EFFECTS OF DIETARY PROTEIN AND PHOSPHORUS RESTRICTION ON THE PROGRESSION OF CHRONIC RENAL FAILURE

Kathleen Zeller, M.D.

Medical Grand Rounds

The University of Texas
Health Science Center at Dallas

September 18, 1986

INTRODUCTION

Approximately 80,000 Americans currently require chronic dialysis therapy, and an additional 30,000 can be expected to require such treatment over the coming year. Adding an anticipated 8,000 renal transplants this year, this will amount to a direct cost in excess of $2 billion for 1986. Projections for 1990 are as high as $3.5 billion, and this not including the cost of lost productivity in the work place. In addition, over 10,000 Americans are expected to die in the next year as a consequence of renal failure or related complications stemming from therapy (1). Thus, any therapeutic modalities demonstrated to slow the progression of end-stage renal disease would have a major impact on morbidity, mortality, and national health care costs.

In recent years, evidence has accumulated to suggest that early dietary intervention, in the form of protein restriction, can dramatically alter the natural history of chronic renal insufficiency. Interest in the role of protein intake in renal disease dates back to the early 1900s. In 1919 and 1923, Newburgh, and Newburgh and Clarkson reported that rabbits fed diets containing large amounts of protein developed significant renal structural damage (2). Over the next 30 years, numerous investigators would report a deleterious effect of dietary protein on the course of experimental nephritis, and on the progressive renal failure that occurs after subtotal renal ablation. In 1927, Moise and Smith found that renal lesions developed rapidly in uninephrectomized rats eating a high protein diet (3). Chanutin and Ludewig (1936) reported that increasing the protein content of the diet from 10 to 80% in rats subjected to partial renal ablation resulted in a progressive increase in proteinuria, renal failure, and mortality (4). This was confirmed by Addis (5). In 1939, Farr and Smadel reported that reducing dietary protein to 5% in rats with nephrotoxic serum nephritis resolved clinical and morphologic evidence of the disease. Control rats fed a 40% protein diet died of renal failure within one year (6).

In 1948, Addis suggested that protein intake be restricted in patients with early renal insufficiency. He argued that the excretion of urea required thermodynamic work by the proximal tubule, and therefore catabolism of large amounts of protein put a strain on this segment of the nephron. This conclusion was supported by the early observation that proximal nephron mass in rats increased substantially with high dietary protein intake. By reducing this intake, Addis hoped to decrease the strain on surviving nephrons in diseased kidneys, thus increasing their longevity (5). Subsequent studies would largely invalidate the notion of urea secretion from the proximal tubule being the major mode of urea excretion, or the concept that this is a prime source of renal work. With the advent of hemodialysis and transplantation, interest in the more general concept of dietary intervention in renal disease gradually eroded.

BRENNER HYPOTHESIS

Recently, there has been a renewal of interest in the possibility that protein restriction slows the progression of chronic renal insufficiency. This is largely due to a unique hypothesis and a series of observations that have appeared in the nephrology literature in the past several years.

Simply stated, the hypothesis generated by Dr. Barry Brenner in the late 1970's is as follows:

1. Nephron depletion, resulting from a variety of disease states, produces compensatory hyperperfusion and hyperfiltration in residual nephrons.

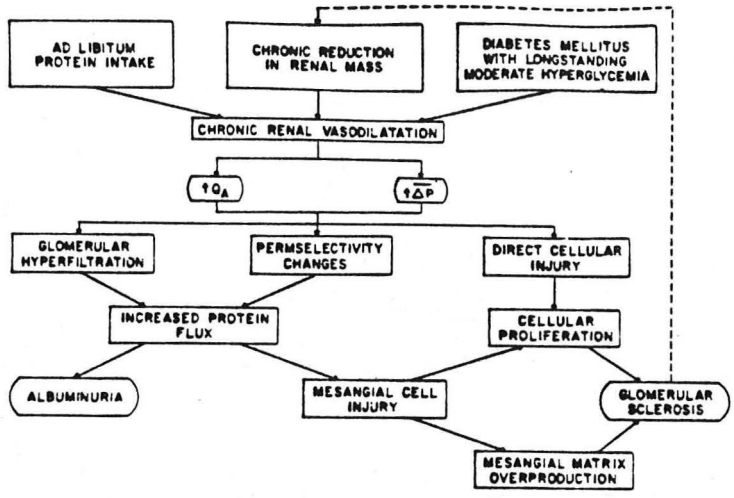
2. The increased glomerular pressures and flows that result from intrarenal vasodilation and hyperperfusion damage the glomerulus and may produce further nephron loss independent of the initial renal insult.

3. Decreasing single-nephron filtration and hyperperfusion by limiting dietary protein intake may slow the progression of renal insufficiency.

In this model of progressive renal disease, it is proposed that an initial insult damages the kidney resulting in compensatory changes by remaining "functioning" tissue. These changes include a decrease in intrarenal vascular resistance promoting arteriolar vasodilation, increased single-nephron blood flow, and therefore increased single-nephron GFR. Brenner hypothesizes that these changes occur in all types of renal disease, but become increasingly significant as fewer functioning nephrons remain (7).

He and others propose that the rise in intraglomerular pressure, resulting from arteriolar dilation, damages the glomerulus directly by altering its permselective properties, and indirectly by augmenting the transcapillary connective flux of plasma proteins. The consequence of both is enhanced protein filtration with accumulation in the mesangium. This then serves as a stimulus to proliferation of mesangial cells and matrix, culminating in glomerulosclerosis. As functioning glomeruli are destroyed, less severely afflicted glomeruli undergo compensatory hyperfiltration, thereby establishing a positive feedback loop resulting in progressive glomerular injury and eventual loss of renal function (8). Protein restriction should normalize glomerular pressures and flows thus breaking this cycle (Figure 1) (7).

Figure 1.



Role of Sustained Increments in Glomerular Pressures and Flows in the Initiation and Progression of Glomerular Sclerosis.

OBSERVATIONS

It is now well established that removal of one human kidney will result in "compensatory" hypertrophy of the other. Glomerular plasma flow and filtration rate increase by about 40% (8). Furthermore, pathologic studies in a variety of human renal diseases reveal marked hypertrophic changes, presumably reflecting "adaptive" hyperfiltration in nephron units least damaged by the original disease process.

Likewise, it has become clear that patients with renal insufficiency secondary to etiologies such as post-streptococcal glomerulonephritis, cortical necrosis, vesicoureteral reflux, or renal agenesis, can progress to end-stage renal disease, even though the initial insult is inactive or corrected. Uncontrolled hypertension or recurrent infection may contribute to this progression, but they do not account for all cases. Patients with renal insufficiency solely secondary to hypertension can develop progressive renal failure despite effective blood pressure control. Similarly, children with corrected vesicoureteral reflux frequently progress to end-stage renal disease despite correction of obstruction and infection (9). Virtually all nephrologists would agree that most patients with GFR's below 25 cc/min will eventually require dialysis or renal transplant, regardless of the original cause of reduced function (10).

In recent years, researchers have also found that GFR does indeed vary in normal humans, depending on dietary protein intake. Pullman (1954) demonstrated a rise in basal GFR (estimated by inulin clearance) of 22 cc/min in twenty normal adults followed for a period of fourteen days, first on a very low protein diet (.3 g/kg/day), and then on a high protein diet (2.6 g/kg/day) (11). Similar results were obtained by Bosch (1983) (using Cr Cl) on five members of the Nephrology Division at Mount Sinai (12). Bergstrom (1985) found substantially smaller changes in inulin clearance (13 cc/min) between a .3 and 2 g/kg protein diet after six days. Both Bosch and Bergstrom went on to demonstrate a further acute increase in GFR in the first three hours following a high protein meal, Bosch finding a 50 cc/min increment in inulin clearance with an 80 gram protein meal, and Bergstrom a 15 cc/min increase in response to 60 grams of protein. Bergstrom also reported that the response to an acute protein load was independent of previous dietary intake. (Patients on a low or high protein diet increased their GFR by approximately the same amount (Table 1) (13).

Table 1.

Effect of a mixed protein-rich meal on renal clearances (mean ± SD)

Clearance (ml/min)	Basal	30–90 min	90–150 min	150–210 min
On high protein diet				
Inulin	112.7±12.1	129.4±18.5**	126.9±8.1**	130.8±11.6**
Creatinine	125.0±12.4	139.4±20.6**	148.4±16.1**	143.3±20.2*
Urea	79.6±14.8	90.1±16.6**	95.7±14.1**	89.9±19.0*
PAH	620±93	654±65	658±65	663±109
Filtration fraction	18.4±2.3	20.2±2.7*	19.4±2.1	20.1±2.9*
On low protein diet				
Inulin	100.1±14.4	107.8±15.0*	111.5±18.7*	112.8±21.1*
Creatinine	116.9±14.2	130.4±16.2	132.8±16.9*	136.0±27.6*
Urea	67.7±11.3	79.4±13.2**	79.9±12.7**	87.8±13.6**
PAH	605±75	680±88**	678±75*	671±115
Filtration fraction	16.6±1.7	15.9±2.1	16.4±1.7	16.9±1.6

* $p<0.05$, ** $p<0.01$ compared to basal values.

These observations, together with anecdotal reports by several nephrologists of a beneficial effect of dietary protein restriction on the course of human renal disease (14), have culminated in a massive research effort, first in animals and then in humans.

ANIMAL MODELS OF RENAL DISEASE

Animal research in this field has primarily used a variety of rat models of renal disease, although more recent investigators have reported results in dogs. Studies that bear on the possible role of dietary

protein restriction fall into one of five major categories. They demonstrate:

1. Nephron Loss Results in Progressive Renal Insufficiency

The most common technique used to produce nephron depletion is subtotal nephrectomy or infarction. In 1932, Chanutin and Ferris first demonstrated in the rat that infarction of greater than 5/6 of the total renal mass was associated with proteinuria, hypertension, and progressive renal dysfunction. Shimamura and Morrison (1974) carefully documented the development of glomerular pathology in the same model. They were able to demonstrate, as early as the 10th week, an increase in glomerular size and hypertrophy of the visceral glomerular epithelial cells. Significant glomerular hyalinization started on the 25th week, and gradually became more extensive. By electron microscopy, the hypertrophic glomerular epithelial cells showed many osmophilic bodies in their cytoplasm, and fusion of foot processes. Beginning on the 30th week, areas of increasing mesangial matrix were evident, and endothelial and epithelial cells disappeared from these areas. The increased matrix eventually occluded capillary lumens and Bowman's space, leading to the formation of obsolescent glomeruli (15).

Progressive injury to remnant glomeruli in the renal ablation model occurs at a rate proportional to the amount of tissue ablated surgically or by infarction. This injury is also reflected in increasing proteinuria. Olsen (1979) demonstrated that there was a 4-fold increase in the protein excretion of rats following 90% renal ablation. When corrected for the reduced nephron mass, this amounted to a 20-fold increase in protein excretion per nephron. Studies using macromolecular tracers found defects in both the charge and size-selective properties of the glomerular basement membrane to account for this (16).

2. Hemodynamic Abnormalities Associated with Nephron Depletion

Kaufman (1975) further examined the functional and hemodynamic abnormalities that occur in the renal ablation model. After removal of 50% of the renal mass, mean nephron GFR increased 60%, and after ablation of 75% of the tissue it increased to 150%. These changes were paralleled by increases in renal growth. In comparison, mean glomerular blood flow rose 90 and 240%, after 50 and 75% nephrectomy, respectively. Using labeled microspheres to examine intrarenal blood flow distribution, he further found a disproportionate rise in blood flow to the inner cortex, and proposed that this was secondary to marked intrarenal vasodilation (17).

At approximately the same time, Brenner characterized the physiological determinants of GFR as the:

1. Initial glomerular plasma flow

2. Systemic oncotic pressure

3. Glomerular transcapillary hydraulic pressure gradient and

4. Glomerular capillary ultrafiltration coefficient (K_f) which represents the product of glomerular capillary hydraulic permeability and the total surface area available for filtration (18).

Deen (1974) then studied glomerular hemodynamics in rats three weeks after unilateral nephrectomy. Using micropuncture techniques, he demonstrated that the elevated GFR in the residual kidney was associated with an 80% increase in single-nephron GFR (SNGFR). Furthermore, this was due to two factors. First, the plasma flow rate in single glomeruli was increased proportionately to the GFR due to pronounced intrarenal vasodilation of both afferent and efferent arterioles. Secondly, the glomerular transcapillary hydraulic pressure gradient was increased, and also contributed to the hyperfiltration. K_f and systemic oncotic pressure did not vary. Ergo, the increased GFR and SNGFR found in the renal ablation model were a consequence of the increased glomerular pressures and flows resulting from renal vasodilation (19).

Since that time, numerous other investigators have demonstrated similar hemodynamic abnormalities in other rat models of renal disease. Azar (1977) showed that intrarenal hemodynamics varied greatly between DOC-salt hypertensive rats who had normal renal function, and those in whom mild dysfunction was produced by unilateral nephrectomy. In established essential hypertension in animals with intact kidneys, there is no increase in glomerular pressure, and glomerular plasma flow tends to be decreased. This is due primarily to an increase in intravascular resistance proportional to the increase in systemic blood pressure. In contrast, Azar found that once nephron loss was established, renal autoregulation failed, and glomerular blood flow increased several-fold secondary to marked intrarenal vasodilation (20).

Glassock (21) found similar hemodynamic abnormalities in rats with nephrotoxic serum nephritis, as did Hostetter in rats made diabetic with streptozotocin and then insulin treated to maintain moderate hyperglycemia (22).

3. Increased Renal Blood Flow Correlates With Progressive Renal Damage

Substantial evidence now exists to suggest that the hemodynamic adaptations to renal damage, that occur in response to a disease state such as diabetes, are in and of themselves causative factors in progressive renal deterioration. Steffes found that unilateral nephrectomy in the diabetic rat greatly hastened the development of typical diabetic lesions. This effect was independent of systemic blood pressure (23). In 1978, Mauer looked at the effects of Goldblatt hypertension on glomerular pathology in diabetic rats. After four months of diabetes, the glomeruli of the unclipped kidney of hypertensive diabetic rats had markedly increased diabetic changes,

including mesangial matrix thickening and mesangial immunoglobin and complement localization, when compared with glomeruli of the contralateral clipped kidney. More importantly, glomeruli of the clipped kidney in hypertensive diabetic rats had less mesangial thickening than glomeruli of normotensive diabetic rats. The authors concluded that alterations in nephron hemodynamics combine with the diabetic state to influence the rate of development of diabetic glomerulopathy in rats (24). Similarly, Berkman and Rifkin observed, during an autopsy on a patient with diabetes and unilateral renal artery stenosis, that Kimmelstiel-Wilson lesions were present in the kidney with the patent renal artery and absent on the contralateral side with the tight renal artery stenosis (25).

Since the articles by Azar and Steffes, numerous investigators have reported a deleterious effect of unilateral nephrectomy on the progressive renal failure associated with a variety of disease entities in the rat, thus suggesting that the hemodynamic abnormalities produced by nephron loss may have broad implications.

4. Protein Restriction Modifies Hemodynamic Abnormalities

In 1980, Ichikawa reported that malnourished Munich-Wistar rats fed a low calorie, low protein diet had SNGFRs that were significantly lower than rats fed a low calorie, high protein diet. This reduced SNGFR was associated with considerably lower values for both the glomerular plasma flow rate (Q_A) and the glomerular ultrafiltration coefficient (K_f), the former, at least in part, a consequence of high total arteriolar resistance. Of note, the transglomerular hydraulic pressure difference (ΔP) was not affected by diet. When Ichikawa further compared these rats with another group fed a high calorie, high protein diet, he found little added effect of the increased caloric intake, confirming that dietary protein content was the important variable (26).

Hostetter went on to explore the effect of reducing dietary protein intake on the hemodynamic abnormalities found in the subtotal nephrectomy model. By putting rats with a 1 5/6 nephrectomy on a low (6%) protein diet for fourteen days, he was able to maintain SNGFR at a level not significantly different from that of control rats without a nephrectomy fed a normal protein diet. Furthermore, this was associated with proportional reductions in the glomerular transcapillary hydraulic pressure gradient and glomerular capillary blood flow. Afferent and efferent arteriolar resistance (R_A and R_E) almost doubled with no change in K_f. Systemic blood pressure was not significantly different between groups (Table 2) (27).

Table 2

SUMMARY OF RENAL CORTICAL MICROCIRCULATION STUDIES

	AP mmHg	P_{GC} mmHg	P_T mmHg	ΔP mmHg	SNGFR nl/min	GFR ml/min	Q_A ml/min	$R_T=R_A+R_E \times 10^{10}$ dyn·s·cm^{-5}
I Nl Rats	112	49	12	37	27.8	.72	74	6.0
II 1 5/6 Neph Rats Nl Diet	128	63	19	44	62.5	.21	187	2.5
III 1 5/6 Neph Rats LP Diet	117	46	14	32	38.2	.16	92	3.9
P, I vs II	<.005	<.001	<.001	<.025	<.005	<.001	<.001	<.005
P, II vs III	NS	<.001	<.025	<.01	<.025	<.001	<.01	NS
P, I vs III	NS	NS	NS	NS	NS	<.001	NS	<.05

Subsequently, Wen (1985) went on to examine the effect of a similar low protein diet on the elevated GFR and renal plasma flow found in diabetic rats with moderate hyperglycemia. Once again, a 40% reduction in these parameters occurred on the low protein diet (28). Recently, Dworkin (1986) found a marked reduction toward normal of the elevated glomerular transcapillary hydraulic pressure gradient found in uninephrectomized DOC-salt rats and spontaneously hypertensive (SHR) rats when these rats were fed a low protein diet for several weeks following surgery (29).

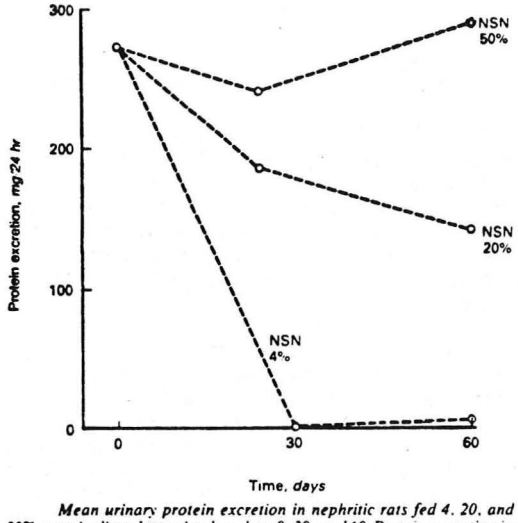
5. Protein Restriction Modifies the Outcome of Renal Disease

Hostetter (1981) initially reported that the early morphologic abnormalities found in rats subjected to a 1 5/6 nephrectomy were blunted by placing the animals on a low protein diet. Likewise, the 20-fold increase in protein excretion found in control rats was eliminated (27). Kenner (1985) compared the effect of a modest protein restriction (14%) versus a high protein diet (37%) in this model (5/6 nephrectomy) and found a significantly higher rate of protein excretion in the rats fed a high protein diet, as well as a 4-fold increase in the rate of renal failure progression and a 7-fold increase in mortality (30). Similar results have been found by Kleinknecht (31), Laouari (32), El-Nahas (33) and Kikuchi (34).

The long-term consequences of dietary protein restriction have also been evaluated in other rat models of renal disease. In 1983, Neugarten

looked at the effects of a low (4.6%), standard (23%) and high (57.5%) protein diet on the course of nephrotoxic serum nephritis. This model of immune nephritis was produced in a typical fashion by injections of goat serum with anti-rat GBM antibody activity, followed later by infusion of rabbit anti-goat gamma globulin. Neugarten found that proteinuria, which exceeded 275 mg/24 hrs at the start of dietary intervention (i.e. while on standard chow), remitted to normal levels (<10 mg/24 hrs) in rats fed the low protein diets, whereas heavy proteinuria continued in nephritic fats fed the 57 and 23% protein diets, with excretion rates of 289 and 133 mg/24 hrs respectively at 60 days (Figure 2) (35).

Figure 2



Mean urinary protein excretion in nephritic rats fed 4, 20, and 50% protein diets determined on days 0, 30, and 60. Protein excretion in control rats did not exceed 11 mg/24 hr.

More importantly, creatinine clearance was not different at this time between nephritic and control rats both fed the 4% low protein diet. Thus, nephritic rats fed the low protein diet demonstrated no loss of renal function. In contrast, nephritic rats fed the standard (23%) or high protein (57%) chow lost approximately 25% of their baseline renal function, a difference that was highly significant (Table 3) (35).

Table 3

THE EFFECT OF DIETARY PROTEIN CONTENT ON NSN: CLINICAL AND LABORATORY FEATURES AT 60 DAYS

	BODY WEIGHT (grams)	BP (mmHg)	URINARY PROTEIN (mg/24 hr)	SERUM ALBUMIN (g/dl)	CREATININE CLEARANCE (ml/24 hr/ 100 g body weight)
Control 4%	315	100	2[b]	2.6[a]	297[b]
Control 20%	371	115	11[b]	3.3[a]	460[b]
Control 50%	418	108	10[a]	3.0[a]	471[b]
NSN 4%	329	103	7	2.6	280
NSN 20%	393	100	133	2.6	294
NSN 50%	448	107	289	2.5	362

[a] $p<.001$ compared to the corresponding nephritic dietary group
[b] $p<.05$ compared to the corresponding nephritic dietary group

Histologic findings at sacrifice confirmed minimal changes in the low protein group, with progressive mesangial expansion, and focal and segmental proliferation and sclerosis correlated with increasing dietary protein. Systemic blood pressure, and dietary calorie and mineral content were identical in all groups. It should be recognized, however, that the 4% low protein diet utilized in this study is insufficient to support normal growth and development. Thus, renal function was stabilized, but possibly at the expense of adequate nutrition (35).

Friend looked at the effects of dietary protein restriction from weaning on the nephropathy of the NZB-NZW mouse (an animal model of lupus glomerulonephritis). He found that protein restriction afforded significant protection with regard to typical histologic abnormalities. When kidney biopsy specimens were read blindly by two observers, the mean renal pathology score was twice as high in the normal diet group. Furthermore, on immunologic analysis he found that those animals on a protein restricted diet demonstrated predominantly mesangial deposition of immunoglobulin and complement, as opposed to those on normal diets who exhibited deposition of immune reactants all along the glomerular basement membrane. Total calorie restriction afforded an even greater benefit, however, in the latter case this was associated with a significant reduction in DNA binding titers that was not evident in the protein-restricted mice. The authors conclude that the beneficial effect of protein restriction was probably mediated by a non-immunologic mechanism (36).

Wen demonstrated that proteinuria and early morphologic abnormalities were prevented by dietary protein restriction in diabetic rats (28). More recently, Rennke (1985), confirmed that these early observations

translate into long-term benefits. They reported results of a morphometric analysis performed in four groups of animals followed for twelve months: moderately hyperglycemic rats on a diet containing either 50% or 12% protein (D50, D12) and non-diabetic controls on similar diets (N50, N12). There was no difference in GBM thickness (th), glomerular volume (Vg), mesangial volume (Vm), segmental glomerular obsolescence (SS) or urinary albumin (Ualb)/24 hrs between diabetic rats fed a low protein diet, and non-diabetic rats fed a high protein diet. Furthermore, diabetic rats fed a high protein diet developed far worse morphometric and functional abnormalities than their low protein counterparts (37).

Table 4

MORPHOMETRIC, MORPHOLOGIC, AND PHYSIOLOGIC ABNORMALITIES IN DIABETIC AND CONTROL RATS AS A FUNCTION OF PROTEIN INTAKE

	th (nm)	$Vg \times 10^{-6}$ (μm^3)	$Vm \times 10^{-5}$ (μm^3)	SS (%)	Ualb (mg/24 h)
D_{50}	329	2.26	2.67	19.6	196
N_{50}	289	1.60	1.81	2.1	29
D_{12}	283	1.66	1.88	2.3	18
N_{12}	258	1.29	1.36	0.7	1

Likewise, Dworkin found that normalizing the elevated glomerular transcapillary hydraulic pressure gradient in uninephrectomized SHR rats, by dietary protein restriction, prevented these rats from developing proteinuria and morphologic evidence of glomerular disease up to 31 weeks after nephrectomy. Uninephrectomized SHR rats fed normal chow developed increasing proteinuria over time, and progressive mesangial expansion and glomerular sclerosis (29).

Finally, Ichikawa recently demonstrated that the amount of dietary protein can condition the severity of renal dysfunction after exposure to an acute pathologic insult. Whole kidney inulin (C_{in}) and PAH (C_{PAH}) clearances were measured in rats after unilateral release of bilateral ureteral obstructions of 24 hour duration. These rats had been fed isocaloric diets containing either 40% casein (high protein diet) or 6% casein (low protein diet) for four weeks. Values for C_{in} and C_{PAH} were markedly depressed in both groups but to a greater extent in high protein fed rats, averaging less than 60% of values measured in low protein fed animals (38).

PHOSPHORUS RESTRICTION - AN ADDITIONAL BENEFIT ?

In 1978, Ibels reported that dietary restriction of phosphate prevented proteinuria, renal calcification, histologic changes, and functional

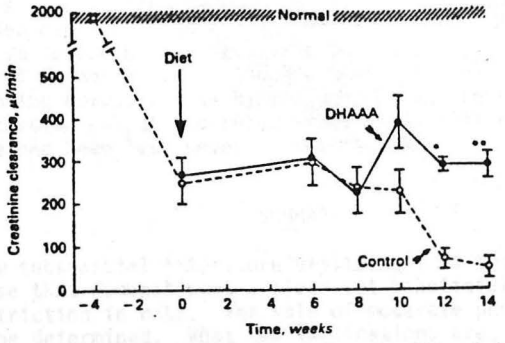
deterioration and death from uremia in rats undergoing 1 3/4 nephrectomy. Animals fed a diet of normal calcium and phosphate content (1.4%, .5%) showed renal deposition of calcium and phosphorus in cortical tubular cells, basement membrane, and interstitium. Phosphate restriction (.04%) markedly reduced the amount of calcium and phosphate deposited in the kidney. Likewise, at four months after surgery, the mean serum creatinine in the animals fed the normal diet was 3.75, as opposed to 1.06 mg/dl in the phosphate-restricted animals. In addition, 19/26 animals on the normal diet had died, as compared with only 2/12 on the phosphorus-restricted diet (39). Similar results were obtained by Karlinsky using the same diets in rats with nephrotoxic serum nephritis (40).

These results, however, were challenged by Laouari. She felt that the protective effect attributed to phosphorus was in fact mediated by an decrease in total food intake. Decreased protein was most likely to be the major beneficial factor. In this study, the authors demonstrated that the severe phosphorus restriction imposed by Ibel and Karlinsky resulted in severe hypophosphatemia, marked anorexia, and growth arrest. When animals subjected to a subtotal nephrectomy were put on a normal or high phosphorus diet, there was little difference in survival (despite a significant increase in mean phosphorus intake per day) if total food intake was restricted to that of rats fed a very low phosphorus diet (41).

In 1983, Kikuchi looked at survival following subtotal renal ablation in rats fed one of four diets: a high protein - normal phosphorus diet, a high protein - low phosphorus diet, a low protein - normal phosphorus diet, and a low protein - low phosphorus diet. The high and low protein diets contained 24 and 6% protein, and the non-restricted and phosphorus-restricted diets .5 and .12% phosphorus, respectively. They reported that protein restriction alone had some benefit on renal deterioration and survival, but that combined phosphorus and protein restriction had a more dramatic effect (34). Unfortunately, this study did not demonstrate comparable quantities of food intake between groups, nor was renal function found to be different by creatinine clearance.

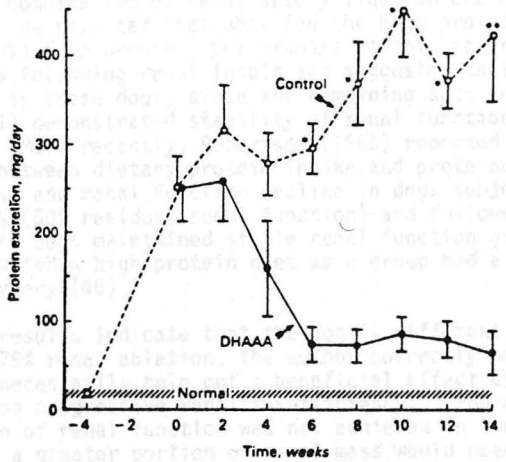
Gimenez found that when male rats with 70% renal ablation were fed a diet containing 2.2% phosphate (very high phosphorus), they had a progressive increase in serum creatinine. Two weeks after surgery, their mean serum creatinine was three times that of comparable partially nephrectomized rats fed a normal phosphate diet (.5%). This deterioration in renal function was prevented by the intraperitoneal injection of 3-phosphocitric acid, an inhibitor of calcium-phosphorus precipitation and crystallization. In this study, care was taken to standardize nutrient content of the diet (42). Most recently, Lumlertgul compared two groups of rats subjected to a subtotal nephrectomy, with one group receiving a phosphorus binder (DHAAA). Both groups of animals were pair-fed identical diets. At fourteen weeks, creatinine clearance in the phosphorus restricted group was 282 µl/min versus 46 µl/min/in the phosphate replete group (Figures 3 and 4) (43).

Figure 3.



Creatinine clearance decreased rapidly at 12 and 14 weeks in phosphate replete rats (open circles) but remained constant in rats consuming DHAAA (closed circles). Values are mean ± SE. *, $P <$ 0.001; **, P 0.005.

Figure 4.



DHAAA treated rats (closed circles) demonstrated reversal of the severe proteinuria of chronic renal failure whereas phosphate replete rats (open circles) demonstrated increasing amounts of proteinuria. Values are mean ± SE. *, $P < 0.001$; **, $P < 0.005$.

Histologic exam of renal tissue from the phosphate replete rats demonstrated more severe glomerular sclerosis, interstitial inflammation with fibrosis, and tubular atrophy and dilation, compared to the phosphorus depleted group (43). It should be noted, however, that this study produced severe hypophosphatemia in the low phosphorus group (2.85 versus 6 mg/dl in normal rats) and may have had a variety of effects such as blunting normal tissue hypertrophy of the remnant kidney, or decreasing cardiac output and renal blood flow, that would not be seen if phosphate had been less severely restricted.

SUMMARY

There is now substantial literature utilizing a variety of rat models of renal disease that demonstrates a clear-cut beneficial effect to dietary protein restriction in rats. The role of moderate phosphate restriction has yet to be determined. What the implications are, however, for human renal disease is less clear. The rat kidney tends to grow throughout the rats' lifetime, which is typically 24 months. In addition, most normal rats who die of old age will die from chronic renal insufficiency. By age 24 months, 60-100% of such animals will have severe glomerulosclerosis associated with proteinuria and hypertension (44). Thus, a beneficial effect to dietary protein restriction in the rat may not translate into a beneficial effect in humans or other species. Studies of dietary protein restriction in dogs have yielded confusing results. In 1983, Polzin evaluated the effects of a low, medium, and high protein diet on dogs in whom chronic renal failure was induced by a combination of renal artery ligation and contralateral nephrectomy. He reported that dogs fed the high protein diet had a high mortality (50%) from uremia. Unfortunately, this occurred in the first several weeks following renal insult and suggested that something else was going on in these dogs, since the remaining dogs in that diet group (50% of total) demonstrated stability of renal function over a 40 week period (45). More recently, Robertson (1986) reported that there was no association between dietary protein intake and proteinuria, morphologic abnormalities, and renal function decline in dogs subjected to 75% nephrectomies (50% residual renal function) and followed for four years. Most surviving dogs maintained stable renal function over this period, although dogs fed a high protein diet as a group had a higher GFR before and after surgery (46).

While these results indicate that the dog is different from the rat in response to 75% renal ablation, the author correctly points out that they do not necessarily rule out a beneficial effect of protein restriction on progressive renal insufficiency. Progressive deterioration of renal function was not achieved in these dogs. It may well be that a greater portion of renal mass would need to be removed to trigger deterioration, or a longer time interval could be required. These experiments have yet to be done.

HUMAN STUDIES

In 1982, Maschio reported the results of a retrospectively controlled trial designed to assess the effects of combined dietary protein and phosphorus restriction on the progression of human renal disease. He studied 75 patients with a variety of renal diseases ranging from chronic pyelonephritis to chronic glomerulonephritis. Patients were divided into three groups as follows:

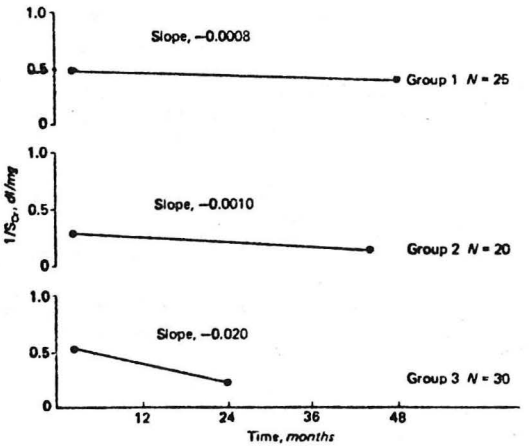
Group 1: 25 patients, Cr 1.5-2.7, low protein, low phosphate diet.

Group 2: 20 patients, Cr 2.9-5.4, low protein, low phosphate diet.

Group 3: 30 patients, Cr 1.6-4.7, retrospectively determined control diet.

Dietary histories for the prior two years were obtained at the start of the study on Group 3 patients by a trained dietician. Protein intake was estimated at approximately 70 grams/day with 900 mg mean phosphorus intake. This compares to the study diet which consisted of .6 g/kg body weight/day protein (60-70% high in biologic value) (equivalent to 40 g/day total in a 70 kg male) and 700 mg phosphorus. To put this in perspective, the current RDA for protein is .8 g/kg/day with most Americans taking in an average of 1.5 g/kg (or 105 gm/day in a 70 kg male). In this study, renal function deterioration was calculated using linear regression analysis of the relationship between time and the reciprocal of serum creatinine for each group. The follow-up period was 18-76 months, with data obtained on the control group from retrospective chart review. Mean blood pressure was comparable in all groups at the start of the study. These results (Figure 5) (47) demonstrate a 20-fold increase in the rate of progression of the control group over the two treatment groups.

Figure 5



The authors also note that there was no evidence of progressive phosphorus and protein depletion in the two treatment groups, although specific nutritional assessment techniques were not reported (47). Criticisms of this particular study include the retrospective controls, the diversity of renal diseases analyzed, and the lack of continued blood pressure reporting during the study. In addition, compliance data was not presented, and renal function changes were only reported as changes in the reciprocal of serum creatinine.

In 1983, several researchers published their individual experiences with protein restricted diets in a special edition of Kidney International devoted to this topic. Their study design and results are summarized in the Appendix.

The study reported in this same issue by Barsotti was the first attempt at a controlled trial. In this study, nineteen controls with a variety of renal diseases were followed monthly for eleven months, while on a diet containing .8 g/kg/day protein and 12 mg/kg/day phosphorus. The treatment group consisted of twenty patients with comparable disease entities followed on a diet consisting of .5 g/kg/day protein and 7 mg/kg/day phosphorus. (Prior to the study interval these patients had been following the control diet.) The mean creatinine clearance in each group at the start of the study was approximately 30 cc/min, and renal function was followed by serum creatinine and creatinine clearance. Blood pressure was reported and was comparable over the study interval. Compliance with the protein restriction was verified by assessment of mean urinary urea nitrogen at monthly intervals. Results are as follows (Table 5) (48):

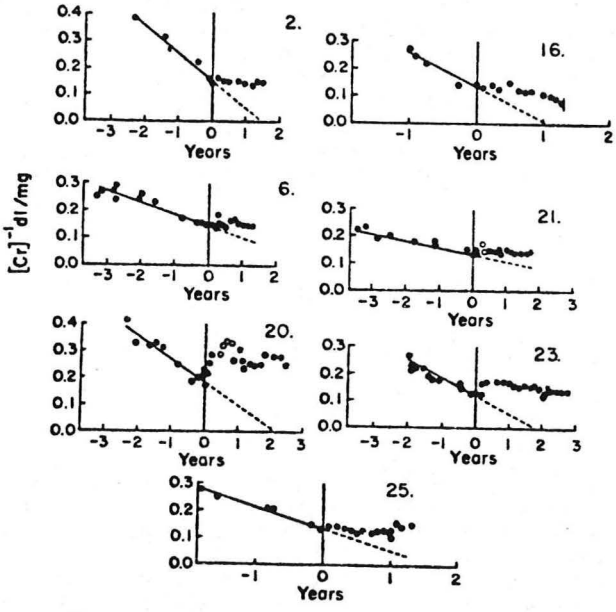
Table 5

	Δ SERUM CREATININE (mg/dl/month)	Δ CREATININE CLEARANCE (cc/min/month)
CONTROLS		
Pre-Study .8g/kg/protein 12 mg/kg phosphorus	+0.08±0.07	-0.50±0.66
During Study .8g/kg/protein 12 mg/kg phosphorus	+0.08±0.01	-0.44±0.10
TREATMENT GROUP		
Pre-Study .8g/kg/protein 12 mg/kg phosphorus	+0.073±0.05	-0.59±0.7
During Study .5g/kg/protein 7 mg/kg phosphorus	-0.03±0.08	+0.1±0.4

Criticisms of this study include the lack of randomization and the large category of renal diseases reported as "chronic glomerulonephritis" without further specifics. Two patients in the control group had an unexpectedly rapid deterioration after entering the study (i.e. slope changes despite no change in diet) and without these patients the group rates of progression would have been slower. Finally, compliance data was not normalized for body weight, such that true compliance could not be assessed. Simply put, this means that a 50 kg patient eating 2 g/kg/day protein could not be differentiated from a 100 kg patient eating 1 g/kg/day. Thus, the data reported could have been achieved despite gross noncompliance.

In 1984, Mitch reported the effects of supplementing a very low protein diet (20-30 gram mixed quality protein) with a ketoanalogue, amino acid mixture (11 grams)in 24 patients with severe renal failure (creatinine clearance 2-15 cc/min). Looking at the seventeen patients for whom prior information was available (mean pre-study intake 56 g protein/day), he compared their course pre and post-institution of the diet, and found that the reciprocal of serum creatinine remained stable in six of seven patients with an initial serum creatinine $\leq$ 8 mg/dl for an average of two years (Figure 6) (49).

Figure 6.



Effect of Therapy on Progression of Chronic Renal Failure in Patients with Serum Creatinine (Cr) Levels <8 mg per deciliter at the Start of Treatment.

This was further verified in these patients by measurement of creatinine clearance. Four additional patients experienced a significantly decreased rate of progression compared with their previous course, as assessed by 1/cr versus time. Criticisms of this study include the retrospective controls, use of serum creatinine and creatinine clearance as the sole markers of GFR with such advanced renal insufficiency, no mention of blood pressure, no compliance data, and no anthropometric assessment.

The paper by Rosman in 1984 is the only published prospective, randomized, controlled trial of dietary protein restriction in renal failure. Two hundred twenty-eight patients with diverse etiologies of renal insufficiency were stratified for age, sex and renal function, and then randomized to one of four groups:

A1: 70 patients, creatinine Cl 31-60 ml/min/1.73m^2, control diet
A2: 40 patients, creatinine Cl 10-30 ml/min/1.73m^2, control diet
B: 66 patients, creatinine Cl 31-60 ml/min/1.73m^2, low protein diet
C: 52 patients, creatinine Cl 10-30 ml/min 1.73m^2, low protein diet

The mean protein intake of A1 patients was 70 g/day versus .6 g/kg/day (40 g/day in 70 kg male) in the corresponding treatment group B. The mean protein intake of A2 patients was 55 g/day versus .4 g/kg/day (30 g/day in 70 kg male) in group C. All patients were treated with aluminum hydroxide to maintain normal serum phosphorus levels. Blood pressure was controlled to comparable levels in all groups throughout the study, and group compliance was assessed by urinary urea nitrogen although this was not normalized for individual weight. Renal function deterioration was followed over a minimum of eighteen months and was reported as the change in the reciprocal of serum creatinine with time (Table 6) (50).

Table 6

	Slope of 1/cr vs Time	
	CrCl 10-30 ml/min	CrCl 31-60 ml/min
Control	-.037	-.036
Treated	-.016	-.007
	p<.01	p<.05

The authors also noted that protein restriction resulted in a significant decrease in proteinuria (p<.02) but specific data was not reported. There were no differences at 9 month intervals in the following parameters which were reported - body weight, blood pressure, hematocrit, serum calcium and serum albumin. Group compliance, assessed at three month intervals, was greater than 90%. While this is clearly the most thorough study to date, concerns about this study are multiple. The

randomization protocol did not produce an even distribution of diagnoses between groups, and since these numbers were small this could be important. Likewise, a number of patients were classified simply as "chronic glomerulonephritis" as in prior studies. Furthermore, protein intake was not normalized for body weight in controls, and compliance in treated patients was likewise not normalized. Creatinine clearance data was not reported in this study, nor was any other direct assessment of GFR. Finally, the nutritional adequacy of their diet can be questioned. While weight and serum albumin did not change, no other nutritional information such as anthropometric data was supplied. The continuous fall in total 24 h urine creatinine output of Group C patients over the study interval would suggest progressive muscle wasting, and this would not be surprising, since the .4 g protein/kg/day supplied by this diet is well below minimum recommendations to maintain neutral or (+) nitrogen balance in a majority of normal individuals.

Unanswered Questions

1. How should we assess the progression of chronic renal failure?

   It is clear that in order to evaluate the effectiveness of a specific therapy on the course of renal disease we need to deal with a relatively homogeneous population at the start. In addition, patients should demonstrate progressive loss of renal function over time. Disease processes such as membranous glomerulonephritis that exhibit significant variability in their course (1/3 of patients remain stable) probably should be excluded, at least in initial evaluations.

   A widely used method of assessing renal failure progression is to plot the reciprocal or the logarithm of plasma creatinine against time. Mitch and Rutherford have shown that greater than 80% of patients with a variety of different disease entities will have a linear course when plotted in this fashion. This implies a constant rate of loss with the reciprocal method, and a constant fractional loss with the logarithm method (51,52).

   In most studies, reciprocal creatinine concentrations before and after the introduction of a low protein diet have been compared. Unfortunately, serum creatinine is not an adequate measure of changes in GFR, particularly when dietary protein is altered. Creatinine is formed from the nonenzymatic irreversible dehydration of creatine. About 2% of total body creatine is converted to creatinine daily. Creatine is produced by endogenous synthesis from amino acids but is also ingested preformed in the diet. Thus, a low protein diet entails an immediate reduction in the creatine pool which can result in a 15% or greater loss in creatinine production per 24 hours. This means that serum creatinine will fall when a patient begins a low protein diet despite no change in GFR (53,54). While Mitch and Walser have reported that a new

steady state of creatinine excretion is achieved within four months, this will only be true provided that muscle mass remains constant, a hypothesis to be tested in the long-term evaluation of low protein diets (55).

Clearly, direct measurement of GFR is more reliable than measurement of serum creatinine. Creatinine clearance may not be the best marker for the reasons noted previously, as well as the fact that GFR is usually overestimated when there is poor renal function. It is also not clear whether tubular handling of creatinine might also be affected by protein intake. For these reasons, clearance of a radioactive marker such as I^{125} iodothalamate, which behaves much like inulin, would be optimal (56).

2. What are the effects of other variables?

In a recent paper, Bergstrom reported that the progression of renal failure was significantly slower in control patients after they had entered a prospective study which called for more frequent follow-up visits. They also found a significant association between the retardation of progression and improved blood pressure control (57). It is likely that close monitoring of other variables such as urinary tract infections, and calcium and phosphorus balance will have a beneficial effect. Future studies will need to carefully control for these variables (56).

3. How should compliance be assessed?

As mentioned previously, urinary urea nitrogen has been used frequently to assess compliance. Changes in dietary protein intake are primarily reflected in urea nitrogen excretion. Non-urea losses tend to remain relatively fixed, and can be estimated by a factor proportional to weight. Thus, urea nitrogen appearance (UNA) is an objective way to assess compliance accurately, provided that complete urine specimens are obtained, allowance is made for changes in body weight and total body water, and results are normalized for body weight, and take into account differences in proteinuria. This, in combination with frequent dietary histories by a trained dietician, should provide a reasonable assessment of protein intake (55).

4. How should nutritional status be followed?

If low protein diets are to be regarded as safe, it is necessary to show that malnutrition does not occur. A number of different parameters have been evaluated to assess nutritional status. These include body weight, anthropometry, serum albumin and transferrin, and nitrogen balance studies.

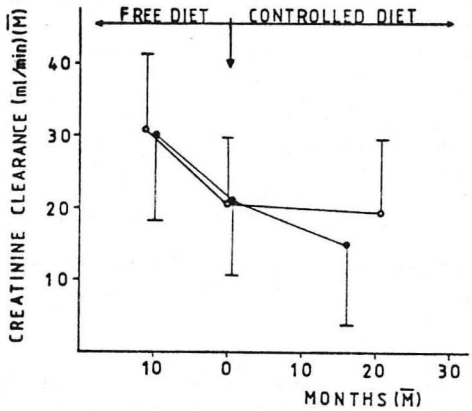
Substantial muscle loss has been observed by several investigators in patients on some low protein diets, without a change in serum

albumin and transferrin, indicating the need for careful anthropometric follow-up. Likewise, formal nitrogen balance studies can only be done at infrequent intervals and may not reflect intermittent periods of catabolism. Combined serial measurements over time offer the most complete nutritional information (56).

5. Is their an additional benefit to phosphorus restriction?

Until recently, all studies looking at the effects of dietary protein restriction combined this with moderate phosphorus restriction. Barsotti attempted to clarify this issue by comparing the decline in creatinine clearance between two groups of patients fed low protein diets, one with a moderate phosphorus restriction (CLND) and the other severely restricted in phosphorus intake (LPLND). Creatinine clearance data was compared for each patient pre and post-institution of their diet (Figure 7) (58).

Figure 7



The changes of C_{cr} in the two groups of patients during the follow-up period of free mixed diet, and during the periods in which they were following the LPLND (O) (mean urinary urea 7.6 g/day; mean urinary Pi 365.3 mg/day) and CLND (●) (mean urinary urea 8.2 g/day; mean urinary Pi 628.8 mg/day).

While the authors conclude that these results demonstrate an additional beneficial effect to phosphorus restriction, this study suffers from many of the design flaws described previously. The control data appears retrospective and the patients are not randomized. There is no assessment of blood pressure during the control or treatment periods, and information concerning etiology of renal insufficiency is scanty. Thus, it remains to be determined whether phosphorus plays a separate role in the progression of chronic renal failure, and future studies should

address this issue as well as the issue of deleterious side effects.

6. What is the "best" low protein diet?

Providing that low protein diets are found to be effective in slowing the progression of renal insufficiency, it will be necessary to determine the optimal daily intake of protein and other nutrients. The RDA for normal adults for protein is .8 g/kg/day. The RDA is based on the average protein (N) lost by individuals on a protein free diet (.45 g/kg/day) plus two standard deviations above that (.15 g/kg/day), to cover 97% of the population plus an increment (.2 g/kg/day) to cover the less efficient use of dietary protein as intake is increased from a point of (-) nitrogen balance to neutral or (+) nitrogen balance (59). Most, but not all, investigators have found that protein intake can be reduced to .55 - .6 g/kg/day, provided that 60-70% of the protein is high in biologic value (high content of essential amino acids). Such diets may also require a higher than usual total energy intake (35-50 kcal/kg/day) to maintain neutral N balance (60,61,62). It is unclear, however, that this level of intake will provide (+) nitrogen balance in all patients with chronic renal insufficiency over extended periods of time. This is particularly questionable in patients with other medical problems. Thus, there is a need for careful, short-term balance studies and more long-term nutritional evaluation.

Ketoanalogues of essential amino acids may allow patients to achieve neutral nitrogen balance despite a lower daily nitrogen intake. Several studies have suggested that uremic patients may actually prefer to ingest .3 g/kg/day protein of mixed quality with supplements of essential amino acids or ketoanalogues in preference to a .6 g/kg/day (60-70% HBV) diet (63,64). Whether this will be true in otherwise healthy patients with moderate renal insufficiency is unclear. Such supplements can cause unpleasant GI side effects that patients tolerate poorly. It is also unclear whether the further nitrogen reduction offered by ketoanalogues will be beneficial, or whether other properties of these medications such as their ability to raise serum calcium and lower serum phosphorus will have additional effects. Thus, each diet will need to be evaluated separately in a variety of disease entities before specific dietary recommendations can be made.

DIETARY PROTEIN AND ALTERED RENAL HEMODYNAMICS - POSSIBLE MECHANISMS

The mechanism by which ingested protein enhances GFR has not been established, although the absorption of amino acids from the intestine into the circulation appears to be required. O'Connor and Summerill have clearly shown that the rise in GFR following a meat meal in dogs

cannot be reproduced by feeding urea, sulfate, or acid in quantities equivalent to that produced by catabolism of the meal (65,66). Moreover, increases in GFR in dogs and humans are induced by intravenous infusion of mixed or individual amino acids or by administration via NG tube. The effect of free amino acids on GFR is probably not direct, since unilateral renal artery infusion of amino acids in the dog produces bilateral increases in GFR (67). Similarly, studies in the isolated perfused kidney of the rat demonstrate little direct effect of infused amino acids on filtration (68). For this reason, it has been suggested that a circulating hormone is responsible. Both growth hormone and glucagon have been suggested as possible effectors, since each is released in response to amino acid infusion or oral protein ingestion, and each has been shown to produce a rise in GFR when infused (69). Moreover, it has been found that somatostatin, which inhibits the endogenous release of both hormones, will prevent the phenomena of protein-induced renal hyperemia (70). Recently, Hirschberg (1985) found that normal and GH deficient adults demonstrated a comparable rise in GFR and renal blood flow (RBF) during arginine infusion, thus negating the importance of GH as an effector in this response (71). Premen (1985) looked at the effect of glucagon infusion at a level comparable to that found postprandially in dogs. Neither RBF nor GFR was significantly altered from its respective fasting control value. A plasma glucagon concentration more than ten times greater than that measured postprandially was required to achieve the rise in GFR demonstrated after the meat meals. Thus, glucagon does not appear to be the primary mediator of protein-induced renal hyperemia (72).

Other investigators have suggested that angiotensin II, which appears to be generated locally in the kidney as well as in the systemic circulation, and/or renal prostanoids may represent a common effector system by which many hormones influence the GFR. Acute and chronic protein loading in normal and subtotal nephrectomized rats is associated with a significant rise in the glomerular production of the vasodilatory prostaglandins PGE_2 and PGI_2 (73,74,75). Similar results have been found in moderately hyperglycemic diabetic rats who also exhibit renal hyperperfusion and hyperfiltration (76,77). Administration of the nonspecific prostanoid synthesis inhibitor, indomethacin, significantly reduces prostaglandin production and prevents the rise in GFR associated with protein ingestion or the diabetic state (73,76). However, prostaglandins frequently function as modulators of the action of other vasoactive substances such as angiotensin II. Thus, the reported increases in local prostaglandin production may simply represent a response to an as yet unidentified primary effector system.

Finally, in a series of elegant experiments, Seney (1985) demonstrated that the tubuloglomerular feedback (TGF) system in rats is rendered less responsive by a high protein diet. This system serves to adjust glomerular vascular resistance and the glomerular ultrafiltration coefficient (two determinants of GFR known to be altered by protein intake) in response to variations of some correlate of the early distal tubule flow rate. (As distal tubular flow increases, GFR normally

falls.) Thus, a reduction in the function of the TGF system by high dietary protein intake reduces the normally present suppression of GFR effected by TG feedback, causing filtration rate to rise (78). Other investigators, however, have found that single-nephron GFR remains elevated even when the effects of TG feedback are eliminated, suggesting that additional factors are also operative (79).

STUDIES IN PROGRESS

The National Institutes of Health is currently sponsoring a multicenter trial entitled "The Modification of Diet in Renal Disease (MDRD)" (80). The purpose of this study is to evaluate the effects of 2 low protein diets on the course of mild, moderate and severe renal insufficiency in a variety of diseases. Nine centers across the country are involved, and a total of 540 patients will be enrolled over the next three to four years. Patients are evaluated by retrospective chart review to determine that their disease is indeed progressive. Active collagen vascular disease, systemic infection, uncontrolled hypertension, and insulin-requiring diabetes mellitus are criteria for exclusion. Patients age 18-40 years with GFRs 25-80 cc/min/1.73 m^2 and patients age 41-75 with GFRs 25-(120-age) cc/min/1.73 m^2 will be randomized to a low protein diet containing .55-.6 g/kg protein and 5-10 mg/kg phosphorus or a normal protein diet containing 1-1.4 g/kg protein and 16-20 mg/kg phosphorus. Patients with GFRs between 10 and 24 cc/min/1.73m^2 will be randomized to either the low protein diet just described or a very low protein diet containing .28 g/kg protein and 4-10 mg/kg phosphorus with amino acid and ketoanalogue supplements. Patients will be followed monthly and compliance monitored by urinary urea nitrogen. Decline in renal function will be followed by Glofil clearance at three month intervals, and nutritional status assessed by repetitive anthropometric evaluation, and serum protein determinations. Total follow-up will range from 24-45 months, thus final results will not be available before 1991.

Here at the University of Texas Health Science Center, we have now had a similar study ongoing for thirty months in Type I diabetic patients with moderate to severe renal insufficiency. Currently, thirty-eight patients are enrolled and randomized to one of three diets:

1. .6 g/kg protein (70-80% high biologic value)
   1000 mg phosphorus (supplemented)
   1000 mg calcium (supplemented)
   2 g sodium

2. .6 g/kg protein (70-80% high biologic value)
   500-600 mg phosphorus
   1000 mg calcium
   2 g sodium

3. control diet containing greater than 1 g/kg protein
   1000 mg phosphorus
   2 gm sodium

Patients are monitored by the same techniques as in the MDRD study. A total of 72 patients is desired and enrollment is continuing. Final results should be available within twenty months.

APPENDIX

RETARDATION OF THE PROGRESSION OF RENAL INSUFFICIENCY
IN PATIENTS TREATED WITH LOW PROTEIN DIETS

Alvestrand, 1983 (81)

20 PATIENTS, ANALYZED RETROSPECTIVELY, 8 SERUM CREATININES OBTAINED OVER MINIMUM OF 200 DAYS PRE AND POST-DIET

ANALYZED AS 1/cr VS TIME VS PRE-STUDY COURSE INDIVIDUALLY AND AS POPULATION MEAN

DIET: 15-20 gm/day MIXED QUALITY PROTEIN SUPPLEMENTED WITH VARIABLE ESSENTIAL AMINO ACIDS OR KETOACIDS

MEAN ENTRY SERUM CREATININE 9.85±0.44 mg/dl

POLYCYSTIC KIDNEY DISEASE	9
CHRONIC GLOMERULONEPHRITIS	2
INTERSTITIAL NEPHRITIS	3
ANALGESIC NEPHROPATHY	2
CONGENITAL	1

RESULTS

SLOPE 1/CREATININE VS TIME $(\mu M/\ell)^{-1}$/MONTH

PRE-STUDY	LOW PROTEIN DIET
-0.23±0.026	-0.022±0.020

MUSCLE WASTING NOT OBSERVED

CRITICISMS

- NO DATA PROVIDED ON: POPULATION CHARACTERISTICS
  HYPERTENSION
  COMPLIANCE
  PATIENT SELECTION CRITERIA
- VARIABLE PRE-STUDY DIET
- VERY ADVANCED RENAL FAILURE AT ENTRY
- NON-RANDOMIZED, RETROSPECTIVE SERIES

LOW PROTEIN DIET SUPPLEMENTED BY KETO ACIDS IN CHRONIC RENAL FAILURE: A PROSPECTIVE CONTROLLED STUDY

Gretz, 1983 (82)

PROSPECTIVE TRIAL, NON-RANDOMIZED
138 PATIENTS

31 TREATED (STUDY HOSPITAL)	107 CONTROLS (NEARBY HOSPITAL)
7 CHRONIC GLOMERULONEPHRITIS	25
5 POLYCYSTIC KIDNEY DISEASE	45
19 INTERSTITIAL NEPHRITIS	37

30 gm PROTEIN DIETS SUPPLEMENTED WITH UNSPECIFIED PROGRAM OF KETO ACIDS, 35-40 kcal/kg/day

HYPERTENSION CONTROLLED "AS NECESSARY"

PROGRESSION OF RENAL INSUFFICIENCY ANALYZED AS TIME FROM SERUM CREATININE 6 mg/dl TO 10 mg/dl

RESULTS

MEDIAN MONTHS CREATININE 6 TO CREATININE 10

DISEASE	CONTROL	TREATED	
CHRONIC GLOMERULONEPHRITIS	5.2	16.3	P=.059
POLYCYSTIC KIDNEY DISEASE	10.5	27.3	p=.033
INTERSTITIAL NEPHRITIS	8.7	17.4	p=.0002

CRITICISMS

NO DATA REPORTED ON:

1. PRE-STUDY COURSE
2. COMPLIANCE
3. NUTRITIONAL ADEQUACY
4. CONCOMITANT MEDICAL CONDITIONS
5. PROTEINURIA
6. HYPERTENSION
7. DIET OF CONTROL GROUP

STUDY/CONTROL PATIENTS FOLLOWED AT DIFFERENT CENTERS

NO DATA PRESENTED ON POPULATION CHARACTERISTICS TO ESTABLISH "COMPARABLE POPULATIONS", IN A NON-RANDOMIZED TRIAL

ENTRY AND EXCLUSION CRITERIA NOT REPORTED

REFERENCES

1. Private Communication, Department of Health and Human Services, Health Care Financing Administration, Office of Research and Demonstrations, August, 1986.

2. Newburgh LH, Clarkson S: Renal injury produced in rabbits by diets containing meat. Arch Int Med 32:850-869, 1923.

3. Moise TS, Smith AH: Effect of high protein diet on the kidneys. Experimental study. Arch Path 4:530-542, 1927.

4. Chanutin A, Ludewig S: Experimental renal insufficiency produced by partial nephrectomy. V. Diets containing whole dried meat. Arch Int Med 58:60-80, 1936.

5. Addis T: Glomerular Nephritis: Diagnosis and treatment. New York, Macmillian, 1948.

6. Farr LE, Smadel JE: The effect of dietary protein on the course of nephrotoxic nephritis in rats. J Exp Med 70:615-627, 1939.

7. Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease. The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 307:652-659, 1982.

8. Hostetter TH, Rennke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med 72:375-380, 1982.

9. Mitch WE, Steinman TI: Can the course of chronic renal failure be altered by diet? The Kidney 16:31-35, 1983.

10. Blachley JD: The role of dietary protein in the progression and symptomatology of chronic renal failure. Am J Med Sci 288(5):228-34, 1984.

11. Pullman TN, Alving AS, Dern RJ, Landowne M: J Lab and Clin Med 44(2):320-332, 1954.

12. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S: Renal functional reserve in humans - effect of protein intake on glomerular filtration rate. Am J Med 75:943-950, 1983.

13. Bergstrom J, Ahlberg M, Alvestrand A: Influence of protein intake on renal hemodynamics and plasma hormone concentrations in normal subjects. Acta Med Scand 217:189-196, 1985.

14. Walser M: Does dietary therapy have a role in the predialysis patient? Am J Clin Nutr 33:1629-1637, 1980.

15. Shimamura T, Morrison AB: A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. Am J Pathol 79(1):95-106, 1975.

16. Olsen JL, Hostetter TH, Rennke HG, Brenner BM, Venkatachalam MA: Altered charge-and-size selective properties of the glomerular wall: a response to reduced renal mass. Kidney Int 16:857, 1979.

17. Kaufman JM, Siegel NJ, Hayslett JP: Functional and hemodynamic adaptation to progressive renal ablation. Circ Res 36:286-293, 1975.

18. Brenner BM, Humes HD: Mechanics of glomerular ultrafiltration. N Engl J Med 297:148-154, 1977.

19. Deen WM, Maddox DA, Robertson CR, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. Am J Physiol 227:556-562, 1974.

20. Azar S, Johnson MA, Hertel B, Tobian L: Single-nephron pressures, flows and resistances in hypertensive kidneys with nephrosclerosis. Kidney Int 12:28-40, 1977.

21. Glassock R, Bennett C, Kayser B, Martin C, Marsh D: Glomerular hemodynamics in nephrotoxic serum nephritis. Amer Soc Neph Abstracts p 91A, 1978.

22. Hostetter TH, Troy JL, Brenner BM: Glomerular hemodynamics in experimental diabetes. Kidney Int 19:410-415, 1981.

23. Steffes MW, Brown DM, Mauer SM: Diabetic glomerulopathy following unilateral nephrectomy in the rat. Diabetes 27:35-41, 1978.

24. Mauer SM, Steffes MW, Azar S, Sandberg SK, Brown DM: The effects of Goldblatt hypertension on development of the glomerular lesions of diabetes mellitus in the rat. Diabetes 27:738-744, 1978.

25. Berkman J, Rifkin H: Unilateral nodular diabetic glomerulosclerosis (Kimmelsteil-Wilson): report of a case. Metabolism 22:715-722, 1973.

26. Ichikawa I, Purkerson ML, Klahr S, Troy JL, Martinez-Moldonado M, Brenner BM: Mechanism of reduced glomerular filtration rate in chronic malnutrition. J Clin Invest 65:982-988, 1980.

27. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 241 (Renal Fluid Elec Physiol 10):F85-F93, 1981.

28. Wen SF, Huang TP, Moorthy AV: Effects of low-protein diet on experimental diabetic nephropathy in the rat. J Lab Clin Med 106(5):589-97, 1985.

29. Dworkin LD, Feiner HD: Glomerular injury in uninephrectomized spontaneously hypertensive rats. A consequence of glomerular capillary hypertension. J Clin Invest 77:797-809, 1986.

30. Kenner CH, Evan AP, Blomgren P, Aronoff GR, Luft FC: Effect of protein intake on renal function and structure in partially nephrectomized rats. Kidney Int 27:739-750, 1985.

31. Kleinknecht C, Salusky I, Broyer M, Gubler MC: Effect of various protein diets on growth, renal function, and survival of uremic rats. Kidney Int 15:534-541, 1979.

32. Laouari D, Kleinknecht C, Gubler MC, Broyer M: Adverse effect of proteins on remnant kidney: dissociation from that of other nutrients. Kidney Int 24 (Suppl 16):S248-S253, 1983.

33. El-Nahas AM, Paraskevakou H, Zoob S, Rees AJ, Evans DJ: Effect of dietary protein restriction on the development of renal failure after subtotal nephrectomy in rats. Clin Science 65:399-406, 1983.

34. Kikuchi H, Matsushita T, Hirata K: Improved dietary treatment with low protein and phosphorus restriction in uremic rats. Kidney Int 24 (Suppl 16): S254-S258, 1983.

35. Neugarten J, Feiner HD, Schacht RG, Baldwin DS: Amelioration of experimental glomerulonephritis by dietary protein restriction. Kidney Int 24: 595-601, 1983.

36. Friend PS, Fernandes G, Good RA, Michael AF, Yunis EJ: Dietary restrictions early and late. Effects on the nephropathy of the NZB x NZW mouse. Lab Invest 38(6):629-632, 1978.

37. Rennke HG, Sandstrom D, Zatz R, Meyer TW, Cowan RS, Brenner BM: The role of dietary protein in the development of glomerular structural alterations in long term experimental diabetes mellitus. Amer Soc Neph Abstracts p 140A, 1985.

38. Ichikawa I, Purkerson ML, Yates J, Klahr S: Dietary protein intake conditions the degree of renal vasoconstriction in acute renal failure caused by ureteral obstruction. Am J Physiol 249 (Renal Fluid Elec Physiol 18): F54-F61, 1985.

39. Ibels LS, Alfrey AC, Haut L, Huffer WE: Preservation of function in experimental renal disease by dietary restriction of phosphate. N Engl J Med 298:122-126, 1978.

40. Karlinsky ML, Haut L, Buddington B, Schrier NA, Alfrey AC: Preservation of renal function in experimental glomerulonephritis. Kidney Int 17:293-302, 1980.

41. Laouari D, Kleinknecht C, Cournot-Witmer G, Habib R, Mounier F, Broyer M: Beneficial effect of low phosphorus diet in uraemic rats: a reappraisal. Clin Sci 63:539-548, 1982.

42. Gimenez L, Walker WG, Tew WP, Hermann JA: Prevention of phosphate-induced progression of uremia in rats by 3-phosphocitric acid. Kidney Int 22:36-41, 1982.

43. Lumlertgul D, Burke TJ, Gillum DM, Alfrey AC, Harris DC, Hammond WS, Schrier RW: Phosphate depletion arrests progression of chronic renal failure independent of protein intake. Kidney Int 29:658-666, 1986.

44. Blachley JD: The role of dietary protein in the progression and symptomatology of chronic renal failure. Am J Med Sci 228(5):228-34, 1984.

45. Polzin DJ, Osborne CA, Hayden DW, Stevens JB: Influence of reduced protein diets on morbidity, mortality, and renal function in dogs with induced chronic renal failure. Am J Vet Res 45(3):506-516, 1984.

46. Robertson JL, Goldschmidt M, Kronfeld DS, Tomaszewski JE, Hill GS, Bovee KC: Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. Kidney Int 29:511-519, 1986.

47. Maschio G, Oldrizzi L, Tessitore N, D'Angelo A, Valvo E, Lupo A, Loschiavo C, Fabris A, Gammaro L, Rugiu C, Panzetta G: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. Kidney Int 22:371-376, 1982.

48. Barsotti G, Morelli E, Giannoni A, Guiducci A, Lupetti S, Giovannetti S: Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: a controlled trial. Kidney Int 24(Suppl 16):S278-S284, 1983.

49. Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, Tungsanga K: The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. N Engl J Med 311:623-629, 1984.

50. Rosman JB, terWee PM, Meijer S, Piers-Becht TP, Sluiter WJ, Donker AJ: Prospective randomized trial of early dietary protein restriction in chronic renal failure. Lancet 2(8415):1291-1296, 1984.

51. Mitch WE, Buffington GA, Lemann J, Walker M: A simple method of estimating progression of chronic renal failure. Lancet 2:1326-1328, 1976.

52. Rutherford WE, Blondin J, Miller JP, Greenwalt AS, Varva JD: Chronic progressive renal disease: rate of change of serum creatinine concentration. Kidney Int 11:62-70, 1977.

53. Blachley JD: The role of dietary protein in the progression and symptomatology of chronic renal failure. Am J Med Sci 288(5):228-234, 1984.

54. El-Nahas AM, Coles GA: Dietary treatment of chronic renal failure: ten unanswered questions. Lancet 1:597-600, 1986.

55. Mitch WE: Nutritional therapy in renal failure. Ann Rev Med 35:249-264, 1984.

56. El-Nahas AM, Coles GA: Dietary treatment of chronic renal failure: ten unanswered questions. Lancet 1:597-600, 1986.

57. Bergstrom J, Alvestrand A, Bucht H, Gutierrez A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-ups and better blood pressure control. Clin Nephrol 25 (1):1-6, 1986.

58. Barsotti G, Giannoni A, Morelli E, Lazzeri M, Vlamis I, Baldi R, Giovannetti S: The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. Clin Nephrol 21(1):54-59, 1984.

59. Holliday MA: Nutrition therapy in renal disease. Kidney Int 30:S3-S6, 1986.

60. Ford J, Phillips ME, Toye FE, Luck VA, Wardener HE: Nitrogen balance in patients with chronic renal failure on diets containing varying quantities of protein. Brit Med J 1:735-740, 1969.

61. Bergstrom J, Furst P, Ahlberg M, Noree LO: The role of dietary and energy intake in chronic renal failure.

62. Kopple JD, Sorensen MK, Coburn JW, Gordan S, Rubini ME: Controlled comparison of 20-g and 40-g protein diets in the treatment of chronic uremia. Am J Clin Nutr 21:553, 1968.

63. Kampf D, Fischer H, Kessel M: Efficacy of an unselected protein diet (25g) with minor oral supply of essential amino acids and keto analogues compared with a selective protein diet (40g) in chronic renal failure. Am J Clin Nutr 33:1673-1677, 1980.

64. Lee HA, Talbot S, Rowlands A, Jackson MA: Dietary management of chronic renal failure with oral amino acids. Nutr Metab 24:50-63, 1980.

65. O'Connor WJ, Summerill RA: The excretion of urea by dogs following a meal of meat. J Physiol 256:93-102, 1976.

66. O'Connor WJ, Summerill RA: Sulphate excretion by dogs following ingestion of ammonium sulphate or meat. J Physiol 260:597-607, 1976.

67. Epstein FH, Brosnan JT, Tange JD, Ross BD: Improved function with amino acids in the isolated perfused kidney. Am J Physiol 243:F284-292, 1982.

68. Maack T, Johnson V, Tate SS, Meister A: Effects of amino-acids on the function of the isolated perfused rat kidney. Fed Proc 33:305, 1974.

69. Johannesen J, Lie M, Kiil F: Effect of glycine and glucagon on glomerular filtration and renal metabolic rates. Am J Physiol 233(1):F61-F66, 1977.

70. Castellino P, Coda B, DeFronzo RA: The effect of intravenous amino-acid infusion on renal hemodynamics in man. Am Soc Neph Abstracts p 145A, 1978.

71. Hirschberg R, Kleinman K, Glassock R, Kopple JD: Effect of arginine infusion on renal plasma flow and GFR in normal and growth hormone deficient man. Am Soc Neph Abstracts p 41A, 1985.

72. Premen AJ, Hall JE, Smith MJ: Postprandial regulation of renal hemodynamics: role of pancreatic glucagon. Am J Physiol 248:F656-F662, 1985.

73. Stahl RA, Kudelka S, Schollmeyer P: Glomerular prostaglandins modulate GFR in rats with reduced renal mass on high protein intake. Am Soc Neph Abstracts p 169A, 1985.

74. Schambelan M, Hutchison FN, Kayser GA, Blake S: Dietary protein intake modulates glomerular production of eicosanoids in rats with Heymann nephritis. Am Soc Neph Abstracts p. 195A, 1985.

75. Levine MA, Kirschenbaum MA, Chaudhari A, Wong MW, Bricker NS: Effect of a protein bolus on GFR and glomerular prostanoid synthesis in normal and uremic rats. Am Soc Neph Abstracts p 190A, 1985.

76. Schambelan M, Blake S, Sraer J, Bens M, Nivez MP, Wahbe F: Increased prostaglandin production by glomeruli isolated from rats

with streptozotocin-induced diabetes mellitus. J Clin Invest 75:404-415, 1985.

77. Craven PA, DeRubertis FR: Glomerular prostaglandins in the hyperfiltration of early diabetes. Am Soc Neph Abstracts p 183A, 1985.

78. Seney FD, Wright FS: Dietary protein supresses feedback control of glomerular filtration in rats. J. Clin Invest 75:558-568, 1985.

79. Schnermann J, Gokel M, Weber PC, Schubert G, Briggs JP: Tubuloglomerular feedback and glomerular morphology in Goldblatt hypertensive rats on varying protein diets. Kidny Int 29:520-529, 1986.

80. Protocol for the cooperative clinical study of dietary modification on the course of progressive renal disease, 1986.

81. Alvestrand A, Ahlberg M, Bergstrom J: Retardation of the progression of renal insufficiency in patients treated with low-protein diets. Kidney Int 24 (Suppl 16):S268-S272, 1983.

82. Gretz N, Korb E, Strauch M: Low-protein diet supplemented by ketoacids in chronic renal failure: a prospective, controlled study. Kidney Int 24 (Suppl 16):S263-267, 1983.