

The Contented Kidney

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This lecture could not be updated in time for the lecture notebook. Updates will be given at the time of the lecture.

The information is presented as follows:

Western Perspective

- Review of kidney function
- Review of common causes of kidney failure
- Identifying those at high risk and prevention of kidney failure
- Supporting the person in chronic kidney failure
- Supporting the person on dialysis
- Supporting the person with a kidney transplant
- Herbs used to support kidney function and how they are thought to work, as well as a list of herbs used to treat complications of kidney failure, dialysis, kidney transplantation or drug side effects
- Research abstracts
- Case histories

Eastern Perspective - by Heiner Freuhauf

1. Traditional etiology and pathogenesis
2. Modern Case Studies

Review of Kidney Function

The kidneys weigh about 100-160 grams each. Each kidney is about the size of a clenched fist. They are responsible for ridding the body of waste material and controlling the volume and composition of body fluids. Specific functions include:

- Regulation of water and electrolyte balances: filter and reabsorb potassium, magnesium, chloride, sodium, calcium, hydrogen, and phosphate ions;
- Maintain blood pressure: maintain adequate water volume, filter and reabsorb sodium, synthesis of renin, kinins, prostaglandins;
- Filter and excrete metabolic waste products: urea (from metabolism of amino acids), uric acid (from nucleic acids), creatinine (from muscle creatine) (urea and creatinine also secreted); end products of hemoglobin breakdown such as bilirubin;
- Filter and excrete foreign chemicals;
- Secrete hormones: erythropoietin (acts on the stem cells of the bone marrow to stimulate red blood cell production - 90% made in kidney, 10% in liver), renin, kinins, prostaglandins;
- Involved with gluconeogenesis: kidney forms glucose from amino acids and other precursors during prolonged fasting. It rivals the liver;
- Regulation of acid-base balance (along with the lungs): bicarb reabsorption and hydrogen ion secretion;
- Maintenance of calcium and phosphorus

balance: hydroxylation of vitamin D to 1-25 dihydroxycholecalciferol, filtration and reabsorption of phosphate and calcium (dependant on PTH);

- Maintenance of hematocrit/hemoglobin: synthesis of erythropoietin.

About 21% of the cardiac output flows to the kidneys. Plasma is filtered and processed about 60 times per day. Each kidney has about 1 million nephrons (functional unit of the kidney). The nephron consists of the glomerulus where fluid and some solutes are filtered from the blood, and the tubule which converts the fluid into urine through reabsorption of solutes and fluid, as well as secretion of solutes and fluid into the tubules. Most plasma substances pass freely into the glomerular filtrate with the exception of proteins. Once in the tubule, water and specific solutes are reabsorbed as well as secreted via the peritubular capillaries. Waste products such as urea, creatinine, uric acid and urates are poorly reabsorbed. Foreign substances and chemicals are also poorly reabsorbed. Some waste products such as creatinine and BUN are additionally secreted from the blood into the tubules. Electrolytes, such as sodium ions, chloride ions, and bicarbonate ions are highly reabsorbed, so little appear in the urine. Nutritional substances, such as amino acids and glucose, are completely reabsorbed. In a healthy individual, they do not appear in the urine even though filtered by the glomerular capillaries. The kidney can't regenerate new nephrons. Renal injury, disease and aging will decrease the number of nephrons. After age 40, the functional nephrons begin to decrease by 10% every 10 years due to benign nephrosclerosis. The remaining nephrons adapt to take on the increased work load. 70% of the functional nephrons can be lost before clinical symptoms appear. When kidney function fails, the resulting kidney failure, if untreated, is lethal within a few days. Death is due to a combination of acidosis, a high concentration of potassium and accumulation of fluid.

Statistics

There were 392,023 people under treatment for end stage renal disease in 2001. Of these people the primary disease causing ESRD was 35.3% due to diabetes mellitus, 23.3% due to hypertension, 15.5% due to glomerulonephritis and 4.3% due to cystic kidneys. the rest was due to various causes. There were 15,331 kidney transplants in 2001.

List of Risk Factors

- Age. The kidney begins to get smaller at about age 35-40. After age 40, the functional nephrons begin to decrease by 10% every 10 years due to benign nephrosclerosis.
- Race. In 2003 blacks had the highest rate per million of ESRD, then Native Americans, then Asians and then whites.
- Gender. Men have a higher risk for developing chronic kidney disease than women.

- Family history. - Family history is a factor in the development of both diabetes and high blood pressure, the major causes of chronic kidney disease.
- Genetic susceptibility to kidney disease such as polycystic kidney disease.
- Insulin-dependent diabetics - Insulin dependent diabetics have all been found to have histological evidence of glomerulosclerosis when renal biopsies have been undertaken. 35% will develop clinical nephropathy, usually about 15-20 years after diagnosis. 5-15% of type II diabetics will also develop nephropathy.

Lab Analysis is Important for Prevention

All insulin-dependent diabetics and to a lesser degree type II diabetics, patients with severe hypertension and patients with genetic susceptibility to kidney disease should have yearly exams and blood chemistry screens as well as a urinalysis twice per year. Any evidence of urinary kappa light chains, microalbuminuria or severely high cholesterol could be the first clue to nephron damage.

Common Causes of Kidney Failure

There are two main categories of kidney failure: acute renal failure and chronic renal failure.

Acute Renal Failure (ARF)

In this form of kidney failure, the kidneys stop functioning properly because of a sudden illness, a medication or medical condition that causes one of the following:

1. Prerenal ARF is due to heart failure with reduced cardiac output and low blood pressure, or conditions associated with diminished blood volume and low blood pressure, such as severe hemorrhage.

A severe drop in blood pressure or interruption in the normal blood flow to the kidneys can occur during major surgery, severe burns with fluid loss through burned skin, massive bleeding (hemorrhage) or a heart attack that severely affects heart function. Blood clots that travel to the kidney also can cause acute kidney failure.

As long as renal blood flow does not fall below 20% of normal, acute renal failure can usually be reversed if the cause is corrected before renal cell damage occurs. When the blood flow to the kidneys decreases, the glomerular filtration rate (GFR) also decreases. This decreases the kidney's work load, and therefore decreases the kidney's requirement for energy and oxygen. Ischemia can not persist for more than a few hours at below 20% blood flow, or the kidney will experience intrarenal ARF.

2. Intrarenal ARF due to abnormalities of the kidney itself, including direct damage to kidney cells or to the kidneys' filtering units, (blood vessels, glomeruli or tubules. Examples follow below) which can be caused by an

inflammation of the kidneys called glomerulonephritis, toxic chemicals, medications and infections.

- Acute Nephritic Syndrome (Acute Glomerulonephritis; Postinfectious Glomerulonephritis) – A common cause of acute glomerular capillary damage. 95% of patients with acute glomerulonephritis had damage occur to the glomeruli 1-3 weeks after an infection elsewhere in the body. Antigen-antibody complexes are deposited in the glomeruli. Glomeruli become blocked by inflammation. In the past, Postinfectious Glomerulonephritis was usually caused by streptococcus; currently, glomerulonephritis is increasingly caused by staphylococcal and gram-negative bacteria.

- Tubular necrosis due to severe renal ischemia - The epithelium is destroyed due to severe ischemia (prerenal ARF causing intrarenal failure) and inadequate supply of nutrients and oxygen to the tubular epithelial cells. Tubular cells slough off and plug up the nephrons. This blocks urine outflow. Most common cause is a prerenal occurrence of ARF, such as circulatory shock.

- Tubular necrosis due to poisons, toxins or medications which destroy the tubular epithelial cells. Examples are carbon tetrachloride, heavy metals, ethylene glycol, insecticides and medications such as tetracyclines and cisplatin.

- Interstitial nephritis is due to vascular, glomerular or tubular damage that destroys individual nephrons or involves primary damage to the renal interstitium. Conditions that cause primary interstitial damage are acute pyelonephritis and acute allergic interstitial nephritis. Pyelonephritis can be due to bacterial infections from the bladder (most commonly due to Escherichia coli, from fecal contamination of the urinary tract) or via the blood stream. Drugs or poisons can also induce primary damage to the renal interstitium.

3. Postrenal ARF due to bilateral obstruction of the urinary collecting system anywhere from the calices to the urethra. (Blocked urine flow from the kidney.) The most common cause being kidney stones caused by precipitation of calcium, urate or cystine. It can also be due to bladder tumors or an enlarged prostate. Blockage of urine flow within the kidney also can cause sudden kidney failure, as can occur with major muscle injury.

With moderate acute renal failure, there is retention of water, waste products of metabolism, and electrolytes. This causes edema and hypertension. Excessive retention of potassium can be fatal. Another possibly fatal problem is metabolic acidosis due to inability to excrete sufficient hydrogen ions.

Acute renal failure may be treated and the person may never have another problem or it can be the instigating factor for chronic renal failure. Chronic renal failure may show up immediately or many years down the road.

Chronic Renal Failure

Chronic renal failure is due to irreversible loss of large numbers of functioning nephrons. Clinical symptoms occur when there are less than 30% normal functioning nephrons. In general, chronic renal failure occurs due to the same reasons acute renal failure occurs, but the progression is slower. Often the initial insult to the kidney leads to progressive deterioration of kidney function and increased loss of nephrons over time until the person reaches end-stage renal failure and is placed on dialysis or receives a kidney transplant. When nephrons are lost, other nephrons take on a larger load. They adapt and excrete normal amounts of water and solutes until the kidney is reduced to 20-30% normal nephron mass. Over the years, the glomeruli are injured. It is thought this injury is caused by the increased pressure and stretch from the increased blood pressure on the glomeruli. This eventually causes sclerosis and further destruction of the kidneys. The only method known by conventional medicine to slow the glomerular damage down is to lower blood pressure and glomerular hydrostatic pressure by using drugs such as angiotensin-converting enzyme inhibitors to block formation of angiotensin II.

In chronic kidney failure, the functioning of the kidney gradually declines, usually over a period of years. Most commonly, it is caused by illnesses such as diabetes, uncontrolled high blood pressure or chronic kidney inflammation (glomerulonephritis or pyelonephritis). It also can occur because of long-term exposure to lead, mercury or certain drugs, especially painkillers.

The most common causes of end stage renal failure is diabetes mellitus, hypertension and glomerulonephritis.

Diabetic nephropathy is the most common cause of renal failure. Almost all insulin-dependant diabetics have histological evidence of glomerulosclerosis. 35% will develop clinical nephropathy, usually about 15-20 years after diagnosis. 5-15% of non-insulin dependant diabetics also develop nephropathy. The younger the age of onset of IDDM, the longer the duration, and the more frequent the episodes of ketoacidosis, the more likely the diabetic is to have diabetic nephropathy. Renal failure accounts for 48% of the diabetic deaths in those who acquire IDDM before age 20.

Hypertension and atherosclerosis can be a primary cause of renal damage. However, renal failure can also induce hypertension and lead to increased renal damage. Even in "normal" people benign nephrosclerosis takes place which diminishes normal kidney function to 60% by age 80. Benign nephrosclerosis in association with severe hypertension can lead to rapidly progressing malignant nephrosclerosis.

Chronic glomerulonephritis is a slowly progressive disease often leading to irreversible renal failure. It can be a primary disease following acute glomerulonephritis or secondary to

systemic diseases, such as diabetes or lupus erythematosus. It usually begins with precipitated antigen-antibody complexes in the glomerular membrane. There is inflammation, thickening, and eventually, fibrous tissue.

Signs & Symptoms of Renal Failure

Patients with slightly diminished renal reserve are asymptomatic and renal dysfunction can only be detected by lab tests. Mild to moderate renal failure may bring about vague symptoms such as nocturia, fatigue and decreased mental acuity.

- Changes in urination -making more or less urine than usual, feeling pressure when urinating, changes in the color of urine, foamy urine, or having to get up at night to urinate.
- Edema or even CHF, there is swelling of the feet, ankles, hands, or face (Due to fluid the kidneys can't remove taking up residence in these tissues.)
- Fatigue or weakness (a build-up of wastes or anemia can cause these symptoms when the kidneys begin to fail.)
- Muscle cramps or twitching
- Shortness of breath due to anemia as well as the build up of fluid in the lungs.
- Ammonia breath or an ammonia or metal taste in the mouth -waste build-up in the body can cause bad breath, changes in taste, or an aversion to protein foods like meat.
- Back or flank pain -due to kidney location on either side of the spine
- Itching -waste build-up in the body can cause severe itching, especially of the legs.
- Loss of appetite
- Nausea and vomiting
- Hypertension
- Yellow brown skin or even uremic frost
- Dark circles under the eyes
- More hypoglycemic episodes, if diabetic
- Positive tests (See tests under "Renal Tests")

Renal Tests

Urinary kappa light chains

This test detects kidney disease early on. It detects small amounts of tiny protein molecules that are entering the urine due to leaky blood vessels in the kidneys called polyclonal kappa light chains. They are the first proteins to leak through tiny pores in the blood vessels of the kidneys that may have been affected by disease. This test requires a small amount of fresh urine.

Microalbuminuria

This less costly test can now be performed qualitatively (by dipstick) in your doctor's office, or quantitatively at outside laboratories. Like the urinary kappa light chain

test, it indicates there are leaky vessels in the kidneys, but at a later stage, since albumin is a slightly larger molecule.

A quantitative measurement requires a 24-hour urine specimen.

24-hour urinary protein

This test detects kidney damage at a later stage than the preceding two tests; it also requires a 24-hour urine collection.

Creatinine clearance

Creatinine is a chemical by-product of muscle metabolism, and is present in your bloodstream all the time. Measuring the clearance of creatinine from the body is a way of estimating the filtering capacity of the kidneys. In diabetics, test values are usually higher than normal when a person is spilling a lot of sugar in the urine, and eventually lower than normal when the kidneys have been damaged by years of elevated blood sugars. You may see an appropriate drop in creatinine clearance when blood sugars are normalized and urine glucose vanishes.

The creatinine clearance test requires a 24-hour urine collection and a small amount of blood to measure serum creatinine. The most common cause of abnormally low values for this test is failure of the patient to collect all the urine produced in a 24-hour period. Therefore, if other kidney tests are normal, tests with low values for creatinine clearance should be repeated for verification.

When it is impractical to make a 24-hour urine collection, as for small children, a new test requiring a small amount of blood, *creatinin-c*, can be performed.

Serum beta2 microglobulin

This is a very sensitive test for injury to the tubules of the kidneys. Elevated values can also result from inflammation or infection anywhere in the body. Thus an isolated elevation of serum beta2 microglobulin without the presence of urinary kappa light chains or microalbumin is probably due to some sort of infection. Such elevation is commonplace in people with AIDS.

24-hour urinary glucose

This test too requires a 24-hour collection of urine, and is of value for proper interpretation of the creatinine clearance if the person is diabetic.

Several factors cause false positive results in some of the above tests. Strenuous or prolonged lower-body exercise (which would include motorcycle or horseback riding) in the 48 hours preceding the tests can cause false positives. Additionally, if on the day the tests are to be performed the patient is menstruating or has a fever, a urinary tract infection, or active kidney stones, they should postpone the tests until these conditions have cleared.

Prevention can be undertaken by attending to the causative factors via treatment of hypertension, diabetes, or other causative factors. Additionally, the herbs and food supplements that follow can be used to support kidney function.

Issues and Treatment of Renal Failure

Following are general issues which need to be considered in acute renal failure, chronic renal failure, dialysis and renal transplantation. Treatments listed are for renal health support, treatment of complicating factors surrounding renal failure, and treatment of the side effects resulting from conventional treatments. Only those treatments which appear to be beneficial and safe to use for prevention, as well as treatment of kidney failure, are included. There are methods for treating some of these conditions which have purposely been left out, since they may harm kidney function, or their effects on kidney function are unknown. The most significant treatments are listed below and are examined in detail on pages 8-16 of this newsletter.

Acute Renal Failure

Chinese data suggests that patients with acute renal failure who are treated right away, have an 89.6% - 92.1% chance of recovering normal kidney function.

There are many causes of acute kidney failure but a common cause which can be prevented, or treated in conjunction with dialysis, is acute failure due to acute nephritic syndrome (acute glomerulonephritis; postinfectious glomerulo-nephritis). 95% of patients with acute glomerulonephritis have damage occur to the glomeruli 1-3 weeks after an infection elsewhere in the body. Antigen-antibody complexes are deposited in the glomeruli. The glomeruli become blocked by the inflammation.

Give the kidney supportive and protective herbs and supplements. See "Herbs and Food Supplements to Support Kidney Function on pages. 8-15 See Case # 2 from Dr. Sharol Tilgner.

Acute failure is generally hard to prevent due to the suddenness and rapidity of the event. In some cases, such as postinfectious nephritis, it can often be prevented. Additionally important, it is necessary to support the kidneys through the acute crisis and make sure it does not become chronic kidney failure. Preventing chronic kidney failure is a better goal than treating chronic kidney failure. If the progression of chronic renal failure is fairly far along, anything you can do to slow down complete kidney failure and stave off the eventuality of dialysis will allow the person more time without this stressful process. Prevention of kidney failure is even better than treating kidney failure. It can best be accomplished by targeting high-risk groups for kidney failure.

Acute Renal Failure Prevention

WH30+, the Chinese herbal preparation composed of Rheum Palmatum, Salvia Miltiorrhiza, Cordyceps Sinensis, Leonurus Sibiricus, Epihedium Macranthum, Radix Astragali, and Radix Codonopsis Pilosulae, is used to treat kidney deficiency in humans.

An acute renal failure and chronic renal failure rat model were introduced by glycerol injection (i.m.) and fed with adenine-excessive diet, respectively. WH30+ was administered to rats at the dose of 50 mg/kg/day from 10 days before the diseases were induced until the rats were sacrificed. The body weight of rats with acute renal failure without treatment was significantly lower than those treated with WH30+ ($p < 0.05$). Overall, serum creatinine and urea nitrogen were elevated significantly ($p < 0.01$) in renal failure rats compared to control. Treatment with WH30+ improved both serum creatinine and urea nitrogen slightly in both models. The WH30+-treated rats with acute renal failure had significantly ($p < 0.05$) greater creatinine clearance than those without treatment. The results of the study show that WH30+ is more effective in the prevention of acute renal failure than chronic renal failure. (2.5)

For additional information on preventing and treating acute renal failure, see the prevention and treatment of chronic renal failure which has many treatments that can also be used in acute renal failure. Specific areas to review are: 1) Prevention of Renal Failure due to toxins 2) Prevention of Renal Ischemia-Reperfusion Injury 3) Herbs and Food Supplements Used to Support Kidney Function

Chronic Renal Failure – Prevention

Diagnosis is not usually known until much of function is lost. If you have high-risk individuals, such as insulin-dependent diabetics, chronically hypertensive individuals, and individuals with a family history of kidney failure, they can be treated preventatively or at a minimum should be monitored for a rise in uremic indices with the use of a blood chemistry screen once per year and urinalysis twice per year. They should be treated at the first sign of renal damage. The key factor is treating these individuals in the early stages, as opposed to waiting for extensive sclerosis and loss of functional nephrons.

The most important tool you have for prevention of renal failure is recognition of the leading causes of renal failure. You can prevent or slow down renal failure best if you treat in the early stages. Clinical symptoms show up when there is 70% destruction of functional nephrons. You don't want to wait for clinical symptoms to show up.

- #1 cause of renal failure - IDDM (35%)
- #2 cause of renal failure - Hypertension (23%)
- #3 cause of renal failure - Glomerulonephritis (15%)

#4 cause of renal failure - Cystic kidneys (4%)

Look for early signs of renal failure in lab work by testing for urinary kappa light chains. Urinary Abnormal blood cholesterol may be the first and only sign if not testing for urinary kappa light chains or microalbuminuria. High cholesterol levels are seen in renal failure. The levels may be as high as 400 or 500. (I have seen levels twice that high.) Watch for microalbuminuria. Albumin is the major protein in the blood. In the early stages of kidney damage small amounts of albumin leak through the kidney and appear in the urine. If found soon enough, it is possible to stop or reduce further damage to the kidney and improve long term health. A single high test result does not mean that kidney damage is present. If the first result is high, the test should be repeated twice in the next six months. If two out of the three results are high, kidney damage is indicated. Yearly physicals and blood chemistry screen as well as a twice yearly urinalysis is necessary in the high-risk groups mentioned above.

Chronic Renal Failure – Treatment

Chinese data suggests 10.9%-13.2% of patients with chronic renal failure are able to fully recover normal kidney function.

Once a person has been diagnosed with chronic renal failure, they generally have less than 30% of nephron function left. At this stage, you attempt to recover function, and prolong current kidney function as long as possible, as well as treat life-threatening or irritating symptoms which are a part of the disease process.

The Role of Antioxidants in Renal Failure

Renal failure is accompanied by oxidative stress, which is thought to be caused by enhanced production of reactive oxygen species and impaired antioxidant defense. End Stage Renal Disease patients have been found to have reduced anti-oxidant systems such as vitamin C and Selenium deficiency and reduced intracellular levels of vitamin E, reduced activity of the glutathione system, at the same time they are rich in oxidants. Additionally pro-oxidant activity is increased due to advanced age in some patients, as well as diabetes, chronic inflammation and non-biocompatibility of dialysis membranes and solutions. (32) Therapeutic interventions aimed at reducing oxidative stress in chronic renal failure patients are as follows:

- the use of biocompatible membranes in dialysis, ultrapure dialysate, and removal of endogenous foci of infection
- hemolipodialysis, and electrolysed reduced water for dialysate preparation
- administration of antioxidants (alpha-tocopherol, ascorbic acid, N-acetylcysteine, reduced glutathione, CoQ10, alpha lipoic acid, l-carnitine, Ginkgo biloba, Sily-

bum marianum. *Salvia miltiorrhiza*)

- substances possibly affecting oxidative stress indirectly (erythropoietin, sodium selenite).(31,31.5)

Three components of **Salvia miltiorrhiza**, salvianolic acid A, B and rosmarinic acid were found to have antioxidant activity. (123)

Ginseng saponin protects the kidney from oxidative stress. (2,3)

Curcumin protected against kidney injury by suppressing free radicals and increasing kidney glutathione content and glutathione peroxidase activity (endogenous antioxidants). Curcumin also eliminated kidney microsomal and mitochondrial lipid peroxidation. (39)

Coptis chinensis decreased serum malondialdehyde level while the glutathione/glutathione disulfide ratio and the activities of the antioxidation enzymes, superoxide dismutase and catalase, were higher in rats with renal ischemia-reperfusion damage compared with controls. (44)

Renal DNA of rats given *Coptidis Rhizoma* extract orally showed a significantly lower DNA fragmentation rate, which was dose-dependent, implying that the extract afforded the kidneys protection against oxidative stress-mediated apoptosis during the process and ameliorated renal function impairment. (44)

Vacinium spp: In 2004 the USDA examined 100 foods and found that wild blueberries were the second highest in antioxidants while cultivated blueberries were number 5.

Patients can improve cellular defense against chronic inflammation and oxidative stress with regular use of L-carnitine, most likely by modulating the specific signal transduction cascade activated by an overproduction of proinflammatory cytokines and oxidative stress. (25) For detailed information on L-carnitine, see "Supporting the Person on Dialysis"

Treatment with **coenzyme Q10**, a known antioxidant, improves renal function in patients with chronic renal failure and decreases the need for dialysis in patients on chronic dialysis.

Quercetin protects the kidney against damage inflicted by reactive oxygen species(28, 28.5, 29)

Vitamin C: Acute administration of vitamin C (3 gram IV) reduces oxidant stress in renal failure and improves NO-mediated vessel dilatation. (109)

See the section called "Support the Person on Dialysis" for more information on vitamin C.

Alpha Lipoic Acid is an interesting antioxidant. Antioxidants have distinctive characteristics. For example, vitamin C protects only the watery portions of cells from free-radical attack; vitamin E protects lipid membranes. Alpha-lipoic acid possesses amazing antioxidant abilities. It has the ability to neutralize free radicals occurring in both watery and lipid regions of cells. It is a wonderful all around antioxidant for the body. Lipoic acid extends itself to other antioxidants (vitamins C and E, as well as glutathione and CoQ10), regenerating them for continued service and greater efficiency.

Lipoic acid is effective in rats for the prevention of early diabetic glomerular injury, proving more effective than high doses of either vitamins A or C. (34,35,97) It is also useful in preventing some types of tubular damage,(37) as well as angiotensin II renal damage. (38)

In one study, parameters of glomerular injury were examined in diabetic rats after 2 mo on unsupplemented diets and in diabetic rats that received the lowest daily dose of dietary lipoic acid (LA) (30 mg/kg body wt), VE (100 IU/kg body wt), or vitamin C (VC; 1 g/kg body wt), which detectably increased the renal cortical content of each antioxidant. The study demonstrated that dietary supplementation with LA prevents early glomerular injury in the diabetic rat. Neither LA nor VC prevented glomerular hyperfiltration whereas both of them suppressed albuminuria. The LA suppressing it to the levels of the control group. LA but not VC or VE also reduced cortical tubular cell content of TGF-beta in the diabetic rats. The data showed the effects of LA were not due to enhancing VE or VC availability in the renal cortex. LA did significantly increase glutathione levels in the renal cortex (has been reported before) and the glutathione content correlated with the reductions in the urinary albumin excretion (UAE) glomerular and tubular content of TGF-beta and glomerular collagen IV in the diabetic rats but not with reductions in either renal mass or GFR. Increased nervous system glutathione content in response to LA use for peripheral nerve injury in diabetic rats has been shown in the past. This suggests that increased glutathione content in both nerve and renal tissue can protect them from damage in diabetes mellitus. The data in this study indicates that LA is effective in the prevention of early diabetic glomerular injury and suggest that this agent may have advantages over high doses of either VE or VC. (97)

Ginkgo biloba: is a PAF receptor antagonist(16) It inhibits PAF-induced formation of reactive oxygen species by mesangial cells, and prevents PAF induced decreases in renal blood flow, decreases in GFR and decreases in urinary sodium excretion. (10) Ginkgo also inhibits glomerular destruction. (16), reduces proteinuria. (16), reduces histopathological lesions in nephrotoxic rabbits. (8), prevents acute rat renal failure induced by glycerol injection. (16), increases the chance of graft survival and decreases the number of acute rejection episodes after surgery. (16), prevents or decreases cisplatin injury to the kidney without

effecting the antitumor activity of cisplatin. (16)

Antioxidants & Renal Toxins

Be careful of anything that will increase excretion of toxins via the kidney. Going on a heavy metal purge may not be the best thing if the persons kidneys are not healthy.

Cisplatin: Cisplatin-induced nephrotoxicity is a chemotherapy side effect that appears to be related to an increase in lipid peroxidation and oxygen free radicals in a kidney. This makes antioxidants a key feature in preventing this terrible side effect of cisplatin chemotherapy.

Lipoic Acid: In cisplatin-induced nephrotoxicity in rats, graded doses of lipoic acid effectively prevented a decrease in renal antioxidant defense system and prevented the increase in lipid peroxidation, platinum content and plasma creatinine concentrations in a dose-dependent manner. (37)

N-acetylcysteine: (See Radiocontrast Nephropathy for details on N-acetylcysteine.)

In-vitro research compared the antioxidants **glutathione**, **N-acetylcysteine**, the iron chelator deferoxamine, *Ginkgo biloba* extract or the xanthine derivate torbafylline in their ability to protect renal cortical slices that were incubated with different cisplatin concentrations. All agents inhibited cisplatin lipid peroxidation; however, at a cisplatin concentration of 1.0 mg/ml, none of them prevented the decline of cisplatin-induced p-aminohippurate (PAH) uptake. The two strongest agents were deferoxamine and N-acetylcysteine. (17)

Silibinin: Research with rats shows silibinin to be of use in renal protection from cisplatin and perhaps may be useful in protecting renal function from other damaging factors. Infusion of silibinin given prior to cisplatin resulted in significant decrease in glomerular and tubular toxicity. (20)

In vitro research showed mesangial cell protection with use of silibinin. (20.25)

Research shows cisplatin damage to glomerular and tubular renal function can be totally or partly ameliorated by IV silibinin given to rats, one hour prior to cisplatin administration. (21)

Ginkgo biloba prevents or decreases cisplatin injury to the kidney without effecting the antitumor activity of cisplatin. (16)

The Ayurvedic herbal formula called Cystone, protects against cisplatin-induced nephrotoxicity without interfering with its antitumor activity. (81) Cystone is made up of:
Shilapushpa (*Didymocarpus pedicellata*) 130 mg

Pasanabheda (<i>Saxifraga ligulata</i> Syn. <i>Bergenia ligulata / ciliata</i>)	98 mg
Manjishtha (<i>Rubia cordifolia</i>)	32 mg
Nagarmusta (<i>Cyperus scariosus</i>)	32 mg
Apamarga (<i>Achyranthes aspera</i>)	32 mg
Gojiha (<i>Onosma bracteatum</i>)	32 mg
Sahadevi (<i>Vernonia cinerea</i>)	32 mg
Shilajeet (Purified (Mineral Pitch))	26 mg
Hajrul yahood bhasma (Lime silicate calcx)	32 mg

Cystone was found to protect tumor-bearing mice from cisplatin-induced nephrotoxicity, when given i.p. 1 h before cisplatin. At 1000 mg/kg, it showed 46, 57 and 66% protection on body weight, BUN and serum creatinine levels, respectively. (81)

Another study suggests that Cystone's kidney protection may be mediated through its ability to inhibit lipid peroxidation. Cystone was given intraperitoneally 1 h before cisplatin. At 500 and 1000 microg/ml, it inhibited lipid peroxidation induced by cisplatin in renal cortical slices by 62.7 and 71.6%, respectively. Renal functions like urine to serum creatinine ratio and creatinine clearance showed significant improvement, as did BUN, while the rats also lost less weight than the rats given cisplatin alone. However, cystone did not protect against the increased excretion of urinary protein and decreased WBC count caused by cisplatin. (82)

Capsaicin: Research with rats shows capsaicin (from Capsicum) has a protective effect against cisplatin-induced nephrotoxicity and lipid peroxidation in rats. (70)

Selenium: Selenium is used as an agent for reducing the nephrotoxicity and bone marrow suppression induced by cisplatin. 4000 micrograms per day of Se as Seleno-Kap-pacarrageenan were administered from 4 days before to 4 days after chemotherapy. The cisplatin dosage was iv administration in 60-80 mg/m² on the first day. Selenium reduced the nephrotoxicity and bone marrow suppression induced by cisplatin. (69)

Selenium, administered intravenously or intraperitoneally, has been shown to provide protection against cisplatin-induced nephrotoxicity in rats. Oral Selenium given to rats treated with cisplatin shows protective effect on the kidneys. When sodium selenite was given prior to CP, rats showed less GFR decline, delayed urinary volume increases, and no urinary NAG isoenzyme B activity increment. It is suggested that a single oral dose of sodium selenite given prior to CP administration, although not preventing deterioration of renal function, partially protects rats from early proximal tubular injury. (67)

The effects of the sodium selenite administration by gavage of 2 mg per kg of body wt. 24 h and 1 h prior to a

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Herbs and Food Supplements Used to Support Kidney Function

Name of product: *Ginkgo*

Form used in research: Ginkgolide B mostly

Amount used by practitioners:

40mg-60mg 24% *Ginkgo* - start patient on 1 capsule BID. If no headaches occur, can increase to 2 capsules BID-TID. Decrease if there is a problem with headaches or hemorrhage (especially need to watch bleeding time if using hemodialysis.)

Ginkgo liquid extract 1:1 strength fresh herb - Start patient on 1/2 teaspoon BID. If no headaches occur, can increase to 1 teaspoon BID-TID. Decrease if there is a problem with headaches or hemorrhage (especially need to watch bleeding time if using hemodialysis.)

Use as much *Ginkgo* as you can without causing side effects. If you get side effects, back off.

Actions:

- PAF receptor antagonist(16): *Ginkgo* inhibits 1)PAF-induced formation of reactive oxygen species by mesangial cells, 2)PAF-induced decreases in renal blood flow, 3) PAF induced decreases in GFR and urinary sodium excretion. (10)
- A mixture of ginkgolides A, B, and C with a molar ratio 2:2:1. called BN5206 reduced cyclosporin-induced nephrotoxicity. (7) It has been shown the *Ginkgo* decreases cyclosporin toxicity without affecting cyclosporin's immuno-suppressive effects. (7) Other invitro studies confirm that *Ginkgo* protects the kidney from cyclosporin damage. (56,57)
- *Ginkgo* inhibits glomerular destruction. (16)
- *Ginkgo* inhibits tubular and interstitial damage due to cyclosporin use without altering immuno-suppressive effects.(7)
- *Ginkgo* reduces proteinuria. (16)
- *Ginkgo* reduces histopathological lesions in nephrotoxic rabbits. (8)
- *Ginkgo* abolishes the adriamycin-induced lethality and proteinuria in rats and produces significant reversal of the glomerular alterations induced by the drug. (16)
- *Ginkgo* prevents acute rat renal failure induced by glycerol injection. (16)p
- *Ginkgo* is shown to increase the chance of graft survival and decrease the number of acute rejection episodes after surgery. (16)
- *Ginkgo* prevents or decreases cisplatin injury to the kidney without effecting the antitumor activity of cisplatin. (16)

Name of product: Fish oil & other Oils

Forms and amount used in research:

- 6 grams 30% C20:5 omega-3 (EPA) and 20% C22:6 omega-3 per day.
- 12 grams per day of 300 mg EPA and 200 mg DHA and 1 IU vitamin E capsule, per day.

Amount used by practitioners: 6 grams per day - Hard to get patient to take these large quantities because they experience bad breath and unpleasant tasting eructations. Additionally, the extra calories are a concern.

- One practitioner finds using 1000 - 1200 mg per day for 7 to 14 days initially can be followed thereafter with only 600 mg per day to decrease inflammation when used in conjunction with a full treatment plan of diet, herbs, protomorphogens and homeopathy.

Actions:

- Renal protection in patients taking cyclosporin: increase of GFR, decreased serum creatinine levels and serum urea, effective renal plasma flow rose, lowering of blood pressure, and maintenance of renal vascular resistance in patients given fish oil. (9, 11)
- Omega-3 fatty acids inhibit thromboxane A2 production. TA2 is implicated in inflammatory conditions of the kidneys.
- Dietary high alpha-linolenate perilla oil suppresses PAF production in rat kidney during systemic endotoxemia. (101)
- alpha-linolenic acid (omega - 3)-rich perilla oil diet inhibits kidney tumors as compared to linoleic acid (omega - 6)-rich safflower or soybean oil diet. (102)

- There was renal injury observed in rat groups fed safflower oil with a high n-6/n-3 ratio and rapeseed oil with presumed minor components that was accompanied by increased expression of the TGF-beta, renin and fibronectin genes. (100)
- DHA suppresses renal injury and gene expression as compared with soybean oil. (100)
- One study showed rats fed rapeseed oil- and safflower oil-supplemented diets developed more severe proteinuria than those fed soybean oil-supplemented diet used as a control, but there were no significant differences in blood pressure. In contrast, a DHA-supplemented diet inhibited the development of proteinuria and suppressed hypertension. (100)

Name of product: *Salvia miltiorrhiza*

Form used in research: tea, magnesium lithospermate B (a tetramer of caffeic acid), salvianolic acid A and B, rosmarinic acid

Amount used by practitioners:

Tea - used as an ingredient in multi-herb Chinese herbal teas.

Research suggests tea as the most active form although tincture appears to be useful. Not enough data yet.

Tincture - 1 teaspoon BID.

Actions:

- *Salvia* reduces accumulation of methylguanidine and guanidinosuccinic acid levels in uremia (oxidation products which accumulate in uremic situations). (8)
- A constituent, magnesium lithospermate B has been shown to decrease blood urea nitrogen, serum creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphate in uremic rats whose uremic state had been induced by an adenine diet. (5)
- Magnesium lithospermate B activates the kallikrein-kinin system in the rat kidney to promote the production and secretion of prostaglandin E2, inducing dilation of the renal vascular system, increase in renal blood flow and glomerular filtration rate. PGE2 also inhibits proliferation of mesangial cells (in glomeruli) and acts antagonistically against vasoconstriction brought about from Thromboxane A2. (5)
- Magnesium lithospermate B may help prevent the development of hypertension through excretion of urinary sodium and by improving renal hemodynamics. (5)
- Three components of *Salvia*, salvianolic acid A, B and rosmarinic acid were found to have antioxidant activity. (123)

Name of product: *Panax ginseng*

Form used in research: Crude herb

Amount used by practitioners: Generally used in Chinese teas in conjunction with other herbs.

Actions:

- Suppresses uremic toxins such as creatinine, methylguanidine, and guanidinosuccinic acid (GSA), decreased urinary excretion of protein and inhibited mesangial proliferation, showing the arrest of progressive renal disorder from subtotal nephrectomy. (2,3)
- Using cultured mesangial cells, there was considerable suppression of mesangial cell proliferation. (2,3)
- Ginseng saponin protects the kidney from oxidative stress. Ginseng's action as a free radical scavenger is important since free radical production is implicated in progressive kidney disorders. (2,3)

Name of product: *Rheum officinalis*

Form used in research: Crude herb or tea

Amount used by practitioners: Generally as part of a Chinese tea.

Actions:

- Increases glomerular filtration, and decreases cholesterol and triglyceride levels. Rheum may relieve diabetic nephropathy by improving lipid metabolism. (1)
- Aqueous extract (tea) has shown lowered blood glucose levels. This may be another reason it has been useful in diabetic nephropathy. (1)
- Aqueous extract increases urinary excretion of urea nitrogen and creatinine, probably due to increased glomerular filtration. (1)
- Improved uremic indices in a clinical trial where it proved much more effective in preventing chronic renal failure (CRF) progression than an ACE inhibitor and together they worked synergistically to prevent CRF. (18)
- Has been found in a clinical trial to lower cholesterol and triglyceride levels in patients with chronic kidney failure. This may help in preventing the development of glomerulosclerosis. (18)

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Name of product: Modified Wen - Pi -Tang a Chinese herbal extract

Form used in research: freeze dried hot water extract(tea):

Amount used by practitioners: *Rheum officinale*-12 grams, *Panax ginseng*-15 grams, *Peonia lactiflora*-15 grams, *Angelica acutiloba*-15 grams, *Polygonum multiflorum*-15 grams, *Pinellia ternata*-10 grams , *Coptis japonica*-8 grams, *Evodia rutecarpa*-2 grams

Actions:

In research with rats, decreased serum urea nitrogen by 26% at 50 mg/kg and 40% at 200 mg/kg compared with controls. The serum creatinine was decreased by 34% at 200 mg/kg. (2)

Name of product: *Cervi cornu vernum*

Form used in research: Alcohol insoluble fraction of an aqueous extract.

Amount used by practitioners: Crude antler

Actions:

- Reduces anemia and reduces the uremic state. (4)
- In rats with adenine-induced renal anemia, the alcohol insoluble fraction of an aqueous extract of *Cervi Cornu Vernum* lowered uremic toxins, such as urea nitrogen, creatinine, and GSA and raised RBC, HB and Ht levels. (4)
- The antler extract contained a high amount of complex polysaccharides including chondroitin sulphate-like glucosaminoglycans. (4)

Name of product: *Vaccinium myrtillus*

Amount used by practitioners:

- 250 mg of 25% anthocyanidin extract BID
- Consume berries liberally
- Liquid extract 1:1 strength - 1/2 teaspoon BID

Actions:

- *Vaccinium* is used to treat bruising from uremic bruising or prednisone-induced bruising.
- *Vaccinium* strengthens capillary walls and reduces capillary leakage by supporting crosslinkage of collagen and inhibiting collagenase and elastase. It also inhibits platelet aggregation and acts as an antioxidant.
- Also consider the herbs *Crataegus*, *Centella*, and *Calendula*.

Name of product: *Taraxacum officinalis*

Amount used by practitioners: Liquid extract of leaf - 1/2 teaspoon BID-TID

Actions: diuretic.

Name of product: *Capsicum spp.*

Form used in research: Capsaicin

Amount used by practitioners: Can use capsaicin, whole *Capsicum* or oleoresin creams or ointments. Needs to be applied externally 3-4 times per day minimum for dialysis induced itching.

Actions:

- *Capsicum* is effective for dialysis-induced itching.
- Chronic treatment given in small frequent doses for a cumulative action that causes an anti-inflammatory response. Capsaicin, a constituent in Cayenne, causes release of substance P from sensory neurons (substance P sends messages of pain to the nervous system) and depletes it on repeated treatment. This diminishes the sensation of pain. It also appears to reduce the itching sensation. Topical use of Capsaicin or whole *Capsicum* can initially cause burning, stinging and redness before it depletes substance P. These reactions usually disappear with repeated application after about 72 hours. It needs to be applied 2-3 times per day for effect, since fewer applications will not continue deplete substance P.

Forms and amount used in animal research internally:

- Capsaisin has a protective effect against cisplatin-induced nephrotoxicity and lipid peroxidation in rats when used at 10mg/kg/d. (70)

Name of product: Silibinin from *Silybum marianum*

Form used in research: Silibinin

Amount used by practitioners: - Not used yet but could try 1 tablespoon powdered crude herb in AM and PM or 1/2-1 teaspoon 1:3 tincture 2-3 times per day. Also available in standardized silymarin (silibinin is part of silymarin) forms.

Actions: Protects the kidney from both glomerular damage and tubular damage from cisplatin without compromising cisplatin. (20, 20.25, 21).

Name of product: *Quercetin - flavonoid*

Amount used by practitioners: - not yet used, research available on rats. Use water soluble form as other forms such as quercetin dihydrate are poorly absorbed and need to be taken in large amounts. In fruits and vegetables, quercetin is bound to sugars that make it absorbable. 500 mg 3-4 times per day is used for other serious conditions.

Amount used in research:

- oral administration of 2-30 mg/kg in rats (136mg - 2000 mg/day in a 150# human) used in studies were protective to the rat kidneys in the research.. Doses of 100 mg/kg (6800mg/day in humans) had a deleterious effect on the kidney (28)
- oral administration of 10 mg/kg per day was given orally to rats (29)

Actions:

- quercetin reduces cisplatin toxicity in cultured tubular epithelial cells. (27)
- quercetin protects the kidney against damage inflicted by reactive oxygen species(28, 28.5)
- quercetin shown to be protective in the face of oxidative damage to the kidneys of rats(29)
- quercetin pretreatment shown to reduce the kidney damage from ischemia-reperfusion injury and its inflammatory sequelae. Pretreatment with quercetin resulted in preservation of histological integrity, with a decrease in tubular damage and interstitial inflammation. (40)

Name of product: *Carnitine*

Amount used by practitioners:

- According to the National Kidney Foundation consensus conference panel, the recommended dose of intravenous L-carnitine is 20 mg/kg total body weight, administered following the end of dialysis.
- A suggested aoral dose of cetyl-L-carnitine dosage is 500-1000 mg twice daily.

Robert Crayhon, a carnitine expert, suggests avoiding carnitine supplements after 3 p.m. to preserve a restful night's sleep. Because increased energy production, a hallmark of carnitine, fosters a greater generation of free radicals, carnitine should always be used with an antioxidant program.

Actions and form/amounts used:

- A National Kidney Foundation panel in 2002 decided L-carnitine is appropriate for 1) unresponsive anemia, 2) Intradialytic hypotension, 3) cardiomyopathy, 4) muscle weakness. The panel recommended a IV dose of 20 mg/kg total body weight, administered following the end of dialysis. They gave no oral recommendation due to their lack of experience with oral administration. (121)
- 1 g was injected postdialysis intravenously via venous route of the dialytic set, three times a week. Reduced the total necessary weekly maintenance dose of rHuEPO by 20% in dialysis patients.(23)
- Treatment with 500 mg/day carnitine taken orally for 2 months reduced serum levels of TG and VLDL, and increased HDL, and albumin in HD patients in this study. (22)
- MHD patients received intravenous injections of L-carnitine 20 mg/kg three times weekly at the end of each hemodialysis treatment for 6 months. The carnitine-treated group showed a statistically significant decrease in serum C-reactive protein and increase in serum albumin and transferrin, blood hemoglobin, and body mass index. (24)
- Patients on hemodialysis taking carnitine have a reduction in muscle cramps as well as intradialytic hypotension. This has been reported since the early 1980's.
- Administration of L-carnitine to chronic hemodialysis patients is associated with lower hospital

utilization.(72)

Name of product: *Perilla frutescens*

Actions and form/amounts used: Tea and rosmarinic acid (see rosmarinic acid information below)

- Fresh leaves boiled in water for one hour (weight:1:20) and the decoction frozen until administration. 50 mg/kg in a low dose group, another group was given a high dose Perilla decoction at 500 mg/kg (30)
 - Perilla suppressed proteinuria (30)
 - Perilla decreased mesangial cell proliferation in HIGA mice (30)
 - Significantly suppressed mesangial IgA deposition in HIGA mice (30)
 - Significantly suppressed serum IgA levels in HIGA mice (30)
 - Stronger as a whole decocted herb than when compared to it's constituent rosmarinic acid
 - A perilla decoction suppressed the proliferation of mesangial cells in vivo at doses of 100 and 500 mg/kg/d in rats, This was due to an inhibition of the glomerular infiltration of macrophage/monocytes and of the production of circulating growth factors. (103)
 - Shown to suppress proteinuria, decrease mesangial cell proliferation in HIGA mice and significantly suppressed mesangial IgA deposition in HIGA mice, as well as significantly suppress serum IgA levels in HIGA mice (30)
- These actions in (30) were dose dependant.

Name of product: *Rosmarinic acid*

Forms and amount used in research:

- 50 mg/kg in HIGA mice (30)

Actions:

- Suppressed proteinuria (30)
- Decreased mesangial cell proliferation in HIGA mice (30)
- Significantly suppressed mesangial IgA deposition in HIGA mice (30)
- Significantly suppressed serum IgA levels in HIGA mice (30)
- Inhibits cultured mesangial cell proliferation induced by platelet -derived growth factor. (30.5)

Name of product: *Lipoic Acid*

Amount used by practitioners:

- Research data on animals is all that is available at this time
- German practitioners have used 600-1800 mg per day to improve diabetic conditions. Side effects include rare reports of a skin rash, hypoglycemia, and, if chronically used, interference with the actions of biotin. (If the daily dose of alpha-lipoic acid exceeds 100 mg, co-supplement with biotin.) Individuals deficient in vitamins B1 (such as alcohol abusers) and vitamin B12 should emphasize the B vitamins when supplementing with lipoic acid. Additionally alpha-lipoic acid frequently changes insulin requirements. Higher doses of alpha lipoic acid should be administered under the observation of a qualified practitioner.

Forms and amount used in research:

- There is a lot of research but at this point it is all on animals. See below:

Actions and form/amounts used in animals:

- 30 mg/kg body wt per day orally in rats. Lipoic acid prevented or ameliorated all of the following changes that occurred in diabetic rats: increased urinary excretion of albumin and transforming growth factor, renal insufficiency, glomerular mesangial matrix expansion, and glomerulosclerosis in association with depletion of glutathione and accumulation of malondialdehyde in renal cortex. (35)
- Significant attenuation ($P < 0.01$) of renal deterioration occurred in ARF rats (occlusion of renal artery) treated with 100 mg/kg LA given by intraperitoneal injection. Administration of LA to rats prior to development of ischaemic ARF prevents renal dysfunction and tissue injury, possibly through the suppression of overproduction of ET-1 in the postischaemic kidney. (36)
- Lipoic acid (25 mg, 50 mg and 100 mg/kg, intraperitoneally) were given as a pretreatment to different groups of rats who were then given 16 mg/kg of cisplatin intraperitoneally. There was a dose dependent protective reaction from the Lipoic acid. (37)
- The body makes only small amounts of alpha-lipoic acid; in fact, just enough to avoid deficiency states. By and large, foods that contain mitochondria (such as red meats and organ meats) are regarded as good sources of lipoic acid. Other sources are spinach, potatoes, brewer's yeast, and wheat germ. For most individuals, supplementation appears the most reliable approach to provide therapeutic levels of lipoic acid.
- Supplementation is often taken with a full spectrum antioxidant and for many conditions around 250-500 mg

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a day appear adequate. The optimum dose for renal protection in humans is unknown, and will change if used preventatively or for treatment. To get the dosage in the above oral research on rats, a 150 pound person would need to ingest 2000mg per day. This is similar to the larger amounts ingested by diabetics. For the last 30 years.

Name of product: Curcumin

Amount used by practitioners:

- Research data on animals is all that is available at this time

Forms and amount used in research:

- There is a lot of research but at this point it is all on animals. See below:

Actions and form/amounts used in animals:

- rats given both ADR and curcumin were given 200 mg kg⁻¹ body weight of curcumin in 1% gum acacia orally for 7 days prior to a single ADR inject of of 7.5 mg kg⁻¹ body weight, dissolved in 0.1 ml saline through the tail vein. Treatment with curcumin significantly protected against proteinuria, albuminuria, hypoalbuminaemia and hyperlipidaemia. Curcumin inhibited the increase in urinary excretion of N-acetyl-beta-D-glucosaminidase (a marker of kidney tubular injury), fibronectin and glycosaminoglycan and blood cholesterol. The data also demonstrated that curcumin protected against kidney injury by suppressing free radicals and increasing kidney glutathione content and glutathione peroxidase activity (endogenous antioxidants). Curcumin also eliminated kidney microsomal and mitochondrial lipid peroxidation. (39)
- curcumin pretreatment has been shown to reduce the kidney damage from ischemia-reperfusion injury and its inflammatory sequelae. Pretreatment with curcumin resulted in preservation of histological integrity, with a decrease in tubular damage and interstitial inflammation. (40)
- The antioxidant effects of curcumin (0.5 grams/100grams) and its derivative tetrahydrocurcumin (0.5 grams/100grams) against iron chelate, ferric nitrilotriacetate (5 mg/kg body intraperitoneally) were both found to be protective with tetrahydrocurcumin being a more promising chemopreventive agent against renal cancer. (41)

Name of product: *Chard -Beta vulgaris L. var. cicla*

Forms and amount used in research:

- An aqueous chard extract from dried chard leaves (100 grams) was extracted with 1000 ml distilled water and boiled for 30 minutes. It was filtered and evaporated to dryness and redissolved in distilled water and administered at 2 grams/kg/day (43)

Actions:

- Protection of rat Kidneys from diabetes induced by streptozotocin which was observed by normalization of serum creatinine and almost normal serum urea while kidney tissue itself had normal parameters 42 days post streptozotocin.(43)

Name of product: *Coptis chinensis*

Forms and amount used in research:

- rhizomes were powdered and extracted with distilled water at 100 degrees C for 1 hr in a 1:10 dilution of rhizome:water . The filtrate was concentrated in vacuo and lyophilized to yield a residue. The yield of the extract was 19.7% by weight of the original material and was composed of 20.8% berberine, 6.1% coptisine and 5.2% palmatine. and a dose of 62.5mg or 125mg/kg body wt./day was given to rats 10 days or 30 days prior to renal ischemia-reperfusion being induced. (44)

Actions:

- serum malondialdehyde level was lower, while the glutathione/ glutathione disulfide ratio and the activities of the antioxidation enzymes, superoxide dismutase and catalase, were higher in ischemia-reperfusion damaged rats given Coptis than controls. (44)
- renal DNA of rats given Coptidis Rhizoma extract orally showed a significantly lower DNA fragmentation rate, which was dose-dependent, implying that the extract afforded the kidneys protection against oxidative stress-mediated apoptosis during the process and ameliorated renal function impairment. (44)

Name of product: N-acetylcysteine

Amount used by practitioners:

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- Research data on animals is all that is available at this time
- For DM a suggested NAC dosage is 600 mg a day on an empty stomach for optimal absorption.
- 1200 mg orally for prevention of radiocontrast media nephropathy, twice daily plus hydration before and after the procedure (105)
- Note: When taking NAC, it is recommended that two to three times as much vitamin C be taken conjunctively because of the prolonged presence of the oxidized form of L-cysteine.

Actions and form/amounts used in animals:

- Unilateral nephrectomized rats were subjected to 45 minutes of renal pedicle occlusion followed by 1 hour of reperfusion. 150 mg NAC/kg was injected s.c. on two occasions, 15 min before ischemia and immediately before the reperfusion period. I/R induced nephrotoxicity, as evidenced by increases in BUN and creatinine in rats, was reversed by NAC. The decrease in GSH and increases in MDA, MPO and PO induced by I/R indicated that renal injury involves free radical formation. NAC reversed these oxidant responses, and protected rat renal proximal tubules from in vitro simulated reperfusion injury. (45)
- NAC and vitamin E, are effective against ADR-induced peroxidative damage in rat kidney. Treatment with NAC and vitamin E (50 mg/kg b.w., i.p.) 1 day prior to ADR administration maintained near normal activities of the enzymes, significantly reduced lipid peroxidation and prevented the necrosis caused by ADR, thereby proving to be an effective thiol replenishing agent and antioxidant. (47)
- In-vitro research compared the antioxidants glutathione, N-acetylcysteine, the iron chelator deferoxamine, *Ginkgo biloba* extract or the xanthine derivative torbafylline in their ability to protect renal cortical slices that were incubated with different cisplatin concentrations. All agents inhibited cisplatin lipid peroxidation; however, at a cisplatin concentration of 1.0 mg/ml, none of them prevented the decline of cisplatin-induced p-aminohippurate (PAH) uptake. The two strongest agents were deferoxamine and N-acetylcysteine. (17)

Name of product: Selenium

Amount used by practitioners:

- 4000 micrograms per day of Se as Seleno-Kappacarrageenan were administered from 4 days before to 4 days after chemotherapy. The cisplatin dosage was iv administration in 60-80 mg/m² on the first day. Selenium reduced the nephrotoxicity and bone marrow suppression induced by cisplatin. (69)

Name of product: Vitamin E

Amount used by practitioners:

- 800-1600 IUs

Forms and amount used in research:

- Vitamin E reduced coronary vascular disease in chronic hemodialysis patients. (92)
- The addition of vitamin E to established cyclosporine therapy allows for a decrease in the amount of cyclosporine. Combining vitamin E and cyclosporine requires medical supervision to avoid cyclosporine toxicity. (52)

Name of product: CoQ10

Amount used by practitioners:

- CoQ10 dosage is 100-300 mg/day. Use higher doses up to 600mg if there is neurological or cardiac impairment. Needs to be in oil to be absorbed properly. Purchase in oil or put powder in oil and rub into gums. (increased absorption in gums and will decrease periodontal dz.)

Forms and amount used in research:

- Treatment with **coenzyme Q10** improves renal function in patients with chronic renal failure and decreases the need for dialysis in patients on chronic dialysis. Coenzyme Q10 has shown a significant reduction in serum creatinine, blood urea and a significant increase in creatinine clearance and urine output in a 4-week trial period. Additionally in this same study, the subjects on dialysis had significant decreases when given coenzyme Q10. (33)
- CoQ10 is protective of the new kidney in renal transplant recipients. It works as an antioxidant without any alterations of serum concentration of creatinine and cyclosporine A. (33.4)

Name of product: Cystone

Cystone is a polyherbal ayurvedic preparation, used to prevent the nephrotoxicity and antitumor activity of cisplatin in

rats.

Forms and amount used in research:

- Given i.p. 1 h before cisplatin. At 1000 mg/kg, it showed 46, 57 and 66% protection on body weight, BUN and serum creatinine levels, respectively.
- Treatment of cisplatin alone to tumor bearing mice resulted in significant antitumor activity as measured by tumor appearance, tumor volume and tumor weight. Pre-treatment with cystone (1000 mg/kg) did not reduce the antitumor activity of cisplatin. These results suggested that cystone protects against cisplatin-induced nephrotoxicity without interfering with its antitumor activity. The present study has many clinical implications in cisplatin chemotherapy.(81)
- Cystone was found to protect rats partially but significantly against cisplatin-induced renal toxicity, when given intraperitoneally 1 h before cisplatin. At 500 and 1000 microg/ml, it also inhibited lipid peroxidation induced by cisplatin in renal cortical slices Renal functions like urine to serum creatinine ratio and creatinine clearance showed significant improvement when cystone was given 1 h before cisplatin. However, cystone did not protect increased excretion of urinary protein and decreased WBC count caused by cisplatin. The present study suggests that the cystone protects kidney against cisplatin-induced toxicity and the protection may be mediated through its ability to inhibit lipid peroxidation. (82)

Name of product: Cordyceps sinensis

Actions and form/amounts used in research:

- It is a parasitic fungus that has been used in Chinese medicine for nephritis for a long time.
- Cordyceps sinensis (CS) has a protective effect on aminoglycoside (AG) induced nephrotoxicity. It ameliorates renal tubular injury as evidenced by less prominent increment of BUN, SCr, sodium excretion, urinary n-acetyl-beta-d-glucosaminidase (NAGase) and less severity of histopathological changes as compared with control. In addition, the use of CS could promote an earlier recovery of renal oxygen consumption insulin clearance, and sodium absorption in isolated perfused kidney from CS treated intoxicated rat than that from control. Researchers think the possible mechanisms of CS on drug-induced nephrotoxicity include: (1) Accelerating the regeneration of tubular cells; (2) Protecting the sodium pump activity of tubular cells; (3) Attenuating the tubular cell lysosome hyperfunction stimulated by phagocytosis of AG as well as decreasing the tubular cell lipoperoxidation in response to toxic injury; (4) Reducing the tissue Ca⁺⁺ content. (2.7)
- May be helpful in treating IGA nephropathy. In vitro and rat research give the indication that this fungus could be useful in treatment of IGA nephropathy. (2.9) Other research that backs this up is research showing this herb is useful in management of autoimmune disorders. (2.4)
- Tang Bailing capsule, (a dry powder preparation of Cordyceps sinensis mycelia) was shown to protect to be useful in the place of asathioprine after renal transplantation It effectively prevents the rejection response after renal transplantation, protects renal and liver function, stimulates hemopoietic function, improves hypoproteinemia and hyperlipidemia, reduces infection. The researchers thought it was an ideal immunosuppressor after organ transplantation. (2.6)
- Cordyceps sinensis (CS) has a protective effect from cyclosporine A nephro-toxicity (CsA-Nx) Both acute and chronic experiments showed that CS could protect the kidney from CsA-Nx and ameliorate the glomerular and interstitial injuries. (2.8)

Name of product: Carnosine (an amino acid peptide)

Amount used by practitioners:

- A suggested carnosine dosage is 1000 mg/day.

Forms and amount used in research:

- has demonstrated in several studies to be a safe and effective antiglycating agent. Because carnosine structurally resembles the sites that glycating agents attack, it appears to sacrifice itself to spare the target (88). Carnosine also bolsters proteolytic pathways, a function that enhances the disposal of damaged and potentially destructive proteins.

Name of product: WH30+, a Chinese herbal preparation

Forms and amount used in research:

- Composed of Rheum Palmatum, Salvia Miltiorrhiza, Cordyceps Sinensis, Leonurus Sibiricus, Epihedium Macranthum, Radix Astragali, and Radix Codonopsis Pilosulae, is used to treat kidney deficiency in humans.
- Treatment with WH30+ improved both serum creatinine and urea nitrogen in rats. The rats with acute renal failure had significantly greater creatinine clearance than those without treatment. The results of the study show that WH30+ is more effective in the prevention of acute renal failure than chronic renal failure. (2.5)

Name of product: Urtica spp. seed

Amount used by practitioners:

- 2 -5 ml (about 1/2 - 1 teaspoon) three times per day of a 1:5 hydroethanolic extract (tincture/liquid extract)

Forms and amount used in research:

2-5 ml (about 1/2 - 1 teaspoon) three times per day of a **1:5 hydroethanolic extract (tincture/liquid extract)**

Actions and form/amounts used in research:

- Significant decrease in creatinine levels in two patients. (125)

Feedback from Practitioners

For all autoimmune related kidney disease, David Winston gets good results with Cordyceps as a tincture, tea or pill. In addition he uses Rhubarb Root (very small doses), Salvia miltiorrhiza and unprocessed Rehmannia, along with Nettle seed. as well as immune amphoteric (Ganoderma, Grifola, Panax, Withania, Tinospora, etc).

In general he uses Nettle Seed Tincture, as a simple tincture of the mature seed in doses of 1-2 ml TID. He also uses Rheum, Salvia and unprocessed Rehmania.

Chanchal Cabrera has had "Stunning results" in 3 cases of incipient renal failure with tinctures of Althea off. radix, Plantago lanceolata, Equisetum arvense, Parietaria diffusa, Aphanes / alchemilla arvensis 1:3 or 1 : 4 tinctures dosed at 10 mL qid and also supplemented with general kidney tonic teas - names not given

Dr. Tom Kruzel has found Salvia miltiorrhiza, fish oil 1000 - 1200 mg per day for 7 days, then 600 mg per day for inflammation. He also uses renal protomorphogens, homeopathy, constitutional hydrotherapy, food allergens (ABO blood type diet and knowing their secretor status), CoQ10, vitamin C to bowel tolerance, Vitamin E 800-1600 IU's, Siberian ginseng rather than Panax as he has had rises on liver enzymes using it over long periods.

My personal opinion**For prevention or treatment of toxins from drugs, environmental etc.**

Silybum marianum, Ginkgo biloba, CoQ10, Cordyceps sinensis, Urtica spp. seed, Selenium, Vitamin C.

For general kidney support in renal failure

No food allergens, CoQ10, Cordyceps sinensis, Urtica spp. seed, Vitamin C, Vitamin E, Salvia miltiorrhiza, fish oil or perilla oil, Rheum palmatum, flax meal for part of protein consumption and renal support.

Autoimmune related disease:

See David Winstons suggestions above

Dialysis

Same items as in general kidney support plus carnitine, but be careful of vitamin C - may cause oxaluria - see data in dialysis section to decide on dosage.

Pretransplant Care

General surgery prep as well as specifics for preventing renal ischemia-reperfusion injury:

Lipoic acid, N-acetylcysteine, Ginkgo 24% - not enough to increase clotting time to much (use dialysis as indication)

Transplant Care

Ginkgo biloba, CoQ10, Cordyceps sinensis, Rheum palmatum, Urtica spp. seed, Silybum marianum, Salvia miltiorrhiza, fish or perilla oil, magnesium may need to be supplemented.

Vitamin C Here

)and ascorbic acid (3 gram at least 2 hour before the procedure and 2 gram in the night and the morning after the procedure as well as hydration) as well as the use of fenoldopam.

single CP intraperitoneal injection of 5 mg per kg of body wt. followed by its daily administration for the 7 subsequent days on these parameters, were examined. It was found to decrease the effect of cisplatin on serum creatinine, and renal malondialdehyde levels, as well as kidney necrosis but did not affect the other parameters such as renal glutathione, and decreased creatinine clearance. (68)

Selenium based amino acid conjugates have shown to be protective against cisplatin renal toxicity with Se-Methyl-L-selenocysteine providing the strongest protection. The precise molecular mechanism by which selenols, generated by beta-lyase, provide protection against cisplatin-induced cytotoxicity, however, remains to be established. (66)

Adriamycin: Adriamycin (ADR), a cytotoxic antineoplastic drug, is used in the treatment of various solid tumors. However it has significant toxicities including nephrotoxicity and is associated with nephrotic syndrome. It is characterized by heavy proteinuria, albuminuria, hypoalbuminemia and hyperlipidemia. Reactive oxygen species have been suspect in the development of this nephrosis.

Curcumin: Curcumin from *Curcuma longa* was shown to be a potent inhibitor of adriamycin nephrosis. In research curcumin (200 mg kg⁻¹ body weight of curcumin in 1% gum acacia orally for 7 days prior to a single ADR injection of 7.5 mg kg⁻¹ body weight, dissolved in 0.1 ml saline through the tail vein.) prevented kidney injury and restored kidney function. Treatment with curcumin significantly protected against proteinuria, albuminuria, hypoalbuminaemia and hyperlipidaemia. Curcumin inhibited the increase in urinary excretion of N-acetyl-beta-D-glucosaminidase (a marker of kidney tubular injury), fibronectin and glycosaminoglycan and blood cholesterol. The data also demonstrated that curcumin protected against kidney injury by suppressing free radicals and increasing kidney glutathione content and glutathione peroxidase activity (endogenous antioxidants). Curcumin also eliminated kidney microsomal and mitochondrial lipid peroxidation. The data suggest that administration of curcumin is a promising approach in the treatment of kidney disease. (39)

Ginkgo: Given preventively, or even curatively, BN 52021 (gingko extract) abolishes the adriamycin-induced lethality and proteinuria in rats. This protection is associated with a significant reversal of the glomerular alterations induced by the extract. BN 52021 also prevents acute rat renal failure induced by glycerol injection. (16)

Adriamycin-injected rats treated with PAF-acether antagonists had a low proteinuria, if any, and no ultrastructural glomerular alterations. **Ginkgo extract (BN 52021)** was one of the a PAF-acether antagonists. (46)

N-acetyl cysteine (NAC) and **vitamin E**, are effective against ADR-induced peroxidative damage in rat kidney. Treatment with NAC and vitamin E (50 mg/kg b.w., i.p.) 1

day prior to ADR administration maintained near normal activities of the enzymes, significantly reduced lipid peroxidation and prevented the necrosis caused by ADR, thereby proving to be an effective thiol replenishing agent and antioxidant. (47)

Other Toxicities

Coptis chinensis: Coptis rhizome extract and its alkaloids can ameliorate the in vitro cell damage associated with peroxynitrite generation in renal tubular cells. The various alkaloids have distinctive mechanisms of action, such as peroxynitrite scavenging, protection from DNA damage and control of the cell cycle. Furthermore, the data suggest that among the Coptis rhizome alkaloids, coptisine is the most effective for protection against SIN-1-induced cellular injury in terms of its potency and content. (44.5)

Curcumin: Acute renal proximal tubular necrosis has been shown to be caused by iron chelate, ferric nitrilotriacetate as consequence of free radical-mediated oxidative tissue damage that eventually leads to a high incidence of renal cell carcinoma. The antioxidant effects of **curcumin** and its derivative **tetrahydrocurcumin** against the toxin were both found to be protective with tetrahydrocurcumin being a more promising agent. (41)

Cordyceps sinensis: Cordyceps sinensis (CS) has a protective effect on aminoglycoside (AG) induced nephrotoxicity. It ameliorates renal tubular injury as evidenced by less prominent increment of BUN, SCr, sodium excretion, urinary n-acetyl-beta-d-glucosaminidase (NAGase) and less severity of histopathological changes as compared with control. In addition, the use of CS could promote an earlier recovery of renal oxygen consumption insulin clearance, and sodium absorption in isolated perfused kidney from CS treated intoxicated rat than that from control. Researchers think the possible mechanisms of CS on drug-induced nephrotoxicity include: (1) Accelerating the regeneration of tubular cells; (2) Protecting the sodium pump activity of tubular cells; (3) Attenuating the tubular cell lysosome hyperfunction stimulated by phagocytosis of AG as well as decreasing the tubular cell lipoperoxidation in response to toxic injury; (4) Reducing the tissue Ca⁺⁺ content. (2.7)

Radiocontrast Induced Nephropathy

Contrast media associated acute renal failure represents the third cause of in-hospital renal function deterioration after decreased renal perfusion and post-operative renal insufficiency. This complication has a mortality rate ranging from 3.8% to 64% depending on the increase of creatinine concentration. The mechanism of contrast induced renal failure is not fully understood. It appears to be a result of direct media contrast induced renal tubular epithelial cell toxicity and renal medullary ischemia. A main mechanism appears to be alteration in renal dynam-

ics probably caused by imbalances between vasodilatory and vasoconstrictor factors, including the activities of nitric oxide, prostaglandins, endothelin and reactive oxygen species. Primary attempts for the prevention of contrast media-induced nephropathy should include a systematic review of a patient's characteristics and risk stratification. Patients at the greatest risk for contrast media-induced nephropathy can be defined as those having preexisting impaired renal function, diabetes mellitus, and congestive heart failure. Other risk factors include; age above seventy years, female gender, dehydration and use of high volume contrast media. The more expeditious use of iso-osmolar non-ionic contrast media has reduced the incidence of contrast media related renal dysfunction. (104) Recommendations to prevent contrast-associated nephrotoxicity are periprocedural hydration, use of a low osmolality contrast and limiting the amount of contrast agent. Additionally, there is positive data on effectiveness of prophylactic administration of antioxidant compounds such as n-acetylcysteine (1200 mg orally twice daily plus hydration before and after the procedure) and ascorbic acid (3 gram at least 2 hour before the procedure and 2 gram in the night and the morning after the procedure as well as hydration) as well as the use of fenoldopam. (105)

N-acetylcysteine has actions relevant to radiocontrast-induced nephropathy (RCIN) that include vasodilatation, enhancement of renal medullary blood flow, and antioxidant properties. The supplement's pharmacokinetics are remarkable for almost complete first pass metabolism after oral administration, resulting in no free drug reaching the circulation. After intravenous administration, extensive reaction with tissue and plasma proteins greatly limits the amount of circulating free drug. Given the difficulty achieving free drug in the systemic circulation, it is highly likely that the drug works via its metabolites. The primary mechanism may be through L-cysteine as a cellular source for glutathione production. A 2004 review of clinical studies of N-acetylcysteine in the prevention of RCIN have yielded highly mixed results; five were dramatically positive, and eight others had no demonstrable efficacy at all. (99)

The Role of Dietary Oils In Renal Health

A study has noted that Omega 3 (n-3) fatty acid-rich oils, such as fish oil, perilla oil and flaxseed oil as well as ethyl docosahexaenoate (DHA - the daughter of Omega 3's) prolonged the survival time of stroke-prone spontaneously hypertensive rats (SHRSP) rats by approximately 10% as compared with linoleate (n-6)-rich safflower oil. Rapeseed oil with a relatively low n-6/n-3 ratio unusually shortened the survival time by approximately 40%, suggesting the presence of minor components unfavorable to SHRSP rats. The effects of dietary oils and DHA on renal injury and gene expression related to renal injury in SHRSP rats was examined.

There was renal injury observed in rat groups fed safflower oil with a high n-6/n-3 ratio and rapeseed oil with presumed minor components that was accompanied by increased expression of the TGF-beta, renin and fibronectin genes. It was also found that dietary DHA suppresses renal injury and gene expression as compared with soybean oil.

Rats fed rapeseed oil- and safflower oil-supplemented diets developed more severe proteinuria than those fed soybean oil-supplemented diet used as a control, but there were no significant differences in blood pressure. In contrast, the DHA-supplemented diet inhibited the development of proteinuria and suppressed hypertension. (100)

Dietary high alpha-linolenate perilla oil suppresses PAF production in rat kidney during systemic endotoxemia. (101)

Research results indicate that the alpha-linolenic acid (n-3)-rich perilla oil diet inhibits development of mammary gland, colon and kidney tumors as compared to linoleic acid (n-6)-rich safflower or soybean oil diet. (102)

See Fish oil Information also in the "Herbs and Food Supplements Section"

The Role of Protein

Protein consumption increases metabolic wastes which the kidney must remove from the body. The person needs to get the proper amount of protein to offset loss and maintain a neutral nitrogen balance. This is different for each individual.

Choosing the type of ingested protein to consume has been shown to be as beneficial if not more beneficial than restricting protein consumption.

Consumption of soybean and soy-based food products, as the source of plant protein, has been shown to retard the development and progression of chronic renal disease. Flax seed meal has also been shown to be beneficial. It reduced proteinuria and glomerular and tubulointerstitial lesions in obese SHR/N-cp rats. Flaxseed meal is more effective than soy protein in reducing proteinuria and renal histologic abnormalities in rats. The reduction in proteinuria and renal injury was independent of the amount of protein intake and glycemic control. (83)

Low casein and soy feeding ameliorates polycystic kidney disease in Han: SPRD-cy rats, reducing both tubular remodeling and interstitial inflammation and fibrosis, while flax seed diets kidney protective effect appears to be through moderation of associated interstitial nephritis. The soy diet alters the renal content of polyunsaturated fatty acids and enriched renal betaine content with retention of citric acid cycle metabolites despite increased excretion. The flax seed diet alters renal content of poly-

unsaturated fatty acids and promotes the formation of less inflammatory classes of renal prostanoides. The flax seed diet also enriched renal content of betaine and succinate. Amelioration of Hans:SPRD-cy rat polycystic kidney disease by diet is associated with alteration in the handling of citric acid cycle metabolites and betaine, and also in content of polyunsaturated fatty acids in kidneys and liver. (84) A second research article also shows flaxseed ameliorates polycystic kidney disease in rats through moderation of the associated chronic interstitial nephritis.(87)

Flax oil was also studied to see if it had beneficial effects on kidneys. Research on rats shows that indeed it is beneficial. (85) This is important as taking too much flax meal in usually necessitates the person increase their liquid also. This may not be possible if the person needs to restrict fluid such as when on dialysis.

Human research shows flaxseed may be renoprotective in lupus nephritis. (86)

Food Allergens

It is extremely important to identify food allergens and address them. This can make all the difference in the world. This is for all patients with renal failure, not just those with IGA Nephropathy. An elimination diet with reintroduction of foods or use of the, Dr. D'Adamo's "blood type diet" (see *Eat Right for Your Type* by Dr. Peter D'Adamo) can be helpful for many people looking for a way to identify food allergens. The biggest food allergens are foods with gluten (such as wheat, oats, barley) and milk as well as milk products. Cow milk seems to be more problematic than goat milk. Pasturized milk is an especially bad culprit. Additional foods that show up as allergens are corn, soy and the solanaceae family which includes plants such as tomatoes, eggplant, peppers etc. Everyone is different and although these foods are seen as allergens more often than others, it is good to work with the person on an individual basis.

Control hypertension

Hypertension is a major problem. It is a complication of renal disease as well as a causative factor. Although hypertension is a problem, sometimes a little extra pressure is all that is keeping the kidney filtering through the glomerulus.. Neither herbs nor drugs control renal induced hypertension very well. Herbal diuretics, such as *Taraxacum* leaf, can be helpful. *Zea mays* is another herb which benefits inflamed kidneys and acts as a diuretic.

There are many herbs that are beneficial in hypertension. A few of them are Cayenne (*Capsicum* spp.), Coleus (*Coleus forskoli*), Cramp bark (*Viburnum opulus*), Dong gui (*Angelica sinensis*), False hellebore (*Veratrum viride*), Garlic (*Allium sativa*), Ginger (*Zingiber officinale*), Hawthorne (*Crataegus* spp.), Linden flower (*Tilia* spp.), Mistletoe (*Viscum album*),

Motherwort (*Leonurus cardiaca*), Passionflower (*Passiflora incarnata*), Rauwolfia (*Rauwolfia serpentina*), Sage root (*Salvia miltiorrhiza*), Skullcap (*Scutellaria lateriflora*), Valerian (*Valeriana officinalis*) *Veratrum is more useful in emergencies as it* has to be given in small doses every 4 hours for best results and can also be toxic as can *Viscum* and *Rauwolfia*. Although I use herbs in renal hypertension, the results are moderate. Generally it takes a mix of drugs, herbs, diet and lifestyle for these people to get their blood pressure into acceptable ranges.

Diet is once again of prime importance in relation to allergies.

Control Angiotensin II

The body responds to decreased glomerular hydrostatic pressure and consequent decreased glomerular filtration by ultimately increasing angiotensin II. This is one of the body's ways of increasing glomerular filtration rate via increasing hydrostatic pressure. This is bad news for the person with glomerular damage as angiotensin II can further induce renal injury. Angiotensin II is associated with perivascular inflammation, cell proliferation, and increased superoxide production in the vascular wall. The antihypertensive drugs that are angiotensin-converting enzyme inhibitors (ACE inhibitors) have been shown to slow the progression of kidney disease that is due to high blood pressure or diabetes.

Lipoic acid may be able to protect against the Ang II-induced inflammatory response and end-organ damage. Research suggests it protects the kidney against Ang II-induced renal injury through anti-inflammatory / antioxidant mechanisms. (38)

Rheum improved uremic indices in a clinical trial where it proved much more effective in preventing chronic renal failure (CRF) progression than an ACE inhibitor and together they worked synergistically to prevent CRF. (18)

Control hypercholesterolemia

Hypercholesterolemia is a sign of chronic renal failure but is also thought to be a causative factor of additional kidney damage by some.

- Dietary fiber, exercise, herbs, nutritional supplements to lower cholesterol can be used if felt necessary. I find statins to be frightening and caution folks about them. If someone insists on taking statins they should at least replenish their CoQ10 which is depleted by statins. *Panax*, *Curcuma* and *Rheum* support normal kidney function while also being beneficial to lower cholesterol. *Allium* which is commonly used to lower cholesterol is indirectly beneficial to the kidneys via its cardiovascular activity. Be cautious with some herbs that may not be wise to use such as *Commiphora mukul*. This author has seen extremely high levels of cholesterol in one person who had a cardiac surgeon marvel at how the person lacked atherosclerotic plaques. Might just be that

the incredible amount of antioxidants he was taking was keeping inflammation down, which is really the culprit in starting atherosclerosis. I am more concerned about decreasing inflammation in a person's body than I am with lowering cholesterol.

Support blood vessel integrity, including glomerular capillaries & peritubular capillaries

- Uremic bruising or bruising from prednisone use can be treated with *Vaccinium myrtillus*. (See pages 8-15)
- Capillary damage is also a problem in hypertension where glomerular sclerosis takes place. In theory, herbs such as *Crataegus* can be used for both the hypertension as well as support of capillary integrity in the glomerulus. See case history #4. Other blood vessel tonics would include, Blueberry/Huckleberry (*Vaccinium* spp.), Calendula (*Calendula officinalis*), Ginger (*Zingiber officinale*), Ginkgo (*Ginkgo biloba*), Gotu kola (*Centella asiatica*), Linden flower (*Tilia* spp.)

Support diuresis

- *Taraxacum officinalis* leaf - one teaspoon BID-TID, *Zea mays* (fresh), *Allium sativa*, *Petroselinum crispum* root. *Petroselinum* was used as a diuretic in one case of renal failure without any apparent irritation of the kidneys. The other herbs appear to be safe diuretics in chronic renal failure.

Decrease work load on the kidney

- Introducing water soluble fibers to the diet such as pectins and mucilages from foods such as apples and flax may mediate acidosis by providing a hydrogen trap in the colon. It is thought that the fermentable fibers may help neutralize the acidic concentration.
- Use enemas with charcoal. Use plain hot water at 104-110 degrees Fahrenheit. Dissolve one to five tablespoons of charcoal in two quarts of water. For a retention enema use one tablespoon per one cup of lukewarm water. Use once to twice per day. (*Home Remedies* by Agatha Thrash M.D.)
- Keep the skin pores open and assist the skin in removal of metabolic wastes:
 - 1) Fever treatment of 100-101 degrees Fahrenheit for edema, to induce water loss through diaphoresis. Monitor blood pressure during this process. (*Home Remedies* by Agatha Thrash, M.D.)
 - 2) Hot mud packs. Daily packs for two weeks showed considerable amounts of uric acid excretion through the skin. Sometimes the percentage of uric acid in the sweat reached a value equal to or exceeding that in the blood (*Home Remedies* by Agatha Thrash, M.D.).

Maintain energy

Low energy can be due to anemia, toxemia or depression as well as other problems the person may be experiencing. The

anemia is due to lack of erythropoietin.

Erythropoietin is primarily made by the kidney. The kidney makes 90% of the erythropoietin while the liver makes 10% of the body's erythropoietin. When the kidneys fail, the red blood cell count falls severely.

- Erythropoietin treatment is given via injection and is expensive. You may be able to substitute *Cervi Cornu Vernum* (unossified horns of stags) for part of erythropoietin (see "Herbs and Food Supplements" for information on *Cervi cornu vernum*.)
- Iron supplementation is usually necessary.

Adaptagens can be helpful in some cases of fatigue. The person is under an incredible amount of stress and adrenal support is often helpful. There are a couple adaptagens that are also useful in kidney disease.

- *Panax ginseng*, *Centella asiatica* are both adaptogens that are safe and even beneficial for renal support.

Maintain calcium levels & 1-25 dihydroxycholecalciferol

- Muscle spasms are a painful problem for the person with chronic kidney failure. It appears to be at least partially due to low calcium levels due to the lack of 1-25 dihydroxycholecalciferol. This leads to decreased intestinal absorption of calcium and decreased renal absorption of calcium as well as decreased absorption of calcium from the bone too. Calcium and 1-25 dihydroxycholecalciferol both need to be supplemented as well as using hot water bottles for acute spasms.

Restless Legs

- Restless legs can be treated with calcium and vitamin B complex.

Immunoglobulin A nephropathy (Berg-er's)

IgA nephropathy is a form of mesangial proliferative nephritis with IgA deposition. The disorder can appear as acute, rapidly progressive, or chronic glomerulonephritis; or as visible or microscopic hematuria.

Cordyceps sinensis is a parasitic fungus that has been used in Chinese medicine for nephritis for a long time. In vitro and rat research supports use of this fungus in treatment of IGA nephropathy specifically. (2.9) Other research that backs this up is research showing this herb is useful in management of autoimmune disorders. (2.4)

Rheum palmatum may be useful in IGA nephropathy as it has been shown to improve renal function by inhibiting the production of IL-6 and lowering immune inflammatory response. (80)

Perilla frutescens has been shown to suppress proteinuria,

decrease mesangial cell proliferation in HIGA mice and significantly suppressed mesangial IgA deposition in HIGA mice, as well as significantly suppress serum IgA levels in HIGA mice (30)

It has been shown to be stronger as a whole decocted herb than when compared to its constituent rosmarinic acid which is also renal protective. A perilla decoction suppressed the proliferation of mesangial cells in vivo at doses of 100 and 500 mg/kg/day in rats. This was due to an inhibition of the glomerular infiltration of macrophage/monocytes and of the production of circulating growth factors. (103)

Control hyperglycemia, if diabetic

- Diet, exercise, nutritional supplements as appropriate in diabetes, *Allium sativa*, *Vaccinium myrtillus*, *Panax ginseng*, *Rheum officinalis*, *Silybum marianum*, *Cinnamomum* spp., *Trigonella foenum graecum* are herbs that are helpful and safe. *Vaccinium* spp., *Panax* and *Rheum* are useful in lowering the uremic index as well as useful for DM. These herbs should all be safe in use in the majority of patients with chronic kidney disease. See case history # 3.

Many of the same nutritional supplements used for renal support are also useful in DM. Some are, L-carnitine (500-1000 mg/day), alpha lipoic acid (600-1800 mg/day - see cautions), Co Q10 (100-300, 600 mg/day if cardiac or neurological problems), NAC (600mg/day), Vitamin C up to bowel tolerance, Vitamin E (400-1200 IU/day with at least 200 of gamma tocopherol). Additionally, Omega 3 fatty acids are also useful in both renal support and DM.

An interesting plant used for diabetes that is also renal protective is Chard. An aqueous chard extract from dried chard leaves (100 grams) was extracted with 1000 ml distilled water and boiled for 30 minutes. It was filtered and evaporated to dryness and redissolved in distilled water and administered at 2 grams/kg/day (43) It protected the rat Kidneys from diabetes induced kidney damage via streptozotocin. This was observed by normalization of serum creatinine and almost normal serum urea while kidney tissue itself had normal parameters 42 days post streptozotocin.(43)

Glycation, Lipoxidation, Diabetes & Renal Disease

Glycation and Lipoxidation are both problematic in uremia. Glycation is a reaction occurring between proteins, and glucose (advanced glycation end products or AGEs) while lipoxidation is a reaction between proteins and lipids (advanced lipoxidation end products or ALEs). They are recognized as a major contributors to aging as well as the complications arising from diabetes and kidney disease. More is known about AGEs than ALEs. Once AGEs are formed, they interact with neighboring proteins to produce pathological crosslinks that toughen tissues. It has been speculated that no other molecules have the potential

toxic effects on proteins and lipids as AGEs and ALEs.

Diabetic individuals form excessive amounts of AGEs earlier in life than nondiabetics, a process that disrupts the normality of organs that depend on flexibility for function. AGEs impair proteins, DNA, and lipids as well as triggering a cascade of destructive events as AGEs cling to cellular binding sites. One of the consequences of AGEs is a 50-fold increase in free-radical formation. Because diabetes increases the number of AGEs, the kidneys are under specific attack. Not only do AGEs attack the kidney, but a decrease in renal function appears to increase AGE's. It is thought that this increase may be due to activation of the renin-angiotensin system. (89)

By opposing glycation, glomerular damage and the resulting inflammation and renal degeneration are reduced.

Carnosine (an amino acid peptide) has demonstrated in several studies to be a safe and effective antiglycating agent. Because carnosine structurally resembles the sites that glycating agents attack, it appears to sacrifice itself to spare the target (88). Carnosine also bolsters proteolytic pathways, a function that enhances the disposal of damaged and potentially destructive proteins.

lipoic acid can lower lipid peroxidation and protein glycosylation. (90)

Lipoic acid is effective in rats for the prevention of early diabetic glomerular injury, proving more effective than high doses of either vitamins A or C. (34,35)

Cordyceps sinensis is thought to decrease the tubular cell lipoperoxidation in response to toxic injury (4)

Cystone, a Chinese herbal formula was found to inhibit lipid peroxidation induced by cisplatin in renal cortical slices (2.7)

Pyridoxamine (a form of B6) A study was undertaken to determine whether inhibition of formation of AGEs and ALEs is a mechanism of action common to a diverse group of therapeutic agents that limit the progress of diabetic nephropathy. The ACE inhibitor enalapril, the antioxidant vitamin E, the thiol compound lipoic acid, and the AGE/ALE inhibitor pyridoxamine on the formation of AGE/ALE were studied. All protected against nephropathy in streptozotocin diabetic rats. All interventions limited the progression of nephropathy, without affecting glycemia at the doses studied, but the maximal benefit was achieved with pyridoxamine, which also limited dyslipidaemia and AGE/ALE formation. These experiments indicate that the more effective the renoprotection, the greater the inhibition of AGE/ALE formation. The order of efficacy was: pyridoxamine (650 mg.kg(-1)/day(-1)) > vitamin E (200 mg.kg(-1)/day(-1)) > lipoic acid (93

mg.kg(-1)/day(-1), approximately enalapril (35 mg.kg(-1)/day(-1)). Pyridoxamine also significantly inhibited AGE/ALE accumulation in tissues; effects of other agents were mixed, but the degree of renoprotection was consistent with their effects on AGE/ALE formation. (98)

Homeopathy

- Homeopathy for mental, emotional support as well as to decrease the progression of the disease.

Protomorphogens

- Renatrophin and Renafood - both Standard Process examples

Counseling

- Counseling is often necessary.

Renal Cancer

Acute renal proximal tubular necrosis has been shown to be caused by iron chelate, ferric nitrilotriacetate as consequence of free radical-mediated oxidative tissue damage that eventually leads to a high incidence of renal cell carcinoma. The antioxidant effects of curcumin and its derivative tetrahydrocurcumin against iron chelate, ferric nitrilotriacetate were both found to be protective with tetrahydrocurcumin being a more promising chemopreventive agent. (41)

Research results indicate that the alpha-linolenic acid (n-3)-rich perilla oil diet inhibits development of mammary gland, colon and kidney tumors as compared to linoleic acid (n-6)-rich safflower or soybean oil diet. (102)

Supporting the Person on Dialysis

When there is complete kidney failure, the only options generally available are dialysis and a kidney transplant. In 2001, there were 287,494 US citizens undergoing dialysis. In 2005 there are over 400,000 people undergoing dialysis. There are two types of dialysis available, peritoneal and hemodialysis. Peritoneal involves an umbilical shunt into the peritoneum whereby dialysate can be filtered through the peritoneum multiple times throughout the day. This type of dialysis can be done in the convenience of your own home or at work. It does have a liability of possible peritoneal infection. Hemodialysis is undertaken in a dialysis unit where the person spends 3-4 hours, 3-4 days per week. A vein is expanded to a larger size by connection between an artery and a vein in the arm (a fistula). Over time this vein becomes very dilated and has rapid flow in it. Once this occurs, two needles can be placed into this vein and they can be connected to a hemodialysis machine. If there is not enough time to create this enlarged vein or the person is anatomically not able to do this it will then require a fake shunt or graft to be placed in the person's arm. Neither peritoneal dialysis or hemodialysis is pleasurable. In acute kidney failure, emergency dialysis is via the carotid artery.

(For dialysis patient treatment use the same regime as listed under treatment of chronic renal failure for the most part. In addition the following information is specific to the person on dialysis.)

Researchers at Johns Hopkins have found that in people with end-stage kidney disease (ESRD), choosing peritoneal dialysis over hemodialysis increases their risk of dying by 50 percent. (121)

In peritoneal dialysis, the membrane lining of the body cavity is used as a substitute filter to do the work of the kidneys. A tubelike catheter, permanently implanted into the abdominal cavity, is used to inject up to 3 liters of waste-absorbing fluid into the cavity, where it remains for anywhere from two to six hours before it needs to be drained. The process must be performed four to six times per day, or patients can use a mechanical device, called a "cycler," overnight.

In hemodialysis, a patient's vein or catheter tubing is used to pump blood outside of the body and through a machine, called a dialyzer, which filters out waste. The cleansed blood is then pumped back into the body. The treatment lasts approximately three to four hours, and needs to be performed approximately three times per week at a dialysis center or appropriate health clinic.

Currently, more than 400,000 Americans require one of the two kinds of dialysis to remove waste products and excess water from the blood because their failing kidneys have less than 15 percent of their normal function remaining. By 2030, the number of Americans needing dialysis is expected to jump to 2 million, due in part to rising rates of diabetes, the leading cause of kidney failure.

Initial results showed that during the first year of treatment, patients choosing peritoneal dialysis were doing as well as patients on hemodialysis. Death rates early in the study were 21 percent and 24 percent, respectively, which were not different enough to be significant, statistically speaking. However, the Hopkins team noted that patients starting treatment with peritoneal dialysis were healthier overall, and more of them had graduated from high school, were married, or had jobs than those on hemodialysis.

When these differences were taken into account, the researchers discovered that while healthy patients did well on either form of dialysis, hemodialysis was of greater benefit for those patients with coexisting illnesses, such as cardiovascular disease. The risk of death among 135 patients with cardiovascular disease who were using peritoneal dialysis was nearly twice that of 459 similar patients on hemodialysis. After one year of dialysis treatment, the risk of death for patients who started on peritoneal dialysis was greater than the risk of death for patients who started on hemodialysis.

Dialysis side effects

- Length of time during each dialysis session is important. Longer sessions will decrease the possibility of sudden

electrolyte changes and sudden loss of water, inducing consequent muscle spasms, headaches and a general sick feeling.

- Salt cravings are common after dialysis, especially when shorter dialysis runs are given.
- Keep phosphorus and potassium blood levels in normal range. Avoid phosphorus and potassium-containing foods and liquids (*increased potassium due to decreased GFR, use of ACE inhibitors or due to destruction of distal tubules and cortical collecting tubules*). Note that Dandelion, which is used as a diuretic by many herbalists, contains a large amount of potassium and you may think it would be cause for alarm. Mineral content is highest in capsules, lower in decocted teas, while liquid extracts contain minimal amount of minerals. Use of the liquid extract in two cases made no difference in potassium serum levels. I suggest use of the liquid extract only.

The type of dialytic systems along with the loss of antioxidant substances via dialysis may contribute to peripheral blood mononuclear cell (PBMC) activation and the production of inflammatory mediators, such as cytokines, oxygen radicals, and complement fragments, that may sustain a state of chronic microinflammation responsible for the pathogenesis of a variety of diseases. Additionally, during hemodialysis, oxidative stress may influence several intracellular signaling enzymes, potentially leading to PBMC activation and proinflammatory cytokine production. This makes dialysis patients prime candidates for antioxidant therapy. The antioxidants listed elsewhere in this lecture should be reviewed for use in dialysis.

Carnitine

Some of the adverse hemodialysis consequences are due to carnitine deficiency. Examples of these conditions include **difficult-to-treat anemia, cardiomyopathy, muscle weakness, and intradialytic hypotension**. Patients receiving dialysis are at risk for the development of dialysis-related carnitine deficiency (DCD) because of the extensive removal of carnitine (levocarnitine, L-carnitine) from the blood during dialysis with subsequent depletion of tissue carnitine stores, inadequate dietary ingestion, and reduced renal synthesis of carnitine. Plasma free carnitine can be reduced by as much as 75% in a dialysis session, due to its small molecular weight and water solubility. Coupled with inadequate dietary ingestion (meat and dairy) and reduced renal synthesis this leads to depletion of tissue carnitine stores. Some patients may have lower levels of carnitine than others. They include older patients, patients with left ventricular hypertrophy and left atrial enlargement, females and patients on aspirin therapy. (26) The National Kidney Foundation convened a consensus conference in September 2002 to address the use of L-carnitine in dialysis patients and in November 2002, the Centers for Medicare & Medicaid Services (CMS) issued a Program Memorandum containing payment instructions for intravenous levocarnitine administered to dialysis patients

Carnitine exists as free carnitine and as acylcarnitines. The sum of free and acylcarnitine is referred to as total carnitine. In healthy

individuals, approximately 98% of total carnitine is distributed in skeletal muscle, with the remainder found in the heart, liver, kidneys and blood. (113) Skeletal muscle and heart tissue are highly dependent upon fatty acid oxidation as a source of energy. With chronic kidney disease, in the absence of dialysis, free and total carnitine concentrations increase, as does the acyl to free carnitine ratio. An acyl to free carnitine ratio >0.4 may indicate insufficient carnitine to buffer accumulation of excess acyl groups within the mitochondria, a condition referred to as carnitine insufficiency. (114) DCD often occurs in patients receiving maintenance hemodialysis. Some scientists and clinicians refer to this problem as a functional deficiency or as a dialysis-related carnitine disorder. This syndrome consists of reduced tissue and plasma free and acylcarnitine concentrations and an increase in the ratio of plasma acylcarnitine to free carnitine. Clinical problems and symptoms that have been associated with DCD include anemia, intradialytic hypotension, cardiomyopathy, and skeletal muscle dysfunction. (115) The cause of Carnitine deficiency in dialysis patients is multifactorial. A major contributing factor is the recurrent loss of carnitine during hemodialysis. (113)

Recent studies have confirmed that patients exhibit a gradual and significant decline in plasma free carnitine concentrations during the months following the initiation of hemodialysis. (113) Predialysis carnitine concentrations are below the normal range and are reduced further during each dialysis session. During the interdialytic interval, the plasma concentrations gradually rise, reflecting redistribution of levocarnitine from tissue stores into plasma. Biopsy studies have confirmed that long-term hemodialysis is associated with depletion of muscle carnitine stores, presumably due to redistribution of muscle carnitine into plasma and subsequent loss in dialysate. While acyl carnitines are also removed from the blood by dialysis, their removal is not as efficient as that seen for free carnitine. Therefore, an increase in the plasma acylcarnitine to free carnitine ratio occurs. The clinical importance of this observation is not well understood.

There has been a lot of research on the use of Carnitine in hemodialysis patients. Although it is not all in agreement. The following seems to be true overall:

Carnitine supplementation in hemodialysis patients at 500 mg/day carnitine taken orally for 2 months reduces serum levels of TG and VLDL-C, and increases HDL-C, HDL(2)-C and albumin in HD patients. (22) Carnitine given post dialysis, 3 times per week, 1 gram IV, has been shown to improve anemia and decrease the necessary dose of erythropoietine by 20%. (23) Low serum albumin (<3.8 g/dl) is found in half of all maintenance hemodialysis patients and is a marker for malnutrition and inflammation and is related to increased mortality. Research has shown intravenous injections of L-carnitine 20 mg/kg given to these patients, thrice weekly may suppress inflammation, particularly among those patients with C-reactive protein $>$ or $=3$ mg/dL, and also increased serum albumin and transferrin, blood hemoglobin, and body mass index. (24).

Patients on hemodialysis taking carnitine have a reduction in muscle cramps as well as intradialytic hypotension. This has been reported since the early 1980's.

Administration of L-carnitine to chronic hemodialysis patients is associated with lower hospital utilization. Patients with cardiovascular disease prior to receiving carnitine, and those with anemia and hypoalbuminemia derived the greatest benefit from carnitine therapy. (72)

The National Kidney Foundation panel in 2002 decided L-carnitine is appropriate for 1) unresponsive anemia, 2) Intradialytic hypotension, 3) cardiomyopathy, 4) muscle weakness. The panel recommended a IV dose of 20 mg/kg total body weight, administered following the end of dialysis. They gave no oral recommendation due to their lack of experience with oral administration. (121) Their report recommendations for the diagnosis and treatment of DCD are as follows:

Plasma carnitine measurement While the panel suggested that the diagnosis of DCD should be based on clinical signs and symptoms rather than any specific laboratory test, the panel did acknowledge the CMS requirement for the documentation of a low plasma free carnitine concentration as a prerequisite for reimbursement for levocarnitine treatment.

Anemia They recommended the administration of L-carnitine for dialysis patients who (111) are unable to maintain a target hemoglobin/hematocrit (11-12 g/dL/33-36%) with use of erythropoietin-based products, and (b) require recombinant human erythropoietin doses >300 units/kg/week intravenously or >200 units/kg/week subcutaneously (or an equivalent dose of other erythropoietin-based products), in spite of adequate iron stores (transferrin saturation >20%, ferritin >100 ng/mL), and without any other identifiable cause of anemia or hyporesponse to erythropoietin." The panel noted the scientific evidence for an inverse correlation between plasma carnitine concentrations and erythropoietin dose requirements. The suggested beneficial effect of levocarnitine is improved stability of the red blood cell membrane leading to enhanced red blood cell survival.(119)

Intradialytic hypotension They recommended administration of L-carnitine for hemodialysis patients who, without clinically identifiable causes, repeatedly experience symptomatic intradialytic hypotension that requires a therapeutic intervention." The basis for this recommendation is that cardiovascular dysfunction is a common cause of intradialytic hypotension and scientific evidence exists suggesting that levocarnitine therapy can improve the cardiovascular response to hypotensive episodes occurring during hemodialysis.(120)

Cardiomyopathy They recommended administration of L-carnitine for dialysis patients who have: New York Heart Association (NYHA) functional class III-IV or American College of Cardiology/American Heart Association (ACC/AHA) Stage C-D heart failure symptoms, OR symptomatic cardiomyopathy with documented impaired ejection fraction, AND not responded adequately to standard medical therapy."

Muscle weakness and diminished quality of life They recommended the administration of L-carnitine for selected patients with symptoms such as muscle weakness and fatigability that affect their quality of life.

With each of these recommendations, the panel urged that patients be monitored closely with objective measures of response to L-carnitine.

The panel advised that, in all cases, L-carnitine therapy should be discontinued if no clinical improvements occurred within 9 to 12 months after the initiation of L-carnitine therapy. L-carnitine pharmacology and dosing **According to the NKF consensus conference panel, the recommended dose of intravenous L-carnitine is 20 mg/kg total body weight, administered following the end of dialysis.** Continued treatment with this dose will result in repletion of skeletal muscle carnitine stores, although distribution of carnitine from plasma to tissue is a slow process, requiring weeks to months for equilibration to occur. There is no justification for repeated measurements of plasma free carnitine during or following intravenous administration of L-carnitine. Medicare will provide reimbursement as follows:

- for those patients who have been on dialysis for a minimum of three months.
- Patients must have documented carnitine deficiency, defined as a plasma free carnitine concentration <40 µmol/L.
- Levocarnitine must be prescribed for one of the two following indications:
 - Erythropoietin-resistant anemia (persistent hematocrit <30% with treatment) that has not responded to standard erythropoietin dosage with iron replacement, and for which other causes have been investigated and adequately treated, or
 - Hypotension on hemodialysis that interferes with delivery of the intended dialysis despite application of usual measures deemed appropriate (e.g., fluid management). Such episodes of hypotension must have occurred during at least two dialysis treatments in a 30-day period.
- Reimbursement will not continue if the patient does not demonstrate improvement within six months of initiation of treatment

Hemodialysis and Cardiovascular Risk & Role of Oxidative Stress

Hyperhomocysteinemia and oxidative stress occur in hemodialysis and peritoneal dialysis treatment both. The concomitant presence of hyperhomocysteinemia and oxidative stress appears to represent an important factor for the occurrence of vascular alterations and cardiac diseases, the main cause of death among dialysis patients. Cardiovascular disease accounts for about 40% of deaths in most large dialysis registries. Different degrees of hyperhomocysteinemia have been observed in all hemodialysis patients and in 95% of the peritoneal dialysis patients. Oxidative stress defined as an imbalance between oxidant and antioxidant forces has been observed in all dialysis patients, but was more intense in hemodialysis individuals. In hemodialysis patients lipoperoxidation and protein oxidation are associated with lower concentrations of antioxidants such as erythrocyte vitamin E and vitamin C. (79.) (See the "Role of Antioxidants" earlier in this article as well as following data.)

Folic acid and other antioxidant vitamins should be considered in hemodialysis in order to reduce homocysteine levels to lower values, that may be beneficial in minimizing the cardiovascular risk in this group. In research the first folate dose (2.5 mg after each dialysis session in humans) reduced by half the initial concentrations of homocysteine

(44.92 +/- 22.05 to 20.56 +/- 6.79 microM; $p < 0.05$) but did not normalize its values. The second dose (15 mg) did not show an additional effect, but it was at this time that lipoperoxidation was significantly reduced, although the protein oxidation showed no change. It was concluded that the first dose of folic acid was efficient in reducing homocysteine concentrations, without normalization of values. The participation of hyperhomocysteinemia in oxidative stress appeared to be partial, but in combination with dialysis treatment, may contribute to the induction of an oxidative environment in this group. The possible antioxidant action of folate must also be considered in this case, acting directly against lipoperoxidation or through hyperhomocysteinemia control. (75)

Microcirculatory disturbance in hemodialysis patients seems to be associated with endothelial damage caused by oxidative stress. According to human research, combined supplementation with **vitamin C and vitamin E** (vitamin C (200 mg daily) and vitamin E (600 mg daily) administered for 6 months) may be of clinical benefit in improving the cutaneous microcirculation by reducing oxidative stress. (76)

One study indicates that uremic patients are characterized by impaired endothelium-dependent vasodilation of the brachial artery, an abnormality related to renal failure severity in CKD patients and to delivered dialysis dose in HD patients. Oxidative stress seems to play a crucial role in worsening endothelial dysfunction in HD patients, while in pre-dialysis patients other pathways probably account for the impaired endothelium-dependent vasodilation. These results could have clinical relevance, since studies show that endothelial dysfunction predicts the development of cardiovascular events in patients with coronary artery disease. Therefore, it is conceivable that endothelial function reduction could be one of the mechanisms leading to the increased CV risk, a well known feature in chronic uremic patients. Oral vitamin C, (2gram) was given before dialysis and 2 hr after dialysis. After vitamin C administration, dilation was significantly enhanced in HD ($4.7 \pm 2.4\%$; $p < 0.01$ vs. baseline), but not in CKD patients. Vitamin C load reduced oxidative stress markers, and increased plasma antioxidant capability in both Chronic kidney disease patients as well as hemodialysis patients. (91) This is probably due to a relationship of vitamin C with nitric oxide. It has been shown that endothelial release of nitric oxide is potentiated by vitamin C, E and lipoic acid.

In a controlled clinical trial, antioxidant therapy with vitamin E reduced coronary vascular disease in chronic hemodialysis patients. (92)

Cigarette smoking further increases plasma-circulating products of lipid peroxidation in hemodialysis patients, which are already increased in nonsmoking hemodialysis patients as compared to matched healthy controls. There

is also lower plasma levels of ascorbate in hemodialysis patients who smoke. This suggest that these patients may be more susceptible to oxidative tissue damage caused by smoking. (106).

Coenzyme Q10 : Treatment with **coenzyme Q10** improves renal function in patients with chronic renal failure and decreases the need for dialysis in patients on chronic dialysis. Coenzyme Q10 has shown a significant reduction in serum creatinine, blood urea and a significant increase in creatinine clearance and urine output in a 4-week trial period. Additionally in this same study, the number of subjects on dialysis were significantly decreased when given coenzyme Q10. (33)

Control dialysis-induced low serum albumin levels

Low serum albumin concentration < 3.8 g/dL, is a marker of malnutrition-inflammation complex syndrome and, is observed in approximately half of all maintenance hemodialysis patients in the United States. It is strongly associated with increased mortality.

A study showed that nutritional intervention could greatly increase the serum albumin level. The nutritional intervention included one can of Oxepa and one can of Nepro to be taken together orally during each routine hemodialysis session for 4 weeks. Each can contained 237 mL fluid. Oxepa provides 355 calories and 14.8 g protein per can, includes **maltodextrin, medium-chain triglycerides, borage oil, and refined and deodorized fish oil**, and is designed for critically ill patients with inflammation and oxidative stress. Each can of Oxepa additionally includes **1,020 mg gamma-linolenic acid, 3,100 mg caprylic acid, 1,080 mg eicosapentaenoic acid, 75 mg taurine, 2,840 IU vitamin A activity, 75 IU vitamin E, and 200 mg vitamin C**. Nepro provides 475 calories and 16.7 g protein per can; includes **high-oleic safflower oil, corn syrup solids, and fructo-oligosaccharides**; and is tailored for the nutritional needs of MHD patients. Oxepa and Nepro also contain **L-carnitine, 43 mg and 62 mg**, respectively. (71)

Vitamin C Status in Hemodialysis Patients

The status of ascorbic acid (AA) in dialysis patients is the subject of debate. Some reports have found AA to be deficient in dialysis patients, while others have found that AA is not deficient. In an attempt to confirm AA serum concentrations in dialysis patients. A recent (2004) study analyzed the concentrations of AA as well as its metabolites using the specific determination of AA with chemical derivatization and the HPLC method. They studied 131 patients under maintenance hemodialysis therapy (HD), 23 patients with chronic renal failure (CRF) and 48 healthy controls (C). They found the frequency of AA deficiency in dialysis patients is extremely high. AA deficiency in HD patients may result in high serum levels of thiobarbituric reactive substances, which reflect increased oxidative stress. Adequate AA

supplementation should therefore be considered in such patients. (108)

The other debate is around hyperoxaluria. It appears that hemodialysis patients given IV vitamin C to treat the deficiency end up with a possible risk for oxalate supersaturation.(122)

Vitamin C & Erythropoietin-hyporesponsive anemia & Iron Overload in hemodialysis patients

This study has demonstrated that short-term low dose intravenous ascorbic acid therapy can facilitate iron release from reticuloendothelial system but also increase iron utilization in both diabetic and non-diabetic hemodialysis patients with iron overload. Therefore, IVAA is a potential adjuvant therapy to treat erythropoietin-hyporesponsive anemia in iron-overloaded patients. (77)

A prospective, randomized, double blind, cross-over study showed a large percentage (64% -67%) were responsive to vitamin C therapy(500 mg IV, three times a week,) as an effective adjuvant therapy to EPO in hemodialysis patients. It resulted in a significant increase in hemoglobin levels and a significant decrease in EPO-hemoglobin ratio. Transferrin saturation also increased with vitamin C treatment. (78)

In hemodialysis patients with a functional iron deficiency, treatment with intravenous ascorbic acid (100 mg, three times a week, after hemodialysis) can prevent iron overload due to treatment with intravenous iron, and provide a useful adjuvant means of maintaining hemoglobin and serum iron levels. (93)

Four weeks treatment using Sorbifer Durules tablets (100 mg Fe²⁺ and 60 mg vitamin C) led to a significant rise of the hematocrit and haemoglobin in blood, iron and vitamin C in serum. This treatment did not affect the oxalic acid plasma level. Oral treatment with Sorbifer Durules, one tablet/24 hours, was adequate for maintaining the serum iron concentration in haemodialyzed patients during treatment with recombinant human erythropoietin. This treatment prevented at the same time the development of vitamin C deficiency in serum and a further rise of plasma oxalic acid in these patients.(94).

The Role of Serum Calcium x Serum Phosphorus & Their Relationship to Vascular Calcification

Serum phosphorus (P) and the product of serum calcium x serum P (Ca x P), are frequently elevated in end-stage renal disease patients on maintenance hemodialysis (HD). Elevated P and Ca x P are associated with vascular calcification in dialysis patients. (110)

Control dialysis-induced itching (also for renal-failure-induced itching)

- Capsaicin, a constituent in *Capsicum* has been shown to be effective for dialysis-induced itching. Whole *Capsicum* extracts can be used also. Creams or salves are used externally.

Ginkgo cautions

- *Ginkgo* is an extremely beneficial herb for renal support, but it will increase bleeding time so be wary since the anticoagulant heparin is given during dialysis. If your patient has trouble clotting after dialysis, the heparin level will need to be decreased or eradicated except for the amount in the dialysate fluid which can't be decreased. The *Ginkgo* may also need to be decreased if decreasing the heparin is not enough.

Pre Renal Transplant

Usual preparation for surgery is helpful with the addition of prevention of renal ischemia-reperfusion injury which will be something every kidney graft will go through. continuing to support the kidneys is useful as you will now be preparing to support the new kidney.

Prevention of Renal Ischemia-Reperfusion Injury

In renal transplants the kidney is without blood supply for a period of time and then is reperfused suddenly with blood. This can actually be harmful to the kidney and create what is called renal ischemia-reperfusion injury.

Lipoic acid has been shown to be beneficial when used as a pretreatment prior to creating renal ischemia in rats. (36)

Quercetin and **Curcumin** reduce ischemia-reperfusion injury and its inflammatory sequelae in rats. Pretreatment with quercetin or curcumin resulted in preservation of histological integrity, with a decrease in tubular damage and interstitial inflammation. (40)

N-acetylcysteine reduces ischemia-reperfusion injury in rats. I/R induced nephrotoxicity, as evidenced by increases in BUN and creatinine, was reversed by NAC. The decrease in GSH and increases in malondialdehyde, myeloperoxidase and peroxide induced by I/R indicated that renal injury involves free radical formation. NAC reversed these oxidant responses, and protected rat renal proximal tubules from in vitro simulated reperfusion injury. (45)

Coptis chinensis rhizome water extract was protective against ischemia-reperfusion injury when given orally to rats. Greater activity was found in rats given the extract

for 30 days than in rats given the extract for 10 days prior to ischemia-reperfusion. In addition, the serum malondialdehyde level was lower, while the glutathione / glutathione disulfide ratio and the activities of the antioxidation enzymes, superoxide dismutase and catalase, were higher in rats given *Coptidis Rhizoma* extract . (44)

Post Renal Transplant

The general issues which need to be considered are:

- Treat renal ischemia-reperfusion injury now if you did not do anything to prevent it prior to surgery - or continue treating it. See above information.
- Control hypertension - see above information.
- Control hypercholesterolemia - see above information.
- Control hyperglycemia if diabetic - see above information.
- Decrease renal inflammation to new kidney if causative factor still exists and support the new kidney - see above information.
- Support blood vessels, including glomerular capillaries - see above information.
- Decrease prednisone bruising - see above information.
- Treat cyclosporin-induced gout.

1 teaspoon Flaxseed oil BID.

Urtica spp, leaf is quite beneficial with gout, but must be used long term for one month or more. Can use one cup of tea TID, if there is no edema or 1/2 teaspoon 1:1 fresh liquid extract BID, if there is edema. Never use *Urtica* which has been harvested after it goes into bud stage. This can irritate the kidneys and cause nephritis. Other herbs for gout that can be used are Burdock root & Seed (especially seed - but don't use too much as it can be over stimulating to the kidney also), Celery seed, also Vitamin C to bowel tolerance as well as eating a quart or more of black cherries or using black cherry juice can relieve gout. You can mix your herbal formula in with the cherry juice for fun and effect.

- CoQ10 is protective of the new kidney in renal transplant recipients. It works as an antioxidant without any alterations of serum concentration of cyclosporine A. (33.4)
- Research shows *Ginkgo biloba* may decrease the chance of delayed graft function and rejection. (16)
- Research has shown *Ginkgo* and fish oil effectively protect the transplanted kidney from damage due to cyclosporin. *Silybum marianum* may also protect the kidney from cyclosporin damage (See Herbs and Food Supplements).
- Sun M, Yang YR, Lu YP, Gao R, Wang L, Wang J, Tang Bailing capsule, (a dry powder preparation of *Cordyceps sinensis mycelia*) was shown to protect the kidney and be useful in the place of asathioprine after renal transplantation It effectively prevents the rejection response after renal transplantation, protects renal and liver function, stimulates hemopoietic function, improves hypoproteinemia and hyperlipidemia, reduces infection. The researchers thought it was an ideal

immunosuppressor after organ transplantation. (2.6)

- Most of the same supplements used for renal failure can be used to protect the new kidney. Read through the entire section of "Post Renal Transplant" for any exceptions

Platelet Activating Factor (PAF), its Role in Renal Failure & Transplant

PAF differs from other known biochemical mediators in being a glycerophospholipid. It is also called PAF-acether or AGEPC (acetyl glyceryl ether phosphoryl choline). It is released by basophils and mast cells in immediate hypersensitivity reactions and macrophages and neutrophils in other inflammatory reactions. It is an extremely potent mediator of bronchoconstriction and of the platelet aggregation and release reactions.

It is an inflammatory mediator that plays an important role in allergic and inflammatory processes, including ischemic renal failure. Evidence for involvement of PAF in renal immune injury has been provided by the observations that PAF is released during kidney hyperacute allograft rejection. It has been proposed that PAF participates in glomerular immune complex deposition in experimental serum sickness and also in systemic lupus erythematosus. Research shows it is released by isolated perfused kidneys and glomeruli as well as by suspensions of medullary cells, although not by tubules. The mesangial cells are thought to be the major source of PAF in the glomerulus. PAF has been shown to cause renal vasoconstriction and release of inflammatory agents, such as prostaglandins and thromboxane B2 in the kidney. There are specific binding sites for PAF.

Platelet Activating Factor Antagonists

PAF antagonists interfere with the binding of PAF to its cellular receptors. Ginkgolides from *Ginkgo biloba*, kadsurenone and other lignans isolated from *Piper futokadsurae*, and gliotoxin-related compounds from various fungi and bacteria constitute three groups of naturally occurring platelet-activating factor antagonists. Of the 3 naturally occurring PAF antagonists, *Ginkgo* is the most available and most researched.

1) *Ginkgo biloba*: A mixture of Ginkgolides ABC in 2:2:1 ratio inhibit most of the biologic effects induced by PAF. Ginkgolide BN 52021 (Ginkgolide B), has been shown to be a receptor antagonist for PAF. (16) Ginkgolides inhibit PAF-induced release of thromboxane B2 and prostaglandins from primary cultures of human and rat glomerular mesangial cells. BN 52021 also inhibits PAF-induced formation of reactive oxygen species from cultured mesangial cells and destruction of the glomeruli. In addition, this antagonist inhibits PAF-induced decreases in renal blood flow, glomerular filtration and urinary sodium excretion (10).

2) *Perilla oil* : Dietary high alpha-linolenate perilla oil suppresses PAF production in rat kidney during systemic endotoxemia, and which is mainly due to the decrease in alkylacyl-GPC content, altered fatty acid compositions of the

precursor lipids and lower CoA-independent transacylase activity. (101)

- **Forskolin, from** *Coleus forskohlii*, Inhibits Platelet Activating Factor (PAF) by competitive inhibition. PAF has the following properties: increased bronchial permeability and smooth muscle contraction. A 40% decrease in PAF binding was observed after pretreatment with forskolin. This antagonistic action on PAF by forskolin is not via the stimulation of cAMP, but by another direct stimulation mechanism. **This herb may be another important herb to use. Needs to be studied.**

Treat diseases, such as hepatitis B and C, from transplant

- *Glycyrrhiza* is usually used for hepatitis but is contraindicated with severe hypertension. Other herbs used in hepatitis which appear to be safe to use for the renal transplant patient are *Silybum*, *Phyllanthus spp.* and *Bupleurum chinense/falcatum*. Additional herbs to use are *Ceanothus spp.* and *Echinacea*. I have used both in renal transplant patients but you have to be careful of Immunomodulators in general as you do not want to cause kidney rejection. The main thing here is to support the liver. For the most part herbs that are called antivirals are usually herbs that act on the immune system. So all immunomodulators and antivirals are suspect of causing renal rejection. **See case history #5.** Lithospermate B from *Salvia miltiorhiza* has been shown to have preventive effect on experimental hepatitis induced by carbon tetrachloride or α -galactosamine/lipopolysaccharide in vitro and in vivo. (42) This would be an herb you are already giving to the patient to support their kidney any way.

Protect the kidney & liver from cyclosporin

Cyclosporin A (CsA) is a potent and effective immunosuppressive agent. It is a fungal cyclic polypeptide (multi-amino acid compound from a fungus) which suppresses both humoral and cell-mediated immunity and is therefore used in organ transplantation but its use is frequently accompanied by severe renal toxicity. The causes for the nephrotoxicity of CsA have not been fully elucidated. Intrarenal vasoconstriction induced by several different mediators, both in humans and experimental animals have been proposed. Both the afferent and efferent renal arterioles seem to be effected.

- **Ginkgo biloba** - One research article shows Ginkgolides A, B, and C inhibiting cyclosporin damage to the kidney. *Ginkgo* reduces tubular and interstitial damage without affecting cyclosporin's immuno-suppressive effects (7).
- Research in rats given cyclosporin A, shows resveratrol (5 and 10 mg/kg) significantly improved the renal dysfunction; tissue and urine total nitric oxide levels, renal

oxidative stress and prevented the alterations in renal morphology. Concurrent administration of L-NAME blocked the protective effect of resveratrol indicating that resveratrol exerts its protective effect by releasing nitric oxide. These results clearly demonstrate the pivotal role of nitric oxide in etiology of CsA nephrotoxicity and indicate the renoprotective potential of resveratrol in CsA nephrotoxicity (74)

- *Cordyceps sinensis* (CS) has a protective effect from cyclosporine A nephro-toxicity (CsA-Nx) Both acute and chronic experiments showed that CS could protect the kidney from CsA-Nx and ameliorate the glomerular and interstitial injuries. (2.8)
- *Silybum* and *Ginkgo* are used for liver protection from cyclosporin damage.

Herbal Side Effects

- Herbs or drugs which can alter the cytochrome p450 system will alter the half lives of immuno-suppressive drugs. Immunosuppressive drugs should be monitored closely when using herbs with unknown cp450 activity.
- Chronic *Glycyrrhiza* use increases aldosterone in the body by increasing the half life of aldosterone. This increases sodium reabsorption and potassium excretion by the kidney. Long term use can induce hypertension in normotensive persons. Hypertension is something the person with a kidney transplant already has to deal with, you don't want to add to it.
- Caution with all treatments which may affect the immune system since the person is using immunosuppressive drugs. Increasing the activity of her/his immune system may cause rejection of the transplant.

Cyclosporine interactions

Cyclosporine Interactions with Dietary Supplements

Magnesium

- Cyclosporine has been associated with low blood magnesium levels. (48,49,50) Monitor the level of magnesium in red blood cells, rather than in serum, as the red blood cell test may be more sensitive for evaluating magnesium status.

Potassium

- Cyclosporine can cause excess retention of potassium, potentially leading to dangerous levels of the mineral in the blood (hyperkalemia). (51) Potassium supplements, potassium-containing salt substitutes (No Salt®, Morton Salt Substitute®, and others), and even high-potassium foods (primarily fruit) should be avoided by people taking cyclosporine. Some wines have potassium sorbate added to them as a bacterial growth retardant.

Vitamin E

- Twenty-six liver transplant patients (both adults and children) unable to achieve or maintain therapeutic cyclosporine blood levels during the early post-transplant period were given water-soluble vitamin E in the amount of 6.25 IU / 2.2 pounds of body weight two times per day. (52) Addition of vitamin E in the early post-transplant period reduced the required amount of cyclosporine and the cost of cyclosporine therapy by 26%. These results imply that the addition of vitamin E to established cyclosporine therapy allows for a decrease in the amount of cyclosporine. Combining vitamin E and cyclosporine requires medical supervision to avoid cyclosporine toxicity.

Quercetin

- In a study in animals, oral administration of quercetin (50 mg per 2.2 pounds of body weight) at the same time as cyclosporine decreased the absorption of cyclosporine by 43%. (53)

Cyclosporin Interactions with Herbs

Scutellaria baicalensis

- In a study in rats, oral administration of Chinese skullcap at the same time as cyclosporine significantly reduced the absorption of cyclosporine. Chinese skullcap did not interfere with the availability of cyclosporine when cyclosporine was given intravenously. (54)

Ginkgo biloba

- One research article (16) showed *Ginkgo* may increase the level of cyclosporin in graft recipients.
- *Ginkgo* reduces tubular and interstitial damage without affecting cyclosporin's immuno-suppressive effects (7).

St. John's wort (*Hypericum perforatum*)

This herb is a known inducer of the cytochrome P3A4 enzyme system as well as P-glycoprotein. It appears that *Hypericum* may reduce plasma levels of cyclosporine. *Hypericum* with known varying amounts of hyperforin was studied and it was found that the extracts with increased hyperforin decreased cyclosporine more than the extracts with less hyperforin. (55)

Two case reports also describe heart transplant patients taking cyclosporine who showed signs of acute transplant rejection after taking St. John's wort extract. (58) Reduced plasma concentrations of cyclosporine were found.

Similar drops in cyclosporine blood levels were reported in 45 kidney or liver transplant patients who began taking St. John's wort. (59)

A literature search performed using Medline, Biological Abstracts, Cochrane Library, AMED, PsycINFO and Embase (all from their inception to September 2003) to identify known drug interaction with St John's wort indicates that St John's wort is a potent inducer of CYP 3A4 and P-glycoprotein (PgP), although it may inhibit or induce

other CYPs, depending on the dose, route and duration of administration. Data from human studies and case reports indicate that St John's wort decreased the blood concentration cyclosporine amongst other drugs. (60,61) Several cases were reported that St John's wort decreased cyclosporine blood concentration leading to organ rejection.

Piperine

- Piperine, a constituent from *Piper nigrum* or Black Pepper inhibits certain cytochrome P450 enzymes and P-glycoprotein. This leads to increased levels of cyclosporin. (65)

Interactions with Foods and Other Compounds

Food

Food increases the absorption of cyclosporine. (62) A change in the timing of food and cyclosporine dosing may alter cyclosporine blood levels, requiring dose adjustment.

Grapefruit juice

Grapefruit juice can significantly increase the bioavailability of cyclosporin. The predominant mechanism for the elevated drug bioavailability caused by grapefruit juice interaction is the inhibition of cytochrome P-450 3A4 in the small intestine, resulting in a significant reduction of drug presystemic metabolism. An additional mechanism is the inhibition of P-glycoprotein, a transporter that carries drug from the enterocyte back to the gut lumen, resulting in a further increase in the fraction of drug absorbed. A single exposure to one glass of grapefruit juice can usually produce the maximal magnitude of this interaction. (62) Eleven medically stable patients (seven males, four females) receiving cyclosporine following kidney transplantation were instructed to take their usual dose of cyclosporine with water for 1 week (Phase 1), with grapefruit juice (8 ounces) for 1 week (Phase 2) and again with water for 1 week (Phase 3). Cyclosporine concentrations increased in 8 of 11 patients when given with grapefruit juice (mean increase 32%; range -4 to 97%) and declined in 10 of 11 when subjects resumed taking cyclosporine with water (mean decrease 27%). (63)

Red wine

Ingestion of red wine along with cyclosporine has been found to reduce blood levels of the drug. Red wine caused a 50% increase in the oral clearance of cyclosporine. However, half-life was not affected, suggesting that red wine decreased cyclosporine absorption. (64) Individuals taking cyclosporine should, therefore, not consume red wine at the same time as they take the drug. It is not known whether red wine consumed at a different time of the day would affect the availability of cyclosporine.

Constipation after surgery

- After surgery, get the bowels moving with *Rheum* and acupuncture.

Weight gain

- Expect an average 35# weight gain from surgery and steroids.

Other helpful suggestions

- Emotional support
- Be aware of mood fluctuations from OKT3 (a drug given immediately after transplant surgery) and steroids and counsel the patient about these drugs and their psychological side effects.
- Nurture self through massage and other supportive methods.
- Energy work such as Qi Gong or Neuromodulation technique can be helpful.
- Hydrotherapy
- Rest is absolutely necessary.
- Healthy diet, eradicate allergenic foods, exercise when appropriate.

The Use of Herbs or Nutrients that Prevent Scarring To Prevent Kidney Rejection

Tissue remodeling depends on mesenchymal cells (fibroblasts and myofibroblasts) and is a prominent feature of chronic renal-transplant rejection. Current research has shown that they originate from the recipient rather than the donor. The presence of mesenchymal cells of host origin in the vascular and interstitial compartments of renal allografts undergoing chronic rejection provides evidence that a circulating mesenchymal precursor cell has the potential to migrate to areas of inflammation. (96)

The rejection appears to be a normal reaction to a wound. The mesenchymal cells are circulating through the blood stream, constantly on the lookout for damaged tissue, traveling to the transplant site and colonizing the area, creating an environment in which the donor organ cannot survive. It is not known why on some occasions the repair leads to perfect healing, but other times the repair is imperfect leading to the chronic scarring that is part of rejection. Scarring of an organ, which occurs during the post-surgical healing process, is actually quite damaging, constricting blood vessels leading to the organ and causing it to fail prematurely.

It might be possible to mitigate or prevent kidney rejection by developing methods of blocking these scar-promoting cells. One of the best herbal methods for preventing scar tissue formation is *Centella asiatica*. *Centella* should be studied in this aspect. Additionally it has historical use in chronic renal disease formulas used in China. Vitamin A which is an agent that gets used to improve tissue healing has had positive and negative effects in relationship to renal scarring. Renal scarring due to pyelonephritis was shown to improve in rats given vitamin A, while vitamin A administration in renal nephropathy did not significantly affect the clinical and pathological course of renal ablation

nephropathy in rats. Furthermore, high doses of vitamin A might even damage renal tissue. (107) It has not been studied in post renal transplant rejection episodes that I know of.

EFFECTS OF HERBS

Salvia miltiorrhiza - A traditional Chinese medicinal herb used for treatment of hemorrhage, menstrual disorders, swelling, and coronary heart disease. *Salvia's* active ingredients include diterpenoids, polyphenolic acids, and a flavanone. The crude extract as well as its diterpenoids and flavanone have shown antimicrobial activity, inhibit blood platelet aggregation, dilate coronary arteries, and increase coronary blood flow without affecting heart rate in vitro and in vivo. They also have preventive effects on development of respiratory distress syndrome. The crude extract and polyphenolic acid have been found to improve renal function in vitro and in vivo. (13)

Salvia miltiorrhiza reduces accumulation of methylguanidine and guanidinosuccinic acid levels in uremia. Methylguanidine and guanidinosuccinic acid (oxidation products) have been reported to cause platelet dysfunction, hemolytic activity, glucose-metabolism disturbance and inhibition of lymphocyte transformation. This demonstrates protection of the body in uremic situations, and also indicates *Salvia's* action as a possible free radical scavenger (8,123). (Active oxygen has been shown to be involved with proliferation of mesangial cells.)

The constituent, magnesium lithospermate B, a tetramer of caffeic acid, has been shown to decrease blood urea nitrogen, serum creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphate in uremic rats whose uremic state had been induced by an adenine diet. It activates the kallikrein-kinin system in the rat kidney to promote the production and secretion of prostaglandin E2, inducing dilation of the renal vascular system, and increasing the renal blood flow and glomerular filtration rate. PGE2 also inhibits proliferation of mesangial cells (in glomeruli) and acts antagonistically against vasoconstriction brought about from Thromboxane A2. PGE2 has been found to inhibit tubular reabsorption of sodium in one study. PGE2 has been demonstrated to have a protective role in the maintenance of hypertension which accompanies renal disease. Magnesium lithospermate B may therefore ameliorate the development of hypertension through excretion of urinary sodium and by improving renal hemodynamics. (5)

Ginkgo biloba A mixture of Ginkgolides ABC in 2:2:1 ratio inhibit most of the biologic effects induced by PAF. Ginkgolide BN 52021 (Ginkgolide B), has been shown to be a receptor antagonist for PAF. (16) One research article shows Ginkgolides A, B, and C inhibiting cyclosporin damage to the kidney. *Ginkgo* reduces tubular and interstitial damage without affecting cyclosporin's immuno-suppressive effects (7). Ginkgolides inhibit PAF-induced release of thromboxane B2 and prostaglandins from primary cultures of human and rat glomerular mesangial cells. BN 52021 also inhibits PAF-

induced formation of reactive oxygen species from cultured mesangial cells and destruction of the glomeruli. (Ginkgo is known to be an antioxidant which is important since free radical production is implicated in progressive kidney disorders.) In addition, this antagonist inhibits PAF-induced decreases in renal blood flow, glomerular filtration and urinary sodium excretion (10). The use of BN 52021 reduces proteinuria and the histopathological lesions in nephrotoxic rabbits. Given preventively, or even curatively, BN 52021 abolishes the adriamycin-induced lethality and proteinuria in rats. This protection is associated with a significant reversal of the glomerular alterations induced by the extract. BN 52021 also prevents acute rat renal failure induced by glycerol injection. BN 52021 given intravenously prior to renal graft surgery and for 4 days after surgery has been shown to increase the chance of graft survival and decrease the number of acute rejection episodes after surgery. (16)

Panax ginseng - Oral Ginseng has been shown to decrease uremic toxins such as creatinine, methylguanidine, and guanidinosuccinic acid. One study found oral ginseng suppressed uremic toxins, decreased urinary excretion of protein and inhibited mesangial proliferation, demonstrating the arrest of progressive renal disorder from subtotal nephrectomy. In experiments using cultured mesangial cells, there was considerable suppression of mesangial cell proliferation. Due to ginseng's role as a free radical scavenger. Another study shows *Ginseng* saponin protecting the kidney from oxidative stress. *Ginseng's* action as a free radical scavenger is important since free radical production is implicated in progressive kidney disorders. (2, 3)

Perilla frutescens

Perilla has been shown to suppress proteinuria, decrease mesangial cell proliferation in HIGA mice and significantly suppressed mesangial IgA deposition in HIGA mice, as well as significantly suppress serum IgA levels in HIGA mice (30) It has been shown to be stronger as a whole decocted herb than when compared to its constituent rosmarinic acid which is also renal protective. A *perilla* decoction suppressed the proliferation of mesangial cells in vivo at doses of 100 and 500 mg/kg/d in rats. This was due to an inhibition of the glomerular infiltration of macrophage/monocytes and of the production of circulating growth factors. (103)

Rheum officinalis - Increases glomerular filtration, and decreases cholesterol and triglyceride levels. Interactions of lipids with advanced glycosylation have been implicated in the genesis of diabetic microangiopathy in the kidney. *Rheum* may relieve diabetic nephropathy by improving lipid metabolism. Experimental research with aqueous extract has shown lowered blood glucose levels. Aqueous extract also increases urinary excretion of urea nitrogen and creatinine, probably due to increased glomerular filtration. (1, 2)

Rheum may be useful in IGA nephropathy as it has been shown to improve renal function by inhibiting the production of IL-6 and lowering immune inflammatory response. (80)

A communication from Lei Leishi on *Rheum* is as follows:

1) Effects of *Rheum* on intrinsic renal cells - *Rheum* had a remarkable suppressive effect on the growth of both renal tubular and mesangial cells in vitro. The constituent of *Rheum* called emodin appears to be highly active in suppressing the growth of mesangial and tubular cells in vitro.

2) An experimental study with nephrectomized rats was started at the 4th week post-nephrectomy. The rats were divided into 4 groups. Group A - control group; group B - nephrectomized and fed with whole extract of *Rheum officinale*; group C - nephrectomized, and fed Enalapril; group D - nephrectomized but not treated. The survival rate at the end of 12 weeks was 75% for group B, 71% for group C, and 61% for group D. The BUN level of the rats treated with *Rheum* was significantly lower than that of the Enalapril group. (He does not state what this was.) *Rheum* and Enalapril both suppressed the degree of azotemia, reduced the urinary protein excretion and lowered serum creatinine. *Rheum* also exerted a prominent beneficial effect on the lipid metabolism of the uremic rats. It lowered the level of cholesterol and LDL, but elevated the HDL level.

3) A clinical trial to evaluate effectiveness of *Rheum* in vivo was undertaken. 151 patients with chronic kidney failure were treated with either *Rheum* or an ACE inhibitor (Captopril), as well as the combination of both. All the patients were followed an average of 32.5 months. The average mean serum creatinine at start up was 328+ 92.8. The frequency of end-stage renal failure in the ACE inhibitor group was 54.3%, the *Rheum* group was 25.9%, the combined regimen was 13.1%. Long-term follow up demonstrates that the progression rate of CRF is retarded and that the nutritional status and quality of life is improved. (18)

Coptis chinensis rhizomes have been shown to be protective against oxidative stress in rat kidneys. It appears to raise levels of glutathione, superoxide dismutase and catalase. It may be helpful in protecting the transplanted kidney from ischemia-reperfusion damage. (44)

Coptis chinensis: *Coptis* rhizome extract and its alkaloids can ameliorate the in vitro cell damage associated with peroxynitrite generation in renal tubular LLCPK cells, and that the various alkaloids have distinctive mechanisms of action, such as peroxynitrite scavenging, protection from DNA damage and control of the cell cycle. Furthermore, the data suggest that among the *Coptis* rhizome alkaloids, *coptisine* is the most effective for protection against SIN-1-induced cellular injury in terms of its potency and content. (44.5)

Silibinin Protects Against Cisplatin-induced Nephrotoxicity without Compromising Cisplatin (20)

Cordyceps sinensis: *Cordyceps sinensis* (CS) a parasitic fungus, may be helpful in treating IGA nephropathy. It is a parasitic fungus that has been used in Chinese medicine

for nephritis for a long time. In vitro and rat research give the indication that this fungus could be useful in treatment of IGA nephropathy. (2.9) Other research that backs this up is research showing this herb is useful in management of autoimmune disorders. (2.4)

Sun M, Yang YR, Lu YP, Gao R, Wang L, Wang J, Tang Bailing capsule, (a dry powder preparation of *Cordyceps sinensis* mycelia) was shown to protect to be useful in the place of asathioprine after renal transplantation. It effectively prevents the rejection response after renal transplantation, protects renal and liver function, stimulates hemopoietic function, improves hypoproteinemia and hyperlipidemia, reduces infection. The researchers thought it was an ideal immunosuppressor after organ transplantation. (2.6)

Cordyceps sinensis (CS) has a protective effect from cyclosporine A nephro-toxicity (CsA-Nx). Both acute and chronic experiments showed that CS could protect the kidney from CsA-Nx and ameliorate the glomerular and interstitial injuries. (2.8)

It has a protective effect on aminoglycoside (AG) induced nephrotoxicity. It ameliorates renal tubular injury as evidenced by less prominent increment of BUN, SCr, sodium excretion, urinary n-acetyl-beta-d-glucosaminidase (NAGase) and less severity of histopathological changes as compared with control. In addition, the use of CS could promote an earlier recovery of renal oxygen consumption, insulin clearance, and sodium absorption in isolated perfused kidney from CS treated intoxicated rat than that from control. Researchers think the possible mechanisms of CS on drug-induced nephrotoxicity include: (1) Accelerating the regeneration of tubular cells; (2) Protecting the sodium pump activity of tubular cells; (3) Attenuating the tubular cell lysosome hyperfunction stimulated by phagocytosis of AG as well as decreasing the tubular cell lipoperoxidation in response to toxic injury; (4) Reducing the tissue Ca⁺⁺ content. (2.7)

Ephedra distachya, *Terminalia chebula*, *Geranium thunbergii* - Like *Rheum* these are tannin-containing herbs. In one experiment, these herbs showed benefits in reducing uremic indices in animals. Animal research indicates many condensed tannins or proanthocyanidin containing herbs seem to improve uremic indices. (15) (This is probably due to their ability to act as antioxidants and to make the blood vessels more flexible and resilient.)

Astragalus membranaceus - Acts as a diuretic when the kidneys are weak. It provides support for the kidneys and has been used in Chinese medicine for treatment of chronic nephritis. *Astragalus* is thought to increase renal blood flow. It is anti-inflammatory, hepatoprotective and an antioxidant. It helps restore normal tissue tone and function.

Curcuma longa - Turmeric - Curcumin, a constituent in *Curcuma* has a lot of research on it but it is all in rats. It protects against kidney injury by suppressing free radicals and increasing kidney glutathione content and glutathione

peroxidase activity (endogenous antioxidants). Curcumin also eliminated kidney microsomal and mitochondrial lipid peroxidation. (39)

Curcumin pretreatment was shown to reduce the kidney damage from ischemia-reperfusion injury and its inflammatory sequelae. Pretreatment with curcumin resulted in preservation of histological integrity, with a decrease in tubular damage and interstitial inflammation. (40)

The antioxidant effects of curcumin (0.5 grams/100grams) and its derivative tetrahydrocurcumin (0.5 grams/100grams) against iron chelate, ferric nitrilotriacetate (5 mg/kg body intraperitoneally) were both found to be protective with tetrahydrocurcumin being a more promising chemopreventive agent against renal cancer. (41)

Beta vulgaris L. var. cicla - Chard

Chard extracts have been shown to decrease blood glucose levels in diabetic research in the past. One study observed antidiabetic effects such as regenerative effect on beta cells of the pancreas both morphologically and biochemically. This would be beneficial to DM patients as a preventative for renal failure as well as support the diabetic with renal failure. Additionally the plant is known as an antioxidant due to the leaves being rich in vitamin C. Antioxidants appear to play a profound effect on protection of the kidney and vitamin C has been shown itself to be protective.

Chard tea extract has been shown to protect rat kidneys from streptozotocin damage which was observed in normalization of serum creatinine and almost normal serum urea while kidney tissue itself had normal parameters 42 days post streptozotocin. (43)

Zea mays - A soothing diuretic and antiseptic. It supports normal kidney anatomy and physiology. Glycoproteins in corn silk produce interferon, inhibit IgE formation and enhance IgG and IgM formation. They also have antiviral and antitumor activities.

Evodia rutecarpa - Reduced uremic state in rats. (2)

Peonia lactiflora - Reduced uremic state in rats. (2)

Stevia rebaudiana - May induce nephrotoxicity - specifically, at the proximal convoluted tubules. This herb should be avoided or used with caution by all persons with renal disorders. (14)

The Committee for Veterinary Medicinal Products in Europe put out a summary report on the plant *Lespedeza capitata*. Following are excerpts from it.

Lespedeza capitata's (Round-headed bush clover) main constituents are flavonoids, belonging to a group of phenolic compounds. In research, rabbits with induced uremia showed significant reduction of urea blood levels when 1 ml/kg bw of the tincture (15% alcoholic solution) was given via gavage. Dogs and cats showing signs of renal failure were treated with 1 ml/kg bw once or

twice per day through several days or weeks. Oliguria and albuminuria disappeared and urea concentration decreased significantly.

Research on toxicity showed the plant to be quite safe for peritoneal and intramuscular administration in rats, mice, guinea pigs, rabbits, dogs and cats. Oral toxicity was not examined.

There may be some benefit of isoflavones and lignans on renal tissue, but the research I have read has been a bit sketchy so far.

References and Abstracts

1. Takako Yokozawa, et al., "Effects of **Rhubarb** Extract in Rats with Diabetic Nephropathy". *Phytotherapy Research*, 97;11:73-75.

Diabetes was induced in rats by subtotal nephrectomy and injection of streptozotocin. One group was given water and the other was administered an aqueous rhubarb extract orally for 80 consecutive days. Rats given the rhubarb extract showed a significant decrease in blood glucose levels. Although there was not a significant difference in the blood urea nitrogen or creatinine, the rhubarb extract group was excreting much more urinary urea nitrogen and creatinine toward the end of the experiment than the control group. The enhancement of the urinary creatinine was most likely due to increased glomerular filtration rate since tubular reabsorption does not occur and only small quantities are secreted. This was a good indicator of improved glomerular filtration taking place. Additionally, there was a significant decrease in the cholesterol and triglyceride levels in the rhubarb extract group compared with the control group. Interactions of lipids with advanced glycosylation has been implicated in the genesis of diabetic microangiopathy in the kidney. Hence, the author of the research article thought the rhubarb extract may be relieving diabetic nephropathy by improving lipid metabolism.

2. Takako Yokozawa, et al., "A Study on the Action of a Modified **Wen-Pi-Tang** Prescription, Using Uremic Toxins in Blood as Indices". *Phytotherapy Research*, 94;8:456-460.

Renal failure was induced in rats via an adenine diet. The rats were given individual crude herbs as well as two formulas. Each formula contained various mixtures of the crude drugs. The formulas were then further separated into groupings which contained different percentages of the herb *Rheum officinale*, which seems to have significant ability to support normal kidney function. One formula performed much better than the other. This formula, containing *Rheum officinale*, *Panax ginseng*, *Peonia lactiflora*, *Angelica acutiloba*, *Polygonum multiflorum*, *Pinellia ternata*, *Coptis japonica* and *Evodia rutecarpa*, decreased serum urea nitrogen by 26% at 50 mg/kg and 40% at 200 mg/kg compared with controls. The serum creatinine was decreased by 34% at 200 mg/kg. The experiments showed the following herbs to individually decrease serum urea nitrogen and creatinine. They are listed from the most significant to the least significant: *Rheum*, *Evodia*, *Peonia* and *Panax*. *Angelica* raised serum urea nitrogen when given alone. *Polygonum* and *Coptis* raised serum urea

nitrogen and creatinine when given alone. The formula listed above given in 200 mg/kg dosage with 13% *Rheum* decreased serum urea nitrogen by 31% and serum creatinine by 30%. At 43%, *Rheum* decreased serum urea nitrogen by 28% and serum creatinine by 35%. Although different percentages of *Rheum* did not affect this formula much, it did affect the other formula significantly. This other formula, although not as effective as the one mentioned above, did improve in its effectiveness when the *Rheum* was increased as follows; Serum urea nitrogen improved from a 13% decrease with 13% concentration of *Rheum* to a 27% decrease with 43% concentration of *Rheum*. Serum creatinine improved from 2% increase at 13% *Rheum* to 29% decrease at 43% *Rheum*. This second formula is not listed due to its toxicity as well as its inability to equal the formula listed above. What is significant is the drastic decrease of serum urea nitrogen and creatinine when the *Rheum* was increased in the formula.

- 2.4 Yang LY, Huang WJ, Hsieh HG, Lin CY. " H1-A extracted from *Cordyceps sinensis* suppresses the proliferation of human mesangial cells and promotes apoptosis, probably by inhibiting the tyrosine phosphorylation of Bcl-2 and Bcl-XL." *J Lab Clin Med*. 2003; Jan;141(1):74-83.

H1-A, a pure compound used in traditional Chinese medicine, is effective in the treatment of autoimmune disorders of MRL lpr/lpr mice. We have previously reported that after 8 weeks of oral therapy with H1-A, 40 microg/kg/day, MRL lpr/lpr mice demonstrated significantly less proteinuria, lower serum creatinine levels, and less renal mesangial proliferation than mice in an untreated group. To clarify the pharmacologic properties of H1-A, we studied its cellular and subcellular effects in cultured human mesangial cells. Our results show that H1-A inhibits cell proliferation and promotes the apoptosis of interleukin (IL)-1- and platelet-derived growth factor (PDGF)-BB-activated human mesangial cells in vitro. Uptake of tritiated thymidine was nearly totally suppressed by the addition of 12.5 micromol/L H1-A (counts per minute decreased from 3905 +/- 70 to 141 +/- 5). The population of S-phase cells decreased from 15.5% +/- 1.7% to 10.0% +/- 0.3%, and G0 + G1 phase cells increased from 68.8% +/- 0.07% to 74.6% +/- 0.05%. This suppression was not a result of cytotoxicity. Apoptosis of human mesangial cells was detectable after treatment with 12.5 or 25 micromol/L H1-A. Using immunoprecipitation and immunoblotting, we found that H1-A inhibits tyrosine phosphorylation of human mesangial proteins and that Bcl-2 and Bcl-XL were probably among these proteins. These findings suggest that H1-A modulates some subcellular signal-transduction pathways and changes the balance between proliferation and apoptosis of mesangial cells in vitro or in vivo. H1-A may be effective in the management of autoimmune disorders, and the modulation of the signal transduction proteins Bcl-2 and Bcl-XL may represent a target for future pharmacologic interventions.

- 2.5 Ngai HH, Sit WH, Wan JM. " The nephroprotect-

tive effects of the herbal medicine preparation, WH30+, on the chemical-induced acute and chronic renal failure in rats." *Am J Chin Med.* 2005;33(3):491-500.

In this study, they evaluated the renal protective effects of a Chinese herbal preparation WH30+ in male Wistar rats with glycerol-induced acute renal failure and adenine-induced chronic renal failure. WH30+ is a Chinese herb preparation composed of *Rheum Palmatum*, *Salvia Miltiorrhiza*, *Cordyceps Sinensis*, *Leonurus Sibiricus*, *Epihedium Macranthum*, *Radix Astragali*, and *Radix Codonopsis Pilosulae*, which has been used to treat kidney deficiency in human. An acute renal failure and chronic renal failure rat model were introduced by glycerol injection (i.m.) and fed with adenine-excessive diet, respectively. WH30+ was administered to rats at the dose of 50 mg/kg/day from 10 days before the diseases were induced until the rats were sacrificed. A reduction in body weight ($p < 0.01$) was observed in rats with chronic renal failure, but there was no difference between treatment groups. However, the body weight of rats with acute renal failure without treatment was significantly lower than those treated with WH30+ ($p < 0.05$). Overall, serum creatinine and urea nitrogen were elevated significantly ($p < 0.01$) in renal failure rats compared to control. Treatment with WH30+ improved both serum creatinine and urea nitrogen slightly in both models. The WH30+-treated rats with acute renal failure had significantly ($p < 0.05$) greater creatinine clearance than those without treatment. The results of the study show that WH30+ is more effective in the prevention of acute renal failure than chronic renal failure.

2,6 Sun M, Yang YR, Lu YP, Gao R, Wang L, Wang J, Tang K. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* "Clinical study on application of bailing capsule after renal transplantation" *Xi Yi Jie He Za Zhi.* 2004; Sep;24(9):808-10. [Article in Chinese]

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OBJECTIVE: To observe and assess the immunosuppressive effect of applying bailing capsule (BLC, a dry powder preparation of *Cordyceps sinensis* mycelia), after renal transplantation, its influence on other systems of organism, and to explore the possible therapeutic mechanism.
METHODS: One hundred and twenty-one recipients of renal homo-allograft were randomly divided into two groups. The 64 cases in Group A was treated with cyclosporin A (Cs A) + prednisone (pred) + azathioprine (Aza), the 57 in Group B treated with Cs A + pred + BLC. They were followed-up for 1-2 year by checking up blood routine, urine routine, liver and renal function, blood electrolytes, glucose and lipids, and uric acid for 2 times every week in the first month after transplantation, followed by proper re-examination of these items according to various condition.
RESULTS: There was no significant difference between the two groups in aspects of graft survival rate, occurrence of reject reaction, renal function recovery, blood electrolytes and blood glucose levels. However, as com-

pared with Group A, in Group B, levels of urinary erythrocytes and leucocytes, blood alanine transaminase (ALT), aspartate aminotransferase (AST), total cholesterol, uric acid as well as the incidence of infection were significantly lower, and blood high density lipoprotein, serum total protein, albumin, RBC and WBC count were significantly higher. **CONCLUSION:** BLC could effectively prevent the reject response after renal transplantation, protect renal and liver function, stimulate hemopoietic function, improve hypoproteinemia and hyperlipidemia, reduce the infection, etc., therefore, it is an ideal immunosuppressor after organ transplantation.

2.7 Li LS, Zheng F, Liu ZH. "Experimental study on effect of *Cordyceps sinensis* in ameliorating aminoglycoside induced nephrotoxicity" *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 1996 Dec;16(12):733-7.

In order to evaluate the effect of *Cordyceps sinensis* (CS) on aminoglycoside (AG) induced nephrotoxicity, gentamicin was imposed on the young and old rats with CS administration. The renal tubular injury was ameliorated as evidenced by less prominent increment of BUN, SCr, sodium excretion, urinary NAGase and less severity of histopathological changes as compared with control. In addition, the use of CS could promote an earlier recovery of renal oxygen consumption insulin clearance, and sodium absorption in isolated perfused kidney from CS treated intoxicated rat than that from control. Possible mechanisms of CS on drug-induced nephrotoxicity include: (1) Accelerating the regeneration of tubular cells; (2) Protecting the sodium pump activity of tubular cells; (3) Attenuating the tubular cell lysosome hyperfunction stimulated by phagocytosis of AG as well as decreasing the tubular cell lipoperoxidation in response to toxic injury; (4) Reducing the tissue Ca^{++} content.

2.8 Zhao X, Li L. "Cordyceps sinensis in protection of the kidney from cyclosporine A nephrotoxicity]" *Zhonghua Yi Xue Za Zhi.* 1993 Jul;73(7):410-2, 447. Article in Chinese
 This research explored the protective effect of *cordyceps sinensis* (CS) on cyclosporine A nephro-toxicity (CsA-Nx) and the possible mechanism, we studied the kidney changes induced by CsA in rats by light microscopy (LM), electronic microscopy (EM) and morphometrical analysis. At the 15th day after receiving CsA, prominent vacuolation and necrosis were noted microscopically in proximal tubular cells and mitochondria swelling electronmicroscopically. Morphometrical study showed that the epithelial areas of both proximal and distal tubules in the CS group were larger than those of the control group. There were obvious vacuolation (90%) and necrosis in proximal tubular cells at different stages of chronic CsA-Nx. Interstitial edema with mild fibrosis was observed. Mitochondria abnormality was seen electronmicroscopically. Morphometrical analysis showed that the epithelial cell areas of tubules and glomeruli were smaller in the CsA group than

those in the CS group. Both acute and chronic experiments showed that CS could protect the kidney from CsA-Nx and ameliorate the glomerular and interstitial injuries.

2.9 Lin CY, Ku FM, Kuo YC, Chen CF, Chen WP, Chen A, Shiao MS. "Inhibition of activated human mesangial cell proliferation by the natural product of *Cordyceps sinensis* (H1-A): an implication for treatment of IgA mesangial nephropathy." *J Lab Clin Med.* 1999 Jan;133(1):55-63.

Cordyceps sinensis (CS) is a parasitic fungus that has been used as a Chinese medicine for a long time in the treatment of nephritis. Today, the hypothesis about the pathogenesis of immunoglobulin A nephropathy (IgAN) is that nephritogenic IgA immune complexes (IgAIC) go to the kidney to stimulate resting mesangial cells to release cytokines and growth factors. These cytokines and growth factors cause mesangial cell proliferation and release matrix, chemical mediators that lead to the glomerular injury. However, nephritogenic IgAIC in humans is still unknown. To solve this problem previously, we established an in vitro model that showed that cultured human mesangial cells (HMC) stimulated with interleukin-1 (IL-1) plus IL-6 can cause mesangial cell proliferation, increasing production of chemical mediators and superoxide anion. An in vivo model also proved that this culture medium may lead to renal injury with hematuria and proteinuria. Therefore, to fractionate the crude components that can be used in the treatment of patients with IgAN, we cultured HMC, and then an HMC activating model with HMC incubated with IL-1 and IL-6 was established. We fractionated the crude methanolic extracts from fruiting bodies of CS with the use of this in vitro inhibition of HMC activation model as our assay method. In brief, the fruiting bodies were extracted by silica gel column chromatography. One out of 6 column fractions, F-2, significantly inhibited the HMC activation by IL-1 plus IL-6. The acute toxicity test with male Institute of Cancer Research mice showed no liver toxicity or mutagenicity. Then we established an IgAN animal model with R36A (Pneumococcal C-polysaccharide purified from *Streptococcus pneumoniae*) as antigen and anti-R36A IgA monoclonal antibody to form nephritogenic IgA-IC, which can induce hematuria and proteinuria in mice with IgA deposition in the mesangial area. The mice in the IgAN model fed with 1% F-2 in diet had significant reduction of hematuria and proteinuria together with histopathologic improvement. Therefore this fraction was then purified by silica gel column chromatography and high-performance liquid chromatography, which got a purified compound H1-A, which can suppress the activated HMC and alleviate IgAN (Berger's disease) with clinical and histologic improvement. These results give us a new regimen for the treatment of patients with IgAN in the future.

3. Takako Yokozawa, et al., "Increase of Active Oxygen in Rats after Nephrectomy is Suppressed by **Ginseng** Saponin". *Phytotherapy Research*, 96;10:569-572.

Previous studies by this author found that in nephrectomized rats given oral *ginseng* there was suppression of uremic toxins, decreased urinary excretion of protein and inhibited mesangial proliferation showing the arrest of progressive renal disorder from subtotal nephrectomy. Additionally, in experiments using cultured mesangial cells, *ginseng* markedly suppressed cell proliferation, suggesting a role as a radical scavenger. This is important since free radical production is implicated in progressive kidney disorders.

This researcher investigated *Panax ginseng*'s possible protective role in renal failure as a free radical scavenger. Rats had 2/3 of their left kidney resected and total excision of their right kidney. One group of rats was given water while the other was given *ginseng* saponin 25 mg/kg orally for 30 consecutive days. The *ginseng* saponin mixture was composed mainly of ginsenoside-Rb1 (13.5%), Rb2 (8.1%), Rc (9%), Rd (4.5%), Re (6.5%), Rf (3.2%), and Rg1 (4.3%). The effect of *ginseng* saponin on reactive oxygen species scavenging enzymes was examined compared with the control group and the normal rats. Enzyme activities were significantly decreased in the control group compared with the normal group. The values were 39% lower for superoxide dismutase (SOD) activity, 39% lower for catalase activity, and 13% lower for glutathione peroxidase (GSH-Px) activity. The enzyme activities were not as decreased in the *ginseng* group as compared to the normal group. The values were 19% lower for SOD activity and were 2% better than the normal group for catalase activity, while 13% lower for GSH-Px activity. The catalase activity and the SOD activity were significantly better in the *ginseng* saponin group.

The decrease in activity of SOD, catalase and GSH-Px suggests failure of the free radical scavenging system in the nephrectomized rats. Catalase is an antioxidative enzyme present in intracellular granule peroxisomes of animals. It was significantly increased in the animals given *ginseng* saponin. There were no changes in the GSH-Px, an enzyme localized in the matrix of the mitochondria which, like catalase, acts to eliminate H₂O₂. This information suggests that the H₂O₂ scavenging by *ginseng* saponin takes place in the peroxisomes.

The authors speculated from this research that *ginseng* saponin protects the kidney from oxidative stress. They also mention in the discussion that creatinine, methylguanidine and guanidinosuccinic acid were also decreased in the rats given the *ginseng* saponin, suggesting that the elimination of free radicals leads to relief of renal disorder.

4. Takako Yokozawa, et al., "The Ethanol-insoluble Fraction of an Aqueous **Cervi Cornu Vernum** Extract Improves the Condition of Renal Anemia in Rats Fed an Adenine Diet". *Phytotherapy Research*, 94; 8:276-280.

Erythropoietin is used to support RBC production in patients with renal anemia. However, it has side effects of hypertension, increase of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and potassium, producing headaches and thrombosis. In Chinese medicine, *Cervi Cornu Vernum* (unossified horns of stags) is used to stimulate the hematogenic

system and activate blood and body fluid energy. It is used for treating anemia. In light of this, the current researcher investigated *Cervi Cornu Vernum's* benefit on renal anemia. An alcohol soluble fraction, an alcohol insoluble fraction as well as a water soluble fraction of deer antler were investigated.

Renal anemia was induced in rats by feeding them an adenine diet. One group was the control group, one group was fed a water soluble fraction of *Cervi Cornu Vernum*, one group an alcohol soluble fraction, and one group an alcohol insoluble fraction of an aqueous extract. The rats were fed this diet for 30 days. At the end of 30 days, the blood and erythrocyte indices of each group were compared. They were also compared with blood indices of a group of normal rats. The RBC's in the control group decreased to 5.89 (normal group 7.67), Hb was 10.43 (normal group 14.4), Ht 30.68 (normal group 45.51), MCV 58.71 (normal group 59.63), MCH 18.78 (normal 19.10) and MCHC 31.85 (normal group 31.88). The alcohol insoluble fraction had the best RBC indices of the 3 fractions: RBC 6.74, Hb count of 11.82, Ht count of 36.58, MCV of 58.90, MCHC of 32.72. The alcohol insoluble fraction also decreased serum urea nitrogen, methylguanidine and guanidinosuccinic acid significantly. There was no change in creatinine level. The alcohol insoluble fraction group also had a significant increase in total albumin and total protein in the serum.

The fact that *Cervi Cornu Vernum* both reduces renal anemia and reduces the uremic state is significant. Renal anemia is attributable to abnormal hematogenesis, hemolysis or exsanguination. With renal damage, erythrocytes are less likely to be produced and more likely to be broken or lost than under normal conditions. Additionally, in advanced uremia, hematogenesis in the bone marrow is inhibited and there is an acceleration of hemolysis by uremic toxins. Therefore, unlike Erythropoietin which is used to treat renal anemia, *Cervi Cornu Vernum* would improve renal anemia by decreasing the uremic state as well as hematogenic stimulation. The alcohol insoluble fraction contained a high proportion of complex polysaccharides including chondroitin sulphate-like glucosaminoglycans. The author believes *Cervi Cornu Vernum* has a direct action on the erythropoietic system, not just via the decreased uremia. This thought is due to other research with herbal formulas which have a significant benefit on uremic conditions but only mild effects on renal anemia.

5. Takako Yokozawa, et al., "Renal Responses to **Magnesium Lithospermate B** (MLB) in Rats with Adenine-induced Renal Failure". *Phytotherapy Research*, 93;7:235-239.

Renal failure was induced in rats by feeding them an adenine diet. During the adenine feeding period, an aqueous solution of MLB (isolated from an aqueous extract of *Salvia miltiorrhiza* root) was administered orally at a dose of 10 mg/kg body weight per day in drinking water. The control rats received tap water. On days 12 and 24 of this feeding period, urea nitrogen, creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphate were examined. Additionally, renal tissue blood flow and mean blood pressure were measured. In the group given MLB, the blood urea nitrogen was decreased by 17% at day 12 and 36% on day 24 in comparison with the

control group. Serum creatinine decreased by 29% on day 12 and 12% on day 24 compared with the control group's levels. Serum methylguanidine level was not changed on day 12 but on day 24 it decreased by 57% that of the control group. Serum guanidinosuccinic acid level was decreased by 32% on day 12 and day 24 was decreased by 44% of the control group's levels. Serum inorganic phosphate was increased by 57% in the control group. In the magnesium lithospermate B group, there was a 16% decrease in the level as compared with the control rats. Urinary excretion of creatinine increased by 14% that of the control group. The excretion of urinary urea increased by 65% that of the control group. Urinary sodium excretion increased by 47% that of the control group. Renal tissue blood flow was decreased by 36% on day 12 and 62% on day 24 in the control group. In the MLB rats there was an increase of 51% blood flow on day 12 and a 31% increase on day 24 as compared with the control group. The blood pressure in the MLB group was decreased by 7% on day 12 and 8% on day 24 in comparison with the control group.

It is known that rats on adenine diets will show an increase in serum levels of urea nitrogen, creatinine, and inorganic phosphate as the period of adenine feeding continues. The fact that the levels decreased in this experiment suggests MLB may have a protective effect in the progression of renal failure. There was also a suppressive effect on the decrease in renal blood flow as well as the increase in blood pressure. The authors theorize the increased renal blood flow is due to increased formation of PGE2. PGE2 is thought to act on the mesangial cells in the glomeruli and small vessel system of the kidney, causing vasodilation. It also acts as an antagonist against the vasoconstriction effect from thromboxane A2. A previous experiment showed MLB increases urinary excretion of PGE2 and it was attributed to an increase of prostaglandin production in the renal tissue.

PGE2 is also thought to be involved in modulating sodium metabolism. It is interesting to note the urinary sodium excretion decreased as renal failure progressed. In the group given MLB there was significantly increased urinary sodium excretion with a decrease in mean blood pressure.

This study suggests that the chronic administration of MLB to rats with renal failure can ameliorate hypertension by increasing the excretion of sodium and improving renal hemodynamics.

6. Ye Guoji, et. al., "Effects of Polysaccharides Purified from **Salvia miltiorrhiza** radix on Experimental Nephrosis in Rats". *Phytotherapy Research*, 94;8:237-341.

Puromycin aminonucleoside was used to induce renal nephrosis in rats. One group was given a polysaccharide fraction obtained from a hot-water extract of *Salvia miltiorrhiza*. The rats given *Salvia* were broken up into two subgroups: One group was given *Salvia* in oral form, the other group was given an intramuscular injectable form. Both groups showed a significant decrease of urinary protein excretion and an improvement in the levels of serum albumin, cholesterol and lipid peroxide. The extent and severity of lesions of the

epithelial cells in the glomerulus were significantly less in the rats given the *Salvia* extract.

Puromycin aminonucleoside-induced nephrosis has been reported to enhance permeability in the glomerular basement membrane (GBM) due to damage to the charge selective barrier as well as that of the size selective barrier. Some authors have observed nephrosis and damage to the anionic charge barrier which may be the cause of the urinary protein excretion. This polysaccharide fraction of *Salvia* has a polyanionic nature due to carboxyl groups of galacturonic acids. When *Salvia's* carboxyl groups have been removed, the extract's effect on experimental nephrosis has been canceled. The author suggests this *Salvia* fraction may stabilize and restore the GBM structure by its polyanionic nature and lead to improvement of Puromycin aminonucleoside nephrosis.

7. E. Pirotzky, et. al., "Cyclosporin-Induced Nephrotoxicity: Preventive Effect of a PAF-Acether Antagonist, BN 52063". *Transplantation Proceedings*, 88;XX:3(3)665-669.

Rats were given Cyclosporin, a drug which is given to renal graft recipients to decrease renal graft rejection, but it has a nephrotoxic side effect. In this experiment, the Cyclosporin caused an increase in serum urea nitrogen and a reduction in glomerular filtration rate. An experimental group was also given an extract of *Ginkgo* called BN 52063 from Sandoz Pharmaceuticals in Switzerland. It is a mixture of ginkgolides A, B, and C with a molar ratio 2:2:1. The concomitant administration of the BN 52063 with the Cyclosporin did not inhibit its immunosuppressive effect. The BUN and GFR remained similar in the BN 52063 group in comparison to the control group (no drug or BN 52063 given). There was a greater increase in BUN and GFR in the BN 52063 group when the Cyclosporin levels were increased significantly. On histological view, the BN 52063 markedly reduced the tubular and interstitial damage at all dosages of Cyclosporin. The authors concluded BN 52063 significantly protected the kidneys from Cyclosporin damage without altering the effect of the Cyclosporin on graft rejection. BN 52063 has also been shown to protect cardiac grafts from rejection when used alone or in combination with azathioprine or Cyclosporin.

8. Takako Yokozawa and Hikokichi Oura, "Effects of Dan Shen Preparations on Blood and Urine Components in Rats with Renal Failure". *Phytotherapy Research*, 93; 7:231-234.

These researchers previously isolated magnesium lithospermate B, a tetramer of caffeic acid, as an active constituent affecting rats with renal failure. Magnesium lithospermate B was found to activate the kallikrein-kinin system in the kidney, thereby promoting the production and secretion of prostaglandin E₂, inducing dilation of the renal vascular system. This resulted in an increase in renal blood flow and glomerular filtration rate, and acceleration of the excretion of uremic toxins, thus improving uremic symptoms. This present study compares the effects of Dan Shen and Dan Shen compound injections on blood and urine components of rats with renal failure. Renal failure was induced in rats via a 18% casein diet with .75% adenine. During the feeding, 1 ml of compound Dan Shen containing 1 gram of Dan Shen (*Salvia miltiorrhiza*) and Jiang Xiang (*Dalbergie odorifera*) per ml, or non-compound Dan Shen

was injected intraperitoneally daily for 12 days. Control rats were injected with an equal volume of saline. On day 12, a 24 hour urine collection was performed and blood was collected for analyses. The BUN in the control rats was 56.2+/-3.2mg/dl while the rats given compound and noncompound Dan Shen were 44.2+/-3.8 mg/dl (21% decrease) and 44.8+/-1.4 mg/dl (20% decrease) respectively. In rats given the compound Dan Shen injection, the methylguanidine levels were decreased by 61%, the inorganic phosphorus levels by 18% and the malondialdehyde levels by 15%. The creatinine levels were reduced, but not significantly. The non-compound Dan Shen decreased methylguanidine levels by 7%, the inorganic phosphorus levels by 18% and the malondialdehyde levels by 2%. In regards to the urine components, the following results were obtained. The rats injected with the compound Dan Shen had an increase in urinary urea excretion of 11%, creatinine excretion of 12% and sodium excretion of 31%, with a slight increase in inorganic excretion. The non-compound Dan Shen had almost no change in urea or methylguanidine levels. There were no significant changes in urinary excretion of creatinine and potassium with the compound or non-compound Dan Shen.

In rats given the compound Dan Shen injection, the blood levels of urea nitrogen, methylguanidine, inorganic phosphorus and malondialdehyde were significantly decreased, as well as the excretion of methylguanidine. The excretion of creatinine and sodium was significantly increased. In contrast, rats given the non-compound Dan Shen injection showed a significant decrease in blood levels of urea nitrogen and inorganic phosphorus only. The magnesium lithospermate B was .82 mg/ml in the compound formula and the noncompound Dan Shen showed almost no lithospermate B, leading the authors to conclude that it was artificially processed. It was thought that the effects seen in the compound were largely due to the Lithospermate B component. However, the effects did not seem relative to the amounts of lithospermate in the formula. Therefore, the authors theorized that there is an effect from the Jiang Xiang itself or a synergistic effect between it and Dan Shen.

As previously stated, there was a significant decrease in the blood and urine levels of methylguanidine and the blood level of malondialdehyde in rats given the compound Dan Shen formula. Previously, these researchers found in vitro that creatol is produced from creatinine in the presence of hydroxyl radicals and oxidized to methylguanidine via creatone A and creatone B. They also reported that hydroxyl radicals are involved in the in vivo production of creatol from creatinine, that the production of creatol from creatinine is a rate limiting step in methylguanidine production. Therefore, the methylguanidine level seems to reflect a state of oxidative stress in the body. This was previously indicated by experiments using radical scavengers or by the measurement of 8-hydroxydeoxyguanosine content in renal tissue. The results of the present study show that the compound Dan Shen injection somewhat improves such states of oxidative stress in an in vivo situation. These findings are significant, (along with Yokozawa's research) indicating that the involvement

of active oxygen in the proliferation of mesangial cells could be inhibited by magnesium lithospermate B.

9. Stooft, et al., "Does **Fish Oil** Protect Renal Function in Cyclosporin-Treated Psoriasis Patients?" *Journal of Internal Medicine*, 89;226:437-41.

Cyclosporin A (CyA), a fungal cyclic polypeptide, has been shown to suppress both humoral and cell-mediated immunity by affecting early steps of T-cell activation. It is the most extensively used immunosuppressive drug currently used in organ transplantation. It is also used in various immune-mediated diseases such as diabetes mellitus or multiple sclerosis. One of the major side effects of CyA is CyA-induced nephrotoxicity due to possible altered hemodynamics. Glomerular filtration rate is reduced in experiments following CyA administration, probably due to an increased production of thromboxane A₂. Histological examination after prolonged CyA administration reveals tubular damage.

This study examined recalcitrant plaque form psoriatic patients taking 2.5 or 5 mg/kg of CyA for 12 weeks. The groups were divided into group 1 using 2.5 or 5 mg/kg CyA, group 2 using 5 mg/kg CyA combined with 12 grams of fish oil per day for 12 weeks. The fish oil contained 300 mg EPA, and 200 mg DHA and 1 IU vitamin E per capsule. Whole blood CyA levels were checked weekly and every fortnight after 1 month. When renal function deteriorated (increase in serum creatinine level above 30% baseline) or serum potassium levels rose dangerously, the CyA dose was adjusted.

There is a correlation between the actual blood CyA concentration and the degree of loss of renal function in the individual patient. Only those patients of both groups with nearly identical CyA levels were compared. This research found a great difference in variability of susceptibility to CyA induced renal dysfunction. The mean CyA induced impairment of GFR was significantly less in the CyA-Fish Oil group as compared to the CyA group. The numbers were 8.7+/-6.8% vs 18+/-9.6%. Serum creatinine levels rose 11.8+/-10.3% in the CyA/Fish Oil group compared with 21.5+/-26.3% in the CyA group. Calculated renal vascular resistance increased by 19.8+/-14.5% in the CyA group, but didn't change at all in the CyA/Fish oil group.

10. Hosford et. al., "**Natural Antagonists of Platelet-activating Factor**". *Phytotherapy Research*, 88; 2:(1)1-25.

This article covers research on 3 different antagonists of platelet-activating factor. They are **Ginkgolides** from *Ginkgo biloba*, **kadsurenone** and other **lignans isolated from *Piper futokadsurae*** and **gliotoxin-related compounds** from various fungi and bacteria.

Platelet-activating substance is a potent mediator of anaphylaxis and inflammation. It is involved in graft rejection and renal disease. There are specific binding sites for PAF. PAF antagonists interfere with the binding of PAF to its cellular receptors.

Platelet-activating factor is released by isolated perfused rat kidneys and glomeruli as well as by suspensions of medullary cells, although not by tubules. The mesangial cells are thought to be the major source of PAF in the glomerulus. PAF has been shown to cause renal vasoconstriction and release of inflammatory agents, such as Prostaglandins and TXB₂ in the kidney.

All three categories show promise as PAF antagonists and their ability to decrease inflammatory damage in the body, including kidney damage. The most widely studied and most readily available category is the plant *Ginkgo biloba*. Ginkgolides from *Ginkgo biloba* inhibit PAF-induced release of thromboxane B₂ and prostaglandins from primary cultures of human and rat glomerular mesangial cells. BN 52021 (Ginkgolide B) also inhibits PAF-induced formation of reactive oxygen species from cultured mesangial cells and inhibits destruction of the glomeruli. (*Ginkgo* is known to be an antioxidant, which is important since free radical production is implicated in progressive kidney disorders.) In addition, this antagonist inhibits PAF-induced decreases in renal blood flow, glomerular filtration and urinary sodium excretion.

11. Van Der Heide, et. al., "The Effects of Dietary Supplementation with **Fish Oil** on Renal Function in Cyclosporin-Treated Renal Transplant Recipients". *Transplantation*, 90;49:523-527.

Effects of daily supplementation of 6 grams of fish oil (30% C20:5 omega-3 (EPA) and 20% C22:6 omega-3) for 3 months on renal function variables were compared with a placebo control of 6 grams of corn oil, (50% C18:2 omega-6) 9 months after grafting. Ten patients took placebo and 11 patients fish oil. Baseline renal function tests were undertaken. After 3 months, renal function tests were performed again. Nothing improved in the placebo group. In the fish oil group, GFR rose by 20.3% and ERPF (effective renal plasma flow) by 16.4%. In the fish oil group, total renal vascular resistance fell by 21.1% and mean arterial blood pressure fell by 8.6%. Serum creatinine and serum urea fell in the fish oil group. Creatinine clearance rose in the fish oil group.

12. H. Y. Chung, et. al., "Acute Effect of **Salvia Miltiorrhiza** Radix Extract on Renal Function in Renal-Impaired Rats", *Chem. Pharm. Bull*, 1988;36:(1)274-278.

The acute effect of *Salvia miltiorrhiza* extract on renal function was investigated in rats with adenine diet induced renal failure. Glomerular filtration rate, renal plasma flow and renal blood flow progressively decreased as renal impairment increased due to extended administration of adenine. Treatment with the extract increased GFR, RPF and RBF. The extract was ineffective in rats with severe renal failure (24th day of adenine administration).

13. Hua Gao and Eric J. Lien, "Chemistry & Pharmacology of **Salvia miltiorrhiza** Radix". *International Journal of Oriental Medicine*, 92;17:(3)125-133.

The active ingredients of *Salvia* are diterpenoids, polyphenolic acids and a flavanone. The crude extract and its major

constituents have been found to have anti-blood-platelet aggregation action, antimicrobial, coronary dilating and uremic preventive activities. They have shown preventative effects on the development of respiratory distress syndrome.

14. Chaivat Toskulkao, Deechakawan, et. al., "The Low Calorie Natural Sweetener **Stevioside**: Nephrotoxicity and its Relationship to Urinary Enzyme Excretion in the Rat". *Phytotherapy Research*, 94;8:281-286.

The constituent, stevioside, given as a subcutaneous injection caused proximal convoluted tubule damage, increasing serum BUN and creatinine as well as stimulating urinary enzyme level changes indicative of renal damage. There is prior research to this experiment indicating the nephrotoxicity of stevioside.

15. Yokozawa, Fujioka and Oura, "Confirmation that **Tannin-containing Crude Drugs** Have a Uremic Toxin-decreasing Action". *Phytotherapy Research*, 1995;9:1-5.

Nine crude herbs containing tannins (condensed or non-hydrolyzable tannins such as epicatechin, catechin, epigallocatechin and gallic acid) were studied for their effects on rats with renal failure. All the tannin-containing herbs showed an effect against uremic toxins. *Ephedra distachya*, *Terminalia chebula*, and *Geranium thunbergii* markedly reduced blood urea nitrogen, creatinine, methylguanidine, and guanidinosuccinic acid. (This is from an abstract from a Tokyo journal. I have only this limited information.)

16. Grino, J., "BN 52021: A **Platelet Activating Factor Antagonist** for Preventing Post-Transplant Renal Failure - A Double-Blind, Randomized Study". *Ann. Intern. Med.*, 1994;121:345-347.

BN 52021 improved post-transplant renal function in patients receiving kidney cadaveric transplantation. 14 patients received BN 52021 intravenously immediately before surgery and immediately afterward up until 4 days post-transplant. 15 patients received intravenous placebo. The donors of the BN 52021 group were also given BN 52021 intravenously while the placebo donors were given placebo. Post-transplant renal failure was 0% in the BN 52021 group and 33% in the placebo group. Mean values of creatinine decreased faster after transplantation in the BN 52021 group than in the placebo group. The median number of days to reach a serum creatinine level less than 300 micromol/liter was slightly less in the BN 52021 group than the placebo group. Median diuresis at the first day after transplantation was higher in the BN 52021 group than the placebo group. At one week, the cyclosporin levels were similar, but at 2 weeks, the BN 52021 group was significantly higher than the placebo group. Acute rejections in the first 3 months were 14% for the BN 52021 group and 33% for the placebo group. After 3 months, the actual graft survival was 100% in the BN 52021 group and 93% in the placebo group.

17. Inselmann, Blohmer, Kottny, et. al., "Modification of

Cisplatin-Induced Renal p-Aminohippurate Uptake Alteration and Lipid Peroxidation by Thiols, **Ginkgo biloba Extract**, Deferoxamine and Torbafylline". *Nephron*, 1995;70:425-429.

Renal cortical slices were incubated with different cisplatin concentrations in the presence of the following antioxidants: glutathione, N-acetylcysteine, the iron chelator deferoxamine, *Ginkgo biloba* extract or the xanthine derivative torbafylline. All agents tested inhibited cisplatin lipid peroxidation; however, at a cisplatin concentration of 1.0 mg/ml, none of them prevented the decline of cisplatin-induced p-aminohippurate (PAH) uptake. The two strongest agents were deferoxamine and N-acetylcysteine. Deferoxamine was the most effective antioxidant with complete inhibition of cisplatin-induced lipid peroxidation but only preventing the decrease in PAH uptake at a cisplatin concentration of .3 mg/ml. No association was found between lipid peroxidation and decline of PAH uptake. This suggests that lipid peroxidation may only in part participate in cisplatin-induced alteration of PAH uptake.

18. Leishi, "**Rheum officinale**: A New Lead in Preventing Progression of Chronic Renal Failure". *Chin. Med. J.*, 1996;109(1):35-37.

This was a communication about clinical research and cell culture studies as well as animal experimentation conducted by Li Leishi, a Chinese researcher. He communicated the following:

- 1) Effects of *Rheum* on intrinsic renal cells - *Rheum* had a remarkable suppressive effect on the growth of both renal tubular and mesangial cells in vitro. The constituent of *Rheum* called emodin appears to be highly active in suppressing the growth of mesangial and tubular cells in vitro.
- 2) An experimental study with nephrectomized rats was started at the 4th week post-nephrectomy. The rats were divided into 4 groups. Group A - control group; group B - nephrectomized and fed with whole extract of *Rheum off.*; group C - nephrectomized, and fed Enalapril; group D - nephrectomized but not treated. The survival rate at the end of 12 weeks was 75% for group B, 71% for group C, and 61% for group D. The BUN level of the rats treated with *Rheum* was significantly lower than that of the Enalapril group. (He does not state what this was.) *Rheum* and Enalapril both suppressed the degree of azotemia, reduced the urinary protein excretion and lowered serum creatinine. *Rheum* also exerted a prominent beneficial effect on the lipid metabolism of the uremic rats. It lowered the level of cholesterol and LDL, but elevated the HDL level.
- 3) A clinical trial to evaluate effectiveness of *Rheum* in vivo was undertaken. 151 patients with chronic kidney failure were treated with either *Rheum* or an ACE inhibitor (Captopril), as well as the combination of both. All the patients were followed an average of 32.5 months. The average mean serum creatinine at start up was 328+ 92.8. The frequency of end-stage renal failure in the ACE inhibitor group was 54.3%, the *Rheum* group was 25.9%, the combined regimen was 13.1%.

Long-term follow up demonstrates that the progression rate of CRF is retarded and that the nutritional status and quality of life is improved.

19. Hase, Kasimu, et. al., "Preventive Effect of Lithospermate B from *Salvia miltiorrhiza* on Experimental Hepatitis Induced by Carbon Tetrachloride or D-Galactosamine/Liposaccharide". *Planta Medica*, 1997;63:22-26.

A water extract from *Salvia* showed a protective effect on cultured rat hepatocytes against carbon tetrachloride (CCL4) induced necrosis. They isolated the active constituent which turned out to be lithospermate B (a salt of lithospermic acid B), a tetramer of caffeic acid. Lithospermate B was found to have substantial activity in vitro as well as in vivo with induced hepatic injuries by CCL4 or D-galactosamine/lipopolysaccharide.

20. Bokemeyer, C., et. al., "Silibinin Protects Against Cisplatin-induced Nephrotoxicity without Compromising Cisplatin or Ifosfamide Anti-Tumor Activity". *Br. J. Cancer*, 1996;74(12): 2036-2041.

Cisplatin is commonly used in the treatment of testicular cancer, but one of its many side effects is nephrotoxicity. Long term damage affects the proximal tubular apparatus and is detected by increased urinary excretion of brush border enzymes, such as L-alanine-aminopeptidase, and magnesium. In this study the flavonoid of *Silybum*, silibinin was used as a renal protectant for cisplatin-induced nephrotoxicity in rats. Silibinin given by itself had no effect on rat renal function. Infusion of silibinin given prior to cisplatin resulted in significant decrease in glomerular (indicated by creatinine clearance and serum urea level) and tubular toxicity (excretion of brush-border enzymes and magnesium). Silibinin did not change the cytotoxic activity of cisplatin or 4-hydroperoxy-ifosfamide in vitro. This proves silibinin to be of use in renal protection from cisplatin and perhaps may be useful in protecting renal function from other damaging factors.

- 20.25 Wenzel S, Stolte H, Soose M., "Effects of silibinin and antioxidants on high glucose-induced alterations of fibronectin turnover in human mesangial cell cultures". *J Pharmacol Exp Ther.* 1996; Dec;279(3):1520-6.

Incubation of Human mesangial cells (HMC) with high glucose induced fibronectin (FN) alterations via oxygen-free radicals which was completely counteracted by either silibinin or a radical scavenger cocktail. Silibinin alone had no effect on either protein synthesis or culture growth. The study further substantiates the proposed role of silibinin in the amelioration of glucose cytotoxicity in renal cells.

21. Gaedeke, J. et. al., "Cisplatin Nephrotoxicity and Protection by Silibinin". *Nephrol. Dial. Transplant.* 1996; Jan; 11(1):55-62.

Two groups of rats were followed. Both groups received an injection of cisplatin (5 mg/kg body weight, i.v.) the second

group additionally received (200 mg/kg body weight, i.v.) 1 hour prior to the cisplatin. The cisplatin caused decreases of creatinine clearance, increases in proteinuria and in the urinary activity of the proximal tubular enzymes alanine aminopeptidase and N-acetyl-beta-D-glucosaminidase and in renal magnesium wasting. The effects of cisplatin on creatinine clearance and proteinuria were completely prevented with the pretreatment of silibinin. Proximal tube impairment was ameliorated (decreased enzymuria and magnesium wasting. Treatment with silibinin drastically decreased morphological alterations of the S3-segment of the proximal tubule 4 days after cisplatin administration. This research shows cisplatin damage to glomerular and tubular renal function can be totally or partly ameliorated by silibinin.

22. Argani H, Rahbaninoubar M, Ghorbanihagjo A, Golmohammadi Z, Rashtchizadeh " Effect of L-Carnitine on the Serum Lipoproteins and HDL-C Subclasses in Hemodialysis Patients". *N.Nephron Clin Pract.* 2005 Aug 9;101(4):c174-c179

Treatment with 500 mg/day carnitine taken orally for 2 months reduced serum levels of TG and VLDL-C, and increased HDL-C, HDL(2)-C and albumin in HD patients in this study.

Methods: Forty HD patients with a mean (+/- SD) age of 53 +/- 13 years were treated with 500 mg/day carnitine taken orally for 2 months. Patients were used as their own controls (prior to treatment). There was a significant decrease in serum TG (2.22 +/- 0.99 vs. 1.93 +/- 1.07 mmol/l, p < 0.01) and VLDL-C (0.93 +/- 0.36 vs. 0.81 +/- 0.34 mmol/l, p = 0.01) and a marked increase in HDL-C (0.9 +/- 0.16 vs. 1.06 +/- 0.24 mmol/l, p < 0.05), HDL(2)-C (0.17 +/- 0.06 vs. 0.27 +/- 0.14 mmol/l, p < 0.05) and albumin (37 +/- 4 vs. 42 +/- 5 g/l, p = 0.01) levels. The serum levels of total cholesterol (4.61 +/- 0.89 vs. 4.5 +/- 0.95 mmol/l, p = 0.1), LDL-C (2.78 +/- 0.85 vs. 2.6 +/- 0.89 mmol/l, p > 0.05), HDL(3)-C (0.73 +/- 0.1 vs. 0.79 +/- 0.17 mmol/l, p > 0.05), hemoglobin, hematocrit, and intradialytic blood pressure did not change after the treatment although the researchers had hoped thought they might.

23. Kadiroglu AK, Yilmaz ME, Sit D, Kara IH, Isikoglu B. " The evaluation of postdialysis L-carnitine administration and its effect on weekly requiring doses of rHuEPO in hemodialysis patients." *Ren Fail.* 2005;27(4):367-72.

This study evaluated the effect of postdialysis administration of parenteral L-carnitine supplementations on hematological parameters and also on weekly required dose of the recombinant human erythropoietine (rHuEPO) in hemodialysis (HD) patients. 34 stable patients (17 male, 17 female) were enrolled in the study who were on rHuEPO therapy and a regular maintenance hemodialysis at 5 h, three times a week with bicarbonate dialysate and with biocompatible membranes. rHuEPO was administered

subcutaneously at 80-120 U/kg/week. The patients were divided into two groups: Group 1, rHuEPO therapy (n=17) and Group 2, rHuEPO therapy + L-carnitine (n=17). L-carnitine (L-carnitine ampul, Santa Farma) 1 g was injected postdialysis intravenously via venous route of the dialytic set, three times a week. The patient's hemoglobin (Hgb), hematocrit (Hct), serum iron (Fe(+2)), total iron-binding capacity (TIBC), transferrin saturation index (TSI), and serum ferritin (Fer) levels were followed during the 16-week period. In group 1, Hgb: 7.9-10.8 g/dl, Hct: 25.3-32.5%; in group 2, Hgb: 10.2-11.8 g/dl, Hct: 30.6-35.4%, respectively ($p < 0.05$). The target Hgb/Hct values were achieved at the end of the study in both groups. Both groups were the same according to their serum Fe(+2) markers ($p > 0.05$). But unlike serum Fe(+2) markers, there were significant differences on weekly requiring doses of rHuEPO therapy between groups. While in group 1, the mean weekly requiring dose of rHuEPO was 6529 U/week (120 U/kg/week) at the beginning of the study, and maintenance weekly requiring dose of rHuEPO was 3588 U/week (66 U/kg/week) at the end of the study, in group 2, they were 4882 U/week (80 U/kg/week), and 1705 U/week (28 U/kg/week), respectively. According to these values, the total reduction in weekly requiring dose of rHuEPO was 45% in group 1, and 65% in group 2; the net gain was 20% in group 2 ($p < 0.05$).

24. Savica V, Santoro D, Mazzaglia G, Ciolino F, Monardo P, Calvani M, Bellinghieri G, Kopple JD, "L-carnitine infusions may suppress serum C-reactive protein and improve nutritional status in maintenance hemodialysis patients". *J Ren Nutr.* 2005; Apr;15(2):225-30.

This study evaluated MHD patients to evaluate the effects of L-carnitine on maintained hemodialysis patients treated by observing inflammation and protein-energy nutritional status. MHD patients were assigned to receive intravenous injections of L-carnitine 20 mg/kg (n = 48) or placebo (n = 65) thrice weekly at the end of each hemodialysis treatment for 6 months. The carnitine-treated group showed a statistically significant decrease in serum C-reactive protein and increase in serum albumin and transferrin, blood hemoglobin, and body mass index. Conversely, in the placebo-treated group, a significant decrease was reported for serum albumin, serum transferrin, and body mass index, whereas the other considered measures did not change significantly. These preliminary findings suggest that in MHD patients, L-carnitine therapy may suppress inflammation, particularly among those patients with C-reactive protein $> \text{or} = 3 \text{ mg/dL}$, and may improve protein-energy nutritional status.

25. Pertosa G, Grandaliano G, Simone S, Soccio M, Schena FP, "Inflammation and carnitine in hemodialysis patients". *J Ren Nutr.* 2005; Jan;15(1):8-12.

Uremic patients have enhanced inflammatory responses and an increased oxidative load. This affects lipids, CHO's, and proteins. This study examines the antioxidative bal-

ancing effects of L-Carnitine by evaluating the effect of L-carnitine supplementation on the peripheral blood mononuclear cell (PBMC) responses to oxidative stress induced by different hemodialysis membranes. Regular L-carnitine supplementation in HD patients were shown to improve cellular defense against chronic inflammation and oxidative stress, most likely by modulating the specific signal transduction cascade activated by an overproduction of proinflammatory cytokines and oxidative stress.

26. Steiber AL, Weatherspoon LJ, Spry L, Davis AT. "Serum carnitine concentrations correlated to clinical outcome parameters in chronic hemodialysis patients." *Clin Nutr.* 2004; Feb;23(1):27-34.

The purpose of this study was to determine whether any correlations exist between carnitine status and selected clinical parameters in hemodialysis (HD) patients. The subjects (n=49) were 60+/-16 (mean+/-SD) years of age and 48% male. Fifteen percent of the subjects had type 1 diabetes mellitus (DM), 29% had type 2 DM, and 25% had left ventricular hypertrophy (LVH). The serum-free and total carnitine, and acylcarnitine concentrations were: 40.3+11.8 micromol/l, 22.8+/-7.3, and 17.5+/-5.9 micromol/l, respectively. The serum acylcarnitine to free carnitine ratio (A/F) was 0.80+/-0.27. Blood urea nitrogen (BUN), parathyroid hormone and ejection fraction were positively correlated and age and left atrial dilation (cm) were negatively correlated with serum total carnitine ($P < 0.05$). BUN and hematocrit were positively correlated ($P < 0.05$) and age was negatively correlated with free carnitine. Subjects who used mannitol or were male had significantly higher concentrations of both free and total carnitine, respectively ($P < 0.05$). Subjects using aspirin had lower concentrations of serum total carnitine ($P < 0.10$).

27. Kuhlmann MK, Horsch E, Burkhardt G, Wagner M, Kohler H, "Reduction of cisplatin toxicity in cultured renal tubular cells by the bioflavonoid quercetin". *Arch Toxicol.* 1998; Jul-Aug;72(8):536-40.

Quercetin (QC), a polyphenolic compound widely distributed in fruits and vegetables sensitizes cancer cells to cisplatin (CP). This study was undertaken to see if it also increases the susceptibility of the kidneys to cisplatin toxicity. The effects of various bioflavonoids on CP toxicity in an in vitro model of cultured tubular epithelial cells (LLC-PK1) was examined. Viability of LLC-PK1 cells, as assessed by lactate dehydrogenase (LDH) release and MTT-test, was affected by CP (100-400 micromol) in a time and dose dependent fashion. Pretreatment of cells with QC for 3 h significantly reduced the extent of cell damage. The protective activity of QC was concentration dependent, starting at 10-25 micromol and reaching a plateau between 50 and 100 micromol. Other bioflavonoids (catechin, silibinin, rutin) did not diminish cellular injury, even at higher concentrations (100-500 micromol). Quercetin itself showed some intrinsic cytotoxicity at concentrations exceeding 75 micromol. Our data indicate that quercetin reduces cisplatin toxicity in cultured tubular epithelial cells. The exact mechanism of protection is unclear, though scavenging of

free oxygen radicals may play an important role.

28. Singh D, Chander V, Chopra K. "The effect of quercetin, a bioflavonoid on ischemia/reperfusion induced renal injury in rats". *Arch Med Res.* 2004; Nov-Dec;35(6):484-94. The effect of quercetin against the damage inflicted by reactive oxygen species (ROS) during renal I/R was investigated in Sprague-Dawley rats using histopathological and biochemical parameters. In one set of experiments, animals were unilaterally nephrectomized and subjected to 45 min of left renal pedicle occlusion, and in another set both renal pedicles were occluded for 45 min followed by 24 h of reperfusion. Quercetin (2 mg/kg, 30 mg/kg, i.p. and 100 mg/kg, p.o.) was administered 2 h prior to ischemia. At the end of the reperfusion period, rats were sacrificed. Thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH) levels, glutathione reductase (GR), catalase (CAT), and superoxide dismutase (SOD) activities were determined in renal tissue. Serum creatinine and blood urea nitrogen (BUN) concentrations were measured for the evaluation of renal function. Ischemic control animals demonstrated severe deterioration of renal function, renal morphology and a significant renal oxidative stress. Pretreatment of animals with quercetin (2 mg/kg and 30 mg/kg, i.p.) markedly attenuated renal dysfunction, morphological alterations, reduced elevated TBARS levels and restored the depleted renal antioxidant enzymes, whereas the (100 mg/kg, p.o.) dose of quercetin failed to revert the renal I/R induced changes. ROS appear to play a causal role in I/R induced renal injury and quercetin exerts protective and deleterious effects in the kidney, depending upon the dose.

28.5 Singh D, Chander V, Chopra K.. "**Quercetin**, a bioflavonoid, attenuates ferric nitrilotriacetate-induced oxidative renal injury in rats". *Drug Chem Toxicol.* 2004; May;27(2):145-56. An iron chelate, ferric nitrilotriacetate (Fe-NTA), induces acute proximal tubular necrosis as a consequence of lipid peroxidation and oxidative tissue damage, that eventually leads to high incidence of renal adenocarcinomas in rodents. This study investigated the effect of quercetin, on Fe-NTA-induced nephrotoxicity in rats. One hour after a single intraperitoneal (i.p.) injection of Fe-NTA (8 mg iron/kg), a marked deterioration of renal architecture and renal function was observed. Fe-NTA induced a significant renal oxidative stress demonstrated by elevated thiobarbituric acid reacting substances (TBARS) and reduction in activities of renal catalase, superoxide dismutase and glutathione reductase. Pretreatment of animals with quercetin (2 mg/kg, i.p.) 30 minutes before Fe-NTA administration markedly attenuated renal dysfunction, morphological alterations, reduced elevated TBARS and restored the depleted renal antioxidant enzymes. These results clearly demonstrate the role of oxidative stress and its relation to renal dysfunction, and suggest a protective effect of quercetin on Fe-NTA-induced nephrotoxicity in rats.

29. Anjaneyulu M, Chopra K. "Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats". *Clin Exp Pharmacol Physiol.* 2004; Apr;31(4):244-8. Oxidative Stress is linked to microvascular complications and end stage renal disease in diabetics. Diabetes was induced in

Sprague-Dawley rats with a single intravenous injection of STZ (45 mg/kg). Four weeks after STZ injection, quercetin (10 mg/kg per day) was given orally for 4 weeks in both control and diabetic rats. Plasma glucose levels and bodyweights were measured at 4 and 8 weeks after the STZ injection. At the termination of the experiments, urine albumin excretion, urine output, serum creatinine, blood urea nitrogen, creatinine and urea clearance were measured. The renal oxidative stress marker malonaldehyde, glutathione levels and the anti-oxidant enzymes superoxide dismutase and catalase were measured in kidney homogenate. Streptozotocin-injected rats showed significant increases in blood glucose, polyuria, proteinuria and a decrease in bodyweight compared with age-matched control rats. After 8 weeks, diabetic rats exhibited renal dysfunction, as evidenced by reduced creatinine and urea clearance, and proteinuria along with a marked increase in oxidative stress, as determined by lipid peroxidation and activities of key anti-oxidant enzymes. Treatment with quercetin significantly attenuated renal dysfunction and oxidative stress in diabetic rats. This study shows the anti-oxidative mechanism most likely being responsible for the nephroprotective action of quercetin.

30. Makino, Ono, Matsuyama, Nogaki, Miyawaki, Honda, & Muso. "Suppressive effects of **Perilla frutescens** on IgA nephropathy in HIGA mice". *Nephrology Dialysis Transplantation* 2003; 18: 484-490.

Mice that spontaneously develop high levels of serum immunoglobulin A (IgA) along with mesangial IgA deposition were used in this study to test Perilla for protective effects of Perilla on the kidney. One group of mice were given a low dose Perilla decoction at 50 mg/kg, another group was given a high dose Perilla decoction at 500 mg/kg, another group was given rosmarinic acid at 50 mg/kg (a known active constituent of Perilla and calculated to be equal to the dose of rosmarinic acid in the high dose Perilla decoction), and there was a control group. These were all fed orally in drinking water for a period of 16 weeks. Perilla suppressed proteinuria (control 14.1±1.6), (low dose group 11.5±0.9), (high dose group 9.6±2), (rosmarinic acid group 9.4±1.8). Perilla decreased the average number of cells in the glomerular cross-sections in a dose dependent manner. Rosmarinic acid significantly suppressed IgA deposition but not as well as high dose Perilla and additionally it did not suppress IgG deposition. Serum IgA itself was decreased in a dose dependant manner in the Perilla groups. Rosmarinic acid also depressed the IgA levels significantly but not as much as either of the Perilla groups. IgA from cultured peyer's patches of Perilla treated mice were significantly reduced compared with controls. The peyer's patches in the rosmarinic acid group was only slightly decreased compared with controls. However the spleen cells derived from the Perilla treated mice and rosmarinic acid mice both released significantly less IgA than cells from the control group with the rosmarinic acid having the most effect. The results suggest that Perilla decoction suppressed IgA production in the intestinal immune system in vivo while the rosmarinic acid did not do much to the peyer's patches. It is assumed something other than rosmarinic acid in Perilla is associated with this gut activity.

The decoction contained several polysaccharides that exert a variety of effects on the immune system including serum interferon-activity *in vivo* and suppression of histamine degranulation from mast cells *in vitro*. They are thought to have a direct effect on the intestinal mucosal immune system. The spleen results suggest that rosmarinic acid had a IgA reduction effect after being absorbed into circulation. The authors thought the suppression of IgA was via generation of the Th1 response in the mice. The perilla decoction caused suppression of IgA nephropathy-like features in HIGA mice. Rosmarinic acid and other not yet known constituents in the decoction may synergistically suppress IgA production, which in turn is thought to down regulate glomerular IgA deposition, proteinuria and mesangial cell proliferation.

30.5 Makino T, Ono T, Muso E, Yoshida H, Honda G, Sasayama S. "Inhibitory effects of rosmarinic acid on the proliferation of cultured murine mesangial cells". *Nephrol Dial Transplant*. 2000; Aug;15(8):1140-5.

In this study they examined the effects of rosmarinic acid on cultured murine mesangial cell proliferation. Cultured murine mesangial cells were stimulated by growth factors with or without rosmarinic acid, and [(3)H]thymidine incorporation was measured in regard both to signal transduction and to cell cycle dependency. In other experiments, mRNA extracted from the cells was analysed by Northern blotting. Rosmarinic acid inhibited the cell proliferation induced by platelet-derived growth factor (PDGF) ($P < 0.01$; IC(50) values, 1.4 microg/ml) or tumour necrosis factor- α ($P < 0.01$; IC(50) values, 3.8 microg/ml), and these effects involved both the G(0)/G(1) and G(1)/S phases of the cell cycle. Rosmarinic acid also suppressed the mRNA expressions of PDGF and c-myc in PDGF-stimulated mesangial cells. Rosmarinic acid appears to inhibit cytokine-induced mesangial cell proliferation and suppresses PDGF and c-myc mRNA expression in PDGF-stimulated mesangial cells. Rosmarinic acid in Labiatae herbs might be a promising agent to prevent mesangial cell proliferation.

31. Luciak M.. "Antioxidants in the treatment of patients with renal failure". *Rocz Akad Med Bialymst*. 2004;49:157-161.

A review of antioxidant use in renal failure.

Renal failure is accompanied by oxidative stress, which is caused by enhanced production of reactive oxygen species and impaired antioxidant defense. The suggested therapeutical interventions aimed at reducing oxidative stress in chronic renal failure patients are as follows: 1) the use of biocompatible membranes, ultrapure dialysate, and removal of endogenous foci of infection; 2) haemolipodialysis, and electrolysed reduced water for dialysate preparation; 3) administration of antioxidants (alpha-tocopherol, ascorbic acid, N-acetylcysteine, reduced glutathione); 4) substances possibly affecting oxidative stress indirectly (erythropoietin, sodium selenite). As currently available

data have, as yet, provided rather limited evidence for the clinical benefit of antioxidant interventions, at present it is untimely to give practical recommendations with regard to antioxidant treatment of patients with renal failure.

31.5 Francesco Locatelli, Bernard Canaud, Kai-Uwe Eckardt, Peter Stenvinkel, Christoph Wanner and Carmine Zoccali. "Oxidative stress in end-stage renal disease: an emerging threat to patient outcome" *Nephrol Dial Transplant* 2003; 18: 1272-1280 Consensus Paper

Patients affected by end-stage renal disease (ESRD) experience an excess of morbidity and mortality due to cardiovascular disease (CVD), which cannot be fully explained by the classical CVD risk factors. Among emerging CVD risk factors, oxidative stress is currently being given emphasis. Methods. We achieved a consensus on key points relating to oxidative stress in ESRD patients. Results. ESRD patients are subjected to enhanced oxidative stress, as a result of reduced anti-oxidant systems (vitamin C and selenium deficiency, reduced intracellular levels of vitamin E, reduced activity of the glutathione system) and increased pro-oxidant activity (advanced age, high frequency of diabetes, chronic inflammatory state, uraemic syndrome, bioincompatibility of dialysis membranes and solutions). Oxidative stress and inflammation are deeply interrelated, as different oxidant free radicals are generated by phagocytic cells in response to inflammatory stimuli: both are related to endothelial dysfunction, as the endothelium is a source and a target of oxidants and participates in the inflammatory response. There is growing evidence, from experimental and clinical studies, that oxidative stress may be implicated in the pathogenesis of atherosclerosis and other complications of ESRD, namely dialysis-related amyloidosis, malnutrition and anaemia. Given that free radicals have very short half-lives (seconds), the clinical assessment of oxidative stress is based on the measurement of different stable oxidized compounds (such as lipid peroxidation products, advanced glycation and oxidation lipid and protein products, nucleic acid oxidation derivatives) or antibodies directed against oxidized epitopes (such as anti-oxidized low-density lipoprotein antibodies). At the same time, both enzymatic anti-oxidants (superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic antioxidants (glutathione, vitamin C, vitamin E, negative inflammatory proteins) can be evaluated. However, many laboratory methods assessing various oxidative stress components still have to be standardized. Moreover, it is still uncertain whether it is better measuring plasma and/or intracellular concentrations or activities of these components. The possibility of improving patient outcome by therapeutic interventions aimed at reducing oxidative stress, e.g. by vitamin C or vitamin E supplementation, currently is to the fore, but results so far have remained inconclusive. Conclusions. It is important to consider oxidative stress as a potentially important source of patient morbidity and mortality, although this knowledge is not yet immediately applicable in the clinical arena. Further

well-designed, randomized controlled clinical trials with anti-oxidants (e.g. vitamin E, vitamin C, N-acetyl cysteine, L-arginine) are required to establish evidence-based recommendations for clinical practice.

32. Chen J, He J, Ogden LG, Batuman V, Whelton PK. "Relationship of serum antioxidant vitamins to serum creatinine in the US population". *Am J Kidney Dis.* 2002; Mar;39(3):460-8.

Several clinical studies have reported that serum vitamin A levels were higher but serum vitamin C levels were lower among patients with end-stage renal disease. However, the relationship of antioxidant vitamins to renal function had not been studied in the general population. This study examined the relationship of serum antioxidant vitamin levels to serum creatinine levels and risk for hypercreatininemia in a representative sample of 6,629 non-Hispanic whites, 4,411 non-Hispanic blacks, and 4,480 Mexican Americans aged 18 years or older who participated in the Third National Health and Nutrition Examination Survey. Serum vitamin A level was positively and significantly associated with serum creatinine level, whereas serum vitamin C level was inversely and significantly associated with serum creatinine level. This study provides supports the hypothesis that antioxidant vitamins may have an important role in the pathogenesis of chronic renal failure.

33. Singh RB, Khanna HK, Niaz MA., "Randomized, double-blind placebo-controlled trial of coenzyme Q10 in chronic renal failure: Discovery of a new role". *Journal of Nutritional & Environmental Medicine.* 2000; 10(4) 281-288
 Purpose: This study examines whether treatment with coenzyme Q10 can improve renal function in chronic renal failure. Design: Randomized, double-blind, placebo-controlled trial. Materials and Methods: Subjects (n = 21) with available records of chronic renal failure on dialysis or not on dialysis (serum creatinine 5 mg dl-1 or above) were randomly divided into intervention (n = 11) and control (n = 10) groups. The intervention group was administered coenzyme Q10 (60 mg TID) and the placebo group inert fibre (cellulose, 1 g TID) for a period of 4 weeks. The coenzyme Q10 group showed a significant reduction in serum creatinine, blood urea and a significant increase in creatinine clearance and urine output compared to the placebo group after the 4-week trial period. The baseline values of these parameters were comparable between the two groups. The frequency of dialysis and the proportion of subjects on dialysis were comparable at baseline. However, after 4 weeks, the subjects on dialysis were significantly fewer in the coenzyme Q10 group than the placebo group (36.2% vs. 90.0%, p < 0.02). Plasma levels of antioxidant vitamins A, E and C and beta-carotene showed a significant increase whereas thiobarbituric acid reactive substances, diene conjugates and malondialdehyde showed a significant reduction in the coenzyme Q10 group compared to the control group. Treatment with coenzyme

Q10 improves renal function in patients with chronic renal failure and decreases the need for dialysis in patients on chronic dialysis. Long-term follow-up is necessary to confirm these results.

33.2 Singh RB, Khanna HK, Niaz MA "Randomized, Double-Blind Placebo-Controlled Trial of Coenzyme Q10 in Chronic Renal Failure: Discovery of a New Role," , *J Nutr Environ Med,* 2000;10:281-288.36843

In studying 21 patients with chronic renal failure who were on or off dialysis (serum creatinine levels of 5 mg/dl or above), 11 were assigned to an intervention group that received coenzyme Q10 at 60mg, 3 times daily, compared with 10 subjects who received a placebo (cellulose) at 1 g, 3 times daily. There was a significant reduction in serum creatinine and blood urea and a significant increase in creatinine clearance and urine output in the coenzyme Q10 group versus the placebo group after the 4-week trial. After 4 weeks, the subjects on dialysis were significantly fewer in the coenzyme Q10 group (36.2%) than in the placebo group (90.0%). There was a significant increase in plasma levels of vitamins A, E, C and beta-carotene, whereas thiobarbituric acid reactive substances, diene conjugates and malondialdehyde showed a significant reduction in the coenzyme Q10 group compared with the control group. Q-Gel®, which is a hydrosoluble coenzyme Q10, was used as the coenzyme Q10 substance in this study.

33.4 Dlugosz A, Kuzniar J, Sawicka E, Marchewka Z, Lembas-Bogaczyk J, Sajewicz W, Boratynska M. "Oxidative stress and coenzyme Q10 supplementation in renal transplant recipients." *Int Urol Nephrol.* 2004;36(2):253-8.

This study was to evaluate the protective role of CoQ10 in renal transplant recipients on lipid peroxidation and lipids parameters, as well as its influence on antioxidant enzymes, neutrophils chemiluminescence and urinary enzymes. The study was performed in 11 long term allograft recipients treated additionally with CoQ10 90 mg/day in three doses, 30 mg each for four weeks. The malonyldialdehyde (MDA) and 4-hydroxynonenal (4-HNE), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and the basic parameters of lipid metabolism such as total cholesterol (TC), high and low density lipoproteins (HDL, LDL), triglycerides (TG), atherogenicity indicators [LDL/HDL; (TC-HDL)/HDL] were evaluated. The chemiluminescence of neutrophils (luminol, fLMP-method) were measured and the activity of N-acetyl-beta-D-glucosaminidase (NAG), alanylaminopeptidase (AAP), elastase, alpha-1-antitrypsin. All parameters were estimated before and after CoQ10 treatment. Statistically significant changes were noticed with the LDL and atherogenicity indicators (p < 0.01) (decrease) as well as HDL level (p < 0.001) (increase).

Also the significant decrease of fMLP stimulated PMNL chemiluminescence ($p < 0.05$) confirms the antioxidative properties of CoQ10. The significant increase of NAG activity ($p < 0.05$) can't be the result of nephrotoxic effect, because NAG-B is unchanged. Serum concentration of creatinine and cyclosporine A in renal allograft recipients was unchanged after CoQ10 treatment. The presented data shows that further study with CoQ10 treatment in renal transplant in larger numbers and over longer periods should be considered.

34. Melhem et al., "Effects of Dietary Supplementation of alpha-Lipoic Acid on Early Glomerular Injury in Diabetes Mellitus". *J Am Soc Nephrol.* ,2001; 12:124-133.

This study, examines the effect of Lipoic acid on glomerular injury in streptozotocin diabetic rats after 2 mo on unsupplemented diets and in diabetic rats that received the lowest daily dose of dietary LA (30 mg/kg body wt), VE (100 IU/kg body wt), or vitamin C (VC; 1 g/kg body wt), which detectably increased the renal cortical content of each antioxidant. Blood glucose values did not differ among the diabetic groups. At 2 mo, inulin clearance, urinary albumin excretion, fractional albumin clearance, glomerular volume, and glomerular content of immunoreactive transforming growth factor-(TGF-) and collagen 1 (IV) all were significantly increased in unsupplemented diabetic rats compared with age-matched nondiabetic controls. With the exception of inulin clearance, LA prevented or significantly attenuated the increase in all of these glomerular parameters in diabetic rats, as well as the increases in renal tubular cell TGF-seen in diabetic rats. At the dose used, VE reduced inulin clearance in diabetic rats to control levels but failed to alter any of the other indices of glomerular injury or to suppress renal tubular cell TGF-in diabetic rats. VC suppressed urinary albumin excretion, fractional albumin clearance, and glomerular volume but not glomerular or tubular TGF- or glomerular collagen 1 (IV) content. LA but not VE or VC significantly increased renal cortical glutathione content in diabetic rats. These data indicate that LA is effective in the prevention of early diabetic glomerular injury and suggest that this agent may have advantages over high doses of either VE or VC.

35. Melhem et al., "-Lipoic Acid Attenuates Hyperglycemia and Prevents Glomerular Mesangial Matrix Expansion in Diabetes". *J Am Soc Nephrol* 13: 108-116, 2002.

This study examined the effects of chronic Lipoic acid supplementation (30 mg/kg body wt per d) on nephropathy in diabetic rats after 7 mo of diabetes. Compared with control rats, diabetic rats developed increased urinary excretion of albumin and transforming growth factor, renal insufficiency, glomerular mesangial matrix expansion, and glomerulosclerosis in association

with depletion of glutathione and accumulation of malondialdehyde in renal cortex. Lipoic acid prevented or ameliorated all of these changes in diabetic rats. Because chronic Lipoic acid supplementation also attenuated hyperglycemia in diabetic rats after 3 mo, its effects on renal injury were compared with treatment of rats with sufficient insulin to maintain a level of glycemic control for the entire 7-mo period (D-INS) equivalent to that observed with Lipoic acid during the final 4 mo. Despite superior longitudinal glycemic control in D-INS, urinary excretion of albumin and transforming growth factor, glomerular mesangial matrix expansion, the extent of glomerulosclerosis, and renal cortical malondialdehyde content were all significantly greater, whereas cortical glutathione content was lower than corresponding values in diabetic rats given Lipoic acid. Thus, the renoprotective effects of Lipoic acid in diabetic rats was not attributable to improved glycemic control alone but also likely reflected its antioxidant activity. The combined antioxidant and hypoglycemic actions of Lipoic acid both may contribute to its utility in preventing renal injury and other complications of diabetes.

36. Takaoka M, Ohkita M, Kobayashi Y, Yuba M, Matsumura Y., "Protective effect of alpha-lipoic acid against ischaemic acute renal failure in rats". *Clin Exp Pharmacol Physiol.* 2002; Mar;29(3):189-94.

This study, examined the protective effect of alpha-lipoic acid (LA), in rats with ischaemic acute renal failure (ARF). Ischaemic ARF was induced by occlusion of the left renal artery and vein for 45 min followed by reperfusion, 2 weeks after contralateral nephrectomy. Blood urea nitrogen (BUN), plasma concentrations of creatinine (Pcr) and urinary osmolality (Uosm) were measured for the assessment of renal dysfunction. Creatinine clearance (Ccr) and fractional excretion of Na⁺ (FENa) were used as indicators of glomerular and tubular function, respectively. Renal function in ARF rats decreased markedly 24 h after reperfusion. Intraperitoneal injection of LA at a dose of 10 mg/kg before the occlusion tended to attenuate the deterioration of renal function. A higher dose of LA (100 mg/kg) significantly ($P < 0.01$) attenuated the ischaemia/reperfusion-induced increases in BUN (19.1 +/- 0.7 vs 7.2 +/- 0.7 mmol/L before and after treatment, respectively), Pcr (290 +/- 36 vs 78.1 +/- 4.2 micromol/L before and after treatment, respectively) and FENa (1.39 +/- 0.3 vs 0.33 +/- 0.09% before and after treatment, respectively). Treatment with 100 mg/kg LA significantly ($P < 0.01$) increased Ccr (0.70 +/- 0.13 vs 2.98 +/- 0.27 mL/min per kg before and after treatment, respectively) and Uosm (474 +/- 39 vs 1096 +/- 80 mOsmol/kg before and after treatment, respectively). Histopathological examination of the kidney of ARF rats revealed severe lesions. Tubular necrosis ($P < 0.01$), proteinaceous casts in tubuli ($P < 0.01$) and medullary congestion ($P < 0.05$) were significantly

suppressed by the higher dose of LA. A marked increase in endothelin (ET)-1 content in the kidney after ischaemia/reperfusion was evident in ARF rats (0.43 +/- 0.02 ng/g tissue) compared with findings in sham-operated rats (0.20 +/- 0.01 ng/g tissue). Significant attenuation ($P < 0.01$) of this increase occurred in ARF rats treated with the higher dose of LA (0.24 +/- 0.03 ng/g tissue). These results suggest that administration of LA to rats prior to development of ischaemic ARF prevents renal dysfunction and tissue injury, possibly through the suppression of overproduction of ET-1 in the postischaemic kidney.

37. Somani SM, Husain K, Whitworth C, Trammell GL, Malafa M, Rybak LP, "Dose-dependent protection by lipoic acid against cisplatin-induced nephrotoxicity in rats: antioxidant defense system" *Pharmacol Toxicol.* 2000; May;86(5):234-41.

This study investigated the effect of graded doses of lipoic acid pretreatment against cisplatin-induced nephrotoxicity. Male Wistar rats were divided into six groups and treated as follows: 1) vehicle (saline) control; 2) cisplatin (16 mg/kg, intraperitoneally); 3) lipoic acid (100 mg/kg, intraperitoneally); 4) cisplatin plus lipoic acid (25 mg/kg); 5) cisplatin plus lipoic acid (50 mg/kg) and 6) cisplatin plus lipoic acid (100 mg/kg). Rats were sacrificed three days after treatment, and plasma as well as kidneys were isolated and analyzed. Plasma creatinine increased (677% of control) following cisplatin administration alone which was decreased by lipoic acid in a dose-dependent manner. Cisplatin-treated rats showed a depletion of renal glutathione (GSH), increased oxidized GSH and decreased GSH/GSH oxidized ratio (62%, 166% and 62% of control), respectively which were restored with lipoic acid pretreatment. Renal superoxide dismutase, catalase, glutathione peroxidase (GSH peroxidase) and glutathione reductase activities decreased (62%, 75%, 62% and 80% of control), respectively, and malondialdehyde content increased (204% of control) following cisplatin administration, which were restored with increasing doses of lipoic acid. The renal platinum concentration increased following cisplatin administration, which the authors thought was possibly decreased by chelation with lipoic acid. This research suggests that the graded doses of lipoic acid effectively prevented a decrease in renal antioxidant defense system and prevented an increase in lipid peroxidation, platinum content and plasma creatinine concentrations in a dose-dependent manner.

38. Mervaala E, et al., "Lipoic acid supplementation prevents angiotensin II-induced renal injury". *Kidney Int.* 2003; Aug;64(2):501-8.

NEEDS DETAILS OF AMOUNTS

Angiotensin II (Ang II)-induced renal injury is associated with perivascular inflammation, cell proliferation, and increased superoxide production in the vascular wall. This research examines lipoic acid's ability to protect against

the Ang II-induced inflammatory response and end-organ damage. The effects of lipoic acid supplementation for three weeks were examined in double transgenic rats (dTGR) and Sprague Dawley (SD) rats. Lipoic acid effectively prevented Ang II-induced glomerular and vascular damage in the kidneys and completely prevented the development of albuminuria. Ang II-induced leukocyte infiltration and cell proliferation in the kidney were attenuated. The redox-sensitive transcription factors nuclear factor (kappa) B (NF-kappa B) and activator protein-1 (AP-1) in the kidneys were increased in dTGR compared with SD, and were effectively reduced. Renal glutathione levels were much higher in dTGR than in SD, while the opposite was true for cysteine levels. These results suggested increased renal glutathione oxidation in dTGR, leading to cysteine shortage. Lipoic acid partly prevented renal cysteine depletion and increased hepatic cysteine and glutathione concentrations. This effect was accompanied by increased hepatic gamma-glutamylcysteine synthetase mRNA expression. The authors concluded that the in-vivo results suggested that lipoic acid protects against Ang II-induced renal injury through anti-inflammatory/antioxidative mechanisms.

39. Narayanan Venkatesan et al., "Curcumin Prevents Adriamycin Nephrotoxicity in Rats". *British Journal of Pharmacology.* 2000;(120)231-234.

This study examined the effect of curcumin on adriamycin (ADR) nephrosis in rats. ADR-induced kidney injury was remarkably prevented by treatment with curcumin. The rats given both ADR and curcumin were given 200 mg kg⁻¹ body weight of curcumin in 1% gum acacia orally for 7 days prior to a single ADR injection of 7.5 mg kg⁻¹ body weight, dissolved in 0.1 ml saline through the tail vein. Results indicated that treatment with curcumin prevented the kidney injury and restored kidney function. Treatment with curcumin significantly protected against proteinuria, albuminuria, hypoalbuminaemia and hyperlipidaemia. Curcumin inhibited the increase in urinary excretion of N-acetyl-beta-D-glucosaminidase (a marker of kidney tubular injury), fibronectin and glycosaminoglycan and blood cholesterol. The data also demonstrated that curcumin protected against kidney injury by suppressing free radicals and increasing kidney glutathione content and glutathione peroxidase activity (endogenous antioxidants). Curcumin also eliminated kidney microsomal and mitochondrial lipid peroxidation. The data suggest that administration of curcumin is a promising approach in the treatment of kidney disease.

40. Shoskes DA., "Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents." *Transplantation.* 1998; Jul;27;66(2): 147-52.

This study examined the effects of quercetin and curcumin, on ischemia-reperfusion in rats. Rats underwent 30 min of left renal pedicle occlusion with simultaneous

right nephrectomy and were pretreated with quercetin or curcumin. Serial serum creatinine was measured, and renal expression of the chemokines regulated upon activation, normal T-cell expressed and secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), and allograft inflammatory factor (AIF) was quantified by polymerase chain reaction. Pretreatment with quercetin or curcumin resulted in preservation of histological integrity, with a decrease in tubular damage and interstitial inflammation. On day 2 after ischemia-reperfusion, quercetin pretreatment decreased the mean serum creatinine level from 6.5 ± 1.4 to 3.3 ± 0.5 mg/dl ($P=0.06$). On day 7, the creatinine level for control animals was 7.5 ± 1.5 mg/dl, which was significantly decreased by pretreatment with quercetin, curcumin, or both together (creatinine levels: 1.6 ± 1.3 , 1.8 ± 0.2 , and 2.0 ± 0.4 mg/dl, respectively; all $P < 0.05$ vs. untreated). By semiquantitative polymerase chain reaction, RANTES, MCP-1, and AIF were detected at high levels in kidneys on day 2 but not in normal kidneys. Pretreatment with quercetin or curcumin strongly attenuated this expression. Quercetin and curcumin reduce ischemia-reperfusion injury and its inflammatory sequelae.

41. Okada K, Wangpoengtrakul C, Tanaka T, Toyokuni S, Uchida K, Osawa T. J "Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice". *Nutr.* 2001 ;Aug;131(8):2090-2095.

Protective effects of curcumin (U1), one of the major yellow pigments in turmeric and its derivative, tetrahydrocurcumin (THU1), against ferric nitrilotriacetate (Fe-NTA)-induced oxidative renal damage were studied in male ddY mice. Single Fe-NTA treatment (5 mg Fe/kg body intraperitoneally) transiently causes oxidative stress, as shown by the accumulation of lipid peroxidation products and 8-hydroxy-2'-deoxyguanosine in the kidney. Mice were fed with a diet containing 0.5 g/100 g U1 or THU1 for 4 wk. THU1 significantly inhibited 2-thiobarbituric acid reactive substances and 4-hydroxy-2-nonenal-modified proteins and 8-hydroxy-2'-deoxyguanosine formation in the kidney; U1 inhibited only 4-hydroxy-2-nonenal-modified protein formation. To elucidate the mechanisms of protection by U1 and THU1, the pharmacokinetics and radical-scavenging capacities of U1 and THU1 were investigated by HPLC and electron spin resonance spin trapping with 5,5-dimethyl-1-pyrroline-N-oxide, respectively. Induction of antioxidant enzymes was also investigated. The amounts of THU1 and its conjugates (as sulfates and glucuronides) in the liver and serum were larger in the THU1 group than in the U1 group. The amounts of U1 and its conjugates were small even in the U1 group. These results suggest that THU1 is more easily absorbed from the gastrointestinal tract than U1. Furthermore, THU1 induced antioxidant enzymes, such as glutathione peroxidase, glutathione S-transferase and NADPH: quinone reductase, as well as or better than U1 and scavenged Fe-NTA-induced free radicals in vitro better than U1. These results suggest that U1 is converted to THU1 in vivo and that THU1 is a

more promising chemopreventive agent.

42. Hase K, Kasimu R, Basnet P, Kadota S, Namba T. "Preventive effect of lithospermate B from *Salvia miltiorrhiza* on experimental hepatitis induced by carbon tetrachloride or D-galactosamine/lipopolysaccharide." *Planta Med.* 1997; Feb;63(1):22-6.

The water extract from the root of *Salvia miltiorrhiza* Bunge showed a protective effect on cultured rat hepatocytes against carbon tetrachloride (CCl₄)-induced necrosis. A further study was carried out to isolate the active constituent. Activity guided fractionation of the extract and chemical analysis gave us lithospermate B (a salt of lithospermic acid B), a tetramer of caffeic acid. Lithospermate B was also found to have a potent hepatoprotective activity in not only in vitro but also in vivo experimental liver injuries induced by CCl₄ or D-galactosamine (D-GalN)/lipopolysaccharide (LPS).

43. R. Yanardag et. al., "The Effects of Chard (*Beta vulgaris* L. var. *cicla*) Extract on Kidney Tissue, Serum Urea and Creatinine Levels of Diabetic Rats". *Phytotherapy Research.* 2002;16;758-761. An aqueous chard extract from dried chard leaves (100 grams) was extracted with 1000 ml distilled water and boiled for 30 minutes. It was filtered and evaporated to dryness and redissolved in distilled water before administration. There were 4 groups. #1 untreated, non-diabetic, #2 chard extract group, #3 diabetic animals, #4 diabetic animals given chard. The chard extract was given to the rats by gavage at a dose of 2 grams/kg every day for 28 days; 14 days after experimental animals were made diabetic. On days 7,14,21,28, 35 and 42 blood samples were taken for serum urea and creatinine levels. On day 42 the kidney tissues were examined. Groups #1 and #2 had normal parameters. Group #2 had significant degenerative change in the kidney tissue while group #4 given chard extract had minimal or absent damage. The mean serum creatinine levels in group #1 was 0.36 ± 0.18 , group #3 was 0.53 ± 0.24 while group #4 was 0.32 ± 0.19 . The mean serum urea for group #1 was 27.81 ± 6.10 , group #3 was 54.53 ± 19.38 while #4 was 39.50 ± 14.51 . I would add that part of this effect may be due to the fact that chard extracts have been shown to decrease blood glucose levels in diabetic research in the past. One study observed antidiabetic effects such as regenerative effect on beta cells of the pancreas both morphologically and biochemically. Additionally the plant is known as an antioxidant due to the leaves being rich in vitamin C. Antioxidants appear to play a profound effect on protection of the kidney and vitamin C has been shown itself to be protective.

44. Cho EJ, Yokozawa T, Rhee SH, Park KY., "The role of *Coptidis Rhizoma* extract in a renal ischemia-reperfusion model." *Phytomedicine.* 2004; Nov;11(7-8):576-84.

The effect of *Coptidis Rhizoma* extract (roots were powdered and extracted with distilled water at 100 degrees C

for 1 hr in a 1:10 dilution of rhizome:water. The filtrate was concentrated in vacuo and lyophilized to yield a residue. The yield of the extract was 19.7% by weight of the original material and was composed of 20.8% berberine, 6.1% coptisine and 5.2% palmatine. and a dose of 62.5mg or 125mg/kg body wt./day) on ischemia-reperfusion in rats was examined. The blood levels of urea nitrogen and creatinine increased significantly more in rats subjected to 24-h reperfusion than those subjected to 6-h reperfusion following 1-h ischemia, indicating functional kidney damage was more severe after the longer reperfusion time. These parameters were reduced by oral administration of *Coptidis Rhizoma* extract. Greater activity was found in rats given the extract for 30 days than in rats given the extract for 10 days prior to ischemia-reperfusion. In addition, the serum malondialdehyde level was lower, while the glutathione / glutathione disulfide ratio and the activities of the antioxidation enzymes, superoxide dismutase and catalase, were higher in rats given *Coptidis Rhizoma* extract orally for 30 consecutive days prior to 1-h ischemia and 24-h reperfusion in comparison with control rats given water. These results indicate that *Coptidis Rhizoma* has a protective action against the renal dysfunction caused by the ischemia and reperfusion process. Furthermore, renal DNA of rats given *Coptidis Rhizoma* extract orally showed a significantly lower DNA fragmentation rate, which was dose-dependent, implying that the extract afforded the kidneys protection against oxidative stress-mediated apoptosis during the process and ameliorated renal function impairment.

44.5 Yokozawa T, Satoh A, Cho EJ, Kashiwada Y, Ikeshiro Y. "Protective role of *Coptidis Rhizoma* alkaloids against peroxynitrite-induced damage to renal tubular epithelial cells." *J Pharm Pharmacol*. 2005; Mar;57(3):367-74. A study was conducted to elucidate and compare the protective activity of alkaloids from *Coptidis Rhizoma* (berberine, coptisine, palmatine, epiberberine, jatrorrhizine, groenlandicine and magnoflorine) using an LLC-PK(1) cell under peroxynitrite (ONOO(-)) generation model. Treatment with 3-morpholinopyridone (SIN-1) led to an increase in cellular ONOO(-) generation in comparison with non-treated cells. However, *Coptidis Rhizoma* extract and its alkaloids, except for berberine, reduced the cellular ONOO(-) level. In addition, DNA fragmentation induced by SIN-1 was significantly decreased by the extract, and also by coptisine, epiberberine, jatrorrhizine, groenlandicine and magnoflorine. Moreover, treatment with berberine, coptisine, palmatine and epiberberine exerted a protective effect against G(0)/G(1) phase arrest of cell cycle induced by SIN-1. The increase in cellular ONOO(-) generation, DNA damage and disturbance of the cell cycle by SIN-1 resulted in a decrease in cell viability. However, *Coptidis Rhizoma* extract, epiberberine, jatrorrhizine, groenlandicine and magnoflorine significantly increased cell viability even at a concentration as low as 10 microg mL(-1). These findings demonstrate that *Coptidis Rhizoma* extract and its

alkaloids can ameliorate the cell damage associated with ONOO(-) generation in renal tubular LLC-PK(1) cells, and that the various alkaloids have distinctive mechanisms of action, such as ONOO(-) scavenging, protection from DNA damage and control of the cell cycle. Furthermore, the data suggest that among the *Coptidis Rhizoma* alkaloids, coptisine is the most effective for protection against SIN-1-induced cellular injury in terms of its potency and content.

45. Sehirlir AO, Sener G, Satiroglu H, Ayanoglu-Dulger G., "Protective effect of N-acetylcysteine on renal ischemia/reperfusion injury in the rat.", *J Nephrol*. 2003 Jan-Feb;16(1):75-80.

The protective effect of N-acetylcysteine (NAC) against the damage inflicted by reactive oxygen species during renal I/R was investigated in Wistar Albino rats using biochemical parameters. Animals were unilaterally nephrectomized, and subjected to 45 min of renal pedicle occlusion followed by 1h of reperfusion. N-acetylcysteine (150 mg/kg, s.c.) or saline was administered twice, 15 min prior to ischemia and immediately before the reperfusion period. At the end of the reperfusion period, rats were killed by decapitation. For biochemical analysis, the lipid peroxidation product malondialdehyde (MDA) and glutathione (GSH) levels, myeloperoxidase (MPO) activity and protein oxidation (PO) were tested. Serum creatinine and BUN concentrations were measured for the evaluation of renal function. I/R induced nephrotoxicity, as evidenced by increases in BUN and creatinine, was reversed by NAC. The decrease in GSH and increases in MDA, MPO and PO induced by I/R indicated that renal injury involves free radical formation. Since NAC reversed these oxidant responses, and protected rat renal proximal tubules from in vitro simulated reperfusion injury, it seems that NAC protects kidney tissue against oxidative damage.

46. Paso F, Sanchez Crespo M, Braquet P, Hernando L. Eur J., Role of platelet-activating factor in adriamycin-induced nephropathy in rats. *Pharmacol*. 1987; Jun 12;138(1):119-23.

The effect of steroids, heparin and specific PAF-acether antagonists (BN 52021 and triazolobenzodiazepines) on proteinuria and renal histological changes induced in rats by adriamycin was studied. Adriamycin evoked a marked proteinuria that was unaffected by methylprednisolone and slightly reduced by heparin. In contrast, adriamycin-injected rats treated with PAF-acether antagonists had a low proteinuria, if any, and no ultrastructural glomerular alterations. These data suggest that PAF-acether could play a major role in the occurrence of proteinuria and that PAF-acether antagonists might provide a new therapeutic approach in certain human nephropathies.

47. Periandavan Kalaiselvi et. al., "Counteracting adriamycin-induced oxidative stress by administration of N-acetyl cysteine and vitamin E". *Clin Chem Lab Med*.

2005;43(8):834-40.

Adriamycin (ADR), a cytotoxic antineoplastic drug, is used in the treatment of various solid tumors. However it has significant toxicities including nephrotoxicity. In the present study, the effects of N-acetyl cysteine (NAC) and vitamin E, known antioxidants, were investigated on ADR-induced peroxidative damage in rat kidney. Adult male albino rats of Wistar strain were administered ADR as a single dose (10 mg/kg body weight, i.v.). Histopathological studies indicated that ADR-treated kidney sections show focal tubular necrosis and casts. ADR-injected rats showed a significant decline in the activities/levels of enzymic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and glutathione-S-transferase) and non-enzymic antioxidants (thiols, vitamin C and vitamin E) with high malondialdehyde levels. The extent of nephrotoxicity was evident from the increased activities of urinary marker enzymes (alkaline phosphatase, lactate dehydrogenase and gamma-glutamyltransferase). Treatment with NAC and vitamin E (50 mg/kg b.w., i.p.) 1 day prior to ADR administration maintained near normal activities of the enzymes, significantly reduced lipid peroxidation and prevented the necrosis caused by ADR, thereby proving to be an effective thiol replenishing agent and antioxidant.

48. June CH, Thompson CB, Kennedy MS, et al. Profound hypomagnesemia and renal magnesium wasting associated with the use of cyclosporine for marrow transplantation. *Transplantation* 1985;39:620-4.

49. Thompson CB, June CH, Sullivan KM, Thomas ED. Association between cyclosporine neurotoxicity and hypomagnesemia. *Lancet* 1984;ii:1116-20.

50. June CH, Thompson CB, Kennedy MS, et al. Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. *Transplantation* 1986;41:47-51.

51. Perazella MA. Drug-induced hyperkalemia: Old culprits and new offenders. *Am J Med* 2000;109:307-14 [review].

52 Pan SH, Lopez RR Jr, Sher LS, et al. Enhanced oral cyclosporine absorption with water-soluble vitamin E early after liver transplantation. *Pharmacotherapy* 1996;16:59-65.

53. Hsiu SL, Hou YC, Wang YH, et al. Quercetin significantly decreased cyclosporin oral bioavailability in pigs and rats. *Life Sci* 2002;72:227-35.

54. Lai MY, Hsiu SL, Hou YC, et al. Significant decrease of cyclosporine bioavailability in rats caused by a decoction of the roots of *Scutellaria baicalensis*. *Planta Med* 2004;70:132-7.

Scutellaria baicalensis root decoction at doses of 1g/kg

and 2g/kg decreased oral cyclosporin peak plasma level by 62.9% and 79.6% respectively while it does not effect intravenous cyclosporin. This eludes to there being an interaction between the decoction and the cyclosporin at the intestinal absorption site. Surprisingly, the administration of baicalin and baicalein increased the cyclosporin peak plasma levels, with the baicalin increase being tremendous.

55. Mai I, Bauer S, Perloff ES, Johne A, Uehleke B, Frank B, Budde K, Roots L, " Hyperforin content determines the magnitude of the St John's wort-cyclosporine drug interaction. ". *Clin Pharmacol Ther.* 2004; Oct;76(4):330-40.

This study compared the effects of 2 SJW preparations with high and low hyperforin (HYF) content on the pharmacokinetics of cyclosporine (INN, ciclosporin) (CSA). In a crossover study, 10 renal transplant patients were randomized into 2 groups and received SJW extract (900 mg/d) containing low or high concentrations of HYF for 14 days in addition to their regular regimen of CSA. After a 27-day washout phase, patients were crossed over to the other SJW treatment for 14 days. Blood concentrations of CSA were measured by immunoassay. The study showed a significant difference between the effects of the 2 SJW preparations on CSA pharmacokinetics (area under the plasma concentration-time curve within one dosing interval [AUC 0-12], $P < .0001$, ANOVA). AUC 0-12 values (monoclonal) with high-HYF SJW comedication were 45% lower (95% confidence interval [CI], -37% to -54%; $P < .05$, Student-Newman-Keuls test) than for low-HYF SJW. The dose-corrected AUC 0-12 for CSA (monoclonal) decreased significantly compared with baseline by 52% (95% CI, -46% to -56%; $P < .05$) after 2 weeks of comedication with high-HYF SJW. Values of peak concentration in plasma and drug concentration at the end of one dosing interval were affected to a similar extent, with reductions by 43% (95% CI, -36% to -48%) and 55% (95% CI, -48% to -60%), respectively. In addition, a 65% (95% CI, 53% to 85%; $P < .05$) increase in daily CSA doses was required during high-HYF SJW treatment. In contrast, coadministration of low-HYF SJW did not significantly affect CSA pharmacokinetics and did not require CSA dose adjustments compared with baseline. CONCLUSION: HYF content of SJW extracts significantly affects the extent of the pharmacokinetic interaction between CSA and SJW.

56. Barth SA, Inselmann G, Engemann R, Heidemann HT. Influences of Ginkgo biloba on cyclosporine A included lipid peroxidation in human liver microsomes in comparison to vitamin E, glutathione and N-acetylcysteine. *Biochem Pharmacol* 1991;41:1521-6.

57. Bagnis C, Deray G, Dubois M, et al. Prevention of cyclosporine nephrotoxicity with a platelet-activating factor (PAF) antagonist. *Nephrol Dial Transplant* 1996;11:507-13.

58. Rauschitzka F, Meir P, Turina M, et al. Acute transplant

rejection due to Saint John's wort. *Lancet* 2000;355:548-9 [letter].

59. Breidenbach T, Hoffmann MW, Becker T, et al. Drug interaction of St. John's wort with cyclosporin. *Lancet* 2000;355:1912 [letter].

60. Zhou S, Chan E, Pan SQ, Huang M, Lee EJ. "Pharmacokinetic interactions of drugs with St John's wort." *J Psychopharmacol.* 2004; Jun;18(2):262-76.

A literature search was performed using Medline (via Pubmed), Biological Abstracts, Cochrane Library, AMED, PsycINFO and Embase (all from their inception to September 2003) to identify known drug interaction with St John's wort. The available data indicate that St John's wort is a potent inducer of CYP 3A4 and P-glycoprotein (PgP), although it may inhibit or induce other CYPs, depending on the dose, route and duration of administration. Data from human studies and case reports indicate that St John's wort decreased the blood concentrations of amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, methadone, midazolam, nevirapine, phenprocoumon, simvastatin, tacrolimus, theophylline and warfarin, whereas it did not alter the pharmacokinetics of carbamazepine, dextromethorphan, mycophenolic acid and pravastatin. St John's wort decreased the plasma concentration of the active metabolite SN-38 in cancer patients receiving irinotecan treatment. St John's wort did not alter the pharmacokinetics of tolbutamide, but increased the incidence of hypoglycaemia. Several cases have been reported that St John's wort decreased cyclosporine blood concentration leading to organ rejection. St John's wort caused breakthrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives. It also caused serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors (e.g. sertraline and paroxetine). Both pharmacokinetic and pharmacodynamic components may play a role in these interactions. .

61. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB, "Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects." *Clin Pharmacol Ther.* 2003; Jan;73(1):41-50.

The effects of 12 days' pretreatment with St John's wort on the disposition of selected in vivo probe drugs were determined in 21 young healthy subjects. Midazolam after oral and intravenous administration was used to assess CYP3A activity in both the intestinal epithelium and the liver, whereas the disposition of fexofenadine after an oral dose was assumed to be a measure of MDR1 function, and the oral plasma concentration-time profile of cyclosporine (INN, ciclosporin) was considered to reflect both CYP3A and MDR1 activities. St John's wort markedly affected the plasma concentration-time profiles of all of the drugs, with associated increases in their clearance. With midazolam, the enhancement was considerably less after intravenous administration (approximately 1.5-fold) than after oral

administration (approximately 2.7-fold), and estimated intestinal and hepatic extraction ratios were higher by approximately 1.2- to 1.4-fold. By contrast, the oral clearances of fexofenadine and cyclosporine were equally increased by approximately 1.6-fold and 1.9-fold, respectively; these changes were both statistically less than for midazolam's oral clearance and greater than its estimated intestinal extraction. Although the disposition of all 3 drugs was altered by St John's wort, the extent of induction measured by oral clearance was different with CYP3A activity (midazolam), apparently increasing more than MDR1 function (fexofenadine), whereas with cyclosporine the change in oral clearance appeared to be more closely associated with the increase in MDR1 rather than CYP3A, despite the fact that both proteins are importantly involved in its disposition. These discordances indicate that, although a common molecular mechanism may be involved, the quantitative aspects of induction are complex and depend on the particular drug and the relative contributions of CYP3A and MDR1 in its disposition.

62. Palumbo G, Bacchi S, Palumbo P, Primavera LG, Sponta AM. , " Grapefruit juice: potential drug interaction". *Clin Ter.* 2005; May-Jun;156(3):97-103.

The predominant mechanism for the elevated drug bioavailability caused by grapefruit juice interaction is the inhibition of cytochrome P-450 3A4 in the small intestine, resulting in a significant reduction of drug presystemic metabolism. An additional mechanism is the inhibition of P-glycoprotein, a transporter that carries drug from the enterocyte back to the gut lumen, resulting in a further increase in the fraction of drug absorbed. Some calcium channel antagonists, benzodiazepines, HMG-CoA reductase inhibitors and cyclosporine are the most affected drugs. A single exposure to one glass of the grapefruit juice can usually produce the maximal magnitude of the interaction.

63. Ducharme MP, Provenzano R, Dehoorne-Smith M, Edwards DJ. "Trough concentrations of cyclosporine in blood following administration with grapefruit juice." *Br J Clin Pharmacol.* 1993 Nov;36(5):457-9.

Eleven medically stable patients (seven males, four females) receiving cyclosporine following kidney transplantation were instructed to take their usual dose of cyclosporine with water for 1 week (Phase 1), with grapefruit juice (8 ounces) for 1 week (Phase 2) and again with water for 1 week (Phase 3). Trough blood samples were obtained at the end of each phase for measurement of cyclosporine concentration using a specific monoclonal whole blood radioimmunoassay. Cyclosporine trough concentrations averaged 116.9 +/- 51.6 ng ml(-1) in the first phase, 145.3 +/- 44.7 ng ml(-1) with grapefruit juice (P < 0.05 compared with the first and third phases) and 111.2 +/- 56.1 ng ml(-1) in the third phase. Cyclosporine concentrations increased in 8 of 11 patients when given with grapefruit juice (mean increase 32%; range -4 to 97%) and declined in 10 of 11

when subjects resumed taking cyclosporine with water (mean decrease 27%). These results suggest that grapefruit juice increases trough concentrations of cyclosporine in blood, possibly by inhibiting pre-hepatic gut wall metabolism, and could be useful in optimizing therapy with this drug.

64. Tsunoda SM, Harris RZ, Christians U, et al. Red wine decreases cyclosporine bioavailability. *Clin Pharmacol Ther* 2001;70:462-7.

In vitro data suggest that red wine may interact with CYP3A4 substrates such as cyclosporine. A randomized, 2-way crossover study was conducted with 12 healthy individuals. Subjects received a single 8-mg/kg dose of oral cyclosporine with water (control) and with 12 oz of red wine (Blackstone Merlot, 1996; Blackstone Winery, Graton, Calif). Whole blood was analyzed for cyclosporine and 6 metabolites by specific fluorescence polarization immunoassay and tandem liquid chromatography-mass spectrometry. Blood levels of cyclosporine were compared between the 2 arms. Red wine caused a 50% increase in the oral clearance of cyclosporine. Systemic exposure as measured by the area under the concentration-versus-time curve (AUC) and peak concentration (C(max)) were significantly decreased by red wine. However, half-life was not affected, suggesting that red wine decreased cyclosporine absorption. In vitro, the solubility of cyclosporine in red wine appeared to be lower than in water. Administration of cyclosporine with red wine causes a significant decrease in cyclosporine exposure. Because cyclosporine is a narrow therapeutic range compound, caution may be warranted with concomitant intake of red wine and cyclosporine.

65. Rajinder K. "Piperine, a Major Constituent of Black Pepper, Inhibits Human P-glycoprotein and CYP3A4". *J Pharm and Experimental Therapeutics*, 2002;302(2):645-650.

This study investigated the influence of piperine on P-glycoprotein-mediated, polarized transport of digoxin and cyclosporine in monolayers of Caco-2 cells. By using human liver microsomes they determined the effect of piperine on CYP3A4-mediated formation of the verapamil metabolites D-617 and norverapamil. Piperine inhibited digoxin and cyclosporine A transport in Caco-2 cells with IC50 values of 15.5 and 74.1

66. Rooseboom M, Schaaf G, Commandeur JN, Vermeulen NP, Fink-Gremmels J "Beta-lyase-dependent attenuation of cisplatin-mediated toxicity by selenocysteine Se-conjugates in renal tubular cell lines." *J Pharmacol Exp Ther*. 2002; Jun;301(3):884-92.

Cisplatin [cis-diamminedichloroplatinum(II)] is a widely used antitumor drug with dose-limiting nephrotoxic side effects due to selective toxicity to the proximal tubule. In the present study, the chemoprotective potential of three selenocysteine Se-conjugates, Se-methyl-L-selenocysteine, Se-(2-methoxyphenyl)-L-selenocysteine, and Se-(2-chlo-

robenzyl)-L-selenocysteine, belonging to three structural classes, against the nephrotoxic effects of cisplatin was investigated. Selenocysteine Se-conjugates have previously been proposed as kidney-selective prodrugs of pharmacologically active selenols because of their active uptake and bioactivation by cysteine conjugate beta-lyases in the kidney. To elucidate whether chemoprotection is beta-lyase-dependent wild-type LLC-PK(1) cells, possessing a very low beta-lyase activity, and LLC-PK(1) cells stably transfected with full-length cDNA coding for rat kidney cysteine conjugate beta-lyase/glutamine transaminase K (R1J) were used. The results indicate that all three selenocysteine Se-conjugates were able to attenuate the cisplatin-induced loss of viability in R1J cells but not in the parental LLC-PK(1) cells, as determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and neutral red uptake. In addition, cisplatin-induced reactive oxygen species (ROS) production was determined using 2',7'-dichlorodihydrofluorescein diacetate. The selenocysteine Se-conjugates were able to decrease ROS levels after cisplatin exposure in both cell types. However, this ROS-protective effect was more profound in R1J cells. Se-Methyl-L-selenocysteine provided the strongest protection. The protective activity against cisplatin-induced cytotoxicity and ROS generation was blocked by aminooxyacetic acid, a selective inhibitor of pyridoxal 5'-phosphate-dependent cysteine conjugate beta-lyases, further supporting the role of beta-lyase in the observed chemoprotection. The precise molecular mechanism by which selenols, generated by beta-lyase, provide protection against cisplatin-induced cytotoxicity, however, remains to be established.

67. Camargo SM, Francescato HD, Lavrador MA, Bianchi ML. "Oral administration of sodium selenite minimizes cisplatin toxicity on proximal tubules of rats." *Biol Trace Elem Res*. 2001; Dec;83(3):251-62.

Cisplatin (c-DDP) is a widely used antineoplastic drug whose main side effect is nephrotoxicity. Selenium, administered intravenously or intraperitoneally, has been shown to provide protection against c-DDP-induced nephrotoxicity in rats. In the present study, the protective effect of orally administered sodium selenite on c-DDP toxicity was further examined. Animals treated with c-DDP alone showed increased urinary volume, decreased creatinine clearance (GFR), and a rise in urinary N-acetyl-(beta-D-glucosaminidase) (NAG) isoenzyme B activity. When sodium selenite was given prior to c-DDP, rats showed less GFR decline, delayed urinary volume increases, and no urinary NAG isoenzyme B activity increment. It is suggested that a single oral dose of sodium selenite given prior to c-DDP administration, although not preventing deterioration of renal function, partially protects rats from early proximal tubular injury.

68. Francescato HD, Costa RS, Rodrigues Camargo SM, Zanetti MA, Lavrador MA Bianchi MD., "Effect of

oral selenium administration on cisplatin-induced nephrotoxicity in rats." *Pharmacol Res.* 2001 Jan;43(1):77-82.

Cis-diamminedichloroplatinum(II) (CP), an important antineoplastic drug, shows remarkable toxicity to the kidney. Methods to reduce CP nephrotoxicity include the use of sodium selenite. The aim of the present study was to investigate the interaction between orally administered selenium and CP in the rat. After observing the effects of CP on body growth rate, urinary volume, serum creatinine, serum selenium levels, creatinine clearance, renal malondialdehyde, and glutathione levels, as well as on renal light microscopically visible lesions, the effects of the sodium selenite administration by gavage of 2 mg per kg of body wt. 24 h and 1 h prior to a single CP intraperitoneal injection of 5 mg per kg of body wt. followed by its daily administration for the 7 subsequent days on these parameters, were examined. CP increased renal malondialdehyde, renal glutathione, and serum creatinine and decreased creatinine clearance. Lipid peroxidation is one of the mechanisms by which CP induces renal damage. Selenium treatment decreased the effect of CP on serum creatinine, and renal malondialdehyde levels, but did not affect the other parameters with the exception of kidney necrosis which was also diminished by this treatment.

69. Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ, Luo L, Xu PM, Zhao YN, Zhao YB, Cheng G. "The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients." *Biol Trace Elem Res.* 1997 Mar;56(3):331-41.

The effect of selenium (Se) in reducing the toxicity of cisplatin in cancer patients was studied. Forty-one patients were randomized into group A (20 patients with Se administration in first cycle of chemotherapy as study cases and without Se in second cycle of chemotherapy as control) and group B (21 patients without Se in first cycle of chemotherapy and with Se in second cycle of chemotherapy). The 4000 micrograms per day of Se as Seleno-Kappacarrageenan were administered from 4 before to 4 d after chemotherapy for study cases. The serum Se increased from 70.4 +/- 22.86 to 157.04 +/- 60.23 ng/mL ($P < 0.001$) in patients received Se. The cisplatin dosage was iv administration in 60-80 mg/m² on the first day. The results showed that the peripheral WBC counts on day 14 after initiation of chemotherapy in study cases was significantly higher than the controls (3.35 +/- 2.01 vs 2.31 +/- 1.38 [$\times 10^9$]/L), $p < 0.05$). On the other hand, the consumption of GCSF for the cases was significantly less than the controls (110.1 +/- 82.2 vs 723.6 +/- 192.6 IU, $p < 0.05$). The volumes of blood transfusion for the study group were also significantly less than the controls (0 vs 62 +/- 38 mL, $p < 0.05$). The nephrotoxicity of cisplatin was measured by urine enzymes (NAG, GGT, AAP, LAP, and ALP) were determined prior to and at 2, 24, 48, and 72 h after initiation of chemotherapy. The urine enzymes NAG, GGT, AAP, and ALP after chemotherapy for cases were significantly lower than the controls. No toxicity of Seleno-Kappacarrageenan was

noted. The above results suggest that the Se can be used as an agent for reducing the nephrotoxicity and bone marrow suppression induced by cisplatin.

70. Yuka SHIMEDA, a,bYoshihiko H IROTANI,* ,aYouko A KIMOTO, aKyoko S HINDOU, a,cYoshio I JIRI, d Takako NISHIHORI, a,eand Kazuhiko T ANAKA a a "Protective Effects of Capsaicin against Cisplatin-Induced Nephrotoxicity in Rats" *Biol. Pharm. Bull.* 2005; 28(9) 1635—1638.

In the present study, we investigated the effect of the dietary antioxidants, capsaicin (Cap), against cisplatin-induced lipid peroxidation and nephrotoxicity in rats. Nephrotoxicity induced by treatment with a single dose of cisplatin (5mg/kg body weight i.p.). The animals were divided into 4 groups. Cap (10mg/kg/d) was given by gavage from the same day of cisplatin injection. Cisplatin administration resulted in significant increases in the kidney weight as a percentage of the total body weight, urine volume, serum creatinine, and blood urea nitrogen by about 132, 315, 797, and 556% in comparison with the control rats, respectively ($p < 0.05$). Also, the renal tissue from the cisplatin-treated rats showed significant decreases in the kidney glutathione (GSH) content and superoxide dismutase (OD) activity and a significant increase in malondialdehyde (MDA) production in comparison to the values at 0h ($p < 0.05$). Seven days after Cap plus cisplatin treatments, the renal damage induced by cisplatin recovered to a statistically significant level. In addition, Cap prevented the rise of MDA and the reduction of SOD activities. These results suggest that Cap has a protective effect against cisplatin-induced nephrotoxicity and lipid peroxidation in rats.

71. Kalantar-Zadeh K, Braglia A, Chow J, Kwon O, Kuwae N, Colman S, Cockram DB, Kopple JD. "An anti-inflammatory and antioxidant nutritional supplement for hypoalbuminemic hemodialysis patients" *J Ren Nutr.* 2005 Jul;15(3):318-31.

A low serum albumin concentration < 3.8 g/dL, a marker of malnutrition-inflammation complex syndrome, is observed in approximately half of all maintenance hemodialysis (MHD) patients in the United States and is strongly associated with increased mortality. It was hypothesized that an oral nutritional intervention with anti-inflammatory and antioxidant properties taken during routine dialysis sessions is well tolerated and corrects hypoalbuminemia in MHD patients. Among all MHD outpatients of three selected HD shifts (n = 81 patients), 21 subjects had a serum albumin level < 3.8 g/dL. One patient who was hospitalized before the intervention was excluded. The other three dialysis shifts, with 82 MHD outpatients including 20 hypoalbuminemic subjects, were observed as concurrent controls. The nutritional intervention included one can of Oxepa and one can of Nepro to be taken together orally during each routine hemodialysis session for 4 weeks. Each can contains 237 mL fluid. Oxepa provides

355 calories and 14.8 g protein per can, includes maltodextrin, medium-chain triglycerides, borage oil, and refined and deodorized fish oil, and is designed for critically ill patients with inflammation and oxidative stress. Each can of Oxepa includes 1,020 mg gamma-linolenic acid, 3,100 mg caprylic acid, 1,080 mg eicosapentaenoic acid, 75 mg taurine, 2,840 IU vitamin A activity, 75 IU vitamin E, and 200 mg vitamin C. Nepro provides 475 calories and 16.7 g protein per can; includes high-oleic safflower oil, corn syrup solids, and fructo-oligosaccharides; and is tailored for the nutritional needs of MHD patients. Oxepa and Nepro also contain L-carnitine, 43 mg and 62 mg, respectively. MAIN OUTCOME MEASURES: Serum albumin pretrial and posttrial. RESULTS: Studied outpatients (12 men and 8 women) were aged 60.4 +/- 13.0 (SD) years. Three patients had started MHD treatment between 1.5 and 3 months before the intervention. Nine patients were diabetic. Preintervention serum albumin, 3.44 +/- 0.34 g/dL (mean +/- SD) increased to 3.68 +/- 0.34 g/dL (P = .001) 4 weeks after the start of the intervention. In 16 patients, serum albumin level increased by 0.2 to 1.3 g/dL, whereas in 4 patients the serum albumin level decreased by 0.2 to 0.6 g/dL. Three patients reported diarrhea, and one diabetic patient had increased serum glucose values. No other side effects were noted. In 20 control outpatients not receiving nutritional intervention, serum albumin did not change from 3.46 +/- 0.20 to 3.47 +/- 10.44 g/dL (P = .47). CONCLUSIONS: In hypoalbuminemic MHD patients, a short-term in-center nutritional intervention with one can of Nepro and one can of Oxepa during HD is practical, convenient, well-tolerated, and associated with a significant increase in serum albumin level. Well-designed randomized placebo-controlled clinical trials are needed to verify the safety and effectiveness of this nutritional intervention and its impact on clinical outcome in hypoalbuminemic MHD patients.

72. Kazmi WH, Obrador GT, Sternberg M, Lindberg J, Schreiber B, Lewis V, Pereira BJ. "Carnitine therapy is associated with decreased hospital utilization among hemodialysis patients." *Am J Nephrol*. 2005; Mar-Apr;25(2):106-15. Epub 2005 Mar 10.
Carnitine deficiency is common among dialysis patients, and some studies have shown improvements in anemia, and cardiac and skeletal muscle function upon administration of L-carnitine. We hypothesized that L-carnitine may be associated with decreased hospital utilization in these patients. METHODS: The Fresenius Medical Care North America dialysis database was used for this retrospective analysis. Adult patients who received carnitine for at least 3 months, and had at least 3 months of pre-carnitine follow-up were included in the study. Hospitalization and hospital day rates were compared before and during carnitine therapy, and with a matched population. RESULTS: Carnitine therapy at a mean dose of 1.5 +/- 0.7 g per administration for an average of 9.7 +/- 5.4 months was associated with a significant reduction in hospital utilization. Patients with cardiovascular disease, defined as

hospitalizations for angina, myocardial infarction, arrhythmia, congestive heart failure, cerebral vascular disease or peripheral vascular disease prior to receiving carnitine, and those with anemia and hypoalbuminemia derived the greatest benefit from carnitine therapy. In a multivariate analysis, compared to 3 months prior to the initiation of carnitine, the adjusted relative risk for hospitalization was 11, 11, and 15% lower at 3, 6, and 9 months, respectively. Among patients with cardiovascular disease, the reduction in risk was even more significant (24, 31, and 34% lower at 3, 6, and 9 months, respectively). Similar results were observed with adjusted relative risk for hospital days. CONCLUSION: Administration of L-carnitine to chronic hemodialysis patients is associated with lower hospital utilization.

73.

74. Chander V, Tirkey N, Chopra K. "Resveratrol, a polyphenolic phytoalexin protects against cyclosporine-induced nephrotoxicity through nitric oxide dependent mechanism." *Toxicology*. 2005 May; 15;210(1):55-64.
The present study investigated the possible protective effect of resveratrol on CsA-induced nephrotoxicity and to explore the possible mechanism involved in resveratrol's effect. Eight groups of rats were employed in this study, group 1 served as control, group 2 rats were treated with olive oil (vehicle for CsA), group 3 rats were treated with CsA (20 mg/kg, s.c. for 21 days), groups 4, 5 and 6 received CsA along with resveratrol (2, 5 and 10 mg/kg, p.o. 24 h before and 21 days concurrently), respectively, group 7 rats were treated with NOS inhibitor, L-NAME (10 mg/kg) along with resveratrol and CsA and group 8 rats received L-NAME along with CsA. CsA administration for 21 days resulted in a marked renal oxidative stress, significantly deranged the renal functions, reduced the tissue and urine nitrite levels and markedly altered the renal morphology. Treatment with resveratrol (5 and 10 mg/kg) significantly improved the renal dysfunction; tissue and urine total nitric oxide levels, renal oxidative stress and prevented the alterations in renal morphology. Concurrent administration of L-NAME blocked the protective effect of resveratrol indicating that resveratrol exerts its protective effect by releasing nitric oxide. These results clearly demonstrate the pivotal role of nitric oxide in etiology of CsA nephrotoxicity and indicate the renoprotective potential of resveratrol in CsA nephrotoxicity

75. Chiarello PG, Vannucchi MT, Moyses Neto M, Vannucchi H. "Hyperhomocysteinemia and oxidative stress in hemodialysis: effects of supplementation with folic acid." *Int J Vitam Nutr Res*. 2003; Nov;73(6):431-8.
This study evaluated two different doses of folic acid and their effects on the control of hyperhomocysteinemia, and on pro-oxidant and antioxidant changes in a group of 32 hemodialysis (HD) patients. Blood samples were collected in a group of patients at three different times:

before (basal; B), after the first (S1), and after the second (S2) three-month supplementation periods, and compared to samples from a group of healthy individuals. Analysis of vitamins (C, E, folate, and B12), oxidant parameters (lipid and protein oxidation), and homocysteine were performed. Hyperhomocysteinemia of different degrees was observed in all patients on HD (45.30 +/- 24.89 microM). Oxidative stress was also detected, with lipoperoxidation and protein oxidation being associated with lower concentrations of antioxidant substances (vitamins E and C). The first folate dose (2.5 mg after each dialysis session) reduced by half the initial concentrations of homocysteine (44.92 +/- 22.05 to 20.56 +/- 6.79 microM; $p < 0.05$) but did not normalize its values. The second dose (15 mg) did not show an additional effect, but it was at this time that lipoperoxidation was significantly reduced, although the protein oxidation showed no change. It was concluded that the first dose of folic acid was efficient in reducing homocysteine concentrations, without normalization of values. The participation of hyperhomocysteinemia in oxidative stress appeared to be partial, but in combination with dialysis treatment, may contribute to the induction of an oxidative environment in this group. The possible antioxidant action of folate must also be considered in this case, acting directly against lipoperoxidation or through hyperhomocysteinemia control. Routine supplementations of folic acid and other antioxidant vitamins should be considered in hemodialysis in order to reduce homocysteine levels to lower values, that although not normal, may be more beneficial in minimizing the cardiovascular risk in this group.

76. Sato M, Matsumoto Y, Morita H, Takemura H, Shimoi K, Amano I. " Effects of vitamin supplementation on microcirculatory disturbance in hemodialysis patients without peripheral arterial disease." *Clin Nephrol.* 2003 Jul;60(1):28-34.
Dysfunctional endothelium caused by oxidative stress is thought to play a role in pathogenesis of a variety of conditions including atherosclerosis. We investigated whether a microcirculatory disturbance in hemodialysis (HD) patients was associated with increased oxidative stress and endothelial injury. **PATIENTS AND METHODS:** Transcutaneous oxygen tension (TcPO₂) on the dorsum of the foot at rest was measured as a marker of microcirculation in 33 patients undergoing HD without clinical manifestations of peripheral arterial disease and 20 healthy controls. Furthermore, in order to examine whether TcPO₂ was affected by antioxidants, oral supplementation with a combination of vitamin C (200 mg daily) and vitamin E (600 mg daily) was administered for 6 months to 8 patients with microcirculatory disturbance (TcPO₂ values of 50 mmHg or less). Serum biochemical parameters including vitamins were also measured. **RESULTS:** Mean TcPO₂ value was significantly lower in HD patients than in control subjects (47.9 +/- 13.5 mmHg versus 62.4 +/- 11.9 mmHg, $p < 0.001$). After vitamin supplementation, TcPO₂ values remarkably

increased (40.6 +/- 10.0 mmHg versus 57.4 +/- 6.5 mmHg, $p < 0.005$). Serum vitamin C and vitamin E levels increased significantly as well, while serum levels of thrombomodulin, a marker of endothelial injury, and thiobarbituric acid reactants, a marker of lipid peroxidation, were significantly decreased in comparison with those before supplementation. **CONCLUSIONS:** Our results suggest that the microcirculatory disturbance in HD patients seems to be associated with endothelial damage caused by oxidative stress. Combined supplementation with vitamin C and vitamin E may be of clinical benefit in improving the cutaneous microcirculation by reducing oxidative stress.

77. Lin CL, Hsu PY, Yang HY, Huang CC. " Low dose intravenous ascorbic acid for erythropoietin-hyporesponsive anemia in diabetic hemodialysis patients with iron overload." *Ren Fail.* 2003; May;25(3):445-53.
Inadequate iron mobilization and defective iron utilization may cause recombinant erythropoietin (rEPO) hyporesponsiveness in hemodialysis (HD) patients with iron overload. The effect of intravenous ascorbic acid (IVAA) in HD patients selected on the basis of iron overload and EPO resistance also has been proven. However, it is uncertain whether IVAA still works in diabetic ESRD patients with hyperferritinemia. Therefore, the aim of this study focusing on diabetic ESRD patients was to analyze the potential effect of low dose IVAA on improvement of anemia and erythropoiesis-related parameters when compared with control period. **PATIENTS AND METHOD:** This study consisted of 22 chronic hemodialysis patients with type II diabetes in a single dialysis unit. In studies of this type, all eligible patients are followed up, but the primary comparison is still between different sequentially treatment including control period and post-IVAA period in same patients. IVAA patients received ascorbic acid, 100 mg each administered intravenously three times per week for eight weeks of treatment and four months of post-treatment follow-up. **RESULTS:** The demographic characteristics of 22 diabetic uremic patients show that mean age is 63.6 +/- 10.2 years old. The ratio of sex (M/F) = 10/12. Mean duration of HD is 46.7 +/- 33.2 months. As for the urea kinetic study between these two periods including KT/V, nPCR, and URR, there is no significantly different. As for anemia-related parameters, Hb and Hct increased significantly in post-IVAA period after 3 months compared with control period, while MCV did not increase significantly. Serum ferritin significantly decreased at study completion. The same situation is for iron. As for TS, it significantly increased at one month and further markedly increased at subsequent three months. **CONCLUSION:** This study has demonstrated that short-term low dose IVAA therapy can facilitate iron release from reticuloendothelial system but also increase iron utilization in diabetic hemodialysis patients with iron overload. Therefore, IVAA is a potential adjuvant therapy to treat erythropoietin-hyporesponsive anemia in iron-overloaded patients.

78. Keven K, Kutlay S, Nergizoglu G, Erturk S. "Randomized, crossover study of the effect of vitamin C on EPO response in hemodialysis patients." *Am J Kidney Dis.* 2003; Jun;41(6):1233-9.

Vitamin C has been reported to be an effective adjuvant agent in the treatment of anemia in iron-overloaded hemodialysis patients. This study evaluated its effect on erythropoietin (EPO) response in a prospective, randomized, double-blind, crossover study. METHODS: Sixty-three patients were randomly divided into two groups. Group 1 was treated with intravenous vitamin C, 500 mg, three times a week, and group 2, with placebo for 6 months. During the second 6-month period, group 1 was treated with placebo, and group 2, with the same dose of vitamin C. Thirty patients in group 1 and 28 patients in group 2 completed the study. Hemoglobin levels, weekly EPO dose, and ratio of EPO to hemoglobin as an index of EPO need were determined at both baseline and the end of the two periods, together with other parameters known to be associated with EPO response. RESULTS: Twenty patients in group 1 (66.7%) and 18 patients in group 2 (64.3%) were responsive to vitamin C. In both groups, vitamin C resulted in a significant increase in hemoglobin levels ($P < 0.0001$ for both) and a significant decrease in EPO-hemoglobin ratio ($P < 0.0001$, $P = 0.019$). Transferrin saturation also increased with vitamin C treatment in both groups ($P = 0.009$, $P = 0.005$). All these parameters remained stable with placebo in both groups. Other parameters did not change throughout the study. CONCLUSION: Vitamin C can be used as an effective adjuvant therapy to EPO in hemodialysis patients. Further studies are needed to determine possible predictors of hematologic response to vitamin C.

79. Chiarello PG, Vannucchi MT, Vannucchi H "Hyperhomocysteinemia and oxidative stress during dialysis treatment." *Ren Fail.* 2003; Mar;25(2):203-13.

The concomitant presence of hyperhomocysteinemia and oxidative stress may represent a determinant factor for the occurrence of vascular alterations and cardiac diseases, the main cause of death among dialysis patients. This study analyzed the occurrence of hyperhomocysteinemia and oxidative stress and their possible relationship in dialysis patients. METHODS: Antioxidant substances, homocysteine, folate, and vitamin B12 were determined in blood from 32 patients on hemodialysis (HD), 21 patients on peritoneal dialysis (PD), and 12 healthy individuals. RESULTS: Different degrees of hyperhomocysteinemia were observed in all HD patients and in 95% of the PD patients (45.30 ± 24.89 microM in HD and 35.50 ± 26.53 microM in PD). Oxidative stress defined as an imbalance between oxidant and antioxidant forces was observed in all dialysis patients, but was more intense in HD individuals. In this group, lipoperoxidation and protein oxidation were associated with lower concentrations of antioxidants such as erythrocyte vitamin E and vitamin C. CONCLUSIONS: Hyperhomocysteinemia and oxidative stress occur in both

types of dialysis treatment, possibly contributing to the establishment of complications in these patients.

80. Song H, Wang Z, Zhang F. "Investigation of urinary interleukin-6 level in chronic renal failure patients and the influence of Rheum palmatum in treating it", *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2000; Feb;20(2):107-9 article in Chinese

This randomized, clinical trial assessed the clinical significance of urinary interleukin-6 (IL-6) level in chronic renal failure (CRF) patients and the effect of Rheum palmatum (RP) in treating it. METHODS: RP and captopril were given to the study group, while captopril was given to the control group alone, and level of urinary IL-6 was determined by sandwich-ELISA. RESULTS: Urinary IL-6 level in CRF patients was obviously higher, than that in healthy control ($P < 0.01$). After treatment, the urinary IL-6 and serum creatinine reduced significantly in the study group ($P < 0.05$), and there was significant difference compared with that in the control group ($P < 0.05$). CONCLUSIONS: Determination of urinary IL-6 level is useful in studying the severity of immune inflammation of CRF. RP improves renal function by inhibiting the production of IL-6 and lowering immune inflammation.

81. Rao M, Praveen Rao PN, Kamath R, Rao MN. "Reduction of cisplatin-induced nephrotoxicity by cystone, a polyherbal ayurvedic preparation, in C57BL/6J mice bearing B16F1 melanoma without reducing its antitumor activity." *J Ethnopharmacol.* 1999 Dec ;15;68(1-3):77-81.

The effect of cystone, a polyherbal ayurvedic preparation, on the nephrotoxicity and antitumor activity of cisplatin is studied in C57BL/6J mice bearing B16F1 melanoma. Intraperitoneal administration of cisplatin 6 mg/kg, resulted in significant reduction of body weight, elevation of blood urea nitrogen (BUN) and serum creatinine levels on day 5. Cystone was found to protect tumor-bearing mice from cisplatin-induced nephrotoxicity, when given i.p. 1 h before cisplatin. At 1000 mg/kg, it showed 46, 57 and 66% protection on body weight, BUN and serum creatinine levels, respectively. Treatment of cisplatin alone to tumor bearing mice resulted in significant antitumor activity as measured by tumor appearance, tumor volume and tumor weight. Pre-treatment with cystone (1000 mg/kg) did not reduce the antitumor activity of cisplatin. These results suggested that cystone protects against cisplatin-induced nephrotoxicity without interfering with its antitumor activity. The present study has many clinical implications in cisplatin chemotherapy.

82. Rao M, Rao MN. "Protective effects of cystone, a polyherbal ayurvedic preparation, on cisplatin-induced renal toxicity in rats." *J Ethnopharmacol.* 1998 Aug;62(1):1-6. Cystone, a polyherbal ayurvedic preparation, was found to protect rats partially but significantly against cisplatin-induced renal toxicity, when given intraperitoneally 1 h be-

fore cisplatin. At 500 and 1000 microg/ml, it also inhibited lipid peroxidation induced by cisplatin in renal cortical slices by 62.7 and 71.6%, respectively. The rats pretreated with cystone (1000 mg/kg i.p.) had significantly lower blood urea nitrogen (BUN) and serum creatinine (33.8 and 0.92 mg/dl, respectively) compared to cisplatin alone (51.5 and 1.41 mg/dl, respectively). The control animals had 17.1 and 0.63 mg/dl, respectively. The cystone treated animals lost 5.63 g body weight compared to 12.5 g for cisplatin alone treated animals on day 5. Renal functions like urine to serum creatinine ratio and creatinine clearance showed significant improvement when cystone was given 1 h before cisplatin. However, cystone did not protect increased excretion of urinary protein and decreased WBC count caused by cisplatin. The present study suggests that the cystone protects kidney against cisplatin-induced toxicity and the protection may be mediated through its ability to inhibit lipid peroxidation.

83. Velasquez MT, Bhathena SJ, Ranich T, Schwartz AM, Kardon DE, Ali AA, Haudenschild CC, Hansen CT. "Dietary flaxseed meal reduces proteinuria and ameliorates nephropathy in an animal model of type II diabetes mellitus." *Kidney Int.* 2003; Dec;64(6):2100-7. Varying the type or source of dietary protein intake can have beneficial effects on chronic renal disease. Consumption of soybean and soy-based food products, as the source of plant protein, can retard the development and progression of chronic renal disease. We studied the obese spontaneously hypertensive/NIH-corpulent (SHR/N-cp) rat, a model of obesity and type II diabetes mellitus that consistently develops nephropathy resembling diabetic nephropathy. We specifically sought to determine whether changing the source of protein intake from animal protein, casein, to plant protein in the form of either soy protein concentrate or flaxseed protein in the diet has a different impact on renal function and nephropathy in this model. **METHODS:** Male obese SHR/N-cp rats were randomly assigned to one of three diets containing either 20% casein, 20% soy protein concentrate, or 20% flaxseed meal. Except for the protein source, all three diets were identical and contained similar amounts of protein, fat, carbohydrates, minerals, and vitamins. All animals were maintained on these diets for 6 months. At the end of the study, blood sampling and 24-hour urine collections were performed for renal functional measurements, and the kidneys were harvested and examined for histologic evaluation. **RESULTS:** All three groups had similar amounts of food intake and body weight gain and exhibited fasting hyperglycemia and hyperinsulinemia. Plasma glucose levels did not differ among the three groups, but plasma insulin concentration was significantly lower in rats fed flaxseed meal than those fed either casein or soy protein concentrate. Mean plasma creatinine, creatinine clearance, and urinary urea excretion also did not differ significantly between the three groups. By contrast, urinary protein excretion was significantly lower ($P < 0.01$) in rats fed flaxseed than in rats fed either casein or soy protein concentrate. Morpho-

logic analysis of renal structural lesions showed that the percentage of abnormal glomeruli with mesangial expansion and the tubulointerstitial score (an index of severity of tubulointerstitial damage) were significantly reduced in rats fed flaxmeal compared to those fed casein or soy protein concentrate. **CONCLUSION:** We conclude that dietary protein substitution with flaxseed meal reduces proteinuria and glomerular and tubulointerstitial lesions in obese SHR/N-cp rats and that flaxseed meal is more effective than soy protein in reducing proteinuria and renal histologic abnormalities in this model. The reduction in proteinuria and renal injury was independent of the amount of protein intake and glycemic control.

84. Bankovic-Calic N, Ogbori MR, Nicman E. "Effect of a modified low protein and low fat diet on histologic changes and metabolism in kidneys in an experimental model of polycystic kidney disease" *Srp Arh Celok Lek.* 2002; Jul-Aug;130(7-8):251-7. [Article in Serbian] Dietary protein restriction slows progression in numerous animal models of renal diseases. Flax seed has also demonstrated useful anti-inflammatory properties in a number of animal models and human diseases. We undertook several studies to determine if feeding with low protein casein, soy diet and flax seed diet would ameliorate renal injury in Han:SPRD-cy rat model of polycystic kidney disease. **METHODS:** Male offspring of Han:SPRD-cy heterozygotes received protein modified diet: ad libitum LP 8% casein in test or 20% casein in control group for 8 weeks; 20% heat treated soy protein or 20% casein in control group two separate studies for 8 weeks ad libitum and pair feeding in 6 weeks; and 10% flax seed diet or control rat chow for 8 weeks from weaning. Tissue was harvested for histological assessment and metabolic changes in lipids, citric acid metabolites and osmolytes. Morphometrically after histochemical and immunohistochemical staining cystic changes, renal tubular proliferation and apoptosis, number of interstitial cells/macrophages infiltration and interstitial fibrosis were measured. Gas chromatography was used for lipid analysis in renal and liver tissue. 1-HNMR spectroscopy was used for urine and tissue organic anion and osmolytes content analysis. **RESULTS IN PROTEIN MODIFIED DIET:** Casein low protein as well as soy protein fed animals demonstrated reduced PKD pathology: significant reduction in cystic changes, interstitial inflammation and fibrosis and also reduction in tubular cells proliferation and apoptosis. Pair feeding protocol in second soy diet study confirmed that significant effect on renal histology was not because of protein deprivation and growth retardation. 1-H NMR spectroscopy revealed that progression of chronic renal failure in Han:SPRD-cy rat PKD is associated with renal depletion of citric acid cycle metabolite and betaine. Amelioration of PKD by soy protein diet is associated with renal retention of citric acid cycle anions, despite increased excretion and preservation of betaine in renal tissue. Soy feeding increased both hepatic and

renal content of linoleic acid and increased renal alpha linolenic acid content, while decreased arachidonic hepatic content. RESULTS IN FLAX SEED SUPPLEMENTATION IN DIET: Flax seed fed animals had moderate decrease in cystic size and less interstitial inflammation and fibrosis while there were no differences in epithelial cell apoptosis and proliferation. Lipid analysis revealed significant renal enrichment of 18 and 20 carbon omega 3 polyunsaturated fatty acids. In flax fed animals there was an increased urinary citrate excretion without significant changes in urinary ammonia excretion, so increased citrate excretion was not due to alkaline effect of the diet. Kidney tissue ¹H NMR spectroscopy revealed that disease amelioration was associated with tissue retention of succinate and betaine. CONCLUSION: Effect on histology: Low casein and soy feeding ameliorates Han:SPRD-cy rat polycystic kidney disease reducing both tubular remodeling and interstitial inflammation and fibrosis, while flax seed diet effect appears to be through moderation of associated interstitial nephritis. Metabolic effect: Soy diet alters the renal content of polyunsaturated fatty acids and enriched renal betaine content with retention of citric acid cycle metabolites despite increased excretion. Flax seed diet alters renal content of polyunsaturated fatty acids and promotes the formation of less inflammatory classes of renal prostanoides. Flax seed diet also enriched renal content of betaine and succinate. Amelioration of Han:SPRD-cy rat polycystic kidney disease by diet is associated with alteration in the handling of citric acid cycle metabolites and betaine, and also in content of polyunsaturated fatty acids in kidneys and liver. Metabolic pathways in dietary modified renal pathology have to be established.

85. Ogborn MR, Nitschmann E, Bankovic-Calic N, Weiler HA, Aukema H. "Dietary flax oil reduces renal injury, oxidized LDL content, and tissue n-6/n-3 FA ratio in experimental polycystic kidney disease." *Lipids*. 2002; Nov;37(11):1059-65.

As whole flaxseed is beneficial in the treatment of experimental renal disease, we undertook a study to determine whether previously documented benefits of whole flaxseed could be reproduced with dietary low-lignan flax oil (FO), a rich source of alpha-linolenic acid, in experimental polycystic kidney disease. Male offspring of Han:SPRD-cy heterozygous rats were fed a synthetic diet containing FO or corn oil (CO) for 8 wk from the time of weaning. Renal inflammation, fibrosis, proliferation, cystic change, and oxidized-LDL were assessed morphometrically. Hepatic and renal lipid composition was assessed using GC. FO feeding produced hepatic and renal enrichment of n-3 PUFA and an increase in C18:>C18 PUFA ratios (18-carbon PUFA compared to longer-chain PUFA), with a reduction in proportion of hepatic long-chain PUFA. The FO-based diet was associated with lower mean cystic change by 29.7% (P = 0.018), fibrosis by 21.7% (P = 0.017), macrophage infiltration by 31.5% (P < 0.0001), epithelial proliferation by 18.7% (P = 0.0035), and ox-LDL detection by 31.4% (P < 0.0001) in

Han:SPRD-cy heterozygotes. Serum creatinine was significantly lower in FO-fed diseased animals. A small hypocholesterolemic effect was noted in all animals fed FO. FO feeding moderates renal injury, modifies the profile of substrates available for elongation to eicosanoid precursors, and inhibits the elongation of C18 PUFA in this model. The consumption of FO-based products may prove a more practical way of obtaining health benefit than attempts to increase dietary content of unrefined seed.

86. Clark WF, Kortas C, Heidenheim AP, Garland J, Spanner E, Parbtani A " Flaxseed in lupus nephritis: a two-year nonplacebo-controlled crossover study." *J Am Coll Nutr*. 2001; Apr;20(2 Suppl):143-8.

The objective of this study was to determine the renoprotective effects of ground flaxseed in patients with lupus nephritis. METHODS: Forty patients with lupus nephritis were asked to participate in a randomized crossover trial of flaxseed. Twenty-three agreed and were randomized to receive 30 grams of ground flaxseed daily or control (no placebo) for one year, followed by a twelve-week washout period and the reverse treatment for one year. At baseline and six month intervals, serum phospholipids, flaxseed sachet counts, serum creatinine, 12-hour urine albumin excretion and urine albumin to creatinine ratios, serum viscosity and plasma lipids were measured. RESULTS: There were eight drop-outs and of the 15 remaining subjects flaxseed sachet count and serum phospholipid levels indicated only nine were adherent to the flaxseed diet. Plasma lipids and serum viscosity were unaltered by the flaxseed supplementation whereas serum creatinine in the compliant patients during flaxseed administration declined from a mean of 0.97+/-0.31 mg/dL to a mean of 0.94+/-0.30 mg/dL and rose in the control phase to a mean of 1.03+/-0.28 mg/dL [p value <0.08]. Of the fifteen patients who completed the study, similar changes were noted [p value <0.1]. The nine compliant patients had lower serum creatinines at the end of the two-year study than the 17 patients who refused to participate [p<0.05]. Microalbumin at baseline declined in both control and flaxseed time periods, but there was a trend for a greater decline during flaxseed administration [p<0.2]. CONCLUSIONS: Flaxseed appears to be renoprotective in lupus nephritis, but this interpretation is affected by under powering due to poor adherence and potential Hawthorne effects.

87. Ogborn MR, Nitschmann E, Weiler H, Leswick D, "Flaxseed ameliorates interstitial nephritis in rat polycystic kidney disease." *Bankovic-Calic N Kidney Int*. 1999; Feb;55(2):417-23.

Flaxseed has demonstrated useful antiinflammatory properties in a number of animal models and human diseases. We undertook a study to determine if flaxseed would also modify clinical course and renal pathology in the Han:SPRD-cy rat. METHODS: Male Han:SPRD-cy rats were pair fed a 10% flaxseed of control rat chow diet for eight weeks from weaning. Tissue was harvested for analysis

of cystic change, apoptosis, cell proliferation, and fibrosis. Tissue was also harvested for lipid analysis using gas chromatography. RESULTS: Animals thrived on both diets. Flaxseed-fed animals had lower serum creatinine (69 vs. 81 $\mu\text{mol/liter}$, $P = 0.02$), less cystic change (1.78 vs. 2.03 ml/kg , $P = 0.02$), less renal fibrosis (0.60 vs. 0.93 ml/kg , $P = 0.0009$), and less macrophage infiltration (13.8 vs. 16.7 cells/high-power video field) of the renal interstitium than controls. The groups did not differ in renal tubular epithelial cell apoptosis and proliferation. Lipid analysis revealed significant renal enrichment of 18 and 20 carbon omega 3 polyunsaturated fatty acids (total omega 6:omega 3 ratio 3.6 vs. 9.1, $P < 0.0001$). CONCLUSIONS: Flaxseed ameliorates Han:SPRD-cy rat polycystic kidney disease through moderation of the associated chronic interstitial nephritis. The diet alters renal content of polyunsaturated fatty acids in a manner that may promote the formation of less inflammatory classes of renal prostanoids.

88. Brownson C, Hipkiss AR. " Carnosine reacts with a glycated protein." *Free Radic Biol Med.* 2000 ; May 15;28(10):1564-70.

Oxidation and glycation induce formation of carbonyl (CO) groups in proteins, a characteristic of cellular aging. The dipeptide carnosine (beta-alanyl-L-histidine) is often found in long-lived mammalian tissues at relatively high concentrations (up to 20 mM). Previous studies show that carnosine reacts with low-molecular-weight aldehydes and ketones. We examine here the ability of carnosine to react with ovalbumin CO groups generated by treatment of the protein with methylglyoxal (MG). Incubation of MG-treated protein with carnosine accelerated a slow decline in CO groups as measured by dinitrophenylhydrazine reactivity. Incubation of [(14)C]-carnosine with MG-treated ovalbumin resulted in a radiolabeled precipitate on addition of trichloroacetic acid (TCA); this was not observed with control, untreated protein. The presence of lysine or N-(alpha)-acetylglycyl-lysine methyl ester caused a decrease in the TCA-precipitable radiolabel. Carnosine also inhibited cross-linking of the MG-treated ovalbumin to lysine and normal, untreated alpha-crystallin. We conclude that carnosine can react with protein CO groups (termed "carnosinylation") and thereby modulate their deleterious interaction with other polypeptides. It is proposed that, should similar reactions occur intracellularly, then carnosine's known "anti-aging" actions might, at least partially, be explained by the dipeptide facilitating the inactivation/removal of deleterious proteins bearing carbonyl groups.

89. Bohlender JM, Franke S, Stein G, Wolf G. "Advanced glycation end products and the kidney." *Am J Physiol Renal Physiol.* 2005 Oct;289(4):F645-59.

Advanced glycation end products (AGEs) are a heterogeneous group of protein and lipids to which sugar residues are covalently bound. AGE formation is increased in situations with hyperglycemia (e.g., diabetes mellitus) and is

also stimulated by oxidative stress, for example in uremia. It appears that activation of the renin-angiotensin system may contribute to AGE formation through various mechanisms. Although AGEs could nonspecifically bind to basement membranes and modify their properties, they also induce specific cellular responses including the release of profibrogenic and proinflammatory cytokines by interacting with the receptor for AGE (RAGE). However, additional receptors could bind AGEs, adding to the complexity of this system. The kidney is both: culprit and target of AGEs. A decrease in renal function increases circulating AGE concentrations by reduced clearance as well as increased formation. On the other hand, AGEs are involved in the structural changes of progressive nephropathies such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy. These effects are most prominent in diabetic nephropathy, but they also contribute to renal pathophysiology in other nondiabetic renal diseases. Interference with AGE formation has therapeutic potential for preventing the progression of chronic renal diseases, as shown from data of animal experiments and, more recently, the first clinical trials.

90. Jain SK, Lim G. " Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-treated human erythrocytes." *Free Radic Biol Med.* 2000; Dec;29(11):1122-8.

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na(+) + K(+))-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na(+) + K(+))- and Ca(++)-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R stereoisomers) in a shaking water bath at 37 degrees C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na(+) + K(+))- and Ca(++)-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na(+) + K(+))- and Ca(++)-ATPases in high glucose-treated RBC. There were no differences in lipid peroxidation, GHb and (Na(+) + K(+))- and Ca(++)-ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na(+) + K(+))- and Ca(++)-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or

inhibit the development of neuropathy in diabetes.

91. L. Ghiadoni¹, A. Cupisti¹, Y. Huang¹, P. Mattei², H. Cardinali¹, S. Favilla¹, P. Rindi², G. Barsotti¹, S. Taddei¹, A. Salvetti¹ "Endothelial dysfunction and oxidative stress in chronic renal failure" *J Nephrol* 2004; 17: 512-519

Uremic patients have an increased incidence of cardiovascular disease (CVD), endothelial dysfunction and oxidative stress that can contribute to cardiovascular (CV) events. To assess the relationship between endothelial dysfunction, oxidative stress and renal failure severity, we studied 40 patients (age 57 ± 7 yrs, 24 males) affected by chronic kidney disease (CKD) K/DOQI stage 3-5 (serum creatinine (Cr) 5.6 ± 2.2 mg/dL) on conservative treatment, 20 uremic patients (age 57 ± 12 yrs, 13 males) on hemodialysis (HD) and 30 healthy controls (56 ± 12 yrs, 20 males). Before and 2 hr after oral vitamin C (2 g) administration, we measured brachial artery endothelium-dependent vasodilation (flow mediated dilation (FMD)) to reactive hyperemia following 5 min of forearm ischemia and the response to sublingual glyceryl trinitrate (GTN). Measurements were made by high-resolution ultrasound and computerized analysis. FMD was lower in CKD patients than in controls (5.3 ± 2.2 vs. $6.9 \pm 2.8\%$; $p < 0.01$) and was further reduced in HD patients (3.6 ± 2.7 ; $p < 0.01$ vs. CKD patients). Response to GTN was similar in all groups. FMD was related to Cr clearance ($r = 0.42$; $p < 0.01$) in CKD patients, while it related inversely to $Kt/V_{\text{small}} > \text{urea}$ ($r = -0.52$; $p < 0.05$) in HD patients. After vitamin C administration, FMD was significantly enhanced in HD ($4.7 \pm 2.4\%$; $p < 0.01$ vs. baseline), but not in CKD patients. Response to GTN was unaffected. However, vitamin C load reduced oxidative stress markers, and increased plasma antioxidant capability in both groups. In conclusion, the reduced endothelium-dependent dilation in the brachial artery of CKD patients is related to renal failure severity. HD patients showed a more marked alteration, which seems to be related, at least in part, to increased oxidative stress. In conclusion, this study indicates that uremic patients are characterized by impaired endothelium-dependent vasodilation of the brachial artery, an abnormality related to renal failure severity in CKD patients and to delivered dialysis dose in HD patients. Oxidative stress seems to play a crucial role in worsening endothelial dysfunction in HD patients, while in pre-dialysis patients other pathways probably account for the impaired endothelium-dependent vasodilation. These results could have clinical relevance, since studies show that endothelial dysfunction predicts the development of CV events in patients with coronary artery disease (8-10). Therefore, it is conceivable that endothelial function reduction could be one of the mechanisms leading to the increased CV risk, a wellknown feature in chronic uremic patients.

92. Usberti M, Gerardi GM, Gazzotti RM, Benedini S, Archetti S, Sugherini L, Valentini M, Tira P, Bufano G,

Albertini A, Di Lorenzo D. "Oxidative stress and cardiovascular disease in dialyzed patients." *Nephron*. 2002; May;91(1):25-33.

Oxidative damage has been suggested to play a key role in accelerated atherosclerosis and to be involved in cardiovascular disease (CVD) of dialyzed patients who are at risk of increased oxidative stress. The purpose of the present study was to examine the relationship between the severity of CVD and some markers of oxidative stress and antioxidant activity in our hemodialyzed (HD) and peritoneal dialysis (PD) patients. Methods: Plasma reactive oxygen metabolites, malondialdehyde and 4-hydroxynonenal (MDA-4HNE), thiols, alpha-tocopherol, and total antioxidant status (TAS) were measured in 55 HD and in 16 PD patients. CVD was considered as the result of variably combined cardiac, cerebral, and vascular pathologies which were scored and grouped in a single CVD index and analyzed with respect to the markers of the oxidative status. 16 normal subjects served as controls. Results: All patients showed evidence of increased oxidative stress which was more severe in HD than in PD patients and which was exacerbated by HD. When cardiac, cerebral, and vascular diseases were analyzed separately, plasma MDA-4HNE and TAS were significantly higher in more severely affected HD patients, but not in PD patients. In HD patients the CVD index was directly correlated with both MDA-4HNE and TAS ($r = 0.42$, $p < 0.01$; $r = 0.39$, $p < 0.01$) and inversely correlated with alpha-tocopherol ($r = -0.32$, $p < 0.05$). MDA-4HNE and TAS were directly correlated in HD patients and inversely correlated in control subjects. Conclusions: Our data show that, in spite of increased antioxidant defense, there is a relationship between the degree of lipid peroxidation and the severity of CVD in HD patients. Moreover, these data underscore the utility of MDA-4HNE, alpha-tocopherol, and TAS in the evaluation of cardiovascular disease.

93. Ogi M, Horiuchi T, Abe R, Wakabayashi M, Wakabayashi T. "Comparison of intravenous ascorbic acid versus intravenous iron for functional iron deficiency in hemodialysis patients" *Nippon Jinzo Gakkai Shi*. 2004;46(8):804-9. [Article in Japanese]

The effect of intravenous ascorbic acid was compared with that of intravenous iron in the treatment of functional iron deficiency, as defined as serum ferritin levels over 300 ng/ml and serum iron levels below 50 microg/dl, in patients on chronic hemodialysis. Thirteen patients on chronic hemodialysis with functional iron deficiency received intravenous injections of ascorbic acid, 100 mg, three times a week, after hemodialysis. The therapy was continued until serum ferritin decreased to below 300 ng/ml (3 months at the maximum). The iron and control group were composed of patients who had serum iron levels below 50 microg/dl within 3 months after serum ferritin rose to over 300 ng/ml. Seven patients with the iron group received more than a total of 10 intravenous injections of saccharated ferric oxide (40 mg/dose) after hemodialysis,

and seven patients with the control group received no iron preparation during the 3 months. In the ascorbic acid group, while hemoglobin did not change from 10.9 +/- 0.5 g/dl (mean +/- SE) during the three-month period, serum iron increased significantly from 37 +/- 4 microg/dl to 49 +/- 4 microg/dl after one month ($p < 0.01$), and remained elevated until the end of the three-month period. Serum ferritin decreased significantly from 607 +/- 118 ng/ml to 354 +/- 30 ng/ml after 3 months ($p < 0.01$). In the iron group, hemoglobin and serum iron increased significantly from the respective pre-treatment levels during the 2-month period, and serum ferritin rose significantly after 3 months. In the control group, hemoglobin, serum iron and ferritin levels decreased significantly from the respective pre-treatment levels during the 3 months. The recombinant erythropoietin dose remained stable for three months in the ascorbic acid, iron, and control groups, respectively. These results suggest that in hemodialysis patients with a functional iron deficiency, treatment with intravenous ascorbic acid can prevent iron overload due to treatment with intravenous iron, and provide a useful adjuvant means of maintaining hemoglobin and serum iron levels.

94. Derzsiova K, Mydlik M, Boldizsar J, Hribikova M, Petrovicova J. "Oral administration of iron with vitamin C in haemodialyzed patients" *Vnitr Lek.* 2001 Apr;47(4):210-4. [Article in Slovak]
One tablet of Sorbifer Durules contains 100 mg Fe²⁺ and 60 mg vitamin C. The authors examined in a short-term study 24 haemodialyzed patients with chronic renal failure of different etiology. The investigation was divided into three parts. During the first 4 weeks the patients did not receive Fe²⁺ nor vitamin C. During the subsequent four weeks the patients had Sorbifer Durules, one tablet/24 hours. This period was followed by another four weeks when the patients went again without Fe²⁺ and vitamin C treatment. At regular intervals, i.e. on days 0, 28, 56 and 84 the authors assessed the packed cell volume, blood haemoglobin and serum iron level, the total iron binding capacity, transferrin saturation, ferritin, and vitamin C in serum as well as the plasma oxalic acid level. Four weeks treatment using Sorbifer Durules led to a significant rise of the packed cell volume and haemoglobin in blood, iron and vitamin C in serum. This treatment did not affect the oxalic acid plasma level. Oral treatment with Sorbifer Durules, one tablet/24 hours, was adequate for maintaining the serum iron concentration in haemodialyzed patients during treatment with recombinant human erythropoietin. This treatment prevented at the same time the development of vitamin C deficiency in serum and a further rise of plasma oxalic acid in these patients.

95. Savikko J, Taskinen E, Von Willebrand E. "Chronic allograft nephropathy is prevented by inhibition of platelet-derived growth factor receptor: tyrosine kinase inhibitors as a potential therapy." *Transplantation.* 2003; Apr

27;75(8):1147-53.

Chronic allograft nephropathy (CAN) is the primary reason for late allograft loss in kidney transplantation, and currently there is no treatment available for it. Platelet-derived growth factor (PDGF) is suggested to be a major mitogen mediating mesenchymal cell proliferation in CAN. It has been shown that PDGF is already induced at acute renal allograft rejection, indicating a link between acute rejection and subsequent development of CAN. However, the definite effect of PDGF on the pathogenesis of CAN is still unknown. We investigated the role of PDGF in CAN by inhibiting PDGF by imatinib (STI571), a selective PDGF receptor tyrosine kinase inhibitor. METHODS: Kidney transplantations were performed from Dark Agouti (DA) to Wistar-Furth rats, and syngenic control transplantations were performed from DA to DA rats. All allograft recipients were immunosuppressed with cyclosporine A (1.5 mg/kg/day subcutaneously). One group of the animals was also treated with imatinib (10 mg/kg/day orally). Serum creatinine levels and cyclosporine A concentrations were measured once per week until the animals were killed. Grafts were harvested 5 and 90 days after transplantation for histology and immunohistochemistry. RESULTS: Only very few histologic chronic changes, similar to syngenic grafts, were seen in imatinib-treated allografts compared with control allografts. Creatinine values of imatinib-treated allograft recipients and infiltration of inflammatory cells, PDGF ligand, and receptor induction were also at the same level as in syngenic grafts. CONCLUSIONS: Our results demonstrate that imatinib prevents CAN almost completely, indicating that PDGF plays an important role in its pathogenesis. On the basis of our findings, imatinib could be a potential intervention in preventing CAN in clinical kidney transplantation.

96. Grimm PC, Nickerson P, Jeffery J, Savani RC, Gough J, McKenna RM, Stern E, Rush DN. "Neointimal and tubulointerstitial infiltration by recipient mesenchymal cells in chronic renal-allograft rejection." *N Engl J Med.* 2001 Jul 12;345(2):93-7.
Tissue remodeling depends on mesenchymal cells (fibroblasts and myofibroblasts) and is a prominent feature of chronic renal-transplant rejection. It is not known whether the mesenchymal cells that participate in remodeling originate locally or from circulating precursor cells. METHODS: We obtained biopsy specimens of renal allografts from six male recipients of an allograft from a female donor, four female recipients of an allograft from a male donor, two male recipients of an allograft from a male donor, and two female recipients of an allograft from a female donor. All the allografts were undergoing chronic rejection. All but two specimens were obtained within six months after transplantation. We used immunohistochemical methods to identify mesenchymal cells with smooth-muscle alpha-actin and in situ hybridization to identify mesenchymal cells with Y-chromosome DNA. RESULTS: No Y-chromosome bodies were identified in the

case of the two renal-allograft specimens in which both the donor and the recipient were female. In the case of the two renal-allograft specimens in which both the donor and the recipient were male, approximately 40 percent of mesenchymal cells contained a Y-chromosome body. In the case of the six specimens in which the donor was female and the recipient was male, a mean (+/-SD) of 34+/-16 percent of mesenchymal cells in the neointima, 38+/-12 percent of such cells in the adventitia, and 30+/-7 percent of such cells in the interstitium contained the Y-chromosomal marker, indicating that they originated from the recipient rather than the donor. In the case of the four renal-allograft specimens in which the donor was male and the recipient was female, the respective values were 24+/-15 percent, 33+/-9 percent, and 23+/-8 percent, indicating a persistent population of donor mesenchymal cells. **CONCLUSIONS:** The presence of mesenchymal cells of host origin in the vascular and interstitial compartments of renal allografts undergoing chronic rejection provides evidence that a circulating mesenchymal precursor cell has the potential to migrate to areas of inflammation.

97. Melhem M, Craven P, and Frederick R. "Effects of Dietary Supplementation of α -Lipoic Acid on Early Glomerular Injury in Diabetes Mellitus" *J Am Soc Nephrol* 2001 ; 12: 124-133.

Antioxidants, in particular vitamin E (VE), have been reported to protect against diabetic renal injury. α -Lipoic acid (LA) has been found to attenuate diabetic peripheral neuropathy, but its effects on nephropathy have not been examined. In the present study, parameters of glomerular injury were examined in streptozotocin diabetic rats after 2 mo on unsupplemented diets and in diabetic rats that received the lowest daily dose of dietary LA (30 mg/kg body wt), VE (100 IU/kg body wt), or vitamin C (VC; 1 g/kg body wt), which detectably increased the renal cortical content of each antioxidant. Blood glucose values did not differ among the diabetic groups. At 2 mo, inulin clearance, urinary albumin excretion, fractional albumin clearance, glomerular volume, and glomerular content of immunoreactive transforming growth factor- β (TGF- β) and collagen 1 (IV) all were significantly increased in unsupplemented D compared with age-matched nondiabetic controls. With the exception of inulin clearance, LA prevented or significantly attenuated the increase in all of these glomerular parameters in D, as well as the increases in renal tubular cell TGF- β seen in D. At the dose used, VE reduced inulin clearance in D to control levels but failed to alter any of the other indices of glomerular injury or to suppress renal tubular cell TGF- β in D. VC suppressed urinary albumin excretion, fractional albumin clearance, and glomerular volume but not glomerular or tubular TGF- β or glomerular collagen 1 (IV) content. LA but not VE or VC significantly increased renal cortical glutathione content in D. These data indicate that LA is effective in the prevention of early diabetic glomerular injury and suggest that this agent may have advantages over high doses of either

VE or VC.

98. Alderson NL, Chachich ME, Frizzell N, Canning P, Metz TO, Januszewski AS, Youssef NN, Stitt AW, Baynes JW, Thorpe SR. "Effect of antioxidants and ACE inhibition on chemical modification of proteins and progression of nephropathy in the streptozotocin diabetic rat." *Diabetologia*. 2004; Aug;47(8):1385-95. Epub 2004 Jul 28.

This study was designed to determine whether inhibition of formation of AGE and advanced lipoxidation end-products (ALE) is a mechanism of action common to a diverse group of therapeutic agents that limit the progress of diabetic nephropathy. We compared the effects of the ACE inhibitor enalapril, the antioxidant vitamin E, the thiol compound lipoic acid, and the AGE/ALE inhibitor pyridoxamine on the formation of AGE/ALE and protection against nephropathy in streptozotocin diabetic rats. **METHODS:** Renal function and AGE/ALE formation were evaluated in rats treated with the agents listed above. Plasma was monitored monthly for triglycerides, cholesterol, creatinine and TNF- α , and 24-h urine samples were collected for measurement of albumin and total protein excretion. After 29 weeks, renal expression of mRNA for extracellular matrix proteins was measured, and AGE/ALE were quantified in skin and glomerular and tubular collagen. **RESULTS:** Diabetic animals were both hyperglycaemic and dyslipidaemic, and showed evidence of early nephropathy (albuminuria, creatinaemia). All interventions limited the progression of nephropathy, without affecting glycaemia. The order of efficacy was: pyridoxamine (650 mg.kg(-1).day(-1)) > vitamin E (200 mg.kg(-1).day(-1)) > lipoic acid (93 mg.kg(-1).day(-1)) approximately enalapril (35 mg.kg(-1).day(-1)). Pyridoxamine also significantly inhibited AGE/ALE accumulation in tissues; effects of other agents were mixed, but the degree of renoprotection was consistent with their effects on AGE/ALE formation. **CONCLUSIONS/INTERPRETATION:** All interventions inhibited the progression of nephropathy at the doses studied, but the maximal benefit was achieved with pyridoxamine, which also limited dyslipidaemia and AGE/ALE formation. These experiments indicate that the more effective the renoprotection, the greater the inhibition of AGE/ALE formation. For optimal protection of renal function, it would be beneficial to select drugs whose mechanism of action includes inhibition of AGE/ALE formation.

99. Steven Fishbane et al., "N-Acetylcysteine In The Prevention Of Radiocontrast-Induced Nephropathy" *J Am Soc Nephrol* 2004 ;15: 251-260,

N-acetylcysteine is a remarkably active agent shown to be useful in a variety of clinical settings. The drug has actions relevant to radiocontrast-induced nephropathy (RCIN) that include vasodilatation, enhancement of renal medullary blood flow, and antioxidant properties. The drug's pharmacokinetics are remarkable for almost complete first pass metabolism after oral administration, resulting in no free drug reaching the circulation. After intravenous

administration, extensive reaction with tissue and plasma proteins greatly limits the amount of circulating free drug. Given the difficulty achieving free drug in the systemic circulation, it is highly likely that the drug works via its metabolites. The primary mechanism may be through L-cysteine as a cellular source for glutathione production. Clinical studies of N-acetylcysteine in the prevention of RCIN have yielded highly mixed results; five were dramatically positive, and eight others had no demonstrable efficacy at all. The following will review the individual studies, attempt to reconcile the divergent results, and propose future research needs.

100. Miyazaki M, Takemura N, Watanabe S, Hata N, Misawa Y, Okuyama H. "Dietary docosahexaenoic acid ameliorates, but rapeseed oil and safflower oil accelerate renal injury in stroke-prone spontaneously hypertensive rats as compared with soybean oil, which is associated with expression for renal transforming growth factor-beta, fibronectin and renin." *Biochim Biophys Acta*. 2000; Jan 3;1483(1):101-10.

We have noted that n-3 fatty acid-rich oils, such as fish oil, perilla oil and flaxseed oil as well as ethyl docosahexaenoate (DHA) prolonged the survival time of stroke-prone spontaneously hypertensive rats (SHRSP) rats by approximately 10% as compared with linoleate (n-6)-rich safflower oil. Rapeseed oil with a relatively low n-6/n-3 ratio unusually shortened the survival time by approximately 40%, suggesting the presence of minor components unfavorable to SHRSP rats. This study examined the effects of dietary oils and DHA on renal injury and gene expression related to renal injury in SHRSP rats. Rats fed rapeseed oil- and safflower oil-supplemented diets developed more severe proteinuria than those fed soybean oil-supplemented diet used as a control, but there were no significant differences in blood pressure. In contrast, the DHA-supplemented diet inhibited the development of proteinuria and suppressed hypertension. The mRNA levels for renal TGF-beta, fibronectin and renin were higher in the rapeseed oil and safflower oil groups after 9 weeks of feeding of the experimental diet than in the soybean oil and DHA groups. The fatty acid composition of kidney phospholipids was markedly affected by these diets. These results indicate that the renal injury observed in the groups fed safflower oil with a high n-6/n-3 ratio and rapeseed oil with presumed minor components is accompanied by increased expression of the TGF-beta, renin and fibronectin genes, and that dietary DHA suppresses renal injury and gene expression as compared with soybean oil.

101. Oh-hashii K, Takahashi T, Tanabe A, Watanabe S, Okuyama H. "Dietary alpha-linolenate suppresses endotoxin-induced platelet-activating factor production in rat kidney." *Lipids*. 1999 Jan;34(1):31-7.

In comparison with dietary high-linoleate safflower oil, high alpha-linolenate perilla oil decreased alkylacyl- and alkenylacyl-glycerophosphocholine (GPC) content in rat

kidney by roughly 30 and 25%, respectively. The fatty acid composition was also modified by high alpha-linolenate oil; arachidonic acid (AA) level in alkylacyl-GPC, a platelet-activating factor (PAF) precursor, decreased by 30% along with concomitant increases in the n-3 fatty acid levels. PAF contents under resting conditions were similarly low in the two dietary groups. Fifteen minutes after endotoxin administration, PAF and lyso-PAF contents increased significantly, and the PAF content in the high alpha-linolenate group was 60% lower than in the high linoleate group; the lyso-PAF contents also tended to be lower. Lyso-PAF acetyltransferase and CoA-independent transacylase activities in kidney microsomes increased significantly after endotoxin administration, while PAF acetylhydrolase activity in the cytosol was relatively unchanged. The lyso-PAF acetyltransferase and PAF acetylhydrolase activities did not differ between the two dietary groups, but the CoA-independent transacylase activity was roughly 30% lower in the high alpha-linolenate group. In agreement with in vitro study, our present study demonstrates that dietary high alpha-linolenate suppresses PAF production in rat kidney during systemic endotoxemia, and which is mainly due to the decrease in alkylacyl-GPC content, altered fatty acid compositions of the precursor lipids and lower CoA-independent transacylase activity.

102. Hirose M, Masuda A, Ito N, Kamano K, Okuyama H. "Effects of dietary perilla oil, soybean oil and safflower oil on 7,12-dimethylbenz[a]anthracene (DMBA) and 1,2-dimethylhydrazine (DMH)-induced mammary gland and colon carcinogenesis in female SD rats." *Carcinogenesis*. 1990 May;11(5):731-5.

The effects of diet supplemented with perilla oil, which contains a large amount of n-3 alpha-linolenic acid, and n-6 linoleic acid rich soybean and safflower oil supplemented diets on 7,12-dimethylbenz[a]anthracene (DMBA)- and 1,2-dimethylhydrazine (DMH)-induced mammary gland and colon carcinogenesis were investigated in female SD rats. Groups of 23 or 24, 5 week old animals were first given three s.c. injections of 40 mg/kg body wt DMH followed by a single intragastric administration of 50 mg/kg body wt DMBA within 2 weeks of the commencement. Starting 1 week after the DMBA treatment, they were administered pellet diet containing 10% perilla oil, soybean oil or safflower oil for the succeeding 33 weeks. Histological examination revealed that the resultant numbers of mammary tumors per rat were significantly lower in rats given perilla oil diet (4.4 +/- 2.5) than in the soybean oil diet group (6.5 +/- 3.9). Furthermore, colon tumor incidence was significantly lower in animals receiving the perilla oil supplement (18.2%) than in those given safflower oil diet (47.4%), and the numbers of colon tumors per rat tended to be lowest in rats administered perilla oil. Also the incidence of nephroblastomas in rats receiving perilla oil diet (0%) was significantly lower than that for the soybean oil diet group (23.8%). The results thus indicate that the alpha-linolenic acid (n-3)-rich perilla oil

diet inhibits development of mammary gland, colon and kidney tumors as compared to linoleic acid (n-6)-rich safflower or soybean oil diet.

103 Makino T, Nakamura T, Ono T, Muso E, Honda G. "Suppressive effects of *Perilla frutescens* on mesangioproliferative glomerulonephritis in rats." *Biol Pharm Bull.* 2001 Feb;24(2):172-5.

Leaves of *Perilla frutescens* var. *crispa* DECNE. (perilla, Labiatae) are used as a garnishing vegetable in East Asian countries as well as an herbal medicine prescribed in Kampo medicines such as Saiboku-to. A previous in vitro study revealed that a decoction of perilla leaves inhibits the proliferation of murine-cultured mesangial cells. In the present study, we evaluated the in vivo anti-proliferative effects of a perilla decoction using rat mesangio-proliferative glomerulonephritis induced by an intravenous injection of rabbit anti-rat thymocyte serum (ATS). Leaves of perilla were boiled, and the decoction was orally administered to the rats as drinking water at doses of 100 and 500 mg/kg/d from the day of ATS-injection (day 0) to day 8, when rats were sacrificed. In the histological evaluation, the total number of glomerular cells, proliferating cell nuclear antigen (PCNA) positive cells, and macrophage/monocyte antigen-positive cells in the glomerulus, was significantly decreased in perilla-treated rats. A significantly lower level of proliferation was induced by the serum of the perilla-treated rats than by that of the controls. These results suggest that the perilla decoction suppresses the proliferation of mesangial cells in vivo by an inhibition of the glomerular infiltration of macrophage/monocytes and of the production of circulating growth factors.

104. Habeb M, Agac MT, Aliyev F, Pehlivanoglu S, Ongen Z. "Contrast media-induced nephropathy: clinical burden and current attempts for prevention" *Anadolu Kardiyol Derg.* 2005; Jun;5(2):124-9. [Article in Turkish] Contrast media-induced nephropathy is the third most common cause of hospital acquired acute renal failure. With the increasing use of contrast media in diagnostic and interventional procedures it has become one of the major challenges encountered during routine cardiology practice. Despite clinical importance it is an under-recognized event with major morbidity and mortality. Risk of developing contrast media-induced nephropathy depends mainly on patients preexisting characteristics and physicochemical properties of the contrast agent. Primary attempts for the prevention of contrast media-induced nephropathy should include systematic review of patient's characteristics and risk stratification. Patients at the greatest risk for contrast media-induced nephropathy can be defined as those having preexisting impaired renal function, diabetes mellitus, and congestive heart failure. Other risk factors include; age above seventy years, female gender, dehydration and use of high volume contrast media. The more expeditious use of iso-osmolar non-ionic contrast media reduced the incidence of contrast media related renal dysfunction.

Currently, the only widely proven method of reducing the risk of contrast-induced nephropathy is adequate pre and postprocedural hydration. In addition, prophylactic use of free radical scavenger N-acetylcysteine has been shown to prevent contrast media-induced nephropathy in some moderate-scale clinical trials and a meta-analysis. Despite the attempts to reduce the risk of contrast nephropathy, this clinical event affects over 25% of high risk patients and mortality remains to be high.

105. Briguori C, Airoidi F, Morici N, Colombo A. "New pharmacological protocols to prevent or reduce contrast media nephropathy." *Minerva Cardioangiol.* 2005; Feb;53(1):49-58. Related Articles, Links

Contrast media associated acute renal failure represents the third cause of in-hospital renal function deterioration after decreased renal perfusion and post-operative renal insufficiency. Although generally benign, this complication shows a mortality rate ranging from 3.8% to 64%, depending on the increase of creatinine concentration. The mechanism by which contrast-induced renal failure occurs is not well understood. Contrast agent-associated nephrotoxicity appears to be a result of direct contrast induced renal tubular epithelial cell toxicity and renal medullary ischemia. Furthermore, a key mechanism seems to be alteration in renal dynamics, probably caused by imbalances between vasodilator and vasoconstrictor factors, including the activities of nitric oxide, prostaglandins, endothelin and reactive oxygen species. Recommendations to prevent contrast-associated nephrotoxicity are: 1) periprocedural hydration, 2) use of a low osmolality contrast, and 3) limiting the amount of contrast agent. Recently, considerable interest has resulted from the preliminary positive data on the effectiveness of prophylactic administration of antioxidant compounds (such as acetylcysteine and ascorbic acid) and fenoldopam.

106. Lim PS, Wang NP, Lu TC, Wang TH, Hsu WM, Chan EC, Hung WR, Yang CC, Kuo IF, Wei YH. "Evidence for alterations in circulating low-molecular-weight antioxidants and increased lipid peroxidation in smokers on hemodialysis." *Nephron.* 2001; Jun;88(2):127-33.

Cardiovascular disease is the major cause of mortality in dialysis patients, accounting for about 40% of deaths in most large registries. Oxidative stress has been strongly implicated in the pathogenesis of these events. As end-stage renal disease is a state of elevated free radical activity, the aim of the present study was to investigate the negative impact of smoking in 57 male hemodialysis patients. METHODS: The patients, who were 20-85 years of age (mean age 51.0 +/- 14 years), had been on hemodialysis for at least 6 months before participating in this study. Fasting blood sampling for serum lipid, albumin, urate and lipophilic antioxidants such as tocopherols, carotenes, ascorbate and lipid peroxides was performed. RESULTS: The plasma malondialdehyde (MDA) concentration was significantly higher in hemodialysis patients who smoked

compared to hemodialysis patients who were nonsmokers (1.92 ± 0.52 vs. 1.59 ± 0.42 nmol/ml, $p = 0.006$). No association was found between levels of MDA in smokers and parameters such as body mass index, serum cholesterol, serum triglycerides and smoking index. There were no significant differences in the plasma levels of uric acid, alpha-tocopherol, gamma-tocopherol, delta-tocopherol, alpha-carotene, beta-carotene and retinol between the two groups. A significantly lower level of plasma ascorbate was observed in hemodialysis patients who smoked compared to the nonsmoking hemodialysis patients or healthy controls (4.59 ± 4.0 vs. 9.57 ± 4.0 and 10.16 ± 4.6 microg/ml, $p < 0.05$). Moreover, in smokers, the plasma levels of ascorbate were negatively correlated with the levels of plasma MDA ($r = -0.43$, $p < 0.001$) of each patient. Partial correlation analysis of the plasma levels of the measured antioxidants and the smoking index revealed a negative correlation between the plasma levels of lipid-normalized lycopene and the smoking index ($r = -0.53$, $p < 0.05$). CONCLUSION: Our data suggest that cigarette smoking further increases plasma-circulating products of lipid peroxidation, which are already increased in nonsmoking hemodialysis patients as compared to matched healthy controls. The lower plasma levels of ascorbate in hemodialysis patients who smoke suggest that these patients may be more susceptible to oxidative tissue damage caused by smoking. Copyright 2001 S. Karger AG, Basel

107. Soylu A, Kavukcu S, Sarioglu S, Astarcioglu H, Turkmen M, Buyukgebiz B. "The effect of vitamin A on the course of renal ablation nephropathy." *Pediatr Nephrol.* 2001 ;Jun;16(6):472-6.

Renal scarring due to pyelonephritis was shown to improve in rats given vitamin A. We evaluated the effect of vitamin A in a renal ablation nephropathy model. Four groups, each including 7 rats with 5/6 nephrectomy, were formed: group I (no vitamin A), group II (60 kIU vitamin A), group III (120 kIU vitamin A), and group IV (180 kIU vitamin A). Four sham-operated rats comprised the control group. After 6 weeks of 5/6 nephrectomy, the rats were sacrificed and serum creatinine, vitamin A, and beta-carotene levels were determined in addition to histopathological evaluation of the remnant kidneys. The tubulointerstitial and glomerular changes were graded as "0-3" and "0-5" respectively, in accordance with the severity of the lesions. Tubulointerstitial score (TIS), mean glomerulosclerosis score (MGS, arithmetical mean of the sclerosis scores of 100 glomeruli), and severity of glomerulosclerosis index (SGI, ratio of the number of glomeruli with grade $>$ or $=$ 3 sclerosis to the total number of glomeruli examined) were calculated for each rat. Serum creatinine levels were higher in the study groups than the control rats ($P < 0.05$), but there was no significant difference between the study groups (although the levels increased as the dose of vitamin A increased). Serum vitamin A levels were significantly higher in the groups given vitamin A than the control rats and group I ($P < 0.05$). In addition, serum vitamin A

levels increased significantly in parallel to increasing doses of vitamin A ($P < 0.05$). Serum beta-carotene levels did not differ between the groups, except for group II, which had lower levels than controls ($P = 0.01$). MGS and SGI were significantly higher in the study groups than control rats ($P < 0.05$), but did not differ between the study groups. Study and control rats were not different with respect to TIS, but there was a difference between the control group and group III ($P = 0.04$). Group II had the lowest MGS, SGI, and TIS scores among the study groups. When all the rats were considered together, vitamin A levels did not correlate with the MGS and SGI, but correlated positively with the TIS ($r = 0.391$, $P = 0.027$). beta-Carotene levels also did not correlate with the MGS, SGI, and TIS. In conclusion, vitamin A administration did not significantly affect the clinical and pathological course of renal ablation nephropathy in rats. Furthermore, higher doses of vitamin A might even damage renal tissue.

108. Hirano H, Tone Y, Otani H, Oya M, Kimura K, Saika Y, Fujii R, Mune M, Ichinose M, Yukawa S. "Levels of serum ascorbate and its metabolites in hemodialysis patients" *Nippon Jinzo Gakkai Shi.* 2004; Jul;46(5):426-33. [Article in Japanese]

The status of ascorbic acid (AA) in dialysis patients is the subject of debate. Some reports have found AA to be deficient in dialysis patients, while others have found that AA is not deficient. In an attempt to confirm AA serum concentrations in dialysis patients, we analyzed the concentrations of AA as well as its metabolites using the specific determination of AA with chemical derivatization and the HPLC method. We studied 131 patients under maintenance hemodialysis therapy (HD), 23 patients with chronic renal failure (CRF) and 48 healthy controls (C). Serum concentrations of AA and the AA metabolites dehydroascorbic acid (DHA) and 2, 3-diketogulonate (DKG) were measured by HPLC. Nine HD patients were taking AA supplements. Seventy-six (62.3%) of the 122 HD patients not taking AA supplements exhibited deficient levels of AA (< 20 microM), while 13 (56.5%) of the 23 CRF patients and 9 (18.8%) of the 48 C showed deficient levels of AA. Analysis of AA metabolites in the normal-range AA (20-80 microM) group revealed that the DHA/AA ratio in HD patients was significantly higher than in C ($3.3 \pm 2.6\%$ and $1.2 \pm 2.2\%$, respectively). The DKG/AA ratio in HD patients was higher than in CRF patients ($3.6 \pm 5.2\%$ vs. $0.9 \pm 1.9\%$), whereas DKG was not detected in C. When compared to serum levels before the start of dialysis, serum AA, DHA and DKG concentrations at the end of the dialysis session decreased by an average of 74.2, 84.0 and 78.8% respectively. In HD patients, serum levels of thiobarbituric reactive substances (TBARS) were significantly lower in the higher AA (> 80 microM) group than in the deficient and normal-range AA groups. In 12 AA-deficient patients, after 1 month of taking AA supplements (200 mg/day), serum AA levels rose to 79.9 microM, while serum TBARS level declined when compared with levels before supple-

mentation. In conclusion, the frequency of AA deficiency in dialysis patients is extremely high. AA deficiency in HD patients may result in high TBARS levels, which reflect increased oxidative stress. Adequate AA supplementation should therefore be considered in such patients.

109. Cross JM, Donald AE, Nuttall SL, Deanfield JE, Woolfson RG, Macallister RJ. "Vitamin C improves resistance but not conduit artery endothelial function in patients with chronic renal failure." *Kidney Int.* 2003; Apr;63(4):1433-42.

Chronic renal failure is associated with impaired endothelium-dependent vasodilation and accelerated atherogenesis. To examine whether endogenous reactive oxygen species (ROS) modify endothelial function in renal failure, we evaluated the effect of the antioxidant vitamin C on endothelium-dependent responses in both the conduit and resistance vasculature of subjects with severe renal impairment. METHODS: Endothelial function of the forearm resistance vasculature was assessed using plethysmography to measure the dilator response to intra-arterial acetylcholine (ACh) (25 to 100 nmol/min). Endothelial function of radial and brachial arteries was assessed using vascular ultrasound to measure the dilator response to flow during reactive hyperemia [flow-mediated dilatation (FMD)]. Studies were performed before and after administration of vitamin C by intra-arterial infusion (25 mg/min) in 33 predialysis patients or by intravenous infusion (3 g) in 17 hemodialysis patients. RESULTS: Parenteral administration of vitamin C resulted in a 100-fold increase (intra-arterial studies) and a 4.5-fold increase (intravenous studies) in serum antioxidant activity. Vitamin C administration increased the dilator response to ACh in resistance vessels ($P = 0.01$), but did not alter the dilator response to flow in conduit vessels of either dialysis ($P = 0.3$) or predialysis subjects ($P = 0.8$). In the presence of the nitric oxide (NO) synthase inhibitor NG-monomethyl-L-arginine (L-NMMA), there was no effect of vitamin C on resistance vessel endothelial function. In all cases the dilator response to the endothelium-independent dilators was unaffected by vitamin C. CONCLUSION: Acute administration of vitamin C reduces oxidant stress in renal failure and improves NO-mediated resistance vessel dilatation.

110. Boaz M, Weinstein T, Matas Z, Green, Smetana S. "Peripheral vascular disease and serum phosphorus in hemodialysis: a nested case-control study." *Clin Nephrol.* 2005; Feb;63(2):98-105.

Serum phosphorus (P) and the product of serum calcium x serum P (Ca x P), are frequently elevated in end-stage renal disease patients on maintenance hemodialysis (HD). Elevated P and Ca x P have been associated with vascular calcification in dialysis patients. OBJECTIVE: To examine the role of P and Ca x P as risk factors for incident peripheral vascular disease (PVD) in HD patients with pre-existing CVD. METHODS: This nested case-control study is

drawn from the 11 incident PVD events reported in the cohort of the Secondary prevention with antioxidants of cardiovascular disease in end-stage renal disease (SPACE): a randomized placebo-controlled trial. PVD was defined clinically and confirmed ultrasonographically. Each individual with a PVD event was matched for SPACE treatment group (vitamin E or placebo), age (in 4-year categories) and gender with two individuals who had no CVD end point during the follow-up period. RESULTS: Serum P and Ca x P levels were significantly higher in PVD patients than in controls. In univariate logistic regression analysis, only serum P predicted PVD in this population (OR 2.02, 95% CI 1.07 - 3.81, $p = 0.03$). In multivariate analysis, adjustment was made for variables dissimilar by PVD status including underlying renal disease, diabetes, smoking, history of angina pectoris, prescription for vitamin D3, erythropoietin, calcium channel blockers and aspirin. In this model, serum P remained the only significant predictor of incident PVD (OR 2.4, 95% CI 1.01 - 5.74, $p = 0.04$). CONCLUSIONS: Findings of the present study are consistent with a role for serum P and Ca x P in the pathogenesis of PVD in HD patients.

111. Hoppel C. The role of carnitine in normal and altered fatty acid metabolism. *Am J Kidney Dis* 2003;41(Suppl 4):S4-S12.

112. Bellinghieri G, Santoro D, Calvani M, et al. Carnitine and hemodialysis. *Am J Kidney Dis* 2003;41(Suppl 1):S116-S122.

113. Evans A. Dialysis-related carnitine disorder and levocarnitine pharmacology. *Am J Kidney Dis* 2003;41(Suppl 4):S13-S26.

114. Goral S. Levocarnitine's role in the treatment of patients with end-stage renal disease: a review. *Dial Transplant* 2001;30:530-8.

115. Eknoyan G, Latos DL, Lindberg J. Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. *Am J Kidney Dis* 2003;41:868-76.

116. Golper TA, Goral S, Becker BN, et al. L-carnitine treatment of anemia. *Am J Kidney Dis* 2003;41(Suppl 4):S27-S34.

117. Pauly DF, Pepine CJ. The role of carnitine in myocardial dysfunction. *Am J Kidney Dis* 2003;41(Suppl 4):S35-S43.

118. Miller B, Ahmad S. A review of the impact of L-carnitine therapy on patient functionality in maintenance hemodialysis. *Am J Kidney Dis* 2003;41(Suppl 4):S44-S48.

119. Arduini A, Holme S, Sweeney JD, et al. Addition of L-carnitine to additive solution-suspended red cells at 4 degrees C reduces in vitro hemolysis and improves in vivo viability. *Transfusion* 1997;37:166-74.

120. Ahmad S, Robertson HT, Golper TA, et al. Multicenter trial of L-carnitine in maintenance hemodialysis patients. II. Clinical and biochemical effects. *Kidney Int* 1990;38:912-8.

121. Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS, Levin NW, Sadler JH, Kligler A, Powe NR " Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. ", *Ann Intern Med.* 2005 Aug 2;143(3):174-83. The influence of type of dialysis on survival of patients with end-stage renal disease (ESRD) is controversial. OBJECTIVE: To compare risk for death among patients with ESRD who receive peritoneal dialysis or hemodialysis. DESIGN: Prospective cohort study. SETTING: 81 dialysis clinics in 19 U.S. states. PATIENTS: 1041 patients starting dialysis (274 patients receiving peritoneal dialysis and 767 patients receiving hemodialysis) at baseline. MEASUREMENTS: Patients were followed for up to 7 years and censored at transplantation or loss to follow-up. Cox proportional hazards regression stratified by clinic was used to compare the risk for death with peritoneal dialysis versus hemodialysis. RESULTS: Twenty-five percent of patients undergoing peritoneal dialysis and 5% of hemodialysis patients switched type of dialysis. After adjustment, the risk for death did not differ between patients undergoing peritoneal dialysis and those undergoing hemodialysis during the first year (relative hazard, 1.39 [95% CI, 0.64 to 3.06]), but the risk became significantly higher among those undergoing peritoneal dialysis in the second year (relative hazard, 2.34 [CI, 1.19 to 4.59]). After stratification, the survival rate was no different for patients who had the highest propensity

122. Canavese C, Petrarulo M, Massarenti P, Berutti S, Fenoglio R, Pauletto D, Lanfranco G, Bergamo D, Sandri L, Marangella M., " Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. ", *Am J Kidney Dis.* 2005 Mar;45(3):540-9. Ascorbate supplementation for patients on regular dialysis treatment (RDT) is advised to obviate deficiency and improve epoetin response in those with functional iron deficiency. However, clear-cut safety concerns regarding hyperoxalemia are still poorly understood. This study tries to establish safety/efficacy profiles of ascorbate and oxalate during long-term intravenous ascorbate supplementation. METHODS: A prospective study was performed in 30 patients on RDT showing ascorbate deficiency (plasma ascorbate < 2.6 mg/L [<15 micromol/L]): 18 patients were administered intravenous ascorbate during 18 months (250 mg/wk, subsequently increased to 500 mg), and 12 patients were taken as reference untreated cases. Plasma ascorbate and oxalate assays and dialytic balance determinations were performed (ion chromatography and reverse-phase high-performance liquid chromatography, respec-

tively) at baseline, during treatment, and 12 months after withdrawal. RESULTS: Plasma ascorbate levels increased dose dependently with supplementation (1.6 \pm 0.8 mg/L [9.1 \pm 4.6 micromol/L] at baseline, 2.8 \pm 1.8 mg/L [15.9 \pm 10.1 micromol/L]) with 250 mg of ascorbate, and 6.6 \pm 2.8 mg/L [37.5 \pm 16.0 micromol/L] with 500 mg/wk of ascorbate), but only normalized with greater dosages for several months in 94% of patients. Baseline plasma oxalate levels increased from 3.2 \pm 0.8 mg/L (35.8 \pm 8.8 micromol/L) to 3.6 \pm 0.8 mg/L (39.5 \pm 9.1 micromol/L) and 4.5 \pm 0.9 mg/L (50.3 \pm 10.4 micromol/L) with 250 and 500 mg, respectively ($P < 0.001$). The calcium oxalate saturation threshold was exceeded by 7 of 18 patients (40%) during 6 months therapy with 500 mg/wk. Ascorbate dialysis removal increased from 37.8 \pm 23.2 mg (215 \pm 132 micromol) to 99.6 \pm 51.7 mg (566 \pm 294 micromol) during supplementation ($P < 0.001$), with corresponding increases in oxalate removal from 82.5 \pm 33.2 mg (917 \pm 369 micromol) to 111.2 \pm 32.6 mg/L (1,236 \pm 362 micromol; $P < 0.01$). Withdrawal reverted plasma levels and dialysis removal to initial values. Values for untreated patients did not change during 1 year of follow-up. CONCLUSION: Patients on RDT may resolve ascorbate deficiency with intravenous supplementation of 500 mg/wk, but this implies a significant risk for oxalate supersaturation. Oxalate measurements are strongly recommended during long-term ascorbate therapy.

123. Huang YS, Zhang JT. "Antioxidative effect of three water-soluble components isolated from *Salvia miltiorrhiza* in vitro", *Yao Xue Xue Bao.* 1992;27(2):96-100. The antioxidative effect of three water-soluble components isolated from *Salvia miltiorrhiza* has been investigated. All the three components were found to inhibit both NADPH-vit C and Fe(2+)-cysteine induced lipid peroxidation (malondialdehyde formation) in rat brain, liver and kidney microsomes in vitro. The order of their inhibitory effect is as follows: salvianolic acid A, salvianolic acid B and rosmarinic acid. The inhibitory effect on lipid peroxidation induced by NADPH-Vit C was more than that induced by Fe(2+)-cysteine. In addition, the three compounds lowered the production of superoxide anion radical (O₂⁻) in xanthine-xanthine oxidase system. The order of their potency was similar to that in antilipoperoxidation. The above results suggest that the three components have strong antilipoperoxidant activity in vitro, which may be partly through scavenging O₂⁻.

124. Zima T, Kamenikova L, Janebova M, Buchar E, Crkovska J, Tesar V. , The effect of silibinin on experimental cyclosporine nephrotoxicity. *Ren Fail.* 1998 May;20(3):471-9. The immunosuppressive drug cyclosporine A (CsA), is metabolized by cytochrome P-450 IIIA. It causes acute reversible as well as chronic largely irreversible nephro-

toxic effects. This effect is based on vasoconstriction of the afferent and efferent glomerular arterioles which leads to a reduction in glomerular plasma flow and glomerular filtration rate. The mechanisms of the vasoconstriction are unclear with a number of different pathways under discussion. Silibinin is the main constituent of silymarin. Silibinin inhibits lipid peroxidation on hepatic microsomes and mitochondria of rats and is also able to reduce the activity of various monooxygenases. Cyclosporin-induced lipid peroxidation and affected cytochrome P-450 may even contribute to cyclosporine nephrotoxicity. We examined the possibility that silibinin had a protective effect as a result of its radical scavenging properties. Silibinin, 5 mg/kg BW i.p., was administered 30 min before cyclosporine application at dose of 30 mg/kg BW daily i.p. The biochemical parameters, total malondialdehyde (MDA) in whole blood and kidney homogenates and specific content of cytochrome P-450 in microsomal liver suspension were estimated. Three groups were studied: controls (con), cyclosporine alone (CsA), and cyclosporine plus silibinin (CsA + Sili). Creatinine was significantly increased after 2 weeks in both cyclosporine treated groups compared to controls (CsA 60.2 +/- 10.6 versus 45.8 +/- 10.4 $\mu\text{mol/L}$, $p < 0.05$; and CsA + Sili 72.0 +/- 8.3 versus 45.8 +/- 10.4 $\mu\text{mol/L}$, $p < 0.001$) and glomerular filtration rate (GFR) was significantly decreased ($p < 0.0001$) in the same groups. Total MDA was elevated only in CsA rats (2.26 +/- 0.35 $\mu\text{mol/L}$, $p < 0.05$) in comparison with controls (1.60 +/- 0.44 $\mu\text{mol/L}$, $p < 0.05$) and with rats treated by CsA + Sili (1.65 +/- 0.27 $\mu\text{mol/L}$, $p < 0.05$). The specific content of cytochrome P-450 in microsomal liver suspension was increased in group CsA + Sili (1.179 +/- 0.115 nmol/mg prot) compared to control group (0.775 +/- 0.086 nmol/mg prot., $p < 0.05$) and also CsA group (0.806 +/- 0.098 nmol/mg prot., $p < 0.05$). In conclusion, silibinin decreased cyclosporine-induced lipid peroxidation without a protective effect on GFR. These data indicate that this pathway is not be important in cyclosporine-induced nephrotoxicity. Administration of both drugs (CsA + sili) increased the specific content of cytochrome P-450 in liver microsomes. This suggests that the effect of silibinin on cyclosporine biotransformation in the liver is via cytochrome P-450.

125. Jonathan Treasure, "Urtica Semen Reduces Serum Creatinine Levels," *Journal of the American Herbalists Guild*, 2003;4 (2);22-25.

Chronic renal failure marks the most severe of the potential end stages of chronic kidney infection and other systemic diseases involving the kidneys, such as diabetes. Patients with renal failure essentially suffer a near complete collapse of kidney function and as a result become internally poisoned by nitrogenous compounds. If kidney function is not restored, which in chronic cases is virtually impossible with modern medical treatments, or if the body's

toxic load cannot be expelled by other means, this condition is severe and usually leads to death quickly. Since the advent of the modern medical procedures of kidney dialysis and kidney transplants, chronic renal failure has lost much of the immediacy of its life threatening quality. For most dialysis and transplant patients, however, the quality of life remains low. Much time has to be spent in dialysis (often three days per week, each treatment day being accompanied by a recovery day after the procedure), and both dialysis and transplant patients need to take strong medications which usually are accompanied by side effects.

The technical accomplishments of modern medicine in the field of renal failure are contrasted by an obvious lack of preventative or curative approaches in both the allopathic and holistic arenas of Western medicine. It may therefore be of value to take a look at traditional approaches in China, where the occurrence and treatment of kidney exhaustion has been reported for 2,000 years.

According to a recent survey, renal failure is the third most prominent cause of death in the People's Republic of China, outranked only by cancer and chronic lung disease. Until recently, expensive treatment options such as dialysis or transplant surgery were reserved for government cadres or high paying foreign clients. Due to the urgency of this situation, the P.R.C. Ministry of Health has actively encouraged research into traditional treatment methods. In the absence of other opportunities, moreover, many Chinese patients have long turned to traditional methods, especially Chinese herbal medicine. We are therefore able to consult both 2,000 years of recorded experience in the treatment of renal failure and various conditions preceding the condition (most notably chronic glomerulonephritis), and a prolific body of modern medical literature on treating both acute and chronic renal failure with Chinese herbs.

Although Chinese clinical textbooks remain cautious in regard to curative treatment outcomes (average remission rate reported to be around 11%-13%), all studies strongly convey the message that herbal treatments can significantly improve the patients' sense of well being and extend their life span. Positive results are usually reported in 75%-80% of all cases. In a Western context, the knowledge and application of traditional Chinese treatment methods may help to prevent a patient's deterioration to this state or, if dialysis has already commenced, to reduce the frequency of hemodialysis or hemofiltration. In transplant patients, moreover, herbal treatment may address the underlying cause of the condition which has not been resolved by the surgery, thus preventing a potential recurrence of dysfunction in the new kidney.

With these goals in mind, this article attempts to provide an overview of traditional Chinese views on chronic kidney failure, as well as to introduce modern clinical approaches that have been inspired by the knowledge of Western medicine.

Traditional Etiology and Pathogenesis

Classical Chinese clinical handbooks are generally organized according to a traditional system of disease classification. Since the systems are based on different diagnostic parameters, there is no direct link between modern and traditional systems of nomenclature, and one needs to search a variety of traditional categories to find the equivalent of the modern condition, in this case kidney failure/uremia. The most relevant categories found in traditional Chinese textbooks are urine retention (longbi), [urine and feces] retention and [food] rejection (guange), kidney wind (shenfeng), and kidney exhaustion (shenlao). These concepts were defined 2,000 years ago in fundamental texts such as *The Yellow Emperor's Classic of Medicine* (Huangdi Neijing) and the *Treatise on Diseases Caused by Cold* (Shanghan Lun).

To understand the traditional reasoning for urinary problems, it is useful to first take a look at how premodern physicians in China viewed the physiology of healthy urination. Zhang Jingyue, the famous Ming Dynasty compiler of classical Chinese medical thought, writes in the "Urine Retention" section of his *Collected Works*:

Since the bladder is the fu organ in charge of storing water, water naturally enters into this organ. And since water is always transformed by qi, meaning that if there is qi there will be [moving] water, we can understand how water gets expelled from this organ. In other words, if water encounters qi it turns into exiting urine. The Classic states: 'Once the qi transforms [water], it can come out.' It is the process of transformation, therefore, that causes water to end up in the bladder, and once it is in there, it is transformation that causes it to come out. If water comes out without having undergone any transformative processes, it must also have entered the bladder without the application of transformative force. Qi transformation, in other words, is involved in both the ingoing and the outgoing processes. This is the true meaning of what the Classic refers to as "qi transformation," a comprehensive term that does not just apply to things coming out. Due to these intricately intertwined dynamics between qi and water, the following can be said: as long as there is qi within water, qi is water; as long as there is water within qi, water is qi. All pathologies, therefore, that involve a deficiency of qi and result in urine retention are always caused by an exhaustion of true yang in the lower burner [source qi] and a fundamental depletion of the original ocean [source water], by fire and water not communicating, by yin and yang breaking apart. Qi, in this case, is just qi, and water is just water. The solitary water thus accumulates and does not move. Potential outcomes of such a situation in which qi does not transform water maybe atrophy of the water fu organ [bladder], or, if water accumulates but is not excreted, processes of decay and putrefaction. Always remember, therefore, that it is the inability of source qi to transform [water] that is at the root of this condition, and that diuretics will thus not be able to force the gates open; that it is the absence of yang within yin that is the true reason, and that bitter and cold medicines will only cause the patient to deteriorate even further.

In the light of this assessment, most traditional approaches

to kidney failure focus on rectifying deficiencies of qi, yang, yin, or a combination thereof. Traditional organ networks involved are primarily the kidney which, once deficient, loses its ability to differentiate the "clear and the turbid;" the spleen, which is recognized as the body's main generator of qi and thus governs all postnatal (metabolic) processes of transformation, especially those involving moisture (due to the spleen's earth/taiyin nature); and the liver, which is in charge of "smooth flow," "expulsion of the old," and, in conjunction with the kidney, "stores prenatal water." Modern approaches tend to focus more on dispelling excess poisons such as uric acid from the bloodstream, a fact that traditional commentators did not know as such, but based on their own diagnostic parameters had early on described as "turbid damp toxins entering the blood."

As for the causative origins of renal failure, traditional etiology gives a variety of reasons, the most prominent being the following: 1) constitutional deficiency of spleen and kidney; 2) mental and physical exhaustion; 3) unhealthy dietary habits which further injure a constitutionally weak spleen; 4) repeated "wind invasion" (cold/flu, infections) from external sources, which further weaken a constitutionally weak spleen and kidney.

Traditional clinical texts report a wide variety of diagnostic and therapeutic approaches to the condition. Below, I will list the most important traditional categories, including the diagnostic features which define each category and the representative remedies which are most often referenced. I would like to underscore, however, that these categories (and their representative treatment suggestions) should be understood as very general guidelines only. Most patients suffering from chronic renal failure present with much more complex symptom pictures, involving both deficiencies (spleen, kidney, or liver) and excess (water, turbid damp, phlegm, or blood stasis) at the same time.

1) Qi Deficiency of Spleen and Kidney

Typical symptoms: pale complexion, physical weakness, shortness of breath, heavy extremities; poor appetite, bloating, diarrhea or loose stool; sticky mouth, poor taste sensation, no thirst or some thirst but little desire to drink; sore lower back and knees; cold extremities; nocturia; tongue pale, fat, toothmarked; pulse deep and weak.

Representative remedies: Buzhong Yiqi Tang, Baoyuan Tang.

2) Yang Deficiency of Spleen and Kidney

Typical symptoms: very pale or ashen complexion, mental and physical fatigue; poor appetite, diarrhea, edema; sticky mouth, poor taste sensation, no thirst; sore and cold lower back and knees or general aversion to cold; profuse nocturia; tongue pale, fat, with obvious toothmarks; pulse deep and weak.

Representative remedies: Zhenwu Tang, Shipi Yin.

3) Yin Deficiency of Liver and Kidney

Typical symptoms: yellowish complexion, hollow features,

dry mouth with bitter or unpleasant taste, likes to drink with a general preference for cold drinks, dry eyes, constipation, sore lower back and knees, heat sensations in palms/soles, dizziness, tinnitus, tongue pale pinkish or red, with no coating or thin yellow coating, pulse fine or fine and wiry.

Representative remedies: Qi Ju Dihuang Tang, Zhi Bai Dihuang Tang, San Jia Fumai Tang.

4) Qi and Yin Deficiency

Typical symptoms: combination of a) qi deficiency symptoms of spleen and kidney, and b) yin deficiency symptoms of liver and kidney.

Representative remedies: Shen Qi Mai Wei Dihuang Tang, Da Buyuan Jian plus.

5) Deficiency of Yin and Yang

Typical symptoms: combination of a) yang deficiency symptoms of spleen and kidney, and b) yin deficiency symptoms of liver and kidney.

Representative remedies: Shenqi Wan, Dihuang Yinzi, Jisheng Shenqi Wan.

6) Turbid Damp Obstructing the Center

Typical symptoms: nausea and vomiting; sticky mouth with urine taste, no thirst; greasy white tongue coating; pulse slippery or soggy.

Representative remedies: Wuzhuyu Tang, Xiao Banxia Jia Fuling Tang, Xuanfu Daizhe Tang, Wenpi Tang.

7) Damp Heat Obstructing the Center

Typical symptoms: nausea and vomiting; sticky/dry mouth with urine taste, possibly bitter taste, preference for cold drinks; burning sensation with (inhibited) urination; greasy yellow tongue coating; pulse slippery, possibly rapid.

Representative remedies: Huanglian Wendan Tang, Banxia Xiexin Tang, Suye Huanglian Tang, Fangfeng Tongsheng San.

8) Water Effusion (Due to Spleen and Kidney Yang Deficiency)

Typical symptoms: obvious edema; fat tongue with moist coating; soggy pulse.

Representative remedies: Wuling San, Fuling Guizhi Baizhu Gancao Tang.

9) Blood Stasis (In the Lower Burner)

Typical symptoms: dark lips and complexion; fixed, stabbing lower back pain; numbness in extremities, rough skin; tongue presents with purplish color and stasis in sublingual veins; congested pulse.

Representative remedies: Guizhi Fuling Wan, Danggui Shaoyao San, Xuefu Zhuyu Tang.

Due to the complexities of the condition, both traditional and modern Chinese medicine physicians would rarely prescribe these traditional “kidney deficiency,” “edema,” and “nausea” remedies in unmodified form, but rather utilize them as informational quarries that provide the basic material for a more individualized approach. To more concretely illustrate how modern Chinese TCM kidney experts address uremia and kidney failure, I have selected a variety of representative case studies published in Chinese medical journals. Note that many of these studies have incorporated Western knowledge of renal pathology and laboratory research of Chinese herbs. The prominent use of rhubarb (dahuang), especially, is due to the recent discovery that this herb can lower nitrogen compounds in the blood. Many Chinese medicine kidney specialists like to prescribe rhubarb both internally and externally (as an enema) to induce diarrhea, attempting to purge toxins that are usually excreted in the urine via the “big exit.” Almost all contemporary TCM physicians therefore instruct their patients to take rhubarb, a cooling, detoxifying, blood moving, and purgative herb—in powdered form if their constitutional remedy, which is usually of a more tonic nature, does not already include this herb.

In a similar fashion, the modern realization that kidney failure is accompanied by compromised microcirculation in the kidneys has caused many TCM physicians to include blood moving herbs, especially *Salvia* (danshen), in their formulas. As is the case with so many “discoveries” in modern TCM, however, both the use of rhubarb and blood moving herbs for kidney failure has precedents in classical herb usage. The 6th century remedy Wenpi Tang (Warm the Spleen Decoction), for instance, features the unusual combination of the cooling herb rhubarb (dahuang) and the warming herb aconite (fuzi). This brilliantly designed formula, in turn inspired by herbal combinations first mentioned in the 2nd century herbal classic, *Shanghan Lun*, reflects the early realization that kidney collapse, in addition to the patient’s constitutional yang deficiency, most often involves toxic heat that must be purged urgently.

1) Source: *A Clinical Handbook for Diagnosis and Treatment in Chinese Western Combination Medicine*, 1994.

Indications: Uremia, renal failure.

Ingredients and Administration: powdered (and encapsulated) rhubarb (dahuang), take 3-9 g per day along with constitutional kidney tonics. At the same time, the book recommends a regimen of daily retention enemas with a decoction of the following herbs: rhubarb (dahuang) 15-30g, oyster shell (mulu) 30g, sophora flower (huaihua) 30g, possibly processed aconite (fuzi) 15-30g.

2) Source: *Clinical Experiences of Diagnosing and Treating Diseases of the Kidney and Bladder*; and *Monograph On Nephritis and Uremia*.

Indications: Uremia.

MODERN CASE STUDIES

It is important to understand that the categories outlined above are very general in nature and list constitutional formulas that have not been specifically designed for kidney failure.

Ingredients and Administration: *Perilla* leaf (zisuye) 30g, *Codonopsis* (dangshen) 15g, white *Atractylodes* (baizhu) 15g, *Pinellia* (banxia) 9g, *Coptis* (huanglian) 3g, *Serissa foetida* (liuyuxue) 30g, green mung beans (ludou) 30g, *Salvia* (danshen) 30g, processed *Aconite* (fuzi) 9g, rhubarb (dahuang) 9-15g, cardamon (sharen) 3g, fresh ginger (shengjiang) 6g; decoct, divide into 2 doses, and drink in one day.

Typical Modifications: for mild edema in the legs, add *Lobelia* (banzhilian); for itchy skin, add *Dictamnus* (baixianpi) and *Kochia* (difuzi); for lower back pain and cast urination, add *Sambucus* (qianqianhuo); for ascites and severe obstruction of both bowel movements and urination, grind up equal amounts of the following herbs, encapsulate the herb powder, and take 3.6g per day (in 4 doses) along with the standard decoction: black pharbitis (heichou), white pharbitis (baichou), fennel (xiao huixiang), rhubarb (dahuang).

Notes: This formula has been designed on the basis of the classic formula Warm the Spleen Decoction (Wenpi Tang) by Dr. Xu Songnian, one of China's eminent authorities on the traditional treatment of kidney disease. He labeled it Wenshen Jiedu Tang (Warm the Kidney and Resolve Toxin Decoction), as which it is often quoted as a representative formula for the treatment of life threatening uremia (in both acute and chronic renal failure patients). Dr. Xu's approach focuses on the expulsion of toxic pathogens from all three burners, putting into action the "excess priority" theory which asserts that the deficiency symptoms of renal failure patients cannot be rectified unless excess toxins are resolved first.

Clinical Trial Outcome: 17 patients with uremia due to renal failure were treated with Wenshen Jiedu Tang. 2 reported obvious results (symptoms improved, kidney functions restored), 6 good results (symptoms improved, kidney functions improved), and 4 showed no improvement (5 patients apparently unaccounted for in the source from which I was translating).

3) Source: New Traditional Chinese Medicine, 1986.

Indications: Uremia.

Ingredients and Administration: rhubarb (dahuang) 15g, processed *Aconite* (fuzi) 15g, hoelen (fuling) 15g, perilla leaf (suye) 10g, *Pinellia* (banxia) 10g, fresh ginger (shengjiang) 10g, *Coptis* (huanglian) 5g, cardamon (sharen) 5g; decoct and drink in one day. Concurrently, administer a daily retention enema with a decoction of the following herbs: rhubarb (dahuang) 15g, sophora flower (huaihua) 15g, *Viola* (zihua diding) 15g, dandelion (pugongying) 30g, oyster shell (sheng muli) 30g, moutan (mudanpi) 10g; boil down to 300 ml, administer once per day, which ensures that the patient has diarrhea 3-5 times per day. Continue this combined regimen for 7-10 days, then rest for 3-5 days, then start the next treatment period.

Notes: This approach, reported by Dr. Chen Xian, is comparable to the previous study. It employs the traditional method of "warming the kidneys while purging the turbid" (wenyang xiezhuo).

Clinical Trial Outcome: Of 45 uremic patients, 14 markedly improved, 13 improved, 12 showed no results, and 6 died.

4) Source: Shanxi Journal of Medicine and Pharmacology, 1982.

Indications: Nephrogenic azotemia.

Ingredients and Administration: raw rehmannia (sheng dihuang) 15-30g, *Dioscorea* (shanyao) 20g, hoelen (fuling) 15-20g, *Plantago* seeds (cheqianzi) 15g, *Aurantium immaturus* (zhishi) 10g, morus bark (sangbaipi) 10g, *Eucommia* (duzhong) 10g, alisma (zexie) 10g, alcohol treated rhubarb (jiu dahuang) 6-10g (boil separately for 15 minutes, add to rest of decoction at time of consumption); decoct, divide into two doses, and drink in one day.

Notes: This remedy is called Renal Azotemia Drink (Shen Dan Jian). Based on the traditional Rehmannia Six Formula (Liuwei Dihuang Wan), it is a typical example for the yin deficiency approach to renal failure. Note that even this tonic prescription still has a strong focus on purging excess heat and toxic damp.

Clinical Trial Outcome: In a case trial, 30 patients with uremia due to kidney failure (presumably both chronic and acute types) were treated with this remedy. At the end of the study, 17 were reported to have gone into remission, 7 basically into remission, and 6 improved.

5) Source: New Traditional Chinese Medicine, 1987.

Indications: Chronic renal failure.

Ingredients and Administration: *Pinellia* (banxia) 12g, bamboo skin (zhuru) 12g, *Eupatorium* (peilan) 12g, *Citrus* (chenpi) 9g, aurantium (zhike) 9g, hoelen (fuling) 20g, *Centella asiatica* (jixuecao, bengdawan) 30g, hu-chang (huzhang) 30g, *Leonurus* (yimucuo) 30g, *Salvia* (danshen) 30g, excrementa bombycis (cansha) 15g; decoct and drink in one day. Concurrently, do a daily retention enema with a decoction of the following herbs: rhubarb (dahuang) 30g, sophora flower (huaihua) 30g, (bengdawan) 30g.

Typical Modifications: for yang deficiency, add processed aconite (fuzi) and fresh ginger (shengjiang); for qi deficiency, add astragalus (huangqi); for damp heat, add coptis (huanglian); for constipation, add rhubarb (dahuang); for loss of consciousness, add Sedate the Palace Pills With Ox Gallstone (Angong Niuhuang Wan).

Notes: This formula was reported by Dr. Hong Tieguo, and reflects another version of the "excess priority" approach to renal failure. Virtually none of the herbs used are tonic in nature. The focus is clearly to remove phlegm, toxic damp, and stagnating blood.

Clinical Trial Outcome: At the conclusion of treatment, of 156 chronic renal failure patients participating in the study, 34 were reported as in remission, 75 as improved, and 47 as without results. Some of the patients also received Western medications, depending on their symptom profile.

6) Source: The Journal of Traditional Chinese Medicine, 1988.

Indications: Kidney dysfunction in chronic nephritis patients.

Ingredients and Administration: *Salvia* (danshen) 30g, *Leonurus* (yimucuo) 30-60g, red peony (chishao) 15-30g, tang-kuei (danggui) 15-30g, *Ligusticum* (chuanxiong) 15-30g.

Typical Modifications: for yang deficiency of spleen and kidney, add processed aconite (fuzi), epimedium (yinyanghuo), morinda (bajitian); for qi and yin deficiency, add *Astragalus* (huangqi), *Codonopsis* (dangshen), white *Atractylodes* (baizhu), *Scrophularia* (xuanshen), ophiopogon (maimendong); for yin deficiency of liver and kidney, add *Cornus* (shanzhuyu), morus fruit (sangshenzi), lycium fruit (gouqizi), raw rehmannia (sheng dihuang); for blood stasis obstructing the collaterals, add anteaterscales (chuanshanjia), rhubarb (dahuang), liquidambar (lulutong).

Notes: This formula was designed by Dr. Hong Shuyun. The design is based on Four Things Decoction (Siwu Tang), replacing rehmannia (dihuang) with *Salvia* (danshen), which enhances the blood moving properties of the original formula and has shown some promise in trials with nephritis patients, and adding leonurus (yimucuo), an herb with an affinity to the lower abdomen which enhances water metabolism, breaks up blood stasis, and guides the effect of the formula specifically to the kidneys. This remedy is a typical example of the clinical approach of the blood moving school, which generally assumes that a) all serious and "strange" diseases involve blood stasis (see especially Wang Qingren's influential Qing Dynasty text, *Rectifying Mistakes in the Medical Classics*, Yilin Gaicuo), and b) all structural change and atrophy in the body needs to be addressed by improving microcirculation.

Clinical Trial Outcome: Of 21 patients treated, the average clearance of urinary creatinine was 36.51% before treatment, and 70.53% after treatment.

FOOTNOTES

1. See Jiang Suli, ed., *A Collection of Famous and Experimental Formulas for Difficult and Recalcitrant Disease*. (Yinan Bingzheng Ming Yan Fang Jiyao). Beijing: Hualing Chubanshe, 1990, vol. 1, p.444.

2. See He Shaoqi, ed., *An Internal Medicine Handbook for Contemporary TCM Physicians* (Xiandai Zhongyi Neike Xue). Beijing: Zhongguo Yiyao Keji Chubanshe, 1991, p.372.

3. Quoted in Chen Guiting and Yang Sishu, eds., *A Clinical Handbook for Diagnosis and Treatment in Chinese Western Combination Medicine* (Shiyong Zhong Xi Yi Jiehe Zhenduan Zhiliao Xue), Beijing: Zhongguo Yiyao Keji Chubanshe, 1994, p.500-501.

4. For formula ingredients and herbal amounts in the traditional remedies mentioned, see one of the many Chinese herbal formula textbooks, such as Bensky and Barolet, *Chinese Materia Medica: Formulas and Strategies*.

5. Chen Guiting and Yang Sishu, p. 503.

6. As quoted in Zhang Haoliang, ed., *Clinical Formulas for the Diseases of the Urinary Tract and the Reproductive System* (Miniao Shengzhi Xi Bing Shiyong Fang), Yangzhou: Jiangsu Kexue Jishu Chubanshe, 1994, p. 123-24.

7. New Traditional Chinese Medicine (Xin Zhongyi) 3/1986, p.23.

8. Zhang Haoliang, p. 124.

9. New Traditional Chinese Medicine (Xin Zhongyi) 7/1987, p. 40.

10. Journal of Traditional Chinese Medicine (Zhongyi Zazhi) 4/1988, p. 271.

