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New hope for the supply-and-demand crisis of kidney transplantation?

In the USA alone, there are over 64,000 people awaiting kidney transplant. This growing need is further exacerbated by the decreasing number of kidneys available from deceased donors, and patients can currently expect to wait several years for a healthy kidney to become available.

However, researchers from the University of Michigan Health System (MI, USA) have offered new hope. In a recent US-wide Scientific Registry of Transplant Recipients (SRTR) study, it was found that kidneys from expanded criteria donors (ECDs) – older donors and those with certain preexisting kidney or other medical problems whose kidneys were often not used in the past – are adding to the pool of kidneys available for transplant and subsequently increasing the survival rate for certain patients with end-stage renal disease.

The study, published in the December 7th issue of the *Journal of the American Medical Association*, set out to gauge which patients benefit from opting for an ECD kidney transplant now, rather than waiting for a non-ECD kidney. The outcome of 109,127 US patients who were on dialysis for kidney failure and had been added to an organ waiting list between 1995 and 2002 was measured, and their progress

followed through July 2004.

Coauthor Robert A Wolfe, Professor Emeritus of Biostatistics, explained, “We calculated the average lifetime for patients who accept an ECD organ compared to those who remained on dialysis with the option of accepting a non-ECD transplant at a later time, in order to help patients choose between these options. The answer depends upon the patient’s situation, so different patients might make different choices based on their particular situation and their willingness to trade off an earlier transplant with an ECD kidney versus a higher chance of failure of the transplant.”

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Factors such as age, gender, ethnicity, the cause of kidney disease and the local waiting time for a non-ECD kidney were all taken into account. A total of 7790 candidates received an ECD kidney, 41,052 a non-ECD deceased donor transplant, 15,203 a living donor transplant, and 45,082 either died before

receiving a transplant or were still waiting for a donor kidney.

Overall, ECD kidneys were shown to have the greatest benefits, in terms of survival, for patients over the age of 40 years and those who would need to wait more than 44 months for a non-ECD kidney to become available, with a 17% long-term lower risk of dying. Only diabetic patients were found to benefit from ECD kidneys in areas where waiting times were shorter. For patients younger than 40 years, there was no significant advantage to accepting an ECD kidney.

“ECD kidneys are clearly a good solution in certain situations,” says Robert M Merion, the Clinical Transplant Director for the SRTR, which is administered by the University Renal Research and Education Association (URREA). “This study’s results allow us, with greater clarity than before, to maximize the benefits of ECD kidneys for patients, and match patients with a transplant option that will offer them the best chance for survival.” While this study focuses on survival rates of kidney transplant patients, Merion promotes further research to address quality-of-life issues for patients who remain on dialysis and those who opt for an ECD kidney transplant.

Discovery of stroke-vulnerable neurons could lead to targeted stroke therapy

Researchers at the University of Central Florida (FL, USA) and the University of Calgary (Rome, Italy) have discovered the molecular event that results in neurons in the hippocampus becoming vulnerable to damage following stroke. It is hoped that the discovery, published in the March 2, 2006, issue of *Neuron*, will lead to the development of targeted drugs for stroke therapy.

The group found a pinpoint alteration in mRNA during the construction of AMPA receptors and that by amending this alteration in the mRNA, these ‘vulnerable’ neurons could be protected from ischemic injury. Further investigation discovered the enzyme responsible for editing this mRNA. The enzyme, CREB, has been previously shown to be reduced in neurons vulnerable to ischemic damage and the study authors showed that by switching this enzyme ‘on’ in these neurons, a positive effect was observed.

The authors commented that “To date, most clinical stroke trials targeting glutamate receptors [AMPA or NMDA] have failed, possibly because receptor antagonists also block the physiological actions of glutamate in noninjured neurons.” They continued that AMPA receptor subunit editing “is an initial intracellular event that gates glutamate receptor injurious signals in forebrain ischemic insult.”

Priority Paper Alerts

Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate.

Rahman M, Pressel S, Davis BR *et al.* *Ann Intern. Med.* 7, 144(3), 172–180 (2006).

This *post hoc* subgroup analysis examined hypertensive patients over the age of 55 years with one or more risk factors for coronary heart disease (CHD) in a multicenter, randomized, double-blind, placebo-controlled trial and compared rates of CHD and end-stage renal diseases (ESRD) events in order to determine whether glomerular filtration rate (GFR) independently predicts risk for CHD. The efficacy of first-step treatment with a calcium-channel blocker or an angiotensin-converting enzyme inhibitor in modifying cardiovascular disease (CVD) outcomes in high-risk patients with hypertension stratified by GFR was also examined. Results indicated that older, more high-risk patients with hypertension and reduced GFR are more likely to develop CHD than ESRD. In addition, a low GFR independently predicts increased risk for CHD. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of the level of renal function.

Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients.

Schiff H. *Nephrol. Dial. Transplant.* (2006) Epub ahead of print.

Report of 433 patients with clinically diagnosed severe acute tubular necrosis (ATN) that necessitated renal-replacement therapy in a prospective cohort study in order to assess the need for short- and long-term dialysis, and to define risk factors for lack of renal recovery. Results demonstrated an overall in-hospital mortality rate for the cohort of 47% and at discharge, 57% of surviving patients (226) had normal renal function, 33% mild-to-moderate renal failure, and 10% severe renal failure. After a period of 1 year, 76 of the surviving patients had died and one patient had progressed to end-stage renal disease from chronic renal failure. The study concluded that the majority of critically ill patients with prior normal renal function who survive the precipitating cause of ATN, will recover a sufficient portion of renal function.

Intensive therapy shows promise in the relief of diabetic neuropathy

The February issue of *Diabetes Care* has published the results of a study demonstrating that patients receiving intensive diabetes therapy show a lower prevalence of neuropathy than those receiving conventional therapy.

Participants in the study were recruited from the Diabetes Control and Complications Trial (DCCT), and had been randomized to receive either intensive therapy (at least three injections of insulin/day) or conventional therapy (on more than two injections/day). After completion of the DCCT trial, participants in the intensive group were encouraged to maintain intensive therapy, and those in the conventional group were encouraged to begin intensive therapy.

Neuropathy was assessed annually using the Michigan Neuropathy Screening Instrument (MNSI). A total of 1257 subjects participated in the first neuropathy assessment. Results demonstrated a lower prevalence of neuropathy in the intensive group compared with the conventional group (17.8 vs 28.0%, respectively). Signs and symptoms of neuropathy remained less prevalent among the intensive group despite similar levels of glycemic control. The intensive therapy group were 64 and 45% less likely to have signs and symptoms of neuropathy compared with those who received conventional therapy.

The trial concluded that the benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years.

Taste receptors living outside the body?

Scientists from the Monell Chemical Senses Center (PA, USA), have been able, for the first time, to maintain taste receptor cells outside the body in culture, paving the way for further research into taste and its function with regard to nutrition, health and disease.

Nancy Rawson, a cellular biologist and principle investigator explained, "The success of this technique may provide hope for people who have lost their sense of taste due to radiation therapy or tissue damage, who typically lose weight and become malnourished. This system gives us a way to test for drugs that can promote recovery."

Rawson and her team have been working on growing taste receptor cells outside of the body in order to further research into the process of taste cell differentiation, growth and turnover. Rather than working with

mature taste cells, basal cells, the undifferentiated precursors, from rat taste buds were extracted and placed into a tissue culture system containing nutrients and growth factors. The basal cells were able to divide and differentiate into functional taste cells in this environment.

The new cells were maintained for up to 2 months. Their characteristics were similar to mature taste cells in several key respects and the cells responded to either bitter or sweet taste stimuli with increases of intracellular calcium, a key property characteristic of mature taste cells.

Through the use of cultured taste cells, scientists have more precise control over the cell's surrounding environment, in addition to better access to subcellular mechanisms, allowing them to investigate previously unanswered questions.

Persistent nerve injury to blame for complex regional pain syndrome-I

According to findings from a report published in the February issue of the journal *Pain*, complex regional pain syndrome (CRPS) is caused by persistent nerve injury that affects nociceptive small fibers. The disease, which involves post-traumatic limb pain and autonomic abnormalities that continue despite the healing of inciting injuries, is a debilitating pain syndrome, the causes of which have been previously unknown. This has made diagnosis, treatment and research difficult and controversial.

The current study tested the hypothesis that CRPS type I is caused by persistent minimal distal nerve injury (MDNI), specifically the distal degeneration of small-diameter axons, the nerve fibers that subserve pain and autonomic function. The trial examined 18 adults with CRPS-I (formerly known as reflex

New study results have revealed that the debilitating disease, CRPS-I is caused by persistent nerve injury

sympathetic dystrophy) – as defined by the International Association for the Study of Pain – affecting their arms or legs. Three sites on the participants, CRPS-affected and matching contralateral limb were studied; the CRPS-affected site, and nearby unaffected ipsilateral and matching contralateral control sites. A total of seven adults with chronic leg pain, edema, disuse and prior surgeries from trauma or osteoarthritis provided symptom-matched controls. Quantitative mechanical and thermal sensory testing was performed followed by quantitation of epidermal

neurite densities within immunolabeled skin biopsies.

The results revealed, unexpectedly, that CRPS-I was often associated with medical procedures. Sensory testing revealed the CRPS-affected sites were highly sensitive to mechanically- and heat-induced pain. Axonal densities, although highly correlated between the ipsilateral and contralateral control sites, were diminished at the CRPS-affected sites in 17 of the 18 patients by an average of 29%. The control subjects had no painful-site neurite reductions indicating that pain, disuse, or prior surgeries alone, do not explain CRPS-associated neurite losses. The researchers concluded that these results confirm that post-traumatic focal MDNI affecting nociceptive small fibers is associated with CRPS-I.

Testosterone shown to improve quality of life in men with Alzheimer's disease

New studies have shown that a testosterone gel can enhance the quality of life for men with Alzheimer's disease (AD), but seems to have little effect on cognition. Previous studies have reported that testosterone levels are lower in men with AD than their counterparts without the neurological disorder.

Po H Lu and colleagues from the University of California (CA, USA), assessed the effects of daily treatment with testosterone or placebo gel in 16 men with AD and 22 healthy men. However, although the active therapy was also linked to improvements in some cognitive functions, these were not statistically significant and no overall effect on cognition was noted. Testosterone also showed quality of life benefits in the healthy control group, but the improvements did not reach statistical significance. Furthermore, no effect on cognition or mood was seen with testosterone in this group.

Lower doses of tissue plasminogen activator are safer

Researchers from Johns Hopkins have found that lower doses of the thrombolytic drug reduce mortality rates in patients with intracerebral hemorrhage.

Results from a Johns Hopkins study, presented at the International Stroke Conference (FL, USA), show that the optimal dose of tissue plasminogen activator (tPA) following an intracerebral hemorrhage (ICH) is lower than the 3 mg dose studied previously. Administration of 1 mg tPA reduced the rate of continued bleeding and subsequent death in these stroke patients.

Treatment of hemorrhagic stroke is less well developed than that for ischemic stroke. During an ICH, blood often extends into the ventricles of the central brain, increasing the risk of death and disability. Up to a half of ICH sufferers die and survivors are often left with significant disabilities. Daniel Hanley (Johns Hopkins, MD, USA) said,

“10 years ago, the mortality rate for this type of stroke was at 80%. 1 year ago, it was 50%. In this study it was 13%.”

Previously, Hanley had investigated a 3 mg dose of tPA in 26 patients, demonstrating the safety of this therapy. In 23% of these patients, continued bleeding was observed and the fatality rate was 19%. In the more recent study, 16 patients received either 0.3 or 1 mg tPA administered through a catheter every 6–12 h for up to 4 days or until the brain ventricles opened. No patients who received 0.3- or 1-mg doses suffered from continued bleeding in the brain and the mortality rate was lower.

Analysis of the cerebral spinal fluid showed that the 1-mg dose remained at therapeutic levels for longer periods of time than 0.3 mg and also cleared the clot more rapidly from the 3rd and 4th ventricles.

Following these promising results, Hanley plans to use the 1-mg dose in a randomized, controlled, Phase III trial of 500 patients.