Kidney International, Vol. 42 (1992), pp. 1266–1282

NEPHROLOGY FORUM

Glucose homeostasis and the kidney

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Case presentations

Patient 1. A 41-year-old woman was admitted to The Methodist Hospital for evaluation of nausea, vomiting, and blurred vision. The gastrointestinal symptoms began the night before admission and were not associated with abdominal pain or diarrhea. She had first experienced blurred vision, most notable in her left eye, a few hours before she sought medical attention; her eyes were not painful and had no discharge. Insulin-dependent diabetes mellitus had been present for 30 years and was complicated by progressive renal insufficiency. Chronic maintenance dialysis had been initiated one month before admission because of end-stage renal failure. Continuous ambulatory peritoneal dialysis (CAPD) was the modality chosen, and she had completed a course of training 4 days before admission. She was given insulin, 20 U NPH and 10 U regular in the morning, and 10 U NPH at night; glucose levels were consistently below 250 mg/dl during the period of CAPD training. She had had one episode of hyperglycemia in the previous year but had not experienced ketoacidosis. Other complications of diabetes included hypertension, controlled with nifedipine, and diabetic retinopathy, for which she had received laser surgery. The patient reported self-administration of illicit intravenous drugs 10 years earlier but denied recent use. She gave a history of 30-pack-years of tobacco usage and social binge drinking but denied chronic alcohol intake. Physical examination revealed a well-nourished white female in no distress. Her temperature was 36.9°C; blood pressure, 178/88 mm Hg supine; heart rate, 88 beats/min; and respiratory rate, 20 breaths/min.

Funduscopic examination revealed poor visualization of all quadrants in both eyes but no papilledema. The left pupil did not react to light. The lungs were clear; the abdomen was soft, and the area surrounding the dialysis catheter was unremarkable. Laboratory findings revealed: sodium, 110 mEq/liter; potassium, 5.1 mEq/liter; chloride, 82 mEq/liter; total CO_2, 19 mmol/liter; BUN, 75 mg/dl; creatinine, 6.1 mg/dl; and glucose, 1704 mg/dl. An arterial blood sample drawn with the patient breathing room air disclosed a pH of 7.31; PCO_2, 39 mm Hg; PO_2, 50 mm Hg; and O_2 saturation, 84%.

Peritoneal dialysis fluid exchanges were discontinued. She was given oxygen by nasal cannula, 2 liters/min, and vomiting was suppressed with intramuscular administration of metoclopramide. During the first 24 hours after she entered the hospital, in addition to her customary regimen, she was given an extra dose of 10 U of regular insulin subcutaneously every 4 hours. Twelve hours after admission, the blood glucose was 114 mg/dl; subsequent values drawn every 2 hours were 138 mg/dl, 103 mg/dl, and 87 mg/dl. Laboratory data obtained 13 hours after admission disclosed: sodium, 133 mEq/liter; potassium, 3.4 mEq/liter; chloride, 96 mEq/liter; total CO_2, 24 mmol/liter; BUN, 75 mg/dl; creatinine, 6.4 mg/dl; and blood glucose, 100 mg/dl. Arterial blood gas studies revealed a pH of 7.42; PCO_2, 39 mm Hg; PO_2, 60 mm Hg; and O_2 saturation, 91%. The patient was discharged 24 hours after admission.

Patient 2. A 37-year-old man had been receiving hemodialysis treatments 3 times weekly for 3 years following bilateral nephrectomy. The medical history was notable for complex congenital urologic anomalies that required multiple operations, including suprapubic cystostomy and ureteroileal cutaneous anastomosis (ileal conduit) at the ages of 8 and 10 years, respectively. Urolithiasis and several episodes of pyelonephritis subsequently required the surgical removal of stones on three occasions and long-term treatment with antibiotics. He ultimately underwent bilateral nephrectomy because of intrarenal abscesses and recurrent sepsis. The patient also had had two major episodes of gastrointestinal bleeding due to peptic ulcer disease about 10 years prior to the initiation of dialysis.

A combination of aluminum hydroxide and calcium carbonate had been prescribed for the control of persistently elevated serum phosphate levels. For the previous 2 years, he also had

Presentation of this Forum is made possible by grants from Merck Sharp & Dohme International; Amgen, Incorporated; Dialysis Clinic, Incorporated; Parke-Davis, Incorporated; Marion Merrell Dow, Incorporated; Sandoz, Incorporated; and CIBA-Geigy Corporation.

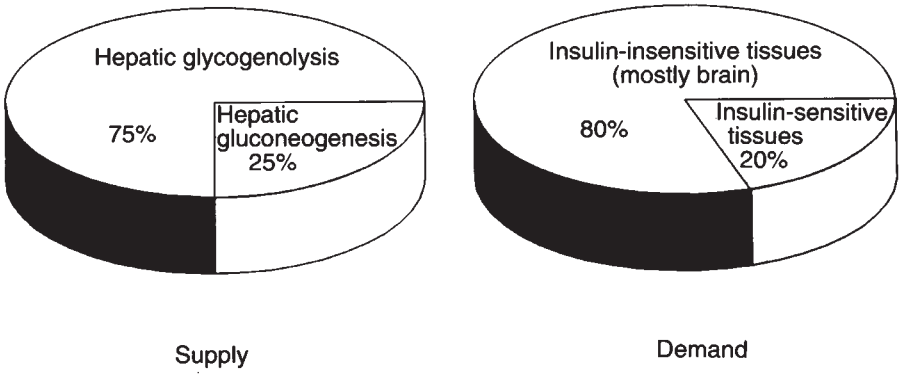

Fig. 1. *Whole body glucose homeostasis in the early fasting state.* (Modified from Ref. 1.)

been given erythropoietin, which had produced a satisfactory red cell count. Representative, predialysis laboratory data were: sodium, 137 mEq/liter; potassium, 4.7 mEq/liter; total CO_2, 24 mmol/liter; chloride, 98 mEq/liter; serum creatinine, 13.2 mg/dl; BUN, 55 mg/dl; calcium, 9.8 mg/dl; phosphorus, 6.9 mg/dl; hemoglobin, 12.7 g/dl; and glucose, 52 mg/dl. Predialysis plasma glucose levels in the fasting state had been persistently low, ranging from 44 mg/dl to 63 mg/dl. None of the medications that he had been given are known to cause hypoglycemia.

Discussion

DR. HORACIO J. ADROGUÉ *(Chief, Renal Section, Veterans Affairs Medical Center, and Professor of Medicine, Baylor College of Medicine, Houston, Texas):* A common feature, the lack of renal function, was associated with opposite deviations in blood glucose in these 2 patients. The first patient's glucose level rose as high as 1704 mg/dl, whereas the second's fell as low as 44 mg/dl. This unusual situation, in which the same disease is associated with both a major increase and a major decrease in the plasma levels of a metabolic substrate, is explained by the complex nature of the interaction between renal function and glucose production and disposal. In this Forum, I will examine the role of the kidney in glucose homeostasis and will discuss the physiologic basis and clinical implications of that role.

Glucose homeostasis

Plasma glucose levels in the normal state can be as low as 60 mg/dl during fasting and exercise and as high as 160 mg/dl after eating. As is well known, glucose levels are determined by the opposing influences of glucose utilization (removal from the circulation) and glucose availability (addition to the circulation). Glucose is, of course, derived both from endogenous and exogenous sources. In the so-called postabsorptive state, that is, under resting conditions after an overnight fast, 80% of glucose utilization occurs in insulin-insensitive tissues; the brain accounts for three-fourths of this amount, and the gut, renal medulla, and blood cells consume the remainder. Insulin-sensitive tissues, including muscle, heart, and adipose tissue, are responsible for only 20% of glucose removal in the postabsorptive state. In this state, the liver is the exclusive site of release of glucose into the circulation. Hepatic glucose derives primarily from glycogenolysis [1]; only 25% of glucose released from the liver derives from gluconeogenesis (glucose synthesized from three-carbon precursors). The major gluconeogenic substrates are lactate, pyruvate, glycerol, and alanine. Depletion of hepatic glycogen stores occurs after 20 to 24 hours of fasting, and the steady removal of glucose from the circulation by extrahepatic tissues produces mild, well-tolerated hypoglycemia (60–80 mg/dl). Sympathetic activity is suppressed by the fasting state. The decreased blood glucose inhibits insulin secretion, thereby reducing glucose consumption by insulin-sensitive tissues and promoting the availability of lipid-derived gluconeogenic precursors and alternate fuels (that is, glycerol and free fatty acids, respectively). The increased availability of fatty acids stimulates ketone production by hepatocytes. The concomitant increase in glucagon secretion increases further ketogenesis and gluconeogenesis. These hormonal adjustments reduce glucose consumption to about one-half the level in the postabsorptive state, the source of glucose under these conditions being gluconeogenesis, almost exclusively of hepatic origin. Non-glucose substrates, including ketone bodies and free fatty acids, provide the remainder of the body's caloric requirements. Although glucose consumption by the brain is reduced in prolonged fasting, the brain still accounts for more than 80% of total-body glucose utilization. If the fasting state persists for several days, renal gluconeogenesis is activated [1, 2]. Plasma glucose levels during the fasting state generally are maintained at levels higher ($\geq$60 mg/dl) than those associated with cerebral dysfunction. A synopsis of glucose demand and supply in the early and late fasting states is depicted in Figures 1 and 2.

Lactate is the other major metabolic fuel that, in addition to glucose, is transferred among body tissues in the so-called Cori cycle. This metabolic cycle allows a continuing supply of energy sources that preserve cell integrity and function [3]. Under normal aerobic conditions, the organs that have an obligatory glycolytic activity consume glucose and produce lactate that is exported through the blood stream. These obligatory glycolytic organs include the brain, muscle, skin, and red cells. In contrast, the liver and renal cortex are responsible for lactate uptake and production of glucose. Glucose is then extracted for consumption in tissues with obligatory glycolysis. The liver has a substantially larger capacity for lactate uptake than does the kidney, partly because of the relative sizes of the organs. The liver therefore is generally regarded as dominant in the process of gluconeogenesis.

Renal tissue is unique in having an extremely low glycogen content; as a result, net glucose production provides a direct

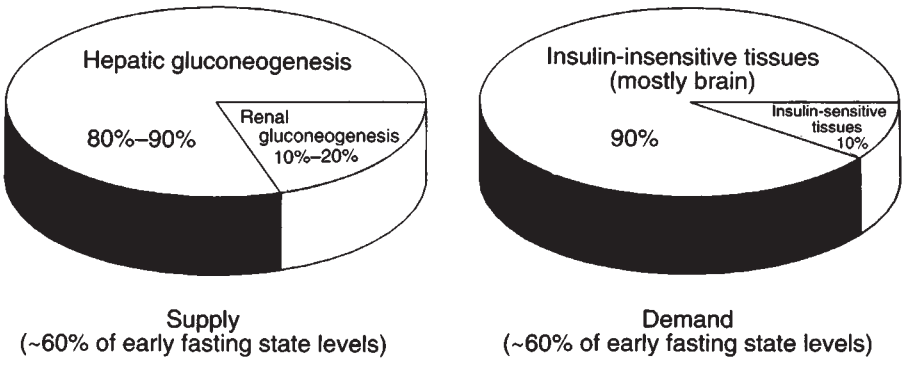

Fig. 2. *Whole-body glucose homeostasis in the prolonged fasting state.* (Modified from Ref. 1.)

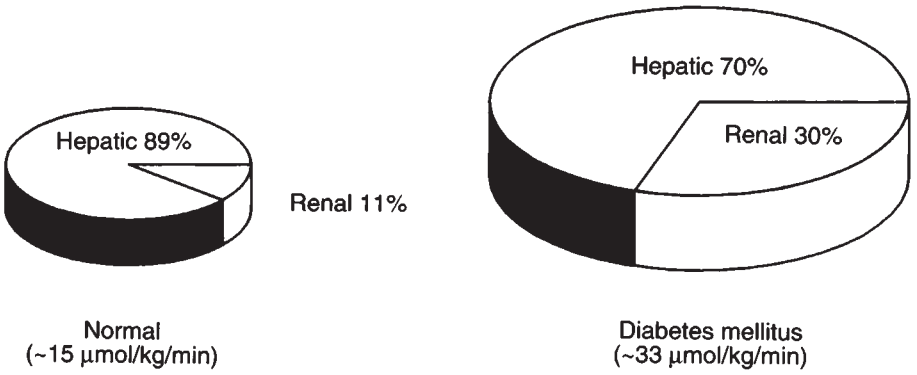

Fig. 3. *Contribution of the kidney to endogenous glucose production in conscious normal and diabetic dogs.* Total glucose production is indicated in parentheses. (From Refs. 21 and 22.)

index of gluconeogenic activity [4, 5]. The renal cortex, like the liver, possesses enzymes that both degrade glucose via glycolysis and produce glucose via gluconeogenesis [6]. Lactate and pyruvate are major substrates for renal and hepatic gluconeogenesis; the kidney also utilizes glutamine, glycine, and citrate, and the liver utilizes alanine. In contrast to the cortex, the renal medulla and papilla are capable only of glycolysis.

Renal glucose production is substantial in the presence of adequate substrates and appropriate hormonal influences. Indeed, in-vitro studies have established that, on a gram-for-gram basis, gluconeogenesis by the renal cortex exceeds that of the liver. Yet the kidney's contribution to extrarenal glucose homeostasis appears small under most conditions assessed in vivo. Only in the presence of sustained hypoglycemia [7, 8], such as in the hepatectomized animal or in prolonged starvation with acidosis [2], is the kidney generally thought to release significant amounts of glucose into the circulation via gluconeogenesis. Increased renal gluconeogenesis also has been documented in animals with decompensated diabetes; the underlying mechanism is thought to be the associated acidemia and not the diabetes-induced defect in carbohydrate metabolism [9–11].

Previous failures at demonstrating the renal release of glucose into the circulation [12–14] might be accounted for by several experimental pitfalls. To date, most in-vivo studies have been performed in animals under general anesthesia, usually pentobarbital, a well-characterized inhibitor of calcium transport; renal glucose production is in part a calcium-dependent process that is stimulated by the addition of the Ca^{++} ionophore A23187 and inhibited by pentobarbital [15–20]. Furthermore, acute studies in vivo generally involved instrumentation of the renal circulation, a maneuver known to significantly reduce the blood flow to the renal cortex, where gluconeogenesis occurs, while preserving blood flow to the renal medulla and papilla, where glycolysis is prominent. Because the arteriovenous difference for glucose in the kidney is small and because of the high renal blood flow rate, it is conceivable that following the acute surgical instrumentation of the anesthetized animal, release of glucose by the kidney into the circulation might not be detected because of an absolutely small (but biologically significant) arteriovenous difference.

In an effort to overcome these shortcomings, we recently examined the renal contribution to extrarenal glucose homeostasis in normal conscious dogs and in diabetic dogs [21, 22]. Preparatory surgery performed at least one week prior to the study included placement of Doppler flow probes on hepatic and renal vessels, and of exteriorized sampling catheters at various sites including the femoral artery, and renal, portal, and hepatic veins. We estimated renal glucose production from the product of renal plasma flow and the arteriovenous difference for plasma glucose plus urinary glucose excretion; the values obtained represent the net renal glucose balance. The net contribution of the kidney to extrarenal glucose stores (homeostasis) in conscious normal dogs following an overnight fast was 1.6 μmol/kg/min, or 11% of total-body glucose production (Fig. 3). Dogs made diabetic by total pancreatectomy at least one week prior to study had a major increase in renal glucose production in the absence of acidemia (blood pH 7.38) or prolonged fasting. The renal glucose production in conscious diabetic dogs that did not receive insulin for the previous 24 hours was 9.9 μmol/kg/min, or 30% of total-body glucose production (Fig. 3). The infusion of regular insulin, 1 U/kg, into the portal vein strongly inhibited renal glucose production in the

absence (2.8 μmol/kg/min) and presence (1.1 μmol/kg/min) of a simultaneous combined adrenergic blockade with propranolol and phentolamine. In the absence of insulin, propranolol infusion reduced renal glucose production by 33%; phentolamine had no measurable effect.

We concluded from these studies that, in the postabsorptive state, the normal kidney participates in delivering glucose to the circulation, yet the kidney's role is modest in comparison to that of the liver. In the diabetic state, however, renal glucose production is substantial, both in absolute terms and as a fraction of total-body glucose production. These findings in conscious normal and diabetic dogs might be applicable to humans. In decompensated human diabetes, with and without metabolic acidosis, renal gluconeogenesis is likely substantial. Renal glucose production, in association with increased hepatic gluconeogenesis and diminished peripheral glucose uptake, contributes to the development of hyperglycemia. It should be recognized, however, that in the presence of normal fluid volume status and renal excretory function, the concomitant glucosuria largely compensates for the excessive renal production of glucose, thereby preventing extreme hyperglycemia.

The contribution of the kidney in the Cori cycle remains undefined, yet it is believed that most glucose regeneration (that is, gluconeogenesis) occurs in the liver. We should recognize, however, that in the presence of significant hyperlactatemia (lactate higher than 5 mEq/liter) and concomitant acidemia, the relative participation of the two organs might change substantially. Although in hyperlactatemia, hepatic lactate uptake increases in production to the lactate load, hepatic glucose release need not increase significantly, presumably because of a simultaneous suppression of hepatic glycogenolysis [23]. If the elevated plasma levels are associated with significant acidemia, hepatic lactate uptake is significantly impaired, and gluconeogenesis is suppressed. In contrast, the combination of hyperlactatemia and acidemia, both of which are typically present during exercise, stimulates renal gluconeogenesis because of stimulation of the key enzyme in the process, phosphoenolpyruvate carboxykinase (PEPCK) [24, 25]. Thus, the renal contribution to extrarenal glucose homeostasis might be very important under some physiologic conditions including exercise. Poor exercise tolerance in uremic patients might be due in part to the impairment in renal gluconeogenesis that alters the normal transfer of fuels among body tissues. Further studies are needed to clarify this important topic. In summary, the renal contribution to extrarenal glucose homeostasis is small under normal conditions and accounts for approximately 10% of total available glucose. In prolonged fasting and in diabetes mellitus, however, the kidney produces 30% or more of the body's endogenous glucose.

I will now consider the hormonal control of renal glucose production in greater detail. The control of renal glucose production has been widely accepted to be closely associated with renal ammoniagenesis and pH regulation [26–29] and to be independent of the effects of insulin and glucagon. Studies that have examined the hormonal influences on renal PEPCK and gluconeogenesis have concluded that insulin has no significant effect on glucose metabolism within the renal cortex [24, 25, 30–32]. The enzyme PEPCK catalyzes the decarboxylation of oxaloacetate to phosphoenolpyruvate and appears as the key regulatory enzyme in renal gluconeogenesis. Alloxan-induced diabetes mellitus in the rat produced either no significant changes or only slightly raised renal PEPCK; the effects on the kidney contrasted dramatically with the profound increase of PEPCK in the liver [24]. Short-term starvation increased the activity of renal PEPCK, but the increase appeared to be unrelated to the levels of insulin and cortisol. Similar effects were observed in normal and adrenalectomized animals, and these changes were considered consequences of the accompanying acidosis [10, 24]. Insulin administration failed to repress PEPCK synthesis in the renal cortex of diabetic rats [25]. In addition, transcription of the gene for renal PEPCK was not affected by diabetes or by glucose refeeding but increased twofold after 24 hours of starvation and decreased significantly after bicarbonate feeding [32]. Furthermore, the suppressive effect of oral glucose administration on the level of renal PEPCK mRNA is independent of insulin [30]. Although insulin is considered the major negative modulator of hepatic PEPCK mRNA transcription and hepatic gluconeogenesis [5], this hormone appears to have no effect on PEPCK in the renal cortex [30, 32]. Moreover, glucagon, a stimulator of hepatic glucose formation, exerted no effect on renal gluconeogenesis [33].

At complete variance with these studies are reports from several investigators of an inhibitory effect of insulin on renal gluconeogenesis [34–37]. A direct inhibitory action of insulin on gluconeogenesis has been shown in canine proximal tubule cells [35–37]. Glucose production in renal cortical slices was higher in samples obtained from diabetic rats than in samples from normals; in addition, insulin administration to the diabetic animals depressed renal glucose production [34]. The suppressive effect of a glucose load on endogenous glucose production was thought to be restricted to the liver, but this effect is likely present in the kidney, as a major reduction of renal PEPCK mRNA occurs after oral glucose administration. The inhibition of renal PEPCK with an oral glucose load was observed in normal euglycemic rats, in rats with insulin-induced hypoglycemia, and in hyperglycemic rats with streptozotocin-induced diabetes [30]. Because of these reports and data collected in our laboratory [21], we conclude that insulin is an important modulator of renal gluconeogenesis and that insulin-deficient states, including prolonged fasting and diabetes mellitus, significantly increase renal glucose production.

Renal physiologists have been interested in gluconeogenesis mostly because of the relationship between the renal production of glucose and that of ammonia [38–41]. The oxidative metabolism of glucose in the renal cortex is not significantly affected by acid-base status [6]; by contrast, gluconeogenesis is markedly stimulated whenever intracellular acidosis develops (for example, in the presence of metabolic acidosis, respiratory acidosis, or potassium depletion) [9–11, 26]. Differences have been identified between the regulation of hepatic and renal gluconeogenesis. Hepatic gluconeogenesis increased in fasted and diabetic rats independently of their acid-base status [11]. By contrast, renal gluconeogenesis increased during fasting and diabetes only when acidosis was present [9–11]. Metabolic acidosis resulting from oral administration of hydrochloric acid or ammonium chloride leads to increased renal ammoniagenesis and gluconeogenesis and increased PEPCK activity in the rat. Ammonium chloride administration, a classic model for evaluating the renal response to metabolic acidosis, inhibits insulin secretion [42–44]. We therefore speculate that an insulin deficit

per se might play a major role in the increased renal ammoniagenesis and gluconeogenesis characteristically observed in acidosis. In addition, insulin resistance develops whenever acidosis is present. I will return to this topic.

Glucagon and cortisol act in a synergistic manner on gluconeogenesis in the liver and possibly in the kidney [45–48]. Despite claims that glucagon exerts no metabolic effects on renal tissue, several studies contradict this assertion. Glucagon stimulates adenylate cyclase activity in various segments of the rat nephron [19, 49, 50]. In addition, the increased plasma levels of amino acids that result from the extrarenal actions of glucagon might stimulate renal glucose production. In normal and in pancreatectomized dogs evaluated when conscious, hypoglycemia resulting from insulin administration raised plasma levels of immunoreactive gut glucagon; this rise in glucagon levels in turn might stimulate renal gluconeogenesis and account for the observed increase in renal blood flow, particularly in the experimental animal with diabetes [51, 52]. Glucocorticoids also increased renal gluconeogenesis in normal and diabetic rats [53, 54]. Furthermore, angiotensin II [55], somatostatin [56, 57], growth hormone [58], and atrial natriuretic peptides [59] stimulate renal glucose production; the atrial natriuretic peptides are elevated in the diabetic rat and have been proposed as potential mediators of hyperfiltration, a process that might be responsible for the development of progressive renal insufficiency. In summary, glucagon, cortisol, and other peptide hormones stimulate renal glucose production and oppose insulin-mediated inhibitory effects on renal gluconeogenesis.

Alpha and beta adrenoreceptors have been identified in the renal cortex [60–63]. Cyclic AMP is the second messenger for beta-1 and beta-2 agonists; alpha-2 agonists inhibit adenylate cyclase and cAMP formation. In contrast, alpha-1 adrenergic effects are calcium mediated. The major endogenous catecholamines known to alter renal function—epinephrine, norepinephrine, and dopamine [64, 65]—derive from renal efferent nerves (norepinephrine and dopamine), from the circulation (epinephrine and norepinephrine), and probably from synthesis within the kidney (dopamine). The neurotransmitters released from the noradrenergic nerve terminals appear to act directly on the renal tubules, including the proximal segment where gluconeogenesis occurs. In rat renal cortex, alpha-1 and -2 adrenoreceptors appear to coexist on proximal tubular cells. Beta-1 and beta-2 agonists likely modulate glucose production by inducing changes in cyclic AMP levels [66, 67]. The observation that cAMP analogues have a significant stimulatory effect on renal PEPCK transcription (mRNA synthesis) is compatible with a stimulatory effect of beta adrenoreceptors on renal glucose production [25]. Stimulation of alpha-1 adrenoreceptors mobilizes phosphatidylinositol, increases production of diacylglycerol and phosphatidic acid, and increases cytosolic calcium; the elevated calcium level in turn might activate protein kinase C and trigger gluconeogenesis [63]. The effects of activation of alpha-2 adrenoreceptors on gluconeogenesis are still poorly defined. Perhaps stimulation of renal gluconeogenesis due to increased sympathetic activity, and increased plasma levels of cortisol and glucagon might account, at least in part, for the hyperglycemia commonly observed in hospitalized patients. Thus, I believe that the sympathetic nervous system likely participates in the regulation of renal gluconeogenesis, especially via a stimulatory role mediated by beta-adrenergic effects [6, 21].

The kidney plays a significant role in disposing of several peptide hormones including insulin, glucagon, and growth hormone [68]. The removal of these hormones from the circulation is followed by their degradation within the renal tissue; urinary excretion of the intact molecules is negligible. The renal disposal of these low-molecular-weight proteins results from glomerular filtration, which precedes tubular uptake and degradation, largely in the proximal nephron. Renal uptake of peptide hormones from the peritubular blood and the subsequent cellular degradation also help eliminate these substances from the circulation. Renal insulin and glucagon extraction amounts to 15% to 40% and 10% to 20%, respectively, under a variety of experimental conditions [68]. We recently examined these parameters in normal conscious dogs and found an extraction of 41% ± 2% for insulin and 9% ± 2% for glucagon; these values were similar in the kidney and liver [22]. The larger mass and total blood flow of the liver as compared with the kidney account for a greater total disposal of both insulin and glucagon by the former organ. Daily renal insulin degradation is approximately 25% of daily pancreatic insulin secretion. The renal extraction, expressed as percentage of load, remains relatively constant over the physiologic range of plasma levels for all peptide hormones. Furthermore, when renal degradation due to end-stage renal disease is diminished, plasma levels of these hormones rise. A decrease in the extraction of insulin by skeletal muscle also has been described in nephrectomized animals [69, 70]. The alteration in hormonal levels plus a defective action of these hormones on target tissues are involved in the pathogenesis of the metabolic derangements observed in renal failure.

Disorders of glucose homeostasis in renal failure

Mild to moderate abnormalities in plasma glucose levels are commonly encountered in patients with renal failure. Interestingly, deranged renal function can result in the development of both hyperglycemia and hypoglycemia. Extreme deviations in plasma glucose are observed less frequently, yet they can lead to symptomatic hyperglycemia with hyperosmolar encephalopathy as well as to life-threatening hypoglycemia.

Hyperglycemia. Hyperglycemia results from an abnormal balance between insulin availability and counterregulation in which the effects of the latter are dominant. The development of renal failure is associated with several metabolic defects in glucose homeostasis that predispose to moderate hyperglycemia [71–73] and account for the syndrome of "uremic pseudodiabetes" (Table 1). Acidemia contributes significantly to the carbohydrate intolerance of renal failure. Acidemia-induced hyperglycemia might be due either to diminished plasma insulin levels or to an effect of acidity on insulin receptor binding and post-binding effects. Alternatively, the carbohydrate intolerance of acidemia might simply reflect the action of counterregulatory hormones, including catecholamines and glucagon.

To better understand the mechanisms responsible for the acidemia-induced insulin insensitivity, let us look at previous observations on the glycemic response to acute respiratory acidosis in the dog in the presence and absence of THAM (Tris-hydroxymethyl-aminomethane). When infused in vivo, THAM rapidly penetrates cells and acts as a proton acceptor.

Table 1. Determinants of glucose intolerance or "pseudodiabetes" in renal failure

Acidemia
Insulin resistance in hepatic and peripheral tissues
Abnormal receptor binding
Postreceptor defect
Increased plasma levels of:
Glucagon[a]
Growth hormone
Parathyroid hormone
Increased plasma levels of substrates for hepatic gluconeogenesis derived from skeletal muscle
Potassium deficiency

[a] Increased tissue sensitivity also is present.

THAM titrates intracellular carbon dioxide to bicarbonate and therefore raises intracellular pH. In the early 1960s, Nahas showed that hyperglycemia is accompanied by an increment in plasma catecholamines during acute respiratory acidosis, but an infusion of THAM, which maintained a constant blood pH during acute hypercapnia, prevented the rise both in plasma catecholamine levels and glycemia [74]. Although the sympathetic system undoubtedly contributes to glucose intolerance in acidemia, our demonstration of persistence of hyperglycemia in the presence of adrenergic blocking agents supports the existence of other mechanisms responsible for the disturbed glucoregulation [75]. Infusion of THAM to normal dogs and humans induced hypoglycemia; the effect was strikingly dependent on the pH level, however. When the blood pH was maintained constant at 7.40 during THAM administration in anesthetized dogs, hypoglycemia developed, but a reduction of blood pH to 7.00 (acute respiratory acidosis) fully prevented changes in the plasma glucose level. Moreover, a further reduction of blood pH to 6.80 during THAM infusion produced hyperglycemia, as opposed to the hypoglycemia observed in isohydric studies. The possibility that the THAM-induced hypoglycemia might be related to an effect of this agent on either insulin secretion, insulin action, or both evolved from the demonstration that a THAM infusion in pancreatectomized dogs deprived of food and insulin for 18 to 24 hours did not reduce plasma glucose levels [74]. Administration of THAM to dogs pancreatectomized hours before the infusion of this compound, however, reduced plasma glucose levels to a level similar to that in normal dogs. These data suggest that increased intracellular pH in peripheral tissues, possibly skeletal muscle, increases glucose metabolism in the presence of insulin and leads to hypoglycemia.

The opposite phenomenon might account for our observations during acute respiratory acidosis: the decrease in extracellular and intracellular (skeletal muscle) pH was associated with hyperglycemia in the presence of normal or increased plasma insulin levels; hyperglycemia appeared to be mediated by reduction of insulin binding to its receptor and decreased tissue sensitivity to the hormone [75]. We concluded that the carbohydrate intolerance found in acidemia is neither the result of decreased plasma insulin levels nor is it prevented by sympathetic blockade. Rather, our insulin infusion studies with euglycemic clamp showed that the abnormal glucoregulation in acidemia results from effects on hepatic and extrahepatic tissues [75]. As Figure 4 illustrates, a sizable reduction in the rate

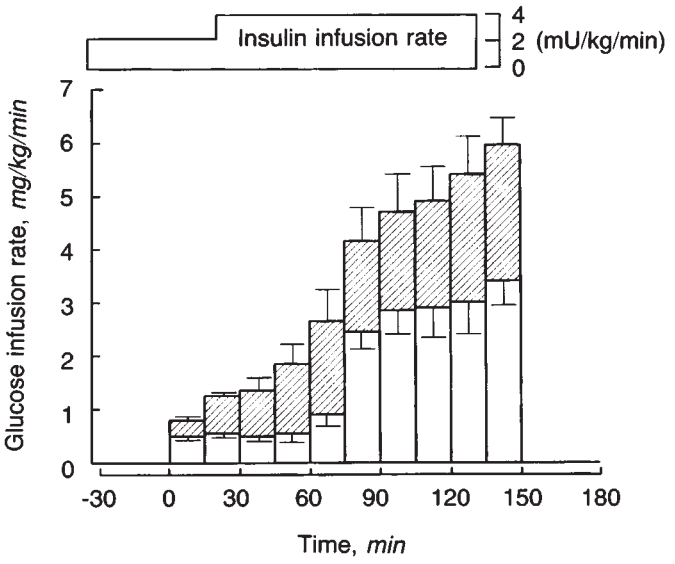

Fig. 4. *Rate of glucose infusion required to maintain euglycemia during insulin infusion studies in normal and acidemic dogs* (pHa = 7.18). Open area in each column represents the value in acidemic dogs; the entire column is the value in normal dogs. (Modified from Ref. 75.)

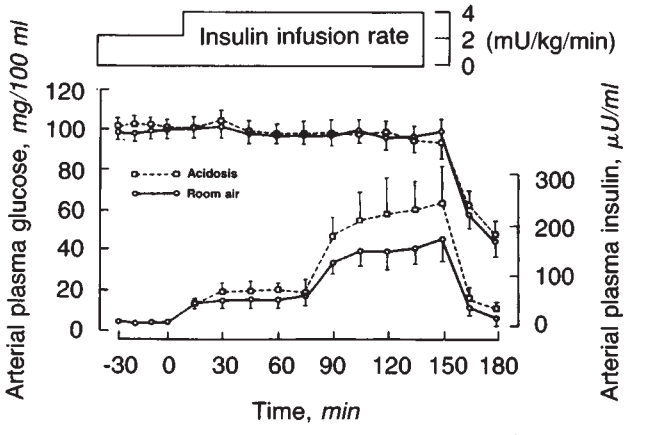

Fig. 5. *Plasma glucose and insulin levels from arterial samples of normal and acidemic dogs during insulin infusion studies with euglycemic clamp* (pHa = 7.18). (Modified from Ref. 75.)

of glucose infusion was required to maintain euglycemia in dogs with severe acidemia (pH = 7.18) during euglycemic clamp. Figure 5 depicts the corresponding arterial plasma levels of glucose and insulin. An identical insulin infusion rate in normal and acidemic animals resulted in higher plasma insulin levels in the latter group; this finding suggested reduced tissue extraction of insulin. We further examined this issue in normal and acidemic dogs exposed to an intravenous glucose load without the exogenous administration of insulin. The ratio of arterial-to-portal vein insulin levels increased significantly at lower blood pH values (Fig. 6); this finding suggested a pH-induced change in hepatic insulin extraction. A direct evaluation of the effect of systemic pH on the hepatic extraction of insulin in the presence and absence of adrenergic blocking agents has conclusively established that acidemia decreases insulin uptake by the liver (Fig. 7). Adrenergic blockade did not significantly alter

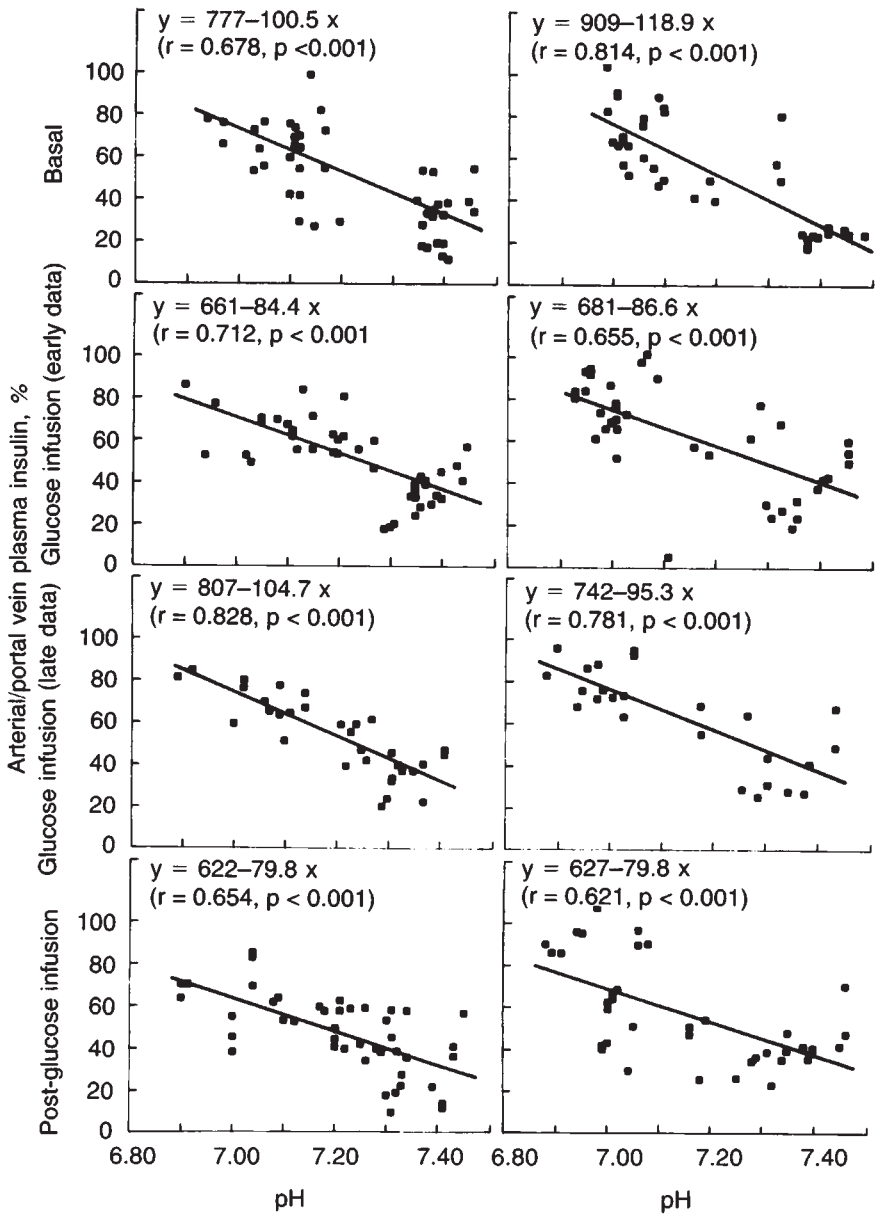

Fig. 6. *Ratio of arterial-to-portal vein plasma insulin levels in basal state, glucose infusion* (1.2 g/kg body wt intravenously over 90 min) *and post-glucose infusion in dogs with intact adrenergic systems* (left) *and adrenergic blockade* (simultaneous phentolamine plus propranolol infusion, right) *as a function of blood pH.*

the effects of acidemia on the ratio of arterial-to-portal vein insulin levels (Fig. 6) or on the hepatic extraction of insulin (Fig. 7). Thus, acidemia per se, independent of the sympathetic nervous system, accounts for the diminished uptake of insulin by the hepatocytes. This effect on the liver led us to propose that an abnormal interaction between insulin and target tissues, hepatic and extrahepatic, might be involved in the acidemia-induced insulin resistance [75]. Consistent with this concept is our recent demonstration of the opposite phenomenon, that is, increased tissue sensitivity to insulin, that occurred in association with increased hepatic insulin extraction in dogs treated chronically with glyburide, an oral hypoglycemic agent widely used in the treatment of type-II diabetes mellitus [76]. We also noted that both metabolic acidosis resulting from the infusion of mineral acids and respiratory acidosis raised plasma levels of both glucagon and glucose [77]. This finding suggests that a primary stimulation of glucagon secretion is the expected response to an increased hydrogen ion concentration in body fluids. Significant pH effects in the insulin-to-glucagon molar ratio in portal vein samples were not found in our studies; the potential effect of changes in glucagon levels during acidosis therefore seems to be properly neutralized by parallel alterations in insulin levels. Thus glucagon's action on its major target organ—the liver—does not appear to have a significant role in the increment in plasma glucose levels observed in acidosis.

The reduced renal extraction of peptide hormones characteristic of renal failure accounts in part for the rise in plasma levels of glucagon, growth hormone, and parathyroid hormone, and these three substances have been implicated in the glucose intolerance of uremia [71–73]. Insulin resistance in renal failure has been documented with direct measurements of glucose

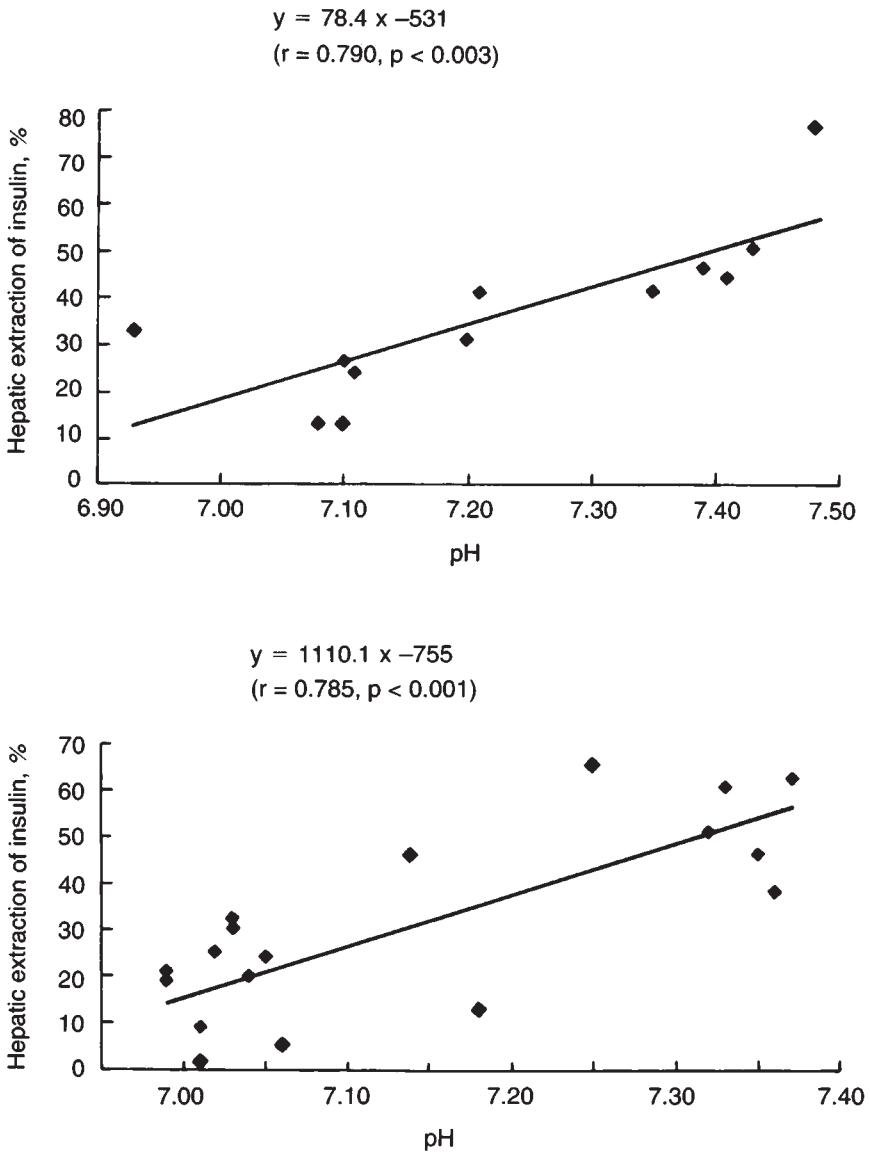

Fig. 7. *Hepatic extraction of insulin in dogs with intact adrenergic systems* (top) *and infusion of adrenergic blocking agents* (bottom, includes phentolamine infusion, propranolol infusion, and simultaneous infusion of both blockers) *as a function of blood pH.* (Reproduced with permission of the American Physiological Society, Ref. 75.)

turnover and involves the skeletal muscle and adipose tissue [72]. Because fasting uremic patients remain normoglycemic despite high plasma insulin levels, an abnormal carbohydrate tolerance must be present. Glucose uptake by the forearm in patients with renal failure who receive an insulin infusion is substantially lower than in normal controls [71]. Furthermore, tissue sensitivity to insulin in uremia increases after dialysis; uremia thus is responsible for the deranged glucose homeostasis [78]. In contrast to the tissue hyporesponsiveness to insulin in uremia, sensitivity to glucagon is heightened [79]. The altered response to the major glucoregulatory hormones in uremia might account for the increased hepatic glucose production and decreased uptake by adipose and muscle tissues. Patients with chronic renal failure had increased hepatic gluconeogenesis from alanine and a relative impairment of peripheral glucose disposal. The increased alanine production from skeletal muscle in chronic uremia results from an accelerated breakdown of muscle proteins, from an inhibition of protein synthesis, or from both mechanisms [80]. The magnitude of the increased hepatic glucose production in renal failure appears to be too small to explain the degree of glucose intolerance observed. Thus in peripheral tissues, the impairment of glucose disposal due to insulin resistance, which probably occurs at the receptor and postreceptor levels, is considered significant. Total-body potassium stores are diminished in uremia, and a potassium-deficient state is present in some of these patients. Glucose intolerance is an important metabolic derangement observed in potassium depletion and results in a deficient insulin release in response to hyperglycemia and a reduced content of glycogen in skeletal muscle [81, 82].

The diminished or absent urinary excretion of glucose at plasma glucose levels higher than the "renal threshold" in patients with renal failure plays a critical role in generating and maintaining severe hyperglycemia [83]. In contrast to this mechanism of glucose retention due to lack of renal function and excretion, "uremic pseudodiabetes" predisposes to only

moderate hyperglycemia. A simple calculation demonstrates the virtual impossibility of maintaining plasma glucose levels substantially higher than 400 mg/dl in the presence of normal renal function because of the magnitude of obligatory glucosuria. The difference between the patient's plasma glucose and the renal "threshold" of approximately 180 mg/dl, multiplied by the daily rate of renal ultrafiltration, allows us to estimate the expected level of glucosuria. Assuming a normal GFR, the amount of glucose that escapes reabsorption at a plasma level of 400 mg/dl is approximately 400 g/day. Whole-body glucose utilization is approximately 200 g/day under euglycemic conditions but, in the presence or absence of insulin, this rate increases in proportion to the glucose concentration during an acute elevation. This effect is substantially intensified, of course, in the presence of high insulin levels. Doubling the plasma glucose concentration in the presence of physiologic levels of insulin doubles glucose consumption. Hyperglycemia increases both oxidative and non-oxidative glucose disposal. Glucose transport increases acutely in tissues having high transport capacity relative to metabolic capacity (brain and red cells) and in those having low transport capacity relative to their metabolic capacity (muscle, heart, adipose tissue). It follows that in patients with severe hyperglycemia and adequate renal function, substantial glucose removal, 600 to 1000 g/day, results from glucosuria plus internal disposal. An equal amount of glucose must enter the circulation to satisfy these demands in steady-state, severe hyperglycemia. However, endogenous glucose production by the liver is suppressed by hyperglycemia, even in the absence of inhibitory effects of the associated changes in insulin and glucagon levels. The inhibitory effect of hyperglycemia on the liver is due to inhibition of both glycogenolysis and gluconeogenesis. Thus, unless an extremely large exogenous source of glucose is present (such as diet or parenteral nutrition), severe hyperglycemia will not be sustained in the absence of renal failure. A possible exception to the obligatory presence of renal failure is the patient with decompensated diabetes, who has an exceptionally high level of endogenous glucose production, that is, in excess of three times the normal value observed in the fasting state.

Renal dysfunction must be present to initiate and sustain extreme hyperglycemia in patients with a full-blown syndrome of hyperglycemic hyperosmolar encephalopathy. The predisposing conditions include the presence of uncontrolled diabetes mellitus and renal failure. This syndrome, usually associated with glucose levels above 600 mg/dl, has high morbidity and mortality rates. Typically, patients are over 50 years of age and have mild type-II diabetes, but as many as 50% have no history of diabetes. The precipitating factors of severe hyperglycemia and hyperosmolar encephalopathy are fluid deficit (Table 2) and glucose load of exogenous and endogenous origin (Table 3). The syndrome often is observed in patients with poor fluid intake (patients who are weak and unable to perceive or respond to thirst because of sedation, stroke, or other causes) and abnormal fluid losses due to osmotic diuresis, vomiting, diarrhea, fever, or diuretics. Patients receiving tube-feeding solutions, parenteral hyperalimentation, and peritoneal dialysis with a high glucose concentration in the dialysate, such as the first patient presented, also are prone to developing this hyperosmolar, hyperglycemic, nonketotic syndrome. The major determinant of marked hyperglycemia in the presence of abnormal glucoregulation is the impaired renal function, due in most cases to volume depletion, which limits or prevents glucosuria. Thus, whenever a major derangement in glucoregulation develops, the overall level of renal function plays a critical role in determining disturbances in the electrolyte [84–86] and nonelectrolyte composition of the plasma, including the blood glucose levels.

Table 2. Fluid deficit as precipitating factor of severe hyperglycemia and hyperosmolar encephalopathy

Physiologic derangement	Clinical entity
Poor water intake	
Relatively preserved CNS function	Elderly/nursing home patients
Major CNS abnormality	Cerebrovascular accident Subdural hemorrhage
Increased urinary fluid loss	Large osmotic diuresis Diuretics
Extrarenal fluid loss	
Gastrointestinal	Gastroenteritis, peptic ulcer disease, gastrointestinal bleeding, pancreatitis
Skin	Heat stroke, burns

Table 3. Exogenous and endogenous glucose load as precipitating factors for severe hyperglycemia and hyperosmolar encephalopathy

Physiologic derangement	Clinical entity
Increased glucose intake	Highly sweetened drinks Enteral or parenteral force-feeding Hyperalimentation Peritoneal dialysis
Increased endogenous glucose production	
Stress	Psychologic/physical trauma
Infection	Pneumonia, pyelonephritis, sepsis
Major illness	Myocardial infarction
Medication	Corticosteroids, phenytoin, calcium-channel blockers

Patients without a history of diabetes mellitus who develop advanced renal failure can exhibit glucose intolerance, manifested as hyperglycemia both after meals and in the fasting state. Dietary management often successfully controls this metabolic abnormality, but hyperglycemia sometimes requires a more aggressive therapeutic approach. In the latter circumstance, neither a calorie-deficient diet nor oral hypoglycemic agents should be used (with the possible exception of glipizide, the most rapid and short-acting sulfonylurea available). The patient must be given carefully titrated insulin therapy; the amount of insulin needed to correct the hyperglycemia cannot be predicted. In spite of the tissue hyporesponsiveness to insulin that accompanies uremia, insulin requirements are characteristically reduced in diabetic patients who develop renal failure [87]. I will discuss the determinants of this paradoxical situation in the next section.

Hypoglycemia. Renal insufficiency is probably the second most common cause of hypoglycemia after insulin therapy [88,

Table 4. Mechanisms of hypoglycemia in renal failure

Diminished glucose availability due to substrate limitation
Defective elimination of drugs that predispose to hypoglycemia
Impaired sympathetic counterregulatory response
Inappropriate elevation of insulin levels and effects
Lack of renal contribution to extrarenal glucose homeostasis

Table 5. Causes of hypoglycemia in renal failure

Physiologic derangement	Clinical entity
Caloric deprivation	Dietary neglect, acute and chronic
	Prolonged fasting
	Chronic malnutrition
	Heart failure
	Neoplasms
	Adrenal, thyroid deficiency
Diminished hepatic release of glucose	Alcohol intake
	Oral hypoglycemic agents
	Beta-blockers, other medications (see Table 6)
	Hepatic disease
Reduced renal release of glucose	Renal failure
Excess peripheral utilization of glucose	Insulin therapy
	Sepsis

Table 6. Drug-induced hypoglycemia

Recreational	Alcohol
Hypoglycemic	Insulin, sulfonylureas
Antihypertensive	Nonselective beta-adrenergic blockers (propranolol, pindolol)
Analgesic	Acetaminophen, salicylates,
Anti-inflammatory	Propoxyphene, phenylbutazone, quinine
Antibacterial	Trimethoprim-sulfamethoxazole, sulfonamides, pentamidine
Antiarrhythmic	Quinidine, disopyramide
Anticoagulants	Warfarin

89]. In a general population of hospitalized patients who developed hypoglycemia, nearly 50% had chronic renal insufficiency [88] and such patients do poorly. Among severe episodes of drug-induced hypoglycemia, more than 75% occurred in patients with renal or hepatic dysfunction or both [89]. Spontaneous hypoglycemia usually develops only in patients with renal failure of prolonged duration; approximately one-half of these patients have had diabetic nephropathy [89]. Contributing factors that play a role in the duration and severity of hypoglycemia in renal failure include the simultaneous presence of undernutrition, hepatic dysfunction, other illness, and drug effects [90, 91]. Diabetes mellitus is the cause of end-stage renal failure in about one-third of ESRD patients, and a significant fraction of these patients require insulin administration; the risk of developing hypoglycemia under these circumstances is exceptionally high.

Let us review the causes and mechanisms of hypoglycemia in renal failure and the distinct signs and symptoms of hypoglycemia in this condition [90–94]. The pathophysiology of hypoglycemia and the clinical conditions in which it develops in patients with renal failure are summarized in Tables 4 and 5. The most important predisposing mechanism to hypoglycemia is diminished glucose availability due to substrate limitation. Deprivation of calories because of poor appetite, upper gastrointestinal symptoms, or simple neglect—particularly in old patients—are leading causes of hypoglycemia. The defective elimination of drugs that predispose to hypoglycemia represents a major mechanism leading to depressed plasma glucose in renal failure. Sympathetic counterregulatory response is depressed in uremia and contributes to hypoglycemia due to inadequate hepatic glycogenolysis and gluconeogenesis. Deficient gluconeogenesis is magnified by the loss of alanine during hemodialysis [89]. The decreased renal insulin extraction can result in hyperinsulinemia, which counteracts tissue insulin resistance and fosters hypoglycemia. However, insulin levels most often are normal in non-diabetic uremic patients. The half-life of endogenous insulin as well as that of exogenous insulin is prolonged in patients with advanced renal failure. The net effect is the possible occurrence of an exaggerated hypoglycemic response, which has been proposed to account in part for the decreased insulin requirements in diabetics with renal failure [87]. The insulin dosage in insulin-treated diabetics decreases as the severity of renal insufficiency increases, and insulin may not be required when end-stage renal failure is reached [89]. Normalization of glucose tolerance tests as a result of the development of renal failure also has been reported in diabetic patients [89]. The presence of fasting hyperinsulinemia in non-diabetic patients with advanced renal failure might be due partly to the presence of significant hyperkalemia. Elevated serum potassium levels such as those commonly found in uremic patients increase the plasma insulin concentration in humans and experimental animals. Clearly, an association exists among hyperkalemia, hypoglycemia, and hyperinsulinemia. It has been difficult to establish with certainty, however, whether the hypoglycemia and relatively high insulin levels observed in non-diabetic patients with renal failure and hyperkalemia are due to the electrolyte abnormality, as many other factors contributing to hypoglycemia are operating simultaneously. Insulin levels also contribute to the modulation of serum potassium [77]. The diminished renal gluconeogenesis characteristic of renal failure adds to the propensity for hypoglycemia. Heart failure, neoplasms and endocrine deficiencies—especially of the adrenal and thyroid glands—also play a role in the development of hypoglycemia in uremic patients. The pathogenesis of hypoglycemia in these diseases varies and includes poor dietary intake, gastrointestinal malabsorption, depletion of glycogen stores, and diminished hepatic gluconeogenesis partly due to insufficient production or delivery of substrates.

The second most important mechanism of hypoglycemia in all patients with renal failure is drug-induced hypoglycemia due to alcohol, insulin, oral hypoglycemic agents, or several drugs that are not effectively eliminated because of renal failure [95]. Table 6 lists the drugs that have been implicated repeatedly in the development of hypoglycemia in patients with normal and abnormal renal function. Other than insulin, the most common exogenous agents causing hypoglycemia in adults presenting to the emergency room are alcohol and sulfonylureas; these two substances account for more than 50% of all cases of irreversible brain damage secondary to hypoglycemia. Renal failure with and without hepatic disease is commonly observed in

patients with severe hypoglycemia due to sulfonylurea therapy and excessive alcohol intake [89, 95]. Several mechanisms are involved in alcoholic hypoglycemia [96]. Inadequate glycogenolysis is due to depletion of glycogen stores as a result of malnutrition, prolonged fasting, and liver disease. Alcohol metabolism depletes hepatic nicotinamide adenine dinucleotide, which is essential for gluconeogenesis from lactate and from other precursors. Ethanol inhibits the hepatic uptake of the gluconeogenic precursors: lactate, alanine, and glycerol. In addition, alcohol inhibits alanine release from skeletal muscle and suppresses counterregulation by inhibiting the release of growth hormone and adrenocorticotrophic hormone. Alcoholic hypoglycemia can develop many hours after alcohol ingestion, even when the patient no longer has detectable blood alcohol levels. Hypoglycemia most commonly occurs in chronically malnourished and fasting alcoholic patients. After a prolonged fast, the normal kidney contributes as much as 45% of endogenous glucose via gluconeogenesis [2], so renal failure substantially increases the risk of alcohol-induced, profound hypoglycemia.

All sulfonylureas currently in use for the treatment of type-II diabetes mellitus have caused severe refractory hypoglycemic coma, primarily in patients with renal failure [95]. Chlorpropamide, the oral agent most frequently implicated in hypoglycemic episodes, is almost exclusively eliminated by the kidney; thus this drug is contraindicated in patients with renal failure. Tolbutamide and acetohexamide also have prolonged half-lives in patients with advanced renal failure and can cause recurrent hypoglycemia in these patients. In contrast to these agents, the second-generation sulfonylureas, including glyburide and glipizide, are metabolized in the liver; the half-lives of these agents remain unaltered in moderate renal insufficiency [89]. However, active metabolic derivatives from glyburide do accumulate in renal failure; thus glyburide should not be used if creatinine clearance is less than 30 ml/min. The short-acting, second-generation drug glipizide also should be avoided in advanced renal failure [89].

Non-selective beta-adrenergic blocking agents such as propranolol and pindolol cause hypoglycemia because they diminish counterregulation to hypoglycemia, including the glucagon-mediated hepatic glycogenolysis and gluconeogenesis. This hypoglycemic effect, more severe in patients with renal failure, has been described both in diabetic and nondiabetic patients. Propranolol is the drug most often associated with hypoglycemia in hemodialysis patients, particularly when a glucose-free dialysate is used [89–92]. The addition of glucose to the dialysate diminishes the risk of hypoglycemia in patients receiving non-selective beta blockers for control of hypertension, angina, or arrhythmias.

The risk of hypoglycemia is substantial in diabetics with renal insufficiency who are given both a sulfonylurea and salicylates. Salicylates and other drugs including phenylbutazone, acetaminophen, propoxyphene, sulfonamides, and warfarin can potentiate the hypoglycemic effect of oral hypoglycemic agents by inhibiting hepatic metabolism of the drug. Trimethoprim-sulfamethoxazole, which also potentiates the effects of oral sulfonylureas, causes hypoglycemia in patients with renal insufficiency, yet this drug has not been held responsible for hypoglycemia in diabetic patients with normal renal function. The risk of hypoglycemia is also present in non-diabetic patients with renal failure receiving any of these compounds. Sulfonamides, like the structurally similar sulfonylureas, decrease plasma glucose levels, especially in patients with renal failure. Moderate amounts of salicylates also can produce hypoglycemia due to renal-failure-induced drug accumulation. Most likely, salicylates and acetaminophen induce hypoglycemia by inhibiting hepatic gluconeogenesis, partly through their ability to uncouple oxidative phosphorylation [95]. By contrast, drug-induced stimulation of insulin secretion has been proposed to account for the development of hypoglycemia with quinine, guanidine, and pentamidine [95]. Disopyramide, a quinidine-like antiarrhythmic drug, also produces hypoglycemia in patients with renal or hepatic dysfunction by a mechanism presumably similar to that of quinine [95]. Excessive peripheral utilization and depressed endogenous glucose production are involved in the hypoglycemia observed in sepsis and after insulin overdose.

Table 7. Signs and symptoms of hypoglycemia in patients with renal failure

Neuroglycopenic manifestations	
~50 mg/dl	Headache, blurred vision, dizziness, lack of coordination
~30 mg/dl	Lethargy, variable degrees of coma
~10 mg/dl	Convulsions, permanent brain damage, death
Sympathetic manifestations:	Usually absent

The existence of an impaired sympathetic counterregulatory response to hypoglycemia in renal failure is important not only from a pathophysiologic point of view, but also in terms of the clinical presentation of hypoglycemia. The typical symptoms of hypoglycemia in adult patients are conveniently classified as those due to sympathetic discharge and those secondary to inadequate glucose delivery to the brain (neuroglycopenia) [97]. The sympathetic symptoms, which generally develop at higher plasma glucose levels than do the neuroglycopenic manifestations, usually are evident when the plasma glucose reaches 50 mg/dl to 70 mg/dl. These symptoms include hunger, irritability, palpitations, tremors, and sweating, and usually are observed in well-nourished individuals who develop acute hypoglycemia. However, patients suffering from hypoglycemia due to severe caloric restriction or renal failure fail to manifest sympathetic-mediated symptoms, and their only manifestations are those of neuroglycopenia (Table 7). Two reasons account for the lack of sympathetic symptoms in the hypoglycemia of renal failure. First, the fasting state inhibits the sympathetic system, whereas feeding results in its stimulation. Thus, overall undernutrition and caloric/substrate limitation in patients with uremia and hypoglycemia suppress the sympathetic response. Second, end-stage renal failure is commonly accompanied by a significant autonomic neuropathy resulting in a lack of sympathetic counterregulation. This defect is magnified in patients with renal failure due to diabetes mellitus in whom the autonomic neuropathy is often severe and the risks of hypoglycemia are highest.

Concluding remarks

The complex role of the kidney in glucose homeostasis accounts for both hyperglycemia and hypoglycemia in advanced renal failure. Among the most important factors that determine whether plasma glucose reaches abnormally high or low values are overall nutritional status, magnitude of current caloric intake, and drug administration. Vacillating blood glucose levels in patients with diabetes mellitus and renal disease make achieving tight metabolic control especially difficult. Because renal failure alters caloric intake and insulin metabolism, insulin requirements can vary markedly. Proper diabetic management demands that clinicians anticipate the possibility of insulin resistance and the need to change insulin dosage; in this context, we should note that glucose intolerance improves with dialysis.

The first patient presented here illustrates extreme hyperglycemia in a woman with type-I diabetes mellitus and end-stage renal failure being treated with continuous ambulatory peritoneal dialysis. The additive effects of anuria, high glucose concentration in peritoneal dialysis fluid (all exchanges were 2.5% dextrose prior to admission), and poor metabolic control of type-I diabetes mellitus accounted for the development of the hyperosmolar hyperglycemic syndrome observed in this patient.

A potentially more serious complication is hypoglycemia in patients with end-stage renal failure. Hypoglycemia is relatively common and has a poor prognosis in patients with renal failure. Patient 2 had persistent hypoglycemia in the absence of a history of a medication that might have been responsible for this abnormality. This patient had had bilateral nephrectomy, so the loss of renal glucose production and renal insulin disposal predisposed him to hypoglycemia; in addition, he had received hemodialysis, as opposed to the first patient, who had received peritoneal dialysis therapy with its attendant, sizable glucose load. Alcohol intake, concomitant liver disease, and sepsis are prominent cofactors in the pathogenesis of hypoglycemia in patients with renal failure. Proper nutrition, the judicious use of any medication that has the potential for inducing hypoglycemia, early detection and treatment of associated diseases, and the use of dialysate fluid with glucose in hemodialysis patients can diminish the risks of this potentially lethal complication.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Insulin resistance and the resultant hyperinsulinemia are now considered risk factors for atherosclerotic vascular disease. To the extent that dialysis ameliorates these metabolic abnormalities of chronic renal failure, hyperinsulinemia might figure as an additional parameter to be considered regarding initiation of dialysis. In your view, how much of the hyperinsulinemia is due to the acidemia of chronic renal failure and how much to the uremia itself? Does this issue strengthen the case for maintaining blood pH close to normal in patients with chronic renal insufficiency? Have there been any studies in uremic animals in which attempts were made to learn how much of the hyperinsulinemia and associated defects of uremia are due to the prevailing acidemia?

DR. ADROGUÉ: Although the association between insulin resistance and an increased risk of atherosclerotic cardiovascular disease is well documented, the roles of insulin resistance and the resultant hyperinsulinemia in the pathogenesis of this illness have not been conclusively established [98–100]. With respect to the hyperinsulinemia observed in patients with chronic renal failure, this abnormality is not always present and, when it occurs, it is often mild. Most patients with uremia have insulin resistance, which should lead to increased insulin secretion unless this process is impaired by renal failure. Consequently, plasma insulin levels can be normal or even low in uremic patients with a decreased insulin secretory response to the intake of nutrients [101]. A precise evaluation of the relative contribution of acidemia and uremia per se in the insulin resistance of patients and animals with chronic renal failure is not available. I believe, however, that acidemia plays a significant role in insulin resistance, and that the maintenance of a blood pH close to normal should be beneficial with respect to the altered glucose homeostasis in end-stage renal failure.

DR. MADIAS: Regarding the pathogenesis of the hyperinsulinemia of uremia, what do we know about insulin release, number of insulin receptors, insulin binding to its receptor, and postreceptor events in this disorder? Is there resistance to insulin's ability to suppress glucose production by the liver in uremia?

DR. ADROGUÉ: The pH dependence of insulin binding to its receptor has been well established in vitro and in vivo [102, 103]. Acidemia decreases insulin binding as well as tissue extraction of plasma insulin [75]. However, uremia without acidosis does not impair insulin binding, insulin-receptor kinase activity, and glycogen synthase activity. Thus uremia per se induces insulin resistance as a result of a postreceptor defect in the insulin-stimulated transport of glucose [104, 105]. The major site of insulin resistance in uremia occurs in the peripheral tissues because suppression of hepatic glucose output by insulin is normal [101]. A substantial improvement in tissue sensitivity to insulin is achieved with dialysis, yet full correction of the defect is not accomplished [106–108].

DR. JORDAN J. COHEN (*Dean, School of Medicine, State University of New York, Stony Brook, New York*): I think we must distinguish between the diabetic patient with renal failure and the non-diabetic with renal failure. We all have seen diabetic patients, such as Patient 1, who develop extreme hyperglycemia consequent to the glucose load from peritoneal dialysate. The explanation for the hyperglycemia in this circumstance seems reasonably straightforward. How common is such extreme hyperglycemia in the non-diabetic patient? Although renal failure can result in glucose intolerance, as defined by reasonable criteria, I can't recall seeing a peritoneal dialysis patient with truly severe hyperglycemia who wasn't diabetic.

DR. ADROGUÉ: I agree in general with your comment. Plasma glucose levels higher than 180 mg/dl are uncommon in non-diabetic patients with uremia who receive chronic peritoneal dialysis. However, severe hyperglycemia is occasionally observed in non-diabetic patients with acute or chronic renal failure who receive multiple rapid exchanges of dialysate (that is, hourly) containing a high glucose concentration (4.25% dextrose) to induce a large net fluid loss. In these circumstances, hyperglycemic hyperosmolar encephalopathy can occur in non-diabetic uremic patients.

DR. COHEN: Even among diabetic patients treated with peritoneal dialysis, the fraction who develop extreme hyperglycemia is small. Do we understand why some diabetics seem to be prone to these very severe degrees of hyperglycemia whereas the majority are not?

DR. ADROGUÉ: I disagree with your comment. Severe hyperglycemia is a major problem commonly observed in diabetics on peritoneal dialysis unless precautions are taken to avoid its development. Regular insulin is usually added to the dialysis fluid to circumvent this problem [109, 110]. Since the amount of glucose absorbed is directly proportional to both the glucose concentration in the dialysate instilled into the peritoneal cavity and to the number of daily dialysate exchanges, the physician must adjust the insulin dosage to fit the particular regimen of peritoneal dialysis recommended for the patient [111]. Diabetics prone to severe hyperglycemia are those involved in frequent and/or substantial dietary indiscretions associated commonly with a large positive fluid balance (characteristically observed on weekends and holidays). The correction of fluid excess in these patients is achieved by increasing the number of daily dialysate exchanges and/or by the use of exchanges with a high glucose concentration; both maneuvers tend to further increase plasma glucose levels. The omission of insulin doses, poor self-monitoring of plasma glucose, and intercurrent infections are other important factors that can lead to uncontrolled diabetes and severe hyperglycemia in uremic diabetic patients on dialysis, especially patients receiving peritoneal dialysis.

DR. COHEN: Is mild to moderate hyperglycemia in the setting of peritoneal dialysis problematic? Do we have any reason to think that a high glucose level is particularly dangerous for such patients if the levels reached do not cause symptoms?

DR. ADROGUÉ: Maintenance of plasma glucose at approximately normal levels is important in uremic diabetic patients in terms of preventing the development and/or decreasing the severity of several acute and chronic complications associated with hyperglycemia. Acute complications of hyperglycemia include a higher risk of severe hyperkalemia and of pulmonary edema due to extracellular fluid volume expansion; these complications result when the high extracellular glucose concentration causes rapid shifts of fluid rich in potassium out of the cells. Chronic complications of hyperglycemia include accelerated atherogenesis and microvascular disease (most notably in the form of diabetic retinopathy), and increased frequency and severity of infection. Because insulin requirements fluctuate widely in uremic diabetic patients on dialysis, very tight glucose control is not a reasonable goal of insulin therapy. It is prudent and feasible to constantly maintain plasma glucose levels between 80 mg/dl and 200 mg/dl. More rigorous glucose control substantially increases the risk of hypoglycemia, the most dread complication in patients with altered glucose homeostasis [110].

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): I have several questions. Which specific cells within the kidney metabolize insulin? Does the site of metabolism vary in patients with different kinds of renal disease? Are there alterations in glucose uptake in the insulin-insensitive tissues in uremic individuals? Finally, is glucose uptake per se altered in uremia?

DR. ADROGUÉ: Renal cells of the proximal tubule extract insulin from the luminal fluid (filtered insulin) and peritubular fluid, and degrade this hormone for final disposal. Although renal ablation can lead to hyperinsulinemia, the high plasma insulin levels observed in uremia must result from inappropriately high secretory rates by the beta cells of the pancreas, since tissue insulin extraction is not a primary modulator of insulin levels [68]. With respect to the metabolism of insulin in renal disease, a reduction in the renal extraction of insulin has been found in disease states characterized by a reduced glomerular filtration rate of $\leq$40 ml/min. When the GFR is less than 20 ml/min, a clinically significant reduction in the renal clearance of insulin is evident [112, 113]. Hyperglycemia in uremic patients, whether diabetic or not, increases glucose uptake in the non-insulin-sensitive tissues. The main defect in glucose metabolism observed in uremia, however, is in glucose disposal by insulin-sensitive tissues, especially the skeletal muscle. A decreased insulin-mediated glucose uptake in skeletal and adipose tissues is also present in uremic non-diabetic patients, and this defect is ameliorated by dialysis.

DR. MADIAS: In various insulin-resistant states, including uremia, insulin-mediated extrarenal potassium uptake, both by liver and muscle, is intact. Obviously, different transport systems mediate glucose uptake and potassium uptake, but could you enlighten us on the current understanding of this dissociation?

DR. ADROGUÉ: Insulin is a major modulator of extrarenal potassium homeostasis and promotes potassium uptake in many cell types, including those from skeletal muscle and liver. The hypokalemic action occurs at a very low insulin concentration, and it is independent of the effect of insulin on glucose uptake [114]. The cellular mechanisms of insulin-mediated potassium uptake include: (*1*) stimulation of the Na-K-ATPase; (*2*) stimulation of the sodium/hydrogen exchanger; and (*3*) depression of ionic conductance of some potassium channels. Stimulation of the sodium-potassium pump by insulin results in the translocation of potassium to the cell interior by the direct action of this pump. The immediate result of insulin-mediated stimulation of Na-K-ATPase on the electric properties of the cell membrane is hyperpolarization of the membrane potential (a more negative cell interior). Secondary effects promoted by insulin-induced hyperpolarization of the cell membrane include a new electrical gradient that favors cellular potassium entry, and deactivation of potassium channels, thereby inhibiting the cellular exit of potassium. Insulin promotes the cellular entry of sodium and the cellular exit of hydrogen by stimulating the sodium/hydrogen exchanger. The entry of sodium increases the potassium-binding capacity of intracellular anions and stimulates the sodium-potassium pump, therefore favoring cellular potassium uptake. Insulin controls gating of the inward rectifier potassium channel of skeletal muscle. This type of potassium channel is relevant, as it accounts for most of the potassium conductance of the skeletal muscle in the resting state. This channel allows potassium to flow into cells much more easily than to exit them. Thus, when the cell membrane is hyperpolarized, the high inward conductance facilitates cellular potassium entry. When the cell membrane is depolarized, the low outward conductance reduces potassium efflux. Insulin exaggerates the inward rectifying properties of this class of potassium channel by a dual effect of stimulation of potassium entry and depression of potassium exit.

DR. ANDREW KING (*Division of Nephrology, New England Medical Center*): I was intrigued by the array of symptoms that

you described for mild to moderate hypoglycemia; these symptoms are commonly observed in the dialysis unit. Have you any idea of the frequency of this type of hypoglycemia? Has anyone defined any long-term risks associated with chronic hypoglycemia and, if so, should we be screening for this?

DR. ADROGUÉ: I believe that symptomatic hypoglycemia is not uncommon in patients on chronic hemodialysis; this view is shared by other investigators [101]. Hypoglycemia occurs in uremic non-diabetic patients, especially in undernourished individuals and those with sepsis, which most commonly develops as a complication of an infected vascular access for chronic dialysis. Hypoglycemia in hemodialysis patients is underdiagnosed because of insufficient awareness of this complication and insufficient screening of plasma glucose levels. I recommend measurement of plasma glucose with routine laboratory evaluation and in uremic patients with evidence of failure to thrive, acute illness, or a change in mental and/or neurologic status. Hypoglycemia associated with renal failure has an ominous prognosis [89]. The addition of glucose to the dialysate in hemodialysis has diminished the incidence and severity of hypoglycemia in this patient population. We should bear in mind that hypoglycemia has the potential for producing sudden death and/or devastating neurologic complications, yet prevention and treatment of hypoglycemia are very effective.

DR. BRIAN PEREIRA (*Division of Nephrology, New England Medical Center*): What is the cause of the kidney's inability to mount gluconeogenesis in patients with end-stage renal disease? Does the uremic state affect the liver's capability for gluconeogenesis?

DR. ADROGUÉ: Patients with end-stage renal failure who develop spontaneous hypoglycemia have diminished gluconeogenesis. Because gluconeogenesis requires an adequate supply of three-carbon precursors (lactate, alanine, glycerol), reduced availability of these substances because of overall malnutrition, poor caloric intake, and a decreased release of lactate by skeletal muscle contributes to reduced glucose production. In addition to substrate limitation, significant alterations also are present in renal failure in the tissues responsible for gluconeogenesis. Renal gluconeogenesis is basically nonexistent in uremic patients, yet the renal production of glucose in normal individuals after prolonged fasting can account for almost one-half of total endogenous glucose production. The presence of relatively high plasma insulin levels in uremia, in spite of the associated normo- or hypoglycemia, inhibits hepatic glucose production. In addition, excessive alcohol intake, chronic liver disease, and accumulation of a number of drugs that decrease hepatic glucose production can lead to further depression of hepatic gluconeogenesis and the development of hypoglycemia in patients with renal failure.

DR. PEREIRA: You mentioned that patients on CAPD absorb a large amount of glucose and consequently release a large amount of insulin, which could have a deleterious effect. In that case, CAPD is probably not the best mode of renal replacement therapy. Are you making that assumption?

DR. ADROGUÉ: Multiple factors are responsible for the carbohydrate intolerance in uremia including insulin resistance, increased levels of anti-insulin hormones (including growth hormone, glucagon, and parathyroid hormone), acidemia, and potassium depletion. The absorption of a large amount of glucose consequent to CAPD using dialysate with a high glucose concentration in patients having carbohydrate intolerance of course involves potentially deleterious metabolic effects. Hyperglycemia can induce glycosylation of proteins in various tissues and thus contribute to accelerated atherosclerosis. Hyperglycemia and the resulting hyperinsulinemia can lead to hypertriglyceridemia and contribute to the abnormal profile of plasma lipoproteins observed in uremia. Glucose absorption in patients treated with CAPD accounts for about 20% of the total daily energy intake and is often associated with weight gain. In spite of the side effects resulting from the glucose present in the dialysate, CAPD represents an excellent modality of renal replacement therapy [115].

DR. KLEMENS MEYER (*Division of Nephrology, New England Medical Center*): I was unnerved by the list of drugs to which you ascribe hypoglycemia. I must say that I was also a little skeptical of it, particularly if the data were drawn from patients who had other underlying reasons for hypoglycemia. You have shown us that hemodialysis patients do have other reasons. I would think it very hard to show that sodium warfarin or acetaminophen was responsible for a meaningful change in blood glucose. I wonder how many of the drugs on your list were carefully studied. How many are on it because of coincidence?

DR. ADROGUÉ: More than 80% of all reported cases of severe drug-induced hypoglycemia have occurred in undernourished patients, most of them having significant hepatic and/or renal disease. Renal failure is the most important predisposing factor for hypoglycemia in patients with diabetes mellitus receiving sulfonylureas. Insulin administration and alcohol ingestion remain the leading causes of disabling and lethal hypoglycemic encephalopathy in uremic and nonuremic patients. Ingestion of aspirin and acetaminophen have resulted in many well-documented cases of symptomatic hypoglycemia. The role of sodium warfarin in drug-induced hypoglycemia appears of lesser importance. Yet all drugs listed in Table 6 are considered to be truly responsible for the development of hypoglycemia [95].

DR. MADIAS: To what extent have researchers studied whether dialysis improves the various abnormalities in glucose homeostasis in uremic patients?

DR. ADROGUÉ: Carefully conducted studies have documented that hemodialysis significantly improves tissue sensitivity to insulin and increases insulin degradation by the liver and skeletal muscle [101]. These effects of dialysis substantially improve the abnormal glucose homeostasis observed in uremic patients.

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): Can you estimate the relative proportion of patients with pseudodiabetes and hypoglycemia? Could there be one or two factors that determine whether a patient will manifest either hypoglycemia or pseudodiabetes? Is the sole difference caloric intake and hepatic gluconeogenesis, or are other factors at play?

DR. ADROGUÉ: I stated earlier that most uremic patients have reduced peripheral sensitivity to insulin's action and evidence of pseudodiabetes. This process leads to either fasting or postprandial hyperglycemia. Yet, these patients are also at risk of hypoglycemia because of marked prolongation of the half-life of insulin and other factors. If diabetes mellitus accompanies uremia, these patients are at increased risk of hyperglycemia

and hypoglycemia. The risk for the development of hypoglycemia is high in uremic patients who are malnourished, have poor caloric intake, ingest significant amounts of alcohol, have concomitant hepatic disease, receive drugs that lead to hypoglycemia (including insulin therapy), receive hemodialysis with a glucose-free dialysate, and develop generalized sepsis.

DR. COHEN: Do you recommend peritoneal dialysis for well-nourished diabetic patients?

DR. ADROGUÉ: Yes, I do recommend CAPD and CCPD as acceptable options among the multiple modalities of renal replacement therapy. The disadvantages of the obligatory glucose load associated with all peritoneal dialysis modalities, as compared with hemodialysis, are counterbalanced by several advantages of PD, including improved control of fluid balance, lower incidence of hypotension and hyperkalemia, and avoidance of the ocular complications (such as bleeding) associated with the use of heparin in hemodialysis.

DR. COHEN: Would you comment on the need for insulin treatment in patients with severe hyperglycemia? On the one hand, as you have noted, insulin resistance is a characteristic feature of patients with renal disease, and has a variety of explanations. On the other hand, the first patient you discussed is typical in that a relatively small amount of insulin was needed to normalize an extremely high blood sugar. This observation raises a question: did the insulin play any role in the treatment of the hyperglycemia, or would the hyperglycemia have subsided just as rapidly on its own?

DR. ADROGUÉ: An additional reduction in peripheral sensitivity to insulin is observed in diabetics who develop renal failure. Yet insulin requirements characteristically diminish in patients with diabetes mellitus when they develop severe renal insufficiency due to decreased caloric intake, prolongation of the half-life of insulin, and other mechanisms. Since increased hepatic glucose production is a characteristic feature of diabetes, and hyperglycemia in these patients fails to fully suppress the hepatic release of glucose, insulin administration is required for the treatment of hyperglycemia. It is unlikely that the hyperglycemia observed in today's first patient would have subsided on its own in the absence of insulin administration.

DR. MADIAS: I was somewhat confused about the effect of acidemia on insulin secretion. I believe that previous workers have shown that ammonium-chloride-induced acidosis suppresses insulin secretion, but I think you mentioned that in your studies insulin secretion was normal or high during acidemia. Haven't you previously shown a difference between the effects of hydrochloric acid and ketoacids on insulin secretion?

DR. ADROGUÉ: A dissimilar insulin secretory response occurs in mineral acid acidosis as compared with organic acid acidosis due to infusion of ketoacids [77]. Whereas metabolic acidosis induced by hydrochloric acid administration fails to significantly alter insulin secretion, a comparable degree of acidemia due to ketoacid infusion increases insulin secretion. We previously proposed that ketones, probably acting as nutrients, stimulate insulin secretion; by contrast, the infusion of hydrochloric acid, which does not have an anion for islet oxidation, fails to stimulate insulin release [77]. The inhibition of insulin secretion observed with ammonium chloride administration depends on the effect of ammonium on the pancreatic islets but not of the simultaneous alteration in systemic acidity. Acidemia of any cause, however, alters insulin binding to its receptor and can produce postreceptor effects. A higher-than-normal plasma insulin level can be observed in acidosis and occurs in association with decreased tissue extraction of insulin by hepatic and extrahepatic tissues.

Acknowledgments

The author is indebted to Debby S. Verrett for skillful assistance in the preparation of the manuscript. The author's work cited in this Forum was supported in part by a Merit Review Grant from the Medical Research Service of the Veterans Affairs and by the American Heart Association, Texas Affiliate.

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