

News

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*****Physician/investigators probe chronic diseases in new clinical research outpatient facility.

DALLAS--Pioneering research on chronic illnesses ranging from diabetes to osteoporosis to multiple sclerosis and others is being conducted by scientists at the General Clinical Research Center Outpatient Service on the campus of The University of Texas Health Science Center at Dallas.

These research studies focus on innovative drug and treatment trials with chronically ill volunteers who have not responded to conventional therapy. They may also aim at understanding how normal volunteers respond to therapies since only by understanding normal body functions can one make assessments on disease states. Some of the studies search for factors which cause diseases to develop.

Research projects often involve both inpatient and outpatient care. The inpatient GCRC facility, located in Parkland Memorial Hospital, is one of 74 such human research facilities funded by the Division of Research Resources, National Institutes of Health, in academic medical centers throughout the United States. The inpatient GCRC, in existence since 1974, is optimal for strict metabolic testing in which a controlled environment is essential. Often a research project will begin with inpatient assessment and then continue with outpatient care.

The newly opened outpatient GCRC facility, housed in the UTHSCD Aston Ambulatory Care Center, is ideal for accommodating long-range research in which outpatients can participate in medical trials with minimal inconvenience. The GCRC anticipates some 5,000 outpatient visits each year, according to GCRC director Dr. Charles Y.C. Pak.

Principle investigators include nationally and internationally recognized authorities in their disciplines. Some of these scientists and their research projects are as follows:

****Two leading authorities in cholesterol metabolism, Drs. David Bilheimer and Scott Grundy, who treated seven-year-old Stormie Jones before and after her historic heart and liver transplant surgery, are researching an experimental drug for lowering blood cholesterol. The drug, mevinolin, has been shown effective in treating people with dangerously high levels of blood cholesterol. "The basic defect in cholesterol metabolism still exists in the patients studied," says Grundy, "but treatment with mevinolin alone or in combination with another drug can bring blood cholesterol levels to about normal." Says Bilheimer, "There are several exciting implications from this study. We now have a prototype for very effective reduction of plasma cholesterol."**

****Some patients don't respond normally to diuretics -- particularly those patients with congestive heart failure, liver disease and some kidney disease, according to pharmacologist Dr. Craig Brater, associate director of the GCRC. These patients seem to develop resistance to diuretic drugs for reasons that are not clear. Brater is investigating the normal response to diuretics, determining how much drug reaches the urinary site of action in the kidney, the drug clearance rates and a multitude of other factors. He is looking at many candidates for mechanisms of diuretic resistance. And he is researching analgesics and antiarthritic medications, known to cause abnormal responses, to study their effect on the kidney.**

****Salt intake may be a risk factor in osteoporosis, according to Dr. Neil Breslau, assistant director of the GCRC. "When a person increases salt intake there is an increase in excretion of calcium as well as sodium. The increase of the two goes parallel in the urine. We are asking 'where does the increased calcium come from?'," Breslau says. In young normal persons, the salt-induced "renal calcium leak" appears to be sustained by an increased amount of calcium absorbed from the intestines. But women with osteoporosis studied in GCRC were not able to adapt to a dietary salt increase, Breslau says, since their calcium absorbed from food did not increase. Because of problems in mineral metabolism, an increase in urinary calcium would have**

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gcrc investigators, add one

to come from bone and not the intestines in these women, he says. Therefore, excessive salt intake is inadvisable in these women.

****Calcium's effect on blood pressure is under investigation by hypertension expert Dr. Norman Kaplan and his associate Dr. C.V.S. Ram. Dietary calcium has recently been hypothesized as being an important nutrient in the determination of hypertension. Studies performed elsewhere show that persons with low calcium diets may be predisposed to hypertension. Kaplan and Ram are looking at the effects of calcium intake on blood pressure in order to provide further understanding. They are also looking at the effects of a calcium channel blocking drug, used for hypertension. The calcium blocker, designed for use in patients with angina or coronary artery spasm, is effective in hypertension. But studies in the GCRC will concentrate on other effects of the calcium blocker -- specifically, whether it may cause changes in mineral metabolism that would result in kidney stones from absorbing too much calcium from the intestines or osteoporosis from absorbing too little calcium from the intestines.**

****Patients who lose large volumes of fluid from intractable diarrhea are the focus of gastroenterologist Dr. Guenter Krejs. Krejs has authored several articles in the New England Journal of Medicine describing the diagnoses of life-threatening hormone-secreting tumors of the gastrointestinal tract that cause large volume diarrhea. These tumors may cause confusing symptoms that are difficult for physicians to diagnose. "From studying normal subjects we know much about the function of the intestine in taking up water, salt and nutrients," says Krejs. "Therefore we can recognize derangements with our techniques and make diagnoses previously overlooked or describe a new mechanism of diarrhea to add to our understanding of these syndromes."**

****Two new orphan drugs for the prevention of kidney stones have been developed in the GCRC by Dr. Charles Y.C. Pak, GCRC director. The first, "sodium cellulose phosphate," was approved by the FDA in December 1982 after 15 years of testing by Pak's group. SCP was found clinically effective in the treatment of "absorptive hypercalciuria," a stone-forming disorder frequently associated with increased absorption of calcium from food. The second drug, with FDA approval pending, is "potassium citrate," a component of citrus fruits. Potassium citrate has been found effective in reducing the rate of stone formation or ceasing stone production in patients with "hypocitraturia," a condition in which a person has a low urinary citrate level.**

****The insulin pump, worn by the diabetic patient for continuous perfusion of insulin, has achieved a reversal in the progressive complication of capillary thickening, according to Dr. Philip Raskin, internationally recognized expert in diabetes. GCRC studies performed by Raskin's team have focused on the various complications of diabetes. An investigation is in progress on treating patients with an inhibitor of the enzyme "aldose reductase" since this enzyme seems responsible for the high levels of "sorbitol" that accumulate in nerves and other tissues in the diabetic. Sorbitol is a form of alcohol derived from glucose metabolism and may play a principle role in diabetes complications, particularly neuropathy and cataracts.**

****Long-range studies on improved hypertension drugs have been conducted by Dr. Gary Reed, hypertension and emergency medicine authority. The original drug for lowering blood pressure by inhibiting the conversion of certain hormones produced by the kidney was tested in the GCRC. Side-effects, however, have limited its use. Reed has been testing a second drug with the same mechanism of action as the first but with an altered chemical structure to avoid the side-effects.**

****Psychiatric illnesses called "affective disorders," including manic-depressive illness in which patients experience wide mood swings from deep depression to extreme elation, are being studied by psychiatrist Dr. John Rush and collaborators Drs. Donna Giles and Michael Schlessler. Work includes looking at biochemical differences that appear to distinguish "biological" depressions, which may be inherited and descend without apparent cause, from learned or psychologically based depressions. By examining altered responses to certain steroids, Rush is trying to identify abnormalities that might predict differential drug response as well as the need for psychotherapy. Also, exciting radiologic studies performed in collaboration with Drs. Frederick Bonte and Michael Devous in the UTHSCD Nuclear Medicine Center indicate certain brain blood-flow abnormalities are found in some forms of depression.**

****Osteoporosis, the most common reason for fractured bones among post-menopausal women, appears to be more than one metabolic bone disease, says Dr. Khashayar Sakhaee, who heads several GCRC osteoporosis studies. His research team has described a cause of osteoporosis which they call "renal leak osteoporosis." Patients with renal leak osteoporosis have an accompanying disorder in which high urinary calcium loss causes too much parathyroid hormone to be secreted. In these patients the kidneys lose a**

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greater than average level of calcium than is absorbed from dietary calcium. One study shows that a diuretic used in a common kidney stone-forming disorder, "hypercalciuria," can control the loss of calcium in the urine of patients with renal leak osteoporosis by controlling the secretion of parathyroid hormone.

**A "modest revolution" in the treatment of autoimmune diseases that effect the central nervous system has taken place in the GCRC, according to neurologist Dr. Richard Tindall. Tindall has looked at new treatments for this group of diseases, which includes multiple sclerosis, myasthenia gravis, Guillain-Barre and polymyositis. Tindall's first GCRC research involved use of a process for clearing the blood of antibodies which destructively attack the body in autoimmune diseases. This process, "plasmapheresis," was one in which a patient's blood is run through a cleaning process and then returned with replacement factors. Results confirm that the process is beneficial in myasthenia gravis and Guillain-Barre, but not in MS. Now new studies involve experimental drugs for the same set of diseases. The first, called "poly ICLC," is an interferon inducer. A drug trial with FDA approval pending involves the use of cyclosporin, the drug used in transplants to suppress rejection, for myasthenia gravis and multiple sclerosis. Tindall says cyclosporin looks promising in both diseases.

**The effects of a low protein diet on diabetic kidney disease is under investigation by one GCRC research team. The research objective, says team leader Dr. Kathleen Zeller, is to determine if the progression of kidney insufficiency in insulin-dependent diabetes can be retarded by a diet restricting protein alone or protein plus phosphate. Evidence has accumulated in recent years to suggest that early dietary protein restriction in diabetes may dramatically alter the natural history of chronic renal insufficiency, says Zeller. Yet the effects of experimental protein restriction must be carefully monitored in a clinical out-patient setting so that signs of patient malnutrition can be monitored.

**Also, frozen metabolic diets have been developed for use in GCRC controlled metabolic studies, according to Dr. Glenn Preminger, an investigator using the diets for his work on new kidney stone drugs. The purpose of the diet is that patients can be put on a fixed diet of known constitution in calcium, sodium and fluid intake and with these strict controls drug treatment studies can be conducted. With the variables of food and fluid fixed, metabolic changes can be attributed to a drug under investigation. "Studies can be done with a minimum of inconvenience to the patient and a hospital stay is avoided," Preminger says.

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