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NUTRITION IN RENAL FAILURE

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INTRODUCTION

Renal insufficiency leads to reduced capacity for the excretion of nitrogenous waste products and impaired electrolyte homeostasis. Since the need to excrete nitrogenous waste products and electrolytes is directly related to the quantities of protein and electrolytes ingested, it is obvious that the severity of the biochemical disturbances in renal failure is increased by higher intakes of these substances. It also follows that reduction of protein and electrolyte intake to minimal requirements will substantially reduce these disturbances. Thus appropriate nutrition is of paramount importance in the therapy of renal failure.

Regular dialysis therapy alters this situation drastically, since both nitrogenous wastes and excess electrolytes are removed. Nevertheless, many of the problems seen in patients on dialysis appear to be related to malnutrition. The causes of malnutrition in dialysis patients are poorly understood.

The optimal nutritional regimen for the pre-dialysis patient would seem to be one that meets all dietary requirements yet minimizes the requirements for renal excretion of wastes. Few attempts have been made to design such nutritional regimens. The ability of the normal kidney to reduce excretion rates to nearly zero has been demonstrated in the past for many substances, including sodium, potassium, chloride, phosphate, and acid. Urea formation can be reduced to low rates by providing only the minimal requirements of amino acids, as such or as nitrogen-free analogs. Thus it should be possible to design a nutritional regimen that minimizes the requirements for renal excretion of most urinary constituents. In a recent experiment (2) rats were infused continuously intragastrically with a mixture designed for this prupose. The animals grew at 3.5 g/day and utilized 67% of administered nitrogen for synthetic purposes. Urinary excretion rates of sodium, phosphate, and urea fell to very low levels. When this same regimen was administered to rats in which renal excretory function was reduced by 90%, growth and nitrogen excretion occurred at the same rate as in control animals (3). After 25 days, blood urea nitrogen was only 42 mg/dl. Rats fed standard diets do not survive such severe renal insufficiency for more

than a few days. These studies emphasize the impact that appropriate nutrition can have on the biochemical consequences of renal failure.

NITROGEN RETENTION

Urea

UREA PRODUCTION, DEGRADATION AND APPEARANCE Urea is hydrolyzed by bacterial urease in the gastrointestinal tract at a rate about 25% of that at which it is produced (in normal subjects), resulting in the release of an average of 3.3 g of ammonia N per day into the portal circulation (182). The colon is the principal site of this reaction (69), but some hydrolysis also occurs in the small bowel, stomach, and mouth. The resulting ammonia is converted back to urea in the liver. Hence total urea production includes this enterohepatic cycle. The difference between urea production and metabolism has been termed urea appearance or urea N appearance. This latter quantity, not total urea N production rate, is one of the components of N balance, since it represents the rate at which N is irreversibly lost from the body as urea.

In chronic renal failure, the rate of urea hydrolysis is no different from that in normal subjects (182). This has never been adequately explained, since intestinal urease is apparently increased in uremic gut (31) and the higher concentration of urea in body fluids should result in an increased rate of hydrolysis.

Urea N appearance is a useful measure for estimating N balance in uremic patients, since N excretion in forms other than urea tends to be nearly constant (105). This indirect estimate of N balance is far simpler than total N analysis of excreta. Further, low values of urea N appearance (4 g per day or less) demonstrate effective N conservation and are generally incompatible with a large negative N balance. The lowest sustained values for urea N appearance reported in patients with chronic renal failure are about 1 g per day (4).

UREA TOXICITY The symptoms and signs of uremic toxicity have long been known to be correlated with the level of blood urea. This is because the accumulation of toxic products of protein catabolism is correlated with the accumulation of urea. Urea itself is not toxic at levels below 100 mg per dl of urea N. This is shown by the absence of uremic symptoms in subjects with normal kidneys who continuously ingest enough protein to maintain blood urea N over 60 mg per dl (145) or who are given urea as a diuretic (50, 123). Furthermore, the addition of urea to the dialysis bath in patients on regular dialysis does not induce any symptoms, provided the amount added is relatively small (84, 88, 93, 122).

At higher concentrations (150 mg per dl or higher), urea is clearly toxic. This is most clearly demonstrated in patients dialyzed against baths containing high concentrations of urea, in whom symptoms such as nausea, vomiting, itching, lethargy, and tremors appear (84, 88, 93, 122).

Whether the toxicity of urea is caused by the substance itself or by a putative increase in intestinal ureolysis has not been established, because these studies have not been repeated in patients in whom bacterial urease was reduced by antibiotics. Evidence from animal studies suggests that increased urea breakdown plays a role. For example, germ-free rats or rats pretreated with oral neomycin (142) survive longer than conventional animals after nephrectomy (56) and have less severe uremic colitis (35). Portal blood ammonia is increased in nephrectomized rats, and the pH, and therefore pNH_3, of cecal contents is increased (142). Immunization against bacterial urease prolongs survival of nephrectomized or ureteral-ligated dogs and protects them against uremic colitis (111).

These findings can be reconciled with the observations summarized above showing that urea degradation is not increased in chronic renal failure by assuming that it is increased when blood urea rises rapidly. If this is correct, suppression of urea degradation by one means or another should be of therapeutic value in acute renal failure in man. Evidently this has not been tried.

An important corollary of the observation that urea is not toxic at blood urea N levels below 100 mg per dl is that attempts to reduce urea selectively in patients with urea concentrations in this range are pointless. Thus the use of microencapsulated urease (39) or sodium benzoate (124) in such patients lacks a rationale.

UREA NITROGEN REUTILIZATION From the earliest studies of nutritional therapy of renal failure (71) the suggestion has recurred that such patients may be able to utilize the ammonia N derived from urea breakdown for synthesis of amino acids. That ruminants can utilize urea N synthetically is well established (30), and there is also evidence that N balance of normal subjects fed urea may improve under certain circumstances (67, 163, 173). The first evidence that this might occur in uremic patients was based on a misinterpretation of isotopic studies using ^{15}N. The appearance of labelled N, administered as urea or as ammonia, in protein was viewed as evidence for such utilization, while it is actually an inevitable consequence of exchange reactions, such as that catalyzed by glutamate dehydrogenase. Even when the net flow of this reaction in vitro is in the direction of ammonia formation, the addition of labelled ammonia will lead to the appearance of labelled glutamate. In the body, glutamate will in turn exchange labelled nitrogen with other amino acids by transamination.

It would appear that studies with labelled N cannot shed light on the existence of urea N reutilization. A more definitive test of this hypothesis was to suppress bacterial degradation of urea in patients on low-protein diets by administering oral neomycin or kanamycin. If urea N were being used synthetically, this measure should have led to deterioration of N balance, with an

associated increase in urea N appearance. However, urea N appearance did not change (127) and N balance improved slightly but significantly (129). The improvement was evidently attributable to reduced endogenous fecal N. Clearly urea N reutilizaiton did not occur in these subjects.

A negative rate of urea N appearance would also be evidence for urea N reutilization. Although very low rates are seen in patients given keto-analogs, negative rates have only rarely been reported (183).

In conclusion, there is no evidence for urea N reutiliation in uremia, even though there is evidence for urea N utilization in normal subjects, at least under certain circumstances.

Ammonia

Urinary ammonia excretion is decreased in renal failure, in relation to the loss of functioning nephrons. This defect contributes to the development of uremic acidosis.

Creatinine and Creatine

As renal insufficiency progresses, urinary creatinine output falls. In severe renal failure, output may be as little as one third of normal (130). This is not the result of accumulation of creatinine in body fluids, because creatinine "appearance," defined as urinary excretion plus change in the body creatinine pool, also falls. Some loss of creatinine in the stool occurs. However, this is far too small to account for the reduced urinary output. It was assumed for many years that a fall in lean body mass, and therefore in the body creatine pool and hence creatinine production, was responsible. However, Jones & Burnett (94) showed that creatinine is extensively metabolized in patients with chronic renal failure. They postulated that creatinine destruction by bacterial enzymes in the gut was responsible, and showed that bowel contents can degrade creatinine. Mitch et al (125) obtained evidence that some creatinine is rehydrated to creatine in such subjects. They also showed that creatinine production is within normal limits in such subjects. Whether the products of creatinine metabolism (other than creatine) are toxic has not been established.

The ratio of urea clearance to creatinine clearance in patients with moderate or severe renal failure averages about 0.6 (183).

Uric Acid

Urinary excretion of uric acid falls progressively as chronic renal failure becomes more severe (57). This is not the result of uric acid accumulation in body fluids; hyperuricemia is common but usually of mild degree. The reduction in uric acid appearance is attributable to uric acid degradation by intestinal bacteria (165) and, in patients on low protein diets, to lower purine intake.

When hyperuricemia is pronounced (over 13 mg per dl in men or 10 mg per dl in women), it should be treated, because functional damage to the kidney may ensue (62). However, treatment of lesser degrees of hyperuricemia with allopurinol has no effect on the rate of loss of renal function (148) and is therefore not indicated.

PROTEIN REQUIREMENTS

In Pre-Dialysis Patients

The principle of restricting protein intake and of optimizing the biological quality of ingested protein has been generally accepted for several decades. These measures increase the efficiency with which ingested nitrogen is utilized for synthetic purposes. They also reduce the ingested quantities of total nitrogen, including nonprotein nitrogen, potassium, phosphorus, and sulfur, thereby reducing the requirements for excretion of urea, uric acid, potassium, phosphate, sulfate, and acid. Thus the tendency of such patients to develop azotemia, acidosis, hyperkalemia, and hyperphosphatemia with all its consequences is diminished.

Obviously the requirements for essential amino acids must be met, or progressive protein deficiency will develop. Furhtermore, the diet must be sufficiently palatable to ensure patient compliance.

Controversy continues over the question of how much protein is required to maintain N balance in patients with renal failure. Many features of the altered metabolism of uremia might promote protein catabolism and hence increase requirements beyond those of normal subjects. Most obvious are proteinuria and occult gastrointestinal bleeding. The latter can be detected in a substantial fraction of chronic uremic patients by isotopic methods (77). It increases protein requirements not only by virture of blood proteins that may not be completely reabsorbed, but also because they cannot be resynthesized with complete efficiency. Likewise, proteinuria increases protein requirements, by more than the daily loss of urinary protein. Hormonal disturbances in uremia may increase protein requirements, including hyperglucagonemia (22) and carbohydrate intolerance (52).

On the other hand, the reduced rates of excretion of non-urea urinary nitrogenous components mentioned above tend to reduce N requirements. Even though urea N reutilization is evidently a myth, N balance can be maintained in some uremic patients on remarkable low intakes (73).

The consensus seems to be that 0.57 g per kg of protein (40 g per 70 kg), predominantly of high biological value, is adequate to maintain N balance in the absence of substantial proteinuria or occult blood loss (104).

In order to maintain blood urea N level below 100 mg per dl on such a regimen, it is necessary for urea clearance to be at least 3 ml per min per 70 kg. This is because this N intake, 6.4 g per 70 kg, minus an average value for non-urea N excretion of 2 g per day (see above), leaves 4.4 g per day of N to be excreted as urea N. Dividing 4.4 by 1.0 gives a urea clearance of 4.4 liters per day or 3.1 ml per min per 70 kg. This corresponds to a creatinine clearance of approximately 5 ml per min per 70 kg and a plasma creatinine concentration of approximately 13 mg per dl.

As noted below, there may be additional reasons for employing forms of dietary therapy other than simple protein restriction at an earlier stage of chronic renal failure, but clearly this approach will not control azotemia adequately if plasma creatinine exceeds 13 mg per dl.

In Children

Additional protein is required for growth in children with renal failure (87).

In Dialysis Patients

Because of the losses of amino acids in the dialysate that occur in hemodialysis patients, amounting to about 8 g per day (14), an intake of 1 g per kg of protein is required to maintain N balance (70). During peritoneal dialysis plasma proteins are also lost in the dialysis fluids. Continuous ambulatory peritoneal dialysis causes the loss of 4–6 g per day of protein (24, 134, 191), and even more when peritonitis develops (134). The dietary protein requirement of patients treated in this manner may be as high as 1.4 g per kg per day (25, 114).

USE OF ESSENTIAL AMINO ACIDS

In Pre-Dialysis Patients

Since L-amino acids first became generally available, a number of workers have reported on their use in chronic renal failure, generally in conjunction with a diet containing 20–30 g per day of protein of mixed quality (0.29–0.43 g per kg per day). The advantage of this diet, as first pointed out by Bergström, Fürst & Norée (19) is that much more variety is possible in the choice of foods when protein quality is not restricted. This makes such diets more acceptable to many patients than diets containing 40 g of protein of predominantly high biological value (95).

The composition and daily dosage of essential amino acids employed in these recent studies has varied considerably. Initially essential amino acids were used in proportions close to their relative requirements in normal man. Alvestrand et al (10), after noting the amino acid composition of intracellular fluid of muscle in such patients (20), increased the proportion of valine and

reduced the proportions of leucine and isoleucine. Improvement in intracellular amino acid concentrations and in N balance was seen.

The problem of designing an ideal formulation of amino acids for use as a dietary supplement in chronic renal failure is as difficult as it is important. Clearly the constituents and their proportions should not be simply the "Rose proportions" of eight essential amino acids. Histidine is clearly an essential amino acid in patients with chronic renal failure and can probably be synthesized only to a very limited extent in normal subjects (107, 108).

In Patients on Dialysis

Partly because of the substantial losses of amino acids that dialysis causes, and partly because malnutrition is common in dialysis patients despite apparently adequate intakes of protein and energy (5, 150, 158, 171), supplements of essential amino acids have been provided in several studies in hopes of improving protein nutrition. Heidland & Kult (85) observed a rise in the plasma levels of several proteins, including transferrin and albumin, when essential amino acids were given intravenously near the end of each hemodialysis for one year. Acchiardo et al (6) administered oral essential amino acids daily for 10 months, in conjunction with 1 g protein per kg per day, to patients on hemodialysis. In comparison with patients receiving a carbohydrate supplement, those on amino acid supplements exhibited an increase in body weight, hematocrit, serum albumin and transferrin, lymphocyte count, and the quantity of trabecular bone; serum triglycerides also rose but serum calcium, phosphate, urea, and cholesterol remained constant, as did nerve conduction velocity. Lamperi et al (110) gave 6–12 g of essential amino acids to patients on continous ambulatory peritoneal dialysis who were receiving 0.9 g per kg per day of protein. In the previous control period, they had been receiving 1.2 g per kg per day of protein. Plasma amino acid levels did not change significantly, but serum albumin rose; hypertriglyceridemia abated.

Thus it would appear that the essential amino acid needs are not fully met in hemodialysis patients eating 1 g per kg per day of protein nor in chronic ambulatory peritoneal dialysis patients consuming 1.2 g per kg per day of protein. Why this is so remains unexplained.

A different approach has been employed by Mitch & Sapir (128), who restricted protein intake to 0.3 g per kg per day, provided 20 g per day of essential amino acids, and reduced dialysis frequency to once every two weeks. Nutrition and N balance were well maintained.

In Patients with Acute Renal Failure

Most patients with acute renal failure are unable to eat normally and require parenteral nutrition. The possibility that parenteral essential amino acids might reduce morbidity and mortality of this disorder was suggested by Abel, Beck &

Abbott (1), who reported hastened recovery of renal function and reduced mortality. Others (15) observed that admininstration of a protein hydrolysate intravenously reduced mortality significantly. Unfortunately, subsequent work has failed to confirm the reduced mortality reported in these initial studies (60, 61, 63, 164). Furthermore, it is not clear whether essential amino acids alone or a mixture containing nonessential amino acids too should be provided (60, 61). Animal work has also yielded conflicting results on this question (137, 168, 170). Thus it remains an open question whether parenteral amino acids are useful in the treatment of chronic renal failure. In future studies in this area, it will become increasingly important to differentiate between patients who exhibit hypercatabolism, with urea N appearance rates of the order of 10 g per day in the absence of N intake, and those who have more normal urea N appearance rates of the order of 4 g per day. Unless protein catabolism can be suppressed in the former group, it is doubtful whether provision of any mixture of amino acids would be beneficial.

USE OF N-FREE ANALOGS OF ESSENTIAL AMINO ACIDS

Principles of Therapy

Since the first step in the major metabolic pathway of four of the essential amino acids (valine, leucine, isoleucine, phenylalanine) is reversible transamination to the corresponding alpha-ketoacid, it is not surprising that these ketoacids can serve as dietary substitutes for the corresponding amino acids. Furthermore, essential amino acids for which transamination is a minor but recognized pathway of metabolism (methionine, tryptophan, and histidine) can also be replaced in the diet by their corresponding keto-analogs. Lysine and threonine do not undergo transamination and therefore cannot be replaced by their keto-analogs. All of these findings have been documented in animals [see (45) for review]. The fact that more than equimolar quantities, particularly of the branched-chain ketoacids, are required to attain growth equal to that promoted by the corresponding amino acids has been attributed to partial degradation of the ketoacids by oxidative decarboxylation. Rat liver contains relatively high activity of branched-chain ketoacid dehydrogenase (97), which may account for the relatively poor growth response of this species to ketoacid-containing mixtures.

Schloerb (156) and Richards et al (147) suggested the use of these compounds in the treatment of chronic renal failure, chiefly on the basis of the now discredited idea of urea N reutilization. Several workers showed that one or more essential amino acids could be replaced in the diet of normal subjects or patients with chronic renal failure by the corresponding ketoacid plus an equimolar quantity of nonessential N, with little or no change in N balance (68, 144, 146, 149). Subsequently the alpha-hydroxy analogs of some of the

essential amino acids (methionine, phenylalanine, and tryptophan) were shown to be adequate dietary substitutes in rats (41). Later work has established that N balance can be maintained in patients with chronic renal failure on virtually protein-free diets in which branched-chain ketoacids are provided in daily doses of 2–3 g per day, phenylalanine as L-phenyllactate, 2 g per day, and methionine as D,L,alpha-hydroxy-gamma-methylthiobutyrate, 2 g per day (131, 132). These doses are all higher than the requirements for the corresponding essential amino acids in normal subjects. Whether lower doses would suffice is not known.

Apart from being N-free substitutes for essential amino acids, these compounds have anabolic properties. Ketoleucine (133) or the three branched-chain ketoacids (154) reduce N losses in fasting obese subjects. Leucine was ineffective in these subjects (133). Ketoleucine improves N balance and reduces muscle protein breakdown in fasting postoperative patients, while leucine does not (153).

Levels of branched-chain ketoacids are lower in the plasma of uremic patients than in normal subjects on the same diet (155).

In Chronic Renal Failure in the Pre-Dialysis Stage

Walser et al (183) administered 5–7 analogs to patients with chronic renal failure without providing equimolar nonessential N and found that urea N appearance was significantly reduced and N balance improved, compared with a subsequent control period. When blood urea was markedly elevated this response failed to occur. Later, the D,L-hydroxy-analog of methionine was substituted for the keto-analog, which is considerably more difficult to synthesize. L-phenyllactate was also shown to be an adequate substitute for phenylpyruvate, and offered the advantage of somewhat improved palatability.

Keto-analogs of tryptophan and histidine, used in two patients in the initial study (183), were replaced by the amino acids as such, because both keto- and hydroxy-analogs of these amino acids are also difficult to synthesize.

The keto-analog of isoleucine exists in two stereoisomeric forms, R(−)- and S(+)-alpha-keto-beta-methylvalerate, the transamination products of L-alloisoleucine and L-isoleucine, respectively. The racemic R,S-mixture was used in all but a few patients in the first study (183) because it is much easier to synthesize and maintains N balance in chronic uremic patients in the absence or near-absence of dietary isoleucine (132, 133). However, when administered in relatively large doses (0.5 mmol per kg per day) it causes plasma isoleucine concentration to fall instead of to rise, for unknown reasons (185). Therefore the S(+) isomer might be preferable.

Numerous studies have been reported in which the keto-analogs of valine, leucine, isoleucine, and phenylalanine, the D,L-hydroxy-analog of methionine, and the other essential amino acids (including histidine) have been

given to patients with chronic renal failure as calcium salts in a daily dose of 6–12 g, along with the remaining essential amino acids and a 20–30 g protein diet. Studies prior to 1981 were summarized by Mitch et al (126). At least seven additional studies have appeared subsequently (17, 18, 55, 66, 78, 157). Improvement in nutritional status, as measured by anthropometry, plasma protein levels, N balance, blood urea N, and serum phosphate has been observed in almost all the patients in these studies. However, in one study (78) no improvement was seen in younger patients with chronic glomerulonephritis, in contrast to the results in older patients or those with polycystic disease. Reduced serum levels of parathyroid hormone have been noted in several studies (55, 66, 157). Testosterone levels and sexual function improved in male patients in one study (66). Effects on the progression of chronic renal failure are dicussed below.

In contrast to these results, two other studies in which nitrogen intake was greater (7–9 g per 70 kg) found no significant benefit from the addition of a ketoacid-containing supplement (33, 83). This is not surprising, since the essential amino acid requirements of these subjects were probably met by the diet. Furthermore, the rate of destruction of ketoacids by oxidative decarboxylation is known to be greater on higher protein intakes (58).

The only side effects noted in these studies have been gastrointestinal distress, variously reported as occurring in up to 15% of patients, and rarely hypercalcemia (91, 180). The calcium salts of branched-chain ketoacids and of phenylpyruvate are particularly unpleasant tasting, and most of these studies have utilized ketoacids in coated granules or tablets. Both of these formulations cause some difficulties with patient acceptance for physical reasons. Another effect noted has been the appearance of alloisoleucine in the plasma, reflecting the transamination of R(−)-alpha-keto-beta-methylvalerate (185).

In most of these studies, the control period has consisted of observations in the same patients while they receive a protein-restricted diet. However, several comparisons of ketoacid-containing supplements with essential amino acids have been reported. In the first (179), a lower rate of urea N appearance and improved N balance was noted in short courses of therapy in patients receiving ketoacids as compared with essential amino acids. In the second (86), patients received essential amino acids for six months followed by a keto-analog-containing mixture for six more months, both given as coated granules of identical appearance. During the ketoacid-treatment period, blood hemoglobin and concentrations of several serum proteins rose; phosphate fell and calcium rose. The third study (33) utilized high N intakes and observed no benefit from either therapy. In the fourth (157), 40 patients received essential amino acids and 50 received ketoacids for an average of 7–9 months. Both groups had severe chronic renal failure (serum creatinine about 10 mg per dl) and were given 0.4 g per kg of protein. In both groups improvement in N balance, de-

crease in blood urea N, and increase in serum transferrin occurred. Acidosis improved, serum phosphate fell, and serum parathyroid hormone levels decreased by 40% only in those receiving ketoacids.

In none of these studies has the concentration of plasma amino acids been reported as returning to normal, although improvement is usually noted.

In Patients on Hemodialysis

Five patients on hemodialysis were given a ketoacid-containing supplement. After 4 weeks improved nutritional status was noted and a reduction in the frequency of dialysis became possible (55). In another study, ketoacid supplementation in dialysis patients led to reduced parathyroid hormone levels within three months (113).

ENERGY REQUIREMENTS FOR NITROGEN SPARING AND ABNORMALITIES OF FAT AND CARBOHYDRATE METABOLISM

According to one report (89), N balance in patients with chronic renal failure improves on constant N intake as caloric intake is increased up to and including 55 kcal per kg per day. It has also been shown that animals with experimental uremia exhibit an excessive protein catabolic response to fasting (187). Thus provision of adequate calories is an important feature of the nutritional therapy of uremia. This is particularly true in children, in whom efforts to improve energy intake may be rewarding in terms of growth. One aspect of dialysis patients' dietary practices that may play a major role in the malnutrition often seen is poor energy intake. According to a recent study, average intake is only 23 kcal per kg per day (158). The recommended dietary allowances for energy are 38 and 36 kcal per kg for men and women aged 23–50 years, and 34 and 33 kcal per kg for men and women over age 50 (47).

Carbohydrate intolerance is characteristic of uremia, and low-protein diets necessarily entail some increase in carbohydrate intake. The principal defect in carbohydrate metabolism is peripheral resistance to insulin (53). Peripheral uptake of glucose is reduced but becomes normal after an amino acid load (51). Hyperglycemia and/or ketosis are rarely seen. Insulin-dependent diabetics usually exhibit a decline in insulin requirements as renal failure progresses.

Abnormalities of fat metabolism are also common in uremic patients, particularly those on dialysis. Hypertriglyceridemia is prominent in patients on continuous ambulatory peritoneal dialysis, probably because of continuous glucose absorption with resultant insulin release (79). It has been attributed both to decreased removal by lipoprotein lipase (12, 38) and to increased production. When the proportion of carbohydrate in the diet is reduced in

pre-dialysis patients or in dialysis patients, hypertriglyceridemia diminishes (151, 152). Increasing the ratio of polyunsaturated to saturated fats in the diet has a similar effect (74, 75, 186), as does exercise (76).

Recently, deficiency of carnitine, owing to its loss into the dialysis bath, has been recognized as a factor in hyperlipidemia. Carnitine is required for the transport of fatty acids across the mitochondrial membrane. Low levels of carnitine are demonstrable in muscle and myocardium of chronic uremic patients. Muscle weakness may also ensue. Oral administration of L-carnitine, 1 g per day, improves muscle strength and reduces hyperlipidemia in dialysis patients with a concomitant increase in serum and muscle levels of carnitine and acetyl carnitine (8, 176). Anemia may also improve, for unknown reasons (174). Intravenous administration of carnitine at the end of each dialysis augments HDL-cholesterol levels (36), a fraction associated with reduced mortality from coronary atherosclerosis, and lowers total serum cholesterol (80). Hormone levels are unaffected (8).

Acetate dialysis causes unique disturbances of energy metabolism. As much as 40% of total oxygen consumption may be accounted for by acetate oxidation. Another moiety of absorbed acetate (about 1/3) enters nonoxidative pathways and may be directed to fat synthesis (159).

PARENTERAL AND ENTERAL ALIMENTATION

The use of intravenous essential amino acids in acute renal failure has been discussed. Parenteral nutrition may also be useful in chronic renal failure, particularly during acute illnesses that cause nausea and vomiting, preventing oral intake. Essential amino acids, glucose, and lipid emulsions are all useful for this purpose. A rapid fall in plasma phosphate may ensue during parenteral alimentation (101).

Continuous nasogastric alimentation in chronic renal failure was briefly described by Meng (121). The results, in terms of reduction of blood urea N and clinical response, were encouraging. Guillot et al (82) fed three children with chronic renal failure by nasogastric tube for 4–45 months. Protein intake (as casein hydrolysate) was 1.5–2 g per kg. Two of the three children grew at normal rates. No attempt was made to minimize the formation of waste products; instead, the rationale was to ensure an adequate intake of nutrients. A different approach was taken by Abras & Walser (4). Patients with severe chronic renal failure were given an average of 76% of their caloric intake and 68% of their nitrogen intake by continuous intragastric infusion of a mixture of oligosaccharides, keto-analogs, and amino acids, designed to minimize the production of waste products requiring renal excretion. Although total N intake averaged only 3.3 g per day, N balance averaged +1.22 g per day. All com-

ponents of waste N excretion fell to very low values. Serum albumin and transferrin remained normal.

The utility of this technique in adults is probably limited to those who are awaiting the maturation of an arteriovenous fistula or are not candidates for dialysis for one reason or another. It might be more generally useful in children or in infants (in whom a gastrostomy or jejunostomy tube would by preferable), since such patients generally do not do well on dialysis.

LONG-TERM EFFECTS ON PROTEIN NUTRITION

In Pre-Dialysis Patients

Over-enthusiatic protein restriction is a potential cause for severe malnutrition in conservatively managed patients. This seems to be relatively uncommon. Several studies of adults treated for months or years with essential amino acids or keto-analogs have documented that protein nutrition is usually well maintained (7, 13, 184). In children, however, growth impairment and malnutrition are common (54, 87, 140, 141).

In Dialysis Patients

Despite apparently adequate protein intake, many patients on dialysis exhibit signs of malnutrition (5, 158, 171). One reason may be poor energy intake. Children fare even worse, and children on continuous ambulatory peritoneal dialysis usually exhibit both growth retardation and protein malnutrition (150). However, children on continuous ambulatory peritoneal dialysis given over 2 g per kg per day of protein and sufficient 1,25-dihydroxy vitamin D plus oral calcium to control hyperparathyroidism may exhibit normal height velocity for bone age (103)

NONDIETARY TECHNIQUES OF CONTROLLING N RETENTION

Other than dialysis, several novel approaches to the control of azotemia have been described. None has been widely accepted.

Adsorbents

Urea and other nitrogenous wastes can be trapped in the gut by giving a variety of adsorbents, including activated charcoal, zirconium, and microencapsulated urease. As noted above, the removal of urea alone offers no benefit unless blood urea N is well above 100 mg per dl. If it is, protein intake is excessive in relation to the amount of renal function remaining, and should be reduced. Since adsorbents do not remove all of the substances found

in high-protein foods that accumulate in the body fluids of uremic patients, their use cannot achieve the same benefit as protein restriction.

One use of adsorbents offers promise, namely, reduction of hyperlipidemia by ingestion of activated charcoal. The mechanism is unknown, but the magnitude of the effect may be substantial (64).

ABNORMALITIES OF DIVALENT ION METABOLISM

Pathogenesis

Hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, vitamin D deficiency, and osteodystrophy are all characteristic of chronic renal failure, especially when it is severe. The primary cause of these disturbances has been debated for years, but still remains uncertain. Although phosphate retention could in theory lead to all of these disturbances, and phosphate restriction in experimental renal failure may prevent or reverse them (96, 160), the difficulty with this explantation is that secondary hyperparathyroidism and, in some cases, hypocalcemia, develop before phosphate retention, either fasting or postprandially, can be demonstrated (100, 178). Resistance to parathyroid hormone is demonstrable at an early stage of renal failure (115). The cause of this abnormality is unknown. Reduced levels of 1,25-dihydroxy vitamin D are usually seen only in late renal failure (42, 98, 161) or in children (139).

Although it was believed for some time that 1,25-dihydroxy vitamin D, the active hormone, is produced only in the kidney, recent work has shown that this may not be correct (16). Nevertheless, plasma levels of this substance are low or undetectable in dialysis patients (109, 161).

Phosphorus Restriction and Aluminum Hydroxide Administration

Despite abundant evidence that dietary phosphorus restriction can prevent or correct secondary hyperparathyroidism in experimental renal failure, this measure is rarely employed in patients. Apparently this is because of a widespread belief that any degree of dietary phosphorus restriction is intolerable. However, the elimination of milk, milk products, cheese, colas, and "instant" powdered beverages will reduce phosphorus intake substantially. When combined with modest protein restriction (40 g per day) these measures will produce a phosphorus intake of approximately 600 mg per day, or half of the usual intake in the United States.

In contrast, basic aluminum salts are frequently employed with the aim of reducing the intestinal absorption of dietary phosphate. Since the maximal phosphate-binding capacity of these gels is 130 mg of phosphorus per g of dry gel (166), at least 5 g per day of gel would be necessary to reduce phosphorus absorption as much as the dietary restriction described above. In practice, the effect on phosphorus absorption of aluminum salts is probably considerably

less, since only a portion of dietary phosphorus exists as or is absorbed as inorganic phosphate. The absorption of phosphorus from phosphopeptides, nucleic acids, phospholipids, and other organic phosphates may not be susceptible to inhibition by aluminum. The use of aluminum salts with no attempt to restrict dietary phosphorus is analogous to the use of diuretics with no attempt to reduce dietary salt. Both practices are indefensible.

Alfrey and associates (9) called attention to the association between dialysis dementia and aluminum accumulation in the brain. Since the kidney is the only route for elimination of absorbed aluminum, higher tissue levels are caused by equal doses in uremic as compared with normal animals. In animals, aluminum salts injected intraperitoneally impair bone mineralization by depositing at the mineralization front. An association between bone aluminum and osteomalacia has been noted in biopsy samples from uremic patients (99).

Initially, this clearcut aluminum toxicity was attributed to aluminum uptake from water used in the dialysis bath. The possibility that oral aluminum salts might cause serious toxicity was discounted, particularly since no such toxicity was evident in patients without renal failure who consume aluminum salts on a chronic basis, unless they became phosphate-depleted. However, recent evidence has established that oral aluminum is at least as important as dialysate aluminum in causing excessive aluminum absorption. For example, reduction of dialysate aluminum levels to zero by use of reverse osmosis for 1 yr failed to alter plasma aluminum in patients taking $Al(OH)_3$ by mouth (169). From these studies it is clear that chronic ingestion of $Al(OH)_3$ is hazardous in patients with renal failure, even if hypophosphatemia does not develop.

Desferrioxamine treatment for 6 months improves osteomalacia in dialysis patients, even though it apparently does not reduce bone aluminum (32).

Calcium Supplements

Intestinal calcium absorption is reduced early in the course of renal failure (46), before vitamin D levels in the plasma fall. Later vitamin D deficiency further aggravates this problem. Both azotemia and acidosis independently augment renal excretion of calcium (118). Calcium balance is commonly negative in uremic subjects, unless calcium supplements are given (46). Hypocalcemia is attributable both to calcium deficiency and to hyperphosphatemia, as indicated by the observation that serum calcium rises towards normal as serum phosphate falls during adminstration of $Al(OH)_3$ (65).

Calcium supplements are also advocated by some as a measure to counteract uremic acidosis. This practice is considerably more common in Europe than in the United States. It appears to be based, at least partially, on a misconception. In order to increase the bicarbonate content of the extracellular fluid, it is obviously necessary to increase the sodium content, since an equivalent increase in the content of calcium or any other cation except sodium would be undesirable. Thus $CaCO_3$ can combat uremic acidosis effectively only by

virtue of calcium-sodium exchange at the bone surface, an inherently limited process, or by suppressing secondary hyperparathyroidism and thereby ameliorating renal wastage of sodium and bicarbonate. Whether this latter effect indeed occurs at all has yet to be demonstrated. Thus it would appear that calcium supplements can have only a transient effect in combating uremic acidosis, and indeed this seems to be the case (21, 117).

Another problem with the use of calcium supplements, in the presence of hyperphosphatemia, is the possibility of aggravating renal insufficiency, owing to deposition of calcium and phosphate in the kidney as discussed in more detail below. In both of the studies cited (21, 117), patients in whom an increase in the serum Ca × P product occurred during $CaCO_3$ treatment also tended to exhibit a rise in serum creatinine. Since this latter change occurred within a few weeks it cannot be attributed to the natural progression of the disease but must have been the result of the $CaCO_3$ administration. This correlation was not noted by these authors and only became apparent on retrospective analysis of their data (181).

Thus a question must be raised as to whether oral calcium supplements are safe in hyperphosphatemic patients, even though they can be used to combat hyperphosphatemia (by inhibiting intestinal phosphate absorption). A better approach would appear to be to attempt to reduce serum phosphate by dietary restriction, and if necessary by short-term $Al(OH)_3$, before adding calcium supplements.

There seems little justification for using calcium salts other than $CaCO_3$ for this purpose. It is true that others are more soluble and might be more effective in achlorhydric patients for this reason. But they all contain much less calcium per g, necessitating greater bulk, and are without exception far more expensive.

There is no question that oral $CaCO_3$ is effective. For example, in one recent study, $CaCO_3$ in a dose of 10–12 g per day was as effective as or more effective than $Al(OH)_3$ 4–5 g per day plus $CaCo_3$ 4–6 g per day on serum phosphate, calcium, and C-terminal as well as N-terminal parathyroid hormone levels in hemodialysis patients (135). Hypercalcemia occasionally occurs, especially in patients on 1,25-dihydroxy vitamin D.

Use of Vitamin D in Various Forms

With the availability of the most potent metabolite of vitamin D, 1-alpha,25-dihydroxycholecalciferol (1,25-dihydroxy vitamin D), interest in the therapeutic use of this vitamin in chronic renal failure has been renewed. However, similar results can be obtained with dihydrotachysterol, a drug available for decades, or with the less expensive analog, 1-alpha-hydroxy vitamin D. All of these drugs increase intestinal calcium absorption and inhibit tubular reabsorption of phosphate. Unfortunately they also promote intestinal absorption of phosphate, so that the net effect is often to increase serum phosphate. By raising serum calcium and probably by a direct action on bone mineralization

they suppress secondary hyperparathyroidism and promote healing of renal osteodystrophy.

In patients on dialysis (the only FDA-approved indication for 1,25-dihydroxy vitamin D), these compounds have proven very useful. In pre-dialysis patients, however, they are potentially very dangerous when employed in the presence of hyperphosphatemia or in near-end-stage patients. Under these conditions they may accelerate the progression of renal failure (43, 48, 136, 189). This effect is usually associated with hypercalcemia (a common problem in their use) but occasionally occurs even when hypercalcemia does not develop.

24,25-Dihydroxy vitamin D may have beneficial effects on bone mineralization without the propensity to induce renal damage (44). It decreases PTH levels in uremic dogs (34) or patients (81) and has little tendency to cause hypercalcemia (29, 34, 44, 81).

In early renal failure, the likelihood of aggravating renal insufficiency is far lower because hyperphosphatemia is not generally present. In such patients, active forms of vitamin D could even slow progression, perhaps by conteracting secondary hyperparathyroidism (see below), despite the fact that circulating levels of 1,25-dihydroxy vitamin D are usually normal in this stage. Children with renal failure usually show improved growth during vitamin D supplementation (37, 40) and may require fewer corticosteroids (172).

Magnesium

Oral administration of magnesium-containing antacids may induce dangerous hypermagnesemia in patients with renal failure, owing to defective renal excretion (143). Nevertheless, if serum magnesium is monitored and these salts are used continuously, they might be effective in reducing intestinal phosphate reabsorption without the potential dangers of $Al(OH)_3$ or calcium salts. In pre-dialysis patients total plasma magnesium is usually close to normal, but ionized magnesium may be low, owing to an increase in the complexed fraction (28). Intracellular magnesium stores are more likely to be high (49) than low (112). Eliminating magnesium from the dialysis solution in patients on continuous ambulatory peritoneal dialysis reduced serum magnesium to normal in association with a loss of 4 mmol per day of magnesium into the dialysate (138).

ABNORMALITIES OF NA, K, WATER, AND ACID BASE BALANCE

Acidosis

Uremic acidosis is caused by accumulation of phosphate, sulfate, and organic acids, impaired ammonia excretion, and renal bicarbonate wastage. The extent

of the last-named process is extremely variable, and extends from the extreme form seen in congenital renal tubular acidosis to essentially zero in some patients. Hence the requirement for $NaHCO_3$ supplements also varies enormously, from zero to as much as 14 mEq per kg in renal tubular acidosis. In patients with renal tubular acidosis this measure alone may induce normal growth (120).

Some improvement in acidosis will result from protein restriction alone, since the major source of acid in acid-ash diets is dietary protein and particularly its sulfur content. Correction of acidosis is important to prevent the continued dissolution of bone salt that it induces, to reduce symptoms directly attributable to reduced pH (which are probably not apparent until serum bicarbonate is 16 mM or lower), and to combat the protein catabolic effect of acidosis. An alkaline-ash diet, comprised mainly of fruits and vegetables, may help but is rather monotonous.

The oral requirement for $NaHCO_3$ must take precedence in determining the optimal sodium intake in pre-dialysis patients. If acidosis cannot be controlled by $NaHCO_3$ and diuretics without progressive increase in extracellular fluid volume, dialysis must be instituted.

Sodium Balance

Chronic uremic patients differ markedly from normal persons in their ability to vary renal excretion of sodium. Normal individuals can reabsorb filtered sodium completely or can excrete over 1000 mmoles of sodium per day. Uremic patients can do neither. They excrete a large, relatively fixed fraction of filtered sodium. Hence, when sodium intake is sharply curtailed, or when extrarenal losses of sodium occur (as for example in diarrheal diseases), renal conservation fails to occur and extracellular fluid volume may become severely depleted. The resultant reduction in glomerular filtration rate is often irreversible. Likewise, when sodium intake is in excess of the ability of the kidneys to excrete sodium, progressive expansion of extracellular fluid volume with resultant edema and congestive heart failure may occur. This also may cause GFR to fall. The regulation of sodium balance is one of the most difficult aspects of conservative management of severe renal failure.

Various techniques have been developed to determine the optimal level of dietary salt in a given patient. Generally the $NaHCO_3$ requirement should be ascertained first, since this will affect the amount of NaCl to be given. Ideally, 24-hr sodium output should then be determined. Providing an amount of NaCl equal to this quantity (in milliequivalents) minus the $NaHCO_3$ intake will then maintain sodium balance.

A more difficult problem is to determine the optimal extracellular fluid volume. Relatively large volume may increase GFR (providing it does not cause heart failure), but there is at least the theoretical possibility that the

resulting hyperfiltration might eventually cause nephron damage (see below). Certainly hypertension will be accentuated.

Reducing extracellular fluid volume will help control hypertension, will reduce or eliminate edema, and could conceivably reduce slow glomerular damage secondary to hyperfiltration. But as noted above, if the reduction is too rapid or too great, irreversible glomerular damage may ensue. Bricker et al (27) showed that gradual reduction of sodium intake, in a small number of patients, was eventually associated with a comparable reduction in sodium excretion and a return of the fractional excretion to a normal or nearly normal value.

The use of furosemide (or other diuretics) is indicated in most cases of moderate or severe renal failure. When furosemide alone does not achieve satisfactory diuresis, furosemide plus hydrochlorothiazide may be more effective (190). When the diuretic is administered chronicaly, the same extracellular fluid volume can be maintained with a higher salt intake, allowing improved palatability of the diet.

Potassium Balance

Most chronic uremic subjects are able to regulate their potassium balance more effectively than their sodium balance. However, a tendency towards hyperkalemia is quite common, especially in the more advanced stages. Fecal excretion of potassium increases (175), but not enough to make up for limited renal excretory capacity. Hence potassium intake must be restricted or else a cation exchange resin in the sodium form must be administered. Modest reduction in potassium intake can be achieved by avoiding high potassium foods such as tomatoes, bananas, and oranges. More severe potassium restriction, applied to a diet already restricted in protein and sodium, poses considerable problems, and most patients will prefer to take the resin, if offered the choice, despite its inconvenience.

A small percentage of patients with chronic renal failure exhibit a tendency to hypokalemia, usually reflecting some degree of hyperaldosteronism. Oral potassium preparations that do not entail any risk of bowel ulceration are now available, and are generally more effective in combatting hypokalemia than attempts to increase the intake of foods relatively high in potassium.

Water Balance

Most chronic uremic subjects retain the ability to maintain normal serum effective osmolality (total osmolality minus urea concentration) through the combined mechanisms of thirst and vasopressin secretion. A few develop hyponatremia, especially those on severely sodium-restricted intake or those with congestive heart failure. In these, water intake must be restricted sufficiently to correct, and subsequently to prevent, hyponatremia.

VITAMINS AND TRACE MINERALS

Water-Soluble Vitamins

Supplements of B vitamins and vitamin C are indicated in most chronic uremic subjects, particularly because of dietary restrictions and partly because of increased requirements. The reason for increased requirements in pre-dialysis patients in not fully understood. Dialysis removes these vitamins. The pyridoxine requirement is 5 mg per day (106). In dialysis patients large pyridoxine supplements (300–600 mg per day) led to a reduction of plasma oxalate values towards normal (23). Pyridoxine supplements also have been reported to restore the plasma concentrations of leucine and valine towards normal in dialysis patients (102). Folic acid has also been recommended in the routine therapy of renal failure.

Fat-Soluble Vitamins

Serum levels of vitamin A and of retinol-binding protein are commonly elevated in uremic subjects (162), owing to the fact that both substances are normally cleared by the kidney. Conceivably, this defect could contribute to the abnormalities of calcium metabolism characteristic of renal failure (59, 188). Hence vitamin A should not be given. The use of active forms of vitamin D is discussed above. Inactive forms have no place in the treatment of renal failure. Thus "multivitamin" preparations are poorly suited for uremic patients. More suitable preparations are available.

Zinc

Zinc concentration is low in plasma, leucocytes, and hair of uremic patients (116). This could be a factor in the reduced taste acuity and sexual dysfunction of such patients. It is caused by dietary protein restriction and by losses in the dialysate. Oral administration of zinc is relatively ineffective in restoring normal zinc levels. Addition of zinc to the dialysate corrects hypogeusia, improves nerve conduction velocity, and restores plasma zinc to normal (167).

After transplantation, abnormalities of zinc metabolism and taste may persist for as long as a year.

EFFECT OF NUTRITIONAL THERAPY ON PROGRESSION

Recent work has raised the possibility, as yet not conclusively proven, that nutritional therapy may retard the rate at which chronic renal failure progresses. This is an exciting prospect that will doubtless receive increasing attention.

For the purposes of this discussion, effects on progression of controlling hypertension or of therapy directed more specifically at disease processes, such

as withdrawal of nephrotoxic analgesic combinations, cortisone, or immunosuppressive therapy, are excluded.

Numerous reports (11, 18, 72, 78, 92, 119, 177, 179, 184) have documented a slower progression of renal insufficiency during reduction in intake of protein and phosphate. Most of these have employed ketoacid supplements in order to reduce protein intake, but similar results have been described with esential amino acid supplements (11, 177) or no supplement (72, 92, 119). None of these studies was prospective and randomized, so that some uncertainty remains as to this purported effect. It also remains to be established whether protein restriction, phosphate restriction, or both are required. The presumed mechanism by which phosphate restriction slows progression is by antagonizing secondary hyperparathyroidism and lowering serum calcium × phosphorus product, both of which should reduce the tendency to renal deposition of calcium characteristic of chronic renal failure (90). The presumed mechanism by which protein restriction is effective is by reducing glomerular hyperfiltration in remaining nephrons, a process that may lead to glomerular injury (26). Further studies of this important problem are needed.

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