ACCELERATED ATHEROGENESIS
IN
CHRONIC RENAL FAILURE

JAMES R. COTTON, M.D.

Medical Grand Rounds
University of Texas Health Science
Center, Dallas

October 6, 1977

INTRODUCTION

In 1976, there were 22,000 patients being maintained on hemodialysis, and an estimated 8,000 new patients are being added to the dialysis rolls annually (1). Unless there are major advances in the prevention and treatment of renal disease and transplant rejection, in the next ten years we can expect to have in excess of 100,000 patients on hemodialysis at an annual cost in the range of 5 to 6 billion dollars per year.

With this expenditure of money and manpower, one would hope that hemodialysis would allow the affected individuals to return to a productive state of existence and to live out a normal life span. Initially it appeared that in most instances both goals would be accomplished. However, at the present time, both rehabilitation and longevity are discouraging.

In both Europe (2) and the United States (3), there is a 10% annual mortality rate in patients on chronic hemodialysis. In 1974 a report from Seattle (4) was the first to point out the high mortality from atherosclerotic vascular disease. In this report, mean age at the start of dialysis was 37 years and the duration of treatment averaged 6.5 years (range, 1-13). Overall mortality was 56.4% and 14 of the 23 deaths could be attributed to atherosclerotic complications: myocardial infarction in 8, strokes in 3, and refractory congestive heart failure in 3. None of these patients were diabetic.

As seen in Table 1, in 1972 heart disease and cerebrovascular disease accounted for 49% of all deaths in the United States, a figure very similar to patients on hemodialysis. However, if one compares mortality statistics in the age range comparable to dialysis patients, only 13.6% of deaths in the United States were due to heart or central nervous system disease in the 24-45 year

age group. Other reports from the National Dialysis Registry (3), the combined European dialysis population (2), and that of the Peter Bent Brigham Hospital (6) also find a similar problem of premature death from atherosclerosis. Thus, hemodialysis patients have a high incidence of cardiovascular related deaths which occur at younger ages than the nonuremic population.

Uremic patients have a number of risk factors for developing premature vascular disease. These include hypertension, variable periods of volume excess, and vascular calcium deposition associated with secondary hyperparathyroidism. While these factors certainly add to the risk of premature vascular disease, each can be controlled or prevented with good medical management. I would therefore like to turn our attention to metabolic derangements which occur in renal failure, because it is these derangements which appear to be responsible for the accelerated atherogenesis.

	No. Patients	No. Deaths	Cardiovascular deaths		Total %
			Heart	Cerebral	
			% of all deaths		
U.S. Population All Ages			38.3	10.7	49.0
U.S. Population Ages 25–45			11.9	1.7	13.6
National Dialysis Registry Bryan [1] Through 1972 Mean Age 43.5	7437	2447	34.5	12.4	46.9
EDTA Parsons et al [2] Mean Age 40	9150	2565	34.7	13.5	48.2
Lindner et al [3] Mean Age 37	39	23	52.2	8.6	60.8
PBBH Home Dialysis Mean Age 48.8	125	34	41.6	16.5	58.1

Table 1. Incidence of cardiovascular deaths in the United States population for 1972, in four reported dialysis populations (5).

CARBOHYDRATE METABOLISM

Glucose Intolerance

Newbauer, in 1901, was the first investigator to describe hyperglycemia in association with renal disease (7). In subsequent years, this observation has been confirmed by multiple investigators. It appears from these reports that fasting blood glucose is normal or only slightly elevated. As seen in Figure 1, when challenged by oral or intravenous glucose, modest hyperglycemia occurs and the rate of decline of the blood glucose is delayed. While this picture resembles early diabetes mellitus, ketosis does not occur and frank hyperglycemia requiring insulin therapy is extremely rare. The incidence of glucose intolerance is very high, ranging 80 to 95% (8,9). An important question to which we will refer to later is at what level of renal failure does glucose intolerance occur? Yasuda (10) examined this question in a study of 22 patients with creatinine clearances ranging from 5 to 96 ml/min. He found that abnormal glucose metabolism occurred when the clearance dropped below 60 cc/min.

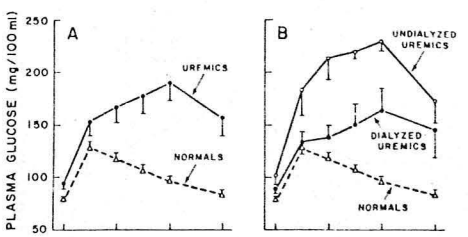


Figure 1. Plasma glucose response to 100g of oral glucose. In panel "A" dialyzed and undialyzed uremics are combined while in panel "B" the groups are shown separately (30).

The effect of hemodialysis on glucose intolerance is controversial. Many studies have used the alkaline cooper of ferricyanide reduction methods to measure glucose. These methods also measure other reducing substances which may be elevated in renal failure and thus give a falsely elevated value (8,11). The glucose oxidose method which does not measure these reducing substances is therefore the best technique for measuring glucose in renal failure. This discrepency is shown in Figure 2. This becomes even more important when analyzing the effects of hemodialysis because dialysis lowers the levels of these reducing substances. Unfortunately, even when the glucose oxidose method is used, some authors have found that dialysis improved glucose tolerance (12,13) while others (14,15,16) have found no improvement. In spite of the controversy, an analysis of these reports reveals that dialysis may improve glucose utilization but rarely is there complete normalization [Fig. 1]. Therefore most patients have a defect in glucose metabolism which occurs early in the course of renal failure, the resulting hyperglycermia is modest, and is only partially corrected by hemodialysis.

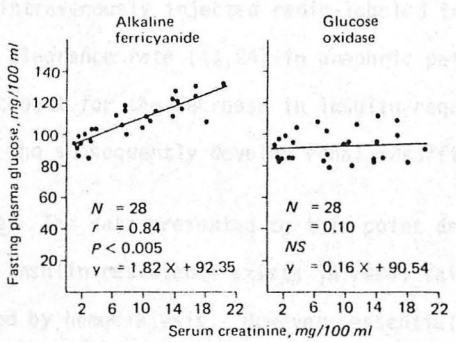


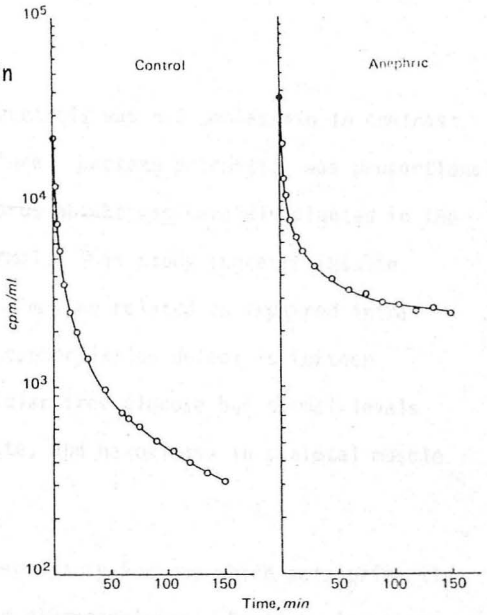
Figure 2. Effect of the method of plasma glucose measurement on the relationship between fasting serum creatinine and plasma glucose concentrations in 28 subjects (11).

Insulin: This important glucoregulatory hormone has been well studied in renal insufficiency. Fasting insulin levels have been found to be normal (12,13,15) or slightly elevated (9,17). The insulin response to hyperglycemia has been reported as normal (18,19) blunted (9,20), or increased (13). However, the levels that appear during the first three minutes after a glucose challenge is usually excessive (13) and all investigators have found that after the peak response occurs, the rate of decline is slower than normal. In studies of patients on hemodialysis, insulin secretion is usually increased in response to a glucose load (15,21), and the rate of decline continues to be delayed.

Insulin degradation by the kidney: In normal subjects, approximately 40-50% of insulin is metabolized by the liver. In the kidney, insulin is filtered at the glomerulus and reabsorbed by the proximal tubule where it is apparently degradated. Thirty to 40% of the insulin entering the renal artery is removed from the circulation as determined by renal artery to vein ratios (22). Only 1.5% or less appears in the urine. It has been estimated that 15-30% of the total insulin secretion is removed by renal mechanisms (23,24). The importance of the kidney in insulin degradation is further supported by studies in which intravenously injected radio-labeled insulin has a markedly reduced metabolic clearance rate (11,24) in anephric patients [Fig. 3]. This could well account for the decrease in insulin requirements observed in diabetic patients who subsequently develop renal insufficiency (25).

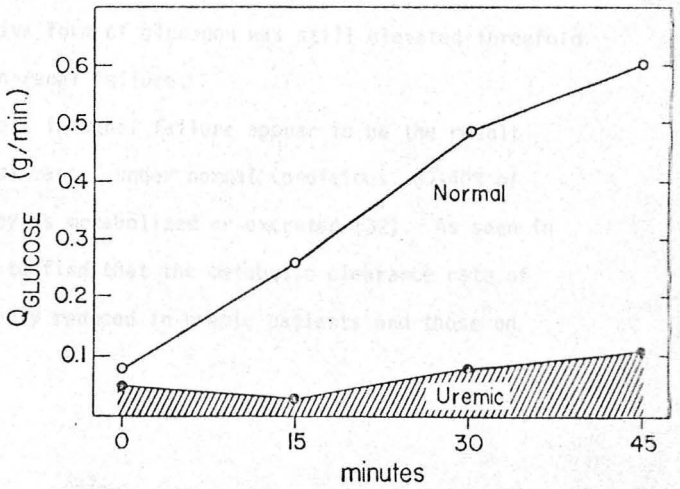
Insulin Resistance: The data presented to this point demonstrates that a relative state of insulin resistance exists in renal failure and is only partially corrected by hemodialysis. However, essentially all the findings presented thus far could be explained by decreased insulin degradation by the

Figure 3. Disappearance curves from plasma of immunoprecipitable ^{131}I-insulin in a normal subject and in an anephric patient (11).



kidneys. Studies by Westervelt (26) reveal additional information concerning this resistant state. He studied net forearm fluxes of glucose, potassium, lactate, and inorganic phosphate after brachial artery insulin infusion in four subjects with renal failure and three normal controls. None were diabetic and the subjects with renal failure all had glucose intolerance. As seen in Figure 4, before insulin infusion, glucose uptake was similar in both groups,

Figure 4. Comparison of extrapolated muscle glucose uptake of subjects weighing 70 kg (155 lb) during insulin infusion. Areas under curves represent cumulative glucose uptake (27).

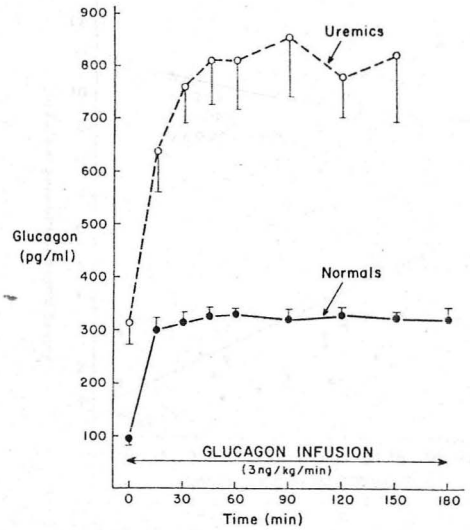


but after the infusion glucose uptake in controls was 8.3 μmoles/min in contrast to 1.6 μmoles/min in those with renal failure. Lactate production was proportional to glucose uptake in both groups. Phosphorus uptake was severely blunted in the uremic group, but potassium uptake was normal. This study suggests insulin resistance occurs at the cellular level and may be related to impaired intracellular glucose phosphorylation. This phosphorylation defect is further supported by the finding of high intracellular free glucose but normal levels of glucose-6-phosphate, fructose-6-phosphate, and hexokinase in skeletal muscle of uremic patients (25).

Glucagon: Glucagon is an important glucoregulatory hormone which acts primarily on the liver to promote gluconeogenesis and glycogenolysis. Fasting elevations in glucagon have been found in renal failure by numberous investigators (13,29,30), and these levels continue to be elevated after hemodialysis (13,29,30). Circulating glucagon is heterogenous in renal failure. With gel filtration there are three peaks: mol. wt. > 40,000 (15%), mol. wt. 9,000 (57%), and mol. wt. 3500 (27%) the latter representing the biologically active form (31). In contrast, only peaks in mol. wt. > 40,000 (54%) and 3500 (46%) are seen in normal subjects. However, the 3500 mol. wt. active form of glucagon was still elevated threefold over normal in individuals with renal failure.

The elevated glucagon levels in renal failure appear to be the result of the loss of functioning renal mass. Under normal conditions, 30-40% of glucagon delivered to the kidney is metabolized or excreted (32). As seen in Figure 5, it is not surprising to find that the metabolic clearance rate of injected glucagon is significantly reduced in uremic patients and those on hemodialysis (30).

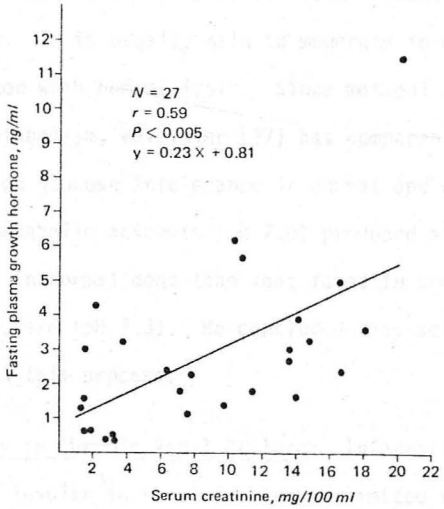
Figure 5. Plasma glucagon concentrations during infusion of exogenous glucagon to normal and uremic subjects (30).



In addition to the elevated circulating glucagon in renal failure, it has been discovered that the liver may be particularly sensitive to glucagon. Soman (33) studied insulin and glucagon binding to liver membranes in 70% and 90% nephrectomized rats. He found that ^{125}I-glucogan binding was increased by 80-120%, and that glucagon (2μM) stimulated adenylate cyclase activity was twofold higher than in controls. In contrast, ^{125}I-insulin binding was reduced 40-50% as compared to controls. Thus, the elevated circulating glucagon and the perference of liver membranes to bind glucagon may certainly contribute to the insulin resistance of renal insufficiency through the gluconeogenic and glycogenolytic effects of this hormone.

Growth Hormone: From Figure 6, growth hormone concentrations are noted to progressively increase with the development of renal failure. However, these elevations do not correlate well with glucose intolerance (9,13,34) and growth hormone is not thought to be a prime factor in the insulin resistance of uremia.

Figure 6. Relationship between serum creatinine and fasting growth hormone concentration in 28 subjects (11).



Potassium deficiency: Hypokalemia blunts pancreatic insulin release and hyperkalemia accelerates insulin secretion. Knochel and Seldin have reviewed these potassium-insulin interrelationships in renal failure (35). They report that in spite of normal or elevated serum potassium levels, the patient with endstage renal disease has a modest total body depletion of potassium. After dialysis therapy, this modest deficit is usually corrected. It should be pointed out that not all dialysis patients have correction of total body potassium, a not too surprising finding in view of present dialyzing procedures which usually use either a 1.0 or 2.0 meq/L potassium dialysate. Seedat (36) found a number of hemodialysis patients to be potassium depleted and the glucose intolerance manifested by these individuals improved with correction of the potassium deficit. The fact that most hemodialysis patients have correction of their potassium deficits, yet continue to manifest glucose and insulin abnormalities make it unlikely that potassium per se is responsible for these abnormalities.

Metabolic acidosis: Metabolic acidosis is found in most patients with end-stage renal disease. It is usually mild to moderate in severity and is improved or corrected with hemodialysis. Since metabolic acidosis is known to alter glucose metabolism, Weisinger (37) has compared the effect of metabolic acidosis on glucose intolerance in normal and uremic dogs. He found that severe metabolic acidosis (pH 7.0) produced significantly less glucose intolerance in normal dogs than that found in uremia where the acidosis was less severe (pH 7.3). He concluded that acidosis did not play an important part in this process.

Insulin Heterogenity in Chronic Renal Failure: Information on the existence of various forms of insulin in renal failure is limited to a report by Mako and associates (17). They found much higher levels of proinsulin (0.62 ng/ml) in twelve uremic patients than in their normal controls (0.16 ng/ml). However, true insulin levels in uremia were also elevated (0.34 ng/ml) over controls (0.24 ng/ml). These investigators report only fasting values and we will have to await further studies before the significance of their findings can be assessed.

As background for understanding the metabolic abnormalities responsible for accelerated atherogenesis, we have established that glucose intolerance occurs early in the course of renal failure. This glucose intolerance is not completely reversed by dialysis and appears to be the result of a relative state of insulin resistance. The insulin resistance in turn appears to be the result of a combination of metabolic events which involve abnormalities of glucagon, insulin, and cellular phosphorylation of glucose.

LIPID METABOLISM

It has long been recognized that patients with nephrotic syndrome have

abnormal elevations in plasma lipids, primarily that of cholesterol, and a number of investigators have attempted to link cardiovascular disease with these lipid abnormalities (38,39,40). However, it was not until 1968 before the first description of lipid abnormalities in nonnephrotic renal failure was made by Bagdade (41). In contrast to nephrotic syndrome, he found that in uremia there was a significant elevation in plasma triglycerides (164 ± 62 mg/100ml) over controls (68 ± 44 mg/100ml) matched for age and weight [Fig. 7]. Numerous other observers have confirmed this hypertriglyceridemic state and the incidence is extremely high ranging from 40-70% (41,43,45). Unfortunately, as seen in Figure 7, hemodialysis fails to reverse this pattern, and in some studies the incidence of hypertriglyceridemia is actually increased (41,43,44). This triglyceride elevation is present early in the course of renal failure (45), occurs equally in both males and females, and may occur at any age. Pennsi's

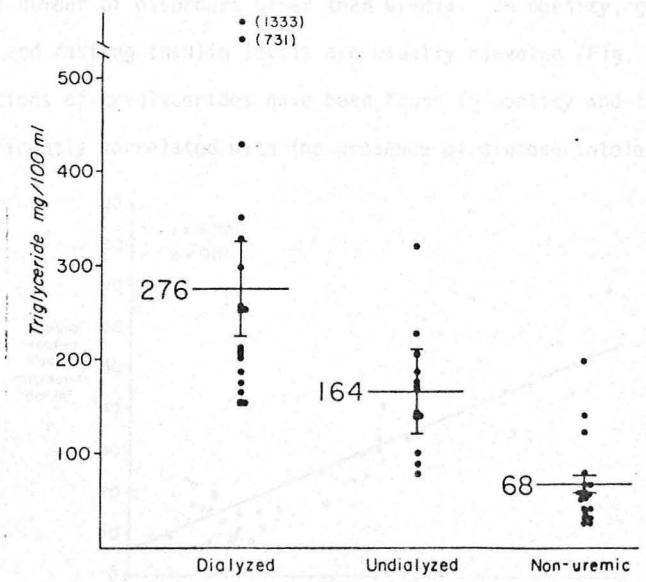


Figure 7. Basal triglyceride concentrations in dialyzed and undialyzed uremic patients compared with normal control subjects (42)

observation of a 93% incidence of elevated triglycerides in a pediatric dialysis population is particularly noteworthy (46). Both undialyzed and dialyzed patients have a Fredrickson's type IV lipoprotein pattern (16,44,45,47), and the excess triglycerides are primarily found in the very low density (VLDL) and, to a lesser extent, the low density lipoprotein (LDL) fractions (47,48). In addition, the high density lipoprotein (HDL) fraction is reduced (49). According to the Framingham study (50), those individuals with elevations in VLDL and/or low levels of HDL have a substantially greater chance of developing coronary artery disease. With the findings of exactly this pattern in renal failure, it is not surprising to find a high incidence of atherogenic complications in association with uremic.

Insulin Resistance and Hypertriglyceridemia: Insulin resistance is known to occur in a number of disorders other than uremia. In obesity, glucose intolerance is common and fasting insulin levels are usually elevated [Fig. 8]. High concentrations of triglycerides have been found in obesity and these elevations are significantly correlated with the presence of glucose intolerance (51).

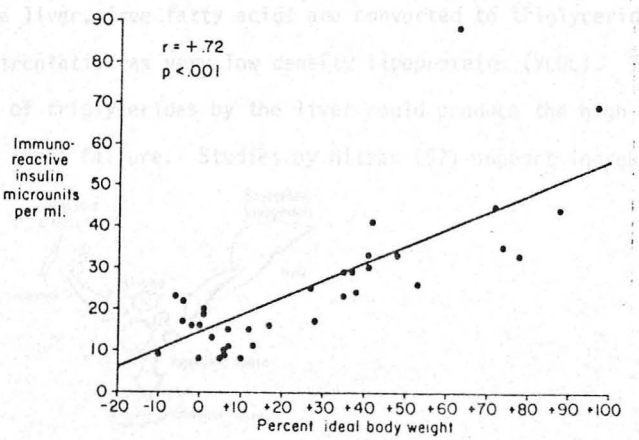


Figure 8. Correlation of basal IRI and obesity expressed as percent ideal body weight in 37 nonuremic subjects (42).

In addition, individuals with endogenous hypertriglyceridemia have been shown to have a similar insulin resistant state (52,53,54).

In renal failure, Bagdade (41), has shown that elevated triglyceride concentrations are found primarily in those patients who have increased basal insulin levels. In addition, Ibels has demonstrated that serum triglycerides are higher in patients with abnormal glucose intolerance (55). Thus, insulin resistance and hypertriglyceridemia appear to be closely linked in renal failure, obesity, and endogenous hypertriglyceridemia.

With knowledge that hypertriglyceridemia is a major atherosclerotic risk factor in renal failure, numerous investigators have attempted to define its source. Generally, two major possibilities exist: increased synthesis or decreased degradation [Fig. 9].

Increased Synthesis: Triglycerides are produced by both the intestine and liver. Those produced by the intestine are transported as chylomicrons. Since elevations in chylomicrons are not a part of the hyperlipidemia of renal failure, it is unlikely that the intestine is important in this process.

In the liver, free fatty acids are converted to triglycerides and released into the circulation as very low density lipoproteins (VLDL). Therefore overproduction of triglycerides by the liver could produce the high levels of VLDL as seen in renal failure. Studies by Nitzan (57) support increased hepatic

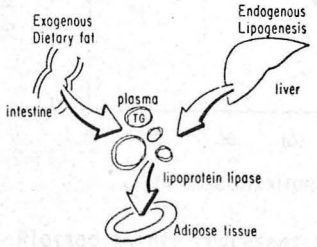


Figure 9. Triglyceride synthesis and removal (56).

synthesis by showing increased 2-C^{14} acetate incorporation into triglycerides in nephrectomized rats. However, other studies in uremic rats show triglyceride production rates to be reduced (58) or normal (59). Direct studies of hepatic production of triglycerides in humans have not been published. An indirect study on humans (60) using glycerol-2-^{3}H to measure triglyceride turnover showed that triglyceride production was subnormal [Fig. 10].

Lipogenesis by the liver requires insulin. The increased insulin secretion and prolonged disappearance rates seen in renal failure could well stimulate the liver to produce an excess of triglycerides. However, we pointed out earlier that studies by Soman (33) show that hepatic membrane binding of insulin was reduced in renal failure and this decreased binding may offset the effects of elevated insulin levels. Thus, while conflicting studies exist, it appears that hepatic triglyceride overproduction is not a primary factor in the hypertriglyceridemia of uremia.

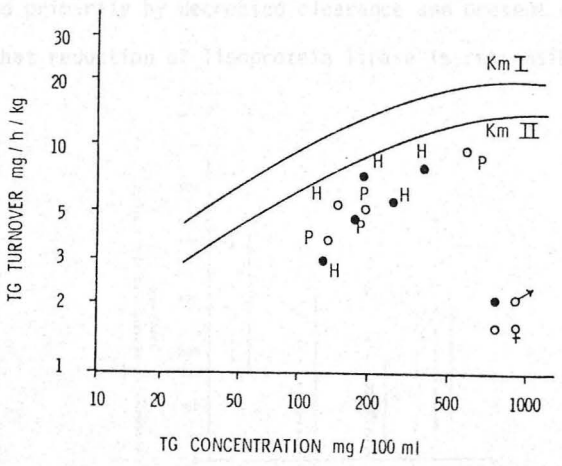


Figure 10. Plotted points represent turnover results compared to triglyceride concentrations in hemodialysis (H) and peritoneal dialysis (P) patients. Normal curves are represented by lines KmI and KmII (60).

Decreased Degradation: The rate of triglyceride removal from the circulation is dependent on the enzyme, lipoprotein lipase. This enzyme is located at or near adipose tissue capillaries and requires insulin for normal function (61). Heparin induces release of this enzyme directly into the circulation and post-heparin lipolytic activity of plasma is used as an indirect means of assessing activity of the enzyme. In uremia, triglyceride clearance has been measured by intralipid infusions and found to be decreased (62). As seen in Figure 11, this decrease in triglyceride clearance appears to be the result of reduced levels of lipoprotein lipase (41,62,63). In addition, uremic plasma from patients with chronic renal failure has been found to inhibit the lipoprotein lipase from rat epididymal adipose tissue (64). Since insulin is required for lipoprotein lipase activity, and insulin resistance is present in both dialyzed and undialyzed uremics, it seems possible, therefore, that any factor which supresses peripheral action of insulin might also supress lipoprotein lipase activity. Thus, in chronic renal failure, hypertriglyceridemia is produced primarily by decreased clearance and present evidence strongly suggests that reduction of lipoprotein lipase is responsible for this decreased clearance.

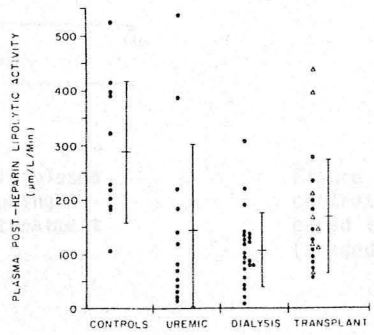


Figure 11. Plasma post-heparin lipolytic activity in healthy control subjects, uremic patients, patients on maintenance hemodialysis, and renal transplant recipients (62).

The Effects of Hemodialysis on Triglyceride Metabolism: The uremic patient is exposed to a number of agents during hemodialysis which might alter triglyceride levels. Large doses of heparin are given during hemodialysis to prevent clotting. With knowledge that heparin activates lipoprotein lipase, one would expect to see a drop in the serum triglyceride concentration during dialysis. Figures 12 and 13 show that as predicted lipoprotein lipase activity increases (62) and triglyceride levels fall (60) rather significantly during dialysis. Similar changes occur when heparin alone is given in large doses, and no change occurs in lipoprotein lipase or triglycerides when simultaneous heparin protamine infusions were given during hemodialysis (63). Therefore, the heparin given during dialysis has a positive effect in lowering triglycerides, but the effect is transient with triglyceride levels returning to basal levels in 12-36 hours (62,63).

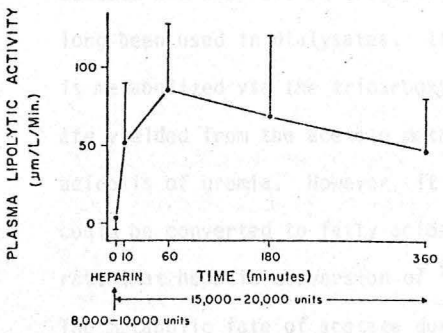


Figure 12. Changes in plasma lipolytic activity during a single hemodialysis treatment in six patient (62).

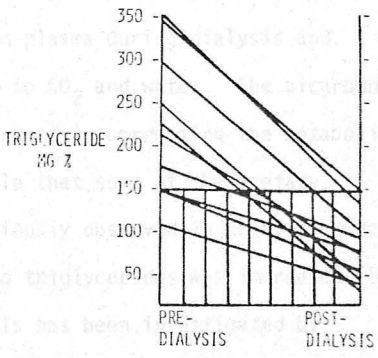


Figure 13. A plot of triglyceride concentration prior to hemodialysis compared to post-hemodialysis figures. (Shaded area represents normal limits)(60)

In an attempt to alter triglyceride levels by removing "uremic toxins," dialysis frequency has been increased. Increase dialysis frequency resulted in both worsening (48,63) and improvement (65). Unfortunately, each of these studies used small numbers of subjects (three or less) and only with larger studies will this question be answered.

The content of dialysate may be important in the reported increased incidence of hypertriglyceridemia after dialysis is initiated. First, most dialysate containes glucose varying from 150 to 250 mg %. Since carbohydrate intake has been closely linked to triglyceride levels, the influence of dialysate glucose has been investigated. Unfortunately, again results are conflicting . When glucose is withheld from the dialysate, triglyceride levels have been found to be unchanged (66) or reduced (48). While glucose content of dialysate remains controversial, increasing attention has been placed on acetate and its role in triglyceride levels in dialysis patients. Acetate has long been used in dialysates. It accumulates in plasma during dialysis and is metabolized via the tricarboxylic acid cycle to CO_2 and water. The bicarbonate yielded from the acetate metabolism is important in correcting the metabolic acidosis of uremia. However, it is also possible that some of the acetate could be converted to fatty acids. It was previously observed in nephrectomized rats that hepatic conversion of ^{14}C - acetate to triglycerides was increased (57). The metabolic fate of acetate during hemodialysis has been investigated by Davidson (67) who found that most of the acetate was oxidized to CO_2. However, a small, but significant amount was incorporated into plasma lipids. From these studies it is feasible that the glucose and acetate contained in most dialysate solutions could further promote hypertriglyceridemia, adding a small but significant burden to the already expanded triglyceride pool.

Dombeck and his associates (68) have made one additional observation concerning the present dialysis practice of prescribing androgens. Oral or intramuscular administration of testosterone or one of its derivitives is commonly given to dialysis patients to promote erythropoesis. Androgens have been effective in raising the hematocrit, and side effects or adverse reactions are rare. However, Dombeck has shown that dialysis patients (all male) had a 42% incidence of hypertriglyceridemia off androgens, and the incidence increased to 67% on androgen therapy. The mean triglyceride level was 198 mg % off androgens and 893 mg % on androgens.

The Role of Parathyroid Hormone in Hypertriglyceridemia: In 1971, Slatopolsky and Bricker demonstrated that as the glomerular filtration rate falls below 60 ml/min, there is a progressive rise in parathyroid hormone levels (69). As pointed out before, glucose intolerance (10) and triglyceride elevations (45) also become manifest early in the course of renal failure. In 1971, Kim (70) found a high incidence of insulin resistance in nonuremic patients with primary hyperparathyroidism and hypercalcemia. During the same year, Lindall studied the relationship between insulin hypersecretion and hyperparathyroidism in the uremic population (71). In this study, Lindall found that dialysis patients without clinical or radiographic evidence of hyperparathyroidism had a normal insulin response to intravenous glucose. In contrast, those with clinical evidence of hyperparathyroidism and one nonuremic patient with primary hyperparathyroidism [Fig. 14] had significantly increased insulin release in response

Time (min)	0	3	6	10	15	30	60
Before operation	12	250	292	182	149	94	69
After operation	12	134	75	74	55	54	42

Plasma insulin in μU/ml; 25 g glucose administered at zero min.

Figure 14. Insulin response to intravenous glucose in one patient with primary hyperparathyroidism (71).

to glucose, and the insulin response returned to normal after parathyroidectomy in both the primary and secondary hyperparathyroid patients. Most, if not all of Lindall's patients had small elevations in serum calcium.

It is known that hypercalcemia stimulates insulin release from tha pancreas. In an attempt to separate the effect of hypercalcemia from parathormone, three investigators studying non-uremic primary hyperparathyroidism (70,72) and uremic secondary hyperparathyroidism (73) have each found the abnormal insulin response to be related to hypercalcemia and not parathormone.

Parathyroid hormone may not be important in insulin resistance but it still may be important in lipogenesis. Adipose fat cell adenylate cyclase is a membranebound enzyme which appears to play a central role in the production of lipolipis. In the rat, a variety of hormones, including catecholamines, ACTH, glucagon, and secretin are capable of activating adipose adenylate cyclase. By contrast, only catecholamines are capable of activating this enzyme in human fat cells. Kather, in two recent publications, has shown that parathyroid hormones can also stimulate adenylate cyclase in both rat (74) and human (75) fat ghost cells. It should be noted that he exposed these fat cells to levels of parathormone which were many times higher than that observed in hyperparathyroidism.

It appears then that the insulin resistance seen in uremic and nonuremic hyperparathyroidism is the result of hypercalcemia. Whether the parathormone levels seen in renal failure significantly alter triglyceride metabolism is yet to be answered.

TREATMENT OF HYPERLIPIDEMIA IN CHRONIC RENAL FAILURE

Clofibrate:

This drug must be used with caution in chronic renal failure. Clofibrate

is primarly excreted by the kidney. When given in the normal therapeutic dose of 1500 mg daily a high incidence of rhabdomyolysis has been reported in hemodialysis patients (76). However, when given as 500 mg every other day, apparently muscle damage ceases to be a significant problem (77). Only a small number of dialysis patients treated with Clofibrate for hypertriglyceridemia have been reported. In both reports reduced dosage was used with improvement in 2/2 in one study (77) and 0/4 in the other (78).

Diet: Two dietary alterations have been studied in an attempt to lower serum triglycerides. One is the reduction in dietary protein. Whenever this is attempted, carbohydrate intake is usually increased to achieve an isocalorie diet. Wochos measured triglyceride levels in 19 patients on a 100 gm protein, 230 gm carbohydrate diet and again after dietary protein had been reduced to 50 gm and carbohydrate increased to 405 grams (41). Mean triglyceride levels on the reduced protein diet increased slightly from 146 ± 15 to 157 ± 15 mg % (not statistically significant).

Sanfelippo and associates (79) studied the effects of dietary alteration in carbohydrate on 12 subjects with chronic renal failure, seven having fasting elevations of triglycerides (> 150 mg %). Two diets were studied. The first was a "conventional" diet which simulated what most subjects were eating at home. It contained 10% of total calories as protein, 59% as carbohydrate, and 40% as fat (polyunsaturated to saturated ratio being 0.2). The second diet contained 10% protein, 35% carbohydrate and 55% of fat (polyunsaturated to saturated ratio of 2.0). Fasting triglyceride levels decreased in all subjects after 11 days on the low carbohydrate diet [Fig. 15]. In spite of the increase in dietary fat, postprandial triglycerides were not different from the "conventional" diet [Fig. 16], and fasting cholesterol levels did not rise. Insulin resistance also improved with carbohydrate reduction.

Figure 15. Effect of diet on fasting plasma levels of triglycerides, cholesterol, glucose and insulin (mean ± SEM). Triglyceride levels were significantly lower on the "low carbohydrate" diet (P<0.001) (79).

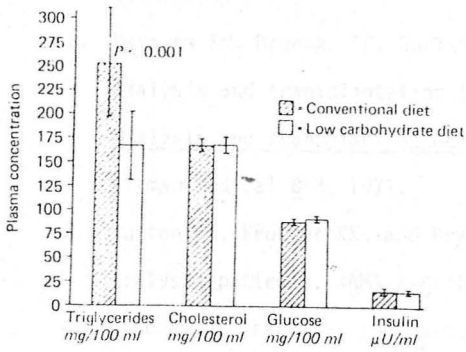
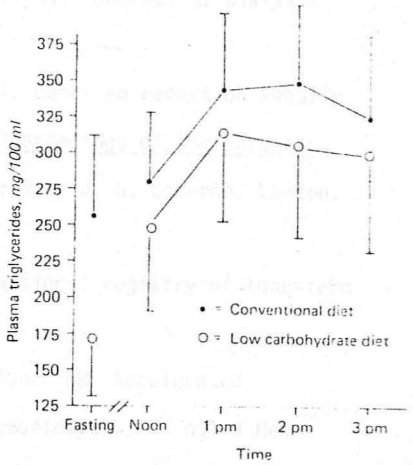


Figure 16. Effect of low carbohydrate diet on fasting and postprandial triglyceride levels (mean ± SEM for the group). Fasting values for that day are also Shown (79).



SUMMARY

Until we unravel the elusive problem of insulin resistance and hypertriglyceridemia of renal failure, accelerated atherogenesis will likely remain the #1 cause of death in dialysis patients. In the meantime, the information presented today suggests strongly that we attempt to identify those patients with triglyceride elevations early in their course of renal failure. Dietary reductions in carbohydrate certainly seem warranted. We must continue to be aggressive in avoiding prolonged periods of hypervolemia, hypertension, or hypercalcemia in an attempt to minimize those cardiovascular risk factors over which we have some control

REFERENCES

1. Burton BJ: Overview of end stage renal disease. Journal of Dialysis 1:1, 1976.
2. Parsons FM, Brunner FP, Gurland HJ, et al: Combined report on regular dialysis and transplantation in Europe. Proceedings of the European Dialysis and Transplant Association. Edited by J. S. Cameron. London. Pitman Medical 8:3, 1971.
3. Burton BT, Krueger KK, and Bryan FA Jr: National registry of long-term dialysis patients. JAMA 218:718, 1971.
4. Lindner A, Charra B, Sherrard D, and Scribner BH: Accelerated atherogenesis in prolonged maintenance hemodialysis. N Engl J Med 290:697, 1974.
5. Lazarus JM, Lowrie EG, Hampers CL, and Merrill JP: Cardiovascular disease in uremic patients on hemodialysis. Kidney Int 7:5167, 1975.
6. Lowrie EG, Lazarus JM, Mocelin AJ, et al: Survival of patients undergoing chronic hemodialysis and renal transplantation. N Engl J Med 288:863, 1973.
7. Newbauer E: Uber hyperglykamic bei hochdrucknephritis und die Beziehungen Zwischenglykamic und glucosurie beim diabetes mellitus. Biochem. Z 25:285, 1910.
8. Westervelt FB and Schreiner GE: The carbohydrate intolerance of uremic patients. Ann Int Med 57:266, 1962.
9. Horton ES, Johnson C, and Lebovitz HE: Carbohydrate metabolism in uremia. Ann Int Med 68:63, 1968.
10. Yasuda K, Sato T, Furuyama T, Yashinaga K: Relationship between insulin response to oral glucose load and creatinine clearance. Diabetes 24:1066, 1975.

11. Reaven GM, Weisinger JR, and Swenson RS: Insulin and glucose metabolism in renal insufficiency. Kidney Int 6:S63, 1974.

12. Navalesi R, Pilo A, Lenzi S, and Donato L: Insulin metabolism in chronic uremia and in the anephric state: effect of the dialytic treatment. J Clin Endrocinol Metab 40:70, 1975.

13. Bilbrey GL, Faloona GR, White MG, and Knochel JP: Hyperglucagonemia of renal failure. J Clin Invest 53:841, 1974.

14. Hutchings RH, Hegstrom RM, and Scribner BH: Glucose intolerance in patients on longterm intermittent dialysis. Ann Int Med 65:275, 1966.

15. Swenson RS, Weisinger J, and Reaven GM: Evidence that hemodialysis does not improve the glucose tolerance of patients with chronic renal failure. Metabolism 23:929, 1974.

16. Arora KK, Trafford JAP, Atkinson MK, and Sheldon J: Changes in glucose tolerance, insulin, serum lipids, and lipoproteins in patients with renal failure on intermittent hemodialysis. Postgrad Med 49:293, 1973.

17. Mako M, Block M, Starr J, Nielsen K, Friedman E, and Rubenstein A: Proinsulin in chronic renal failure and hepatic failure: a reflection of the relative contribution of the liver and kidney to its metabolism. Clin Res 21:631, 1973.

18. Briggs JD, Buchanan KD, Luke RG, and McKiddie MT: Role of insulin and glucose intolerance in uremia. Lancet 1:462, 1967.

19. Cerletty JM and Engbring NH: Azotemia and glucose intolerance. Ann Int Med 66:1097, 1967.

20. Hampers CL, Soeldner JS, Doak PB, and Merrill JP: Effect of chronic renal failure in hemodialysis on carbohydrate metabolism, J Clin Invest 45:1719, 1966.

21. Lowrie EG, Soeldner JS, Hampers CL, and Merrill JP: Glucose metabolism

and insulin secretion in uremic, prediabetic, and normal subjects. J Lab Clin Med 76:603, 1970.

22. Rubenstein AH and Spitz I: Role of the kidney in insulin metabolism and excretion. Diabetes 17:161, 1968.
23. DeFranzo RA, Anders R, Edgar P, and Walker WG: Carbohydrate metabolism in uremia: a review. Medicine 52:469, 1973.
24. Corvilain J, Brauman H, Delcroix C, et al: Labeled insulin catabolism in chronic renal failure and in the anephric state. Diabetes 20:467, 1971.
25. Zubrod CG, Eversole SL, and Dana GW: Amelioration of diabetes and striking rarity of acidosis in patients with Kimmelstiel-Wilson lesions. N Engl J Med 245:518, 1951.
26. Westervelt FB: Insulin effect in uremia. J Lab Clin Med 74:79, 1969.
27. Westervelt FB: Uremia and insulin response. Arch Intern Med 126:865, 1970.
28. Fiaschi E, Campanacci L, Guarnieri GF, et al: Muscle glucose content and hexokinase activity in patients with chronic uremia. Kidney Int 7:S341, 1975.
29. Ganda OP, Aoki TT, Soeldner JS, Morrison RS, and Cahill GF: Hormone-Fuel concentrations in anephric subjects: effect of hemodialysis. J Clin Invest 57:1403, 1976.
30. Sherwin RS, Bastl C, Finkelstein FO, Fisher M, Black H, Hendler R, and Felig P: Influence of uremia and hemodialysis on turnover and metabolic effects of glucagon. J Clin Invest 57:722, 1976.
31. Kuku SF, Jaspan JB, Emmanouel DS, Zeidler A, Kata AI, and Rubenstein AH: Heterogeneity of plasma glucagon. J Clin Invest 58:742, 1976.
32. Lefebvre PJ, Luckx AS, and Nizet AH: Renal handling of endogenous glucagon in the dog: comparison with insulin. Metabolism 23:753, 1974.

33. Soman V and Felig P: Glucagon and insulin binding to liver membranes in a partially nephrectomized uremic rat model. J Clin Invest 60:224, 1977.

34. Davidson MB, Fisher MB, Dabir-Vaziri N, and Schaffer M: The effect of protein intake on the abnormal growth hormone, glucose, and insulin homeostasis of uremia. Metabolism 25:455, 1976.

35. Knochel JP and Seldin DW: The pathophysiology of uremia. The Kidney W. B. Saunders Co. pp 1448-1485, 1976.

36. Seedat YK: Effect of potassium on blood-sugar and plasma insulin levels in patients undergoing peritoneal and hemodialysis. Lancet 2:1166, 1968.

37. Weisinger J, Swenson RS, Greene W, Taylor JB, and Reaven GM: Comparison of the effect of metabolic acidosis and acute uremia on carbohydrate tolerance. Diabetes 21:1109, 1972.

38. Berlyne GM and Mallick NP: Ischemic heart-disease as a complication of nephrotic syndrome. Lancet 2:399, 1969.

39. Porro GB and Bianchessi M: Ischemic heart disease complicating nephrotic syndrome. Lancet 2:804, 1969.

40. Curry RC and Roberts WC: Status of the coronary arteries in the nephrotic syndrome. Am J Med 63:183, 1977.

41. Bagdade JD, Porte D, Curtis FK, and Bierman EL: Uremic Lipemia: An unrecognized abnormality in triglyceride synthesis and removal. Trans Assoc Am Physician 81:190, 1968.

42. Bagdade JD: Uremic Lipemia. Arch Intern Med 126:875, 1970.

43. Hussey HH: Hyperlipidemia in children following long-term hemodialysis or renal transplantation. JAMA 236:1387, 1976.

44. Dombeck DH, Lindholm DD, and Vierira JA: Lipid metabolism in uremia and the effects of dialysate glucose and oral androgen therapy. Trans Amer Soc Artif Int Organs 19:150, 1973.

45. Wachos DN, Anderson CF, and Mitchell JC: Serum Lipids in chronic renal failure. Mayo Clin Proc 51:660, 1976.

46. Pennisi AJ: Hyperlipidemia in pediatric hemodialysis and transplant patients: association with coronary artery disease. Am J Dis Child 130:957, 1976.

47. Bagdade J, Casaretto A, and Albers J: Effects of chronic uremia, hemodialysis, and renal transplantation on plasma lipids and lipoproteins in man. J Lab Clin Med 87:37, 1976.

48. Samar RE, Moncrief JW, Decherd JF, and Popovich RP: Lipoprotein binding and hypertriglyceridemia in chronic uremia. Trans Amer Soc Artif Int Organs 21:455, 1975.

49. Bagdade JD and Albers JJ: Plasma high-density lipoprotein concentrations in chronic hemodialysis and renal-transplant patients. N Engl J Med 296:1436, 1977.

50. Gordon T, Castelli WP, Hjortland MC, Kannel WB, and Dawber TR: High Density Lipoprotein as a protective factor against coronary heart disease. Am J Med 62:707, 1977.

51. Maruhama Y, Yanbe A, Okuguchi F, et al: Relationship between insulin secretory function and endogenous hypertriglyceridemia in obese humans with insulin resistance. Tohoku J Exp Mep 119:357, 1976.

52. Farquhar JW, Frank A, Gross RC, and Reaven GM: Glucose, insulin, and triglyceride response to high and low carbohydrate diets in man. J Clin Invest 45:1648, 1966.

53. Reaven GM: Lerner RL, Stern MP, and Farquhar JW: Role of insulin in endogenous hypertriglyceridemia. J Clin Invest 46:1756, 1967.

54. Olefsky JM, Farquhar JW, and Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. Am J Med 57:551, 1974.

55. Ibels LS and Wilmshurst EG: Glucose intolerance and hypertriglyceridemia in uremic and hemodialysis patients. Sixth International Congress of Nephrology (Abstract) p 936, 1975.

56. Bierman EL: Abnormalities of carbohydrate and lipid metabolism in uremia. Arch Intern Med 126:790, 1970.

57. Nitzan M, Metzgier BE, and Wilber JF: Effects of acute uremia on metabolic fuels and hormones in the rat. Israel J Med Sci 8:771, 1972.

58. Gregg R, Mondon C, Reaven E, et al: Triglyceride metabolism in acutely uremic rats. Clin Res 23:121(A), 1975.

59. Bagdade JD, Yee E, and Wilson DE: Mechanisms of hyperlipidemia in chronic uremia. Clin Res 23:314(A), 1975.

60. Cattran SC, Steiner F, Fenton SSA, and Wilson DR: Hypertriglyceridemia in uremia and the use of triglyceride turnover to define pathogenesis. Trans Amer Soc Artif Int Organs 20:148, 1974.

61. Bagdade JD, Porte D, and Bierman EL: Diabetic lipemia: a form of acquired fat induced lipemia. N Engl J Med 276:427, 1967.

62. Ibels LS, Reardon MF, and Nestel PJ: Plasma post-heparin lipolytic activity and triglyceride clearance in uremic and hemodialysis patients and renal allograft recipients. J Lab Clin Med 87:648, 1976.

63. Gutman RA, Uy A, Shalhoub RJ, Wade AD, O'Connell JMB, and Recant L: Hypertriglyceridemia in chronic nonnephrotic renal failure. Am J Clin Nutr 26:165, 1973.

64. Murase T, Cattran DC, Rubenstein B, and Steiner G: Inhibition of lipoprotein lipase in uremic plasma, a possible cause of hypertriglyceridemia. Metabolism 24:1279, 1975.

65. Cattran SC, Fenton SSA, Wilson DR, and Steiner G: Defective triglyceride removal in lipemia associated with peritoneal dialysis and hemodialysis. Ann Int Med 85:29, 1976.

66. Novarini A, Zuliani U, Bandini L, et al: Observations on lipid metabolism in chronic renal failure during conservative and hemodialysis therapy. Europ J Clin Invest 6:475, 1976.

67. Davidson WD, Morin RJ, Roarke SJ, and Guo LSS: The role of acetate in dialysate for hemodialysis. 10th Ann Contractor's Conf Report, NIAMDD p. 15, 1977.

68. Dombeck DH, Lindholm DD, and Vieira JA: Lipid metabolism in uremia and the effect of dialysate glucose and oral androgen therapy. Trans Amer Soc Artif Int Organs 19:150, 1973.

69. Slatopolsky E, Caglar S, Pennell JP, Taggart DD, Canterbury JM, Reiss E, and Bricker NS: On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog. J Clin Invest 50:492, 1971.

70. Kim H, Kalkhoff RK, Costrini NV, et al: Plasma insulin disturbances in primary hyperparathyroidism, J Clin Invest 50:2365, 1971.

71. Lindall A, Carmena R, Cohen S, and Compty C: Insulin hypersecretion in patients on chronic hemodialysis. Role of parathyroids. J Clin Endocr 32:653, 1971.

72. Yasuda K, Hurukawa Y, Okuyama M, Kikuchi M, and Yoshinaga K: Glucose tolerance and insulin secretion in patients with parathyroid disorders. N Engl J Med 292:501, 1975.

73. Amend WJ, Steinberg SM, Lowrie EG, et al: The influence of serum calcium and parathyroid hormone upon glucose metabolism in uremia. J Lab Clin Med 86:435, 1975.

74. Kather H, Heuck CC, Toschope W, Ritz E, and Simon B: Unchanged hormone sensitivity of rat fat cell adenylate cyclase in uremia. Clin Nephrol 8:324, 1977.

75. Kather H and Simon B: Adenylate cyclase of human fat cell ghosts: stimulation of enzyme activity by parathyroid hormone. J Clin Invest 59:730, 1977.

76. Kijima Y, Sasaoka T, and Kanayama M: Untoward effects of clofibrate in hemodialysis patients. N Engl J Med 296:515, 1977.

77. Kurokawa K: Clofibrate in hemodialysis patients. N Engl J Med 296: 942, 1977.

78. Margolis S and Sapir DG: Serum Lipid and lipoprotein abnormalities in chronic renal failure. 10th Ann Contractor's Conf Report, NIAMDD p 12, 1977.

79. Sanfelippo ML, Swenson RS, and Reaven GM: Reduction of plasma triglycerides by diet in subjects with chronic renal failure. Kidney Int 11:54, 1977.