

A researcher's job is to question. But, there are only so many answers to medical questions that can be obtained in test tubes and animal models. At some point, the ultimate test must be done with humans in a clinical setting.

"Clinical research is how we move health care forward, how we understand our whole bodies better," said Jennifer Larsen, MD, professor of internal medicine.

Dr. Larsen is director of UNMC's Clinical Research Center (CRC).

Clinical research may directly benefit the patient, but often, patients may not see any direct benefit. Three years ago, University Hospital, later to become the Nebraska Health System, and UNMC committed resources to develop a state-of-the-art Clinical Research Center, a place where study conditions can be controlled as much as possible.

Before, clinical research at UNMC was conducted in the hospital and outpatient clinics. Although research continues in many areas across NHS, other projects have moved to the CRC.

"Preliminary results are critical to helping investigators gain more funding. It's the single most important thing an institution can do to facilitate that process," Dr. Larsen said.

Two research questions, two trials...

*Will bone marrow transplants truly help people with autoimmune diseases, such as multiple sclerosis?*

*What role does insulin play in blindness?*

...two volunteers. This is a tale of a man with multiple sclerosis (MS) and a young college student with diabetes. Their reasons for volunteering differ, but what ultimately lies at the foundation of their offer to help is a sincere desire to be part of moving medicine forward.

# A tale of Clinical TRIALS

Story by Elizabeth Kumru  
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## Jim's tale

Jim Duke, a 35-year-old Ames, Neb., attorney was diagnosed with multiple sclerosis in 1993, a year after he earned his law degree. Little did he know it was the beginning of the end of his short criminal law practice.

Last May, he retired when it became too hard to walk, even with the aid of a cane. "I'm much too young to be his damn old," he said in frustration.

Early studies had shown that a treatment for cancer patients could stop MS from progressing or even reverse it in 80 percent of the patients. Duke liked those odds and enrolled in a clinical trial at UNMC.

Even though it was an experimental treatment for MS, he agreed to go through radiation, chemotherapy and a peripheral blood stem cell transplant.



Transplant nurse Katie Maher and Dr. Steven Pavletic evaluate Jim Duke's walking ability. Duke underwent a stem cell transplant in hopes of slowing the progression of multiple sclerosis.

Another medical center in a 20-center national collaboration group that is performing bone marrow transplants to treat MS. The only other medical center in the study that has enrolled patients is the Fred Hutchinson Cancer Center in Seattle, Wash., said principal investigator Steven Pavletic, M.D., assistant professor of oncology-rheumatology.

"Our hope is to reset the immune system to a better functioning state in order to stop the destructive process," he said.

UNMC is known worldwide for establishing the first peripheral blood stem cell transplant program to treat cancer. Last year, UNMC modified the procedure to reset the immune system to treat rheumatoid arthritis. The experimental treatment has been deemed successful in reversing the disease to an earlier stage, said James O'Dell, M.D., professor, rheumatology-immunology, although continued treatment with medication is required.

"The trial for multiple sclerosis was a natural next step," Dr. Pavletic said.

UNMC is one of two medical centers in a 20-center national collaboration group that is performing bone marrow transplants to treat MS. The only other medical center in the study that has



Neurologist Dr. Jinan Al-Omaishi and nurse practitioner Kathleen Healey examine MRI brain scans.

More than 1,800 patients are seen in the NHS rheumatology clinic and more than 450 patients are seen in the multiple sclerosis clinic that was started two years ago.

MS affects approximately one out of 1,600 people, mostly between the ages of 20 and 40. It is one of the major causes of disability in adults under age 65, said Jinan Al-Omaishi, M.D., instructor, neurology. There are an estimated 5,000 people with MS living within a 100-mile radius of Omaha.

Multiple sclerosis is a chronic, often disabling disease of the central nervous system. One-half of the patients become wheelchair bound within 15 years of onset of the disease. During the last stages, the patient is bedridden.

Duke watched as MS changed his life. His fierce independence slipped away from him in bits and pieces.

As his legs grew weaker, Duke sought the help of UNMC's MS clinic and physical therapists in the spring of 1998. By the end of the year it was clear that he was teetering towards a progressive phase of the disease. The clinical trial was his first glimmer of hope.



MRI brain scans illustrate the progression of multiple sclerosis. White spots show the degeneration of myelin. The top scan is of a newly diagnosed MS patient. The bottom scan shows how the disease has progressed.

Patients eligible for the trial must have significantly deteriorated in functional ability in the past year. Duke's ability to walk had deteriorated from using a cane to occasionally needing a wheelchair in the past year.

Acceptance into the program meant a 45-day stay in the Lied Transplant Center where tests were performed and stem cells harvested. A baseline magnetic resonance image (MRI) was taken for later comparisons.

Since his release, Duke has been given other MRI's that indicate no

progression of MS. Though the damage to his nervous system has not been cured, the lack of progression has been seen as a hopeful sign.

“Episodes of MS tend to strike while a person is under stress and there’s nothing more stressful than going through radiation and chemotherapy,” he said.

Since the transplant, Dake has been working with his physical therapist to learn to walk again. It’s a slow process, but a promising one.

“If I can make a little impact in the world by going through this, then I’ve done more than I could ever do as an attorney,” he said.

## *Jessica’s tale*

Jessica Beard, a sophomore at the University of Nebraska-Lincoln, has a double major in communications and French, speaks the language fluently and has toured the country twice. She wants to study in Europe and after graduation, work in corporate public relations using her language skills.

At 19, she is ahead of the game.

Since she was four, Beard has been getting daily insulin shots. She has Type 1 diabetes.

“I’ve learned from a young age how important it is to take care of myself. The disease hasn’t interfered with anything I’ve wanted to do,” she said.



Jessica Beard braved poking and prodding to volunteer to further science.

Having tight control of her diabetes was one of the reasons she was asked by her physician, Dr. Larsen, to participate in a clinical trial.

Two different studies were described to her. Studying how insulin affects the eyes drew her interest.

“One of the consequences of diabetes is blindness. I considered that if I help now and if this research provides useful information, I could be a direct beneficiary



Dr. Samer Nakhle adjusts Beard’s glucose to maintain a consistent level throughout the study

of it years down the road,” Beard said.

The study is a joint project between ophthalmology and endocrinology. Endocrinologist James Lane, M.D., assistant professor, designed the study with Michael Yablonski, M.D., Ph.D., professor and chairman, and physiologist Carol Toris, Ph.D., assistant professor and researcher, in ophthalmology. They were assisted by Samer Nakhle, M.D., endocrinology fellow.

The project builds on two previous studies. Dr. Yablonski showed in 1989 that the production of fluid, called aqueous humor, was reduced in the eyes in people with Type 1 diabetes. Researchers believe that if the flow rate is depressed for any reason, it may allow for a build-up of growth factors in the back of the eye and cause blindness.

But, in a similar study at the Mayo Clinic in Rochester Minn., results were not as dramatic for people with Type 1, and showed no difference for people with Type 2 diabetes.

“Dr. Yablonski wondered if it was actually insulin, and not excessive blood sugar, that caused the difference in the two studies. In this study, we are trying to find out if there are different flow rates for people who have diabetes and if there is any correlation with the degree of retinopathy,” Dr. Toris said.

Causes of retinopathy, inflammation of the retina, are not clearly understood. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20 to 74 years.

For the study, 18 people without diabetes and 15 people with Type 1 diabetes will be tested. Another round of testing will be done with people who have Type 2 diabetes.

The project requires Beard to make several visits to UNMC for check-ups, an eye exam and then two overnight stays in the hospital. Measurements are taken at low and high insulin levels on separate visits two weeks apart.

Once admitted to the hospital, Beard settles in for the night. She gets no dinner. Researchers want tight control of her blood sugar and a nurse checks it every hour.

At 2 a.m., and every five minutes for one-half hour,

he is given special eye drops that will detect fluid movement in her eyes later that morning. The orange drops turn her world yellow. She doesn't get much sleep.

About 7 a.m., after no breakfast, Beard is wheeled into the CRC. An hour later, Beard is hooked up to four different machines. Two IV lines pump insulin and glucose into her left arm. Dr. Nakhle sits to her left and monitors the two pumps. The study requires a steady blood sugar level of 90.

Her right hand is immobilized in a "hot box" that maintains a constant 55 degrees. A port in her right arm provides easy access for a nurse to draw blood every five minutes. Cardiac monitors are patched on her chest.

The routine develops an easy rhythm. Blood is drawn and given to a research technologist, who runs the glucose analyzer. The machine gives him a reading. "It's 89," he says to Dr. Nakhle, who makes a slight adjustment.

Every 45 minutes the routine changes slightly. Dr. Toris walks in and turns the room dark. Curtains are pulled and lights are turned off. The only illumination in the room radiates from a small desk lamp next to Dr. Toris' computer.

Sitting silently in front of Beard is a fifth machine that is now wheeled up to her chair. The machine, a fluorophotometer, measures the flow of eye fluid. Eye pressure and blood flow measurements are taken with another machine.

Beard slides to the edge of her chair and peers into the machine. A blue light measures how much of the orange eye drops remain.

"We look at the disappearance rate. If it's disappearing fast that means the fluid is washing out. If there is not much change that means the fluid flow in the eye is



Ophthalmologist Dr. Yun Liang Wang and physiologist Dr. Carol Toris prepare to take eye fluid and pressure measurements.

slow. It's not washing out. It could mean that the insulin level is making a difference," Dr. Toris said.

"If we do find big differences between the groups, then we can look more closely at the cellular and molecular levels," she said.

"The ultimate goal is to discover a way to prevent this type of blindness."

By 12:30 p.m., all the measurements are completed and Beard is detached from the machines.

"I'm aware of the long-term effects of diabetes and it scares me. I'm glad researchers at UNMC are trying to find some answers," Beard said.

For more information about the MS trial call (402) 559-7857, and for the diabetes trial call (402) 559-7685. *d*

## Studies flourish @ the CRC

More than 57 protocols and 94 investigators are using the Clinical Research Center (CRC) resources at UNMC, said Jennifer Larsen, M.D., professor of internal medicine and director of the CRC.

The CRC also serves as a resource for teaching and training medical students, residents, fellows and other health providers the skills of clinical investigation.

Following is a list of just a few of the studies underway in the CRC. For more information about CRC activities, call (402) 559-7685, or visit the center's website at [www.unmc.edu/crc](http://www.unmc.edu/crc).

- Test erythromycin's effectiveness in reducing nausea for people receiving chemotherapy. Eligible participants must be over age 19 and are about to undergo a stem cell transplant.
- Evaluate the responses of people in a smoking cessation program to genetic counseling. Eligible participants must be over age 19 and have no history of cancer other than certain skin cancers.
- Study the relationship between multiple sclerosis and genetics in families. Eligible participants or family members must have been diagnosed with MS.