

## In the Literature

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This section of News and Views will present updates of recent advances in the medical and scientific literature.

### Early Success of First Permanent Implant of Jarvik 2000 Heart

The use of permanent mechanical pump devices to improve circulatory function in patients with end-stage heart failure has been limited by the size of the devices, the reliance on hospital care for device maintenance, and the life-threatening complications of thromboembolism and infection. In the September 9th issue of *The Lancet*, Westaby and colleagues report on the first permanent implant of the Jarvik 2000 Heart into a 61 year-old man with symptomatic dilated cardiomyopathy, as part of a non-randomised, prospective assessment of the device in patients who are ineligible for cardiac transplantation. The thumb-sized pump was implanted into the apex of the patient's failing left ventricle through a thoracotomy and a tiny vascular graft was constructed to convey blood from the device to the patient's descending aorta. The power cable of the device was passed through the patient's chest and neck to a mounted pedestal behind his mastoid process. This pedestal is connected to an external battery and controller worn on the patient's belt. The single dial controller allows the patient to regulate the device's pumping efficiency according to activity level. Six weeks after implantation, the patient's left ventricular ejection fraction improved from less than 10% at baseline to 30%. His exercise tolerance increased and was accompanied by a decrease in bodyweight and disappearance of peripheral edema and ascites. There was no evidence of significant hemolysis or device-related complications, such as thromboembolism or infection. Although it is too early to draw definitive conclusions regarding the long-term safety and efficacy of the Jarvik 2000 Heart, the authors suggest that this initial intervention provides encouraging evidence for the therapeutic use of permanent mechanical circulatory support in patients with end-stage heart failure.

Westaby S, Banning AP, Jarvik R, *et al.* (2000). *Lancet*. 356: 900-903.

### New Protein Linked to Alzheimer's Disease

Alzheimer's disease is characterized by the accumulation of amyloid- $\alpha$  ( $A\alpha$ ) peptide in the brain that leads to the formation of neurotoxic plaques.  $A\alpha$  is generated from a larger transmembrane precursor,  $\alpha$ -amyloid precursor protein ( $\alpha$ APP), through enzymatic cleavage by a complex of proteins that includes presenilin (PS1) and presenilin 2 (PS2). Missense mutations in PS1 and PS2 have been linked with familial Alzheimer's disease. To date, the search for other proteins involved in the formation of  $A\alpha$  has been unsuccessful. In the September 7th issue of *Nature*, Yu and colleagues report the discovery of a new transmembrane protein, nicastrin, which is involved in the processing of  $\alpha$ APP. Nicastrin was isolated from cultured cells overexpressing PS1 by immuno-

precipitation with antibodies against PS1. The full-length cDNA for nicastrin was cloned and the gene for nicastrin maps to a region of chromosome 1 that has previously been associated with Alzheimer's disease. Further immunoprecipitation experiments with anti-nicastrin antibodies demonstrated that nicastrin interacts with PS1, PS2, and the extracellular portion of  $\alpha$ APP. Mutations that altered these interactions either increased or decreased the proteolytic cleavage of  $\alpha$ APP to yield  $A\alpha$ . Interestingly, experiments in the nematode, *C. elegans*, which knocked out the function of nicastrin yielded offspring with the same phenotype as those in which the Notch-signalling pathway was reduced. Notch is an important transcription factor released from a transmembrane precursor during development to upregulate the expression of genes involved in cell-fate determination. This finding suggests that nicastrin may be involved in a more broadly functioning proteolytic complex of proteins that process transmembrane proteins like  $\alpha$ APP and Notch. The authors speculate that nicastrin may also be a target for therapeutic manipulation in patients with Alzheimer's since it is involved in regulating the production of  $A\alpha$ . Yu G, Nishimure M, Arawaka S, *et al.* (2000). *Nature*. 407:48-54.

### Ondansetron Reduces Drinking among Biologically Predisposed Patients

Early-onset alcoholism is associated with patients who develop alcoholic behavior before the age of 25 and who demonstrate a broad range of anti-social behaviors.

Prior research has linked early-onset alcoholism with dysfunctional handling of the neurotransmitter serotonin in the brain. Selective serotonin (5-HT<sub>3</sub>) receptors are known to be involved in mediating the euphoric effects of alcohol consumption by modulating the brain's dopamine reward system. Johnson and colleagues hypothesized that early-onset alcoholics would experience better drinking outcomes when treated with ondansetron, a 5-HT<sub>3</sub> antagonist frequently prescribed as an anti-nausea medication, when compared with late-onset alcoholics treated with a similar course of ondansetron. 321 patients diagnosed with alcoholism according to DSM-III-R criteria were randomized in a double-blind study to receive either placebo or ondansetron. Patients were followed on a weekly basis and were asked to self-report their alcohol consumption and the number of days during which they had abstained from alcohol. Patients were also evaluated for plasma carbohydrate deficient transferrin (CDT) levels, an objective biological marker of their alcohol consumption. Early-onset alcoholics receiving ondansetron self-reported significantly lower numbers of drinks per day compared with placebo. Moreover, the mean log CDT ratio was significantly reduced in the ondansetron group. In con-

trast, there were no statistically significant findings achieved with the late-onset alcoholics receiving ondansetron when compared with placebo. These results support the theory of a biological basis for alcoholism and propose a targeted pharmacological therapy for a specific subgroup of alcoholics.

Johnson BA, Roache JD, Javors MA, *et al.* (2000). *JAMA*. 284(8): 963-971.

### Use of Deception by Internal Medicine Residents

Although the use of deception by physicians in encounters with their patients has been intensely scrutinized, little is known about the practices of lying by physicians in their interactions with their colleagues. In a survey of 222 internal medicine residents at four teaching hospitals in the United States, respondents were presented with five clinical vignettes and were asked to indicate their willingness to deceive their colleagues in each scenario. 36% of respondents indicated that they were likely to use deception to avoid exchanging call with a fellow resident, while 6% would protect a colleague by substituting their own urine in another resident's drug test. With regard to patient care, 15% indicated that they would misrepresent a diagnosis in a medical record to protect a patient's privacy, 14% would fabricate a patient's laboratory data if asked to recall it by an attending physician during rounds, and 5% would lie to an attending physician about checking a patient's stool for blood to cover up their own medical mistake. The authors of the study suggest that while lying about clinical issues is not common, it is troubling when it occurs. They recommend that professionalism and collegiality should be addressed as part of the medical education curriculum and that educators should consider the possibility that a resident is not telling the truth as part of the differential diagnosis in a patient work-up.

Green MJ, Faber NJ, Ubel PA, *et al.* (2000). *Arch Intern Med*. 160:2317-2323.

### Free Estradiol May Protect Against Dementia in Women

Previous studies have yielded conflicting results on the question of whether estrogen replacement therapy can improve cognitive function or prevent Alzheimer's disease in post-menopausal women. Estrogen receptors are expressed throughout the brain, particularly in regions involved in memory and learning, such as the hippocampus and amygdala. Unlike previous authors who investigated the relationship between total serum estrogen and cognitive performance, Yaffe and colleagues hypothesized that concentrations of non-protein-bound (free) and loosely bound (bioavailable) estradiol might be associated with cognitive function in older women. 425 post-menopausal women aged 65 or older underwent cognitive assessment with a modified mini mental status examination (mMMSE) and measurement of free and bioavailable serum estradiol by radio-immune assay at baseline and six years later. Cognitive impairment (a decrease of 3 points or more in mMMSE score) occurred in five of 94 women in the high tertile for free estradiol and in 17 of 106 women in the low tertile. This association persisted after adjustment for age, education, body mass index, current estrogen use, history of surgical menopause and baseline mMMSE score. The authors speculate that free estradiol might be more important in protecting against cognitive decline because of its increased bioactivity and increased ability to cross the blood-brain barrier, as compared with total estradiol, which is largely bound to sex-hormone binding-globulin in the bloodstream. The authors note that all of the women in the study had relatively low levels of free estradiol and suggest that a low dose of estrogen replacement therapy might be sufficient to prevent cognitive decline, without significantly increasing the risk of negative outcomes, such as breast cancer or thrombosis.

Yaffe K, Lui L-Y, Grady D, Cauley J, Kramer J and Cummings SR. (2000). *Lancet*. 356: 708-712.

### Insulin Independence Following Islet Transplantation in Seven Type I Diabetics

Previous studies of islet transplantation in type I diabetics with poor glycemic control have failed to consistently yield sustained freedom from the need for injected insulin. Many of the immunosuppressive agents used in previous transplantation regimens, such as diabetogenic glucocorticoids, either damage the insulin-producing beta cells of the pancreas or induce resistance to insulin in peripheral tissues. To address this problem, Shapiro and colleagues designed a regimen to transplant pancreatic islets in conjunction with glucocorticoid-free immunosuppressive therapy. Seven type I diabetics with a history of severe hypoglycemia and metabolic instability received islet transplants. All seven patients quickly achieved insulin independence following transplantation of sufficient numbers of islets and remained free of the need for exogenous insulin as of their most recent follow-up (mean: 11.9 months). All patients demonstrated markedly improved glycemic control, indicated by a significant mean decrease in the amplitude of glycemic excursions, a return to the normal range of glycosylated hemoglobin values and absence of episodes of hypoglycemic coma following transplantation. Three and six months after transplantation all patients had detectable serum C-peptide concentrations, indicating that the transplanted islets were producing endogenous insulin. There was no evidence of serious transplant-related complications. In summary, these findings indicate that islet transplantation in conjunction with glucocorticoid-free immunosuppression can result in insulin independence and good metabolic glycemic control in patients with type I diabetes.

Shapiro AMJ, Lakey JRT, Ryan EA *et al.* (2000). *NEJM*. 343(4):230-238.

### New Protein Inhibits Colon Cancer

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Colon cancer is the second-leading cause of cancer deaths in North America and it has been estimated that 50% of people develop colon tumours by the age of 70. Research by Sasaki and colleagues showed that genetic inactivation of the protein p110 $\alpha$  produced an increased rate of colorectal cancers in mice. p110 $\alpha$  is a catalytic subunit of the phosphoinositide-3-OH kinase  $\alpha$ (PI(3)K $\alpha$ ) isoform that is activated by interaction with G-protein coupled receptors. PI(3)Ks are lipid kinases involved in the regulation of basic cellular responses, including cell proliferation, differentiation and protection from apoptosis. The researchers also found that p110 $\alpha$  was not expressed in primary colorectal adenocarcinomas in human patients. When p110 $\alpha$  was introduced into human colon cells lacking it, tumour formation was inhibited. Moreover, overexpression of p110 $\alpha$  in human colon cancer cells with inactivating mutations in tumour suppressor genes (APC and p53) or in colon cancer cells with activating mutations in oncogenes (beta-catenin and K-ras) suppressed tumorigenesis. This data correlates well with their findings that mouse cells lacking p110 $\alpha$  showed an increased expression of a cell death inhibitor (Bcl-2) and some important cell-cycle regulatory molecules (Cyclin D1, Cdk2 and Cdk4). Thus, p110 $\alpha$  is a novel tumor suppressor gene that is able to negatively regulate multiple steps of colorectal tumor progression. It is thought that the prevalence of colon cancer is influenced by environmental factors such as diet. As a result of its involvement with G-protein coupled receptors expressed on the surface of colonic epithelial cells, the authors speculate that p110 $\alpha$  may act as a messenger between environmental influences and cellular functions. Further study on the protein and its functional pathway to inhibit colorectal cancers may lead to improved treatment.

Sasaki T, Irie-Sasaki J, Horie Y *et al.* (2000). *Nature*. 406: 897-902.