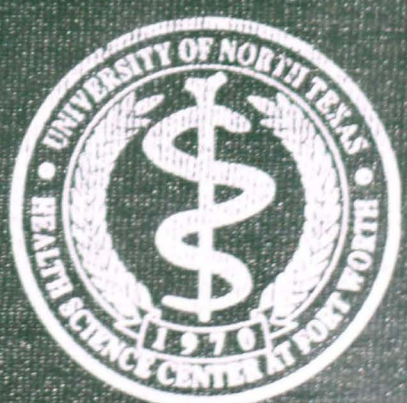
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A LOOK AT DIABETES MELLITUS AND THE EFFECTS OF A STUDY DRUG ON DIABETIC NEPHROPATHY

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A LOOK AT DIABETES MELLITUS AND THE EFFECTS OF A STUDY DRUG ON DIABETIC NEPHROPATHY

INTERNSHIP PRACTICUM REPORT

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BACKGROUND AND LITERATURE REVIEW

Diabetes Mellitus (DM) is sometimes referred to as the silent killer. This is supported by the reality that of the approximately 17 million people who suffer from diabetes in the United States alone, 5.9 million are currently undiagnosed. For many, the diagnosis comes after years of damage have been done. As a result, diabetes accounts for approximately 19% of all deaths in the U.S. of people over the age of 25 (1).

According to the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), this is not a disease that afflicts only the elderly, a certain ethnic group, or a specific sex. In the United States one child or adolescent in every 400 to 500 children and adolescents has Type I diabetes. Therefore 151, 000 Americans under the age of 20 are victims of this disease. In addition, 16.9 million members (8.6%) of the U.S. population over the age of 20 are afflicted, and approximately 7 million of these patients are over the age of 65. Although American Indians appear to have a higher susceptibility to diabetes, at least 7% of the population of each ethnic group in the United States has diabetes. Sex does not appear to affect risk either, as 8.3% of all U.S. men and 8.9% of all U.S. women are diabetics (1).

The stress to the body caused by diabetes places patients at a high risk for other diseases and complications. Heart disease is the leading cause of diabetes related deaths worldwide. Patients with diabetes are 2 to 4 times more likely to suffer from heart disease and stroke than non-diabetic patients. This is enhanced by the fact that 73% of all

diabetic adults have hypertension with blood pressures greater than 130/80. These diseases lead to a myriad of other complications for diabetics. Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness per year, and causes less severe vision problems for many others. Diabetes also accounts for 43% of new patients entering treatment for end-stage renal disease (ESRD) each year, and was the cause of 114, 478 kidney transplants in 1999 alone. Approximately 60 to 70% of all diabetics suffer from some degree of neuropathy (nervous system damage) as well. This especially affects the sensation in the feet causing 60% of non-traumatic lower limb amputations in the U.S (1).

DM is a chronic metabolic disorder in which an absolute or relative deficiency of insulin causes impaired utilization of carbohydrates and enhanced utilization of proteins and lipids (2). The disease is characterized by symptoms of polyuria (increased urination), polydipsia (increased thirst), polyphagia (increased appetite), and fatigue, as a result of persistent hyperglycemia. For diagnostic purposes, hyperglycemia is defined as a fasting plasma glucose (FPG) level of equal to or greater than 126 mg/dl and/or a two-hour postprandial plasma glucose (PPG) level of equal to or greater than 200 mg/dl. The diagnosis is made when such levels are obtained in two of three different screenings.

Once the diagnosis is made, the disease is classified into one of five subclasses including; type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus (GDM), malnutrition related diabetes mellitus, and secondary diabetes mellitus (4). For this review, the focus will be on type 1 and type 2 diabetes. Type 1 diabetes, also known as insulin dependent diabetes mellitus (IDDM), is defined by a complete or almost

complete lack of insulin leading to the presence of ketosis (accumulation of ketone bodies). This lack of insulin not only causes severe hyperglycemia and ketosis, but also an increased appetite accompanied by weight loss (2). Although type 1 diabetes can occur at any age, it typically develops in the first 20 years of life. For this reason, it has also been referred to as juvenile onset diabetes.

Type 2 diabetes is also known as non-insulin dependent diabetes mellitus (NIDDM), because the body produces normal or even elevated levels of insulin. However, the cells of the body resist the effects of the insulin leading to impaired glucose utilization. Unlike type 1 diabetes, patients with NIDDM are usually over the age of 35, obese, and less prone to ketosis. Because the insulin resistance that causes type 2 diabetes usually develops over time and the symptoms are typically less severe, this is the form that is most often undiagnosed before the more serious complications have developed.

In normal healthy individuals, blood glucose is detected by the pancreatic β-cells. These cells take up the glucose and break it down by glycolysis to produce ATP. The ATP produced activates a sulfonylurea receptor, which in turn closes the sulfonylurea receptor/potassium – ATP channel. When this channel closes, K^+ can no longer exit the cell, which leads to the depolarization of the plasma membrane. This in turn causes a calcium channel to open allowing an influx of calcium. Stored insulin is then released from the cell. After being released from the β-cell, insulin is drawn to insulin receptors on muscle, fat, and hepatic cells. In the muscle and fat cells, this insulin-receptor

interaction causes a cascade of signaling events that initiate the translocation of glucose transport proteins (GLUT4) to the cell surface. It is only after GLUT4 reaches the cell surface that the glucose in the blood can be taken up into the cells. In hepatic cells, insulin is not needed for glucose uptake, but it is necessary for glucose utilization and the inhibition of glucose production and secretion.

For the diabetic patient, this system of control is not functional. With type 1 diabetics, the pancreatic β-cells are not adequately producing insulin due to immune mediated destruction of these cells. This destruction happens over time, but patients eventually loose all β-cell function in most cases. When insulin is absent or highly inadequate, the body functions under starvation conditions regardless of the amount of carbohydrates being eaten. In this state, muscle cells are relying on protein metabolism and the breakdown of glycogen stores for energy. At the same time, adipocytes begin breaking down lipids and triglycerides to release free fatty acids and glycerol into the blood stream. Meanwhile, the liver is busy breaking down glycogen and producing glucose. Hepatic cells take up the fatty acids and glycerol liberated by fat cells and breaks them down into ketones. These ketones can build-up in the blood and cause ketosis, and when the disease is untreated, they can mix with the other toxic acids generated by the alternate energy pathways utilized within the body to cause ketoacidosis (a drop in body pH resulting from the interaction of acids and ketones) (5).

On the other hand, type 2 diabetics produce normal to elevated levels of insulin in most cases. Unfortunately, the body has developed a resistance to the action of this

insulin. Typically, this resistance causes the pancreas to increase insulin production in an effort to maintain the pre-diabetic state. Over time this compensation fails and hyperglycemia ensues as the β-cell function decreases (4). As a patient transitions from the pre-diabetic state to a state of hyperglycemia, three pathophysiological changes can be observed. First, the basal hepatic glucose production rate increases as less insulin is being utilized. Second, insulin resistance is becoming more severe due to increased genetic damage or conditions such as increased obesity, a more sedentary lifestyle, or aging. Finally, there is a decrease in β-cell functioning and a decline in insulin secretory ability. This decrease in insulin production could be the result of preprogrammed genetic abnormalities to the β-cells, glucose toxicity, or β-cell exhaustion. If this progression is uninhibited, type 2 diabetes can also reach absolute insulin deficiency and the initiation of a starvation state in the face of increased carbohydrate intake.

Once a patient is diagnosed with diabetes, prompt and effective treatment is paramount in preventing complications and ultimately keeping the patient alive. Therefore, a thorough medical evaluation should be performed to classify the disease as type 1 or type 2, to detect the possible presence of complications, and to formulate a management plan for continuing care (6). According to the American Diabetes Association (ADA), treatment goals should include glycemic control with an HbA1c $\leq$ 7% (the American College of Endocrinologists suggest an HbA1c $\leq$ 6.5%), a blood pressure under 130/80 mmHg, and lipid management with an LDL $\leq$ 100mg/dL and an HDL $\geq$ 45mg/dL.

For type 1 diabetics, the initial form of treatment is insulin therapy accompanied by lifestyle modifications. With type 2 diabetics, it is sometimes possible to gain control over the disease without medication. However, for this to work, the individual must take an active role in his care, and the management plan must take into consideration his age, school or work schedule and conditions, physical activity, eating patterns, social situation and personality, cultural factors, and the presence of complications or other medical conditions (6).

Studies have shown that non-pharmacological treatment plans can have a great impact on glycemic control, as well as the control of hypertension and dyslipidemia, an abnormal lipid level. The main focus of this therapy is on diet and nutrition. Patients are educated by a dietician or nutritional expert on the effects the foods they eat have on their blood sugar, blood pressure, and cholesterol. Depending on the circumstances, certain dietary restrictions may be made in addition to the low carbohydrate diet necessitated by diabetes. These restrictions can include low sodium diets for hypertensive patients, low fat diets for patients with hypercholesterolemia, and low protein diets for patients with or at high risk of developing nephropathy. Also, these plans include education on the role of physical activity in improving blood glucose control, reducing cardiovascular risk factors, contributing to weight loss, and improving overall well being (6). In order for diet and exercise to be successful, patients must be willing to perform self-monitoring of their blood glucose, and understand how to use the test results to modify their diet and exercise to achieve and maintain blood glucose goals and to prevent hypoglycemia.

Finally, smoking is responsible for one of every five deaths in the United States, and studies of diabetics have shown that those who smoke have a heightened risk of macrovascular complications and premature death. Smoking has also been found to have a role in the premature development of the microvascular complications of diabetes and possibly in the development of type 2 diabetes itself (6). Therefore, smoking cessation is another major emphasis of non-pharmacological treatment plans for diabetics, as well as for those at risk for developing type 2 diabetes.

When non-pharmacological treatment is inadequate to achieve normalization or near normalization of metabolic abnormalities, a variety of therapeutic agents are available to the diabetic patient. The non-insulin, oral antidiabetic drugs target one of the three basic abnormalities that contribute to hyperglycemia in type 2 diabetes. These abnormalities are peripheral insulin resistance, excessive glucose production by the liver, and impaired insulin secretion by the pancreas (4). The most commonly used classes of oral agents are sulfonylureas, metformin, and thiazolidinediones (TZDs). Due to the mechanism of action of these drugs, and the pathophysiology of type1 and type 2 diabetes, non-insulin therapy is almost exclusively used for treating type 2 diabetes.

Sulfonylureas work primarily by chronically stimulating pancreatic insulin secretion. This in turn reduces glucose production and secretion by the liver and increases peripheral glucose utilization (4). The sulfonylureas used most commonly today are known as second-generation drugs, and are more potent on a per milligram basis, produce fewer side effects, and interact less frequently with other drugs than the

older products. The three second-generation sulfonylureas are glimepiride, glipizide, and glyburide. The most common side effects of this class of drugs include; weight gain, hypoglycemia, mild gastrointestinal upset, and skin irritations. Hypoglycemia is a major complication of sulfonylureas, and is more prevalent in patients who drink large amounts of alcohol, skip meals, or are elderly (4).

Glimepiride, marketed as Amaryl®, has been shown to improve hyperglycemia without producing clinically significant increase in fasting insulin levels. Therefore, it is the only sulfonylurea that is FDA approved for use along side insulin therapy. In recent studies, glimepiride caused little weight gain or hypoglycemia. The usual maintenance dosage is 1 to 4mg once daily with a maximum dose of 8mg once daily (4).

Glipizide, marketed as Glucotrol® and Glucotrol XL®, is metabolized by the liver to predominantly inactive products, which greatly reduces the risk of hypoglycemia. This makes glipizide particularly well suited for elderly patients and patients with mild renal or liver dysfunction (4). Glucotrol XL® utilizes a controlled delivery system allowing for once daily dosing making compliance greater than that achieved with Glucotrol®, which requires twice a day dosing. The recommended starting dose for glipizide is 5mg twice daily with a maximum recommended dose of 20mg twice daily (4).

Glyburide, marketed as DiaBeta®, Micronase®, and Glynase Pres-Tab®, is also metabolized by the liver and excreted in the urine and bile. However, the by-products retain hypoglycemic activity making glyburide less well suited for patients with liver or kidney dysfunction. For each of these drugs, the duration of action is 16 to 24 hours and

the recommended dosing schedule is 1 or 2 times daily. The recommended starting dose is 2.5 to 5mg daily for DiaBeta® and Micronase® and 1.5 to 3mg daily for the Glynase Pres-Tab®. The maximum recommended dose is 10mg twice daily for DiaBeta® and Micronase® and 6mg twice daily for the Glynase Pres-Tab® (4).

Typically, sulfonylurea therapy is initiated at the lowest possible dose once daily, and increased progressively until the targeted blood glucose levels are achieved. When the daily dose reaches approximately 50% of the maximum recommended daily dose, dosing should be changed to twice daily. In general, sulfonylureas should not be initiated as monotherapy for newly diagnosed obese type 2 diabetics or in diabetics failing nonpharmacologic treatment, as these patients likely suffer from hyperinsulinemia. Also, some evidence has suggested that using sulfonylureas too early may lead to beta cell exhaustion (4).

Metformin, marketed as Glucophage®, works by suppressing excessive hepatic glucose production and increasing glucose utilization in the peripheral tissues (4). Metformin is not metabolized by the body, and is excreted unchanged by the kidneys. The major side effects of this drug include mild diarrhea, anorexia, nausea, and abdominal discomfort. These symptoms are normally transient and dose related, and they decrease with chronic use. Metformin should be initiated at 500mg/day with dinner for a week, then twice daily with meals to reduce the risk of side effects. From this point, the dose should be titrated slowly if needed, not to exceed a maximum recommended daily dose of 2,550mg (4).

Not only is metformin effective in gaining glycemic control, but it has also been found beneficial in lowering triglycerides and LDL cholesterol and in raising HDL cholesterol, as well as promoting weight loss or a reduction in weight gain. Unfortunately, it has also been associated with incidences of lactic acidosis, particularly in patients with renal dysfunction. Therefore, metformin should not be prescribed to patients with a serum creatinine level above 1.5mg/dL for men or 1.4mg/dL for women. Also for this reason, metformin should be discontinued before patients undergo any medical procedure requiring the injection of dyes into the blood stream, and should not be resumed in these patients until the creatinine level is determined to be acceptable. It is also contraindicated in patients with hepatic disease, cardiac insufficiency, alcohol abuse, and any history of lactic acidosis (4).

Metformin is available in several forms for monotherapy and combination therapy. Glucophage XR® is an extended release form of metformin that can be taken once a day with as much efficacy as twice daily dosing with traditional release Glucophage®. Also, a combination pill consisting of metformin and glyburide is available. This drug is called Glucovance®, and was shown to be more effective in lowering blood sugar than either metformin or glyburide alone.

Thiazolidinediones (TZDs) are the newest class of oral antidiabetic agents to be approved by the FDA. These drugs reduce insulin resistance in skeletal muscle, adipose tissue, and the liver. This is accomplished in part by stimulating nuclear receptors called peroxisome proliferator-activated receptors (PPARs) that regulate the transcription of a

number of genes for proteins involved in glucose and lipid metabolism (4). Possibly as a result of the stimulation of lipid metabolism, TZDs also reduce cardiovascular risk factors including markers for vascular inflammation. Therefore, these drugs are not only useful in treating hyperglycemia, but may be used to prevent type 2 diabetes in patients with mild insulin resistance and to prevent premature cardiovascular disease. Currently, two TZDs are available in the U.S., rosiglitazone and pioglitazone.

Rosiglitazone, marketed as Avandia®, is currently indicated for use as a monotherapy or in combination with metformin or sulfonylureas. As a monotherapy, it can be taken once daily with a maximum recommended dose of 8mg, or in two equal daily doses with a maximum recommended dose of 4mg. It is slightly more efficacious when taken twice daily. When being added to metformin or sulfonylureas, the current dose of these drugs should be unchanged. Side effects of rosiglitazone include alanine aminotransferase (ALT) elevations, weight gain, edema (swelling), and anemia (decreased oxygen-carrying capacity of the blood) (4).

Pioglitazone, marketed as Actos®, is the newest TZD. Actos® has been FDA approved for monotherapy, as well as in combination with metformin, sulfonylureas, and insulin. The major side effects of pioglitazone are peripheral edema and weight gain. Although elevations in ALT have not been noted in long-term studies, liver functioning should be monitored regularly. Dosing of pioglitazone is somewhat dependent on concomitant medications with a maximum recommended dose for monotherapy of 45mg and a maximum recommended dose in combination therapy of 30mg. In either case, it

can be taken once daily with or without food (4).

When choosing non-insulin, oral antidiabetic agents for monotherapy or combination therapy in type 2 diabetics, a physician must consider the patient's age, weight, duration of disease, compliance, presence of dyslipidemia, duration and severity of hyperglycemia, presence of kidney, liver, or cardiac disease, and the presence of gastrointestinal problems (4). For example, TZDs and metformin are good choices for newly diagnosed, obese patients who have failed nonpharmacologic interventions because they do not cause hypoglycemia. Also, these two classes of drugs have been shown to lower triglycerides and raise HDL, which helps to control the dyslipidemia found in many type 2 diabetics. However, thin patients are often more insulin deficient, and therefore, sulfonylureas are a better choice of monotherapy in these patients. When patients have severe and prolonged hyperglycemia and insulin therapy wants to be avoided, it is acceptable to start a sulfonylurea at the maximum dose until reasonable metabolic control is attained. Because the classes of oral antidiabetic agents are structurally and functionally unrelated, there are no limitations on using any of these drugs in combination, and this approach often results in better glycemic control than monotherapy. Unfortunately, even combination therapy can fail, and many type 2 patients eventually need insulin therapy as well.

Both type 1 and type 2 diabetics can benefit from insulin therapy. However, for type 1 patients there is no other option for primary treatment. Exogenous insulin administration decreases blood glucose levels by suppressing hepatic glucose production,

increasing postprandial glucose utilization, and improving the abnormal lipoprotein levels seen in patients with insulin resistance (4). Other benefits include decreased effects of glucose toxicity, improved insulin sensitivity, and beta cell secretory function. The major complications of insulin therapy include weight gain, especially in type 2 diabetes, and hypoglycemia, which is more common in type 1 diabetes.

The types of insulin available are animal, human, and insulin analogs. These three types of insulin are used to make several different preparations including fast-acting, short-acting, intermediate-acting, and long-acting insulins. Selection of the appropriate insulin preparation should be based on the desired time course of action. Long or intermediate-acting insulins are needed as basal therapy to suppress hepatic glucose production overnight and between meals, while short and fast-acting preparations are used as bolus insulin to prevent hyperglycemia after meals. Without proper timing of each injection, the insulin offers less protection against hyperglycemia and results in a greater incidence of hypoglycemia.

In the body of a non-diabetic, basal insulin is produced at a nearly constant rate to regulate blood glucose concentrations between meals and overnight. Therefore, basal insulin therapy is needed to provide a constant baseline insulin level regardless of meals or exercise. Ideally, it will allow a patient to skip a meal or exercise without the threat of hypoglycemia. Basal insulin is available therapeutically in three forms. Intermediate-acting insulin is marketed as neutral protamine Hagedorn (NPH) and lente. It has an onset of action of 1 to 3 hours with peak action after 6 to 8 hours. Intermediate-acting

insulin has a duration of action of 16 to 24 hours. The long-acting basal insulin ultralente has a gradual onset of action peaking at 8 to 20 hours depending on numerous factors (4). The newest basal insulin is glargine, also known as lantus, and is an insulin analog. Glargine also has a gradual onset of action, but it does not peak during its 24-hour duration of action. Basal insulin can be used alone as single injection therapy, together with a bolus insulin either separately or mixed for multiple daily injections, or with oral non-insulin therapy for added glycemic control in type 2 diabetes.

The pancreas of the non-diabetic patient and even type 2 diabetics secretes insulin in response to ingested carbohydrates. However, in diabetics this insulin secretion is absent or inadequate to prevent hyperglycemia. Therefore, bolus insulin therapy is necessary with meals to inhibit hepatic glucose production and to regulate utilization of the carbohydrates that are eaten to prevent postprandial hyperglycemia. Regular insulin is a short-acting bolus agent with an onset of action of 30 minutes that peaks after 2 to 5 hours and has a 5 to 8 hour duration of action. Fast-acting bolus insulin includes lispro-humalog and aspart-novolog, both of which have an onset of action of just minutes with a peak action at less than 1 hour. The duration of action for humalog and novolog is 3 to 5 hours. Bolus insulin is typically administered before each meal and in combination with a basal insulin (4).

When a diabetes patient is on insulin therapy, a number of side effects are possible. The majority of these side effects are the result of hypoglycemia. For this reason, it is important that insulin using patients monitor their blood sugar daily, and

often multiple times a day. Insulin users experience daily variations in their blood glucose levels influenced by differences in insulin absorption rates, insulin sensitivity, exercise, stress, diet, rates of food absorption, and hormonal changes (7). Illness, traveling, and changes in routine also influence blood glucose levels. In order to prevent extreme hypoglycemia, these home blood glucose monitoring results must be used to adjust insulin dose and times of dosage. However, there are times when circumstances are beyond control. Therefore, insulin using diabetics must be aware of the symptoms of hypoglycemia, and should always carry at least 15g of carbohydrates to eat in the event of a hypoglycemic reaction. In addition, these patients should carry medical identification to alert others of their insulin use in case of an emergency.

When diabetes is not adequately controlled in some way, microvascular and macrovascular complications can result. The most common microvascular complications are diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) both showed that intensive therapy is highly effective in delaying the onset and slowing the progression of these complications in both type 1 and type 2 diabetes. The intensive therapy used in the studies strived to achieve normal or near normal blood glucose levels. The findings of these studies lead to the glycemic goals advocated by the American Diabetes Association (ADA) including fasting blood glucose levels of 80 to 120mg/dL, postprandial blood glucose levels below 160mg/dL, and a hemoglobin A1c of less than 7% (4).

Diabetic retinopathy consists of retinal changes marked by microaneurysms, exudates, hemorrhages, and occasional neovascularization (2). Retinopathy is associated with both type 1 and type 2 diabetes, and is estimated to be the most frequent cause of new cases of blindness each year among adults between the ages of 20 and 74. The duration of diabetes and the duration and severity of hyperglycemia play a large role in the development and progression of retinopathy. As a result, patients should be educated on the relationship between hyperglycemia and retinopathy along with the role of hypertension in the progression of the disorder. Patients must also understand that the symptoms of diabetic retinopathy do not develop until advanced stages of the disease, and therefore routine eye exams are a necessity.

Diabetic retinopathy progresses through three stages including nonproliferative or background retinopathy, preproliferative retinopathy, and finally proliferative retinopathy. In the nonproliferative stage, background changes are characterized by microaneurysms and hemorrhages. This stage is also associated with macular edema resulting from serous fluid leaks into the area of the maculae. Macular edema is characterized by the presence of hard exudates and bulging blood vesssels (4). The added pressure of the edema on the retina can cause blurred vision. Preproliferative retinopathy is characterized by "beading" of the retinal veins, soft exudates, and irregular, dilated, and tortuous retinal capillaries or newly formed intraretinal vessels (4). In this stage the blurred vision continues with occasional blots in the visual field. The final stage, proliferative retinopathy, is characterized by neovascularization covering over one

third of the optic disk. These fragile vessels most likely develop in response to ischemia and are prone to bleeding. When the new vessels rupture they can cause "floaters" in the visual field, as well as the development of scar tissue on the retina. As the scar tissue contracts, it can displace and detach the retina leading to severe or total vision loss. Currently, the only treatment for diabetic retinopathy is prevention through metabolic control and laser photocoagulation.

Diabetic neuropathy is the most common of the chronic complications of diabetes affecting both type 1 and type 2 diabetics (2). Although the pathophysiology of this complication is not well understood, it has been shown that high blood pressure and high blood sugar levels can lead to metabolic disturbances within the neuron itself. As a result, diabetic neuropathy can affect both the peripheral and the autonomic nervous systems.

Peripheral neuropathy commonly develops in stages, progressing from occasional pain and tingling in the extremities, to a more constant and severe pain often accompanied by burning and stabbing sensations. In the most advanced stages of peripheral diabetic neuropathy, the patient is no longer feeling pain, but is also unable to sense pain, especially in the feet. Along with this decrease in sensation comes a decrease in the deep reflexes as well as decreased muscle strength. Because the loss of sensation occurs gradually in most cases, the patient is generally unaware of it, and is therefore more prone to wounds and burns. For this reason, diabetic patients must be educated on the importance of foot care to prevent ulcers that can lead to necessary amputations.

The autonomic form of diabetic neuropathy can lead to a number of symptoms and dangers for the diabetic patient. The most common symptoms include gastrointestinal irritations due to gastroparesis, a delayed emptying of the stomach. These symptoms include nausea and vomiting of undigested food and abdominal pain. Other symptoms of autonomic neuropathy include diarrhea, constipation, urinary retention or incontinence, decreased sweating, fainting episodes, and impotence (8). Blood sugar and blood pressure control are important in all diabetics to prevent complications including neuropathy and other cardiovascular events such as myocardial infarctions. However, for patients with autonomic neuropathy, this control is vitally important, as the angina associated with most cardiac events may not be present.

Diabetic nephropathy is a complication of diabetes characterized by overt proteinuria, increased systemic blood pressure, and decreased renal function (9). This syndrome affects 20 to 30% of diabetic patients, and is responsible for over 40% of all new cases of end stage renal disease (ESRD) in the United States each year. Diabetic nephropathy is also the most expensive of the diabetic complications to treat. In 1997, the cost for treating diabetics with ESRD was greater than $15.6 billion and the cost rises each year.

Although 20 to 30% of type 1 and type 2 diabetics develop nephropathy, the percentage of patients progressing to ESRD is much smaller for type 2 diabetes than for type 1. This has been attributed in part to the great percentage of patients with type 2 diabetes who have coronary artery disease at the time of diagnosis, and therefore may die

from cardiovascular events before the nephropathy has a chance to progress to ESRD (10). As the treatments and therapies available for coronary artery disease improve, the percentage of patients with type 2 diabetes entering renal replacement therapy programs may increase.

Diabetic nephropathy can be divided into five stages (11). The earliest stage is the onset of diabetic kidney disease characterized by an increased glomerular filtration rate (GFR) and kidney hypertrophy. These changes are not clinically evident, and they are typically reversible with good glycemic control. The second stage consists of increased glomerular basement membrane thickness and a raised mesangial matrix volume. Although the GFR is further elevated in this stage, the urinary albumin excretion rate (UAE) remains unchanged. Therefore, this stage is still not clinically evident in most cases. Stage three usually develops after more than 7 years of diabetes, and is the first clinically evident stage of kidney disease. This stage is referred to as microalbuminuria since the UAE is now elevated between 30 and 300 mg/24h. However, the dipstick test for urinary protein is still negative in this stage. If left untreated, the UAE will increase by approximately 10 to 20 % per year, and an increase in blood pressure is typically detectable in type 1 diabetes at this stage. With type 2 diabetes, hypertension usually precedes nephropathy development. The fourth stage is overt nephropathy and is characterized by an UAE greater than 300 mg/24h and a positive dipstick for protein in the urine. This stage is also referred to as macroalbuminuria or clinical albuminuria. Once a patient reaches this stage, the kidney damage is usually

irreversible and kidney function begins to decline with decreases in the previously elevated GFR of 10mL/min per year. The final stage is ESRD characterized by minimal residual renal function. At this point, the patient will require dialysis or kidney transplantation to stay alive. The average time from diabetes onset to the development of ESRD is 20 to 30 years. However, the time for diabetes diagnosis to ESRD can be much shorter in a type 2 diabetic due to the lag between onset and diagnosis.

Recent studies including the DCCT and the UKPDS have shown that genetic predisposition, hyperglycemia, hypertension, smoking, age, gender, and ethnicity can predispose a patient to the development and progression of nephropathy. It has also been demonstrated that control of factors such as hypertension, smoking, hyperglycemia, hyperlipidemia, and dietary protein intake can delay the progression of nephropathy (12). Therefore, the best treatment plan includes active screening and prevention through control of blood sugar, blood pressure, and lipids.

Screening for nephropathy begins with testing for microalbuminuria on a regular basis. For type 2 diabetics, the screening should be initiated at the time of diagnosis and should be repeated annually until signs of elevated UAE are observed. With type 1 diabetes, microalbuminuria rarely occurs before five years duration of the disease, and it is therefore not recommended to begin screening within the first five years. However, after five years duration of type 1 diabetes, it is recommended to screen annually until signs of microalbuminuria occur. Once an UAE over 30mg/24h is observed, the patient should be screened two more times within six months. If two of the three tests are

positive for microalbuminuria, the diagnosis can be made and treatment should be initiated. Microalbuminuria screening can be performed by measuring the albumin-to-creatinine ratio in a random collection, by performing a twenty-four hour collection to measure UAE and creatinine clearance, or by performing a timed collection (usually four hours or overnight). When using the albumin-to-creatinine ratio, microalbuminuria is present at ratios equal to or greater than 30mg albumin to 1g creatinine (10).

By initiating intensive treatment to bring blood glucose to near normal levels early in the course of diabetes, it may be possible to prevent diabetic nephropathy altogether. The DCCT showed that intensive glycemic control reduced the development of nephropathy by 33% in type 1 diabetics with no signs of microalbuminuria. Similar results have been attained for type 2 diabetes by the UKPDS. However, as nephropathy progresses, glycemic control is less effective in preventing the development of ESRD. Therefore, it is necessary to get hyperglycemia under control early in the disease, obtaining an HbA1c less than 7% to achieve the maximum benefits.

For both type 1 and type 2 diabetes, the rate of decline of renal function, after the onset of overt nephropathy, strongly correlates with hypertension. The degree of albuminuria in patients with microalbuminuria also correlates with hypertension (13). Therefore, it is obvious that controlling blood pressure can prevent the progression of nephropathy. By controlling blood pressure in type 2 patients who are hypertensive at the time of diagnosis, and who have no signs of microalbuminuria at diagnosis, it may be possible to prevent nephropathy completely. Unfortunately, in type 1 diabetes,

hypertension and nephropathy appear to develop simultaneously in most cases, and controlling blood pressure is simply able to slow or prevent the progression of microalbuminuria to ESRD. In light of this evidence demonstrating the role of high blood pressure in diabetic kidney disease and the fact that microalbuminuria is an independent risk factor for coronary artery disease, the ADA recommends a target blood pressure of 130/80mmHg for all diabetic patients.

In addition to hyperglycemia and hypertension, both type 1 and type 2 diabetics have an increased predisposition for hyperlipidemia. Studies have shown that both elevated triglycerides and low HDL correlate with the development of diabetic nephropathy and other cardiovascular complications of diabetes. Unfortunately, there has been no evidence to date showing that either reducing triglycerides or raising HDL plays a role in slowing the progression of nephropathy once it has developed. However, due to the evidence that early control of lipids before nephropathy development could be preventative, and that lipid management can prevent cardiovascular disease, it has been recommended by the ADA to bring the LDL cholesterol of all diabetics below 100mg/dL and the HDL above 45mg/dL in men and above 55mg/dL in women (6).

Currently treatment for diabetic nephropathy begins in the stage of microalbuminuria and is aimed at preventing further progression of the disease. These treatments are most commonly ACE-inhibitors and AGE-inhibitors. Once the patient reaches ESRD, little can be done. At this point the patient begins dialysis and goes on the kidney transplant list.

ACE-inhibitors inhibit the angiotensin converting enzyme blocking the production of angiotensin II, and are commonly used in diabetic and non-diabetic patients to treat hypertension. Although the antihypertensive properties of ACE-inhibitors give compelling reason to use them in preventing nephropathy, these drugs also show renoprotective effects beyond controlling blood pressure (13). ACE-inhibitors work by reducing the constriction of the glomerular capillaries thereby reducing glomerular hyperfiltration (4). In patients with decreased GFRs, ACE-inhibitors may be able to reverse the damage or prevent further decline. In the diabetic arm of the Heart Outcomes Prevention Evaluation (HOPE), the use of ACE-inhibitors in type 2 diabetics with normo- or microalbuminuria and with similar blood pressures resulted in a 24% greater decrease in the rate of progression to overt nephropathy than did placebo (14). For these reasons, Ace-inhibitors have become the first choice of antihypertensive therapy for type 1 and type 2 patients, as well as in normotensive patients with microalbuminuria or macroalbuminuria. In patients who do not tolerate ACE-inhibitors, angiotensin II receptor blockers (ARBs) should theoretically provide almost identical results. However, ARBs have not been validated in clinical studies (13).

Advanced glycation end products (AGEs) arise from the interaction of a sugar with a protein or lipid. The first product in this reaction is a Schiff's base that rearranges to form an Amadori product. The Amadori product then proceeds through a cascade of reactions to give an AGE. When AGEs interact with their receptors, they can induce cell activation, increase oxygen radical formation, increase the formation of cytokines,

growth factors, and adhesion molecules, or cause cell proliferation or apoptosis. Also, AGEs quench the nitric oxide in the body leading to defective vasodilation. The combination of these effects on cells aids in the development of the major cardiovascular complications of diabetes.

In healthy individuals, the kidneys remove AGEs from the plasma through glomerular filtration and eventual urinary excretion. However, in diabetic patients, plasma AGE levels are elevated and become higher as renal function decreases. This accumulation of AGEs increases the transcriptional activation of growth factors including TGF-β1 and types III and IV collagen within mesangial cells. As a result, increased serum AGE levels correlate with the progression of early morphological kidney damage, including thickening of the glomerular basement membrane (15).

The production of AGE-inhibitors has shown great promise in treating and preventing diabetic nephropathy. Aminoguanidine is an AGE-inhibitor that reacts with the carbonyl groups of glucose and Amadori compounds making them unreactive. These drugs have proven to be effective in preventing AGE binding and thereby halting the progression of diabetic nephropathy and causing a decline in proteinuria. Unfortunately, aminoguanidine has the potential to cause serious side effects including flu-like symptoms, the induction of autoantibodies, rapid progressive glomerulonephritis, and anemia (14). Other AGE-inhibitors with alternate modes of action are currently being tested in clinical trials.

When prevention of the progression of nephropathy fails, patients are faced with

the need for dialysis or kidney transplant to stay alive. The cost to patients requiring dialysis is over $50,000 per year on average, and the time required per week for such treatment makes it difficult for these patients to hold a full time job. In addition to being a costly form of treatment, diabetic patients undergoing dialysis have a much lower survival rate than non-diabetic patients. On the other hand, kidney transplantation holds a much higher survival rate for diabetic patients, and is less costly than maintaining dialysis. Therefore, transplantation is the preferred treatment for ESRD due to diabetes. Unfortunately, there are more than 40,000 patients waiting for kidneys, and only an average of 8,000 kidneys available annually. Furthermore, if tight glycemic control is not maintained after the transplant, the progression of nephropathy will begin in the new kidney making the need for subsequent transplants possible in young patients.

Fortunately, this problem can be avoided in type 1 patients by performing a pancreatic transplant along with the renal transplant. Due to the success of pancreatic transplants in providing normal or near-normal glucose levels in type 1 diabetes, there has been some push for pancreatic transplants in type 1 patients with macroalbuminuria. (11) Recent studies have shown that such transplants can decrease UAE and glomerular mesangial volume in the native kidneys over time. This type of treatment would not be warranted in patients with ESRD due to the extent of irreversible and life threatening kidney damage, or in patients with microalbuminuria, as treatment with ACE-inhibitors and tight glycemic control are capable of reversing the kidney damage at this stage.

INTERNSHIP JOURNAL

May 20, 2002:

8:00 – 11:00 - I worked with Debbie Lewis, R.N. completing paperwork from last week's patient visits. This included an introduction to the source documents and how to complete them, as well as the process for copying and filing the neurological assessment forms and faxing them to the sponsor. Then, I learned how to fill out the Clinical Trials Patient Information Form that must be completed and returned to the Clinical Trials Office for a patient that completes a study screening.

11:00 - 1:00 - I watched as Debbie processed urine and stool specimens for shipment to the sponsor and the central lab. This was done according to the protocol provided by the sponsor. The stool sample and ambient urine went to the central lab, and frozen urine samples were shipped on dry ice to the sponsor.

1:00 – 2:15 - Debbie and I reviewed lab results for patient BAS, who has been randomized for the study.

2:15 – 4:15 - Debbie and I reviewed the nephropathy study Case Report Forms (CRFs) for randomized patients and the Prescreening Workbook used for patients prior to randomization. I learned when, where, and how data and lab results are recorded and filed in these.

May 21, 2002:

8:00 – 9:30 - Debbie and I went through study patient charts to file lab results and make certain that all paperwork was up to date.

9:30 – 10:30 - I helped to compile information for a physician within the department who is trying to get involved in clinical trials. We searched the web sites for various sponsor companies and Clinical Research Organizations (CROs) to get instructions for enrolling in their physician networks.

10:30 – 11:00 – Debbie and I reviewed a letter from the monitor containing queries and instructions following the last monitoring visit. Together, we went through patient charts to make the necessary corrections and to answer the queries.

11:00 – 11:30 – I observed as Debbie corresponded with the monitor concerning a patient. Then, we faxed lab results to a screen-failed patient's primary care physician bringing his attention to the abnormal results, and letting him know that the patient did not qualify for enrollment in the nephropathy study.

12:30 – 1:30 - I helped Debbie unpack boxes of lab supplies and store them on the appropriate shelves. Then, I reviewed the protocol start-up checklist, protocol assessment checklist, subject expenses worksheet, employee salary expenses worksheet, and budget worksheet that are used by the department to determine study feasibility.

1:30 – 2:00 - We finished gathering information for the physician wanting to get started in clinical research, and e-mailed the information to her.

2:30 – 4:20 - I worked on journaling the activities of the day, and discussed scheduling my defense with Debbie. Then, I reviewed the informed consent for the study.

May 22, 2002:

8:00 – 11:00 - Debbie and I reviewed lab results, and learned that subjects CMJ and MQY did not qualify for the nephropathy study. Clifton Cage, D.O. was notified, and the patients were called. Then, the patients were dropped from the study by calling the sponsor's Interactive Voice Recognition System (IVRS). Debbie also updated the screening log for the study.

11:00 – 12:00 – Debbie showed me the database used to identify and recruit study subjects.

12:00 – 1:00 - I attended a luncheon provided by pharmaceutical representatives.

2:00 – 3:00 - Debbie and I audited charts to identify possible subjects for an upcoming hypertension/hyperlipidemia study.

3:00 – 3:30 - Debbie showed me a binder she compiled with patients listed by diagnosis. We used this to identify other subjects for the hypertension study.

May 23, 2002:

8:30 – 9:00 - Debbie and I reviewed lab results for nephropathy study subject SCG, and learned that he qualified for the study. We then called IVRS and randomized the subject.

9:00 - 9:30 - Debbie e-mailed the monitor to inform her of the new status of subject SCG.

9:30 - 10:30 - Debbie and I audited more charts for the hypertension study.

10:30 - 11:00 - I helped review four protocols for possible participation, and assisted in completing the investigator questionnaire for the studies.

1:00 - 3:30 - Debbie and I audited more charts for the upcoming hypertension study.

3:30 - 4:00 - I met with Debbie and Dr. Cage to discuss the criteria for the hypertension study, and the pros and cons of applying for the studies Debbie and I reviewed earlier.

4:00 - 4:15 - I helped Debbie locate and copy the Joint National Committee (JNC) VI guidelines for hypertension and the National Cholesterol Education Program (NCEP) III guidelines for hyperlipidemia which will be used in screening for the upcoming study.

May 24, 2002:

8:00 - 9:30 - Debbie and I audited more charts for the upcoming hypertension study.

9:30 - 10:00 - I met with Debbie, Dr. Cage, and the physician we have been helping get

started in clinical trials. We discussed adding her as a sub-investigator under Dr. Cage to gain experience.

10:45–11:00 - I observed as Debbie telephone screened an individual interested in participating in a study. The information was added to the database.

11:00 – 11:15 – Debbie and I discussed her role in seeing patients for another diabetes study involving diabetic education and Osteopathic Manipulation Medicine (OMM).

1:00 - 4:45 - Debbie and I saw patients for the Diabetes/OMM trial. She counseled them on the importance of their diet in controlling their disease, as well as the importance of understanding their medications. I learned a lot about the different attitudes of diabetic patients.

May 28, 2002:

9:30 - 10:30 - Debbie and I audited more charts for the upcoming hypertension study. During this time Debbie also scheduled a time for one of the monitors to come.

10:30 – 11:00 - Debbie and I phoned nephropathy study subjects to remind them of their upcoming appointments.

11:30 – 1:00 - I watched a video produced by the nephropathy study sponsor describing diabetic neuropathy and the neurological assessments to be performed during the study.

1:30 - 1:45 - I filled out the forms to attend the investigator's meeting for the hypertension study.

1:45 - 2:45 - Debbie and I audited more charts for the hypertension study.

3:00 - 3:45 - I attended the Best New Practice Plan Awards Reception.

3:45 - 4:15 - Debbie and I continued auditing charts for the hypertension study.

May 29, 2002:

8:15 - 8:45 - Debbie showed me how to prepare a chart for a new subject to be screened for the nephropathy study.

8:45 - 9:30 - Debbie and I completed paperwork to apply for a study with the physician wanting to get started in research listed as a sub-investigator.

9:30 - 10:00 - Debbie and I printed forms and filed them in the nephropathy study chart for subject SCG

10:00 – 10:30 - A shipment of the nephropathy study drug was received. We checked the bottles against the shipping order, and then the shipping order was signed and copied. The original was returned to the sponsor, and a copy was added to the study binder.

11:00 - 12:30 - Subject JLR came to screen for the nephropathy study. He was consented, and then the medical history, vitals, P-NSS and blood work were completed.

1:15 - 1:45 - JLR returned and Dr. Cage performed the Clinical Neuropathy

Assessment (CNA).

1:45 - 2:40 - I watched as Debbie processed the blood samples for subject JLR. We then went to the Clinical Trials Office to get dry ice. Once back in the lab, we packaged the frozen and ambient specimens for shipment to the central lab.

3:00 - 3:15 - Debbie and I prepared the lab requisition and supplies for processing the 12-hour urine collection that JLR will return tomorrow.

May 30, 2002:

8:00 - 9:00 - I labeled the lab supplies and forms for the week 0 visit for nephropathy study subject SCG. Each tube required his initials and screening number.

9:00 - 9:45 - I processed the 12-hour urine specimen for nephropathy study subject JLR. Frozen specimens will be shipped to the sponsor, and ambient samples will be shipped to the central lab.

9:45 - 10:45 - Debbie and I audited more charts for the upcoming hypertension study.

11:15 – 12:00 - Nephropathy study subject SCG arrived for his week 0 visit. Debbie took his vitals, performed the Positive Neuropathy Symptoms Survey (P-NSS), drew blood work, and dispensed the study drug along with dosing instructions. A urinalysis was collected before he left.

12:45 – 1:30 – The blood and urine samples from the week 0 visit were processed.

1:30 - 1:45 - Debbie and I went to the Clinical Trials Office to get dry ice.

1:45 - 2:30 - I helped Debbie package the labs for JLR and SCG for shipment.

2:30 - 3:15 - I assisted Debbie in transcribing data from the source document to the CRF for nephropathy study subject SCG.

3:30 - 4:00 - I completed the Institutional Review Board (IRB) tutorial to be eligible to conduct research on human subjects at UNTHSC.

May 31, 2002:

8:00 - 11:00 - Debbie and I updated the laboratory shipment log for the labs shipped yesterday, and audited more charts for the upcoming hypertension study.

12:30 – 1:00 - Debbie and I discussed the different medications used to treat diabetic patients, including sulfonylureas, metformin, and thiazolidinediones.

1:00 - 4:00 - Debbie and I saw three subjects for the Diabetes/OMM study. Again, they were counseled on the effects their diet and medications have on their blood sugars. The new patients were asked to keep diet and blood sugar diaries for the next week. Between patients I read selected chapters from Diagnosis and Management of Type 2 Diabetes.

June 2, 2002:

12:30 - 1:15 - Dr. Cage, Debbie, and I landed at O'Hare Airport in Chicago, IL, and took a taxi to the Fairmount Hotel.

2:00 - 7:00 - Dr. Cage, Debbie, and I attended lectures during the Investigators' Meeting for the hypertension study. These lectures included an

overview of the product, an overview of the protocol, the statistical methods to be used, an introduction to on-line meetings, and a panel discussion.

June 3, 2002:

8:30 - 12:00 - Dr. Cage, Debbie, and I attended more lectures during the Investigators' Meeting for the hypertension study. The topics of these lectures included: regulatory documents and procedures, laboratory procedures and surveillance, the drug supply, International Conference on Harmonization (ICH) and Good Clinical Practices (GCPs) guidelines for clinical research, the monitoring plan, site communication and key forms.

1:00 - 3:00 - The Investigators' Meeting continued with lectures on adverse event monitoring, enrollment strategies, a review of the CRF, and a question and answer session.

June 5, 2002:

8:00 - 9:00 - I updated Annita on my internship experience, and provided Dr. Koulen with the overview of my internship that he requested.

9:00 - 9:45 - I completed and printed the adverse event flow sheet, the patient flow sheet, concomitant medication form, and the narrative notes form in order to construct a chart for a new patient screening for the nephropathy

study. I also reviewed the lab values received via fax for JLR. He was informed that he screened failed when he arrived for his screening visit this morning.

10:00 – 10:30 - Debbie and I completed the chart for the new nephropathy study subject (NMB), and gathered the CNA and P-NSS forms and lab supplies that would be needed for the visit.

10:30 – 11:30 - NMB arrived for her pre-screening visit. She had been consented prior to the appointment, and brought her 12-hour urine collection at this time. Once her vitals were taken and Debbie had completed the medical history and P-NSS, Dr. Cage performed the CNA. Then, Debbie completed the visit by drawing the necessary blood work.

11:30 – 12:15 - Debbie and I called the IVRS to enroll NMB and obtain a screening number. Then, the lab requisitions were completed as far as possible before processing the labs.

1:00 - 1:45 - Debbie and I processed the labs for NMB per protocol.

1:45 - 3:15 - Debbie and I went to the Clinical Trials Office to get dry ice. We then packaged the labs for shipping, prepared the shipping labels and air bills, and called to arrange for pick-up. However, we did not receive a collection time with the 12-hour urine collection for NMB. Therefore, the urine could not be shipped today.

3:15 - 4:00 - Debbie called the monitor for the nephropathy study to get clarification

on how to respond to the inclusion criteria that was waived by the sponsor for NMB. The prescreening workbook requires that a check be placed in "yes" or "no" for each criteria individually. Debbie also called NMB, and requested that she call us back with the collection time for the urine.

June 6, 2002:

8:30 - 9:00 - Debbie and I completed the requisition for the 12-hour urine from yesterday. The samples were then placed in the appropriate shipping boxes, and the ambient sample was packed with refrigerator packs.

9:00 - 9:30 - I went with Debbie to the Clinical Trials Office to get dry ice and more Clinical Trials Patient Information Forms. We then returned to the office and packaged the frozen urine specimens for shipment to the nephropathy study sponsor.

9:30 - 10:15 - I assisted in completing the patient screening log and other logs for the nephropathy study. I also completed the Clinical Trials Patient Information Sheet for nephropathy study subject NMB while Debbie completed the Patient Fact Sheet and the screening workbook for NMB. We also filed lab results for JLR in the screening workbook.

10:15 – 11:30 - I completed my journal for the morning, and Debbie reviewed it. Then, Debbie and I searched the labs and Medicine rooms on the floor for

space to store study supplies which will arrive when the new studies start.

12:30 – 12:45 - Debbie called a patient to recruit her for the nephropathy study. She was told about the study and its purpose, and prescreened for qualification. Then, an appointment was made for her to come in for prescreening.

12:45 - 1:30 - Debbie left a message with another potential subject for the nephropathy trial. Then, she called the sponsor for the upcoming hypertension trial to see if the protocol would arrive in time for the July IRB meeting.

1:30 - 3:15 - Debbie and I reviewed the inclusion/exclusion criteria for the upcoming hypertension study. Then, we went over the list of potential subjects we compiled for the study to make certain that they all met certain qualifications.

June 7, 2002:

8:00 - 8:30 - Debbie and I reviewed the lab results received for subject NMB. I entered these values into the patient flow sheet in her chart.

8:30 - 11:30 - I copied and read selection from the book Diagnosis and Management of Type 2 Diabetes, 5th ed.

11:30 – 12:00 - Debbie and I composed a recruiting letter for the hypertension study.

1:00 - 4:45 - Debbie and I saw four patients for the diabetes/OMM study. Each patient was counseled on their diet and how it affects their blood sugar.

The new patients were asked to keep a diary of their diet and daily blood sugar readings to aid in the counseling at future visits.

June 10, 2002:

8:20 - 10:00 - I charted lab results for nephropathy study subject SCG, and filed the lab report in his chart. I also charted the lab results for subject NMB, and noted that she had screen failed due to a low UAE. Then, the IVRS was called to report NMB as a screen fail, and to remove her from the study. The screen failure was also noted on the patient-screening log and in the study binder. Then, lab results were recorded and filed for subjects CMJ, MQY, and BAS. Since BAS was randomized her 24-hour albumin has dropped from 416mg/24hr. to 39.6mg/24hr.

10:00 – 11:00 - Nephropathy study subject NMB came to return her hemocult slide, and at this time was informed of her screen failure for the study. I then began reading an article about 21 CFR 11, and the problems it could cause for clinical trials sites utilizing electronic data capture.

12:15 – 12:45 - I updated my journal and finished the article about 21 CFR 11.

12:45 - 2:30 - I read more of the pages I copied earlier in the week from Diagnosis and Management of Type 2 Diabetes, 5th ed. Then, I helped Debbie compose a cover letter for a study Dr. Cage is interested in participating in . The letter and Dr. Cage's CV were then e-mailed to the sponsor

company.

2:30 - 2:45 - I watched as Debbie transcribed information from the source document to the CRF for nephropathy study subject BAS.

3:00 - 3:45 - I read an article discussing the investigator-prescriber effect, and its implications in clinical trials and prescription writing in the clinic setting.

June 11, 2002:

8:00 - 8:30 - I helped Debbie prepare the chart for subject SJT who will be screened for nephropathy study today. This included completing the patient flow sheet, adverse events flow sheet, concomitant medication form, and the narrative note. We also completed a Clinical Trials Patient Information Sheet.

8:30 - 10:00 - SJT was consented for the nephropathy study, and then the prescreening visit was performed per protocol. In Dr. Cage's absence, P.A. Pagels performed the CNA. Before the subject left, she was given a container and instructions for the 12-hour urine collection and a hemocult slide.

10:00 – 10:45 - I called the IVRS and entered SJT and obtained a screening number. Then, I entered her into the screening log, the consented patients log, the informed consent log, and the referral log. Afterwards, I processed her

labs per protocol as Debbie observed.

10:45 – 11:45 - The CNA and P-NSS forms for SJT were copied and faxed to the sponsor. Then, the originals were filed in the source document and the copy was placed in the screening workbook. Debbie also returned several phone calls and rescheduled appointments for the nephropathy study. Then, she called the Clinical Trials Office to change the dry ice order.

12:45 - 1:15 - The labs I processed earlier were packaged and the shipping labels were prepared. Then, Debbie called to arrange for pick-up.

1:30 - 1:45 - Debbie completed the screening workbook for SJT.

2:00 - 2:30 - Debbie and I reviewed the list of patients who will be seen in the clinic for the next two weeks, and highlighted the diabetic patients. This list will be used for recruiting by the coordinators for the other diabetes studies being conducted within the department.

2:30 - 2:45 - The monitor who arrived after lunch completed his work, and Debbie and I reviewed the queries he left with us. These were taken care of by writing a memo-to-file, and contacting the sponsor's monitor for the study.

2:45 - 4:00 - I continued reading selections from Diagnosis and Management of Type 2 Diabetes 5th ed.

June 12, 2002:

8:40 - 9:00 - I labeled the lab supplies for the week 16 visit for nephropathy study subject BAS. I also reviewed this visit in the protocol. Then, BAS called to reschedule due to illness.

9:00 - 10:00 - I prepared a chart for a new nephropathy screening subject, and gathered the informed consent form, CNA form, and the P-NSS form. When the patient arrived, I placed him in a room to read the consent form.

10:00 - 11:00 - The subject chose not to participate in the study after reading the informed consent and the study schedule. He felt that he might have trouble keeping the visit schedule due to work. He was then asked to complete a diabetes questionnaire for another diabetes study.

An Investigational New Drug Application (IND) Safety Report was received for the nephropathy study, and the appropriate paperwork was completed to report the SAE to the IRB.

12:30 – 12:45 - Debbie composed a cover letter to accompany the SAE report to the IRB. The letter summarized the IND Safety Report in a concise and easy to read manner.

12:45 - 1:30 - The IND Safety Report form along with the cover letter and a copy of the actual IND Safety Report were taken to the IRB Office, and the Clinical Trials Patient Information Sheets for nephropathy study subjects NMB and SJT were taken to the Clinical Trials Office. The original IND

Safety Report and a copy of the cover letter were placed in the study binder, and a copy was e-mailed to Dr. Cage since he is still on vacation.

2:00 - 2:15 - A memo-to-file was composed to explain why labs received this week would not be signed and dated by Dr. Cage until next week. It also noted that clinically significant labs would be handed over to P.A. Pagels for immediate review.

2:30 - 3:00 - I processed the 12-hour urine collection returned by SJT per protocol, and packaged the ambient samples for shipment to the central lab.

3:00 - 3:15 - Debbie and I went to the Clinical Trials Office to get dry ice. We then returned to the lab and packaged the frozen urine samples for shipment to the sponsor.

3:15 - 3:30 - Debbie noted on the laboratory-shipping log and in the narrative note of the source document that the labs for SJT had been shipped.

3:30 - 4:00 - I read more selections from Diagnosis and Management of Type 2 Diabetes 5th ed. During this time, Debbie telephone screened a patient interested in diabetes studies. He did not qualify for the nephropathy study.

June 13, 2002:

8:00 - 9:15 - Debbie had an e-mail this morning informing us that the deadline to submit new studies for the July IRB meeting is June 17. So, Debbie

called the sponsor for the hypertension study to see if the protocol would be arriving in time to make the deadline. We also got a fax with lab results for nephropathy study subject SJT, and they were transcribed into her chart. Then, Debbie called BAS to reschedule her week 16 visit, and to get information about her illness to record it as an AE.

9:15 - 9:45 - I labeled the lab supplies and completed the lab requisition form as well as possible for the week 2 visit for nephropathy study subject SCG.

9:45 - 10:00 - Debbie and I reviewed the Drug Information Association (DIA) website to see what they do. Then, Debbie e-mailed Dr. Cage and asked him to look at the website and see if he wanted to join the DIA.

10:00 – 11:00 - I did a search on MEDLINE for articles pertaining to diabetic nephropathy. Then, I recorded lab results into the chart of nephropathy study subject SJT. During this time Debbie straightened out a problem with the labs we shipped yesterday. The requisitions had been switched, and she had to fax the proper requisitions to the lab and the sponsor.

12:30 - 1:00 - I observed Debbie preparing the nephropathy study drug for dispensing at the week 2 visit for subject SCG. Then, I helped her edit a recruiting flyer for the hypertension study.

1:00 - 1:30 - SCG arrived for his week 2 visit. I watched as Debbie took his vitals and performed the P-NSS. While Debbie drew the necessary blood work, I counted the returned study drug for compliance. Then, a

urinalysis was collected and the new study drug was dispensed along with a container for him to perform a 12-hour urine sample prior to his next visit on June 26, 2002.

1:30 - 2:00 - Debbie and I processed the labs that were collected per protocol and packaged them for shipping. The shipment was then recorded on the laboratory shipment log.

2:00 - 2:30 - I completed the subject and visit information on the P-NSS form, copied the form, and faxed it to the sponsor. Then, I marked the original and copy, and marked the fax date on the original. These were then filed in the CRF and the source document. Then, I completed the Clinical Trials Patient Visit Form to go to the Clinical Trials Office. Finally, I copied several pages from Medical-Surgical Nursing 3rd ed.

2:30 - 3:00 - Debbie and I reviewed lab results for a patient she and Dr. Cage are helping with diabetes control. Then, we calculated the compliance for SCG, and noted that he had taken an extra pill or lost one.

3:00 - 3:45 - I read more from Diagnosis and Management of Type 2 Diabetes 5th ed.

June 14, 2002:

8:00 - 9:00 - Debbie and I reviewed the lab results for nephropathy study subject SJT, and learned that she had screen failed. This was noted in her chart, and she was informed of the results by telephone. Then, she was entered

into the patient log as a screen fail.

9:00 - 10:00 - Debbie and I read articles about study insufficiencies and subject recruitment in "Monitor" magazine published by the ACRP.

10:00 – 11:00 - BAS arrived for her week 16 visit. I watched as Debbie took her vitals and performed the P-NSS. After the P-NSS, Debbie drew the necessary blood work. Then, BAS was asked to complete the questionnaire for another diabetes study currently being conducted. While she did this, Debbie and I gathered the medications that the clinic is providing for her during the study, along with her new study drug, and gave them to her before she left. A urine sample was also collected before she left.

11:00 – 11:30 - Debbie and I processed the labs for BAS per protocol and completed the shipping labels. I also checked and logged the temperatures in the refrigerator and freezer.

12:30 – 12:45 - Debbie and I walked to the Clinical Trials Office and got dry ice. Then, we returned to the lab and packaged the labs processed earlier for shipment. This included completing the shipping labels and calling for pick-up.

12:45 - 1:15 - I filled out the Clinical Trials Patient Visit form for BAS while Debbie completed the narrative note, source document, and the CRF for BAS. The subject did not bring her unused drug to the visit; therefore, the new study drug will not be dispensed until the old drug is returned.

1:20 - 2:40 - Debbie and I saw three patients for the diabetes/OMM study. These patients were counseled on their diet and exercise, and how to use the two to gain better control of their blood sugar.

2:40 - 3:00 - BAS returned her unused study drug and empty container, and new study drug was dispensed to her. Then, Debbie and I counted the returned medication and calculated her compliance. This value was recorded in the source document and the CRF. The dispensed drug and the returned containers were recorded in the drug accountability log.

June 17, 2002:

8:30 - 8:45 - Debbie and I reviewed the lab results obtained for the week 2 nephropathy study visit for SCG. These values were entered in the source document.

9:00 - 11:00 - I read more from Diagnosis and Management of Type 2 Diabetes 5th ed.

12:30 - 4:00 - I called diabetes patients from Debbie's database to recruit patients for the diabetic questionnaire. Together, Debbie and I scheduled over twenty patients for the study

June 18, 2002:

8:00 - 9:00 - Debbie and I gathered the lab supplies needed to redraw the blood work for nephropathy study week 16 visit for BAS. The labs shipped on

Friday were not delivered on Saturday, and therefore, were too old to use when the central lab received them. Debbie also whited out the dates on the old requisition and replaced them with today's date as the lab had instructed her to do.

9:30 - 10:30 - Debbie continued calling patients for the diabetic questionnaire for Dr. Franks, and I reviewed my journal.

10:30 – 11:00 - The week 4 lab kits for nephropathy study subject SCG arrived. I labeled the boxes, supplies, and requisitions, and put them on the shelf.

11:00 – 12:00 - Debbie and I began breaking down the lab kits used to screen patients for the nephropathy study, because the screening period has ended. This will provide room for the supplies that will arrive soon for the neonatal conjunctivitis study.

12:45 - 1:00 - I broke down more lab kits from the nephropathy study.

1:15 - 2:20 - BAS arrived to have her lab work redrawn. The blood was drawn and Debbie and I processed it. Then, we went to the Clinical Trials Office to get dry ice. Upon returning, the labs were packaged and shipped.

2:20 - 2:30 - Debbie noted that the labs were redrawn in the narrative note for BAS, and the laboratory-shipping log was updated.

2:30 - 3:00 - Debbie and I looked through supply catalogs to find a cart for lab supplies that would fit in the lab area. This was found and ordered.

3:00 - 3:30 - Debbie and I broke down more lab kits, and placed the empty boxes in

the hall to be picked up by the custodian.

3:30 - 4:15 - The lab supplies for the conjunctivitis study arrived, and they were counted against the shipping order. Then, the supplies were shelved.

June 19, 2002:

8:00 - 8:40 - Debbie and I prepared for the Site Initiation visit for the neonatal conjunctivitis study. This included logging the temperature in the refrigerator and freezer, copying CVs, reviewing the regulatory documents, and making certain the conference room was reserved.

8:40 - 8:45 - Debbie contacted nephropathy study subject BAS, and scheduled a time for her to come in for an unscheduled CNA due to changes in her neuropathy.

9:00 - 11:30 - The monitor from the conjunctivitis sponsor company arrived for the Site Initiation visit. He first toured the facility, and then he reviewed the source documents, CRFs, and visit procedures with Debbie and I. Then, Dr. Cage came in and asked the questions he had about the study. Finally, Dr. Cage was walked through the exams and lab procedures.

1:15 - 2:00 - Debbie returned the voicemails, one of which was from the conjunctivitis study monitor regarding additional information he needed before he could ship the study drug. Debbie contacted the Clinical Trials Office to get the information for him.

2:00 - 4:00 - Debbie and I continued working to gather the documents needed for the conjunctivitis study. These were placed in the regulatory binder. I also made copies of the informed consent document to have them readily available when patients come in that qualify for the study.

June 20, 2002:

8:00 - 9:30 - Nephropathy study subject BAS arrived for her CNA assessment by Dr. Cage. After the exam, the form was faxed to the sponsor and copied for filing in the source document and the CRF. Debbie completed a form to request payment for an unscheduled visit. The form was printed for filing in the study binder, and e-mailed to the sponsor. A note was also made in the comment section about the unscheduled visit.

9:30 - 10:30 - Debbie and I reviewed and filed lab results for the nephropathy study. The results for subject SCG showed signs of a urinary tract infection (UTI). Therefore, Debbie contacted his primary care physician, and contacted SCG recommending that he visit his doctor.

10:45 – 11:45 - I reviewed some material on diabetes and diabetic complications.

1:15 - 1:45 - Debbie and I opened boxes of materials received for the conjunctivitis study. This included a baby cuff for blood pressure checks, as well as recruiting materials.

1:45 - 2:00 - Debbie and I took the recruiting materials and other paperwork for the

conjunctivitis study to the Clinical Trials Office. The recruiting materials must be approved by the IRB in expedited review.

2:00 - 2:30 - Debbie and I continued assembling the regulatory binder for the conjunctivitis study. This included completing the designation of responsibilities form.

June 21, 2002:

8:00 - 9:00 - I reviewed the inclusion/exclusion criteria, schedule of study visits, and the informed consent for the conjunctivitis study. I also logged the temperature in the refrigerator and the freezer.

10:15 - 10:30 - Debbie and I walked to the UNTHSC pharmacy to get blood glucose monitoring strips for a patient we will see this afternoon for the diabetes/OMM study. He cannot afford the strips at this time.

10:30 – 10:45 - Debbie telephone screened a patient interested in clinical trials. The information will be added to the database for future studies.

12:15 – 12:30 - Debbie showed me the Clinical Trials Enrollment form she must keep for the Clinical Trials Office, and must update monthly for the Clinical Trials meeting.

12:45 - 1:30 - Debbie and I worked on a checklist used to determine eligibility for the conjunctivitis trial, as well as a form for conducting the medical history for this study. We worked on this throughout the day during our free

time.

1:30 - 4:15 - Debbie and I saw three patients for the diabetes/OMM study. These patients were counseled on their diet and exercise, and the affects these have on the blood sugar.

June 24, 2002:

8:15 - 9:30 - I logged the temperatures in the refrigerator and the freezer. Then, I reviewed the list of articles I need to copy for my diabetes research.

9:45 - 10:15 - I read an article about study budget planning and the areas that are the most problematic for most investigators and sponsors.

10:45 – 11:00 - Debbie contacted a sponsor company to determine the status of a trial that a physician within the department had applied for.

11:00 – 11:30 - Debbie and I broke down more lab kits from the nephropathy study.

12:30 - 5:15 - I spent the afternoon in the library continuing my research on diabetes and diabetic nephropathy.

June 25, 2002:

8:30 - 9:30 - Debbie and I reviewed the protocol for the hypertension study which arrived yesterday. I also logged the temperatures in the freezer and the refrigerator.

9:30 - 10:00 - Debbie and I assembled a binder for the hypertension study, adding the

protocol and the regulatory documents we have at this point.

10:00 – 10:30 - I read an article about diabetes while Debbie reviewed my journal.

10:30 – 11:00 - I made copies of the protocol for the hypertension study for Dr. Jones and P.A. Pagels, which I placed in their boxes in the clinic.

12:45 - 2:00 - Debbie and I read an article about the Health Information Privacy Act Amendment (HIPAA) and the implications it will have on clinical research. Then, we developed a Release of Medical Records form that will satisfy the proposed bill.

2:00 - 2:45 - Dr. Cage, Debbie, and I reviewed the chart for nephropathy study subject BAS. Her last neuropathy assessments have shown significant changes. Therefore, Dr. Cage was asked to call the sponsor's neurologist to discuss the situation. The two decided to keep her in the study, but to add additional neuropathy assessments to monitor her change. Dr. Cage asked Debbie and I to make a chart to map her changes.

2:45 - 3:00 - Debbie and I discussed our options for the graph Dr. Cage requested. We decided to use a bar graph to present the data.

3:00 - 3:15 - Debbie and I researched vitamin B_6 and its role in neuropathy.

June 26, 2002:

8:15 - 9:15 - I reviewed two protocol synopses that we received yesterday. Both are

for diabetic nephropathy studies. Then, Debbie and I looked at ophthalmology books to review symptoms and causes of neonatal conjunctivitis.

9:30 - 11:00 - I calculated the urinary albumin/creatinine ratio for the patients who screen failed for the current nephropathy study, in order to get an idea of how may patients might qualify for the studies being reviewed by Debbie and Dr. Cage.

11:00 – 11:15 - Debbie and I reconstructed the chart for nephropathy subject BAS.

11:15 – 12:00 - Debbie, Dr. Cage, and I met and discussed the nephropathy study, and the trials that will be starting soon.

1:00 - 2:00 - Nephropathy study subject SCG came in for his week 4 visit. Debbie took his vitals and performed the P-NSS. Then, the necessary blood work was drawn, and he was asked to provide a urine sample for a urinalysis. Before, he left, the old study drug was taken back, and the new study drug was dispensed. Then, Debbie and I processed his labs per protocol, and went to the Clinical Trials Office to get dry ice. Upon returning, we packaged the labs for shipment.

2:00 - 4:20 - Dr. Cage, Debbie, and I met to discuss the conjunctivitis study. We discussed the entry criteria, flow of visits, action to take if chemical toxicity is expected, etc. We then discussed my internship, and a general outline for my practicum.

June 27, 2002:

8:15 - 8:30 - I copied the P-NSS for the week 4 visit for nephropathy subject SCG. The copy and original were then filed appropriately.

8:30 - 9:30 - Debbie and I completed the physician questionnaire for the two nephropathy studies that we reviewed yesterday.

9:30 - 11:00 - Debbie and I worked on the budget for the hypertension study using the departments form for reviewing budgets and determining study practicality.

12:45 - 1:20 - Debbie and I reviewed the regulatory documents for the hypertension study, and took them to the Clinical Trials Office.

1:20 - 4:30 - I continued helping Debbie evaluate the budget for the hypertension study by gathering information about the clinic's normal fees for procedures that will be required by the study, and determining clinic employee fringe benefits.

June 28, 2002:

8:00 - 9:15 - Debbie and I resumed work on the budget for the hypertension study by completing the subject expense worksheet.

9:15 - 11:30 - Debbie and I made a graph to chart the neuropathy changes and the changes in 24-hour albumin excretion for the two subjects randomized

in the nephropathy study (SCG and BAS).

12:30 - 1:00 - Debbie and I continued working on the budget for the hypertension study.

1:00 - 1:30 - I accompanied Debbie to see a patient for the diabetes/OMM study. The patient has not been able to get strips for his blood glucose monitor, and was therefore not able to complete the blood sugar diary. Therefore, he was reminded of the impact his diet and exercise have on his blood sugar.

1:30 - 2:30 - Debbie and I worked on the budget. We also filed lab results received for nephropathy study subject SJT.

RESULTS AND CONCLUSIONS

The current treatments available for diabetic nephropathy have many shortcomings. The majority of these treatments are only effective in prevention and in slowing the progression of nephropathy from its early stages. Unfortunately, many patients with type 2 diabetes go undiagnosed until the greatest window of opportunity for these therapies has passed. Patients with type 1 and type 2 diabetes who are not adequately controlled in the areas of hyperglycemia, hypertension, and hyperlipidemia may not be able to prevent the development of End Stage Renal Disease (ESRD) with the current therapies. At this time, a patient who reaches advanced stages of overt nephropathy only has a slim chance of avoiding ESRD and its consequences, including a lifetime of dialysis or a kidney transplantation. Therefore, there is a huge need for more efficient drugs to treat and reverse nephropathy.

In order to improve the treatments available for patients with illnesses such as diabetic nephropathy, pharmaceutical companies test the drugs and devices they develop in clinical studies. These trials are divided into four distinct phases, and begin after the FDA has reviewed laboratory safety data and approved human testing.

Phase 1 clinical trials are the first studies of the investigational drug in humans. Therefore, the goal of these studies is to gain a safety profile of the drug. Phase 1 studies are typically short and are conducted in a hospital or research center. During these trials less than 100 healthy volunteers are admitted into the research center and exposed to a

wide range of doses of the study drug. During this time the volunteers are closely monitored with regular blood work, vital sign checks, urinalysis, and recording of intake and output levels, as well as the amount of exercise the subject gets. This close monitoring enables the sponsor to evaluate the absorption, distribution, metabolism, excretion, and duration of action of the drug (3). After a phase 1 trial, the sponsor has an idea of what levels of the study drug can be tolerated, how often dosing should occur, and what side effects to expect.

If the drug proves safe in phase 1 studies, the sponsor will move on to phase 2 trials. These studies are conducted on a slightly larger population of patients who have the disease or condition indicated by the drug. The purpose of phase 2 trials is to evaluate drug efficacy while continuing to monitor safety and side effects. Phase 2 studies are often referred to as dose ranging studies, because the sponsor is hoping to gain an understanding of what dose is needed to gain the desired effect (3). Phase 2 studies are often blinded, meaning that neither the patient nor the physician knows what dose of drug the patient is receiving, or if the patient is actually receiving a placebo. This technique is used to prevent subject and physician bias in reporting results. Once a phase 2 trial is completed, the sponsor knows which dose or doses should be adopted.

Now, it is time to move on to phase 3 trials. These studies incorporate a population of approximately 1000 subjects who have the indicated illness. The goals of a phase 3 trial are to verify the drug's effectiveness, its general risk to benefit ratio, and to monitor any adverse reactions from the long-term use of the drug (3). Therefore, these

studies are much longer than the other phases of clinical trials. Since phase 3 trials are very expensive for the sponsor, only the dose or doses the company plans to market are tested at this point. As with the phase 2 studies, phase 3 trials are typically blinded and patients are randomized into a treatment group. Due to the nature of data obtained during this phase, these studies are typically the most pivotal to the drug development process (3). The New Drug Application (NDA) is filed with the FDA after phase 3 testing is completed, and further testing cannot occur until FDA approval has been granted.

After FDA approval of the new drug has been received, the sponsor company can begin marketing the drug. Phase 4 trials are therefore referred to as post-marketing studies (3). A sponsor conducts phase 4 studies for a multitude of reasons. The most prevalent reason is for marketing purposes. This could be to gain a marketing edge, to refute a marketing issue, or to defend against claims raised by a competitor. Phase 4 studies are typically observational and usually conducted in a smaller number of subjects (3). These studies are typically randomized and may be used to test the efficacy of a new dosage or to reassess a particular safety issue that might have come about with long-term use of the drug. Therefore, the number and purposes of phase 4 studies can vary greatly between drugs.

During my internship, I assisted with a twenty-four week, phase 2, double blinded, placebo controlled trial for a drug being developed to slow, if not prevent, the development of ESRD from overt nephropathy in patients with both type 1 and type 2 diabetes. This drug is a naturally occurring component of vitamin B_6, and is an AGE-

inhibitor (16).

The AGE-inhibitory effect of the study drug was discovered by isolating Amadori products in the pathway to AGE formation. Once the intermediates were isolated, the sponsor's scientists searched for compounds that could specifically block the conversion of these Amadori products into AGEs (16). The study drug was found to be a strong inhibitor of this pathway. In comparison, the common AGE inhibitor, aminoguanidine, was found to be ineffective in blocking the post-Amadori formation AGEs. Therefore, it must block AGE formation at one of the less clinically relevant pathways, and should be less effective in treating nephropathy according to the sponsor's scientists. (16)

This study included type 1 and type 2 patients with clinically diagnosed diabetic retinopathy and a urinary albumin excretion rate (UAE) of greater than 300 mg/24h. Other inclusion and exclusion criteria were applied for the safety of the subjects and greater viability of the data. When patients came in for screening, an informed consent was obtained before any study related procedures were performed. After the informed consent was obtained, the pre-screening visit took place. During this visit, a medical history was obtained and numerous tests were performed to determine baseline conditions of the patient, as well as determining qualification for the study.

Among the baseline assessments were an objective neurological assessment called the Clinical Neuropathy Assessment (CNA) performed by Clifton Cage, D.O., neurological exam performed by Clifton Cage, D.O., and a subjective neurological assessment called the Positive Neuropathy Symptom Score (P-NSS) performed by

Debbie Lewis, R.N. The CNA was completed at the prescreening visit, the screening visit, and weeks 12 and 24, and at the follow-up visit. The neurological exam was completed at the second screening visit and at weeks 6, 12, 24, and at the follow-up visit. Debbie Lewis, R.N. performed the P-NSS at each visit. Tests for inclusion/exclusion purposes, as well as to monitor safety included, HbA1c, liver functions, serum creatinine, stool occult blood tests, screening for antinuclear antibodies (ANA), and general chemistry and hematology tests. The majority of these tests were repeated at each visit or at every other visit. In order to monitor the UAE, patients were required to perform a 12 hour urine collection and return it to the office. This was done following the prescreening visit and prior to visits at weeks 0, 4, 8, 12, 16, 20, and 24. A complete physical examination is performed at the second screening visit and at weeks 6, 12, 24, and at the follow-up visit. Patients are asked about medication changes and adverse events at each visit.

During the enrollment period, 13 subjects were brought in for screening, and 2 subjects were randomized. The majority of patients who screen failed did not have adequate UAEs. If a subject continued to meet all inclusion and exclusion criteria after the screening visit, he or she was randomized into a study drug or placebo group. This was done by calling the sponsor's interactive voice response system (IVRS). The IVRS assigns a randomization number to the subject, and initiates shipment of the study drug. The study drug is dispensed initially at the baseline visit (week 0), and at each subsequent visit the old study drug is taken back and new study drug is dispensed. The recovered

drug was used to calculate subject compliance. Subjects were instructed to take the medication twice daily. Upon subject completion of the study, all study drug and empty containers were collected.

Since the study subjects are randomly assigned to a study group, and the study is being conducted in a double blind fashion, I have little evidence of the study drug's efficacy. However, I can make a few predictions based on the data obtained at this point. First, the UAEs of both randomized patients have dramatically improved since starting the study. For subject BAS, the UAE was 436mg/24hr at baseline, and by week 4 it had dropped to 52.2mg/24hr. Although the UAE has shown some fluctuations over the 20 weeks that she has been in the study, it showed an overall improvement of 396.4mg/24hr dropping from 436mg/24hr (baseline) to its lowest point of 39.6mg/24hr during week 12. However, she has also improved her HbA1c from 7.5 at baseline to 5.8 at week 20, which could account for part of the improvement in the UAE. For subject SCG, the initial UAE was 1339.8mg/24hr with a urine dipstick showing 3+ protein in the urine. His week 4 UAE was down to 1048mg/24hr, a decrease of 291.8mg/24hr, and at his week 6 visit the urine dipstick revealed only a trace of protein in the urine. This subject had good glycemic control at baseline, and has not seen a significant change in his HbA1c value since starting the study. Although it appears that the study drug is improving diabetic nephropathy, there is not enough data at this point to make that statement.

The efficacy and safety of the study drug are also being tested by monitoring changes in diabetic neuropathy of study subjects. This is done by performing the CNA

and the P-NSS on a regular basis. The CNA involves both an objective and a subjective section. During the objective portion of the assessment, Clifton Cage, D.O. observes the subject's motor and sensory abilities. To assess muscle strength and coordination, the subjects are asked to walk on their heels, walk on their toes, rise from a kneeling position, and move their legs against resistance. For the sensory portion of the exam, subjects are asked to close their eyes and report what they feel as their feet and great toes are subjected to soft touch with a cotton ball, pinpricks, vibrations, and movement of joint positions. For each of these tasks, the subject receives a score of normal, decreased, or absent. When this is complete, Clifton Cage, D.O. asks a number of questions concerning peripheral and autonomic neuropathy symptoms. The subjects are asked to answer with "yes" if the symptom is present or "no" if it is not present. If they answer yes, they are then asked about the severity and frequency of the problem.

Debbie performs the P-NSS assessment, typically before the CNA is performed. This exam only involves a subjective portion. Debbie Lewis, R.N. asks the subjects a number of questions relating to the symptoms of peripheral neuropathy. Again, the patients are asked to answer with "yes" if the symptom is present and "no" if the symptom is not present. As with the CNA, all positive answers are followed up with questions about the severity and frequency of the symptom.

Subject BAS has shown the most change in neuropathy symptoms since starting the study. Throughout the study, her answers to the subjective questions have been inconsistent; therefore, I have focused on the objective portion of the CNA to base my

conclusions. At baseline, BAS had decreased soft touch, pinprick, and vibration sensations, but had normal joint position sensations in her right foot. In her left foot, she had absent soft touch and pinprick sensations, decreased vibration sensations, and normal joint position sensations. By week 12, her soft touch sensation was absent in both feet and the pinprick and vibration sensations were decreased in both feet while the joint position remained normal. As a result of dramatic changes in the subject's responses to the subjective questions of the CNA and the P-NSS, a CNA was requested at week 16. This test revealed an absence of the soft touch, pinprick, and vibration sensations in both feet, while the joint position sensation in both feet remained normal. This raised some concern for the subject's safety, and it was decided that the CNA should be repeated at the week 20 visit. This time the subject showed improved results from week 16 in that the vibration sensation in the right foot was only decreased. Based on this, it appears that the neuropathy changes are due more to subject variability than to the study drug. Therefore, the subject was allowed to continue in the study.

For subject SCG, the baseline neuropathy was somewhat worse. He showed to have absent soft touch, pinprick, and vibration sensations in his right foot, with normal joint position sensations. His left foot showed absent soft touch sensation, decreased pinprick and vibration sensations, and normal joint position sensation. Unfortunately, there has not been another CNA performed to date to compare these results to. During the subjective questions of the CNA and the P-NSS, he complained only of tightness and numbness at baseline. However, during the P-NSS assessment at week 4, the subject

complained of prickling and tingling. This could be caused by worsening peripheral neuropathy causing him more pain, or improving neuropathy with a return of sensation. Therefore, at this point there is not enough evidence to say if the study drug is having an effect on diabetic neuropathy.

Participation in a drug study offers countless benefits to subjects. The most obvious is the opportunity to receive a drug that is not currently available on the open market. This is especially beneficial to those patients who have failed with the current treatments. Also, the study drug and all study related procedures are free to the study subjects. This is a way to provide medical care to those patients who can not otherwise afford it. Finally, the frequency of visits mandated by a study provides optimal levels of care to patients, and the likelihood of serious medical problems going unnoticed is greatly diminished. In the case of diabetic patients, this increased contact with a physician and other health care professionals often provides the motivation and education needed to gain control over one's disease. Therefore, drug studies not only provide hope for future patients, but also provide numerous benefits to study participants.

REFERENCES

1. NIDDK National Diabetes Information Clearinghouse; "National Diabetes Statistics General Information and National Estimates on Diabetes in the United States, 2000"; http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#7
2. Stedman's Medical Dictionary. 27th ed. 2000. Philadelphia, PA: Lippincott Williams and Wilkins.
3. Introduction to Clinical Research and Studies. 1999. Dallas, TX: MedTrials Incorporated.
4. Edelman, S.; Henry, R.. Diagnosis and Management of Type 2 Diabetes, 5th ed. 2002. Caddo, OK: Professional Communications , Inc.
5. Genuth, S. (1998) The Endocrine System. In Berne, R. and Levy, M. (ed.), Physiology 4th ed. (pp779-1046). St. Louis, MO: Mosby, Inc.
6. American Diabetes Association. Standards of Medical Care for Patients with Diabetes Mellitus. Diabetes Care 25: S33-49, 2002.
7. American Diabetes Association. Insulin Administration. *Diabetes Care* 25:S112-115, 2002.
8. Luckman, J.; Sorensen, K.C.. Medical-Surgical Nursing. 3rd ed. 1987. Philadelphia, PA: W.B. Saunders Company.
9. Cooper, M.; Gilbert G.; Epstein, M.. Pathophysiology of Diabetic Nephropathy. *Metabolism*, Vol 47, No12, Suppl1 (December), 1998: pp3-6.

10. American Diabetes Association. Diabetic Nephropathy. *Diabetes Care* 25:S85-89, 2002.

11. Stegall, M. D.; et al. Pancreas Transplantation for the Prevention of Diabetic Nephropathy. *Mayo Clinic Proceedings* 2000; 75:49-56.

12. Ritz, E.; Tarng, D.. Renal disease in type 2 diabetes. *Nephrology Dialysis Transplantation* (2001) 16 [Suppl5]: 11-18.

13. Foggensteiner, L.; Mulroy, S.; Firth, J.. Management of diabetic nephropathy. *Journal Of The Royal Society Of Medicine* 2001; 94: 210-17.

14. Remuzzi, G.; Schieppati, A.; Ruggenenti, P.. Nephropathy in Patients With Type 2 Diabetes. *New England Journal of Medicine* April 11, 2002; Vol. 346, No. 15: pp 1145-50.

15. Heidland, A.; Sebekova, K.; Schinzel, R.. Advanced Glycation End Products and the Progressive Course of Renal Disease. *American Journal of Kidney Disease,* Vol 38, No4, Suppl 1 (October), 2001: pp S100-6.

16. Biostratum. Investigator's Brochure. 2001.

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