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**JOURNALS IN  
SCIENCE AND MEDICINE**

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**American Journal  
of Human Genetics**

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**Volume 72, Number 1  
January 2003**

**Association of In Vitro Fertilization with  
Beckwith-Wiedemann Syndrome and  
Epigenetic Alterations of *LIT1* and *H19***

*M.R. DeBaun, E.L. Niemitz,  
and A.P. Feinberg*

Recent data in humans and animals suggest that assisted reproductive technology (ART) might affect the epigenetics of early embryogenesis and might cause birth defects. We report the first evidence, to our knowledge, that ART is associated with a human overgrowth syndrome namely, Beckwith-Wiedemann syndrome (BWS). In a prospective study, the prevalence of ART was 4.6% (3 of 65), versus the background rate of 0.8% in the United States. A total of seven children with BWS were born after ART, five of whom were conceived after intracytoplasmic sperm injection. Molecular studies of six of the children indicate that five of the six have specific epigenetic alterations associated with BWS, four at *LIT1* and one at both *LIT1* and *H19*. We discuss the implications of our finding that ART is associated with human overgrowth, similar to the large offspring syndrome reported in ruminants.

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**Cell**

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**Volume 111, Number 4  
November 15, 2002**

**Biological Progression from Adult  
Bone Marrow to Mononucleate  
Muscle Stem Cell to Multinucleate  
Muscle Fiber in Response to Injury**

*M.A. LaBarge and H.M. Blau*

Adult bone marrow-derived cells (BMDC) are shown to contribute to muscle tissue in a step-wise biological progression. Following irradiation-induced damage, transplanted GFP-labeled BMDC become satellite cells: membrane-ensheathed mononucleate muscle stem cells. Following a subsequent exercise-induced damage, GFP-labeled multinucleate myofibers are detected. Isolated GFP-labeled satellite cells are heritably myogenic. They express three characteristic muscle markers, are karyotypically diploid, and form clones that can fuse into multinucleate cells in culture or into myofibers after injection into mouse muscles. These results suggest that two temporally distinct injury-related signals first induce BMDC to occupy the muscle stem cell niche and then to help regenerate mature muscle fibers. The stress-induced progression of BMDC to muscle satellite cell to muscle fiber results in a contribution to as many as 3.5% of muscle fibers and is due to developmental plasticity in response to environmental cues.

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## Human Reproduction

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Volume 17, Number 3  
March 2002

### The European Study of Assisted Reproduction Families: The Transition to Adolescence

*S. Golombok et al.*

**BACKGROUND:** Findings are presented of the second phase of a European longitudinal study of families created by assisted reproduction. The present investigation reports on data obtained during the child's transition to adolescence. **METHODS:** A total of 102 IVF families, 94 donor insemination (DI) families, 102 adoptive families, and 102 families with a naturally conceived child were compared on standardized interview and questionnaire measures of parenting and children's psychological well-being. **RESULTS:** The assisted reproduction families were similar to the adoptive and natural conception families for many of the measures of the quality of parent-child relationships. To the extent that differences were found between the assisted reproduction families and the other family types, these reflected mainly more positive functioning among the assisted reproduction families, with the possible exception of the overinvolvement with their children of a small proportion of assisted reproduction mothers and fathers. The assisted reproduction children were functioning well and did not differ from the adoptive or naturally conceived children on any of the measures of psychological adjustment. However, only 8.6% had been told about their genetic origins. **CONCLUSIONS:** IVF and DI families with an early adolescent child appear to be functioning well.

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## International Journal of Gynecology and Obstetrics

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Volume 76, Number 3  
March 2002

### Transplantation of the Human Uterus

*W. Fageeh et al.*

Human uterine transplantation was performed on 6 April 2000 on a 26-year-old female who lost her uterus 6 years earlier due to post-partum hemorrhage. The donor, a 46-year-old patient with multiloculated ovarian cysts, underwent a hysterectomy modified to preserve tissue and vascular integrity. The donor uterus was connected in the orthotopic position to the recipient's vaginal vault and additional fixation was achieved by shortening the uterosacral ligament. The uterine arteries and veins were extended using reversed segments of the great saphenous vein, then connected to the external iliac arteries and veins, respectively. Immunosuppression was maintained by oral cyclosporine A (4 mg/kg/body wt.), azathioprine (1 mg/kg/body wt.) and prednisolone (0.2 mg/kg/body wt.). Allograft rejection was monitored by Echo-Doppler studies, magnetic resonance imaging (MRI), and measurement of the CD4/CD8 ratio in peripheral blood by fluorescence activated cell sorter (FACS scan). An episode of acute rejection was treated and controlled on the ninth day with anti-thymocytic globulin (ATG). The transplanted uterus responded well to combined estrogen-progesterone therapy, with endometrial proliferation up to 18 mm. The patient had two episodes of withdrawal bleeding upon cessation of the hormonal therapy. Unfortunately, she developed acute vascular thrombosis 99 days after transplantation, and hysterectomy was necessary. Macro- and microscopic histopathological examination revealed acute thrombosis in the vessels of the uterine body, with resulting infarction. Both fallopian tubes remained viable, however, with no evidence of rejection.

The acute vascular occlusion appeared to be caused by inadequate uterine structure support, which led to probable tension, torsion, or kinking of the connected vascular uterine grafts.

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**Journal of the American  
Medical Association**

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**Volume 288, Number 13  
October 2, 2002**

**Economic and Health Consequences  
of Selling a Kidney in India**

*Madhav Goyal, M.D., et al.*

Among paid donors in India, selling a kidney does not lead to a long-term economic benefit and may be associated with a decline in health. Physicians and policy makers should reexamine the value of using financial incentives to increase the supply of organs for transplantation.

**Volume 288, Number 14  
October 9, 2002**

**Limitations of Direct-to-Consumer  
Advertising for Clinical Genetic Testing**

*S.E. Gollust et al.*

Although direct-to-consumer (DTC) advertisements for pharmaceuticals have been appearing in the mass media for 20 years, DTC advertisements for genetic testing have only recently appeared. Advertisements for genetic testing can provide both consumers and physicians with information about test availability in an expanding market. However, 3 factors limit the value and appropriateness of advertisements: complex information, a complicated social context surrounding genetics, and a lack of consensus about the clinical utility of some tests. Consideration

of several advertisements suggests that they overstate the value of genetic testing for consumers' clinical care. Furthermore, advertisements may provide misinformation about genetics, exaggerate consumers' risks, endorse a deterministic relationship between genes and disease, and reinforce associations between diseases and ethnic groups. Advertising motivated by factors other than evidence of the clinical value of genetic tests can manipulate consumers' behavior by exploiting their fears and worries. At this time, DTC advertisements are inappropriate, given the public's limited sophistication regarding genetics and the lack of comprehensive premarket review of tests or oversight of advertisement content. Existing Federal Trade Commission and Food and Drug Administration regulations for other types of health-related advertising should be applied to advertisements for genetic tests.

**Volume 288, Number 16  
October 23/30, 2002**

**Exercise Type and Intensity in Relation  
to Coronary Heart Disease in Men**

*Mihaela Tanasescu, M.D., et al.*

Total physical activity, running, weight training, and walking were each associated with reduced CHD risk. Average exercise intensity was associated with reduced risk independent of the number of MET-hours spent in physical activity.

**Homocysteine and Risk of Ischemic Heart  
Disease and Stroke: A Meta-analysis**

*Homocysteine Studies Collaboration*

This meta-analysis of observational studies suggests that elevated homocysteine is at most a modest independent predictor of IHD and stroke risk in healthy populations. Studies of the impact on disease risk of genetic variants that affect blood homocysteine concentrations will help determine whether homocysteine is causally related to vascular disease, as may large randomized trials of the

effects on IHD and stroke of vitamin supplementation to lower blood homocysteine concentrations.

**Volume 288, Number 17**  
**November 6, 2002**

**Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women: The Cache County Study**

*Peter P. Zandi et al.*

Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.

**Volume 288, Number 18**  
**November 13, 2002**

**Walking and Leisure-Time Activity and Risk of Hip Fracture in Postmenopausal Women**

*Diane Feskanich, Walter Willett, M.D., and Graham Colditz, M.D.*

Moderate levels of activity, including walking, are associated with substantially lower risk of hip fracture in postmenopausal women.

**Pregnancy in the Sixth Decade of Life: Obstetric Outcomes in Women of Advanced Reproductive Age**

*Richard J. Paulson, M.D., et al.*

Appropriately screened women aged 50 years or older can successfully conceive via oocyte donation and experience similar pregnancy rates, multiple gestation rates, and spontaneous abortion rates as younger recipients. During pregnancy, they appear at increased risk of preeclampsia and gestational diabetes. A majority can expect to deliver via cesarean. However, there does not appear to be any definitive medical reason for excluding these women from attempting pregnancy on the basis of age alone.

**Volume 288, Number 19**  
**November 20, 2002**

**Effects of Hormone Replacement Therapy and Antioxidant Vitamin Supplements on Coronary Atherosclerosis in Postmenopausal Women: A Randomized Controlled Trial**

*David D. Waters, M.D., et al.*

In postmenopausal women with coronary disease, neither HRT nor antioxidant vitamin supplements provide cardiovascular benefit. Instead, a potential for harm was suggested with each treatment.

**Comparison of Mortality Between Private For-Profit and Private Not-For-Profit Hemodialysis Centers: A Systematic Review and Meta-analysis**

*P. J. Devereaux, M.D., et al.*

Hemodialysis care in private not-for-profit centers is associated with a lower risk of mortality compared with care in private for-profit centers.

**Pedophilia**

*P.J. Fagan et al.*

This article addresses the risk factors associated with the psychiatric disorder pedophilia, its treatment, and treatment outcomes. It addresses physician responsibilities associated with case identification of victims and possible roles in the medical management of pedophilia. The essential feature of pedophilia is that an individual is sexually attracted exclusively or in part to prepubescent children. While pedophilia may be limited to fantasies and impulses, pedophilic behaviors are the primary concern of both the mental health and criminal justice systems. Remote risk factors for development of pedophilia often include the individual having been sexually abused as a child. Proximate risk factors for its behavioral expression are prevalence of

comorbid psychiatric disorders and substance abuse disorders. Current treatment goals focus on stopping the behavior and achieving long-term behavioral control in the community. Common treatment methods are cognitive-behavioral, group therapy, and, when appropriate, medications such as androgen-lowering agents that can act as sexual appetite suppressants. Meta-analyses have established that treatment is more effective than nontreatment in preventing recidivism of sexual offenders in general, a finding that has a high probability of application to individuals with pedophilia. Pedophilia is a chronic psychiatric disorder, but it is treatable in terms of developing strategies for preventing behavioral expression. Ultimately, reducing the prevalence of pedophilic behavior requires further collaboration between the criminal justice system and the health care communities.

**Volume 288, Number 20**  
**November 27, 2002**

**Nut and Peanut Butter Consumption and Risk of Type 2 Diabetes in Women**

*Rui Jiang, M.D., et al.*

Our findings suggest potential benefits of higher nut and peanut butter consumption in lowering risk of type 2 diabetes in women. To avoid increasing caloric intake, regular nut consumption can be recommended as a replacement for consumption of refined grain products or red or processed meats.

**Optimal Diets for Prevention of Coronary Heart Disease**

*Frank B. Hu, M.D.,  
and Walter C. Willett, M.D.*

Substantial evidence indicates that diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together

with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight, may prevent the majority of cardiovascular disease in Western populations.

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**Journal of  
Clinical Investigation**

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**Volume 110, Number 8**  
**October 15, 2002**

**Delta-1 Enhances Marrow and Thymus  
Repopulating Ability of Human  
CD34<sup>+</sup>CD38<sup>-</sup> Cord Blood Cells**

*K. Ohishi, B. Varnum-Finney,  
and I.D. Bernstein*

We investigated the effect of Notch signaling, a known regulator of cell fate in numerous developmental systems, on human hematopoietic precursors. We show that activation of endogenous Notch signaling in human CD34<sup>+</sup>CD38<sup>-</sup> cord blood precursors with immobilized Delta-1 in serum-free cultures containing fibronectin and hematopoietic growth factors inhibited myeloid differentiation and induced a 100-fold increase in the number of CD34<sup>+</sup> cells compared with control cultures. Immobilized Delta-1 also induced a multifold expansion of cells with the phenotype of common lymphoid precursors (CD34<sup>+</sup>CD7<sup>+</sup>CD45RA<sup>+</sup>) and promoted the development of cytoplasmic CD3<sup>+</sup> T/NK cell precursors. IL-7 enhanced the promotion of T/NK cell differentiation by immobilized Delta-1, but granulocytic differentiation occurred when G-CSF was added. Transplantation into immunodeficient mice showed a substantial increase in myeloid and B cell engraftment in the marrow and also revealed thymic repopulation by CD3<sup>+</sup> T cells due to cells being cultured for a longer period with immobilized Delta-1. These data suggest that Delta-1 can enhance myeloid and lymphoid marrow-repopulating ability and promote the generation of thymus-repopulating T cell precursors.

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**Nature**

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**Volume 417, Number 6887**  
**May 23, 2002****Transgenic Anopheline  
Mosquitoes Impaired in  
Transmission of a Malaria Parasite***J. Ito et al.*

Malaria is estimated to cause 0.7 to 2.7 million deaths per year, but the actual figures could be substantially higher owing to under-reporting and difficulties in diagnosis. If no new control measures are developed, the malaria death toll is projected to double in the next 20 years. Efforts to control the disease are hampered by drug resistance in the *Plasmodium* parasites, insecticide resistance in mosquitoes, and the lack of an effective vaccine. Because mosquitoes are obligatory vectors for malaria transmission, the spread of malaria could be curtailed by rendering them incapable of transmitting parasites. Many of the tools required for the genetic manipulation of mosquito competence for malaria transmission have been developed. Foreign genes can now be introduced into the germ line of both culicine and anopheline mosquitoes, and these transgenes can be expressed in a tissue-specific manner. Here we report on the use of such tools to generate transgenic mosquitoes that express anti-parasitic genes in their midgut epithelium, thus rendering them inefficient vectors for the disease. These findings have significant implications for the development of new strategies for malaria control.

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**Nature Biotechnology**

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**Volume 20, Number 11**  
**November 2002****Neural Stem Cells Display  
an Inherent Mechanism for  
Rescuing Dysfunctional Neurons***J. Ourednik et al.*

We investigated the hypothesis that neural stem cells (NSCs) possess an intrinsic capacity to “rescue” dysfunctional neurons in the brains of aged mice. The study focused on a neuronal cell type with stereotypical projections that is commonly compromised in the aged brain—the dopaminergic (DA) neuron. Unilateral implantation of murine NSCs into the midbrains of aged mice, in which the presence of stably impaired but nonapoptotic DA neurons was increased by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was associated with bilateral reconstitution of the mesostriatal system. Functional assays paralleled the spatiotemporal recovery of tyrosine hydroxylase (TH) and dopamine transporter (DAT) activity, which, in turn, mirrored the spatiotemporal distribution of donor-derived cells. Although spontaneous conversion of donor NSCs to TH<sup>+</sup> cells contributed to nigral reconstitution in DA-depleted areas, the majority of DA neurons in the mesostriatal system were “rescued” host cells. Undifferentiated donor progenitors spontaneously expressing neuroprotective substances provided a plausible molecular basis for this finding. These observations suggest that host structures may benefit not only from NSC-derived replacement of lost neurons but also from the “chaperone” effect of some NSC-derived progeny.

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## Neurosurgery

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**Volume 51, Number 4  
October 2002**

**Transplanted Neural Stem Cells  
Survive, Differentiate, and Improve  
Neurological Motor Function after  
Experimental Traumatic Brain Injury**

*P. Riess, M.D., et al.*

**OBJECTIVE:** Using the neural stem cell (NSC) clone C17.2, we evaluated the ability of transplanted murine NSCs to attenuate cognitive and neurological motor deficits after traumatic brain injury. **METHODS:** Nonimmunosuppressed C57BL/6 mice (n = 65) were anesthetized and subjected to lateral controlled cortical impact brain injury (n = 52) or surgery without injury (sham operation group, n = 13). At 3 days postinjury, all brain-injured animals were reanesthetized and randomized to receive stereotactic injection of NSCs or control cells (human embryonic kidney cells) into the cortex-hippocampus interface in either the ipsilateral or the contralateral hemisphere. One group of animals (n = 7) was killed at either 1 or 3 weeks postinjury to assess NSC survival in the acute posttraumatic period. Motor function was evaluated at weekly intervals for 12 weeks in the remaining animals, and cognitive (i.e., learning) deficits were assessed at 3 and 12 weeks after transplantation. **RESULTS:** Brain-injured animals that received either ipsilateral or contralateral NSC transplants showed significantly improved motor function in selected tests as compared with human embryonic kidney cell-transplanted animals during the 12-week observation period. Cognitive dysfunction was unaffected by transplantation at either 3 or 12 weeks postinjury. Histological analyses showed that NSCs survive for as long as 13 weeks after transplantation and were detected in the hippocampus and/or cortical areas adjacent to the injury cavity. At 13 weeks, the NSCs transplanted ipsilateral to the impact site expressed neuronal

(NeuN) or astrocytic (glial fibrillary acidic protein) markers but not markers of oligodendrocytes (2'3'cyclic nucleotide 3'-phosphodiesterase), whereas the contralaterally transplanted NSCs expressed neuronal but not glial markers (double-labeled immunofluorescence and confocal microscopy). **CONCLUSION:** These data suggest that transplanted NSCs can survive in the traumatically injured brain, differentiate into neurons and/or glia, and attenuate motor dysfunction after traumatic brain injury.

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## The New England Journal of Medicine

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**Volume 347, Number 10  
September 5, 2002**

**Walking Compared with Vigorous  
Exercise for the Prevention of  
Cardiovascular Events in Women**

*J.E. Manson, M.D., et al.*

These prospective data indicate that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events among postmenopausal women, irrespective of race or ethnic group, age, and body-mass index. Prolonged sitting predicts increased cardiovascular risk.

**Volume 347, Number 11  
September 12, 2002**

**A Randomized Trial Comparing  
Radical Prostatectomy with Watchful  
Waiting in Early Prostate Cancer**

*L. Holmberg, M.D., et al.*

In this randomized trial, radical prostatectomy significantly reduced disease-specific mortality, but there was no significant difference between surgery and watchful waiting in terms of overall survival.

**Quality of Life after Radical  
Prostatectomy or Watchful Waiting**

*G. Steineck, M.D., et al.*

The assignment of patients to watchful waiting or radical prostatectomy entails different risks of erectile dysfunction, urinary leakage, and urinary obstruction, but on average, the choice has little if any influence on well-being or the subjective quality of life after a mean follow-up of four years.

**Volume 347, Number 12  
September 19, 2002**

**Heritability of Mammographic Density,  
a Risk Factor for Breast Cancer**

*N.F. Boyd, M.D., et al.*

These results show that the population variation in the percentage of dense tissue on mammography at a given age has high heritability. Because mammographic density is associated with an increased risk of breast cancer, finding the genes responsible for this phenotype could be important for understanding the causes of the disease.

**Volume 347, Number 14  
October 3, 2002**

**State Expenditures for Tobacco-Control  
Programs and the Tobacco Settlement**

*C. P. Gross, M.D., et al.*

State health needs appear to have little effect on the funding of state tobacco-control programs. Because only a very small proportion of the tobacco settlement is being used for tobacco-control programs, the settlement represents an unrealized opportunity to reduce morbidity and mortality from smoking.

**Volume 347, Number 16  
October 17, 2002**

**Twenty-Year Follow-up of a Randomized  
Study Comparing Breast-Conserving  
Surgery with Radical Mastectomy  
for Early Breast Cancer**

*U. Veronesi, M.D., et al.*

The long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. Breast-conserving surgery is therefore the treatment of choice for women with relatively small breast cancers.

**Twenty-Year Follow-up of a Randomized  
Trial Comparing Total Mastectomy,  
Lumpectomy, and Lumpectomy plus  
Irradiation for the Treatment of Invasive  
Breast Cancer**

*B. Fisher, M.D., et al.*

Lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained.

**Volume 347, Number 17  
October 24, 2002**

**Aspirin and Mortality from  
Coronary Bypass Surgery**

*D. T. Mangano, M.D., for the  
Multicenter Study of Perioperative  
Ischemia Research Group*

Early use of aspirin after coronary bypass surgery is safe and is associated with a reduced risk of death and ischemic complications involving the heart, brain, kidneys, and gastrointestinal tract.



**Outcomes after Total versus Subtotal Abdominal Hysterectomy***R. Thakar, M.D., et al.*

Neither subtotal nor total abdominal hysterectomy adversely affects pelvic organ function at 12 months. Subtotal abdominal hysterectomy results in more rapid recovery and fewer short-term complications but infrequently causes cyclical bleeding or cervical prolapse.

**A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors***K. A. Schulman, M.D., et al.*

Academic institutions routinely engage in industry-sponsored research that fails to adhere to ICMJE guidelines regarding trial design, access to data, and publication rights. Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed.

**Volume 347, Number 19  
November 7, 2002****A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism***K. M. Madsen, M.D., et al.*

This study provides strong evidence against the hypothesis that MMR vaccination causes autism.

**Volume 347, Number 20  
November 14, 2002****Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events***P. M. Ridker, M.D., et al.*

These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score.

**Cyclin E and Survival in Patients with Breast Cancer***K. Keyomarsi et al.*

Levels of total cyclin E and low-molecular-weight cyclin E in tumor tissue, as measured by Western blot assay, correlate strongly with survival in patients with breast cancer.

**Volume 347, Number 21  
November 21, 2002****A Controlled Trial of a Human Papillomavirus Type 16 Vaccine***L. A. Koutsky et al.*

Administration of this HPV-16 vaccine reduced the incidence of both HPV-16 infection and HPV-16-related cervical intraepithelial neoplasia. Immunizing HPV-16-negative women may eventually reduce the incidence of cervical cancer.

**Glycoprotein-D-Adjuvant Vaccine to Prevent Genital Herpes***L. R. Stanberry, M.D., et al.*

These studies suggest that the glycoprotein D vaccine has efficacy against genital herpes in women who are seronegative for both HSV-1 and HSV-2 at base line but not in those who are seropositive for HSV-1 and seronegative for HSV-2. It had no efficacy in men, regardless of their HSV serologic status.

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**Proceedings of the National  
Academy of the Sciences**

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**Volume 99, Number 20  
October 1, 2002**

**From the Cover: Therapeutic  
Neonatal Hepatic Gene Therapy in  
Mucopolysaccharidosis VII Dogs**

*K. P. Ponder et al.*

Dogs with mucopolysaccharidosis VII (MPS VII) were injected intravenously at 2–3 days of age with a retroviral vector (RV) expressing canine beta-glucuronidase (cGUSB). Five animals received RV alone, and two dogs received hepatocyte growth factor (HGF) before RV in an attempt to increase transduction efficiency. Transduced hepatocytes expanded clonally during normal liver growth and secreted enzyme with mannose 6-phosphate. Serum GUSB activity was stable for up to 14 months at normal levels for the RV-treated dogs, and for 17 months at 67-fold normal for the HGF/RV-treated dog. GUSB activity in other organs was 1.5–60% of normal at 6 months for two RV-treated dogs, which was likely because of uptake of enzyme from blood by the mannose 6-phosphate receptor. The body weights of untreated MPS VII dogs are 50% of normal at 6 months. MPS VII dogs cannot walk or stand after 6 months, and progressively develop eye and heart disease. RV- and HGF/RV-treated MPS VII dogs achieved 87% and 84% of normal body weight, respectively. Treated animals could run at all times of evaluation for 6–17 months because of improvements in bone and joint abnormalities, and had little or no corneal clouding and no mitral valve thickening. Despite higher GUSB expression, the clinical improvements in the HGF/RV-treated dog were similar to those in the RV-treated animals. This is the first successful application of gene therapy in preventing the clinical manifestations of a lysosomal storage disease in a large animal.

**Volume 99, Number 21  
October 15, 2002**

**Long-Term Systemic Therapy of Fabry  
Disease in a Knockout Mouse by  
Adeno-Associated Virus-Mediated  
Muscle-Directed Gene Transfer**

*H. Takahashi et al.*

Fabry disease is a systemic disease caused by genetic deficiency of a lysosomal enzyme, alpha-galactosidase A (alpha-gal A), and is thought to be an important target for enzyme replacement therapy. We studied the feasibility of gene-mediated enzyme replacement for Fabry disease. The adeno-associated virus (AAV) vector containing the alpha-gal A gene was injected into the right quadriceps muscles of Fabry knockout mice. A time course study showed that alpha-gal A activity in plasma was increased to ~25% of normal mice and that this elevated activity persisted for up to at least 30 weeks without development of anti-alpha-gal A antibodies. The alpha-gal A activity in various organs of treated Fabry mice remained 5–20% of those observed in normal mice. Accumulated globotriaosylceramide in these organs was completely cleared by 25 weeks after vector injection. Reduction of globotriaosylceramide levels was also confirmed by immunohistochemical and electron-microscopic analyses. Echocardiographic examination of treated mice demonstrated structural improvement of cardiac hypertrophy 25 weeks after the treatment. AAV vector-mediated muscle-directed gene transfer provides an efficient and practical therapeutic approach for Fabry disease.

**Volume 99, Number 25  
December 10, 2002**

**Trehalose Accumulation in Rice  
Plants Confers High Tolerance  
Levels to Different Abiotic Stresses**

*A.K. Garg et al.*

Trehalose is a nonreducing disaccharide of glucose that functions as a compatible sol-

ute in the stabilization of biological structures under abiotic stress in bacteria, fungi, and invertebrates. With the notable exception of the desiccation-tolerant “resurrection plants,” trehalose is not thought to accumulate to detectable levels in most plants. We report here the regulated overexpression of *Escherichia coli* trehalose biosynthetic genes (*otsA* and *otsB*) as a fusion gene for manipulating abiotic stress tolerance in rice. The fusion gene has the advantages of necessitating only a single transformation event and a higher net catalytic efficiency for trehalose formation. The expression of the transgene was under the control of either tissue-specific or stress-dependent promoters. Compared with nontransgenic rice, several independent transgenic lines exhibited sustained plant growth, less photo-oxidative damage, and more favorable mineral balance under salt, drought, and low-temperature stress conditions. Depending on growth conditions, the transgenic rice plants accumulate trehalose at levels 3–10 times that of the nontransgenic controls. The observation that peak trehalose levels remain well below 1 mg/g fresh weight indicates that the primary effect of trehalose is not as a compatible solute. Rather, increased trehalose accumulation correlates with higher soluble carbohydrate levels and an elevated capacity for photosynthesis under both stress and nonstress conditions, consistent with a suggested role in modulating sugar sensing and carbohydrate metabolism. These findings demonstrate the feasibility of engineering rice for increased tolerance of abiotic stress and enhanced productivity through tissue-specific or stress-dependent overproduction of trehalose.

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## Science

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**Volume 298, Number 5600  
December 6, 2002**

**Ectoderm to Mesoderm  
Lineage Switching During  
Axolotl Tail Regeneration**

*Karen Echeverri and Elly M. Tanaka*

Foreign environments may induce adult stem cells to switch lineages and populate multiple tissue types, but whether this mechanism is used for tissue repair remains uncertain. Urodele amphibians can regenerate fully functional, multitissue structures including the limb and tail. To determine whether lineage switching is an integral feature of this regeneration, we followed individual spinal cord cells live during tail regeneration in the axolotl. Spinal cord cells frequently migrate into surrounding tissue to form regenerating muscle and cartilage. Thus, in axolotls, cells switch lineage during a real example of regeneration.