

## 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.

### Progress Towards a Vaccine for Alzheimer's Disease

Alzheimer's Disease (AD) is associated with the formation of neurotoxic plaques due to the accumulation of amyloid- $\beta$  (A $\beta$ ) peptide. However, it is unclear from past research whether the progressive dementia of AD is caused by the abnormal build-up of A $\beta$ . Two papers published in the December 21/28 issue of *Nature* provide compelling evidence for a causative role of A $\beta$  accumulation in AD. Janus *et al.* and Morgan *et al.* studied the functional effects of vaccination with A $\beta$  in transgenic mice predisposed to develop AD. Earlier work demonstrated that when vaccinated with A $\beta$ , mice predisposed to develop AD formed antibodies to A $\beta$  and showed reduced neurotoxic plaque formation. To determine whether A $\beta$  vaccination could protect against the cognitive dysfunction seen in AD, both groups used similar tests of spatial memory. In these tests, the mice had to swim to and mount a platform located invisibly beneath the surface of a pool of water. Janus *et al.* tested "spatial-reference" memory: the platform remained in the same location for every trial over each five-day testing period and the mice were tested longitudinally at four-week intervals to track changes in learning and memory over time. In contrast, Morgan *et al.* tested "episodic-like" memory: the platform remained in the same location for every trial in each day of testing, but was moved about randomly from day to day to test short-term memory. Both groups found that mice vaccinated with A $\beta$  did not show the age-related decline in performance seen in non-immunized controls. Interestingly, both groups found that although vaccination with A $\beta$  reduced the number and size of A $\beta$  plaques, it did not completely eliminate plaque formation. In addition, Janus *et al.* reported no overall decrease in the amount of A $\beta$  peptide. Both groups suggest that either a small or a selective reduction in A $\beta$  levels may be sufficient to protect against AD dementia. In summary, these two papers suggest that A $\beta$  plaque formation may be responsible for the cognitive dysfunction of AD and provide hope that a human vaccine against A $\beta$  may be successful in preventing AD in the future.

Janus C, Pearson J, McLaurin J, *et al.* (2000). *Nature*. 408: 979-82.  
Morgan D, Diamond DM, Gottschall PE, *et al.* (2000). *Nature*. 408: 982-85.

### Hip Protector Reduces Incidence of Hip Fractures in Elderly

Hip fractures are a significant cause of morbidity and mortality in the elderly population. They are usually the result of a fall or other traumatic event producing direct impact to the greater trochanter of the femur superimposed on an underlying structural weakness in the bone caused by osteoporosis. Current methods of hip fracture prevention are aimed at either reducing the risk of falling or reducing the severity of osteoporosis. Kannus and colleagues investigated the use of hip protectors to prevent hip fractures in a large-scale trial in

Finland. The protector used was a padded shield covering the greater trochanter worn inside a pant pocket or on a stretchy undergarment. Their trial involved subjects 70 years old or older receiving care at any of 22 community health-care centres in Finland, who had one or more identifiable risk factors for hip fracture. These included a previous history of falls or fractures, impaired balance or mobility, or cognitive impairment. Randomization to either hip protector or control groups was performed in a 1:2 ratio according to health-care centre. At baseline assessment, there were 446 subjects in the hip protector group and 981 subjects in the control group. During the study, 13 subjects in the hip protector group had a hip fracture, as compared with 67 in the control group. Nine of the 13 fractures sustained in the hip protector group occurred while the subject was not wearing a hip protector. The authors concluded that among elderly adults who are at risk for hip fracture, the risk of fracture can be reduced by 60 percent by the use of a hip protector. Additionally, their calculations suggest that in order to prevent one hip fracture per year, only 41 elderly persons need to use the protector for a year. Although compliance with wearing a hip protector may limit the effectiveness of hip protectors as a fracture prevention device, these findings suggest a powerful method for reducing the risk of fractures and should be considered in all persons at increased risk.

Kannus, P, Parrkari, J, Niemi, S *et al.* (2000). *NEJM*. 343: 1506-1513.

### Fetal Cell Therapy Improves Motor and Cognitive Function in Patients with Huntington's Disease

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease characterized by a progressive loss of GABA-containing neurons in the striatum and cerebral cortex. Although some of the symptoms of HD, such as chorea, psychosis, and depression, can be alleviated by medication, there is currently no effective therapy for this disease in humans. However, in animal models of HD, intrastriatal grafts of fetal striatal neuroblasts were shown to form a striatum-like complex with functional neuronal projections to the cerebral cortex. These reconstituted structures were sufficient to cause a reversal of the motor and cognitive deficits seen in rats and monkeys with HD. In a preliminary report published in *The Lancet*, Bachoud-Lévi and colleagues describe five patients with symptomatic Huntington's disease who received two intrastriatal grafts of neuroblasts, separated by a one-year interval, from 7.5-9 week old human fetuses. Three of the five patients showed graft survival one year after the second graft implantation. Graft survival was demonstrated by increased or stable metabolic activity throughout the striatum on PET imaging when compared with pre-implantation data. Interestingly, the three patients with surviving grafts showed improvements in neuropsychological testing, activities of daily living,

and a reduction in the severity of chorea and bradykinesia. In contrast, the two other patients who showed decreased metabolic striatal activity following graft implantation demonstrated worsened cognitive and motor function 1 year post-implantation. Similarly, a cohort of 22 patients with HD who were assessed in parallel showed worsening chorea and neuropsychological performance. Although these findings are preliminary and have only been demonstrated in a small sample of HD patients, they suggest that there may be a role for fetal cell-replacement therapy in the treatment of HD in the future. A larger multi-centre study is currently in progress to determine the therapeutic benefit of fetal cell-therapy in HD.

Bachoud-Lévi A-C, Rémy P, Nguyen J-P, *et al.* (2000). *Lancet*. 356: 1975-1979.

### Regular Source of Care Among Physicians

Studies of the general population indicate that individuals who use a single physician to manage primary health care needs, known as a regular source of care (RSOC), are more likely to use preventive health services and enjoy shorter lengths of stay when admitted to hospital. Past research also suggests that physicians' personal health habits and disease screening practices influence the preventive health counseling they provide to their patients. Gross and colleagues surveyed all of the physicians who graduated from the Johns Hopkins School of Medicine between 1948 and 1964 to investigate the use of an RSOC among physicians, and to determine whether having a RSOC was associated with the subsequent receipt of preventive health services. 915 physicians completed their survey (77% response rate) and 312 (35%) indicated that they did not have a RSOC. The use of a RSOC varied according to medical specialty, as pathologists, surgeons and internists were less likely to have a RSOC than pediatricians and psychiatrists. Respondents who did not have a RSOC were almost twice as likely to believe that chance or fate determines health outcomes and were less likely to believe that health professionals determine health. Not having a RSOC also predicted not being screened for breast, colon, and prostate cancer, as well as not receiving influenza vaccination. This study did not directly investigate whether having a RSOC influences the quality of care provided by physicians to their patients. The authors suggest that the use of a RSOC and preventive health services among physicians is sub-optimal, given that physicians are not only aware of the purpose and efficacy of preventive services, but also have greater access to these services than the general population. The authors recommend that physician organizations encourage physicians to have a RSOC and that medical education stress the importance of appropriate personal health care to medical students.

Gross CP, Mead LA, Ford DE, and Klag MJ. (2000). *Arch Intern Med*. 160: 3209-3214.

### Cellular Telephone Use is Not Linked to Brain Cancer

There are currently an estimated 500 million cellular telephone users worldwide. Concerns have been raised about the possible adverse health effects associated with cell phone use, especially the possibility that low-power radiofrequency signals transmitted by the antennas might cause brain tumors. The evidence for such thinking is largely anecdotal, as there is no commonly agreed upon scientific mechanism by which a carcinogenic effect of low-power radiofrequency would be mediated, and there is little epidemiological research on exposure to low-power radiofrequency. Two retrospective case-control studies published in the *Journal of the American Medical Association* and the *New England Journal of Medicine* found no association between handheld cellular telephone use and the risk of brain cancer. Muscat and colleagues surveyed 469 primary brain cancer patients and 422 age-matched controls at five US medical centers between 1994 and 1998 and found no statistically significant

differences in the number of years of use, hours per month, or total cumulative hours of cellular phone use between brain cancer patients and controls. Additionally, within the brain cancer patient group, there were no associations between cell phone use and the site or histologic subtype of tumour or cellular phone handedness and tumor laterality. Similarly, Inskip and colleagues conducted interviews with 782 primary brain cancer patients and 799 age-matched controls at four US medical centers between 1994 and 1998 and found no evidence of increased brain cancer risk among persons who used cellular telephones for 60 or more minutes per day or regularly for five or more years. They also did not find any association between cellular phone use and histologic tumour subtype, or cellular phone handedness and tumor laterality. Although these studies are limited by both recall bias and the recent changes in cellular telephone technology as well as their ability to detect whether cellular telephones might increase cancer risk following a long latency period, they suggest that short-term exposure to low-power radiofrequency signals emitted by cellular phones does not cause brain cancer.

Muscat JE, Malkin MG, Thompson S, *et al.* (2000). *JAMA*. 284:3001-07.

Inskip PD, Tarone RE, Hatch ME, *et al.* (2001). *NEJM*. 344:79-86.

### A New Link Between Pesticides and Parkinson's Disease

Although the cause of idiopathic Parkinson's disease (PD) is unknown, epidemiological studies suggest an association with exposure to pesticides and other environmental toxins. The theory of toxin-mediated damage leading to PD was fueled by the appearance of an outbreak of parkinsonism among heroin addicts in California in the early 1980s. This outbreak was linked to MPTP, a chemical compound that had been inadvertently synthesized in the process of heroin production. Further biochemical studies with MPTP demonstrated that a MPTP metabolite can selectively inhibit mitochondrial complex I in dopaminergic neurons and induce acute PD-like symptoms in experimental animals. This evidence was used to develop an animal model of PD. However, the MPTP model does not show the accumulation of Lewy bodies or the systemic inhibition of complex I seen in idiopathic PD in humans. To develop a more accurate animal model of PD, Betarbet and colleagues exposed rats to rotenone, a widely used pesticide derived from the roots of certain plant species. Rotenone-treated rats developed bradykinesia, rigidity, postural instability and a resting tremor that improved with administration of a dopamine analog. Additionally, brain sections from these rats demonstrated progressive degeneration of the substantia nigra, and the surviving nigral neurons showed cytoplasmic inclusions that resembled Lewy bodies. Rotenone administration also produced complex I inhibition throughout the brain. Interestingly, Betarbet and colleagues observed PD-like symptoms at concentrations of rotenone that were insufficient to significantly impair oxidative phosphorylation throughout the brain. They speculate that this finding argues against ATP depletion as a mechanism for the loss of dopaminergic neurons in PD and supports the theory that free radicals, generated from mitochondrial inhibition, may be responsible for the damage. From an epidemiological perspective, these findings also suggest that low levels of environmental rotenone, and other environmental toxins that inhibit mitochondrial complex I, may contribute to the pathogenesis of idiopathic PD.

Betarbet R, Sherer TB, MacKenzie G, *et al.* (2000). *Nature Neuroscience*. 3: 1301-6.