

## **Blood Test Can Predict Pulmonary Complications from Sickle Cell Disease**

*Background:* A pneumonia-like illness known as acute chest syndrome (ACS) is the leading cause of death in patients with sickle cell disease. Although ACS often develops in the course of sickle cell crises (acute, painful events in which the blood vessels are clogged with sickle-shaped cells), it has not been possible to predict whether a given patient would develop ACS.

*Advance:* Researchers studying patients who were hospitalized for sickle cell crises found that elevated levels of an enzyme called secretory phospholipase A<sub>2</sub> are associated with development of ACS. Whereas the classic symptoms of ACS develop with little warning, the enzyme levels in the blood increased 24 to 48 hours before ACS could be diagnosed clinically.

*Implications:* If these results are confirmed by larger clinical studies, enzyme measurements could be used to identify patients with impending ACS. Early diagnosis will allow treatment to be initiated before severe ACS develops, thereby reducing the morbidity, mortality, and costs associated with this complication.

Styles LA, Aarsman AJ, Vichinsky EP, and Kuypers FA: Secretory phospholipase A<sub>2</sub> predicts impending acute chest syndrome in sickle cell disease. Blood 96: 3276-3278, 2000.

## Newly Identified Genetic Defects Cause Sudden Cardiac Death in Young People

*Background:* When a seemingly healthy young person suddenly “drops dead” from cardiac arrest, hypertrophic cardiomyopathy (HCM) is usually the cause. HCM affects 1 in 500 people, and appears to be inherited in approximately 70 percent of cases. However, it varies in both its severity and its underlying mutations, and many of the varieties have not been characterized.

Wolff-Parkinson-White (WPW) syndrome is another cause of sudden death in otherwise healthy young people. It is one of the most common causes of tachyarrhythmia (a heart disorder characterized by a fast and irregular heart beat) in infants and children. About 80 percent of people with WPW symptoms first experience them between the ages of 11 and 50. Sometimes WPW syndrome leads to HCM. Like HCM, it can be inherited.

*Advance:* Researchers studying inherited heart diseases have identified a genetic defect associated with inherited WPW syndrome in two families. The mutation was not detected in people who had sporadic (non-inherited) WPW syndrome.

In a separate study, researchers identified another mutation thought to cause a type of familial HCM independent of WPW syndrome. The newly identified mutation results in only mild hypertrophy (enlargement) of the heart’s left ventricle, but is associated with a high incidence of sudden death.

*Implications:* As with all inherited diseases, understanding the genetic defects responsible for HCM and WPW facilitates pre-clinical diagnosis in affected children and improved genetic counseling for prospective parents. Moreover, associating individual mutations with particular clinical outcomes, as in the familial HCM example illustrated here, has significant prognostic value and can help tailor disease management to the specific needs of the patient.

Gollob MH, Green MS, Tang ASL, Gollob T, Karibe A, Hassan A-S, Ahmad F, Lozado R, Shah G, Fananapazir L, Bachinski LL, and Roberts R: Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. The New England Journal of Medicine 344: 1823-1831, 2001.

Karibe A, Tobacman LS, Strand J, Butters C, Back N, Bachinski LL, Arai AE, Ortiz A, Roberts R, Homsher E, and Fananapazir L: Hypertrophic cardiomyopathy caused by a novel  $\alpha$ -tropomyosin mutation (V95A) is associated with mild cardiac phenotype, abnormal calcium binding to troponin, abnormal myosin cycling, and poor prognosis. Circulation 103: 65-71, 2001.

## **Genetic Mutation Increases Heart Attack Risk for Women on Hormone Replacement Therapy**

*Background:* Designed to assess the effects of hormone replacement therapy (HRT) on coronary heart disease (CHD) and heart attacks in postmenopausal women, the Heart and Estrogen/progestin Replacement Study (HERS) revealed that women taking active hormones had more heart attacks during the first year than women taking placebo pills. One potential explanation for these results in the overall study group is that HRT increases the risk of heart attacks for a subgroup of women. For example, the subgroup may have a genetic trait that counters the protective effect of HRT and places them at risk for CHD.

*Advance:* Researchers found that a mutation in the gene for prothrombin, an enzyme that regulates blood clotting, was associated with an eleven-fold increased risk of heart attacks in women with high blood pressure who used HRT, compared with hypertensive women who did not have the variant and did not take HRT. In contrast, hypertensive HRT users without the variant were not at a significantly increased risk for a heart attack.

*Implications:* The results suggest that HRT may place women who have hypertension at increased risk of heart attack if they also have the prothrombin variant described in this study. If the results are confirmed, postmenopausal women considering HRT may eventually be screened for genetic variants to predict the likelihood of risk or benefit from HRT.

Psaty BM, Smith NL, Lemaitre RN, Vos HI, Heckbert SR, La Croix AZ, and Rosendaal FR: Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. Journal of the American Medical Association 285: 906-913, 2001.

## **MRI Helps Identify Patients Likely to Benefit from Revascularization**

*Background:* Damage from heart attacks occurs when arteries carrying blood to the heart become blocked. Removing the blockage can improve prospects for recovery by allowing damaged areas of the heart to recover. However, revascularization procedures such as bypass surgery and angioplasty are not without risk, and sometimes damage to the cardiac tissue is so severe that it cannot be reversed. Heretofore several methods could distinguish between reversibly and irreversibly damaged cardiac tissue on the outer portion of the cardiac wall, but none could assess the extent of injury at other regions across the wall and all had other limitations.

*Advance:* Researchers recently demonstrated that magnetic resonance imaging (MRI), when used with a contrast agent, offers sufficient resolution to enable identification of damaged areas even in patients who did not know they had experienced heart attacks and can determine the extent of injury even in the central and interior portions of the cardiac wall. Moreover, the technique allows researchers to distinguish between reversibly and irreversibly damaged areas so accurately that only two percent of the cases where tissue was identified as irreversibly damaged improved after revascularization.

*Implications:* The prognostic value of contrast-enhanced MRI will be useful in helping patients and their physicians make informed treatment decisions. Because angioplasty and bypass surgery are not risk-free, using MRI to screen revascularization candidates may help to identify people for whom the risks of these invasive procedures outweigh the benefits.

Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, and Judd RM: The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. The New England Journal of Medicine 343: 1445-1453, 2000.

## **Preschool Communication Problems and Later Academic Performance**

*Background:* Disorders of the speech-sound system, called expressive phonology, are the most prevalent communication difficulties observed in young children. These children form a heterogeneous group, with some having isolated speech-sound disorders, while others have these disorders in combination with other language problems. In some cases, these disorders resolve by school age, but previous studies have suggested that many children may encounter subsequent difficulties in language, reading, and spelling. However, the trajectory of development, resolution, and persistence of these disorders remains unclear.

*Advance:* NIH investigators conducted a longitudinal follow-up study of children with early expressive phonology disorders. Fifty-two children were followed from the preschool years into the third and fourth grades. Children were classified into two groups based on the presence of an early phonology disorder in isolation or the presence of a phonology disorder with other language problems. At follow-up, a small number of children in either group exhibited residual speech sound production errors. However, those children with a history of phonological and other language problems exhibited poorer performance on a number of measures of communication (including phoneme awareness, language, reading decoding, reading comprehension, and spelling). These findings indicate that young children with isolated phonology disorders have better outcomes than do those whose disorder is accompanied by other language impairments. In addition, children with phonology disorders accompanied by additional language disorders are at greater risk for reading, spelling, and language difficulties when they enter an academic setting.

*Implications:* These findings provide important direction to clinicians regarding the prognosis for children with disorders of expressive phonology.

Lewis BA, Freebairn LA, and Taylor HG: Follow-up of children with early expressive phonology disorders. Journal of Learning Disabilities 33: 433-444, 2000.

## Development of Stereocilia Orientation in Hair Cells

*Background:* In humans, sounds are detected in the cochlea, the snail-shaped organ of the inner ear. The cochlea contains thousands of mechanosensory cells referred to as sensory hair cells. These hair cells are arranged in four rows, which travel along the cochlear spiral. Each of these cells has numerous specialized projections, referred to collectively as a “stereocilia bundle” that project into a fluid-filled space within the cochlea. As sound waves pass into the ear, they are converted into pressure waves in the fluid-filled cochlea that induce vibrations of the hair cell stereocilia bundles. Vibrations of the stereocilia bundles lead to the production of chemical signals that are then passed on to the brain via the auditory nerve. Thus, the vibration of the stereocilia bundle forms the biological basis for the perception of sound. Stereocilia bundles are only sensitive to vibrations in a single direction; therefore, the orientation of the bundle is crucial for normal function. In a normal cochlea, stereocilia bundles of all hair cells point in the same direction. However, recent studies suggest that developmental defects can lead to abnormal stereocilia bundle orientation and to hearing loss. However, the cellular and genetic factors that play a role in the specification of bundle orientation are unknown.

*Advance:* Recent experiments conducted by NIH scientists indicate that a secreted signaling protein, referred to as Wnt-7a, is critical for orientating stereocilia bundles of cochlear hair cells. Specifically, the *Wnt-7a* gene is expressed in cells located adjacent to the inner row of the hair cells. Secreted Wnt-7a protein establishes a concentration gradient across the hair cell region. Disruption of this gradient either through the addition of excess Wnt-7a protein, or by blocking of the downstream signaling pathway, leads to the development of disoriented bundles in the embryonic ear.

*Implications:* Developing hair cells detect the gradient of Wnt-7a protein and use this gradient as a mechanism to orient all stereocilia bundles in the same direction.

Dabdoub A, Donohue MJ, and Kelley MW: Wnt-7A mediates stereociliary bundle orientation in the organ of Corti. Journal of the Associates of Research Otolaryngol Abstract 24:165, 2001.

## **Loss of Neurons in a Particular Brain Region is Associated with Onset of Cognitive Decline in Older Individuals**

*Background:* The entorhinal cortex (EC) is a brain region that plays a crucial role in memory processing. Early studies showed a severe loss of neurons in a specific part of the EC in late-stage Alzheimer's disease (AD). More recent studies showed that death of these neurons is one of the earliest changes in AD, along with accumulation of plaques and tangles in specific brain regions. Important questions are whether some of these neurons die even before the onset of any memory problems, or whether neuronal death also occurs in a condition called Mild Cognitive Impairment (MCI). People with MCI have memory problems but have not been diagnosed with AD. MCI is a major risk factor for developing AD.

*Advance:* In the first study, autopsies were done as part of a longitudinal study of aging and dementia in nuns and brothers in the Religious Orders Study. All individuals had detailed clinical evaluations within 12 months of death and were categorized as having no cognitive impairment, mild cognitive impairment (MCI), or mild or moderate AD. Individuals with MCI all had significant losses of layer II EC neurons relative to those with no cognitive impairment, and these losses were as extensive as those in the AD patients. In the second study, autopsies were done on individuals from a longitudinal study whose cognitive status had been assessed within a year before death or whose cognitive status had been assessed by a post-mortem interview with an informant. This study found extensive loss of neurons in the EC in persons with very mild AD. In contrast, persons with no cognitive decline, but with plaques and tangles in their brains, showed no loss of neurons in EC.

*Implications:* These studies indicate that elderly individuals with MCI and very mild AD already have dramatic decreases in the number of neurons in a particular region of the EC. Therefore, these neurons, associated with memory function, degenerate early in cognitively impaired individuals. Importantly, one of the studies showed that there was no neuron loss in individuals who had the neuropathological hallmarks of AD but no memory loss. This suggests that the onset of neuronal loss is associated with the onset of memory loss and that even with the plaques and tangles of AD, there is no memory loss without a change in these EC neurons. Further research is needed to develop methods that can identify at-risk individuals even prior to MCI so that treatments can be initiated that will prevent, delay the initiation of, or slow the degeneration of these critical neurons.

Kordower JH, Chu Y, Stebbins GT, DeKosky ST, Cochran EJ, Bennett D, and Mufson EJ: Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. Annals of Neurology 49: 202-213, 2001.

Price JL, Ko AI, Wade MJ, Tsou SK, McKell DW, and Morris JC: Neuron number in entorhinal cortex and CA1 in preclinical Alzheimer's disease. Archives of Neurology (in press, 2001).

## **Some People with Mild Cognitive Impairment Progress to Alzheimer's Disease and Some Don't: How to Tell**

*Background:* Mild cognitive impairment (MCI) is conceptualized as a transitional state between normal aging and Alzheimer's disease (AD). Individuals with MCI have a demonstrable memory deficit on formal testing, but do not meet the clinically accepted criteria for AD. They do, however, convert to AD at a much higher rate than age-matched groups of cognitively normal individuals. There is still disagreement among scientists as to whether MCI is early-stage AD or a different clinical entity, because there are individuals with MCI who do not progress to AD.

*Advance:* Researchers examined 404 people who had either mild memory loss or no memory problems. The 227 individuals with MCI were placed into one of three categories: fairly confident of dementia, suspicious of dementia, and uncertain of dementia, reflecting the researchers' degree of confidence that the subtle signs of memory loss might indicate the onset of AD. The volunteers were reassessed annually for up to 9.5 years, and at that time all the volunteers with the most severe form of MCI had developed the clinical symptoms of AD but many in the less severe groups had not. In another study, investigators identified 129 individuals who met established criteria for normal control subjects, mild cognitive impairment (MCI), or probable AD, both at entry into the study and at a subsequent clinical evaluation 2-4 years later. Each subject had an MRI scan at baseline and at follow up. The size of the hippocampus decreased in all groups, most rapidly in AD patients, less rapidly in those with MCI, and least in control subjects. Within the control and MCI groups, those who experienced decline in cognitive function over time had a significantly greater decrease in hippocampal size than those who remained clinically stable.

*Implications:* The finding that many individuals labeled as MCI have AD suggests that the true prevalence of AD may be much greater than is currently appreciated. However, not all individuals with MCI progress to AD, and it is important to differentiate between those who do and do not progress. Serial measurements of hippocampal size may be a useful tool for identifying individuals with MCI who will and will not progress to AD.

Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, and Berg L: Mild cognitive impairment represents early-stage Alzheimer disease. Archives of Neurology 58: 397-405, 2001.

Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, and Kokmen E: Rates of hippocampal atrophy correlate with change in clinical status and AD. Neurology 55: 484-489, 2000.

## Imaging Clearance of Plaques by Immunotherapy in Living Mice

*Background:* At present, Alzheimer's disease (AD) can be diagnosed with certainty only with a post-mortem examination that shows the presence of two defining features of the disease, amyloid plaques and neurofibrillary tangles, in particular brain regions. Early diagnosis of AD or Mild Cognitive Impairment (MCI) would be greatly aided by the direct imaging of these pathologic features in the living brain. Conventional imaging techniques, especially repeated magnetic resonance scans over time, may have their greatest value in the area of MCI. To date the utility of these methods for AD research is hindered by their limited resolving power. Researchers, first at Elan Pharmaceuticals and then at several academic institutions, had already shown that in particular transgenic lines of mice, immunization with the amyloid- $\beta$  (A $\beta$ ) peptide could both prevent and remove A $\beta$  aggregates from brain. These mice provided a model to test new imaging techniques for plaques and their clearance from brain tissue.

*Advance:* Investigators used transgenic mice that develop plaques like those present in AD to test a new technique for observing what happens in the living brain when these mice are immunized with the A $\beta$  peptide. The imaging technique used was multiphoton microscopy, which provides a resolving power 100 times greater than that of other non-invasive *in vivo* imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Multiphoton microscopy uses long-wave-length light to excite a standard fluorescent dye. This technique allows sufficient resolution to view very small structures and lesions in brain such as plaques. In this experiment, antibodies specific for amyloid and labeled with a fluorescent dye were placed directly onto the surface of brains of anesthetized 20-month old mice. Investigators showed reversal of existing amyloid- $\beta$  deposits in the brain within three days of treatment with the antibodies.

*Implications:* This research showed that a novel technique, optical imaging, involving the use of specific dyes and markers could be used to track the extent of plaque removal following immunization in a transgenic mouse model of AD. It is likely that methods can be developed that will permit the visualization of plaque as well as its removal from human brain. The research also validates antibody-mediated passive immunization procedures for the removal of plaques from the brain. It remains to be determined if neurons in the brain can survive and function following exposure to the neurotoxic A $\beta$  plaque and to the immune therapy itself.

Bacskai BJ, Kajdasz ST, Christie RH, Carter C, Games D, Seubert P, Schenk D, and Hyman BT: Imaging of amyloid-beta deposits in brains of living mice permits direct observation of clearance of plaques with immunotherapy. *Nature Medicine* 7: 369-372, 2001.

## **Imaging Small Regions of Brain in Humans and Genetically Modified Mice**

*Background:* Since functional magnetic resonance imaging (fMRI) was developed in the early 1990s, studies have focused on how the brain functions during performance of some task, such as learning new information or remembering old. While this technology has revolutionized how we view the activity of the brain, it has several limitations. With fMRI, we can view brain structures that are a few millimeters in size; this resolution is insufficient for evaluating many smaller structures, such as the subregions of the hippocampus important in learning and memory. Another limitation arises in patients with moderate to severe Alzheimer's disease who cannot understand the experimental instructions and therefore cannot perform a mental task while being imaged. Requiring task performance to observe brain activity is even more limiting in studies of rodents and non-human primates where anesthesia is needed to prevent the animals from moving. Because most causes of brain dysfunction produce changes not only in the active, but also in the resting state of brain cells, functional imaging of the resting state might allow early detection of changes in very small regions of the brain.

*Advance:* A new method of fMRI was designed to be sensitive to resting brain cell function. This method is dependent on oxygen use by the brain during rest, and allows visualization of signals from subregions of the hippocampus. Using this technique, researchers found that hippocampal signals are significantly diminished in elderly humans with memory decline when compared to age-matched controls, and that different individuals show dysfunction in different subregions. Among healthy elders, the greater the intensity of the signal from a particular subregion of the hippocampus, the better the memory performance. Because this method does not require the subject to perform a mental task, it also was tested in anesthetized normal and in genetically modified, cognitively impaired mice. In mice genetically modified to carry a mutant Alzheimer's disease gene and that show a memory deficit, the researchers were able to detect functional changes in subregions of the hippocampus in the absence of changes in brain structure detectable by MRI.

*Implications:* This study was able to generate brain maps that highlight the structural and functional architecture of the hippocampal formation based on resting function. The importance of this enhanced resolution is illustrated when attempting to evaluate hippocampal function in life. Cells residing in different subregions are selectively vulnerable to different disease processes. Precise mapping of dysfunction requires a subregional analysis only possible with the new techniques introduced here. These techniques could eventually be used to identify persons with loss of neurons in very specific brain regions, for example in preclinical identification of persons at risk for developing Alzheimer's disease.

Small SA, Wu EX, Bartsch D, Perera GM, Lacefield CO, DeLaPaz R, Mayeux R, Stern Y, and Kandel ER: Imaging physiologic dysfunction of individual hippocampal subregions in humans and genetically modified mice. Neuron 28: 653-664, 2000.

## Bacterial Slime Clogs Cystic Fibrosis Lungs

*Background:* Cystic fibrosis (CF) is one of the most common fatal genetic diseases in the U.S. Approximately 30,000 Americans have the disease and an estimated 8 million are carriers of it. Thick, sticky mucus clogs the lungs and intestines of those with CF, causing malnutrition, frequent lung infections, breathing difficulty, and eventually permanent lung damage. Bacteria, especially *Pseudomonas aeruginosa*, thrive in this thick mucus, causing persistent infection. Most of those with CF die from respiratory failure caused by these infections – often around the age of 30.

*Advance:* Once these bacteria gain a foothold in CF lungs, they are invincible even to long-term antibiotic treatment. Physicians specializing in CF recently joined with microbiologists to reveal why these lung infections are so difficult to treat. The scientists showed that the bacteria in CF lungs encase themselves in a protective slime called a biofilm. Partial to wet surfaces, biofilms are responsible for everything from dental plaque and bathtub soap scum to bacterial colonies that corrode the bottom of ships. Within gluey pockets in the biofilm, colonies of bacteria flourish, nourished by a network of water-filled channels and shielded from the effect of antibiotics. The researchers developed a sensitive lab test that detects biofilms in CF lungs, based on telltale molecules produced by the structures.

*Implications:* This technique could form the basis for a diagnostic test to detect the presence of biofilms in a wide range of medical conditions and industrial processes. The work might also help scientists design drugs to prevent biofilms from forming or to disrupt them after they have become established.

Singh PK, Schaefer AL, Parsek MR, Moninger TO, Welsh MJ, and Greenberg EP: Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. *Nature* 407: 762-764, 2000.

## Identification of a Genetic Risk Factor for Lumbar Disc Disease

*Background:* Lumbar disc disease (LDD) is a common cause of low back pain. It frequently presents as a disc rupture (or herniation). Many of these patients present with sciatica, the radiation of pain from the buttock past the affected knee into the calf or foot (because of direct pressure from the ruptured contents of the disc on an adjacent spinal nerve root). The origins of LDD are multi-factorial, including heavy lifting, twisting, vibration, smoking, taller height and obesity. Studies in identical twins imply that there is also a genetic component to LDD. Recent studies by this same group have identified a genetic substitution in the building blocks of collagen IX, a component of the structural elements that make up the intervertebral disc. The purpose of this study was to determine if other collagen IX gene sequence variations play a role in the development of LDD.

*Advance:* The investigators studied 171 Finnish adults with x-ray confirmed LDD and 321 control adults who were not related and who did not have symptoms of LDD. An analysis of their collagen IX genes was performed. Their search revealed 2 amino acid substitutions that are significantly more prevalent in patients with LDD than in healthy controls. The first substitution occurs in the alpha 2 chain (collagen IX is composed of three amino acid chains), where tryptophan (one of the amino acids) replaces glutamine. The just-found second substitution occurs in the alpha 1 chain, where tryptophan replaces arginine. Both of these substitutions result in a three-fold increase in the risk of clinically significant LDD in the Finnish population.

*Implications:* LDD is a significant public health problem. Although 75 percent of these patients have resolution of their complaints by three months, the remaining 25 percent do not. This latter group has been identified as consuming significant health care dollars used to treat LDD. These findings are the first reported common genetic risk factor for LDD. As noted, these substitutions do not cause LDD, but they result in a three-fold increase in the risk of clinically significant LDD. Further study of the interaction between genetic and environmental factors such as physical stress are needed. A more complete understanding of these risk factors and their mechanisms could lead to rational preventive measures and/or to improved symptomatic care for this pressing public health problem.

Paasilta P, Lohiniva J, Göring HHH, Perälä M, Räänä SS, Karppinen J, Hakala M, Palm T, Kröger H, Kaitila Ilkka, Vanharanta H, Ott J, and Ala-Kokko L: Identification of a novel common genetic risk factor for lumbar disc disease. The Journal of the American Medical Association 285: 1843-1849, 2001.

## Genetic and Molecular Basis of Pseudoxanthoma Elasticum

*Background:* Pseudoxanthoma Elasticum (PXE) is a systemic inherited disorder that involves the elastic tissue in the skin, eyes, and cardiovascular system. It can result in severe and even fatal health problems or may be much milder and clinically difficult to identify unless suspected and pursued vigorously. It is often not visible early in life but, in more severe cases, may manifest in childhood. It had been classically considered a genetic disorder of a structural component, but with the discovery of the gene that is defective in the disease, it is now becoming apparent that this disease actually is a metabolic disorder in which the structural component is secondarily affected.

*Advance:* A consortium of investigators localized the gene underlying PXE a little over a year ago. This gene encodes for a protein that underlies multiple drug resistance in microorganisms but appears to have the function of transporting materials through the membrane of human cells. In a recent study, affected individuals from 4 families were investigated to determine the specific genetic defects underlying the disease in each family. The 4 families were from different ethnic backgrounds, yet the specific defect in all 4 families was exactly the same. The fact that all 4 families had the identical defect implies that this is a genetic “hot spot” and possibly that the same mechanism of mutation leads to this uniformity of mutation in disparate families.

The presumed function of this gene would indicate that PXE is a metabolic disease in which the metabolic alterations are manifested predominately in damage to elastic fibers and tissues in which elastic fibers predominate. This is contrary to the traditional reference to PXE as a classic structural molecule disease. The recognition that this is a metabolic disease offers new hope for the development of treatment based on metabolic modifications including potentially such things as diet manipulation or drug therapy.

*Implications:* The isolation of a gene underlying an inherited disease is quite common at this time. However, the recognition that PXE is likely a metabolic rather than a structural disease opens new potential avenues for the development of therapeutic interventions that will either delay or completely prevent the health effects of the disease. The isolation of the gene and the cataloging of the gene defects underlying the disease, particularly in families where there has been one identified member, will allow the early identification of affected individuals so that treatment can be instituted before the development of signs or symptoms of the disease and, hopefully, early enough to prevent such signs and symptoms from ever developing.

Ringpfeil F, Nakano A, Uitto J, and Pulkkinen L: Compound heterozygosity for a recurrent 16.5-kb alu-mediated deletion mutation and single-base-pair substitutions in the *abcc6* gene results in pseudoxanthoma elasticum. *American Journal of Human Genetics* 68: 642-652, 2001.

Uitto J, Pulkkinen L, and Ringpfeil F: Molecular genetics of pseudoxanthoma elasticum: a metabolic disorder at the environment-genome interface. *Molecular Medicine Today* 7: 13-17, 2001.

## **Epidermolysis Bullosa: Molecular Mechanisms and Treatment Possibilities**

*Background:* Epidermolysis Bullosa (EB) is a group of inherited diseases in which the epidermal cells at different levels in the skin fall apart after trauma, often minor trauma. The most severe forms of the disease are not compatible with life and result in death in early infancy or in childhood. Other forms are milder and are compatible with long life, although with complications. Most of the genes underlying EB have been identified but there are animal models for only a few of the forms of EB. The lack of animal models for some of the variants has limited research. In addition, new syndromes continue to be described, often with different mutations in the same, previously described, genes but which result in somewhat different clinical pictures. Analysis of these mutations helps in our understanding of the disease process and the normal function of these genes and proteins. Treatment for EB is primarily supportive. Much work being done is in the hope of being able to directly affect the underlying abnormalities in this disease in the future.

*Advance:* A new method of genetic manipulation has been devised in which the abnormal genes involved in EB can be turned on by local application of an inducing chemical. This activates the gene in a localized area allowing study of the process without resulting in severe disease that otherwise would be fatal for the animal. Mutation analysis was performed in children affected with a rare form of EB that is associated with abnormalities of the gastrointestinal and urinary tracts to predict the kind of complications to be expected. With this knowledge, the pediatricians involved in the care of these newborns could recognize the defects early and surgically correct them before significant complications could develop. In the lethal form of EB termed Herlitz Junctional EB, the reduced quantities of laminin 5 (a compound of the basement membrane zone) resulted in continued excessive weakness and the skin disease typical of this form of EB.

*Implications:* Advanced techniques such as the inducible system described above are necessary to allow the study of forms of the disease that would be fatal if expressed in the entire mouse or in the entire skin of a mouse. The development of this technology should provide further stimulus for investigations of the molecular basis of EB. The continued development of correlations between specific abnormal genes and the diseases they produce is allowing earlier and earlier diagnosis of disease. In some forms of the disease this early diagnosis will allow heightened clinical preparations for the systemic complications of these forms of EB and will allow prompt intervention to reduce morbidity and mortality in these children.

Cao T, Longley MA, Wang XJ, and Roop DR: An inducible mouse model for epidermolysis bullosa simplex implications for gene therapy. Journal of Cell Biology 152: 651-656, 2001.

Wallerstein R, Klein ML, Genieser N, Pulkkinen L, and Uitto J: Epidermolysis bullosa, pyloric atresia, and obstructive uropathy: a report of two case reports with molecular correlation and clinical management. Pediatric Dermatology 17: 286-289, 2000.

Spirito F, Chavanas S, Prost-Squarcioni C, Pulkkinen L, Fraitag S, Bodemer C, Ortonne JP, Meneguzzi G: Reduced expression of the epithelial adhesion ligand laminin 5 in the skin causes intradermal tissue separation. Journal of Biological Chemistry 276: 18828-18835, 2001.

## **Low Serum Thyroid Stimulating Hormone Levels Increase Risk of Fracture in Elderly Women**

*Background:* Thyroid dysfunction is very common in older women: 8 percent to 13 percent of women over 50 have biochemical evidence of either the overproduction or underproduction of thyroid hormone. Thyroid-stimulating hormone (TSH) acts reciprocally with circulating thyroid hormone and if it is low it can be either from high natural thyroid hormone secretion – hyperthyroidism – or by the over-treatment of low thyroid hormone – hypothyroidism – with synthetic thyroid hormone supplements.

*Advance:* Thyroid stimulating hormone (TSH) levels of 0.1 mIU/L or less (normal level 0.3-5.0mIU/L) mean that circulating thyroid hormone is too high. According to newly published data from the multi-center, prospective Study of Osteoporotic Fractures, very low TSH significantly increases the risk of new hip and vertebral fractures in women over 65 years old. Investigators at the four clinical sites in this study collected blood samples from 9,704 women in 1988, then questioned the subjects every 4 months about the occurrence of fractures.

Measured serum TSH levels in the archived blood of 148 women with new hip fractures and 149 with new vertebral fractures were compared with those of 373 randomly selected women without reported fractures. The risk of hip fracture was more than three times as high among women with low TSH levels than among those with normal levels, a significant difference after adjusting for age, previous hyperthyroidism, self-rated health, current use of estrogen and thyroid hormone, and body weight. The findings were similar for risk of vertebral fracture.

The risk of hip fracture, but not vertebral or any nonspine fracture, was twofold higher for those who reported a history of hyperthyroidism. However, risk of fracture was not associated with thyroid hormone use. Fracture risk is not linked to thyroid hormone itself, if the levels are appropriate for the person taking it, but if thyroid levels are too high, then there clearly is a deleterious effect, whether it is from taking too much or from having a gland that is overactive. The prevalence of thyroid disorders in older women suggests that thyroid function is a significant risk factor for osteoporotic fracture.

*Implications:* This observation has consequences for both the treatment of hyper- and hypothyroidism, conditions that are highly prevalent in postmenopausal women. Normal TSH levels should be sought when treating hyperthyroidism or when thyroid hormone is being administered to treat hypothyroidism. The use of suppressive thyroid hormone therapy for benign conditions should be reconsidered in light of the adverse skeletal consequences of low TSH level. In addition, bone mineral density should be followed in women being treated for thyroid disorders.

Bauer, DC, Ettinger, B, Nevitt, MC, Stone, KL, for the Study of Osteoporotic Fractures Research Group: Risk for Fracture in Women with Low Serum Levels of Thyroid-Stimulating Hormone. Annals of Internal Medicine 134: 561- 134, 2001.

## **Racial Disparities in the Diagnosis and Treatment of Schizophrenia and Depression**

*Background:* A growing body of research suggests significant racial disparities in the delivery of medical care at the level of detection and diagnosis of illness and in receipt of treatment. With respect to psychiatric disorders, studies of persons without schizophrenia have shown that African-Americans are less likely to be diagnosed with an affective disorder and more likely to be diagnosed with a psychotic disorder. These differences could reflect erroneous diagnoses or true differences in prevalence. The uncertainty is troubling, given the significant proportion of people – an estimated 7- to 70 percent – with schizophrenia who have comorbid depression. Depression co-occurring with schizophrenia may be a precursor of relapse; may increase risk for rehospitalization; and is associated with demoralization, hopelessness, and impaired social skills. Most important, depression may place the person with schizophrenia at elevated risk for suicide. An unanswered question has been whether the underdiagnosis of affective disorders found in the absence of schizophrenia would be true of persons with the diagnosis.

*Advance:* Researchers examined the consequences of racial differences in the diagnosis and treatment of depression in people with schizophrenia. A consecutively admitted sample of psychiatric inpatients diagnosed with schizophrenia (n=123) was assessed for depression and for quality of life. Caucasians were seven times more likely to be diagnosed with depression than were African-Americans. Depression was significantly associated with reduced life satisfaction in Caucasians but not African-Americans. In a separate study, investigators examined data from patients diagnosed with schizophrenia (n=685) who were interviewed in the Schizophrenia Patient Outcomes Research Team (PORT) study and found that African-Americans were significantly less likely than were Caucasians to report a past or current diagnosis or current treatment of depression, mania, or anxiety disorders. These researchers also examined claims for Medicare recipients with schizophrenia, using a 5 percent random sample of all people with at least one Medicare service claim (inpatient or outpatient) in 1991 and who were diagnosed as having schizophrenia in any care setting (n=12,440). Among adults under 65, Caucasians were almost one and a half times more likely than African-Americans to have received an ambulatory care mental health service, and 1.3 times more likely to have received individual therapy.

*Implications:* These three studies direct attention to disparities experienced by African-Americans with schizophrenia in the diagnosis and treatment of depression and other affective disorders, and in their use of ambulatory mental health services generally. Although depression is under-diagnosed among African-Americans with schizophrenia, the fact that quality of life ratings were lower among Caucasians with depression casts doubt on the validity of the depression diagnosis using conventional diagnostic tools. The concomitant disparity in service use by Medicare recipients under age 65 implies under-provision of care to African-Americans.

Delahanty J, Ram R, Postrado L, Balis T, Green-Paden L, and Dixon L. Differences in rates of depression in schizophrenia by race. Schizophrenia Bulletin 27: 29-38, 2001.

Dixon L, Green-Paden L, Delahanty J, Lucksted A, Postrado L, and Hall J. Diagnosis and treatment for affective and anxiety disorders in schizophrenia differs by race. Psychiatric Services, (in press 2001).

Dixon L, Lyles A, Smith C, Hoch JS, Fahey M, Postrado L, Lucksted A, and Lehman A. Use and costs of ambulatory care services among Medicare payments to persons with schizophrenia. Psychiatric Services 52: 786-792, 2001.

## **Bipolar Disorder in Children: Exploring a New Diagnostic Entity**

*Background:* Bipolar disorder (manic-depressive illness) is being diagnosed with increasing frequency in children who also have a diagnosis of attention deficit hyperactivity disorder (ADHD). Yet the bipolar disorder diagnosis in children is controversial because 1) the high rate of comorbid ADHD makes differential diagnosis difficult and 2) the long-term course of the childhood onset disorder is not well understood. To address these issues, investigators are conducting a naturalistic follow-up study of a well-characterized sample of 93 children diagnosed with bipolar disorder (with or without comorbid ADHD) who were 7 to 16 years of age at intake, a comparison group of children with a diagnosis of ADHD and no current or past diagnosis of bipolar or major depressive disorder, and healthy children. To document that comorbid ADHD is an age-dependent feature of child mania, the researchers developed an instrument that assesses specific criteria of mania that do not overlap with ADHD or other conduct disorders.

*Advance:* Findings from the ongoing study indicate that, with few exceptions, the children with bipolar disorder had homogeneous diagnostic features (i.e., in rates of mania, mixed mania, psychosis, rapid cycling, or comorbid oppositional defiant disorder (ODD)) across gender, pubertal status, and ADHD diagnosis. Children with comorbid ADHD were more likely to be younger and male, and pubertal children had higher rates of hypersexuality. Children in the bipolar group had significantly greater impairment in their relationships with parents and peers than did those in the ADHD and healthy control groups. Of particular importance in determining the existence of a new disorder, the diagnosis was stable. After 6 months, 86 percent of the children in the bipolar group still met full criteria for the diagnosis, and only 14 percent had recovered. At 1-year follow-up, 37 percent of the children had recovered from mania, and the rate of relapse after recovery was 38 percent.

*Implications:* These findings suggest that with careful assessment of mania and rapid-cycling features, the diagnosis of bipolar disorder in children can be made reliably. Low recovery and high relapse rates at follow-up indicate poor outcome for children with bipolar disorder in this naturalistic study. The children's poor psychosocial functioning deficits need to be addressed through interventions. These children will have to be followed into adulthood to establish if their rapid cycling (78 percent at intake) is limited to childhood or continues into a rapid-cycling adult course of bipolar disorder.

Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, and Soutullo CA: Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty, and comorbid attention deficit hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 10: 157-164, 2000.

Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, and Zimmerman B: One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. American Journal of Psychiatry 158: 303-305, 2001.

Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, and Soutullo CA: Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. Journal of Child and Adolescent Psychopharmacology 10: 165-173, 2000.

## Improved Diagnosis of Oligodendroglioma

*Background:* Malignant gliomas are the most common tumors that arise in the brain. For nearly a century, pathologists have classified gliomas according to the type of glial cell (brain supporting cell) that they resemble. Radiation and surgical removal have been the mainstay of therapy for most types of gliomas because responses to chemotherapy are infrequent and unpredictable. Oligodendrogliomas, which resemble glial cells called oligodendrocytes, are more likely to respond to drug therapy than most gliomas, but distinguishing oligodendrogliomas on the basis of appearance has been difficult. Brain tumors, like all forms of cancer, are genetic diseases – not in the sense that they are inherited but because the uncontrolled growth reflects defects in genes that influence the cells' behavior. So, looking at genes may be a powerful way to discriminate among types of tumors.

*Advance:* Building on their earlier gene findings, a research team has now tested the use of molecular genetic markers for identifying subtypes of oligodendrogliomas and predicting response to chemotherapy. The study, which examined results from 50 patients, demonstrated that tumors could be divided into four subgroups depending on whether they had lost genetic information on portions of chromosomes 1 and 19 (called 1p and 19q) and whether there were mutations in the TP53 gene. Patients with combined losses of 1p and 19q had strong and lasting responses to chemotherapy, with long survival. Other tumors with 1p alterations also respond to drugs, but not as well. Tumors with no loss of 1p which have TP53 mutations may also respond to chemotherapy, but the tumors recur quickly. Tumors with no loss of 1p and no TP53 mutations respond very poorly to chemotherapy.

*Implications:* These findings raise the possibility for the first time that therapeutic decisions at the time of diagnosis might be rationally tailored to particular genetic subtypes of oligodendrogliomas. There are more than 100 types of brain tumors recognized by conventional pathological criteria. For now, the reasons that different tumor types respond differently to therapies may not be clear, but the genetic diagnostic distinctions present important clues to unravel those differences. As understanding of brain tumors at the molecular level progresses, scientists hope to develop therapies that precisely target those defects, and precise molecular diagnosis will be an essential part of that strategy.

Ino Y, Betensky RA, Zlatescu MC, Sasaki H, Macdonald DR, Stemmer-Rachamimov AO, Ramsay DA, Cairncross JG, and Louis DN: Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. Clinical Cancer Research 7: 839-45, 2001.

## Predicting Intractability of Epilepsy in Children

*Background:* Epilepsy is a disorder – really a group of disorders – in which seizures occur, usually unprovoked and unpredictably. It is one of the most common neurological problems, affecting about 1 percent of the U.S. population, with about 125,000 new cases diagnosed each year. Epilepsy can result from many causes, ranging from external insults such as trauma or disease to perhaps more than 100 inherited syndromes. Often the cause is unknown. Although epilepsy can begin at any age, about 30 percent of newly diagnosed cases are children, most younger than 2 years. Seizures can be controlled with drugs in most children – although these drugs are far from ideal – but in some children control of seizures is very poor, or intractable. The medical, social and economic consequences of intractable epilepsy are severe for children and their families.

*Advance:* A new study provides physicians with much needed guidance for predicting early which children with epilepsy will develop intractable forms of the disease. Researchers actively recruited patients from academic centers, private practices, and community clinics to try to gather a widely representative group of children. More than 600 children entered the study at their first diagnosis of epilepsy, and researchers evaluated their status on average (median) five years later. About 10 percent of these children developed intractable epilepsy. The analysis evaluated which of many clinical measures, classifications, and tests best predicted intractability. The study found that clinical classification of epilepsy syndromes, high initial seizure frequency, and certain EEG (brain wave) findings could predict early in the course which children will develop intractable epilepsy.

*Implications:* This study provides solid guidance for physicians and families coping with epilepsy. There are a wide variety of surgical and drug treatments for epilepsy, and this new information will be helpful in developing treatment strategies that might be more aggressive in children whose epilepsy is likely to be intractable than in those whose seizures are easily controlled.

Berb AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, and Beckerman B: Early development of intractable epilepsy in children, a prospective study. Neurology 56: 1445-1452, 2001.

## **Link Between a Common Sleep Disorder and a Risk Factor for Alzheimer's Disease**

*Background:* We spend about one-third of our life asleep. Profound mysteries remain about sleep, such as why sleep is necessary. Whatever the reason, sleep disorders can seriously erode quality of life, and even contribute to early death. Sleep apnea, or prolonged interruptions to breathing while asleep, causes serious sleep deprivation because a person must partially but repeatedly wake to take in air. This disorder is associated with increased risk of cardiovascular disease and heart attack. An important public health concern, sleep apnea affects an estimated 4 percent of adult men and 2 percent of adult women to some degree.

Sleep disturbances are also common in persons with Alzheimer's disease (AD), but the underlying reasons for this association are unclear. Currently, one of the few known risk factors for AD depends on which version of a cholesterol transport protein called apolipoprotein E (ApoE) each of us inherits. While the ApoE 2 subtype may be protective against AD, the presence of the ApoE 4 subtype predisposes a person to both AD and cardiovascular disease.

*Advance:* Because of the connections between sleep, AD and cardiovascular disease, researchers investigated whether the severity of apnea was associated with any of the various circulating ApoE subtypes. Using a large population of middle-aged adults who suffer from sleep apnea, researchers found that individuals who have the ApoE 4 subtype were nearly two times more likely to experience moderate-to-severe apnea than people who express only the ApoE 2 or 3 subtypes. Extrapolating these data to the general population, the researchers suggest that up to 8 percent of moderate to severe sleep apnea might be associated with the ApoE 4 subtype.

*Implications:* The association between ApoE 4, a cholesterol transport protein, and chronic sleep-disordered breathing provides new information about physiological changes in sleep disorders. More importantly, this study brings together previously unexplained links between apnea, cardiovascular disease and AD, and provides the basis for investigating the potential relationships between these debilitating conditions. Improved ability to detect a predisposition for apnea, CVD and AD based on ApoE profile will allow intervention strategies, such as diet and lifestyle modification.

Kadotani H, Kadotani T, Young T, Peppard P, Finn L, Colrain I, Murphy G, and Mignot E: Association between apolipoprotein E e4 and sleep-disordered breathing in adults. Journal of the American Medical Association 285: 2888-2890, 2001.

## Early Prediction of Stroke Recovery

*Background:* A stroke (or brain attack) occurs when the blood supply to a part of the brain is blocked or when a brain blood vessel bursts. In either case, the symptoms of stroke may include sudden numbness or weakness (especially one-sided), and sudden confusion or difficulty with speech, vision, movement, or coordination. Stroke is diagnosed by a neurological exam, blood tests, and by imaging the brain and blood vessels. Early treatment can significantly reduce the severity of the damage done to brain cells and improve the prognosis for recovery. However, therapy must be administered within hours of the stroke to be beneficial. Since it is often several days before all of the effects of a stroke are clear, an early and accurate assessment of prognosis after stroke could greatly benefit a patient's care.

*Advance:* Scientists have developed a new tool to help physicians predict how well a person will recover from a stroke. The procedure combines three types of information during the first several hours the stroke patient is in the hospital. One is diffusion-weighted magnetic resonance imaging (MRI) of the brain, an adaptation of the standard MRI. Another is the score on the NIH Stroke Scale (NIHSS), a widely used clinical measure of neurological dysfunction. The third factor is the time from the onset of symptoms to the time of the brain scan. Surprisingly, the patients who waited longest before receiving the scans were more likely to recover. The combined scale predicts stroke recovery with high sensitivity and specificity.

*Implications:* The combination of the three measures provide a more accurate prediction of stroke recovery than any measure alone. This new diagnostic tool should help physicians manage patients more efficiently and reduce distress and anxiety among patients and families. In addition, the accurate prediction of prognosis should allow physicians to make better decisions about the aggressiveness of treatment, ultimately improving the stroke patient's outcome.

Baird AE, Dambrosia J, Janket SJ, Eichbaum Q, Chaves C, Silver B, Barber PA, Parsons M, Darby D, Davis S, Caplan LR, Edelman RE, and Warach S: A three-item scale for the early prediction of stroke recovery. *Lancet* 357: 2095-2099, 2001.

## Predicting Prognosis in Wilm's Tumor

*Background:* Neurotrophins are natural chemicals that promote cell growth and survival. Neurotrophins were first studied because of their critical role in the development of the nervous system where they influence whether nerve cells multiply, migrate, specialize, and even survive throughout development. Subsequently, the role of these powerful signal molecules in maintaining healthy cells in the adult brain and in other parts of the body have come to light.

Because of their extraordinary capacity to stimulate cell growth and division, neurotrophins and the receptors by which cells detect and respond to these signals can contribute to the progression of brain tumors. Neurotrophins may influence tumor progression by promoting abnormal cell growth or by inhibiting cell death, which is a normal part of the development process. For certain brain tumors, the expression of selected neurotrophins and their receptors is correlated with the clinical outcome for the patient.

*Advance:* Recently scientists have discovered that the expression of neurotrophins and neurotrophin receptors can also be used to predict the outcome for pediatric patients with kidney tumors known as nephroblastoma, or Wilm's tumor. Patients who expressed high levels of one type of neurotrophin receptor along with low levels of another type formed a clear high-risk group, strongly correlated with an unfavorable outcome.

*Implications:* The levels of these neurotrophin receptor subtypes could be used as a new prognostic factor in children with Wilm's tumor. This important finding will translate into improved outcomes for children with Wilm's tumor, since patients with a high risk of relapse can be identified early and treated aggressively while low risk patients can avoid unnecessary treatment toxicity. New cancer therapies for this disease can be designed to selectively target the neurotrophin receptor system. More generally, these findings remind us of the essential unity of biology. Cells throughout the body use variations on the same biological themes to carry out their functions, so research in one area of science often has unanticipated implications for many areas of medicine.

Eggert A, Grotzer MA, Ikegaki N, Zhao H, Cnaan A, Brodeur GM, and Evans AE: Expression of the neurotrophin receptor TrkB is associated with unfavorable outcome in Wilm's tumor. Journal of Clinical Oncology 19: 689-696, 2001.

## A Noninvasive Test to Detect Kidney Transplant Rejection

*Background:* When a patient receives a kidney transplant, the patient's immune system recognizes the transplant as "foreign" and attempts to destroy it. Drugs that suppress the immune system can help to prevent this organ rejection, but still roughly 35 percent of organ transplant recipients suffer an episode of acute (sudden and severe) rejection during the first year after transplantation. As a consequence, doctors must closely monitor the status of a transplanted kidney in order to treat episodes of acute rejection. The best method for monitoring kidney status is the needle biopsy, which involves insertion of a long needle into the kidney through an incision in the skin and removal of a small sample for examination under the microscope. However, needle biopsies are painful and may lead to complications, including failure of the transplant. A noninvasive test for diagnosing immune rejection of the transplant would be welcomed by patients and could improve the outcome of transplantation.

*Advance:* Researchers recently demonstrated that they could detect signs of immune rejection of a transplanted kidney by measuring, in patient urine samples, two RNAs (molecules that are precursors to proteins) that appear to play a role in transplant rejection. The researchers found that the expression of these proteins was higher in urine samples from patients undergoing an episode of acute rejection, which was confirmed by needle biopsy, than in samples from patients with no evidence of acute rejection.

*Implications:* Measurements of the urinary levels of RNAs involved in destroying cells could form the basis for a noninvasive diagnostic test for transplant rejection. Future studies will be aimed at improving the diagnostic accuracy of the test by measuring the urinary levels of other molecules. Refinements of the test should allow doctors to predict acute rejection and start appropriate treatment before the transplanted kidney is irreversibly damaged. In addition, determining which proteins are involved in transplant rejection will provide clues as to potential therapeutic targets for preventing transplant rejection.

Li B, Hartono C, Ding R, Sharma VK, Ramaswamy R, Qian B, Serur D, Mouradian J, Schwartz JE, and Suthanthiran M: Noninvasive diagnosis of renal-allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine. The New England Journal of Medicine 344: 947-954, 2001.

## **Marijuana Use in Early Adolescence Can Lead to Psychiatric Problems as an Adult**

*Background:* There is an age-old question in the addiction and mental health arena: Which comes first – the drug use or the psychiatric disorder? In both clinical and general population samples of adolescents and adults, psychiatric disorders have been found to be related to drug use. Different models for why this relationship occurs have been suggested over the years. Some believe that psychiatric problems precipitate drug use. They suspect that people take drugs to self-medicate for their psychiatric problems. Another model suggests that drug use leads to certain psychiatric disorders. For example, in the case of marijuana, perhaps the toxic effects of marijuana on brain functioning is what leads to anxiety and depression. A third model suggests that psychiatric disorders and drug use are related because of shared common etiological factors. Researchers are shedding some new light on this question.

*Advance:* In a recent study, researchers investigated the nature of the link between marijuana use, depressive symptoms, anxiety, and interpersonal aggression by conducting two sets of interviews two years apart with over 2,200 Colombian teens between the ages of 12 and 17. Trained interviewers talked to adolescents in their homes in three Colombian cities, obtaining information about frequency of marijuana use and symptoms of anxiety and depression. They then performed two sets of analysis. Unlike other studies, this study did not find that anxiety and depression led to increased marijuana use. Instead, the researchers found that marijuana use in early adolescence is associated with higher levels of anxiety, depressive symptoms, and interpersonal aggression in late adolescence, all of which may persist into adulthood. These findings led researchers to conclude that development of drug use preceded psychiatric symptoms in the studied population.

*Implications:* These findings suggest that at certain stages of adolescent development, drug use should be considered a risk factor for the later development of psychiatric disorders and problem behaviors, as well as the inability to assume adult roles in society. The results also confirm the fact that marijuana use in early adolescence is not without consequences and has been shown to precipitate the development of later psychiatric conditions. Thus, marijuana use prevention messages should be targeted to youth prior to the onset of adolescence.

Brook JS, Rosen Z, and Brook DW: The effect of early marijuana use on later anxiety and depressive symptoms. New York State Psychologist 35-39, 2001.

## **Brain Damage Due to Methamphetamine Abuse has Functional Consequences**

*Background:* Methamphetamine is a dangerous and highly addictive drug that has become increasingly popular among our Nation's youth. Studies in animals have shown that methamphetamine can produce profound and long-lasting neurotoxicity to the brain – damaging dopamine, as well as serotonin and monoamine-containing nerve cells. Furthermore, this damage produces cognitive and motor deficits. Now, human imaging studies are showing similar results.

*Advance:* In one study, researchers used a brain imaging technique known as positron emission tomography (PET) to measure levels of a brain protein known as the dopamine transporter (DAT) in former methamphetamine abusers. These transporters are part of the dopamine brain circuit which is key for movement control and feelings of pleasure. Results showed that, on average, DAT levels in a brain area known as the striatum were 25 percent lower in methamphetamine abusers than in control subjects. This reduction was evident even in abusers who had been drug free for at least 11 months. Additionally, the reduction in DAT was correlated with decrements in cognitive and motor functions.

In a second study, researchers used PET to measure glucose metabolism in the brains of methamphetamine abusers, some of whom had not used methamphetamine for almost 3 years. Glucose metabolism is a measure of brain cell activity, and reduced glucose metabolism can be a very sensitive indicator of brain damage and an early indicator of neurodegenerative disease. Results of this study showed a marked overall increase in glucose metabolism in the brains of methamphetamine abusers when compared to nondrug abusers, suggesting an inflammatory reaction. This effect was most marked in the parietal cortex, which is involved in sensation and spatial perception, and was correlated with poor performance on a spatial function test. Researchers also found that there was a reduction in glucose metabolism in two brain regions involved in dopamine pathways, the thalamus and striatum.

*Implications:* These results show that methamphetamine use, at doses taken by human abusers, is associated with reductions in DAT associated with motor and cognitive impairment, and functional changes in behavior, as well as significant changes in glucose metabolism. The fact that functional deficits could be seen after 11 months of abstinence and glucose metabolism changes after 35 months of abstinence indicate the long-lasting nature of these changes. This suggests the potential for long-term health problems associated with methamphetamine abuse. For example, the decrease in glucose metabolism in the thalamus and striatum, brain areas involved in motor functions, suggests that methamphetamine abusers may be at greater risk for neurodegenerative diseases such as Parkinson's. These results emphasize the need to alert the public and clinicians of the long-term brain changes that methamphetamine can cause and highlight the need to develop treatments that improve dopamine brain function and restore cognitive and motor function.

Volkow ND, Change L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Logan J, Wong C, and Miller EN: Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *American Journal of Psychiatry* 158: 377-382, 2001.

Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Wong C, and Logan J: Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers. *American Journal of Psychiatry* 158: 382-389, 2001.

## Understanding E. Coli Pathogenicity

*Background:* A strain of the bacterium *Escherichia coli* (*E. coli*) known as O157:H7 causes an estimated 75,000 illnesses a year in the U.S., according to the Centers for Disease Control and Prevention, including numerous deaths, and is especially dangerous to children, the elderly, and people with weakened immune systems. The food-borne pathogen was first identified in 1982 in an outbreak from contaminated undercooked hamburger patties, and the number of reported cases has risen steadily since then, so that it is now considered a major threat to public health. Since *E. coli* is a normal part of the human gastrointestinal flora, scientists have continually sought an explanation for the extreme pathogenicity of the O157:H7 strain.

*Advance:* Researchers at the University of Wisconsin, Madison, completely sequenced all the 5,450 genes of the O157:H7 strain to seek clues to what makes the organism so dangerous. The research was supported in part by the NIH Shared Instrumentation Grant Program, which provided money for the DNA sequencing and other special equipment. The researchers then compared the sequence with that of the harmless *E. coli* genome, which they had sequenced in 1996, looking for what they thought would be minor differences between the harmless and the pathogenic strains. The sequence comparisons proved otherwise. Although the two strains shared about 3,500 genes, the O157:H7 strain had dramatically increased the size of its genome and had acquired 1,300 genes not found in the harmless strain. The new genes were not inserted at a single site but were scattered throughout the circular genome as clusters or islands of potentially pathogenic genes. Among these banks of foreign genes were genes very similar to those of the bacterium *Salmonella* and the plague-causing organism *Yersinia*. The O157:H7 strain also had genes that code for the extremely potent Shiga toxin, originally found in the dysentery-causing microorganism *Shigella*. How these banks of genes have been exchanged across entire families of bacteria is now a new central mystery in pathology.

*Implications:* There are currently no effective treatments for *E. coli* O157:H7 infections, which cause a severe form of bloody diarrhea and release toxins that damage the kidneys and may cause renal failure. Now that the genes unique to this pathogenic strain have been uncovered by sequencing, scientists have a tangible set of targets for the development of better vaccines and drugs as well as improved diagnostic tools for early identification of this deadly pathogen.

Perna NT, Plunkett G III, Burland V, Mau B, Glasner JD, Rose DJ, Mayhew GF, Evans PS, Gregor J, Kirkpatrick HA, Pósfai G, Hackett J, Klink S, Boutin A, Shao Y, Miller L, Grotbeck EJ, Davis NW, Lim A, Dimalanta ET, Potamousis KD, Apodaca J, Anantharaman TS, Lin J, Yen G, Schwartz DC, Welch RA, and Blattner FR: Genome sequence of enterohaemorrhagic *Escherichia coli* O157:H7. *Nature* 409: 529-533, 2001.

## Diagnosing and Monitoring Sleep Apnea

*Background:* During sleep, many people stop breathing for short periods of time. This condition, known as obstructive sleep apnea, can lead to serious irregular heart rate and is associated with increased risks for high blood pressure, heart attack, and stroke. Detecting sleep apnea has been difficult because it requires expensive direct monitoring of several variables, including nasal air flow and blood oxygen concentration, and the measuring devices can interfere with normal sleep patterns. A few preliminary studies have suggested, however, that sleep apnea might be detectable by analysis of a simple electrocardiogram (ECG).

*Advance:* Scientists at the Research Resource for Complex Physiologic Signals approached this possibility of simplified detection in a novel way. In conjunction with the *Computers in Cardiology 2000* meeting, they sponsored a contest that invited researchers from many disciplines to create algorithms to detect sleep apnea based on a provided set of annotated ECGs. The algorithms were then applied to another set of annotated ECGs that the researchers had never seen. The results were impressive. Among the many participants, four groups created distinctly different algorithms that had an accuracy of 100 percent in detecting sleep apnea. In addition to detecting apnea, the severity of the condition must be determined by measuring the frequency and duration of the periods where breathing has stopped. The ability of the algorithms to make these measurements based on the ECG was also scored, and the top-performing algorithms did as well as trained professionals using the more expensive recording techniques.

*Implications:* These algorithms for detecting sleep apnea will have beneficial medical ramifications, but this innovative cooperative approach to solving difficult signal analysis problems may, in the end, be the most valuable result.

Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK, and Stanley HE: Physiobank, physiotoolkit, and physionet: components of a new research resource for complex physiologic signals. *Circulation* 101: e215-e220, 2000.

Mietus JE, Peng CK, Ivanov PC, Goldberger AL: Detection of obstructive sleep apnea from cardiac interbeat interval time series. *Computers in Cardiology* 27: 753-756, 2000.

## A New Device for Cancer Diagnosis

*Background:* Barrett's esophagus is a condition that develops in some people with chronic heartburn. In this disease, the lining of the stomach grows up into the esophagus where it does not belong. Over time, this tissue can turn into a precancerous type of tissue and then into a cancer known as adenocarcinoma. Virtually all adenocarcinomas of the lower esophagus occur in patients with Barrett's esophagus. The prognosis for patients who are diagnosed with adenocarcinoma of the lower esophagus is quite poor, but the chances of successful treatment increase significantly if the disease is detected at either the Barrett's esophagus or the later pre-cancerous stage. The esophagus of patients who have chronic heartburn can be inspected with an instrument called an endoscope, but these inspections often fail to detect either Barrett's esophagus or the later pre-cancerous stage. Because of this failure, patients at risk for adenocarcinoma of the lower esophagus are subjected to numerous random biopsies. This technique is invasive and expensive and can fail to detect precancerous tissue if the biopsy does not randomly hit the right spot in the esophagus.

*Advance:* Researchers at the Massachusetts Institute of Technology have developed a noninvasive device to diagnose Barrett's esophagus. This device uses three optical techniques: fluorescence, reflectance, and light scattering. The information derived from this combination of observations is quite powerful and seems to allow routine diagnosis of Barrett's esophagus. In addition to providing a reliable diagnosis, this instrument is far less intrusive than the currently used random biopsy protocol. These measurements are made with a very small device on the end of a flexible fiber. The measurement only takes a few seconds and the examined tissue is only exposed to a little light.

*Implications:* This new device will be a great tool to create a comprehensive picture of the changes in tissue that occur as a patient progresses from Barrett's esophagus to the precancerous state and then on to adenocarcinoma of the lower esophagus. Such information should be helpful in allowing doctors to devise a treatment strategy for their patients. Although this study focused on a difficult test case in the throat, there is no reason that this tool cannot be used to examine precancerous tissue in the oral cavity, cervix, lungs, breasts, and the gastrointestinal tract.

Georgakoudi I, Jacobson BC, Van Dam J, Backman V, Wallace MB, Muller MG, Zhang Q, Badizadegan K, Sun D, Thomas GA, Perelman LT, and Feld MS: Fluorescence, reflectance, and light-scattering spectroscopy for evaluating dysplasia in patients with barrett's esophagus. Gastroenterology 120: 1620-1629, 2001.

## **Type 2 Diabetes Detection in High-Risk Individuals**

*Background:* Diabetes mellitus is responsible for pain, disability, or premature death. The most common form, non-insulin-dependent or Type 2 diabetes, affects 16 million, mostly adult, individuals in the U.S., according to the National Institute of Diabetes and Digestive and Kidney Disorders. Early diagnosis and treatment of this malady help to prevent many of the disease symptoms and untimely death. To improve early detection of diabetes, the level of blood glucose that is now considered acceptable in fasting patients has been lowered. However, multiple reports indicate that many people who have acceptable fasting glucose levels still are diagnosed with diabetes on the basis of a 2-hour glucose tolerance test (OGTT), which is considered more accurate. To obtain an overview of the ability of the fasting blood glucose test to diagnose diabetes, researchers compared the results of that test with the OGTT and the blood levels of a type of hemoglobin called HbA<sub>1c</sub>. The amount of HbA<sub>1c</sub> in the blood is considered a sensitive indicator of the glucose status.

*Advance:* Investigators at the Indiana University General Clinical Research Center studied 244 individuals who were at a high risk of developing diabetes because of obesity or a family history of the disease. They found that the fasting blood glucose test was relatively insensitive in detecting diabetes. Between 29 percent and 48 percent of the study participants who had fasting blood glucose levels below the new cut-off value were diagnosed with diabetes according to the OGTT. The HbA<sub>1c</sub> provided better results, but 39 percent of the participants diagnosed with diabetes still were considered normal by the HbA<sub>1c</sub> test. The scientists recommend that for people at risk for Type 2 diabetes, the fasting blood glucose test should be supplemented with the HbA<sub>1c</sub> test to improve diagnostic accuracy.

*Implications:* Ninety-five percent of U.S. citizens with diabetes suffer from the effects of Type 2 diabetes mellitus. Early detection permits appropriate treatment and amelioration of such morbidity and will have a significant impact on American public health.

Perry RC, Shankar RR, Fineberg M, McGill J, and Baron AD: HbA<sub>1c</sub> measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the early diabetes intervention program (EDIP). Diabetes Care 24: 465-471, 2001.

## Improved Prediction of Tissue Damage in Stroke Patients

*Background:* Efforts to limit tissue death in acute stroke patients may be improved significantly by identifying tissue that is receiving reduced blood flow but remains viable. Novel technologies, known as diffusion-weighted and perfusion-weighted magnetic resonance imaging (MRI), have been developed that are highly sensitive and specific in diagnosing acute diminished blood flow to particular areas of the brain. The tissue signatures resulting from the acute MR imaging of the brain may be able to categorize the physiological state of the tissue and therefore help physicians make the most appropriate clinical decisions.

*Advance:* Based on prior studies in rhesus monkeys at the New England Regional Primate Research Center, investigators at the Massachusetts General Hospital and the Massachusetts Institute of Technology designed and analyzed statistical formulas to evaluate the risk of damage for each unit of tissue assessed by MRI. These investigations showed that combining the diffusion-weighted images with the perfusion-weighted images provided greater specificity and sensitivity than algorithms that utilized either of these images alone.

*Implications:* These advanced computer-based technologies that rapidly combine different types of MRI data into a single “risk map” of the brain may enhance medical assessment following stroke. This includes the evaluation of the extent of tissue injury and evolution of this injury following the initial stroke. Because it is essential to provide rapid treatment to stroke patients, the improved diagnostic procedure may help these patients survive without debilitating effects.

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## Childhood Origins of Health Disparities in African-Americans

*Background:* African-Americans experience higher rates of obesity, type 2 diabetes mellitus, hypertension, stroke, and other cardiovascular disease than Caucasian Americans. Data from HANES III, a national assessment of the health and nutrition status of Americans, show that African-American girls are nearly twice as likely as Caucasian girls to be obese. Other data show that adult African-American women are three times more likely to have a stroke than their Caucasian counterparts.

To find out what early childhood factors lead to these conditions, NIH-funded researchers conducted an unprecedented longitudinal study of over 130 African-American and Caucasian children to determine whether the changes in various indices of glucose and insulin activity lead to changes in body fat as the children reached puberty. Insulin is a hormone that helps the body use glucose, or “blood sugar,” by moving it from the blood and storing it as triglycerides in fat cells.

*Advance:* Researchers found that high circulating levels of insulin predicted weight gain for both African-American and Caucasian children. However, they found that African-American children, compared to Caucasian children, had significantly higher fasting insulin and a greater insulin response to both oral and intravenous glucose. Moreover, the African-American children had higher levels of “insulin resistance” – the inability of the body to respond to the effects of insulin. These differences persisted even among African-American and Caucasian children with similar physical activity levels, dietary intake, body fat and socioeconomic status.

*Implications:* Since insulin plays a critical role in storing energy in fat cells, high levels of circulating insulin can lead to obesity in childhood and to diabetes, hypertension, stroke, and cardiovascular disease later in life. Therefore, the high levels of insulin and insulin resistance demonstrated in African-American children can be used as a marker to predict later obesity. In addition, this information will help scientists develop specific pharmacological and behavioral interventions that focus on modifying insulin levels and the body’s response to insulin.

Johnson MS, Figueroa-Colon R, Huang TTK, Dwyer JH, and Goran MI: Longitudinal changes in body fat in African American and Caucasian children: influence of fasting insulin, glucose and insulin sensitivity. Journal of Clinical Endocrinology and Metabolism 86: 3182-3187,2001.

## **New Method to Measure Testosterone Levels May Help Diagnose Infertility in Men**

*Background:* Testosterone, the primary male sex hormone, is critical for normal production of sperm. Low concentrations of testosterone may be responsible for abnormal sperm production in certain men who are infertile. Typically, testosterone levels in men are measured using blood serum samples. However, studies in rats have shown that concentrations of testosterone in the rat testes are significantly higher than in normal blood serum, and that the concentration that is minimally required to maintain sperm production is substantially higher than the levels observed in serum. Unfortunately, there is no comparable information on testosterone concentrations in humans, largely because there has not been a simple, non-invasive, repeatable procedure available to measure testicular testosterone levels. Therefore, NIH-supported investigators sought to develop a minimally invasive technique to obtain accurate and reproducible measurements of testosterone concentrations from the human testes.

*Advance:* For this study, the researchers first developed methods to extract fluid from the rat testis. The method was then adapted for humans. Using samples from 21 men, scientists found that the average concentration of testosterone in intratesticular fluid was approximately 100-fold higher than the concentration of testosterone found in normal human serum.

*Implications:* Scientists have developed a minimally invasive technique for obtaining samples from human testes to measure testosterone levels. Using this technique to obtain samples from men with various degrees of failure to produce sperm will allow scientists to determine the minimum testicular testosterone concentration needed for maintaining normal levels of sperm production. The new method would be essential in conducting research that could provide: 1) important insights for understanding the underlying mechanisms that control human sperm production, 2) a sperm production marker to assess potential causes of male infertility, and 3) a method for assessing the effectiveness of various treatments for men in whom the cause of infertility was previously unknown.

Jarow JP, Chen H, Rosner W, Trentacoste S, and Zirkin BR: Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. Journal of Andrology 22: 640-645, 2001.

## Artificial Intelligence in the Diagnosis of Breast Cancer

*Background:* While one in eight women in the U.S. will be diagnosed with breast cancer in her lifetime, the application of sophisticated screening mammography offers great potential to lessen the impact of this disease. Mammograms detect not only tiny early malignancies but also precancerous and high risk conditions. Early detection reduces risk of death from breast cancer by nearly one-third. The increasing use of digital mammography allows an expanding role for computing, and researchers have been investigating the use of computer-aided diagnosis for imaging studies. If computers can be “taught” to read and assess mammograms, they can serve as a second reader and improve diagnostic accuracy. They offer the added advantage of reliability because they provide objective, consistent results and do not become tired or distracted, as their human counterparts might.

*Advance:* Building on over 15 years of studying computer-aided diagnosis, NIH-supported researchers have obtained FDA approval for an adjunctive computer reading system of digitized film/screen mammograms. The investigators have established a database of mammograms and accompanying family, gynecologic, dietary, and medical histories. They have developed criteria for the computer to recognize cancer in the mammograms based on texture of the breast, and are comparing the computer analysis to current methods of risk assessment based on the Gail model and possession of biomarkers BRCA1 and BRCA2. Findings about breast texture in this set of women may help identify high risk in other women, aiding in selection of patients to be followed closely to maximize the possibility of early detection.

*Implications:* Using computer-aided diagnosis to help identify women at high risk for breast cancer provides an important tool beyond current standard practice to select women to follow closely. Frequent monitoring with optimized analysis will discover cancer earlier, leading to further decreases in advanced disease and mortality from breast cancer.

Huo Z, Giger ML, Wolverton DE, Zhong W, Cumming S, and Olopade OI: Computerized analysis of mammographic parenchymal patterns for breast cancer risk assessment: feature selection. Medical Physics 27: 4-12, 2000.

## HPV Testing Identifies Pap Test Abnormalities Needing Follow-Up

*Background:* Each year, more than 2 million women who receive Pap testing are diagnosed with a condition called atypical squamous cells of undetermined significance (ASCUS). Most of these mild cervical abnormalities resolve on their own without any treatment or intervention, but a minority develop into precancer or cancer. The question of what – if anything – should be done about a diagnosis of ASCUS has long been a major issue in cervical cancer screening. Physicians have had to make decisions about follow-up testing and examinations for ASCUS patients without having a way to identify which of these patients are at risk for developing more serious conditions. Strategies are needed to identify women with clinically significant cervical findings while avoiding excessive follow-up referrals that can needlessly increase health care costs.

*Advance:* The ASCUS/LSIL Triage Study (ALTS) is a multicenter, randomized clinical trial in which investigators evaluated three management strategies for detecting cervical intraepithelial neoplasia (CIN), a precancerous condition that can develop from ASCUS. ALTS involved about 5,000 women who had mildly abnormal Pap tests. About two-thirds of the women had ASCUS, and the rest had a more definite abnormality called low-grade squamous intraepithelial lesion (LSIL). Within each of these categories, women were randomly assigned to one of three different groups. One group had an immediate colposcopy, in which the cervix is examined with a magnifying instrument and biopsy is performed on abnormal areas. A second group had repeat Pap tests. The third group of women were tested for specific types of human papillomavirus (HPV) that are associated with cervical cancer. Women whose HPV results were positive for these virus types had immediate colposcopy with indicated biopsy; those with negative results did not. HPV testing was found to identify nearly all (96.3 percent) of the women with ASCUS abnormalities that needed treatment. Only about 55 percent of women with ASCUS would have been referred to colposcopy if the HPV test had been used for triage in all cases. Thus, HPV testing reduced referrals to colposcopy by about one-half when compared with immediate colposcopy.

*Implications:* HPV testing can provide clinicians with a management strategy tool in making follow-up referrals for ASCUS. A positive HPV test suggests that precancer or, rarely, cancer may be present, as precancers were found in 10–20 percent of ASCUS cases in which the HPV test was positive. Conversely, a negative HPV test provides strong reassurance that precancer or cancer is not present. The other two options evaluated in ALTS – immediate colposcopy with indicated biopsy and follow-up by repeat Pap tests every 6 months – also remain alternatives that may be considered. Patients and physicians may take several factors into account when deciding what to do about ASCUS, such as cost and patient preferences regarding follow-up procedures.

National Cancer Institute, Office of Cancer Communications. HPV testing shows which Pap abnormalities need attention. Press release. <http://rex.nci.nih.gov/massmedia/pressreleases/altsrelease.html>. Accessed July 28, 2001.

Solomon D, Schiffman M, and Tarone R: Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. Journal of the National Cancer Institute 93: 293-239, 2001.

## **New, Highly Accurate Technique for Genetic Diagnosis of Cancer Risk**

*Background:* Twenty percent of patients with colorectal cancer have a family history that suggests a genetic contribution to the disease, common exposures among family members, or a combination of both. Specific genetic mutations have been identified as the cause of inherited cancer risk in some colon cancer-prone families, accounting for perhaps five to six percent of colorectal cancer cases overall. However, conventional genetic testing for inherited susceptibility to colorectal cancer may fail to identify one-quarter to one-half of persons who have such a susceptibility and who would therefore benefit from more aggressive screening programs.

*Advance:* Researchers have developed a technology that dramatically improves the accuracy of genetic tests for susceptibility to inherited cancer. Every person carries two copies of each gene (one inherited from the father, one from the mother). These two copies are known as “alleles,” and conventional genetic tests analyze both potentially mutated alleles at the same time. However, defective alleles can be hidden, or “masked,” by normal genes. The new technology, called “conversion,” separates the two copies of the gene so that they can be analyzed individually. Specifically, researchers can uncover masked mutant genes by uniting human cells with specially designed mouse cells to create mouse-human cell lines. Each cell line contains a copy of the gene that the researchers want to study. The researcher can then look for gene mutations by using conventional DNA sequencing methods. With this new technology, scientists can detect genetic mutations associated with certain kinds of hereditary colorectal cancer nearly 100 percent of the time.

*Implications:* By unmasking mutated genes, these investigators have overcome a major obstacle to testing for genetic mutations in inherited diseases – and identifying people at higher risk for colorectal cancer who would be candidates for screening and preventive interventions. Although conversion has only been tested on colorectal cancer mutations so far, the technique should apply to other hereditary cancers, including breast and kidney cancer, as well as a wide variety of neurological and cardiovascular disease genes.

Yan H, Papadopoulos N, Marra G, Perrera C, Jiricny J, Boland CR, Lynch HT, Chadwick RB, de la Chapelle A, Berg K, Eshleman JR, Yuan W, Markowitz S, Laken SJ, Lengauer C, Kinzler KW, and Vogelstein B: Conversion of diploidy to haploidy. *Nature* 403: 723-724, 2000.

## MR Imaging in Metastatic Lymph Node Detection and Gene Therapy

*Background:* As various imaging techniques become more advanced and refined, they offer an expanding array of diagnostic and therapeutic utilities and the potential to replace more invasive and riskier techniques such as surgical biopsy. Researchers are examining the use of magnetic resonance (MR) probes, radiopharmaceuticals, and optical probes to investigate various targets related to cancer progression. This includes lymph nodes, whose status plays an important role in staging and making treatment decisions for many cancers. Current noninvasive imaging techniques do not identify the cells in a lymph node or give the necessary information about the number and location of metastatic nodes. The information is obtained through biopsy, which often results in complications (such as lymphedema) and may also fail to detect some affected nodes. Sophisticated imaging can also be used for a range of other purposes, including monitoring gene therapy and tracking stem cell activity.

*Advance:* A research group has developed a way of tagging cells magnetically with a tiny particle that attaches to cells without harming them or interfering with their activity. The particle allows for cell visualization on high-resolution MR imaging. Mouse experiments show that the technique is far more sensitive than expected. One study has demonstrated that it is possible to see changes in tagged lymph nodes containing metastases in magnetic resonance images. In another project, researchers have induced into mouse tumors a gene that permits the cells to take up excess amounts of iron. When the mice were injected with a magnetic iron agent, MR imaging detected contrast proportional to the amount of iron the tumors took up. Researchers demonstrated that the labeled cells retain their capability for differentiation, can be visualized by high-resolution MR imaging, and can be retrieved from excised tissues and bone marrow using magnetic sorting techniques. In related work, researchers have labeled human stem cells with an MR-active label and shown that it is possible to track them, using mouse experiments.

*Implications:* Implications for this work can be applied to the specific areas studied and beyond. The work with lymph nodes has the potential for broad applications in the staging of cancer, with the promise of reducing the side effects related to surgical biopsy. In the mouse tumor gene project, the technique could make it possible to image cells injected for gene therapy, to discover their location, and to determine whether the cells are still alive. This would make it possible to follow the progress of gene therapy in a patient over time with MR imaging, with no need for serial biopsy. The stem cell work enables the visualization of significantly fewer cells, even possibly single cells, with MRI. This could prove very useful in studying autoimmune and inflammatory diseases, as well as cancer.

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Weissleder R, Moore A, Mahmood U, Bhorade R, Benveniste H, Chioocca EA, and Basilion JP: *In vivo* magnetic resonance imaging of transgene expression. *Nature Medicine* 6: 351-355, 2000.

Lewin M, Carlesso N, Tung CH, Tang XW, Cory D, Scadden DT, and Weissleder R: Tat peptide-derivatized magnetic nanoparticles allow *in vivo* tracking and recovery of progenitor cells. *Nature Biotechnology* 18: 410-414, 2000.

## Potential Biomarkers to Detect Early Ovarian Cancer Found

*Background:* If ovarian cancer is detected before it spreads beyond the ovaries, the five-year survival rate is 93 percent. Unfortunately, early disease has few symptoms, and fewer than a quarter of the cancers are detected early. That means that at present, only 46 percent of women diagnosed with ovarian cancer will survive longer than five years. Researchers are seeking sensitive and specific noninvasive techniques to detect early ovarian cancer.

Cancer develops as a result of a series of molecular changes within the cell. These changes cause the cell's genes to produce different amounts and types of molecules. If the tumor cells make far more of any particular molecule, and if that molecule is secreted into the blood, it could be used as an easily assessed marker to indicate the presence of the cancer. One such tumor marker, CA125, is fairly effective in identifying late-stage ovarian cancers and in monitoring the response of patients to therapy, but it is not specific enough to detect early stages. Researchers are seeking to develop reliable assay methods and to evaluate candidate genes for their potential use as markers in the blood for early-stage ovarian cancer.

*Advance:* Scientists have identified five genes that appear to produce molecules that could be used as assay markers. After careful preparation of a variety of tissue cells, including normal ovarian tissue and ovarian cancer cells, researchers cloned the genes of the cells. Using a number of different approaches, they analyzed the genes for such factors as how likely the genes were to be different in malignant versus normal ovarian tissue and which genes would produce molecules most likely to be secreted into the blood. The genes that appear to be the most likely candidates for early detection assays are called *mesothelin*, *HE4*, *ESE-1*, *SLPIa*, and *GPR39*. Some of the genes were known before, but information on their differential over-expression in ovarian cancer is new. Researchers have, so far, developed methods to assay *mesothelin* and *HE4* in the blood.

*Implications:* During the past three decades, the advances in treatment of ovarian cancer has had only a modest effect on overall survival. A multimodal strategy for diagnosis appears to be the best way to detect ovarian cancer early and, presumably, reduce the number of deaths from the disease. Early, noninvasive screening, such as this gene assay, could indicate which women should receive the more expensive, but effective, transvaginal sonography. Deaths from ovarian cancer could be substantially decreased.

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## Genetic Testing of Stool Detects Colorectal Cancer

*Background:* Colorectal cancer accounts for the second largest number of cancer deaths in the U.S. Its early detection improves survival, but the current detection methods involve testing for occult, or unseen, blood in the stool, or the rather invasive colonoscopy. Scientists have observed that colorectal cancer cells are shed into the stool, and their goal was to develop reliable, specific molecular genetic tests for cancer detection from stool samples. Colorectal cancer often has a fairly small number of genetic alterations: (1) mutations that activate a cancer-causing gene called *K-RAS*, (2) mutations that inactivate the tumor suppressor genes *APC* and *TP53*, and (3) some mutations of the genes that repair mismatched DNA. These last mutations can be spotted by checking the patterns of certain short DNA sequences such as one labeled BAT26. Finding, isolating, and analyzing the tiny amount of tumor DNA poses daunting technical problems. The vast majority of the DNA found in stools comes from intestinal tract bacteria. Even among the DNA shed by the person, only a small fraction contains the mutations from the tumor.

*Advance:* By using three different assays for K-RAS, TP53, and BAT26 genetic material, scientists were able to isolate and accurately identify the cancers of about three-quarters of their research cohort of patients. The 51 patients in the panel had each been diagnosed or screened positive for colorectal cancer. Researchers analyzed DNA from stool samples taken when the patients' tumors were intact and DNA from samples of the tumors after they were surgically removed. Among the 51 patients, the analysis of the tumor samples indicated that 39 (76 percent) had a mutation in one of the three genes being investigated. Stool analysis detected 36 mutations, or 92 percent of them. Stool analysis for each person showed no mutations that were not present in the tumor analysis. The TP53 and the BAT26 stool samples all matched. The K-RAS matching was significant but not as good, perhaps because the gene may be more easily degraded by compounds present in the stool. The researchers now plan to look at ways to improve K-RAS availability and to look at genes that were not included in this analysis. If they can include detection of the APC tumor suppressor gene, cancer detection through this method could theoretically increase to 90 percent.

*Implications:* This study effectively developed a reliable, reproducible method for the purification, amplification and identification of the minuscule quantities of tumor DNA in stool. In addition, it quantified the small amounts of DNA made available. In addition to potentially improving early detection of colorectal cancer, these lab techniques may be useful for tests to assess other fluids such as sputum in lung cancer patients, urine in bladder and kidney cancer patients, seminal fluid in prostate cancer patients, and mammary duct effluents in breast cancer patients.

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## Use of Saliva in Diagnosis and Management of AIDS

*Background:* Although the risk of transmission is low, current evidence indicates that human immunodeficiency virus (HIV) infection can be acquired through the oral cavity by breastfeeding and oral-genital contact and that the virus can multiply in the tissues of the mouth and throat. The results of recent studies suggest that the oral cavity may be a reservoir for HIV type 1 (HIV-1). The saliva of some infected individuals can contain virus levels greater than those in their blood and can potentially serve as a means to transmit the infection. There also is reason to believe that viral reproduction at different reservoir sites within the same individual may result in the production of HIV-1 variants that differ by the site of production and that, because of their differing origin, may require differing and specific therapeutic approaches.

*Advance:* NIH grantees have examined the genetic composition of viral samples from the saliva and blood plasma of HIV-1 infected individuals. The technology used can rapidly identify the R5 and X4 variants of the HIV virus that have different clinical significance and reflect genetic variations in the outer coat of the virus. The R5 variant usually predominates early in the course of the infection and does not induce formation of the pathologic mass of cellular components called syncytia, while the X4 variant induces syncytia and may evolve from R5 variants during disease progression. The investigators studied matched saliva and plasma samples from 11 infected individuals and found R5 variants in both fluids of all subjects and the X4 variant in the saliva and plasma of 3 subjects. These results suggest that the X4 variant is not excluded from the saliva reservoir and that HIV-1 in saliva and blood may stem from a common source.

*Implications:* These findings indicate that saliva may serve as a noninvasive means for evaluating and monitoring viral reproduction and evolution in HIV-1 infected individuals as well as for selection and evaluation of anti-HIV-1 drug therapy.

Freel SA, Williams JM, Nelson JAE, Patton LL, Fiscus SA, Swanstrom R, and Shugars DC: Characterization of human immunodeficiency virus type 1 in saliva and blood plasma by V3-specific heteroduplex tracking assay and genotype analyses. *Journal of Virology* 75: 4936-4940, 2001.

## Early Detection of Head and Neck Squamous Cell Carcinoma

*Background:* Oral, pharyngeal, or laryngeal cancer is diagnosed in an estimated 41,000 Americans each year. Patients whose cancers are detected and treated early have a much better chance of survival and suffer less treatment-related damage than patients whose disease is diagnosed late. Unfortunately, many head and neck cancers are not detected early, resulting in a poor prognosis. The reasons for late detection range from failure by patients to recognize early symptoms or to seek medical care promptly to difficulty in detecting some tumors during clinical examination. A reliable, noninvasive test to detect head and neck cancer early, perhaps even before it is clinically detectable, would offer a means of reducing morbidity and mortality using current treatment options.

*Advance:* NIH-supported scientists used a technique called microsatellite analysis to detect cancer-specific DNA changes in tumor tissue from 44 patients with head and neck cancer and in cells collected by oral rinsing and swabbing from the cancer patients and from 43 healthy control subjects. They found DNA changes signaling cancer in 38 of the tumors, and found matching genetic alterations, or cancer markers, in the oral samples from 35 of the 38 patients whose tumors contained markers. No cancer-specific genetic changes were found in oral cells collected from the healthy subjects. Cancer markers were detected in both lymph node metastases and oral cells from three patients with unknown primary tumor sites, indicating that microsatellite analysis of saliva can reveal cancer not detectable by oral examination.

*Implications:* The study provides proof of principle for using microsatellite analysis of cells in saliva to detect head and neck cancer – the first step in developing a reliable, noninvasive screening test for these cancers. If the test is validated and refined, it could provide clinicians with a tool for screening at-risk persons for early-stage head and neck cancer and for monitoring patients after cancer treatment.

Spafford MF, Koch WM, Reed AL, Califano JA, Xu LH, Eisenberger CF, Yip L, Leong PL, Wu L, Liu SX, Jerónimo C, Westra WH and Sidransky D: Detection of head and neck squamous cell carcinoma among exfoliated oral mucosal cells by microsatellite analysis. Clinical Cancer Research 7: 607-612, 2001.

## Ultrahigh Resolution Instrument May Improve Diagnosis of Retinal Diseases

*Background:* Optical coherence tomography (OCT) is a non-invasive imaging technique, similar to ultrasound, that promises to have a broad range of applications for the diagnosis and management of a variety of ocular diseases. Of the many applications being investigated, the most eagerly anticipated is the use of OCT for optic nerve measurements in glaucoma patients. Glaucoma is characterized by a distinct pattern of optic nerve damage. However, because current diagnostic methodology only allows the clinician to detect the disease after sufficient nerve loss has occurred, the patient may have already suffered irreversible vision loss by the time a diagnosis is made. Thus, being able to visualize optic nerve damage at its inception has been a long-sought goal in the clinical management of glaucoma.

*Advance:* A new generation of OCT instrumentation is being developed. Currently available OCT instruments have a resolution of 10 micrometers (1 micrometer =  $10^{-6}$ m). The prototype that has been developed this past year resolves retinal structures at the 3 micrometer level. In combination with advances in image processing and the development of methods to determine structural boundaries, high resolution OCT allows medical researchers to see retinal microstructure that could have previously only been seen in tissue preparations. Results from these instruments demonstrate their ability to study intraretinal structures associated with a specific disease non-invasively, providing earlier diagnosis and more precise monitoring of progression. For example, thinning of the retinal nerve fiber layer is an indicator of glaucomatous damage and progression. Ultra-high resolution OCT can potentially detect changes in thickness in this layer down to the single cell level, thus providing greater sensitivity and precision than other ophthalmic imaging instruments.

*Implications:* Ultrahigh resolution ophthalmologic OCT allows more precise examination of retinal morphology for earlier diagnosis and more precise monitoring of ocular pathologies. Practically, this may enable clinicians to intervene before extensive sight is lost and to monitor treatments more effectively. In a disease such as glaucoma where the diagnosis can be delayed because of confounding factors, high resolution OCT would be invaluable. Other uses for this instrument include the diagnosis and management of diabetic retinopathy and macular degeneration. Glaucoma, diabetic retinopathy, and macular degeneration disproportionately affect people over 65. Early detection of these blinding diseases is critical in an aging population.

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## **Simpler Method of Genotyping Hepatitis C (HCV)**

*Background:* An estimated 170 million people worldwide are infected with hepatitis C, a major emerging disease caused by the hepatitis C virus (HCV). Because of the likelihood that developing chronic infection may be associated with some strains of HCV, the genotypic characterization of hepatitis C virus has become increasingly important for the ultimate goal of improved clinical management and public health control. Several methods exist for genotyping hepatitis C virus. Most of these methods, however, are labor intensive, costly, and confined to research or reference laboratories. Simpler and more accessible tests are necessary in countries around the world where hepatitis C virus poses an emerging public health problem, and where there is a limited capacity to diagnose infection at the genotype level.

*Advance:* NIH-supported scientists from the Czech Republic and California have described a new and relatively inexpensive method for characterizing HCV, called restriction site-specific polymerase chain reaction (RSS-PCR). Using this approach, blood samples from patients with hepatitis C were analyzed to predict subtypes. Both the sensitivity and specificity of the RSS-PCR test for the differentiation of HCV subtype 1b from the others were 100 percent. This method can be modified to differentiate any hepatitis C genotype or subtype of interest.

*Implications:* The simplicity and speed of the RSS-PCR method may provide new opportunities to study the epidemiology of HCV infections and the relationship between HCV genotypes and clinical outcome by more laboratories throughout the world. In addition, this approach may be useful for the genotyping of other pathogens that cannot be easily isolated or cultured.

Krekulova L, Rehak V, Wakil AE, Harris E, Riley LW: Nested restriction site-specific pcr to detect and type hepatitis c virus (HCV): a rapid method to distinguish HCV Subtype 1b from other genotypes. Journal of Clinical Microbiology 39: 1774-1780, 2001.

## Penicillin Resistant Meningitis in Salvador, Brazil

*Background:* Penicillin was once the major weapon against *Streptococcus pneumoniae*, the causative agent of severe pneumonia in children under the age of five and for 1 million deaths each year. In many parts of the world, penicillin has been found to be ineffective against this microbe. In developing countries, where poverty and poor health care infrastructure contribute to the elevated rates of life-threatening pneumococcal diseases like meningitis, resistance to antimicrobial therapies such as penicillin has significant repercussions. Understanding the dynamics and risk factors related to the spread of penicillin resistance for *S. pneumoniae* will assist in the development of more effective regimens to prevent and treat disease.

*Advance:* Using population-based data from children, NIH-supported researchers from Salvador, Brazil assessed risk factors for acquiring penicillin resistant pneumococcal disease. An inexpensive and rapid method was used for typing penicillin resistant *S. pneumoniae* in investigations of pneumococcal outbreaks. It was found that approximately 10 percent of children with pneumococcal meningitis showed an intermediate-level resistance to penicillin. Penicillin resistant isolates were significantly associated with an age of two and under, previous antibiotic use, and co-resistance to another antibiotic (trimethoprim-sulfamethoxazole). Researchers also found that a closely related strain, serotype 14, was responsible for more than 50 percent of the cases of penicillin resistance pneumococcal meningitis. These isolates may have spread to other regions of Brazil, further contributing to the recent emergence of penicillin-resistant *S. pneumoniae* in Brazil.

*Implications:* The increasing spread of penicillin-resistant strains of meningitis-causing pneumococcus (particularly serotype 14) suggests that more effective prevention strategies, including those involving new drug regimens, are urgently needed.

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## **Accuracy and Bias in Ratings of Nursing Home Residents' Pain**

*Background:* There are nearly 1.5 million older residents of nursing homes in the U.S. Paid caregivers in nursing homes are largely unlicensed nursing assistive personnel known by a variety of titles such as certified nursing assistant or nurse's aide. Chronic pain is a frequent occurrence among nursing home residents, given the nature of chronic illnesses that are age-related: arthritis and musculoskeletal disorders and injuries, disability-enforced inactivity, neurologic conditions, and diabetes-related pain, for example. However, 20 percent of nursing home residents cannot communicate meaningful information about their pain. Pain is a complex phenomenon with wide variation among individuals. It is affected by mood and other psychosocial factors, and interferes with quality of life, sleep, productivity and utilization of health care services. Many health care providers do not have the background to effectively treat pain nor to assess its presence.

*Advance:* An assessment by structured interview measured licensed practical nurse (LPN) and nursing assistant (NA) estimations of pain in nursing home residents. These estimations were compared for accuracy to the Minimum Data Set for each resident which stems from the residents' own reports of pain and from formal assessments for pain frequency during a seven-day period. Findings for the 252 residents and associated staff revealed that there was no resident gender or race bias in pain estimation by either LPNs or by NAs. However, both LPNs and NAs underestimated nursing home residents' weekly pain frequency, weekly pain intensity, and daily pain intensity. NAs were less likely than LPNs to underestimate chronic pain.

*Implications:* Undertreatment of pain is pervasive in all health care settings and in nursing homes. Undertreatment affects the quality of life of more than half of residents and is related to disruptive behavior of residents. Since the current structure of nursing homes reflects staffing by unlicensed personnel, it is essential that those who have the closest contact with nursing home residents have the skills necessary to detect chronic pain. Certain resident characteristics predicted undertreatment for daily pain: male gender, black race, older age, poorer physical function and cognitive impairment. While education and role modeling of pain assessment (and communicating treatment goals relating to pain management) are needed by nursing home staff, these resident characteristics may assist in targeting specific and more frequent assessment of residents representing those factors.

Engle VF, Graney MJ, and Chan A: Accuracy and bias of licensed practical nurse and nursing assistant ratings of nursing home residents' pain. Journal of Gerontology 56A, M405-M411, 2001.

## **Longitudinal Follow-up of Neonatal Intensive Care Unit Survivors**

*Background:* Many more neonates are living to infancy and childhood, in part because of the utilization of neonatal intensive care units (NICU). Since many major neonatal illnesses are associated with poor school and academic performance, it is important to separate the potential effects of low birth weight from the other neonatal medical status factors that may occur concurrent with low birth weight.

The sample of 188 children followed up to eight years included 39 who were healthy, full-term infants as well as 149 preterm infants recruited from one NICU. The NICU “graduates” were grouped according to nature and extent of problems at discharge from NICU: one group had few clinical problems; another group were clinically ill but without neurologic abnormality; a third group had severe neurologic compromise in the neonatal period; a fourth group was small for gestational age with or without medical problems.

All groups were followed at hospital discharge from NICU, at 18 and at 30 months, as well as at 4 and 8 years. Follow-up included comprehensive assessments. The study had low attrition, and researchers were blinded to the neonatal status of the children.

*Advance:* Change in neurologic classification over time varies as a function of the nature and types of neonatal illness and complications, and these changes affect cognitive and school achievement outcomes. The patterns over the long follow-up indicate that factors other than low birth weight and gestational age alone are important to cognitive and school achievement outcomes. A steady increase in abnormal neurologic status occurred in the two groups of children who were discharged from NICU with major problems.

*Implications:* Though NICU survival has improved, the incidence of diseases and complications in the neonatal period have remained stable. The present study indicates that neonatal medical status is an important variable affecting cognitive and school performance. A child with negative neurologic findings at 18 months or later may require early intervention services at 18 and 30 months of age, speech or physical therapies at preschool age and additional school resources at school age.

McGrath MM, Sullivan MC, Lester BM, and Oh W: Longitudinal neurologic follow-up in neonatal intensive care unit survivors with various neonatal morbidities. *Pediatrics* 106: 1397-1405, 2000.

## **Predicting Left Ventricular Hypertrophy in Young Hypertensive African-American Men**

*Background:* The vast incidence of hypertension means that not every individual with hypertension reasonably can be screened for end-organ damage stemming from the hypertension. Additionally, achieving hypertension control (a relatively normal blood pressure) is not sufficient to determine if end organ damage is occurring or progressing.

While microalbuminuria is a predictor of cardiovascular events in hypertension, if target organ damage such as left ventricular hypertrophy (LVH) and proteinuria is found, more aggressive treatment is recommended by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. African-Americans are at particularly high risk for hypertension-related renal failure and left ventricular hypertrophy. A random spot urine test was used to measure albumin/creatinine ratio, as a predictor of left ventricular hypertrophy.

*Advance:* For African-American subjects, the mean age was 41 years, and the mean blood pressure reading was 157/107. Echocardiogram evidence of left ventricular hypertrophy was present in 27.5 percent of the subjects. A significant correlation was found between echocardiogram evidence of left ventricular mass and urinary albumin/creatinine ratio. The single void, simple, inexpensive urine albumin/creatinine ratio is a predictor of left ventricular mass in young, inner-city, African-American men with hypertension not on medical therapy. The test is practical and less expensive than other tests that might be used to screen for end organ damage.

*Implications:* The population of young, African-American, urban men is particularly difficult to recruit into screening and treatment for chronic disease. Echocardiograms are not always available in an outpatient or store-front health care setting. Having a simple, inexpensive test that helps screen patients who already have evidence of organ damage from untreated or inadequately treated hypertension helps target those patients for special effort, since they have the most to gain from aggressive antihypertensive therapy.

Post WS, Blumenthal RS, Weiss JL, Levine DM, Thiemann DR, Gerstenblith G, and Hill MN: Spot urinary albumin—creatinine ratio predicts left ventricular hypertrophy in young hypertensive African-American men. *American Journal of Hypertension* 13: 1168-1172, 2000.