MEDICAL GRAND ROUNDS

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THE PATHOPHYSIOLOGY AND CLINICAL CHARACTERISTICS OF SEVERE HYPOPHOSPHATEMIA

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INTRODUCTION

Following a hiatus of interest spanning 25 years, hypophosphatemia has again become an important and popular topic. The major reasons underlying this resurgence are the automation of laboratory measurements showing that not only may profound depression of serum phosphorus concentration occur under a variety of circumstances, but also the increasing evidence that it may be associated with serious morbidity. In our particular setting, that is, in the patient population of the VA Hospital, profound hypophosphatemia has been found to occur with rather amazing frequency in patients being treated for severe alcoholic withdrawal and as known for forty years, we may now recall that it is commonly seen in patients recovering from severe DKA. This discussion will concern itself mainly with these two disorders.

Normal Phosphorus Metabolism

A normal 70 kg man contains approximately 23,000 millimoles of phosphorus. About 80% of this is in bone. If his muscle mass is average, that is about 30 kg, about 8% of his total phosphorus will be found in skeletal muscle. The bulk of phosphorus in skeletal muscle and viscera is inside the cell where its average concentration in cell water is 100 millimoles/L. Thus as K is the major intracellular cation, P is the major intracellular anion. The bulk of intracellular phosphorus is organic, existing as intermediary carbohydrates, lipids and proteins. A small but nevertheless critical fraction is inorganic, i.e., phosphate ions. This fraction is crucial because it is in diffusion equilibrium across the cell membrane and as such is the pool from which ATP is resynthesized (1).

Phosphorus has a variety of important biological functions. It is essential for structural integrity of all cells and all known synthetic, as well as catabolic porcesses. It regulates activity of a host of enzymes. It is involved in fuel storage and critical energy transformations. The latter include provision of fuel for transport, conservation of energy sources and maintenance of body temperature. It plays an important role in delivery of oxygen to tissues by regulating the level of 2,3-DPG and ATP in erythrocytes. It is part of an important urinary buffer system permitting excretion of fixed acids. Finally, it is critical in the defense against infectious organisms.

In children, the concentration of inorganic phosphorus in serum (the quantity normally measured by standard laboratory procedures) varies between 4.0 and 7.1 mg/dL (1.3 and 2.3 millimoles/L). In adults, the concentration in serum varies between 2.7 and 4.5 mg/dL (0.9 and 1.5 millimoles/L). In normal persons serum phosphorus is regulated within a fairly narrow range. It tends to decrease slightly after ingestion of carbohydrates or fats. During modest respiratory alkalosis, it may decline approximately 0.5 millimoles/L. In contrast, serum P may increase during states of dehydration and rise transiently after exercise.

The normal adult ingests approximately 1 g of phosphorus daily in the diet although this quantity varies widely. The variation is due to its marked abundance in all natural foodstuffs. Of the quantity absorbed,

approximately 90% is excreted into the urine and 10% into the feces. Renal excretion of phosphorus is regulated by glomerular filtration and tubular reabsorption. The latter is, in a major way, regulated by parathyroid hormone. There is also some evidence that renal tubular secretion of phosphorus might occur; however, the importance of this factor as a means to regulate total body phosphorus in man has not been determined (2). Studies on the distribution, exchange and excretion of radiophosphorus have been published by Levenson and his associates (3).

Phosphorus Deficiency

It should be clearly understood that hypophosphatemia does not necessarily indicate phosphorus depletion. In contrast, serious phosphorus depletion may exist in the presence of a normal or even elevated concentration of inorganic phosphorus in serum. These relationships will be discussed at more length subsequently.

Phosphorus is so abundant in natural foods that phosphorus deficiency in normal man almost never occurs. Several authors (4,5) studied dietary phosphorus deficiency in cattle many years ago and established firmly the role of phosphorus in growth, apparent resistance to infection and fertility. More recently, studies in normal subjects and patients with hypoparathyroidism by Lotz and Bartter (6,7) have established that selective phosphorus deficiency, induced by a deficient diet and ingestion of large quantities of phosphate binding antacids, may in time lead to a rather distinct clinical syndrome. These subjects became anorectic, weak and complained of bone pain. Symptoms appeared only when serum phosphorus concentration fell below 1.0 mg/dL. Clinical improvement occurred rapidly when phosphorus was restored to their artificial 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 the patients with hypoparathyroidism, in no case did hypercalcemia occur. The finding that phosphate virtually disappears from the urine during isolated deficiency induced by this means and the studies on experimental animals conducted by other investigators since that time (8,9) have rather clearly established that parathormone production apparently decreases.

Causes of Moderate Hypophosphatemia

Moderate depressions in the concentration of serum phosphorus are numerous (Table I).

TABLE I. CAUSES OF MODERATE HYPOPHOSPHATEMIA

Hemodialysis	Volume Expansion
Hyperparathyroidism	--Aldosteronism (Licorice)
Starvation	--Saline Infusion
Glucose Administration	--Hypokalemia
Fructose Administration	Hypomagnesemia (?)
Glycerol Administration	Gram Negative Bacteremia
Lactate Administration	(Alkalosis ?)

CAUSES OF MODERATE HYPOPHOSPHATEMIA (Continued)

$NaHCO_3$ Infusion	Insulin Administration
Osteomalacia	Gastrin Administration
Renal Tubular Defects	Glucagon Administration
Pregnancy	Epinephrine Administration
Malabsorption	Corticosteroid Administration
Vitamin D Deficiency	Diuretic Therapy
Acute Gout	Androgen Therapy
Salicylate Poisoning	Recovery From Hypothermia

The adjective "moderate" refers to concentrations of phosphorus in serum ranging between 1.0 - 2.5 mg/dL. Many of the causes of moderate hypophosphatemia do not require extensive elaboration. Of interest, hyperparathyroidism is seldom associated with phosphorus concentrations below 1.5 mg%. In starvation serum phosphorus concentration generally remains normal, but many decline to or slightly below the lower range of normal.

In a normal person, glucose administration leads to release of insulin (10-14). In turn, insulin promotes transport of both glucose and phosphorus into skeletal muscle and liver. The decline in serum phosphorus concentration under such conditions usually 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 (15). In severe disease of skeletal muscle such as muscular dystrophy, hypophosphatemia is less after glucose (16). When glucose is administered to a starving individual (17) or patients with hepatic cirrhosis, this hypophosphatemic response may be much more pronounced (18,19). In contrast to glucose, the administration of fructose may be associated with a more pronounced decline of serum phosphorus concentration, especially if administered intravenously (20). The mechanism of this response to fructose infusion is related to its unregulated uptake by the liver. In normal man, specific kinases exist in the liver which catalyze phosphorylation of glucose (glucokinase) to glucose-6-PO_4 and fructose (fructokinase) to fructose-1-PO_4. Increasing concentrations of glucose-6-PO_4 inhibit the activity of glucokinase, thereby regulating the uptake of both glucose and phosphorus. In contrast, increasing concentrations of fructose-1-PO_4 do not inhibit fructokinase. Thus, fructose phosphorylation is <u>unregulated</u> and in consequence, hypophosphatemia is more pronounced after fructose than glucose (21).

Administration of glycerol intravenously may also depress serum phosphorus concentration by means of its phosphorylation. The quantitative effect of this procedure in man has not been established.

Infusion of sodium lactate may decrease serum phosphorus concentration by three mechanisms: first, lactate is converted to glucose in the liver; second, similar to infusions of sodium bicarbonate, it may be associated with volume expansion and thereby enhance fractional phosphate excretion by the kidney; and third, it induces alkalosis. As will be discussed, induction of acute alkalosis (22) may be associated with slight increases in the rate of glycolysis and thereby promote transfer of phosphorus from

serum to the intracellular space.

Osteomalacia resulting from deficiencies of either phosphate, calcium or both may be associated with modest hypophosphatemia. Defective absorption of filtered phosphate by the renal tubule may occur under a variety of circumstances, exemplified by the Fanconi Syndrome, and certain instances of heavy metal poisoning. Pregnancy is sometimes associated with a slight decline of serum phosphorus. This has no serious implications.

Malabsorption of calcium by the intestine, as seen in patients with steatorrhea, results in a decline of ionized calcium concentration in the serum. This in turn increases production of parathormone that may decrease renal tubular reabsorption of phosphorus and lead to modest hypophosphatemia. Deficiency of vitamin D is also associated with a decline of calcium absorption by the gut and in addition, diminution in parathormone responsiveness of bone. Overproduction of parathormone occurs and hypophosphatemia may result as a consequence of phosphaturia induced by parathormone.

For uncertain reasons, acute gout has been observed in association with hypophosphatemia. Severe pain, hyperventilation and respiratory alkalosis could cause hypophosphatemia in acute gout. In some circumstances, this has followed fructose administration intravenously, which by means of lactic acidosis, liver injury and acute overproduction of uric acid has apparently produced gout. It has been well demonstrated that the rapid decline of intracellular inorganic phosphate concentration after fructose infusion may activate enzymes that are responsible for the rapid depletion of intracellular adenine nucleotides. These nucleotides are irreversibly converted into inosine and in turn, uric acid. Infusion of only 25 g of fructose may damage liver cells by this mechanism. Fructose should probably not be used intravenously, especially in patients likely to have liver disease (23-28).

Acute poisoning with salicylates may be associated with respiratory alkalosis. This may reduce serum phosphorus concentration as a consequence of stimulating intracellular glycolysis.

Acute or chronic states of extracellular fluid volume expansion may lead to increased fractional excretion of phosphorus into the urine and thereby produce modest hypophosphatemia. Reports of hypophosphatemia in patients with primary aldosteronism and in association with hypokalemia (29,30) could be at least partly related to this mechanism.

There is considerable clinical as well as experimental evidence that under certain circumstances hypomagnesemia may cause phosphaturia. Magnesium deficiency is thought to dampen the action of parathormone on bone, a process requiring a normal concentration of magnesium ions. This in turn leads to hypocalcemia. Its relationship to hypophosphatemia will be discussed in a later section.

Hypophosphatemia of modest degree is commonly found in patients with bacteremia due to gram negative organisms (31). Such bacteremia is generally associated with hyperventilation and respiratory alkalosis. In addition to hypophosphatemia, gram negative bacteremia is also commonly associated with hypokalemia, presumably the result of alkalosis.

Hypophosphatemia resulting from insulin administration has been discussed previously. Administration of glucagon may lead to hypophosphatemia and phosphaturia (32). Epinephrine administration may occasionally

lead to hypophosphatemia, perhaps by induction of hyperglycemia. Patients on modestly large doses of cortico-steroids and patients with Cushing's Syndrome are occasionally hypophosphatemic. Serum phosphorus concentration may also decline modestly as a result of either pharmacologic or osmotic diuresis. However, once the active diuretic phase has passed, serum phosphorus concentration tends to become normal or even increase by means of volume contraction.

Of interest, androgen therapy has been associated with rather sharp declines of serum phosphorus and potassium concentration in patients with catabolic illness. This effect is transient and presumably results from incorporation of phosphorus into cells.

In patients recovering from profound or prolonged hypothermia, such as that employed in open heart surgery, hypophosphatemia and/or hypokalemia may occasionally appear in association with inappropriate losses of these substances into the urine (33).

Causes of Profound Hypophosphatemia

There are seven clinical conditions in which serum phosphorus concentration may fall below 1 mg/dL. These are listed in Table II.

TABLE II. CAUSES OF SEVERE HYPOPHOSPHATEMIA

(1) Associated with Alcoholic Withdrawal
(2) Diabetes Mellitus
(3) Pharmacologic PO_4 Binding
(4) Recovery/Diuretic Phase after Severe Burns
(5) "Hyperalimentation"
(6) "Nutritional Recovery Syndrome"
(7) Severe Respiratory Alkalosis

The first two, namely alcoholism and diabetes mellitus, will be subsequently elaborated in more detail.

Pharmacologic binding of phosphorus by either aluminum hydroxide, magnesium hydroxide or aluminum carbonate gels, may be an important cause of morbidity in patients treated for peptic ulcer disease and more recently in patients with chronic renal failure. The availability of such antacids in highly concentrated form (aluminum carbonate) has increased the importance of this problem.

Patients with severe, extensive third degree burns retain large quantities of salt and water. As healing progresses, the retained salt and water are mobilized and excreted into the urine. In the wake of this diuresis, there may occur a sizable loss of phosphate with consequent hypophosphatemia. Simultaneously, they may become anabolic and phosphorus is rapidly taken up by cells. The combined effects of these two factors may rarely result in profound hypophosphatemia. Patients recovering from burns may remain unexplainably hypophosphatemic and hypouricemic for months after their initial injury.

The wide application of "hyperalimentation" by parenteral or oral routes, when administered without adequate phosphorus, is a well-known

cause of severe hypophosphatemia. Its occurrence has permitted characterization of rather distinctive clinical signs and findings. Perhaps of greatest importance, it has provided direct evidence that provision of phosphorus during hyperalimentation prevents such events from occurring.

The nutritional recovery syndrome refers to a constellation of events observed during refeeding of patients with severe and advanced protein-calorie malnutrition. Most of my information on this entity is based upon comments heard over conference tables from military physicians who were responsible for the care of prisoners-of-war released from camps in Europe, Japan or the South Pacific at the conclusion of World War II. It was their contention that overzealous refeeding of these men, especially with simple carbohydrates, was often followed by the appearance of massive edema, ascites, hydrothorax, and other findings consistent with acute congestive heart failure. Thereby, the term "nutritional recovery syndrome" originated. They were well aware of thiamine deficiency and its acute exacerbation by carbohydrate loading. In many instances, they were able to provide thiamine (Brewer's yeast) along with the carbohydrate. However, this did not consistently prevent the development of such findings or death (34). They contended that refeeding with skim milk was associated with a marked decrease in the morbidity of the refeeding syndrome. Unfortunately, measurements of chemical composition of the blood or urine of those patients was so limited because of the inadequate facilities that so commonly prevailed in that situation so as to prevent a meaningful analysis of their observations. In many respects, this syndrome can be reproduced in experimental animals (35).

Although one can never be certain, the observations made by these physicians on the treated malnourished prisoners-of-war lead to speculation that the phosphorus and perhaps potassium content of skim milk might have been highly important in the decline of the morbidity when used to treat severe protein-calorie malnutrition.

Those interested in perusing these highly interesting and shocking reports on disease and the protean nutritional disturbances observed in the P.O.W. and detention camps in Europe and the Far East during and after World War II should read references 36 through 39.

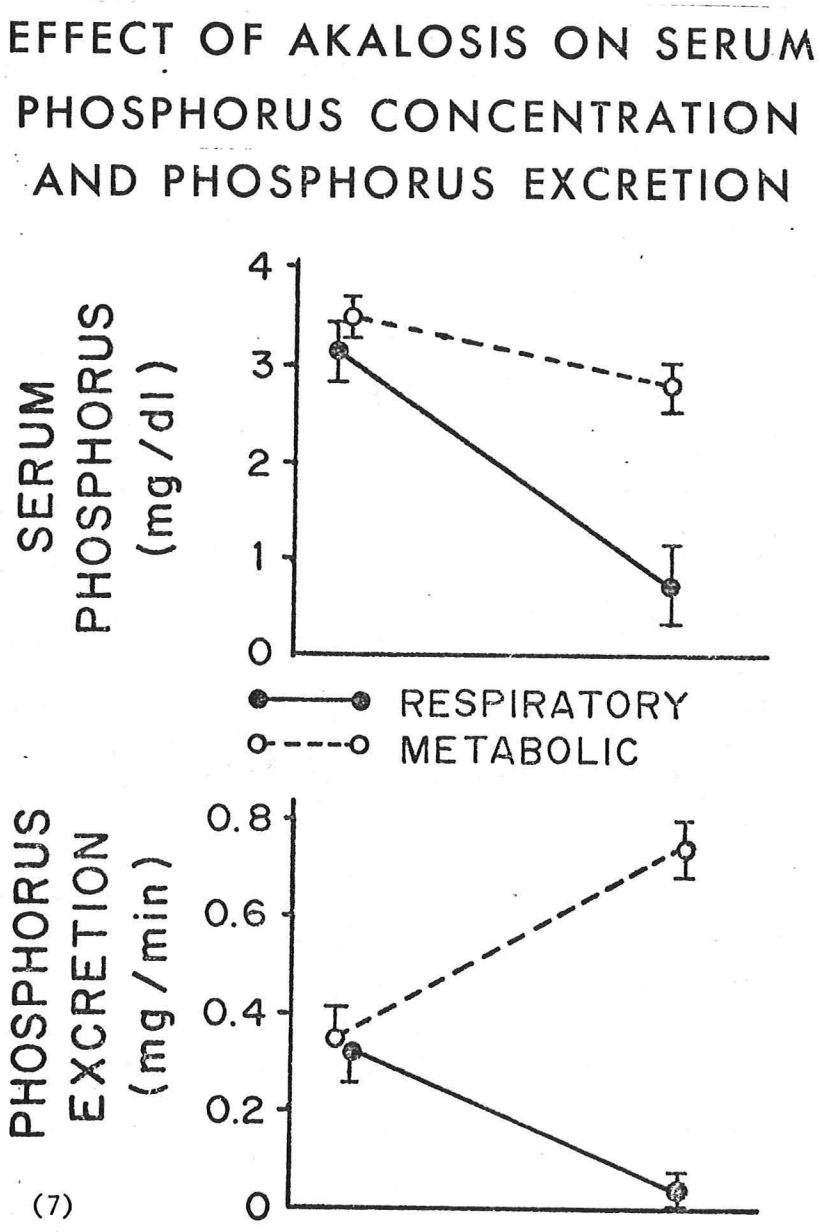
The last cause of profound hypophosphatemia listed in Table II is that associated with severe and prolonged respiratory alkalosis. Mild hyperventilation is well known to induce a slight decline of serum phosphorus concentration. However, that prolonged and intense hyperventilation may lead to a decline of serum phosphorus to values in the vicinity of 0.5 mg/dL is not widely appreciated. As will be pointed out in more detail subsequently, this could have a very important bearing on the appearance of severe hypophosphatemia in patients withdrawing from chronic alcoholism.

There are four very relevant papers concerning hypophosphatemia in patients with respiratory alkalosis. In 1924, Haldane and his co-workers (22) observed that respiratory alkalosis decreased serum phosphorus concentration. In 1946, Rapoport and his associates (40) demonstrated that arterial serum phosphorus concentration fell to values as low as 0.75 mg/dL during voluntary hyperventilation. In the third paper, Okel and Hurst (41) studied the effects of hyperventilation in normal volunteers. The first subject, one of the authors, noted that the first 30 minutes of

hyperventilation demanded expenditure of considerable effort and persistence to maintain the desired alveolar pCO_2 level. However, maintenance of hyperventilation thereafter was virtually effortless. The authors used an infrared apparatus to monitor alveolar CO_2 which was maintained in the range of 2 to 2 1/2%. This is about one-half normal. They described initial symptoms of giddiness, similar to a sensation of alcoholic inebriation. They experienced the usual tingling and numbness. The serum phosphorus measured in three of the subjects fell to values of 0.9, 1.0 and 1.7 within one to two hours. Simultaneously, serum potassium concentration in the same subjects declined only 0.7, 0.8 and 0.3 mEq/L. Magnesium concentration was not affected. The average pH increased from 7.4 to 7.71. Urinary phosphorus excretion declined to virtually undetectable levels. Perhaps of most importance in this study was their observation that once profound respiratory alkalosis was established, it could be sustained in such a subtle manner that it was hardly noticeable by the examiner.

The fourth important paper was published by Mostellar and Tuttle (42). They compared the effects of respiratory alkalosis and metabolic alkalosis on serum phosphorus concentration and phosphorus excretion into the urine. This study was done on normal volunteer subjects. Their results are shown in Figure 1.

FIGURE 1.



Serum phosphorus concentration in the subjects with respiratory alkalosis fell from a mean value of 3.1 to 0.8 mg/dL. Values as low as 0.3 mg% were observed. In contrast, elevation of arterial blood pH by infusion of sodium bicarbonate 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/dL to only 3.0 mg/dL. Their observations on urinary excretion of phosphorus are also of great interest. During respiratory alkalosis, phosphorus virtually disappears from the urine. In contrast, phosphorus excretion nearly doubled during infusion of sodium bicarbonate. The mechanism underlying these differences appears to be quite obvious. In respiratory alkalosis there is a rapid movement of CO_2 from the intracellular space because this gas is highly diffusible. The increase of intracellular pH as a conseqeunce of CO_2 removal activates glycolysis so as to increase formation of phosphorylated carbohydrate compounds within the cell. The source of phosphorus for this reaction 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.

A. Pathogenesis of Phosphate Depletion in Diabetes Mellitus

Patients with adequately controlled diabetes mellitus generally have no recognizable disturbance of phosphorus metabolism. On the other hand, those who develop glycosuria and ketonuria almost invariably lose phosphate excessively into the urine. In 1924, Haldane and his associates (22) showed convincing evidence that metabolic acidosis may cause phosphaturia. These findings were confirmed by Bolger and Peters in 1925 (43) and extended by Guest and Rapoport in 1939 (44)(Figure 2).

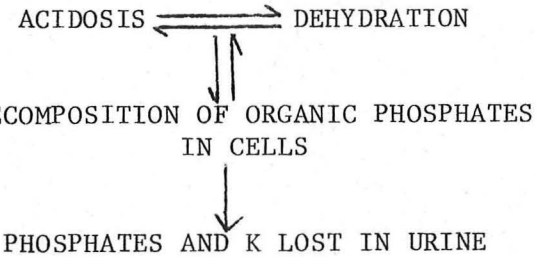


FIGURE 2.

Acidosis tends to decompose organic compounds inside the cell so that inorganic phosphate moves into the plasma and in turn, is excreted into the urine. Coexistent glycosuria and ketonuria would both tend to augment phosphaturia. Of great importance, it was shown (22,44) that return of intracellular organic phosphates to normal after a brief bout of NH_4Cl-induced metabolic acidosis required 7 - 10 days. In contrast, supplementation with phosphorus produced recovery within 24 hours. Suspecting that deficiency of phosphorus might impair glucose utilization, Friedlander (45) showed in 1926 that in patients with diabetes mellitus, utilization of glucose was improved simply by administration of phosphate intravenously without insulin. In support of this was the earlier demonstration by Haldane that glucose utilization was impaired during hyperventilation (46).

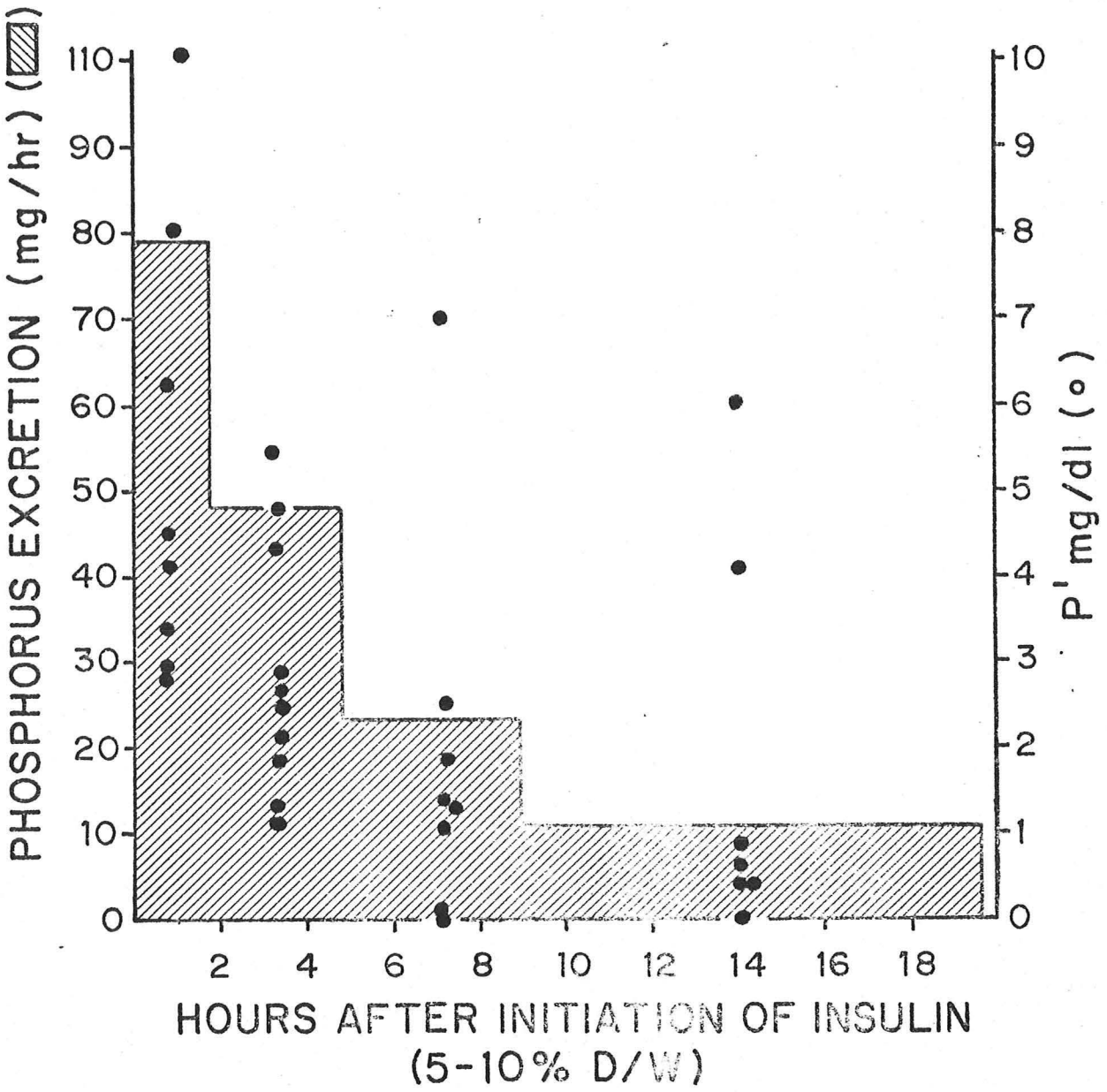
In relevant studies on experimental animals (47) with alloxan diabetes, it was shown that nitrogen excretion generally exceeded that predicted from simultaneous losses of phosphate and potassium with respect to their contents in cellular protoplasm. The excessive quantity of nitrogen was presumably derived from amino acids mobilized from skeletal muscle that were destined for conversion to glucose in the liver. Such data obtained from studies on experimental animals were verified in two clinical studies (48,49) in which patients with insulin dependent diabetes were intentionally deprived of insulin and carefully observed for several days while they developed hyperglycemia, ketonuria and ketoacidosis.

It is worth noting that serum phosphorus may be normal or slightly elevated in patients with untreated diabetic ketoacidosis. This is usually associated with excretion of large quantities of phosphorus into the urine. This was the subject of many additional studies conducted from 1920 through 1950 (47-56). The relationship between urine phosphorus excretion and changes in serum phosphorus concentration is illustrated in Figure 3 (Page 10). This was prepared from data published by Drs. Seldin and Tarail in 1950 (54). In these patients, phosphaturia was substantial on admission. However, with insulin therapy, fluids and correction of the ketoacidosis, serum phosphorus plummeted as also did phosphaturia.

Estimations of the total body phosphorus deficit in patients with diabetic ketoacidosis have been made by "reverse-balance" studies in which the net quantity of phosphorus retained was measured over a period of several weeks. Initial net phosphorus losses were often substantial, extending up to 400 mmoles. These losses were probably underestimated since in most of these studies, the balance period was ended before the patient's weight had returned to normal. I have been unable to find any data on muscle phosphorus content--in patients or animals with diabetic ketoacidosis.

The availability of the electrocardiogram and the flame photometer to measure potassium appear to have stolen the limelight from the enormous amount of work done on phosphorus depletion and hypophosphatemia in patients with diabetic ketoacidosis. The hazardous electrocardiographic alterations with hypokalemia during treatment of diabetic ketoacidosis was first reported in 1946 (57,58). At about the same time, careful and detailed studies by Frank and his associates from Detroit (51,53) described instances in which comatose hypophosphatemic patients awoke following administration

FIGURE 3



of sodium phosphate. This and many other important papers were largely ignored.

The possibility that phosphate depletion and hypophosphatemia might be related to the elevation of CPK activity in some diabetics undergoing treatment for ketoacidosis will be detailed later in the discussion concerning the role of hypophosphatemia in rhabdomyolysis. That hypophosphatemia may be responsible for failure to recover from coma after otherwise successful treatment for diabetic ketoacidosis was discussed in detail at Grand Rounds several years ago by Dr. Madison.

B. THE PATHOGENESIS OF PHOSPHORUS DEPLETION DURING HYPERALIMENTATION OF CACHECTIC PATIENTS

Neither clinical nor experimental starvation is associated with phosphorus deficiency or hypophosphatemia. In these settings there occurs an orderly shrinkage of the cellular mass so that the general relationships between nitrogen, phosphorus, potassium and other intracellular components remains nearly normal. In some of our own recent studies of malnourished dogs given a balanced but calorie-deficient diet, it was found that serum phosphorus concentration remains normal and that muscle phosphorus content actually becomes slightly elevated. Upon refeeding the malnourished animals with a high calorie diet complete in all components except phosphorus, there was a rapid decline of muscle phosphorus content in association with the development of hypophosphatemia. Thus, tissue repair under conditions of phosphorus deprivation creates phosphorus deficiency. In studies conducted in patients (59) it has been well demonstrated that a normal metabolic mixture (meaning a diet containing minerals, electrolytes and nitrogen in proportion to their content inside the normal cells), in conjunction with adequate calories, is mandatory if the tissue being repaired is to obtain normal composition. Deprivation of any single component will impair this process. Therefore, there is nothing mystical about the abnormal cell composition one would encounter during refeeding of a patient with cachexia from almost any cause providing the potential for cellular anabolism exists.

C. PATHOGENESIS OF PHOSPHATE DEPLETION IN THE CHRONIC ALCOHOLIC

A host of factors could be responsible for phosphate depletion in the alcoholic. It occurs in about 50% of those hospitalized (60). Among the obvious causes are poor intake, the use of antacids, diarrhea, and vomiting. Nevertheless, some alcoholics develop hypophosphatemia in the absence of these factors suggesting operation of other mechanisms. I would like to consider four additional possibilities, including (a) ethanol *per se*, (b) magnesium deficiency, (c) alcoholic hypocalcemia and (d) ketoacidosis.

1. Ethanol

In the majority of patients with chronic alcoholism who continue to eat a reasonably normal diet, serum phosphorus will generally be normal or perhaps only slightly diminished. Indeed, it has been our experience that most severe chronic alcoholics, even those whose nutrition has been marginal or clearly inadequate, also display serum phosphorus concentrations which are normal or in the low normal range at the time they are admitted to the hospital. However, in this group of patients, profound hypophosphatemia may occur on the second, third or fourth hospital day.

(a) Effect of Ethanol on Water and Electrolyte Excretion

It would seem appropriate at this point to review the effects of ethanol on the excretion of water and electrolytes by the kidney.

The fact that alcohol has a diuretic action has been well appreciated for many years. The late Maurice Strauss (61) has benevolently assigned recognition of the diuretic effect of ethanol to Shakespeare (62).

ACT II, SCENE III – MACBETH

(Enter Macduff and Lennox)

Macduff: What three things does drink especially provoke?

Porter: Merry sir, nosepainting, sleep, urine. Lechery sir, it provokes and unprovokes; it provokes the desire, but takes away the performance.

William Shakespeare

By all evidence, ethanol inhibits release of ADH from the posterior pituitary and therefore results in diminished reabsorption of water by the kidney when the kidney should otherwise be conserving water (61, 63-65). This effect is not usually pronounced and establishes its relative unimportance as a cause of dehydration. It is notable that the diuretic effect of ethanol is only observed as blood alcohol concentration in blood is rising (65) and may not occur at all in patients who are chronic alcoholics (66).

"Beer Drinkers Hyponatremia"

An interesting disorder of body hydration in beer drinkers has been reported by Hilden and Svendsen (67). They studied 5 patients whose average beer consumption was 5 liters/day but whose intake of food or fluids other than beer was negligible. Each patient had severe hyponatremia (Na^S range 108-127 mEq/L) and modest hypokalemia (range 2.5 - 3.1 mEq/L). Urine osmolality was very low. Since beer contains very little sodium or other nonmetabolizable solutes, the capacity to excrete the necessary volume of dilute urine would be insufficient. The result would be chronic water intoxication. Germane to "beer drinkers hyponatremia" was a comment by another astute observer:

> Water, taken in moderation, might not hurt anybody.
>
> *Mark Twain*

Lucid investigations on a multitude of willing volunteers have established that administration of 50-200 cc of ethanol mixed in water to a normal subject may slightly increase or decrease sodium and chloride

excretion, consistently decrease potassium excretion and increase calcium and magnesium excretion. Although minor variations in these findings have been reported, it can be safely stated that a single dose of ethanol given to a normal person has a proven, important effect on but one electrolyte in terms of its urinary excretion and that is to increase the loss of magnesium. Zinc excretion also consistently rises. However, its importance is not well understood.

The effect of ethanol on phosphorus excretion is far from settled. One group of investigators (68) examined its effects in 7 women and 2 men who were not alcoholics. They infused 50 cc of ethanol in 500 cc of normal saline over a period of 3 hours. Phosphorus excretion rates rose as high as 300 mg/hour. It seems unlikely that 500 cc of isotonic saline over 3 hours could produce sufficient volume expansion to cause phosphaturia of this degree. In fact, there was no evidence of hemodilution. In these patients, it was noted that ethanol produced acute hypercalcemia and a tendency toward elevated serum phosphorus concentrations. Their findings on phosphorus excretion are at odds with those reported by others and such rates of phosphaturia are extreme to say the least. Other investigators (69) found that both normal subjects and chronic alcoholics who were being fed a normal diet, showed a very slight decrease of phosphaturia following administration of ethanol. They also noted a slight rise in the serum concentration of Ca^{++} and PO_4 and a slight decline of K^{+} and Mg^{++}. However, the same group (70) reported that urinary phosphorus excretion became inappropriately elevated in chronic alcoholics ingesting large quantities of ethanol, but only after the appearance of hypomagnesemia. Unfortunately, the latter data were never formally reported.

Ethanol, at least in modest quantities, does not lead to significant release of insulin in normal subjects (71).

2. Hypomagnesemia: Its Possible Role in Phosphate Depletion

It has been rather clearly established that chronic alcoholics may become magnesium deficient and hypomagnesemic (72-76). The proclivity of ethanol to reduce magnesium balance and the possible consequences of Mg^{++} deficiency have been extensively reviewed by Flink (77). An unsettled question concerns the possibility that partial starvation and repeated bouts of ketoacidosis, both occurring with great frequency in severe alcoholics, might play a greater role in Mg^{++} deficiency than ethanol itself.

Detection of hypomagnesemia in chronic alcoholics in large part depends upon timing of blood samples. Many patients display a normal magnesium concentration when admitted to the hospital after which it may fall. In others, serum magnesium concentration may be initially low and subsequently rise even without treatment.

Experimental Mg^{++} deficiency in man leads to an interesting array of disorders. After ingesting a Mg^{++} deficient but otherwise normal diet for several weeks, experimental subjects demonstrate fine and coarse tremors, choreiform and athetotic movements, fasciculations of the tongue, sweating, hyperacusis, delerium, convulsions and coma (78,79).

Table III illustrates the laboratory abnormalities associated with hypomagnesemia.

TABLE III.

EXPERIMENTAL Mg++ DEFICIENCY IN MAN

1. HYPOMAGNESEMIA
2. HYPOCALCEMIA
3. PHOSPHATE: NO CHANGE OR SLIGHT RISE
4. HYPOKALEMIA (INCONSTANT)
5. EXCESSIVE LOSS OF PHOSPHORUS AND POTASSIUM INTO URINE

These include hypocalcemia, a normal or elevated serum phosphorus, sometimes hypokalemia with or without alkalosis and excessive losses of phosphorus and potassium into the urine. These biochemical disturbances are reproducible in the dog (80) but with some difficulty in the rat. In contrast to the Mg++ deficient man or dog, the Mg++ deficient rat becomes hypercalcemic (81,82). However, this can be prevented by a low calcium diet (83) or parathyroidectomy (84). The mechanisms responsible for some of these abnormalities are shown in Table IV:

TABLE IV.

PATHOPHYSIOLOGY OF Mg++ DEFICIENCY

1. PARATHORMONE DEPRESSED
2. PHOSPHATURIA RELATED TO HYPERPHOSPHATEMIA
3. BONE RESPONSE (c-AMP, HYDROXYPROLINE) RESPONSE TO PTH IMPAIRED
4. RENAL RESPONSE (TRP) TO PTH IMPAIRED
5. CALCITONIN NORMAL

Phosphaturia, a feature of experimental Mg++ deficiency (85) leads to phosphorus deficiency (86). Its intensity is directly related to the severity of hyperphosphatemia (78). In dogs, the clearance P falls during hypomagnesemia. This would be compatible with either decreased responsiveness of the renal tubule to PTH or decreased hormone production.

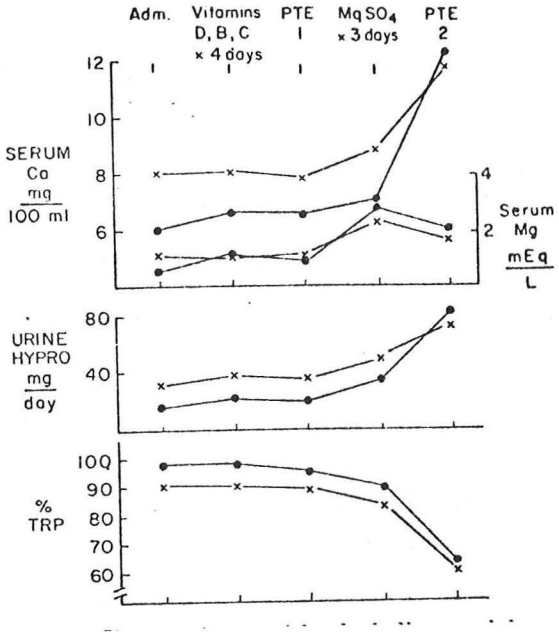
This was initially proposed by Heaton and his co-workers (87) in patients with steatorrhea and malabsorption who were hypomagnesemic and hypocalcemic. Otherwise, hypocalcemia would increase secretion of parathormone which in turn would return serum calcium to normal through its action on bone. It was suggested by Muldowney (88) that either PTH production fell or its effect on bone became blunted. In support of this notion, it was shown that injection of PTH increased phosphate clearance but did not increase serum calcium concentration. More recent studies in Mg++ deficient man (89,90) and dogs (80) have shown that (a) PTH levels either do not rise or even fall despite hypocalcemia (91); (b) that the bone response and renal response to PTH (i.e., increased phosphaturia and cyclic-AMP excretion) were present but blunted (90) and finally (c) calcitonin (89) remains normal. All of the foregoing observers noted that therapeutic administration of Mg++ leads to a rapid correction of serum calcium and of interest, a transient increase of phosphaturia, perhaps the result of a rise in parathormone production.

Although seldom considered, it has been clearly demonstrated in man (78) and rats (86) that Mg++ deficiency leads to a net loss of potassium. It was proposed (86) that since Mg++ ions are required for normal activity of transport ATP-ase, loss of Mg++ may depress activity of the pump so that K would leave the cell and Na would enter. Such changes were actually demonstrated in skeletal muscle of the Mg++ deficient rat (86).

To this point, much of the discussion may seem irrelevant since hypophosphatemia seldom occurs in pure Mg++ deficiency. However, it should be kept in mind that serum phosphorus concentration is usually only slightly depressed in the majority of patients with steatorrhea or chronic alcoholism, before treatment is instituted.

Estep and his associates (92) (Figure 4) studied 20 severe alcoholics who were malnourished, hypocalcemic and hypomagnesemic.

FIGURE 4.



The hypocalcemia was not due to hypoalbuminemia. Administration of parathyroid extract to 13 of the 20 patients showed two patterns of response. In 8, PTH produced no change in serum calcium, hydroxyproline excretion or tubular reabsorption of phosphorus. In 5 others, there was a rise of serum calcium, an increase of hydroxyproline excretion and a decrease in tubular reabsorption of phosphorus. Of great interest, in those who showed no response to PTH, serum Mg ranged from 0.4 to 1.2 mEq/L. In those who responded, serum Mg ranged from 1.7 to 2.3 mEq/L. Administration of Mg++ intravenously for 1 day restored responsiveness to PTH. While their observations suggest that Mg deficiency might explain some of the findings in these patients, the only apparent explanation for the hypocalcemia in those patients who responded to PTH must be that PTH secretion was subnormal.

All of the foregoing appear to underscore the importance of Mg deficiency in the pathogenesis of phosphorus depletion in the alcoholic. This contention is supported by the observations of Matter who showed that phosphate wasting after ingestion of ethanol occurs only after serum Mg++ concentration became abnormally low (70).

The studies by Victor (93) and Wolfe (94) have strongly suggested that hypomagnesemia during alcoholic withdrawal may play an important role in certain CNS manifestations. In these patients, they showed an impressive three-way correlation between hypomagnesemia, respiratory alkalosis and seizure activity. Although not measured, profound hypophosphatemia would have been a virtual certainty in their patients in view of the severity of respiratory alkalosis. Respiratory alkalosis in alcoholic withdrawal and the coincidence of hypokalemia have been stressed by others (95,96) as also has the decline of serum Mg++ concentration during the immediate withdrawal period (66).

3. The Possible Role of Hypocalcemia in the Pathogenesis of Phosphate Depletion in a Patient with Chronic Alcoholism

It has been our observation that most patients with severe advanced alcoholism show a low serum calcium concentration at the time of their admission to the hospital. This usually ranges from 8 to 8.5 mg/100 ml. It often cannot be explained by an abnormally low albumin concentration. Whether or not this represents a low ionized calcium concentration has not been evaluated. Since all alcoholics are not hypomagnesemic, it seems possible that hypocalcemia could stimulate release of PTH and this in turn, phosphaturia. Evidence for this is lacking. Hypocalcemia could also result from interference with calcium transport in the gut (97) or malabsorption which is commonly observed in patients who consume large quantities of ethanol with resulting steatorrhea.

Of interest, two experimental studies have suggested that acute ethanol administration may seriously impair the response of bone to parathormone and thereby induce hypocalcemia (98, 99). In both of these studies, the role of hypomagnesemia was not considered.

4. The Possible Role of Ketoacidosis in the Phosphate Depletion of Chronic Alcoholism

Ketoacidosis must be considered a candidate causing phosphate depletion in chronic alcoholism (63,64,100,100a). Since these patients ingest grossly inadequate diets, ketonuria is a rather common finding.

This is often present at the time the patients are admitted to the hospital but rapidly disappears following administration of even small quantities of glucose. Excessive ketone production thus induced would be quite independent of that observed in certain severe alcoholics who tend to develop Beta-hydroxybutyric acidosis and lactic acidosis consequent to an alteration of their redox state. It would seem strongly possible that repeated episodes of ketoacidosis may serve to decompose organic phosphates within cells and lead to a loss of phosphate in the urine.

Patients with cirrhosis of the liver appear more inclined to develop hypophosphatemia after glucose loads than normal subjects (16). Studies from Dr. Unger's laboratory (101), illustrated in Figure 5, show that patients with alcoholic liver disease overproduce insulin in response to a hyperglycemic stimulus.

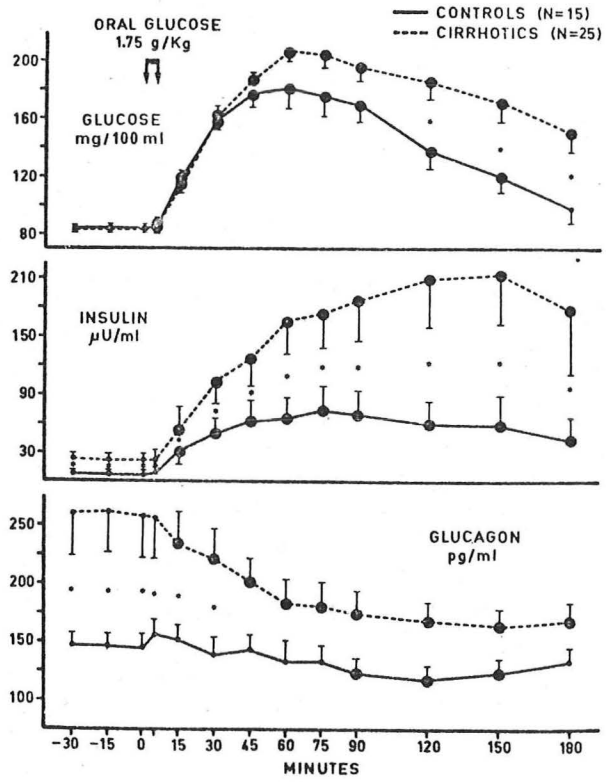


FIGURE 5.

Administration of insulin without glucose may result in a decline of serum phosphorus concentration. The secretion of insulin is particularly exaggerated if glucose is administered by the oral route. Intravenous potassium is also a potent stimulator of insulin release (102). Although never studied in such patients, the possibility exists that simultaneous administration of glucose along with potassium might augment the already exaggerated insulin responsiveness in patients with liver disease. Our own observations in dogs starved for three days have not disclosed an inappropriate overproduction of insulin in the dogs given potassium and glucose. However, these studies would by no means be comparable to the situation prevailing in a patient with alcoholic withdrawal and alcoholic liver disease.

Consequences of Severe Hypophosphatemia

At this time there appears to be at least five definite consequences of severe hypophosphatemia. These are shown in Table V.

TABLE V.

CONSEQUENCES OF SEVERE HYPOPHOSPHATEMIA

DEFINITE

1. **RED CELL DYSFUNCTION**
2. **LEUKOCYTE DYSFUNCTION**
3. **PLATELET DYSFUNCTION**
4. **CNS DYSFUNCTION**
5. **RHABDOMYOLYSIS**

Of these, disordered erythrocyte metabolism and hemolysis have been best characterized.

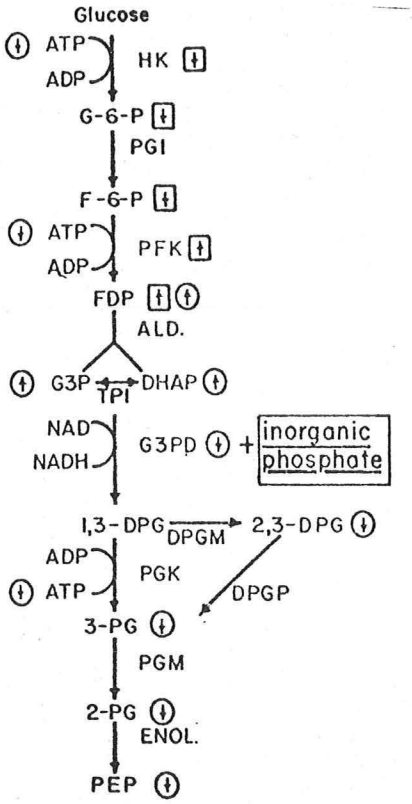
Lichtman demonstrated a correlation between red cell ATP content and serum phosphorus concentration in a patient with uremia (serum creatinine conc. = 16 mg/dL). Patients with uremia usually demonstrate elevated red cell ATP content in direct relationship to their hyperphosphatemia. His patient was treated with hemodialysis, a low protein diet and phosphate binding antacids. As the patient's serum phosphorus concentration progressively fell from about 9 to 1 mg/dL, ATP content declined linearly from about 4 to less than 1 mM/L. Hemolysis did not occur. In normal red cells, cold-storage leads to a similar decline of ATP content. Incubation of such cells with phosphorus and adenosine leads to rapid regeneration of ATP. Using hypophosphatemic uremic serum, Lichtman showed that adenosine did not promote resynthesis of ATP. However, it did when phosphorus concentration was normal. These findings were independent of pH and azotemia. When this patient was hypophosphatemic, he complained of anorexia, nausea, malaise, muscular weakness and mental depression. Correction of hypophosphatemia was associated with marked improvement of these symptoms. Lichtman postulated that a similar decline of ATP might have occurred in other cells of the body and thus explain his patient's symptoms.

In a subsequent study of a 52-year-old woman with steatorrhea (105) 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 cells and impaired lactate production. Similar to his patient with uremia, this

patient did not show evidence of hemolysis. Unfortunately, no comment was made whether or not the patient became symptomatic during hypophosphatemia.

Travis and her associates (106) measured intermediary glycolytic products in red cells of 5 patients whose serum phosphorus concentration fell to 1 mg/dL or less during the course of intravenous hyperalimentation. Directional alterations of these components are illustrated in Figure 6.

FIGURE 6.



The sum of dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (G-3-P), 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 200-600 mumoles/ml. This piling up of "triose phosphates" in red cells occurs because inorganic phosphate is a co-factor necessary for activity of glyceraldehyde-3-phosphate dehydrogenase (G-3-PD) which facilitates conversion of triose phosphates to 1,3-diphosphoglycerate (1,3-DPG). As a consequence, erythrocyte glycolysis below this step is suppressed and not only is formation of 2,3-DPG limited, but also formation of ATP.

According to Travis (106), the decline of ATP has two additional effects. First, low ATP decreases red cell hexokinase activity and thus retards formation of glucose-6-phosphate. 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 demonstrate that administration of intravenous phosphate for 2 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.

It is to be emphasized that gross hemolysis did not occur in any of the patients discussed thus far. This suggests that the effect of ATP depletion per se, albeit important, may not be nearly so critical to the capacity of a red cell to do its job as that related to its content of 2,3-DPG.

It was earlier contended by Guest and Rapoport (44) that the biologic reason for producing 2,3-DPG in the red cell, being as it is no more than an appendage on the glycolytic pathway, was to provide a pool from which inorganic phosphate could be mobilized for resynthesis of ATP. However, later workers found its most important physiological role is that of promoting release of oxygen from oxyhemoglobin (107,108). ATP also has this effect, but to a lesser extent. The interaction of 2,3-DPG and 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 mmHg. This may decline to the vicinity of 16 mmHg in the presence of hypophosphatemia (105). In studies of red cells 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 (106,109). This more rapid recovery of 2,3-DPG than ATP during repletion with phosphorus suggests an important mechanism for survival.

Depletion of red cell 2,3-DPG by metabolic acidosis (110) and its depression in severe hypophosphatemia has been implicated in diabetic coma by means of its inclination to impede delivery of oxygen to tissues (111-113). In support of this was the demonstration by Alberti (114) that decreased red cell 2,3-DPG may be associated with a decreased P_{50} and lactic acidosis. The latter might have been the result of anoxia.

In studies of great potential importance but not confirmed, Bryan-Brown, C.W. has shown that the depressed 2,3-DPG and P_{50} of transfused cells may be rapidly restored following a large dose of methylprednisolone (115).

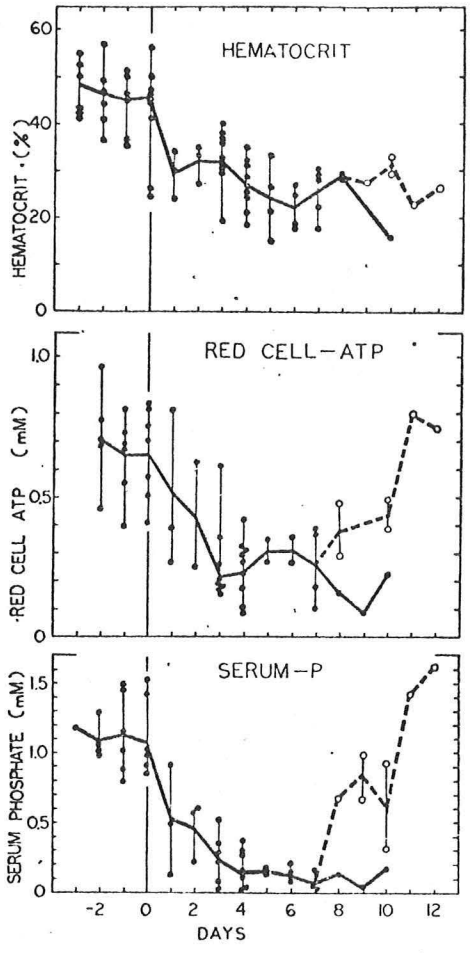
Jacob and Amsden studied a 47-year-old man, a severe alcoholic, who for one week had epigastric pain, diarrhea and profuse vomiting (116). When admitted he was alert, slightly icteric, displayed tachycardia and a respiratory rate of 28/min. He was weak and tremulous. Laboratory findings showed an elevated amylase, a blood pH ranging from 6.98 to 7.06, bicarbonate 1, chloride 102, sodium 135 and K 4.7 mEq/L. Plasma ketones and lactate were elevated. Serum Mg++ was 1.1 mEq/L. Administration of $NaHCO_3$ was associated with the appearance of convulsive seizures and later disorientation, lethargy and apnea. At this time, his serum phosphorus was 0.1 mg/100 ml. During the first 5 hospital days, the patient's hematocrit fell from 44 to 25%, bilirubin rose from 3.0 to 8.0 mg/dL and reticulocytosis appeared. Blood smear showed marked polychromasia and microspherocytosis. Red cell ATP during hypophosphatemia

in this patient was 0.39 umoles/gm hemoglobin. This value is about 11% of normal. Such a low value corresponds to the finding in other disorders of red cell glycolysis that ATP must fall to less than 15% of normal before hemolysis occurs. In the reports of Lichtman (104,105) and Travis (106) hemolysis did not occur and none of their patients showed ATP values below 30% of normal. Hemolysis has been observed in quite similar cases by others (117).

Nakao and his associates (118) were the first to show a correspondence between ATP content of red cells and their viability. Evidence now exists that the skeletal muscle fiber may be analogous to certain structural elements of the red cell (and other cells for that matter). Similar to skeletal muscle, the microfilamentous structures of red cells contain actin and myosin, which also require ATP for proper interaction. These processes, in turn, may be responsible for maintaining normal red cell configuration. Interference with the interaction would in turn alter the structural conformity of the red cell (119-121).

Experimental studies on dogs receiving hyperalimentation after a period of starvation by Yawata and his co-workers (122) have shed light upon the sequence of red cell alterations induced by hypophosphatemia (Figure 7).

FIGURE 7.



In sequence, the cells become spheroidal, dehydrated, rigid and finally, entrapped by the spleen. The changes are prevented or reversed if cellular ATP is maintained by providing phosphate supplements *in vivo* or a brief period of incubation of depleted cells with adenosine and phosphate *in vitro*. Although unexplored, one would predict that rigid, non-deformable red cells would encounter great difficulty in negotiating the capillary circulation of almost any tissue. Thus, ischemia would result not only from failure to unload the oxygen from the red cell (↓2,3-DPG and ↓ATP) but possibly from failure of the cell to arrive at its destination.

To summarize the effects of hypophosphatemia on red cell structure and function, available evidence suggests that hemolysis occurs only when serum phosphrus concentration is less than 0.5 mg/dL and perhaps in the presence of additional influences such as severe acidosis. The latter, quite independently of hypophosphatemia, may inhibit phosphofructokinase and in turn inhibit synthesis of ATP. When the latter falls to extremely low levels, viz., less than 15% of normal, hemolysis may supervene.

Leukocyte Function During Hypophosphatemia

One of the most serious side effects of intravenous hyperalimentation therapy is serious, often fatal infections by bacterial and fungal organisms. There are undoubtedly many reasons why this could occur.

Patients receiving hyperalimentation usually have serious disease with malnutrition and as such are compromised hosts. It was recognized that the cannula, being a foreign body in the circulation, was commonly colonized. Improved techniques and frequent replacement of cannulas have diminished the incidence of infection. As mentioned previously, it has been shown that plasma hypertonicity may inhibit phagocytic activity and thereby increase the chance of infection. Patients with malnutrition tend to be glucose intolerant and thus prone to hyperglycemia. Moreover, it is customary to administer hypertonic solutions for parenteral hyperalimentation.

Suspecting that severe hypophosphatemia may impair resistance to infection, Craddock and his associates (123) examined phagocytic function in dogs given a calorie-restricted diet for 4-6 weeks. This was sufficient to produce a 30% loss of weight. Hypophosphatemia was induced by parenteral hyperalimentation. Compared to studies conducted on the dogs before hypophosphatemia was induced, they observed a 50% depression of chemotactic, phagocytic and bactericidal activity of the granulocytes. Leukocyte ATP content fell. ATP in granulocytes increased and the motility defect was corrected as phosphate was repleted *in vivo* by supplementation of the diet or *in vitro* by incubation of the leukocytes with adenosine and phosphate. These investigators made similar observations on a single patient who became hypophosphatemic during hyperalimentation. The depressed phagocytic, chemotactic and bactericidal activities of this patient's granulocytes were corrected by incubation *in vitro* with adenosine and phosphate and *in vivo* after phosphate supplementation. Once again, it must

be emphasized that these effects are seen only when hypophosphatemia is severe. That respiratory alkalosis and hypophosphatemia may occur in association with gram negative bacteremia has been discussed (31). One group of investigators showed that guinea pigs infected with Salmonella organisms became hypophosphatemic before death. When given phosphate, mortality was significantly reduced and the number of organisms found in their tissues was less (124).

The proposed mechanism by which hypophosphatemia impairs granulocytic function is probably related to impairment of ATP synthesis. The microtubules, by their contractions, regulate the mechanical properties of leukocytes, thus pseudopod and vacuole formation. The microfilaments are in many respects similar to the myofibrils of skeletal muscle and require ATP for their source of energy.

Actin and myosin have been found in the cytoplasm of granulocytes (125). Perhaps of equal importance, Lichtman (126) has emphasized that hypophosphatemia does not only limit mechanical functions of the granulocyte but may also be important to sustain the increased rate of synthesis of phosphoinositides and other organic phosphate compounds that occur during phagocytosis (127). Three reviews related to actin and myosin in "non-muscular" tissues have recently appeared (128-130).

Platelet Disorders and Hypophosphatemia

A perusal of the clinical literature on hypophosphatemia shows no evidence that it is associated with hemorrhage. However, Yawata and his associates (122) studied experimentally malnourished dogs treated with parenteral hyperalimentation. They found that hypophosphatemia was associated with 7 abnormalities of platelet function and structure (Table VI):

ABNORMALITIES OF PLATELETS IN EXPERIMENTAL HYPOPHOSPHATEMIA

TABLE VI.

1. Thrombocytopenia
2. Increased platelet diameter
3. Increased number of megakaryocytes in marrow
4. Marked acceleration of platelet disappearance
5. Impaired clot retraction
6. ATP content diminished 50%
7. Hemorrhage into gut and skin

(1) thrombocytopenia, (2) increase in platelet diameter suggesting shortened platelet survival, (3) megakaryocytosis of the marrow, (4) a 5-10 fold acceleration of the rate of labelled platelet disappearance from blood, (5) impairment of clot retraction, (6) a 44-57% reduction in platelet ATP-content and (7) hemorrhage into the gut and skin. Of note, all these abnormalities are not seen if phosphorus supplements are provided.

The possibility exists that a relationship between profound hypophosphatemia and clinically significant disorders of platelet function could exist. However, even in the experimental studies reported by Yawata et al (122), it seems peculiar why clot retraction was impaired at all since thrombocytopenia and decreased platelet ATP content were only modest in degree. However, these findings could indicate a thrombopathic state.

This potentially important complication of hypophosphatemia in man deserves further study.

EFFECTS OF HYPOPHOSPHATEMIA ON THE CNS

The effects of hypophosphatemia on the CNS have been well characterized in terms of symptoms but poorly defined in terms of pathophysiology. In those patients who have become severely hypophosphatemic, a sequence of symptoms compatible with a metabolic encephalopathy may occur (Table VII) (131).

TABLE VII. SEQUENCE OF CNS SYMPTOMS IN SEVERE HYPOPHOSPHATEMIA

IRRITABILITY
APPREHENSION
MUSCULAR WEAKNESS
NUMBNESS
TINGLING PARESTHESIAS
DYSARTHRIA
CONFUSION
OBTUNDATION
CONVULSIVE SEIZURES
COMA
HALLUCINATIONS ABSENT

This sequence consists of irritability, apprehension, muscular weakness, numbness, paresthesias, dysarthia, confusion, obtundation, convulsive seizures and coma. This clinical syndrome has been observed in patients without other causes for encephalopathy who have been treated with I.V. hyperalimentation and also in patients during withdrawal from chronic alcoholism. In the latter instance, the clinical picture is similar in some respects to delerium tremens. However, the rather distinctive hallucinations of delerium tremens have not been observed. Both conditions may coexist.

The relationship between hypophosphatemia and the decline of red cell 2,3-DPG becomes especially important in tissues where oxygen is necessary for energy production. This could have an important role in the brain where oxidation of glucose through the Krebs Cycle is necessary for synthesis of ATP.

In the report by Travis and her co-workers (106) three of the eight patients who became hypophosphatemic during hyperalimentation developed circumoral and peripheral extremity paresthesias, mental obtundation and hyperventilation. Of great interest, these three patients demonstrated marked shifts of their oxyhemoglobin dissociation curve to the left, and developed P_{50} values of 16.0, 16.5 and 20.9 mmHg. The two patients whose P_{50} values were 16.0 and 16.5 also showed diffuse slowing of their electroencephalogram.

Perhaps the best evidence that hypophosphatemia plays a role in this encephalopathy has been the observation that it does not occur in patients receiving hyperalimentation with preparations containing adequate phosphorus.

Several investigators have examined certain effects of hypophosphatemia during hyperalimentation in experimental animals (Table VIII).

TABLE VIII. **THE CENTRAL NERVOUS SYSTEM IN HYPOPHOSPHATEMIA**

- BRAIN ATP?
- EEG CORRELATES WITH $\downarrow P_{50}$
- PREVENTABLE IN MAN

Yawata and his associates (131a) induced malnutrition and weight loss in dogs by dietary restriction. They described ataxia, convulsions and death as severe hypophosphatemia occurred during hyperalimentation without phosphorus. Although they initially reported a diminution of brain ATP-content to 80% of normal, their subsequent studies were not confirmatory (132). Silvis and his co-workers (133) studied dogs with malnutrition induced by small bowel resection so that their weight had decreased to 50% of normal. Through indwelling intravenous catheters, they infused a solution containing hypertonic glucose and amino acids to provide 140 cal/Kg/day. Control animals (no catheter) were killed at 14 days. Hyperalimented animals had a mean survival of 5.4 days and at this time, a mean phosphorus level of 0.4 mg/dL. Some displayed weakness, convulsions and coma. In animals hyperalimented with the same preparation containing supplemental phosphorus sufficient to prevent hypophosphatemia, survival

was not improved. They concluded that hypophosphatemia was not the cause of death in the starved, hyperalimented animals not given phosphate. Our experience with chronic, indwelling venous cannulas in either normal or potassium-deficient dogs would strongly suggest that the dogs studied by Silvis and his associates may have succumbed to infection related to venous cannulation quite independently of phosphate. Their report contained no observations on this possibility. Furthermore, it is widely appreciated that hyperalimentation of starving, malnourished animals may be complicated by marked hyperglycemia. In our studies, infusion of glucose in dogs starved for only 3 days lead to modest hypophosphatemia. But perhaps most important, they developed marked hyperglycemia and coma. A hyperosmolar state is known to impair leukocytic phagocytosis (123) independently of hypophosphatemia.

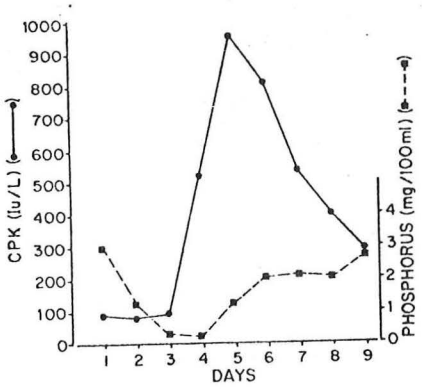
It would seem pragmatic to accept the contention that CNS function may well be impaired by profound hypophosphatemia. Although neither the structural nor the biochemical lesion in the brain has been characterized, one could predict impairment of glucose utilization since it is dependent upon the availability of inorganic phosphorus. Glucose oxidation and therefore ATP production would also fall because of anoxia resulting from diminution of 2,3-DPG. The latter would seem to conform with the abnormalities of CNS function and electroencephalographic disturbances described in patients with profound hypophosphatemia by Travis and her associates (106).

Rhabdomyolysis and Phosphate Deficiency

Clinical observations and a number of experimental studies have provided evidence that skeletal muscle dysfunction may result in phosphate depletion. Lotz and Bartter (6,7) have described muscular weakness in experimental phosphate depletion in man, and several other anecdotal reports (134,135) have reported myalgia in patients who are severely hypophosphatemic.

We have recently reported observations concerning the common occurrence of hypophosphatemia in patients with chronic alcoholism and how this might be related to alcoholic myopathy (136). In patients with severe chronic alcoholism, generally in association with poor nutrition, severe hypophosphatemia may occur which tends to become especially pronounced after they have been hospitalized. Hypophosphatemia usually reaches its nadir on the 2nd to 4th hospital days during administration of large amounts of carbohydrate. It was noted in these patients that when serum phosphorus concentration had been less than 1 mg/100 ml and remained at that level for 1 to 2 days, there often occurred a sharp rise in serum creatine phosphokinase activity. This relationship is illustrated in Figure 8.

FIGURE 8.



This shows serum phosphorus concentration and serum CPK activity in a typical patient with severe chronic alcoholism who had been admitted on many occasions for alcoholic withdrawal. His body weight was subnormal as a result of poor dietary intake. As is ordinarily the case, the patient was treated with intravenous glucose and potassium chloride. Typical for such patients, serum phosphorus concentration was in the lower range of normal at the time of admission, falling from 2.9 mg/dL on the first day to a value of less than 0.5 mg/dL on the third and fourth hospital days. At this time, his serum CPK activity rose sharply. The patient complained of muscle pain and profound weakness. On the next day, obvious swelling of the legs was evident. Heme pigment was detected in the urine. Simultaneously, plasma remained clear suggesting that hemolysis was not responsible for the pigmenturia. Over the following 48 hours, the patient's serum phosphorus concentration rose, presumably the result of phosphorus release from injured skeletal muscle cells. Laboratory findings in such patients are shown in Table IX.

PROMINENT LABORATORY FINDINGS IN RHABDOMYOLYSIS

TABLE IX.

1. HYPERKALEMIA
2. HYPOPHOSPHATEMIA → HYPERPHOSPHATEMIA
3. PROFOUND HYPOCALCEMIA (ONCE NECROSIS IS ESTABLISHED)
4. LATE HYPERCALCEMIA
5. HYPERURICEMIA MAY BE MARKED
6. DISPROPORTIONATE ELEVATION OF CREATININE IN RELATION TO BUN
7. CPK ELEVATION MODEST IN ALCOHOLICS
8. FRANK MYOGLOBINURIA RARE
9. ACUTE RENAL FAILURE RARE

Others (Figure 9) have also observed that many severe alcoholics, even those without overt evidence of muscle cell necrosis and whose CPK activity was normal when admitted, show similar elevations of CPK on the second to the fourth hospital days after admission.

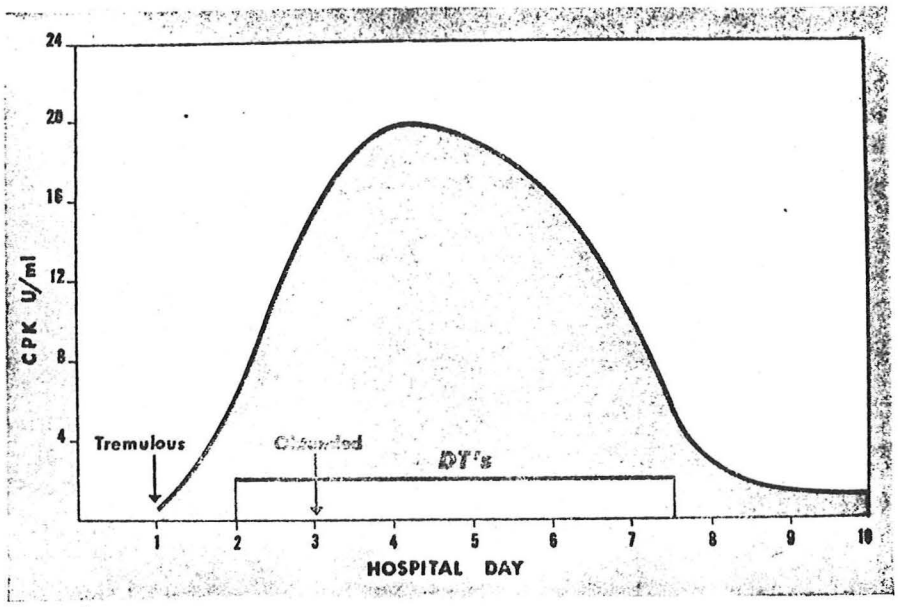
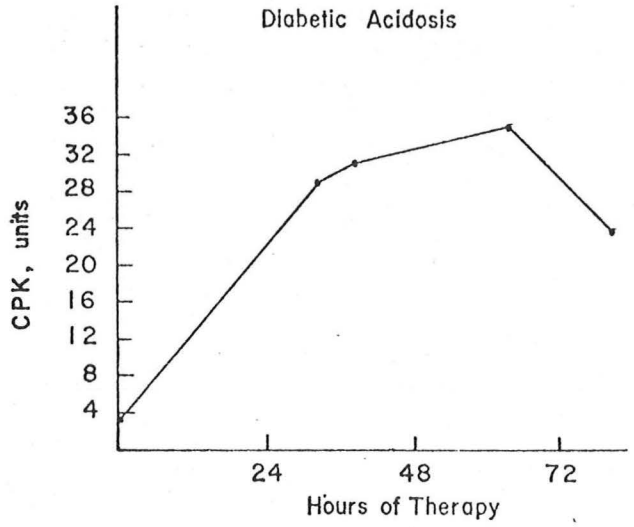


FIGURE 9.

This temporal relationship has also been noted during recovery phase of treatment for diabetic ketoacidosis (Figure 10) (138-142) and by us during refeeding patients with severe protein calorie and malnutrition.

FIGURE 10.



It has been noted that most of these patients have virtually no detectable phosphorus in the urine at the time when their serum phosphorus concentration is lowest.

To further characterize these observations, we examined a number of severe alcoholics who had in most cases been admitted to the hospital because of alcoholic gastritis. The patients were selected on a basis of an initially normal but subsequently elevated serum CPK activity. In all patients, hypophosphatemia preceded the elevation of CPK. By the time our studies were conducted, recovery from hypophosphatemia had occurred spontaneously in some of the patients. It is to be noted that those who showed recovery of serum phosphorus concentration at this time, as indicated in Table X, were those who also showed the most pronounced elevations of CPK activity.

TABLE X.

TABLE
Biochemical Disturbances of Alcoholic Myopathy

Patient	CPK IU/liter	Aldolase ·mU/ml	Pi mg%
1.	800	34.0	3.3
2.	187	34.0	1.0
3.	208	13.2	0.8
4.	1924	30.5	3.1
5.	2470	47.0	2.9
6.	550	18.2	1.9
7.	148	19.2	1.8
Normal Range	25-145	0-6	2.5-4.5

It seems quite likely that this rise of serum phosphorus concentration might have been the result of skeletal muscle injury and cellular release of phosphorus (136,143,144). In these patients we examined skeletal muscle tissue for its content of electrolytes and the resting transmembrane electrical potential difference of the muscle cells. Normal values for these parameters were determined from studies on six normal volunteers. CPK activity in serum of the patients with chronic alcoholism was substantially higher than those observed in normal subjects. At the time the studies were conducted, the average serum phosphorus concentration was 2.1 mg%. However, the range of phosphorus values in these patients varied between 0.8 to 3.3 mg/dL. Muscle sodium and chloride content were elevated. Although some observers have found muscle potassium content to be subnormal in alcoholic myopathy (145), the muscle potassium content in our patients was clearly within normal limits. Some, but not all, of these patients had recieved prophylactic potassium chloride during the immediate days preceding the studies, and this could have accounted for the latter observation. The most striking finding was the markedly subnormal value for total muscle phosphorus content. This averaged 13.2 millimoles/100 g fat free dry solids. In normal subjects, this averages 24.6 millimoles by this method of analysis. The water content of the tissue was also elevated. The resting muscle membrane potential in the patients with chronic alcoholism was subnormal, averaging -70.4 mV compared to a normal value of -86.7 mV. The elevated total tissue chloride, sodium and water content, and a subnormal resting membrane potential suggest that the bulk of the water, sodium and chloride retained was inside the cells. This wold agree with the characteristic electron microscopic findings of intracellular edema in skeletal muscle in patients with alcoholic myopathy (146,147).

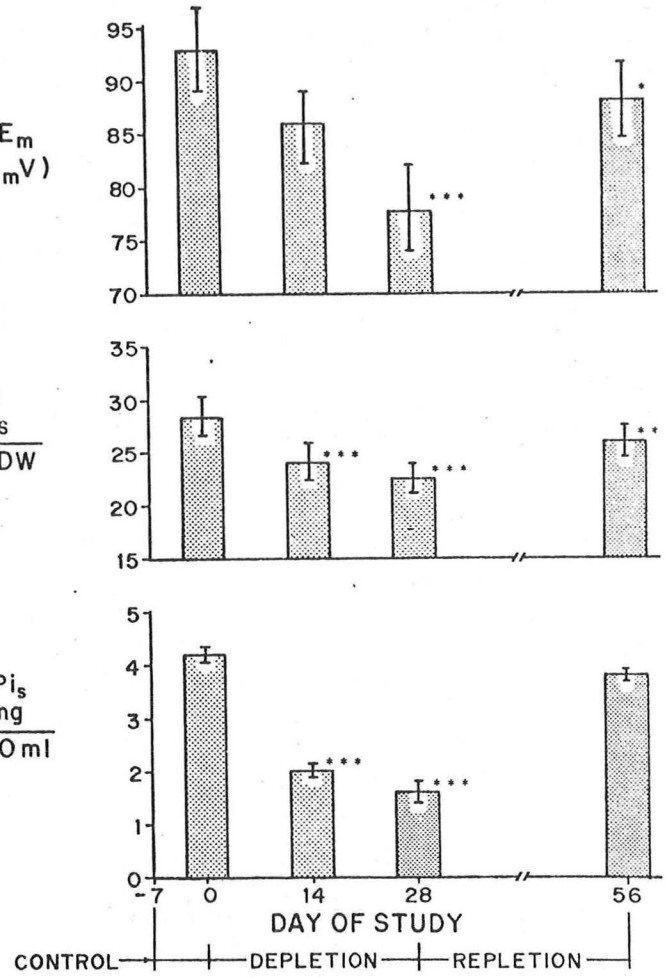
Many theories have been proposed to explain the pathogenesis of myopathy in alcoholics. Thus ethanol may impede sodium and potassium transport in a number of tissues and by inference, has been assumed to assert a similar effect on skeletal muscle. More specifically, Mayer (148) has shown that the resting membrane potential of rat skeletal muscle falls following administration of alcohol. However, based upon the finding that chronic alcoholics may also become acutely and profoundly hypophosphatemic suggests that such hypophosphatemia might be independently implicated in the myopathy noted so commonly in these patients. Although certainly not clear, it seems possible that muscle cell injury could well occur by interference with the chemical processes important in maintaining cellular membrane integrity. Major among such interfering processes could be the inhibition of protein synthesis by ethanol (149) and anoxia from subnormal content of 2,3-DPG in red cells. The relationship of hypophosphatemia, decreased red cell 2,3-DPG and the possibility of cellular anoxia are discussed elsewhere in this review.

Experimental Myopathy Associated with Phosphorus Depletion in the Dog

To elucidate this specific role of phosphate deficiency on skeletal muscle, we examined 8 dogs fed a phosphorus deficient synthetic diet in quantities calculated to maintain their body weight for a period of 28 days. Aluminum carbonate gel was added to the diet to bind phosphate in

the gut. Muscle composition and membrane potential were measured serially throughout the period of depletion and again after repletion. The average values from those studies were shown in Figure 11.

FIGURE 11.



In the top portion of the figure are illustrated average values for muscle membrane potential in the control state. This averaged -93 mV. After the animals had been on the diet 14 days, this value had fallen to -86 mV which was significantly different from the control. By day 28 this value had fallen to a -77.6 mV. At the corresponding periods of study, total muscle phosphorus content fell from 28.2 millimoles/100 g fat free dry solids to 24 millimoles on day 14 and further to 22.4 millimoles on day 28. Before the study was initiated, serum phosphorus concentration averaged 4.2 mg%. By day 14 this had fallen to 2.1; by day 28 the average value was 1.7 mg%. The values determined on day 28 could have been spuriously high since hemolysis was very difficult to avoid at this time. Other determinations of muscle composition in these animals showed that the average content of sodium and chloride rose. Of great interest, there was also a

slight but nevertheless significant drop in potassium content of the muscle. Total water content of the tissue rose by the 28th day of the study.

Such data indicate that dietary deprivation of phosphorus in the dog sufficient to decrease total muscle phosphorus content by an average of only 15% may be responsible for significant increase of muscle sodium chloride, a diminution of potassium and a decline of resting membrane potential. When average muscle phosphorus content decreases by 20%, these findings became more pronounced and the water content of the tissue rises. Similar to the patients with alcoholic myopathy whose serum CPK activity was normal when admitted to the hospital, CPK activity remained normal in these animals. It is to be noted here that the degree of phosphorus depletion in skeletal muscle in the patients with chronic alcoholism was much more profound at the time the studies were conducted than that produced in dogs by phosphorus deprivation for only 28 days.

These findings in many respects are typical of the so-called "sick cell" and closely resemble those induced in the experimental myopathy of potassium deficiency. Such a situation appears to be precarious for cellular integrity. Perhaps of importance is the observation that patients with alcoholism commonly demonstrate normal values for CPK when first admitted to the hospital. Its subsequent rise commonly appears to be preceded by a stressful event such as an increase in muscular work, exemplified by a convulsive seizure in the withdrawing alcoholic, or a further sustained reduction in serum phosphorus concentration induced by administration of a large carbohydrate load. Some evidence also exists that acute respiratory alkalosis may be a factor precipitating acute profound hypophosphatemia in these patients. At any rate, cellular injury under such conditions could become so severe that CPK could leak out, thus reflecting frank cellular destruction. Such a sequence of events could prevail in some alcoholics with myopathy who have become phosphate deficient; their muscle cells could be at the threshold of structural disintegration and any stressful event might bring out overt rhabdomyolysis. Ongoing studies in our laboratory strongly suggest that zealous refeeding of a partially starved dog causes acute elevations of CPK in those animals demonstrating the most profound drop in phosphate concentration. Such evidence tends to support the clinical observations.

It should be noted that Mg^{++} deficiency has been reported to produce a myopathy in the rat (150). Under such conditions, as will be subsequently pointed out, K deficiency would also occur. Potassium deficiency is a known cause of myopathy and rhabdomyolysis (151,152). Whether or not isolated Mg deficiency could induce a myopathy is not clear but appears to be a strong possibility.

Abnormalities of Liver Function in Hypophosphatemia

The first evidence that acute, severe hypophosphatemia, possibly induced by hyperventilation, might be implicated in declining hepatic function and hepatic coma was suggested by Frank and Kern in 1962 (153).

His first patient was a 51-year-old woman with alcoholic cirrhosis and ascites. Serum phosphorus when admitted was 1.9 mg/dL, Ca++ 7.7 mg/dL, and bilirubin 8.2 mg/dL. By hospital day 4, serum P had fallen to 0.5 and Ca++ to 6.8. Bilirubin had risen to 14.1 mg/dL. She became comatose. Over the following few days, her neurological findings cleared as her serum P returned to normal (muscle necrosis ?). We have also observed this sequence of events and have questioned the possibility that auto-correction of hypophosphatemia via release of phosphorus from skeletal muscle might be inadvertently life-saving. Of interest, respiratory alkalosis has generally preceded the drop in serum phosphorus in our patients. This was also noted by Frank and Kern (153).

Rajan, Levinson and Leevy (154) studied 27 malnourished alcoholics with cirrhosis and liver failure. In 17 patients (Group A) serum P was normal and in 10 patients (Group B) it was less than 1.5 mg%. In both groups there was a similar degree of respiratory alkalosis; average pCO_2 and pH were 29.3 mmHg and 7.51 units respectively. Arterial pO_2 was similar in both groups (averaging 71 mmHg). The P_{50} in the hypophosphatemic group was 21.5 mmHg compared to 32.6 mmHg in the normophosphatemic group. The erythrocyte content of 2,3-DPG in the hypophosphatemic group was 2850 mumoles/ml packed cells whereas the corresponding value in the normophosphatemic group was 6900. Hepatic oxygen extraction was reduced. Correction of serum phosphate concentration was associated with a correction of 2,3-DPG, P_{50} and increase in hepatic oxygen extraction. Unfortunately, these results have not yet been reported in more than abstract form and any firm conclusions must be reserved. However, their findings appear to be quite logical and correspond to clinical observations on many patients with chronic alcoholism and hepatic disease, viz., that liver function commonly appears to deteriorate after several days in the hospital at a time when hypophosphatemia becomes most pronounced. Obviously, this is another potentially important complication of hypophosphatemia that requires more detailed study.

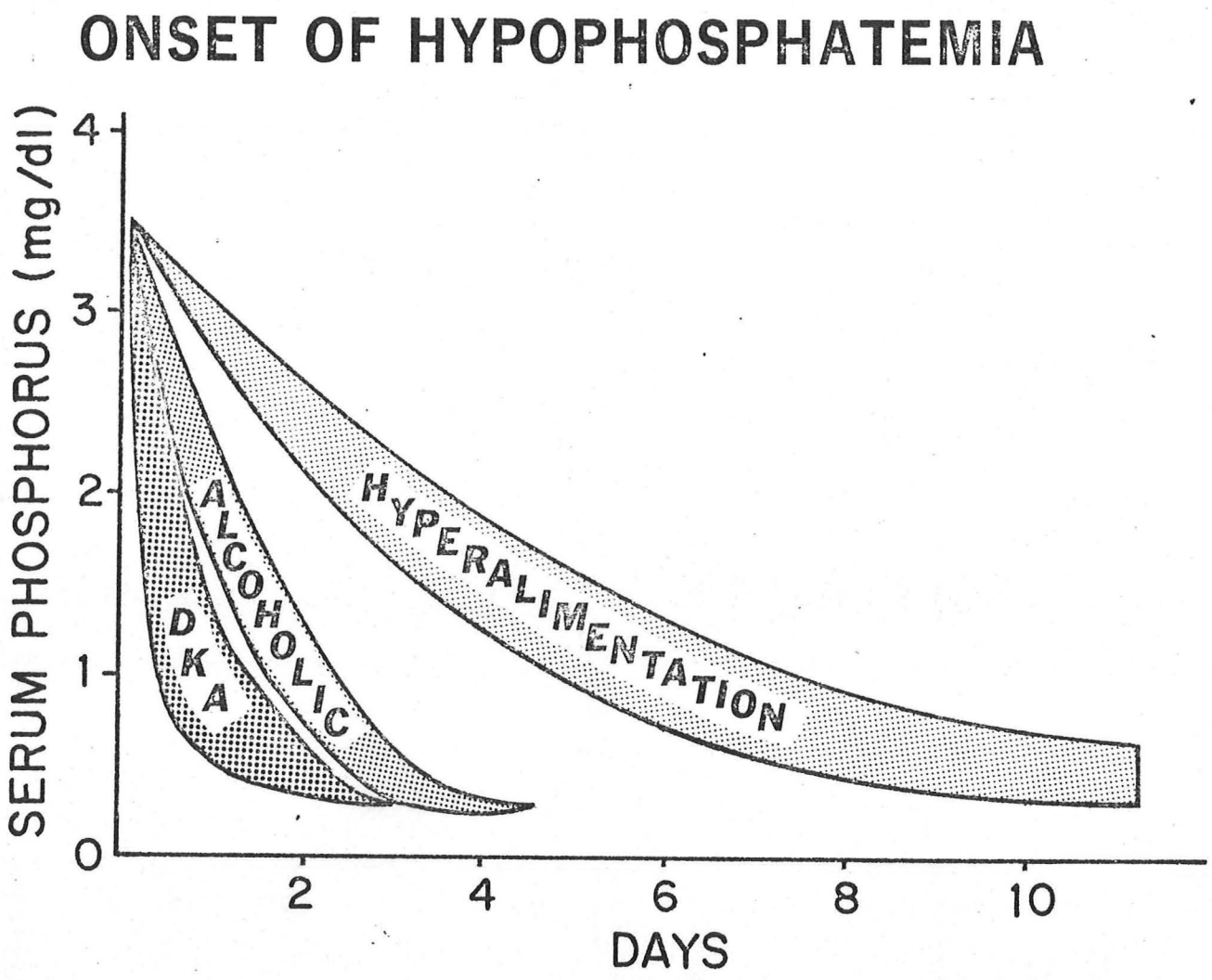
The number of complications that could be ascribed to hypophosphatemia or phosphorus deficiency are limited only by one's imagination. Suspected but unconfirmed are several defects possibly resulting from tissue anoxia. These include congestive heart failure (133) and liver dysfunction (154). Renal bicarbonate wasting and renal glycosuria (155) have been reported and appear to reflect an impairment in proximal tubular function of the kidney. In two young men with severe alcoholic intoxication (156), described findings are suggestive of proximal tubular dysfunction. These include markedly elevated phosphate and uric acid clearances, renal glycosuria and metabolic acidosis. I have personally observed two young, severe alcoholic women who ingested large quantities of Lucky Tiger Aftershave Lotion who demonstrated renal glycosuria, phosphaturia, an alkaline urine depsite severe metabolic acidosis, hypokalemia, hypophosphatemia, hypouricemia, hypomagnesemia and hypocalcemia. Both had pronounced CNS dysfunction but recovered. At that time (1957 and 1962), this brand of aftershave lotion contained maleic acid as a preservative. Maleic acid is a substance utilized experimentally to induce proximal tubular injury. At that time, I concluded that maleic acid was the culprit. However, in view of evidence now available, perhaps

severe hypophosphatemia was solely responsible. Lactic acidosis has been observed (114) in a number of diabetic patients and alcoholics with hypophosphatemia. However, this could have many other equally valid causes.

A Recapitulation

In Figure 12 an attempt is made to illustrate the usual time at which hypophosphatemia appears in patients with the three conditions most commonly associated with profound hypophosphatemia.

FIGURE 12.



In the figure, serum phosphorus concentration is illustrated on the vertical axis and days on the horizontal axis. In patients with diabetic ketoacidosis, the onset of hypophosphatemia is usually prompt; appearing within the first 24 hours and may reach its nadir within the first 24 to 36 hours. In patients with chronic alcoholism its onset tends to be

a bit later, the nadir being observed on the second through the fourth days. In sharp contrast, patients with cachexia who are receiving parenteral hyperalimentation may not become severely hypophosphatemic until about the 6th day of treatment and sometimes not until the 10th day.

In Figure 13, an attempt has been made to put much of the information already presented in perspective.

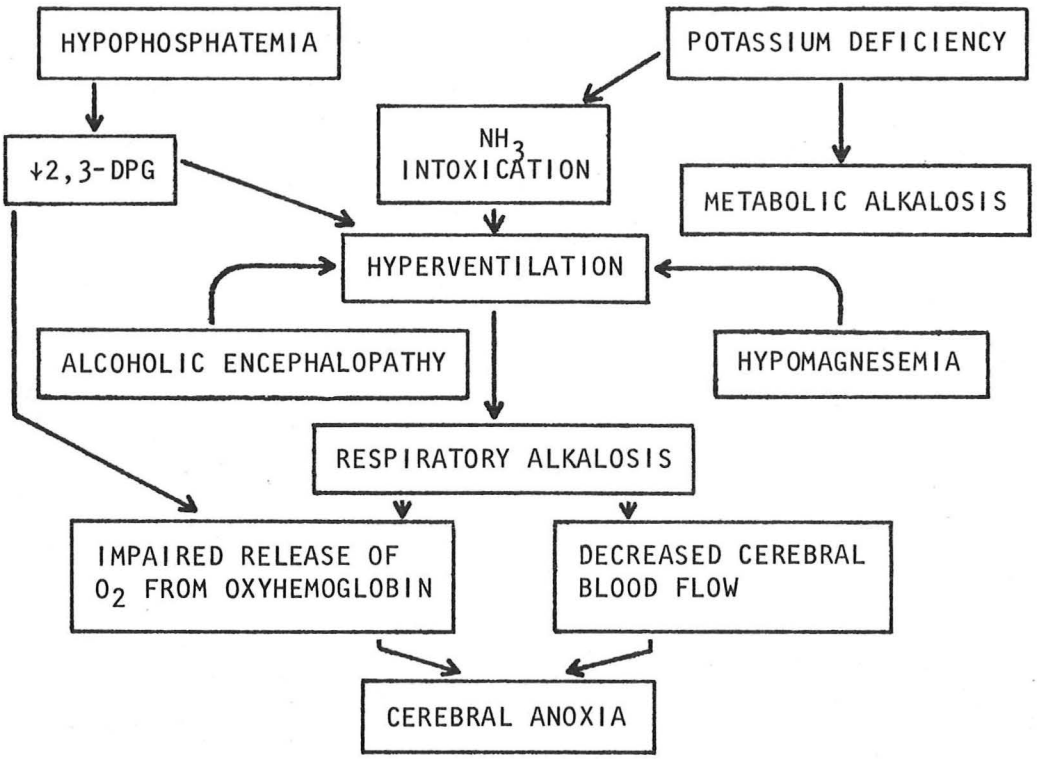


FIGURE 13.

In the upper left hand portion of the figure it is shown that hypophosphatemia may lead to a decline of 2,3-DPG content in the red cell. The most certain consequence of this disturbance is impaired release of oxygen from erythrocytes. Another possible effect shown by the arrow pointing from 2,3-DPG is that of hyperventilation. In the upper right hand corner, it is noted that in patients with alcoholic cirrhosis and portal hypertension, hypokalemia is common and may indirectly be responsible for ammonia intoxication (157). This too has been associated with hyperventilation. Potassium deficiency would also tend to produce metabolic alkalosis which tends to favor the development of hypophosphatemia. In many of these patients hypomagnesemia tends to appear on the second day or so and has been cited as a possible cause of

increased neuromuscular irritability and hyperventilation (93,94). In such patients, metabolic encephalopathy associated with alcoholic withdrawal is probably another valid cause for hyperventilation. Hyperventilation and respiratory alkalosis are emphasized strongly in this scheme. When respirations become driven as they often are in these patients, respiratory alkalosis and hypophosphatemia may become profound. Thus in a patient whose red cell 2,3-DPG is diminished by hypophosphatemia, the only remaining favorable influence to release oxygen into peripheral tissues would be acidosis. Instead, alkalosis, a more common finding, would further impair release of oxygen. Of equal importance, profound respiratory alkalosis is well known to induce a major reduction of cerebral blood flow (103). This has been demonstrated in normal volunteer subjects who were anesthesized, intubated and hyperventilated mechanically. With an average pCO_2 of 19 millimeters of mercury and a pH of 7.78, cerebral blood flow decreased by an average value of 40%. In the withdrawing malnourished alcoholic, whose red cell 2,3-DPG is depressed because of phosphorus depletion, superimposed respiratory alkalosis eliminates the Bohr effect. These influences acting together could virtually eliminate release of oxygen to the brain. Add to this a major decrease in cerebral blood flow resulting from respiratory alkalosis and it is not surprising that one would encounter paresthesias, aphasia, ataxia, mental obtundation and seizures in such patients. This might also explain why major manifestations of hypophosphatemia are seldom observed in patients recovering from diabetic ketoacidosis. Thus, they do not ordinarily develop acute respiratory alkalosis.

Of great interest, where sufficient studies were obtained (93,94, 131,153) such as those on patients who developed paresthesias, convulsions and coma during hyperalimentation, that serum magnesium concentration had fallen and both patients displayed arterial blood pH values exceeding 7.5 and corresponding low values for pCO_2, reflected respiratory alkalosis. I suspect this may be the coup de grâce in such patients.

Treatment of Hypophosphatemia

The remaining issue concerns the advisability of treating hypophosphatemia or prophylactic administration of phosphorus to patients who are virtually certain to become hypophosphatemic.

I feel quite safe recommending treatment for a chronic alcoholic because our studies indicate that they have a pre-existing phosphate deficiency, at least in terms of skeletal muscle. It is quite likely that the same situation exists in diabetic ketoacidosis although measurements of tissue phosphorus content other than in red cells, have not been done. In alcoholics and patients with diabetic ketoacidosis, it seems likely that the pre-existing phosphorus deficiency would adequately explain the rapid onset of hypophosphatemia as soon as cellular anabolism begins. In contrast, all evidence--including tissue analysis--indicates that the cellular content of phosphorus in cachexia or starvation is normal. This might explain why hypophosphatemia does not appear in such a patient

until the 4th to 10th day after initiating treatment. In this circumstance, cellular reconstruction would proceed without phosphorus; phosphorus deficiency would thus be produced.

Potential Hazards of Phosphate Therapy

There are 6 potential hazards associated with administration of phosphate salts. The most important is (1) hyperphosphatemia, which in turn, may induce the second and third complications. These include (2) metastatic deposition of calcium phosphate and resulting (3) hypocalcemia. An equally serious hazard is (4) hyperkalemia if one administers excessive quantities of potassium phosphate.

The remaining two complications are related to (5) the osmotic diuretic effect of filtered phosphate if serum phosphorus rises substantially with dehydration and (6) hypernatremia.

If phosphate salts are used appropriately in patients capable of incorporating phosphate into their cells, hyperphosphatemia does not occur and except for the possibility of hyperkalemia, there is little chance that the foregoing complications will appear.

Contraindications to the Use of Phosphate Salts

1. Hypercalcemia of any cause
2. Hyperphosphatemia
   (a) Renal failure
   (b) Hypoparathroidism
3. Oliguria
4. Evident tissue necrosis

Substances Available for Use

1. Milk. Skim milk or low-fat milk is useful in a patient who can tolerate oral feeding. Milk contains approximately 1.0 gm each of calcium and phosphorus (33mmoles) in each quart. This is especially useful as a safe means to initiate treatment in a cachectic or starved person. It is wise to start slowly and gradually increase the quantity of food offered. If the patient refuses to eat, skim milk with an added amino acid supplement (aminaid) is usually well-tolerated. Otherwise, intravenous routes may become necessary. Due to the fat content of whole milk, diarrhea may occur.
2. $Na_2PO_4 \cdot Na_2HPO_4$, (3:8 w/w: Fleet's). This may be used p.o. in doses of 15-30 cc, t.i.d. (contains 1.63 mmoles P/cc). This usually produces diarrhea.
3. $KH_2PO_4 \cdot K_2HPO_4$ (1.04:1 w/w). As packaged by Travenol in 10 cc vials for incorporating into intravenous fluids, will deliver about 2 mmoles of P/cc.

Under nearly all circumstances, patients likely to develop hypophosphatemia will also require potassium and magnesium. Since hypophosphatemia does not appear to cause difficulty unless serum concentration is less than 1.0 mg%, levels above this can be maintained easily by administering one-half their potassium supplement as KCl and one-half $KH_2PO_4 \cdot K_2HPO_4$.

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