious that each of the various forms of phosphate binding antacids has the same effect on urinary calcium excretion and calcium balance. The potential importance of Spencer's observation that even modest doses of phosphate binding antacids in patients whose calcium intake is marginal leads to a sustained negative balance of calcium, could have far reaching important implications in the pathogenesis metabolic bone disease. Since Spencer's studies (100) were performed only in men, it is very likely that phosphate binding antacid ingestion in conjunction with a modest calcium intake could have far more harmful consequences in women (82).

D. METABOLIC ACIDOSIS

Both clinical observations and experimental evidence indicate that severe metabolic acidosis may occur in the presence of phosphate deficiency and severe hypophosphatemia. As indicated in the foregoing section, removal of phosphorus from the diet and simultaneous administration of phosphate binding antacids leads to prompt mobilization of bone mineral. Hypercalciuria is a prompt and predictable response. As hypophosphatemia becomes more severe, phosphate ions virtually disappear from the urine thereby eliminating the capacity to excrete metabolic hydrogen as titratable acid. Normally, about one-half of metabolic acid produced by metabolism is excreted by exchange of hydrogen ions from the renal cell with sodium ions from the renal tubular lumen. Three mechanisms permit excretion of hydrogen ions. First, disodium hydrogen phosphate (Na_2HPO_4) is converted to monosodium dihydrogen phosphate (NaH_2PO_4) and the hydrogen ions thus excreted are measurable as titratable acidity. Second; ammonia diffuses into the tubular lumen and combines with H+ to become ammonium (NH_4+), which is essentially nonresabsorbable, thereby facilitating excretion of hydrogen ions.

Third, a small quantity of hydrogen is excreted as free hydrogen ions, thus accounting for the pH. Although pH itself does not account for significant quantities of H+ excretion; the low pH produced in the urine facilitates trapping of NH_4+ in the tubular lumen so that it must be excreted.

If phosphate is absent from the urine, one would predict that sufficient metabolic acid could be excreted as NH_4+ to prevent acidosis. Ordinarily, a decline of intracellular pH would augment production of ammonia. However in phosphate deficiency, NH_3 formation decreases (85). It has been proposed that intracellular pH rises in phosphorus deficiency, thereby accounting for the decreased NH_3 production. A rise of intracellular pH in phosphate deficiency has been shown to occur in liver and muscle (102). Whether a similar change occurs in the kidney cell has not been determined. Nevertheless, abundant evidence shows that phosphate deficiency not only reduces excretion of titratable acid as isomers of phosphoric acid but of importance, it also reduces ammonia excretion, thus supporting the theory that the intracellular pH of renal tubular epithilium rises. Thereby,. the decrease in ammonia production and unavailability of buffer phosphate in the urine essentially prevent excretion of metabolic acids.

It seems logical to ask why profound metabolic acidosis does not regularly develop in persons who cannot excrete titratable acid or ammonium into the urine. Although phosphorus deficiency is common, metabolic acidosis in phosphorus deficiency is indeed a rare entity. The explanation for its uncommon occurrence lies in the fact that during mobilization of bone mineral, there also occurs mobilization of carbonate, which is an important component of bone apatite (Fig. 5). During osteolysis associated with phosphorus deprivation, sufficient carbonate is mobilized from bone to titrate all metabolic acid retained in the body. In fact, in studies using animals it has been found that carbonate mobilization may overshoot and result in slight metabolic alkalosis. However, should some event occur that prevents mobilization of bone mineral, then severe metabolic acidosis may occur. This has been described in children with severe lactase deficiency and protein calorie malnutrition during refeeding without providing adequate phosphate in the diet (103). Addition of phosphate to their diet resulted in pronounced increments of titratable acidity into the urine and correction of metabolic acidosis. In experimental phosphorus deficiency, some very interesting results have been observed following administration of certain drugs that impede calcium mobilization from bone. Thus, metabolic acidosis has been observed to supervene very rapidly in the face of phosphorus deficiency in animals following administration of either diphosphonate or colchicine (85).

5
Dis

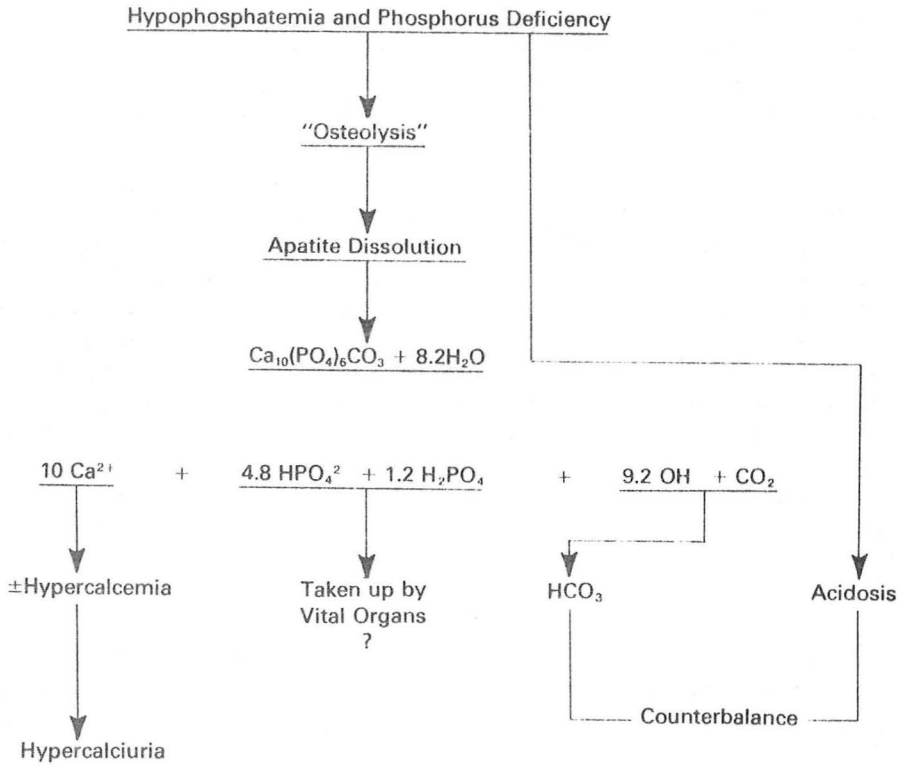


Figure 5 Deprivation of phosphorus stimulates dissolution of the skeleton in an apparent attempt to maintain a normal serum phosphorus concentration. Apatite breaks down to calcium, phosphate, carbonate, and water. Hypercalcemia occurs in children or in adults in any state in which increased bone turnover prevails. Hypercalciuria is a regular feature. Although urine phosphate is sufficiently depressed to prevent acid excretion as titratable acidity, carbonate ions mobilized from apatite titrate metabolic acids sufficiently to prevent metabolic acidosis. If this process is long standing, classical osteomalacia may result.

E. NERVOUS SYSTEM DYSFUNCTION

Dysfunction of the central nervous system has been well characterized in severe hypophosphatemia, especially during the course of hyperalimentation in patients with disease causing severe weight loss. A sequence of symptoms compable with a metabolic encephalapathy has been described by Silvis (108,109). In such patients, hypophosphatemia usually occurs after approximately one week or more of hyperalimentation with solutions of glucose and/or amino acids not containing enough phosphorus to prevent hypophosphatemia. The sequence of abnormalities consist of irritability, apprehension, muscular weakness, numbness, paresthesias, dysarthria, confusion, obtundation, convulsive seizures, coma, and death. Although such a clinical state could be confused with that of delirium tremens in the alcoholic, the lucid visual and auditory hallucinations in the alcoholic usually do not occur in the patient with hypophosphatemia. Obviously both conditions may coexist. Travis and her coworkers (61) described

parathesias about the mouth and the limbs, mental obtundation and hyperventilation in three of eight patients who became hypophosphatemic during hyperalimentation. At the same time, these patients displayed a sharp drop in red cell 2,3-DPG content, a drop in their hemoglobin P_{50} value to levels of 16.0, 16.5 and 20.9 mm Hg. These are exceptionally low values compared to the normal value of 26 mm Hg. They were able to correlate these findings with an abnormality of the electroencephalogram. Both abnormalities disappeared and the patients recovered symptomatically as hypophosphatemia was corrected. Indeed, red cell 2,3-DPG recovered during supplementation with phosphorus despite worsening hypophosphatemia. Most notably, such symptoms do not occur when adequate phosphorus is provided to prevent hypophosphatemia during hyperalimentation. Malnourished dogs treated with hyperalimentation so as to deliberately induce hypophosphatemia results in ataxia, convulsions and death (110). In a similar study, Silvis and his coworkers (111) studied dogs with malnutrition induced by small bowel resection so that their weight had decreased by 50%. Through indwelling intravenous catheters, they infused a solution containing hypertonic glucose and amino acids to provide 140 calories/kg/day. Hyperalimented animals had a mean survival of only 5.4 days and at this time their mean phosphorus level was 0.4 mg/dL. Some animals displayed weakness, convulsions and coma. In other animals hyperalimented with the same preparation but containing supplemental phosphorus sufficient to prevent hypophosphatemia, survival was the same. They concluded that hypophosphatemia was not the sole cause of death in the starved hyperalimented animals not given phosphate. In our own studies, attempts to chronically cannulate dogs for the purpose of parenteral hyperalimentation has almost universally been met with bacteremia and severe sepsis. In addition, it is possible that resection of the small bowel, such as performed in a study by Silvis et al (111), caused other deficiencies that might have been responsible for death despite prevention of hypophosphatemia.

In order to avoid the above possibilities, we prepared a group of dogs by feeding them a nutritionally adequate diet that was restricted in calories so as to produce a weight loss of 30% below their baseline value (43). At this point one group of animals was gavage fed a mixture providing 140 calories/kg/body weight/day that contained essentially no phosphorus and compared to another group of animals gavage fed with a same mixture containing an abundant quantity of phosphate. Those animals deprived of phosphorus during hyperalimentation developed pronounced weakness, fasciculations, profound anorexia and would usually die after about five or seven days. Their serum phosphorus values were well below 1 mg/dL. In contrast, animals fed the same diet containing phosphorus did not have to be gavage fed and displayed no symptoms whatsoever except apparent hunger.

Although central nervous manifestations of phosphorus deficiency appear to occur with regularity in experimental animals and in patients hyperalimented without adequate phosphorus who become hypophosphatemic, to date there has been no systematic study of brain chemical composition or histology to characterize this important complication of hypophosphatemia.

Since the foregoing reports, some important information has emerged on the effects of acute hypophosphatemia and its effects on the central nervous system. The following case reported by Ritz (112) from the University of Heidleberg is representative.

> A 53 year old woman with regional enteritis, anorexia nervosa and food fadism consumed a diet composed of baked

brains and raw liver. She was admitted to the hospital after losing weight from 55 to 40 kg over four months. Physical examination showed marked weight loss, a blood pressure of 90/60 mm Hg, and a pulse of 88/min. She had bilateral pretibial edema. Diffuse muscle wasting was prominent, but neurological examination was within normal limits. Laboratory findings showed a moderate, microcyte anemia. Serum electrolyte concentrations showed a Na of 128 mEq/L, K 3.1 mEq/L, Cl 92 mEq/L, HCO_3 24 mEq/L. Calcium was 6.6 mg/dL and serum phosphorus ranged between 2.8 - 3.7 mg/dL. Plasma urea nitrogen was 9 mg/dL, creatinine 0.6 mg/dL and plasma cholesterol 76 mg/dL. Her xylose absorption was below normal, and fecal fat excretion was 20.9 g/24 hours.

Having failed to gain weight, parenteral nutrition was initiated on the 13th hospital day. The mixture administered each 24 hours containing 418 grams of glucose, 50 grams of synthetic L-amino acids, 100 grams of xylitol (see p), 11 mmoles of lactate, 59 mmoles of acetate and 24 units of regular insulin. The phosphate content of the mixture was 9 mmoles administered each 24 hours. She also received a multivitamin preparation containing thiamine.

Six days later, the patient became progressively restless and complained of circumoral and finger tip tingling followed by generalized numbness. She was lethargic and slightly disoriented but otherwise mentation was normal. She was markedly weak, unable to sit up and had difficulty swallowing. Respirations became labored and her speech assumed a nasal quality. Her temperature rose to 38.5° C. Blood pressure fell to 75/60 mm Hg and her pulse rose to 120/min. Her abdomen became distended and bowel sounds were hypoactive. Weakness advanced to the point at which the patient could not raise her head from her pillow. She showed bilateral ptosis and a diminished gag reflex. Deep tendon reflexes were elicited with difficulty but the plantar response was flexor. Her sensory examination was normal.

Repeated laboratory examinations showed that her hemoglobin had fallen from 11 to 6.6 gm/dL. Her uric acid was 2.0 mg/dL, plasma creatinine 0.4 mg/dL and her serum sodium was 114 mEq/L. Arterial PCO_2 was 54 mm Hg and arterial pH was 7.40. Her calculated total CO_2 was 34 mmoles/L. Serum calcium had fallen to 6.2 mg/dL and serum phosphorus was 0.25 mg/dL. CPK activity was normal.

The patient was given hypertonic sodium chloride, albumin and macromolecular dextran. This did not produce improvement by the 20th hospital day and treatment was begun with potassium phosphate. By the 3rd day of treatment with phosphate, the patient's hypotension, ileus and all neurological signs as well as hypercapnia disappeared. The patient left the hospital against medical advise and died two months later. An autopsy showed regional ileitis with perforation.

Although there is some question concerning the role that hyponatremia might have played in this patient's illness, its correction had no salutory effect. On the other hand, once hypophosphatemia had been corrected, the patient's neurological disorder resolved completely. The fact that her CPK was within normal limits is not an unique observation. Of the large number of patients we have observed at the Veterans Hospital with hypophosphatemia occurring in the wake of alcoholic withdrawal, hyperalimentation, or treatment of diabetic ketoacidosis, rhabdomyolysis is common only in those with alcoholic withdrawal. I can recall but one patient who developed a substantial elevation of CPK activity during the course of hypophosphatemia induced by total parenteral nutrition.

Earlier observations by Travis (74), Silvis (108, 109) and several other investigators (47,113) have underscored the importance of central nervous system complications in patients who slowly develop severe hypophosphatemia during the course of hyperalimentation induced by total parenteral nutrition. However, the symptoms and findings that have not been emphasized until the past few years include ptosis, amblyopia, distortions of color perception, dysphagia, dysphonia, impairment in the ability to swallow secretions, respiratory weakness and hypercarbia in a setting of profound muscle weakness and diminished deep tendon reflexes. As one might suspect, smooth muscle function is also apparently affected by severe hypophosphatemia as evinced by ileus. Although hypophosphatemia with respiratory muscle weakness has been described, in one report (114) the patients were also hypokalemic suggesting that this may have played a role in the muscular manifestations of this condition. However, in the patient described by Ritz (112), it is doubtful that a serum potassium value of 3.1 mEq/L could be responsible for the advanced state of neuromuscular dysfunction. Planas and his associates (114a) have shown increased fatiqability of diaphragmatic contractions in phosphorus-deficient dogs.

F. HYPOPHOSPHATEMIC CARDIOMYOPATHY

Little information has been reported about impairment of myocardial function in patients with hypophosphatemia and phosphorus deficiency. O'Connor and his associates (115) showed that calculated stroke work increased after phosphorus administration in seriously ill patients whose serum phosphorus concentration ranged from 0.7 to 1.4 mg/dL. These improvements were independent of Starling effects and probably represented an improvement in myocardial contractility.

Another report (116) described 3 patients with severe congestive cardiomyopathy and florid heart failure who had become seriously phosphorus deficient by chronic alcoholism (one) or by aluminum hydroxide ingestion (two). Serum phosphorus levels ranged from 0.3 to 0.6 mg/dL. Complete recovery followed phosphorus repletion despite the fact that two of them received no digitalis preparation, diuretics or other drugs usually employed in congestive heart failure. Although this unique observation has not been confirmed, an identical patient has been observed in Tyler, Texas. This patient had long-standing anorexia and consumed large quantities of aluminum hydroxide gel for ulcer disease. She presented in florid biventricular failure. There was no response to diuretics or digitalis. When her serum phosphorus value of 0.1 mg/dL was corrected she recovered completely.

Several noteworthy studies have been conducted on experimental cardiomyopathy.

Fuller and his associates (117) have examined the effects of selective phosphorus deprivation in dogs. The dogs had implanted devises to measure the rate of ascending aortic blood flow, left ventricular pressure and left ventricular contractility. The animals were studied before phosphorus depletion was induced, following 35 days of depletion and again after 56 days of repletion. Phosphorus deficiency was confirmed by serial measurements of muscle phosphorus content and a decline of serum phosphorus concentration from an average control value of 5.2 to 0.9 mg/dL after five weeks of phosphorus depletion.

During phosphorus depletion left ventricular end diastolic pressure increased from a resting control value of 4.2 $\pm$ 0.9 mm Hg to 7.2 $\pm$ 1 mm Hg ($p < 0.001$) while stroke work decreased an average of 34% ($p < 0.01$). Also, both average and peak external left ventricular potential energy decreased 28% and 24% respectively ($p < 0.01$). During phosphorus repletion all four variables returned toward their control values. The authors concluded that chronic phosphorus deficiency reduces the energy generating ability of the left ventricle. Phosphorus depletion caused a reduction in myocardial stroke work independently of the Frank-Starling effect. Upon restoring phosphorus to the diet, all abnormalities cleared rapidly. In other studies (118) the authors have found that the left ventricular ejection velocity and ventricular contractility, measured by implanted pressure transducers in the left ventricular free wall, are both reduced by phosphorus deficiency and returned to normal following phosphorus repletion in the diet. Finally, in unpublished observations, they have shown that the left ventricular response to isoproterenol, which usually increases stroke work, fails to do so in the presence of phosphorus deficiency. As discussed previously (Table IV, p.) such changes occur in association with a significant decline in sarcoplasmic inorganic phosphate. The resulting alteration of the phosphorylation potential and the implication that mitochondrial energy production is reduced, could represent the biochemical counterpart of the heart's decreased capacity for mechanical work. Studies such as these provide strong evidence that chronic phosphorus deficiency impairs myocardial function. Such abnormalities correlate well with the limited clinical observations suggesting that severe phosphorus depletion and severe hypophosphatemia in man, induced by dietary deprivation and simultaneous ingestion of phosphate binding antacids, lead to a state of congestive cardiomyopathy that may disappear completely following phosphorus repletion.

Brautbar and his associates (119) have examined the biochemical effects of phosphorus deficiency on the heart of the rat. They showed that rats made phosphorus deficient for a period up to 12 weeks showed a direct correlation between serum phosphorus values and cellular concentration of inorganic phosphate. There was also a direct correlation between serum phosphorus concentration and muscle cell content of creatine phosphate. In contrast, there was no correlation between serum phosphorus values and tissue content of ATP, ADP or AMP. Of interest, creatine kinase activity decreased in both the sarcoplasm and mitochondria in phosphorus deficient rats. The decrease in creatine phosphate content of rat heart could have been the result of decreased transport activity of creatine or decreased synthesis. Their studies indicated that all steps of myocardial energetics are impaired in phosphorus deficiency and provide a molecular basis for the altered myocardial function observed in phosphorus depleted man and dogs.

The heart in starvation

In persons who have died as a result of starvation or those who die during the course of refeeding for starvation, cardiovascular events are commonly the

mode of death. Besides being abnormally small, the heart in starvation is soft, pale and flabby. The following information is taken from Keyes and his associates (120). The coronary vessels are usually conspicuous, partly because of the disappearance of the normal epicardial fat. Subepicardial edema is sometimes apparent. In 10-20% of the cases described by Porter in 1889, the heart surface showed patches of a white gelatinous material which was easily detached. This was called a "soldiers spot" and was thought to represent degenerating epicardial fat. In 1948, Uehlinger reported observations on prisoners of war who had died during the first weeks of refeeding. They showed marked brown atrophy of the heart. He also noted the patches of gelatinous atrophy, so-called "soldiers spots". Brown atrophy is observed in about 80% of fatal cases of inanition. This is a pathological description composed of five important findings: (1) loss of cross striations, (2) increased nuclei per volume of sarcoplasm, and (3) vacuolar changes, (4) thin, atrophic fibers and, (5) brownish pigment may be seen accumulated in a fusiform pattern on the longitudinal axes of the nuclei. These hearts also tend to show perivascular fibrosis, occasional collections of lymphocytes, condensations of nuclei and fatty infiltration. Degeneration of autonomic ganglia have also been described. Stein and Fenigstein studied 492 adults who died in the Warsaw ghetto in 1942. Eighty-seven percent of these unfortunate victims showed severe atrophy of the heart, indeed the heart weights ranged between 110 to 350 grams. Although the average weight of all of the hearts examined was 19% below the expected value, it is remarkable that some weighed less than 50% of normal.

The following cases described by Weinsier are good examples of myocardial insufficiency in patient hyperalimentated for severe inanition (121).

> The first patient was a 28 year old woman, with anorexia nervosa of at least seven years duration. Her height was 5'4" and her weight was 28 kg. The patient was alert, oriented and in no acute distress. Her weight was thought to be 40% of normal. Her blood pressure was 90/60 mm Hg, pulse 92 and regular. Except for emaciation, her physical examination was normal. Her laboratory data showed a normocytic anemia, BUN 30 mg/dL, creatinine .6 mg/dL, potassium 2.9 mEq/L, calcium 5.1 mg/dL, albumin 2.3 g/dL, phosphorus 2.7 mg/dL and glucose 103 mg/dL. The patient was transfered from the Psychiatric Service to the General Medicine Service for treatment of malnutrition. Her morbid appearance led the physician in charge to comment in the patient's record that because of severe malnutrition it was of "life threatening importance to aliment the patient parenterally". Thus, within several hours after transfer to the Medical Service, total parenteral nutrition was instituted. She received 500 g of glucose, 80 g of amino acids as (Freamine II) in 2 liters of fluid containing 200 mEq of Na, 130 mEq of P, 30 mmoles of phosphate, 16 mEq of magnesium, 15 mEq of Ca and 135 mg of thiamine and other vitamins. The total calories administered per 24 hours were 2,320. On the second day the patient complained of chest pain and was found to have tachycardia. An electrocardiogram showed poor R wave progression across the precordium with ST segment elevation and inverted T waves in the anterior chest leads. Her phosphorus at this time was 1.1 mg/dL, magnesium, 1.1 mg/dL, glucose 668 mg/dL, Na 138 K 3.6, Cl 117 and HCO_3 14 mmoles. Her arterial pH was 7.23

with a PCO_2 of 17 and a PO_2 of 119, thus indicating an acute metabolic acidosis. Later that day, her systolic blood pressure fell to 60 mm Hg and frequent ventricular premature contractions were noted. Her blood pressure was supported with vasoconstrictors and a lidocane drip was begun. Bicarbonate was administered to treat her metabolic acidosis. She received no phosphorus or magnesium despite a phosphorus value of 0.4 mg/dL. By the beginning of the third day, while continuing hyperalimentation, the patient developed pulmonary edema which was followed by a decline of arterial PO_2 to 21 mm Hg and elevation of pCO_2 to 40 mm Hg. Ventilatory support was initiated. Over the next three weeks, repeated pulmonary infections, further deterioration of pulmonary status, gastrointestinal bleeding and myocardial instability with hypotension culminated in death.

The second patient described by Weinsier et al was a 66 year old woman with diarrhea and malabsorption that followed construction of an ileal conduit for uretheral obstruction three months before admission. The patient's height was 5'1" and her weight was 36 kg. Her physical exam demonstrated cachexia and marked muscle atrophy. She had diffuse tenderness of the abdomen but no bowel sounds or signs of peritoneal irritation. There was edema of the hands, feet and sacrum. The cardiovascular and nervous systems were within normal limits.

Laboratory data showed a hematocrit of 38%, blood urea nitrogen=22 mg/dL, creatinine 1.0, P 3.4, HCO_3 17, glucose 48 mg/dL and albumin 1.6 g/dL. Her electrocardiogram showed sinus tachycardia and nonspecific ST-T changes.

Because of the patient's weight loss and cachectic appearance, a note was inscribed in her records "because the patient was critically malnourished she should be hyperalimented without delay". Accordingly, within 12 hours of admission to the hospital, she was begun on 3 liters of fluid a day containing 750 g of dextrose, 120 g of amino acids as Freamine II, 60 mEq of Na, 20 mEq of P, 15 mmoles of phosphate and multivitamins. Twenty four hours after beginning parenteral hyperalimentation, she was noted to be lethargic with a pulse rate of 180/min. and a blood pressure of 50 mm Hg by palpation. She showed no signs of congestive heart failure at that time. Her serum phosphorus level had fallen to 0.7 mg/dL and her electrolytes showed Na 142, K 1.4, Cl 111, and HCO_3 19. Her magnesium was normal and her glucose was 1,010 mg/dL. Her lactate was 2.9 mmoles/L. Arterial blood pH was 7.31, PO_2 59 and PCO_2 24.

On the second day the patient developed respiratory arrest and thereafter required mechanical ventilation. Although her electrolyte and acid-base disturbances were corrected, the patient's subsequent course was downhill and she died on the 6th hospital day. Autopsy findings were com-

patable with ischemic enterocolitis, pneumonitis and adult respiratory distress syndrome.

Considering the pronounced degree of myocardial atrophy seen in severe inanition, one is hardly surprised to observe such events as acute congestive heart failure, volume overload, "adult respiratory distress syndrome" or cardiac arrest due to electrolyte derangements if such a person is hyperalimented with large volumes of high caloric fluids. For example, in the second patient described by Weinsier (121) total parenteral nutrition was begun with a daily dosage of 3 liters of hypertonic fluid that resulted in a serum potassium concentration of 1.4, a phosphorus level of 0.7 mg/dL, metabolic acidosis and a glucose concentration of 1,010 mg/dL. Such electrolyte disturbances alter electrical properties of the heart cell and the phosphate deficiency could also depress ventricular contractility. In addition, not only was the total volume of fluid administered excessively large but also the added influence of severe hyperglycemia would augment the volume overload further. It is clear that while phosphorus deficiency may contribute toward myocardial dysfunction in such patients, the total explanation is much more complex.

It is notable that both patients developed hyperchloremic metabolic acidosis with a normal anion gap. Since measurements of urine pH, titratable acidity or excretion of ammonium were not performed, the precise role of phosphate deficiency in their metabolic acidosis can not be ascertained. Although it is possible that the mixture utilized for parenteral nutrition contained crystalline amino acids that might have been responsible for the metabolic acidosis, Heird and his associates (122) indicate that acidosis does not tend to occur with the use of FREAMINE II. It contains metabolizable salts of arginine and lysine as the acetate rather than the hydrochloride, and has thereby been shown to avoid the complications of metabolic acidosis. Therefore, it is possible that hypophosphatemia decreased titratable acid formation and ammonium production, and thereby was probably responsible for the acidosis (See p. 28).

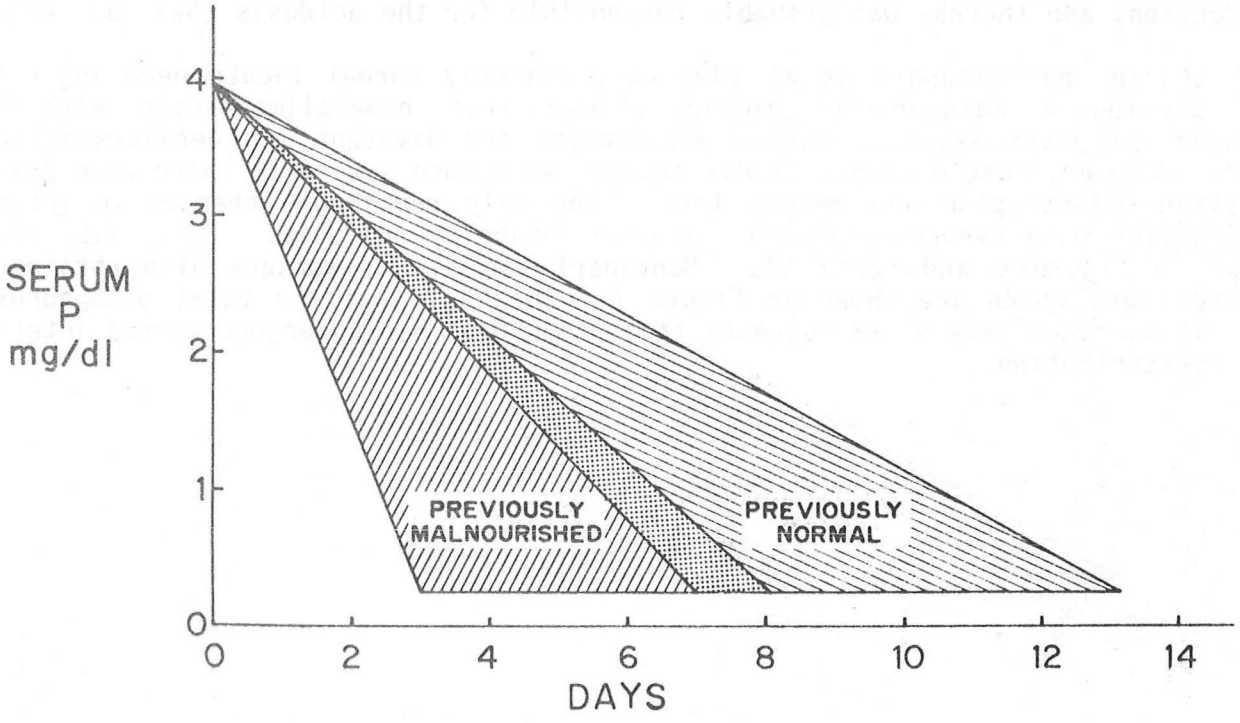
Studies by Montanari et al (30) on previously normal (acute head injury) and previously malnourished humans showed that hyperalimentation without phosphorus caused skeletal muscle electrolyte and divalent ion derangement in both. However, muscle compositional changes were more severe in those with preexisting malnutrition and weight loss. The only remarkable changes in serum composition were hypophosphatemia and mild metabolic acidosis. These data are shown in Figure 6 and Table VI. Montanari and his co-workers also obtained balance data which are shown in Figure 7. The fact that the total phosphorus deficit averaged only 50 mM suggests that phosphorus had undergone marked internal redistribution.

TABLE VI MUSCLE ELEMENTS IN PATIENTS WITH HYPOPHOSPHATEMIA*

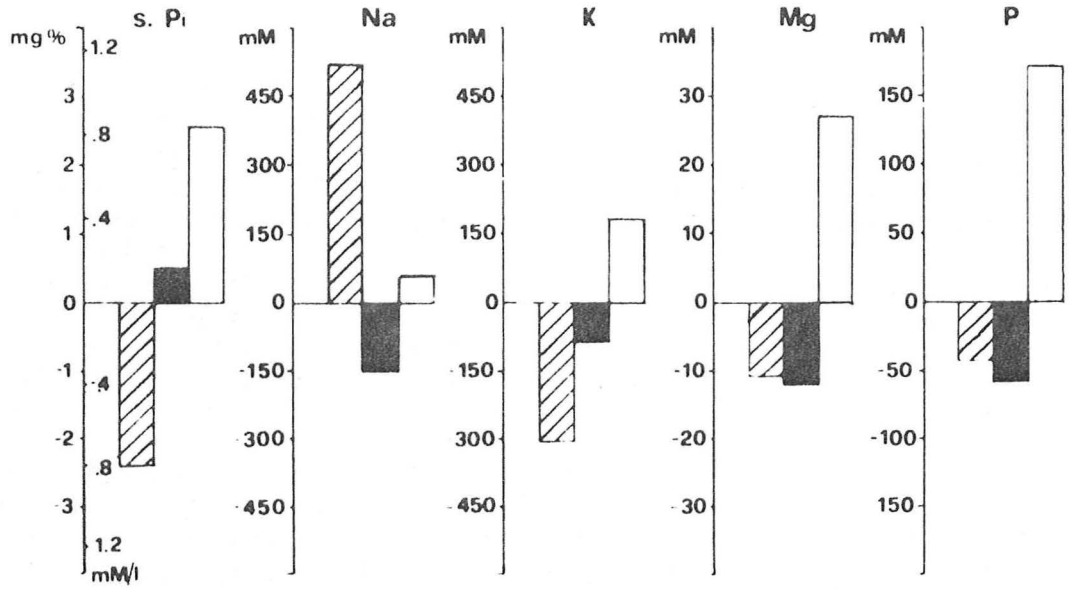
	NORMAL (n=10)	MALNOURISHED (n=11)	WELL-NOURISHED (n=12)
P^i serum (mM/L)	1.2 ± 0.3	0.29 ± 0.03	0.29 ± 0.03
P^m mM/dg	28 ± 0.9	17.7 ± 0.8	25.2 ± 0.9
Na^m mM/dg	13 ± 0.4	25.5 ± 1.8	20.2 ± 1.3
K^m mM/dg	46 ± 5	34.9 ± 1.2	40.6 ± 1.4
K^i mEq/L	182 ± 6	134 ± 6.0	153 ± 6.0

(* All data represent $\bar{x}$ ± 1 S.E.M.)

ACUTE HYPOPHOSPHATEMIA DURING TPN IN MAN : MONTANARI ET AL ADV. EXP. BIOL. MED., 1982



CHANGES OF SERUM Pi AND EXTERNAL BALANCES DURING TPN WITH AND WITHOUT AHPP



Any physician who treats patients with severe malnutrition or anorexia nervosa should be aware that acute administration of large quantitities of calories and large volumes of fluids to any such patient is an unwise therapeutic decision. There should be no hurry. Such patients have often subjected themselves to dietary indiscretion, food fadism, induced vomiting, or laxative and diuretic abuse for many years and have managed to survive. Indeed, despite their wasted appearance, many of them deny illness. Trying to correct their nutritional disorders by overzealous hyperalimentation in the hospital setting is a misadventure which may result in their death.

Although the fatal experiences from the prisoner of war camps in the Philippine Islands and in Europe during World War II are the most commonly cited examples of the so called nutritional refeeding or recovery syndrome (36), such instances were described centuries ago.

> In his description of the seige of Jerusalem by the Romans, Josephus Flavius wrote ... "some of the deserters fled to the Romans. Their faith was worse than if they would have stayed in the city, and the hunger they had left behind was, as they discovered, less lethal than the plenty that the Romans had provided. They arrived blown up by starvation as if by dropsy, then stuffed their empty bellies non-stop 'til they burst - except for those who were wise enough to restrain their appetite and take the unaccustomed food a little at a time." (123).

Dr. Ludlow Pence, staff physician at the VA Medical Center in Dallas, related his experience on American prisoners of war in Germany at the end of World War II. Dr. Pence was assigned to a hospital set up to provide care for these individuals. Many of these men had lost 40% of their normal body weight. When they were given glucose or other carbohydrates, many developed edema, effusions in serious cavities and often died after a few days. While some showed classic findings of wet beri-beri, others did not. The physicians discovered that although the men could seldom tolerate whole cow's milk, when it was diluted 1:1 with water and given in quantities of one ounce per hour, it caused neither vomiting nor diarrhea. After a few days, the quantity was gradually increased and followed by satisfactory recovery.

Such experience resembles that of Schnitker and his associates who treated American prisoners of war in the South Pacific Islands (124). In their experience, death commonly occurred when refeeding was conducted too rapidly with high carbohydrate foods, even when given with Brewer's yeast as a source of thiamine. However, based upon unreported verbal statements, when skim milk was given, neither congestive heart failure, edema nor sudden death appeared. It has been assumed that the content of electrolytes and divalent ions provided in milk might have explained this successful form of treatment. Similar experiences were gained from the use of coconut milk in the South Pacific during World War II. The comosition of coconut milk is essentially identical to blood plasma.

Table VII illustrates the recommendations for hyperalimentation solutions that have been employed at the Massachussetts General Hospital by Ryan (125). For adults, 3 L of these solutions are recommended each 24 hours. This volume contains between 2631 and 2877 calories. Such quantities are clearly excessive as initial treatment for patients with advanced malnutrition or inanition. A number of commerical preparations are available, usually as mixtures of carbohydrates and amino acids to which electrolytes, minerals and vitamins must be added. In my view, the important recommendation for administering such solutions to poorly nourished patients, especially those typified by advanced anorexia nervosa, is to begin very slowly with perhaps 300 - 400 calories on the first day, and gradually increase the total number of calories administered per day while carefully observing the patient physically and chemically so as to avoid problems with hypervolemia or electrolyte disturbance. This requires measurement of daily weight under carefully controlled conditions. An additional measurement that may be useful as an index to avoid excessively rapid refeeding is serum urate. Thus, phosphate trapping and hypophosphatemia can initiate injury in a variety of tissues (126). Release of nucleoproteins from such injured cells can be reflected by a sudden abnormal elevation of serum uric acid. Should hyperuricemia occur in the absence of prerenal azotemia, one might consider additional phosphorus supplementation or a reduction of nutrient administration. Blood samples should be collected at least daily. Urine volume should be monitored and measurements obtained for specific elements in the urine if indicated by changes in their respective values in serum.

TABLE VII COMPOSITION OF SOLUTIONS FOR TPN

INGREDIENTS	CASEIN HYDROLYSATE	CRYSTALLINE AMINO ACIDS	COW'S MILK WHOLE	COW'S MILK SKIM
PROTEIN g/L	23	31.2	37	34
FAT g/L	—	—	34	0.7
CHO g/L	196	209	44	48
K mEq/L	36	40	38	41
Na mEq/L	31	20	21	22
Cl mEq/L	19	26	100	103
P mmol/L	25	26	30	33
Mg mmol/L	3.3	3.3	10.8	11.8
Ca mmol/L	2.3	2.3	29	30
KCal/L	877	959	640	340

Table VII also illustrates the composition of whole cows milk and cows milk from which most of the fat has been removed. With the exception of a difference in fat and carbohydrate content, all of these preparations have a similar concentration of sodium and potassium, whereas milk contains higher values for phosphorus, magnesium, calcium and chloride. Thus, if a patient can tolerate the fat content of whole milk or skim milk, and if they can tolerate lactose, and if they are capable of ingesting oral substances such as these without development of nausea, vomiting or diarrhea, there seems little justification for administering the more expensive synthetic preparations. On the other hand, if a person refuses to eat or vomits the material, these synthetic preparations must be used.

VI. TREATMENT OF HYPOPHOSPHATEMIA

Diabetic Ketoacidosis

Treatment with phosphate salts in the management of diabetic ketoacidosis (DKA) has become exceptionally popular in the United States. This practice has resulted from the fact that nearly all patients with DKA show a decline in serum phosphate following administration of fluids and insulin. Despite the foregoing, recent studies have made routine phosphate therapy in DKA controversial. Keller and Berger (71) compared 12 patients with DKA who were not treated with phosphate with 12 patients who were treated with phosphate. Red cell 2, 3-DPG was depressed in both groups initially, and although the rate of its recovery was more rapid in those treated with phosphate, recovery also progressed rapidly in the untreated group. In practical terms, the difference was probably not sufficient to be important clinically. In addition, restora-

tion of 2, 3-DPG levels in red cells indicates that phosphorus was utilized to synthesize this compound despite moderately severe hypophosphatemia. The lowest average serum phosphorus concentration in those treated without phosphate was 2.2 ± 0.3 mg/dL, whereas in patients treated with phosphate, the lowest average value was 3.6 ± 0.4 mg/dL. Of the 12 patients not receiving phosphate treatment, only three had serum phosphorus levels below 2.0 mg/dL, and these were 1.5, 1.2, and 1.7 mg/dL.

Wilson and his associates (127) have examined the effects of phosphate treatment in 44 patients with DKA. They were unable to show any evidence of clinical benefit in terms of duaration of DKA, dose of insulin required to correct the acidosis, abnormal muscle enzymes, glucose disappearance, morbidity, or mortality.

As indicated previously, acute hypophosphatemia does not ordinarily produce severe complications unless serum levels fall below 1.5 mg/dL. Most patients with diabetic ketoacidosis give a history of loss of diabetic control for a period of only 2 to 5 days before they seek treatment. Such patients nearly always display hyperphosphatemia at the time of admission to the hospital.

Rarely, patients with diabetic ketoacidosis will develop serum phosphorus values below 1.0 mg/dL during treatment, and although specific studies on such a group have not been reported, it would seem likely that serious effects could well occur. Sometimes, patients whose diabetic keotacidosis has been long standing and especially severe will show hypophosphatemia on admission despite severe acidosis. Such patients are usually hypokalemic as well. These two findings doubtless indicate severe, simultaneous deficiencies of phosphorus and potassium, and almost certainly, both need to be replaced.

Based on the foregoing, current evidence suggests that phosphate replacement is probably not necessary in the majority of patients with DKA, especially those whose illness has been of short duration and moderate in severity. This contention appears to be strongly supported by the data of Kono and his associates (72) who showed that correction of intermediary glycolytic abnormalities in DKA occurred promptly by correcting acidosis without phosphate therapy. In all patients with ketoacidosis, serum phosphorus should be measured every 12 hr during the acute illness. If it falls below 1.0 mg/dL, replacement therapy should be initiated.

General Therapeutic Considerations

The general principles of management for phosphorus deficiency and hypophosphatemia are similar to those for deficiency of many other ions or minerals. First, if an individual can tolerate oral administration of the supplement, it should be administered by this route. Milk is an excellent source of phosphorus as well as potassium and calcium. Its phosphorus content is approximately 33 mmol/qt. Many patients with severe phosphorus deficiency cannot tolerate milk because of its content of lactose or fat. Skim milk may be tolerable, but in the event it is not , one might attempt administration of Fleet's enema solution orally, which is buffered sodium phosphate. The dose is 15-30 cc three or four times daily. In the presence of phosphorus deficiency and otherwise normal intestinal function, the capacity for phosphate absorption may be enhanced so that the usual diarrhea with administration of sodium phosphate salts does not occur.

In most instances of severe hypophosphatemia, it is necessary to administer phosphate salts intravenously. One should select an intravenous preparation and become acquainted with its composition. Commercial preparations are readily available. Some of these are shown in Table VIII.

TABLE VIII PHOSPHATE PREPARATIONS FOR INTRAVENOUS USE

Preparation	Composition (mg/ml)	Phospate (mmol/ml)	Sodium (mEq/ml)	Potassium (mEq/ml)
K phosphate	236 mg K_2HPO_4 224 mg KH_2PO_4	3.0	0	4.4
Na phosphate	142 mg Na_2HPO_4 276 mg $NaH_2PO_4H_2O$	3.0	4.0	0
Neutral Na phosphate	10.0 mg Na_2HPO_4 2.7 mg $NaH_2PO_4.H_2O$	0.09	0.2	0
Neutral Na, K phosphate	11.5 mg Na_2HPO_4 2.6 mg KH_2PO_4	1.10	0.2	0.02

Ideally, the compound should be given in a quantity that will not produce hyperphosphatemia. Hypocalcemia and metastatic calcifications are distinct hazards incident to intravenous phosphate salts (128). Infusion of phosphate salts will lower ionized calcium if the product of calcium and phosphorus exceeds 2.4 - 2.5 X 10^{-6} mM (58 mg/dL). Infusion of 1.8 mmol PO_4/kg body weight into normal subjects produces a fall of serum calcium that averages 0.18 mmol/liter (-0.7 mg/dL). In one patient with hypoparathyroidism, 1.3 mmol PO_4/kg body weight reduced serum calcium from 2.1 to 1.8 mM (-1.2 mg/dL). If serum calcium is low before administration of PO_4 salts, an appreciable fall of serum calcium would not be anticipated if the solubility product were not exceeded. In healthy subjects, a fall of calcium produced by PO_4 infusion would be in part corrected by release of parathyroid hrmone. However, if a patient also has severe hypomagnesemia, release of parathyroid hormone would be suppressed (129) and, in turn, hypocalcemia could conceivably become more severe and prolonged. Alkalosis could potentiate the tendency for $CaHPO_4$ formation and thereby enhance hypocalcemia.

Patients being treated for diabetic ketoacidosis, alcoholics in withdrawal, and patients with steatorrhea often have hypophosphatemia, hypomagnesemia, hypocalcemia, and hypokalemia. In such patients, electrolyte replacement solutions should include phosphate, magnesium, and potassium. However, lest the conclusion be made that it might be best to avoid phosphate altogether, the natural course of diabetic ketoacidosis should be considered.

Without phosphate treatment, adults treated for diabetic ketoacidosis may become hypocalcemic (73%) or hypomagnesemic (55%) (130). In a study of nine children with diabetic ketoacidosis given phosphate salts, five became hypocalcemic (131). In the latter study, hypomagnesemia was present in each

patient but fell below 1 mEq/Liter in only one. The dose of phosphate in those children who had the most severe hypocalcemia was greater than 11 mmol/kg per 24 hr. Serum phosphorus was also high. A 9-year-old child with diabetic ketoacidosis has been described by Winter (132) who developed hypocalcemia and hypomagnesemia after administration of more than 5 mmol phosphorus/kg body weight in 29 hr. Administration of intravenous phosphate in adults with diabetic ketoacidosis in doses ranging from 15 to 45 mmol during the first 10 hr of treatment did not result in a significantly greater depression of serum calcium in those receiving phosphate than in those who did not. Keller and Berger (71) infused from 40 to 130 mmol PO_4 into adult patients with diabetic ketoacidosis. The average serum calcium concentration fell from 9.4 to 8.3 mg/dL in those not treated with PO_4 and from 8.7 to 7.8 in those who were treated with PO_4. Based on such data, hypocalcemia occurs in the majority of patients during treatment of diabetic ketoacidosis whether phosphorus is given or not. Nonetheless, if large doses of phosphorus are given, hypocalcemia can be seriously aggravated.

In treating adult patients with hypophosphatemia, a rule of thumb that continues to be successful in our hands has been to administer approximately 20 mmol of sodium or potassium phosphate intravenously each 8 hr. Using this formula, the total daily dose is less than 1 mmol/kg body weight. This amount has generally been adequate to maintain serum phosphorus levels at or above 1.5 mg/dL. This concentration appears to prevent most of the severe consequences of hypophosphatemia and should not cause precipitation of calcium phosphate in tissues.

In treating the complex electrolyte derangements described above in the patient with alcohol withdrawal, it is practical to administer phosphorus, magnesium, and potassium in the same solution. For example, we have employed solutions composed of 1 liter of 5% glucose in 0.45% saline to which has been added 20 mmol of potassium phosphate, 20 mEq of potassium chloride, and 4.0 ml of 50% magnesium sulfate (16 mEq of magnesium). This quantity is infused over 8 hr. We have infused this mixture three times daily for several days in many patients with successful results. The three electrolytes are compatible in solution. Used in such quantities, we have not encountered severe hypocalcemia. Obviously, intravenous phosphorus should not be administered in the presence of hyperphosphatemia.

REFERENCES

1. Carothers, J.E., Kurtz, N.M., and Lemann, J., Jr.: Error Introduced by Specimen Handling Before Determination of Inorganic Phosphate Concentrations in Plasma and Serum. Clin. Chem. 22(11):1909-1912, 1976.

2. Donhowe, J.M., Freier, E.F., Wong, E.T., and Steffeos, M.W.: Factitious hypophosphatemia related to mannitol therapy. Clin. Chem. 27:1765-1769, 1981.

3. Levenson, S.M., Adams, M.A., Rosen, H., and Taylor, F.H.L.: Studies in phosphorus metabolism in man. III. The distribution, exchange and excretion of phosphorus in man using radioactive phosphorus (P-32) as a tracer. J. Clin. Invest. 32:497-509, 1953.

4. Ingwald, J.S.: Phosphorus nuclear magnetic resonance spectroscopy of cardiac and skeletal muscles. Am. J. Physiol. 242:H729-H744, 1982.

5. Kula, R.W., Brumback, R.A., Engle, W.K., and Line, B.R.: Ischemic contracture in muscle phosphorylase deficiency. Clinical scanning and histochemical and autoradiographic studies. Neurology 27:401-402, 1977.

6. Ross, B.D., Radda, G.K., Gadian, D.G., Rocker, G., Esiri, M., and Falconer-Smith, J: Examination of a case of suspected McArdle's Syndrome by ^{31}P nuclear magnetic resonance. N. Engl. J. Med. 304:1338-1342, 1981.

7. Hultman, E.: Studies on muscle metabolism of glycogen and active phosphate in man with special reference to exercise and diet. Scand. J. Clin. Lab. Invest. 19:Suppl. 94:1-63, 1967.

8. Jacobus, W.E., Taylor, G.J., IV, Hollis, D.P., and Nunnally, R.L.: Phosphorus nuclear magnetic resonance of perfused working rat hearts. Nature 265:756-758, 1977.

9. Haussler, M.R., and McCain, T.A.: Basic and Clinical Concepts Related to Vitamin D Metabolism and Action. New Engl. J. Med. 297:974-1050, 1977.

10. Schneider, L.E., Schedl, H.P., McCain, T., and Haussler, M.R.: Experimental Diabetes Reduces Circulating 1, 25-Dihydroxyvitamin D in the Rat. Science 196:1452-1454, 1977.

11. Lee, S.W., Russell, J., and Avioli, L.V.: 25-Hydroxycholecalciferol to 1,25-Dihydroxycholecalciferol: Conversion Impaired by Systemic Metabolic Acidosis. Science 195:994-996, 1977.

12. Fuchs, R., and Peterlik, M.: Intestinal Phosphate Transport. Adv. Exp. Biol. Med. 128:381-390, 1979.

13. Vianna, M.J.: Severe hypophosphatemia due to hypokalemia. JAMA 215:1497-1498, 1971.

14. Hillman, R.W.: Dextrose, Insulin and Epinephrine Tolerance Tests in Cirrhosis of the Liver. Am. J. Dig. Dis. 16:174-179, 1949.

15. Rasmussen, H., and Reifenstein, E.C., Jr.: Williams, R.H. (editor) Textbook of Endocrinolgy. Third Edition, W.B. Saunders Co., Philadelphia, 1962, p. 798.

16. Olgaard, K., Madsen, S., Lund, B., and Sorenson, O.H.: Pathogenesis of hypophosphatemia in kidney neurograft recipients: a controlled total. Adv. Exp. Biol. Med. 128:255-261, 1979.

17. Levy, L.A.: Severe Hypophosphatemia as a Complication of the Treatment of Hypothermia. Arch. Intern. Med. 140:128-129, 1980.

18. Walaas, O., Walaas, E., and Wick, A.N.: The Stimulatory Effect by Insulin on the Incorporation of ^{32}P Radioactive Inorganic Phosphate into Intracellular Inorganic Phosphate, Adenine Nucleotides and Guanine Nucleotides of the Intact Isolated Rat Diaphragm. Diabetologia 5:79-87, 1969.

19. Forsham, P.H., and Thorn, G.W.: Changes in inorganic serum phosphorus during the intravenous glucose tolerance test as an adjunct to the diagnosis of early diabetes mellitus. Proc. Amer. Diabetes Assoc. 9:101-122, 1949.

20. Danowski, T.S., Gillespie, H.K., Fergus, E.B., and Puntereri, A.J.: Significance of blood sugar and serum electrolyte changes in cirrhosis following glucose, insulin, glucagon, or epinephrine. Yale J. Biol. Med. 29:361-375, 1956-1957.

21. Corredor, D.G., Sabeh, G., Mendelsohn, L.D., Wasserman, R.E., Sumder, J.H., and Danowski, T.S.: Enhanced post glucose hypophosphatemia during starvation therapy of obesity. Metabolism 18:754-763, 1969.

22. Danowski, T.S., Gillespie, H.K., Egren, T.J., Mateer, F.M., and Leinberger, M.H.: Muscular dystrophy. V. Blood sugar and serum electrolytes following insulin and dextrose, alone or in combination. Am. J. Dis. Child. 91:429, 1956.

23. Hillman, R.W.: Dextrose, Insulin and Epinephrine Tolerance Tests in Cirrhosis of the Liver. Am. J. Dig. Dis. 16:174-179, 1949.

24. Farber, E.: ATP and cell integrity. Fed. Proc. 32:1534-1539, 1973.

25. Stein, J.H., Smith, W.O., and Ginn, H.E.: Hypophosphatemia in acute alcoholism. Am. J. Med. Sci. 252:78-83, 1966.

26. Ryback, R.S., Eckardt, M.H., and Pautler, C.P.: Clinical Relationships Between Serum Phosphorus and Other Blood Chemistry Values in Alcoholics. Arch. Intern. Med. 140:673-677, 1980.

27. Knochel, J.P.: Hypophosphatemia in the Alcoholic. Arch. Intern. Med. 140:613-615, 1980.

28. Miller, P.D., Heinig, R.E., and Waterhouse, C.: Treatment of Alcoholic Acidosis: The Role of Dextrose and Phosphorus. Arch. Intern. Med. 138:67-72, 1978.

29. Anderson, R., Cohen, M., Haller, R., Elms, J., Carter, N.W., and Knochel, J.P.: Skeletal Muscle Phosphorus and Magnesium Deficiency in Alcoholic Myopathy. Mineral and Electrolyte Metab. 4:106-112, 1980.

30. Montanari, A., Borghi, L., Curti, A., Canali, M., Mergoni, M., Zuccoli, P., Novarini, A., and Borghetti, A.: Acute hypophosphatemia during total parenteral nutrition in man: Its effect on muscle cell composition. Adv. Exp. Med. Biol. 151:229-238, 1982.

31. Blachley, J.D., Ferguson, E.R., Carter, N.W., and Knochel, J.P.: Chronic Alcohol Ingestion Induces Phosphrous Deficiency and Myopathy in the Dog. Trans. Assoc. Amer. Phys. Vol. XCIII:110-122, 1980.

32. Ferguson, E.R., Blachley, J.D., and Knochel, J.P.: Skeletal Muscle Ionic Composition and Sodium Transport Activity in Chronic Alcoholism. Trans. Assoc. Amer. Phys. Vol. XCIV:61-72, 1981.

33. Lotz, M., Zisman, E., and Bartter, F.C.: Evidence for a phosphorus depletion syndrome in man. New Engl. J. Med. 278:409, 1968.

34. Wacker, W.E.C.: Magnesium/Calcium Balances and Steady States of Biological Systems. J. Theoret. Biol. 20:65-78, 1968.

35. Lennquist, S., Lindell, B., Nordstrom, H., and Sjoberg, H.E.: Hypophosphatemia in severe burns. A prospective study. Acta. Chir. Scand. 145:1-6, 1979.

36. Knochel, J.P.: The Pathophysiology and Clinical Characteristics of Severe Hypophosphatemia. Arch. Intern. Med. 137:203-220, 1977.

37. Mostellar, M.E., and Tuttle, E.P., Jr.: The effects of alkalosis on plasma concentration and urinary excretion of inorganic phosphate in man. J. Clin. Invest. 43:138-149, 1964.

38. Knochel, J.P., Haller, R., and Ferguson, E.: Selective Phosphorus Deficiency in the Hyperalimented Hypophosphatemic Dog and Phosphorylation Potentials in the Muscle Cell. Shaul G. Massry, Eberhard Ritz and Henri Jahn, Editors, Volume 128, pp. 323-334, Advances in Experimental Medicine and Biology, Phosphate and Minerals in Health and Disease, Plenum Press, 1980.

38a. Woods, H.F., Eggleston, L.V., and Krebs, H.A.: The Cause of Hepatic Accumulation of Fructose 1-Phosphate on Fructose Loading. Biochem. J. 119:501-510, 1970.

38b. Bode, J.C., Zelder, O., Rumpelt, H.J., and Wittkamp, U.: Depletion of Liver Adenosine Phosphates and Metabolic Effects of Intravenous Infusion of Fructose or Sorbitol in Man and in the Rat. Europ. J. Clin. Invest. 3:436-441, 1973.

38c. Sestoft, L., and Gammeltoft, A.: The Effect of Intravenous Xylitol on the Concentration of Adenine Nucleotides in Human Liver. Biochem. Pharmacol. 25:2619-2621, 1976.

39. Brautbar, N., Leibovici, H., and Massry, S.G.: On the Mechanism of Hypophosphatemia during Acute Hyperventilation: Evidence for Increased Muscle Glycolysis. Mineral Electrolyte Metab. 9:45-50, 1983.

40. Hill, G.L., Guinn, E.J., and Dudrick, S.J.: Phosphorus distribution in hyperalimentation induced hypophosphatmia. J. Surgical Research 20:527-531, 1976.

41. Derr, R.F., and Zieve, L.: Weakness, neuropathy, and coma following total parenteral nutrition in underfed or starved rats: relationship to blood hyperosmolarity and brain water loss. J. Lab. Clin. Med. 92:521-528, 1978.

42. Derr, R., and Zieve, L.: Intracellular Distribution of Phosphate in the Underfed Rat Developing Weakness and Coma Following Total Parenteral Nutrition. J. Nutr. 106:1398-1403, 1976.

43. Knochel, J.P, Barcenas, C., Cotton, J.R., Fuller, T.J., Haller, R., and Carter, N.W.: Hypophosphatemia and Rhabdomyolysis. J. Clin. Invest. 62:1240-1246, 1978.

44. Knochel, J.P., Bilbrey, G.L., Fuller, T.J., and Carter, N.W.: The Muscle Cell in Chronic Alcoholism: The Possible Role of Phosphate Depletion in Alcoholic Myopathy. Ann. N.Y. Acad. Sci. 252:274-286, 1975.

45. Rainey, R.L., Estes, P.W., Neely, C.L., and Amick, L.D.: Myoglobinuria Following Diabetic Acidosis. Arch. Intern. Med. 111:564-571, 1963.

46. Ravid, M., and Robson, M.: Proximal myopathy caused by catrogenic phosphate depletion. JAMA 236:1380, 1976.

47. Chudley, A., Ninan, A., and Young, G.B.: Neurologic signs and hypophosphatemia with total parenteral nutrition. CMA Journal 125:604-607, 1981.

48. Fuller, T.J., Nichols, W.W., Brenner, B.J., and Peterson, J.C.: Reversible Depression in Myocardial Performance in Dogs with Experimental Phosphorus Deficiency. J. Clin. Invest. 62:1194-1200, 1978.

49. Veech, R.L., Lawson, W.R., Cornell, N.W., et al: Cytosolic phosphorylation potential. J. Biol. Chemist 254:6538-6547, 1979.

50. Kreusser, W.J., Kurokawa, K., Aznar, E., and Massry, S.G.: Phosphate depletion. Effect on renal inorganic phosphorus and adenine nucleotides, urinary phosphate and calcium, and calcium balance. Mineral Electrolyte Metab. 1:30-42, 1978.

51. Fuller, T.J.: Unreported observations.

52. Knochel, J.P.: Neuromuscular Manifestations of Electrolyte Disorders. Am. J. Med. 72:521-535, 1982.

53. Ross, B.K., and Hlastala, M.P.: Increased hemoglobin-oxygen affinity does not decrease skeletal muscle oxygen consumption. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51(4):864-870, 1981.

54. Knochel, J.P.: Models of Hypophosphatemia and Phosphate Depletion. Adv. Exp. Biol. Med. 151:191-198, 1982.

55. Kretz, J., Sommer, G., Boland, R., Kreusser, W., Hasselbach, W., and Ritz, E.: Lack of involvement of sarcoplasmic reticulum in myopathy and acute phosphorus depletion. Klin. Wochenschr. 58:833-837, 1980.

56. Knochel, J.P., and Schlein, E.M.: On the Mechanism of Rhabdomyolysis in Potassium Depletion. J. Clin. Invest. 51:1750-1758, 1972.

57. Cronin, R.E., Ferguson, E.R., Shannon, W.A., Jr., and Knochel, J.P.: Skeletal muscle injury after magnesium depletion in the dog. Am. J. Physiol. 243:F113-120, 1982.

58. Guest, G.M., and Rapoport, S.: Rose of acid-soluble phosphorus compounds in red blood cells. Am. J. Dis. Child. 58:1072-1089, 1939.

59. Benesch, R., and Benesch, R.E.: Intracellular organic phosphates as regulators of oxygen release by hemoglobin. Biochem. Biophys. Research Communications. 26:162, 1967.

60. Lenfant, C., Torrance, J.F., Woodson, R.D. et al: Role of organic phosphates in the adaptation of man to hypoxia. Fed. Proc. 29:1115-1117, 1970.

61. Travis, S.F., Sugerman, H.J., Ruberg, R.L., Dudrick, S.J., Delivoria-Papadopoulos, M., Miller, L.D., and Oski, F.A.: Alterations of red cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. New Engl. J. Med. 285:763-768, 1971.

62. Rapoport, S. Dietz, F., and Sauer, G.: Quantitative aspekte des phosphoglyceratzyklus in roten Blutzellen. Act. Biol. Med. Germ. 13:693-702, 1964.

63. Astrup, P.: Relationship of pH to red cell 2,3-DPG content. Adv. Expt. Med. & Biol. 6:67, 1970.

64. Ditzel, J.: Impaired oxygen release caused by alterations of the metabolism in the erythrocytes in diabetes. Lancet 1:721-723, 1972.

65. Ditzel, J.: Importance of plasma inorganic phosphate on tissue oxygenation during recovery from diabetic ketoacidosis. Hormone & Metab. Res. 5:471-472, 1973.

66. Ditzel, J.: The effect of plasma inorganic phosphate on tissue oxygenation during recovery from diabetic ketoacidosis. Printed in "Oxygen Transport to Tissue" Edited by Dicher, H.I., Bruley, D.F. Plenum Publishing Corp. New York, 1973.

67. Haldane, J.B.S., Wigglesworth, D.B., and Woodrow, C.E.: The effect of reaction changes on human inorganic metabolism. Proc. Roy. Soc. B. 96:1, 1924.

68. Bolger, H.A., and Peters, J.P.: The concentration of the blood and of the urine in diabetic toxemia. Arch. Intern. Med. 36:857-873, 1925.

69. Guest, G.M., and Rapoport, S.: Rose of acid-soluble phosphorus compounds in the red blood cells. Am. J. Dis. Child. 58:1072-1089, 1939.

70. Seldin, D.W., and Tarail, R.: The metabolism of glucose and electrolytes in diabetic acidosis. J. Clin. Invest. 29:552, 1950.

71. Keller, U., and Berger, W.: Prevention of Hypophosphatemia by Phosphate Infusion During Treatment of Diabetic Ketoacidosis and Hyperosmolar Coma. Diabetes 29:87-95, 1980.

72. Kono, N., Kuwajima, M., and Tarui, S.: Alteration of Glycolytic Intermediary Metabolism in Erythrocytes During Diabetic Ketoacidosis and Its Recovery Phase. Diabetes 30:346-353, 1981.

73. Lichtman, M.A., Miller, D.R., Cohen, J., and Waterhouse, C.: Reduced red cell glycolysis, 2,3-diphosphoglycerate and adenosine triphosphate concentration, and increased hemoglobin oxygen affinity caused by hypophosphatemia. Ann. Intern. Med. 74:562-568, 1971.

74. Travis, S.F., Sugerman, H.J., Ruberg, R.L., Dudrick, S.J., Delivoria-Papadopoulos, M., Miller, L.D., and Oski, F.A.: Alterations of red cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. New Engl. J. Med. 285:763-768, 1971.

75. Jacob, H.S., and Amsden, P.: Acute hemolytic anemia with rigid red cells in hypo-phosphatemia. New Engl. J. Med. 285:1446, 1971.

76. Nakao, K., Wada, T., and Kamiyana, T.: A direct relationship of adenosine triphosphate level and in vivo viability of erythrocytes. Nature (London) 194:877-878, 1962.

77. Rubin, E., and Rottenberg, H.: Ethanol-induced injury and adaptation in biologic membranes. Fed. Proceedings 41:2465-2471, 1982.

78. Yawata, Y., Hebbel, R.P., Silvis, S., Howe, R., and Jacob, H.: Blood cell abnormalities complicating the hypophosphatemia of hyperalimentation: erythrocyte and platelet ATP deficiency associated with hemolytic anemia and bleeding in hyperalimented dogs. J. Lab. Clin. Med. 84:643-653, 1974.

79. Sarg, M.J., Jr., and Pitchumoni, C.S.: Case Report: Hypophosphatemic hemolytic syndrome of alcoholics - a common city hospital problem. Am. J. Med. Sci. 276:231-235, 1978.

80. Laiken, S., Beck, C.H., and Timms, R.M.: Acute Renal Failure Associated With Hemodialysis and Hypophosphatemia. Western J. Med. 128:343-345, 1978.

81. Ben-Isaac, C., Massry, S.G., Rosenfeld, S., Kleeman, C.R., and Bick, M.: Evidence for humoral factor responsible for the hypercalcuria of phosphate depletion. Proc. Am. Soc. Clin. Invest. 5a, 1974.

82. Dominguez, J.H., Gray, R.W., and Lemann, J., Jr.: Dietary Phosphate Deprivation in Women and Men: Effects on Mineral and Acid Balances, Parathyroid Hormone and the Metabolism of 25-OH-Vitamin D. J. Clin. Endocrinol. Metab. 43:1056-1068, 1976.

83. Kruessser, W., and Ritz, E.: The Phosphate Depletion Syndrome. Contr. Nephrol. 14:162-174, 1978.

84. Pronove, P., Bell, N.H., and Bartter, F.C.: Production of hypercalciuria by phosphorus deprivation on a low calcium intake: a new clinical test for hyperparathyroidism. Metabolism 10:364-371, 1961.

85. Emmett, M., Goldfarb, S., Agus, Z.S., et al: The pathophysiology of acid-base changes in chronically phosphate-depleted rats. J. Clin. Invest. 59:291-298, 1977.

86. Raisz, L.G., and Niemann, I.: Effect of phosphate, calcium and magnesium on bone resorption and hormonal responses in tissue culture. Endocrinoloy 85:446-452, 1969.

87. Baylink, D., Werdegal, J., and Stauffer, M.: Formation, mineralization and resorption of bone in hyperphosphatemic rat. J. Clin. Invest. 50:2519-2530, 1971.

88. Cuisinier-Gleizes, P., Thomasset, M., Sainteny-Debove, F., and Mathieu, H.: Phosphorus deficiency, parathyroid hormone, and bone resorption in the growing rat. Calcif. Tiss. Res. 20:235-249, 1976.

89. Mashima, Y., Ogawa, M., Aoki, Y., Ichiki, M., and Swann, D.K.: Changes in phosphorus distribution during total parenteral nutrition. J. Par. Ent. Nutr. 5:189-192, 1981.

90. deVernejoul, M.C., Marie, P., Kuntz, D., Gueris, J., Miravet, L., and Ryckewaert, A.: Nonosteomalacic osteopathy associated with chronic hypophosphatemia. Calcif. Tissue Int. 34:219-223, 1982.

91. Cooke, N., Teitelbaum, S., and Avioli, L.V.: Antacid-induced osteomalacia and nephrolithiasis. Arch. Intern. Med. 138:1007-1009, 1978.

92. Harrison, J.E., Hitchman, A.J., Hitchman, A., Hasany, S.A., McNeill, K.G., and Tam, C.S.: Differences between the effects of phosphate deficiency and vitamin D deficiency on bone metabolism. Metabolism 29:1225-1233, 1980.

93. Parker, M.S., Klein, I., Haussler, M.R., and Mintz, D.H.: Tumor-Induced Osteomalacia: Evidence of a Surgically Correctable Alteration in Vitamin D Metabolism. JAMA 245:492-493, 1981.

94. Sweet, R.A., Males, J.L., Hamstra, A.J., and DeLuca, H.F.: Vitamin D metabolite levels in oncogenic osteomalacia. Ann. Intern. Med. 93:279, 1980.

95. Compston, J.E., Laker, M.F., Woodhead, J.S., Gazet, J.C., Horton, L.W.L., Ayers, A.B., Bull, H.J., and Pilkington, T.R.E.: Bone Disease After Jejuno-Ileal Bypass for Obesity. Lancet 2(1):1-4, 1978.

96. Fauley, G.B., Freeman, S., Ivy, A.C., Atkinson, A.J., and Wigodsky, H.S.: Aluminum phosphate in the therapy of peptic ulcer. Effect of aluminum hydroxide on phosphate absorption. Arch. Intern. Med. 67:563-578, 1941.

97. Freeman, S., and Freeman, W.M.C.: Phosphorus retention in children with chronic renal insufficiency. Am. J. Dis. Child. 61:981-1002, 1941.

98. Kirsner, J.B.: Effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in man. J. Clin. Invest. 22:47-52, 1943.

99. Shorr, E., and Carter, A.C.: Aluminum gels in the management of renal phosphate calculi. JAMA 144:1543-1556, 1950.

100. Spencer, H., Kramer, L., Norris, C., and Osis, D.: Effect of small doses of aluminum-containing antacids on calcium and phosphorus metabolism. Am. J. Clin. Nutr. 36:32-40, 1982.

101. Spencer, H., and Kramer, L.: Antacid-Induced Calcium Loss. Arch. Intern. Med. 143:657-659, 1983.

102. Gold, L.W., Massry, S.G., Arieff, A.I., and Coburn, J.W.: Renal Bicarbonate Wasting During Phosphate Depletion: A Possible Cause of Altered Acid-Base Homeostasis in Hyperparathyroidism. J. Clin. Invest. 52:2556-2562, 1973.

103. Kohaut, E.C., Klish, W.J., Beachler, C.W., and Hill, L.L.: Reduced renal acid excretion in malnutrition: A result of phosphate depletion. Am. J. Clin. Nutr. 30:861, 1977.

104. Steele, T.H.: Impaired bicarbonate reabsorption in the phosphate-depleted rat. Mineral Electrolyte Metab. 2:74-80, 1979.

105. Schmidt, R.W.: Effects of phosphate depletion on acid-base status in dogs. Metabolism 27:943-952, 1978.

106. Aruda, J.A.L., Julka, N.K., Rubinstein, H., Sabatani, S., and Kurtzman, N.A.: Distal Acidification Defect Induced by Phosphate Deprivation. Metabolism 29:826-836, 1980.

107. Biltz, R.M., Pellegrino, E.D., and Letteri, J.M.: Skeletal carbonates and acid-base regulation. Mineral and Electrolyte Metab. 5:1-7, 1981.

108. Silvis, S.E., and Paragas, P.D.: Paresthesias, weakness, seizures and hypophosphatemia in pateints receiving hyperalimentation. J. Lab. Clin. Med. 62:513-520, 1972.

109. Silvis, S.E., DiBartolomeo, A.G., and Aaker, H.M.: Hypophosphatemia and Neurological Changes Secondary to Oral Caloric Intake. Am. J. Gastroenterology 73:215-222, 1980.

110. Yawata, Y., Craddock, P., Hebbel, R., Howe, R., Silvis, S., and Jacob, H.: Hyperalimentation Hypophosphatemia: Hematologicneurologic dysfunction due to ATP depletion. Clin. Res. 31:729, 1973.

111. Silvis, S.E., and Paragas, P.V., Jr.: Fatal hyperalimentation syndrome. Animal studies. J. Lab. Clin. Med. 78:918-930, 1971.

112. Ritz, E.: Acute hypophosphatemia. Kidney Intern. 22:84-94, 1982.

113. Lee, K.L., Sibbald, W.J., Holliday, R.L., and Linton, A.L.: Hypophosphatemia associated with coma. CMA Journal 119:143-145, 1978.

114. Newman, J.H., Neff, T.A., and Ziporin, P.: Acute Respiratory Failure Associated with Hypophosphatemia. Medical Intelligence 296:1101-1103, 1977.

114a. Planas, R.F., McBrayer, R.H., and Koen, P.A.: Effects of hypophosphatemia on pulmonary muscle performance. Adv. Exp. Med. Biol. 151:283-290, 1982.

115. O'Connor, L.R., Klein, K.L., and Bethune, J.E.: Effect of hypophosphatemia on myocardial performance in man. N. Engl. J. Med. 297:901, 1977.

116. Darsee, J.R., and Nutter, D.O.: Reversible severe congestive cardiomyopathy in three cases of hypophosphatemia. Ann. Intern. Med. 89:867-870, 1978.

117. Fuller, T.J., Nichols, W.W., Brenner, B.J., et al: Reversible depression in myocardial performance in dogs with experimental phosphorus deficiency. J. Clin. Invest. 62:1194, 1978.

118. Fuller, T.J., Nichols, W.W., Brenner, B.J., and Peterson, J.C.: Effects of phosphorus depletion on left ventricular energy generation. Adv. Exp. Biol. Med. 103:395-400, 1977.

119. Brautbar, N., Baczynski, R., Carpenter, C., Moser, S., Geiger, P., Finander, P., and Massry, S.G.: Impaired energy metabolism in rat myocardium during phosphate depletion. Am. J. Physiol. 242:F699-F704, 1982.

120. Keyes, A., Brozek, J., Henschel, A., Mickelsen, O., and Taylor, H.C.: The Biology of Human Starvation. Vol. I. University of Minnesota Press, 1950, pp. 206-207.

121. Weinsier, R.L., and Krumdieck, C.L.: Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am. J. Clin. Nutr. 34:393-399, 1980.

122. Heird, W.C., MacMillan, R.W., and Winters, R.W.: Total parenteral nutrition in the pediatric patient; in Total Parenteral Nutrition, J.E. Fischer, Ed., Little Brown and Co., pp. 277-278.

123. Josephus: The Jewish War. Translated by Williamson, G.A. and Harmondsworth U.K., Penguin Books, 1959, p. 300.

124. Smith, G.S., Smith, J.L., Maneesh, M.S., Simon, J., and Johnson, B.C.: Hypertension and cardiovascular abnormalities in starved-refed swine. J. Nutr. 82:173-182, 1964.

125. Ryan, J.A., Jr.: Complications of Total Parenteral Nutrition. In Total Parenteral Nutrition, J.E. Fischer, Ed., Little Brown and Co., p.93.

126. Morris, R.C., Jr., Nigon, K., and Reed, E.B.: Evidence that the Severity of Depletion of Inorganic Phosphate Determines the Severity of the Disturbance of Adenine Nucleotide Metabolism in the Liver and Renal Cortex of the Fructose-Loaded Rat. J. Clin. Invest. 61:209-220, 1978.

127. Wilson, H.K., Kever, S.P., Lea, A.S., Boyd, A.E., and Eknoyan, G.: Phosphate therapy in diabetic ketoacidosis. Arch. Intern. Med. 142:517-520, 1982.

128. Hebert, L.A., Lemann, J., Peterson, J.R., et al: Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. J. Clin. Invest. 45:1886, 1966.

129. Anast, S., Winnacker, J.L., Forte, L.R, et al: Impaired release of parathyroid hormone in magnesium deficiency. J. Clin. Endocrinol. Metab. 42:707, 1976.

130. Martin, H.E., Smith, K., and Wilson, M.L.: The fluid and electrolyte therapy of severe diabetic acidosis and ketosis. Am. J. Med. 24:376-389, 1958.

131. Zipf, W.B., Bacon, G.E., Spencer, M.L., et al: Hypocalcemia, hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. Diabetes Care 2:265-268, 1979.

132. Winter, R.J., Harris, C.J., Phillip, L.S, et al: Diabetic ketoacidosis induction of hypocalcemia and hypomagnesemia by phosphate therapy. Am. J. Med. 67:897-900, 1979.