

SCIENCE CAPSULES

Sugar May Help Cystic Fibrosis Patients Avoid Infection. A sugar known as xylitol, reported to prevent dental caries and acute ear infections, may offer protection against bacteria that would otherwise infect cystic fibrosis (CF) patients. Researchers demonstrated that xylitol prevents infection in respiratory tissues by lowering the salt concentration of liquid secreted by tissues from CF and non-CF subjects. In addition, xylitol given in the form of a nasal spray significantly decreased the number of staphylococci present in the nasal passages of healthy volunteers. These results support the concept that lowering the salt concentration on airway surfaces enhances the airway's innate antibacterial defense system and suggest that xylitol-like therapeutics may prevent or slow the onset of bacterial infection in CF.

Zabner J, Seiler MP, Launspach JL, Karp PH, Kearney WR, Look DC, Smith JJ, and Welsh MJ: The osmolyte xylitol reduces the salt concentration of airway surface liquid and may enhance bacterial killing. Proceedings of the National Academy of Sciences USA 10: 11614-11619, 2000.

Studies Reveal Differences in Effectiveness of Common Asthma Treatments. Asthma is a chronic lung disease that affects more than 15 million Americans and is estimated to cost the U.S. economy \$12.3 billion a year in health care expenditures and lost productivity. Two NIH studies comparing treatments for adults with mild-to-moderate persistent asthma recently established that long-acting beta-agonists (LABs) are not as effective as inhaled corticosteroids (ICS) for reducing asthma attacks. However, when LABs are used regularly to supplement treatment with ICS, they can improve asthma control and enable substantial reductions in steroid doses. Providing the approximately 6 million patients who have moderate persistent asthma with what is scientifically demonstrated to be the best available treatments not only will reduce their morbidity from the disease, but also will reduce the burden asthma imposes on the U.S. economy.

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, Drazen JM, Ford JG, Israel E, Martin RJ, Mauger EA, Nachman SA, Spahn JD, and Szeffler SJ: Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. The Journal of the American Medical Association 285: 2583-2593, 2001.

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, Ford JG, Israel E, Kraft M, Martin RJ, Nachman SA, Peters SP, Spahn JD, and Szeffler SJ: Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. The Journal of the American Medical Association 285: 2594-2603, 2001.

Phenserine Regulates Translation of β -Amyloid Precursor Protein Message: A New Target for Alzheimer's disease Drug Development. One of the major hallmarks of Alzheimer's disease (AD) is the appearance of senile plaques in brain. These plaques are primarily composed of amyloid β -peptide ($A\beta$), a toxic fragment formed when a larger protein called β -amyloid precursor protein (β APP) breaks down. Researchers are working to develop agents that reduce β APP expression. This study identified a new target for reducing levels of β APP in brain. The

investigators tested a drug called phenserine, originally developed to increase levels of the chemical messenger acetylcholine, which is depleted in the brains of people with AD. They discovered that phenserine can reduce levels of β APP in cells, through a mechanism independent of acetylcholine activity. It does this by inhibiting the formation of β APP. Current research is directed towards the design, synthesis, and development of agents that optimally and safely regulate β APP and A β levels with the aim of slowing or halting the molecular events that lead to AD.

Shaw KTY, Utsuki T, Rogers J, Yu QS, Sambamurti K, Brossi A, Ge YW, Lahiri DK, and Greig NH: Phenserine regulates translation of β -amyloid precursor mRNA by a putative interleukin-1 responsive element, a new target for drug development. Proceedings of the National Academy of Sciences USA 98: 7605-7610, 2001.

Cytokine TGF- β 1 Reduces Plaque Burden in Transgenic Mice. Abnormal accumulation of the amyloid- β peptide (A β) in the brain may be crucial to the development of Alzheimer's disease (AD), but the underlying mechanisms remain unknown. Epidemiological studies as well as studies of inflammation in AD brain have suggested that an overall reduction in brain inflammation might reduce the risk of developing AD. In addition, it is known that high levels of transforming growth factor- β 1 (TGF- β 1, a cytokine that is part of the inflammatory response to injury) can increase the deposition of amyloid in cerebral blood vessels and may have a role in AD pathology. New lines of transgenic mice were established in which the effect of TGF- β 1 on deposition of human A β plaques in the brain and its blood vessels can be examined. Results from this study suggest that particular components of the inflammatory response in brain, for example microglial activation in response to high levels of TGF- β 1, might act to reduce, not elevate, plaque levels in brain tissue. Better understanding of this process could lead to the development of treatments for AD as well as for the hemorrhage that can occur with vascular disease and stroke.

Wyss-Coray T, Lin C, Yan F, Yu GQ, Rohde M, McConlogue L, Masliah E, and Mucke L: TGF- β 1 promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice. Nature Medicine 7: 612-618, 2001.

Treating the Catabolic Effects of Burns. Following severe burn, individuals often have an elevated metabolism characterized by significant breakdown of skeletal muscle mass (catabolism) that can extend well past wound healing and dramatically hinder a return to normal life. In a series of studies, important variables that predict the risk of excessive catabolism have been identified, and anabolic therapies (oxandrolone and recombinant human growth hormone) to counteract these effects have been tested with positive results.

Hart DW, Wolf SE, Chinkes DL, Gore DC, Mlcak RP, Beauford RB, Obeng MK, Lal S, Gold WF, Wolfe RR, and Herndon DN: Determinants of skeletal muscle catabolism after severe burn. Annals of Surgery 232: 455-465, 2000.

Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, Wolfe RR, and Herndon DN: Anabolic effects of oxandrolone after severe burn. Annals of Surgery 233: 556-564, 2001.

Hart DW, Herndon DN, Klein G, Lee SB, Celis M, Mohan S, Chinkes DL, and Wolf SE: Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Annals of Surgery* 232: 827-834, 2001.

Cognitive-Behavioral Therapy for Treatment of Bulimia Nervosa. Investigators in two academic medical centers tested the relative efficacy in ameliorating bulimic symptoms of two forms of psychotherapy – cognitive-behavioral therapy (CBT), an approach that concentrates on defining how a person’s behaviors have an impact on problems that contribute to illness, and interpersonal therapy (IPT), an approach that addresses health problems by focusing strictly on current conflicts and interpersonal problems. Subjects with the eating disorder bulimia nervosa were randomized to receive either CBT or IPT weekly over 20 weeks, and then followed up 1 year post-treatment. Among those completing the full course of treatment, 45 percent of the CBT group versus 8 percent of the IPT group achieved recovery by the end of the acute treatment period. CBT responders also showed quite stable maintenance of their treatment gains, with 40 percent of treatment completers still recovered at the 1-year follow-up point. While IPT acted more slowly, however, it tended to produce delayed improvements that continued to mount subsequent to treatment, such that 27 percent of IPT completers were judged recovered at follow-up (less than for CBT, but not a statistically significant difference). Analysis of change in different symptom clusters indicated that CBT was superior in altering the primary behavioral symptoms associated with bulimia nervosa, whereas both therapies were equivalent in treating depressive symptoms that are also common in these patients (as measured on such dimensions as weight and shape concerns, self-esteem, and interpersonal functioning). The investigators concluded that CBT is to be considered the preferred treatment for bulimia nervosa because it produces clinical benefits more quickly than IPT and, overall, is efficacious with a larger percentage of patients.

Agras WT, Walsh BT, Fairburn CG, and Wilson GT: A multicenter comparison of cognitive-behavioral therapy and interpersonal psychotherapy for bulimia nervosa. *Archives of General Psychiatry* 57: 459-466, 2000.

“Continuation Phase” Psychotherapy Can Help Prevent Recurrence of Depression. Eighty percent of patients who have recovered from major depressive disorder (MDD) relapse in the absence of prophylactic treatment. To reduce this risk, clinicians often prescribe continuation phase antidepressant medication to prevent relapse (should the index episode continue) and maintenance medication to prevent recurrence (i.e., a new episode). Although cognitive therapy (CT) may reduce relapse and recurrence when patients learn to use the associated skills over time, the long term effects of CT have not been well specified. Investigators have developed an intervention called “continuation-phase CT” (C-CT). Initially, they treated patients with major depression for 20 sessions of CT. Unmedicated responders were randomized to either 8 months of C-CT or control (evaluation without CT). Over the 8-month intervention period, C-CT significantly reduced relapse rates more than control (10 percent versus 31 percent). Over 24 months, C-CT significantly reduced relapse and recurrence estimates among patients with early onset MDD (16 percent versus 67 percent in control) and among those with an unstable remission during the acute treatment phase (37 percent versus 62 percent for the control group).

Findings suggest that 8 months of C-CT significantly reduced relapse and recurrence in the highest risk patients with recurrent MDD.

Jarrett RB, Kraft D, Doyle J, Foster BM, Eaves GG, and Silver PC: Preventing recurrent depression using cognitive therapy with and without a continuation phase. Archives of General Psychiatry 58: 381-387, 2001.

Depression in Alzheimer's Disease Patients is Treatable. A recent clinical trial compared treatment with a modern antidepressant (sertraline) to placebo in 22 depressed individuals with Alzheimer's disease. Preliminary results indicated that more of the antidepressant-treated subjects improved compared to the placebo-treated ones. These results underscore the need to treat the depression that co-occurs with Alzheimer's disease.

Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, Brandt J, and Rabins PV: Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the depression in Alzheimer's disease study. American Journal of Psychiatry 157: 1686-1689, 2000.

Antisense Therapy May Make Sense for Alzheimer's Disease. The logic of antisense therapy is quite compelling. The DNA of our genes directs the formation of RNA which cells read out to form proteins. Every DNA and RNA strand has an exact complement, like the two strands of the DNA double helix. So, introducing a molecule that is the exact match (antisense) for an RNA that codes for a harmful protein should lock up the RNA and prevent the production of that protein. In practice, however, success has been limited by the difficulty of delivering antisense molecules where needed. Now, scientists have developed a chemically modified type of antisense molecule directed against amyloid beta protein, which forms clumps in the brains of people with Alzheimer's and contributes to the disease. When introduced intravenously, the antisense agent reversed learning and memory deficits in mice with an Alzheimer's-like disease. Much work is needed before such a treatment could safely be applied to people, but the tantalizing potential of antisense therapy for many diseases may be moving closer.

Banks WA, Farr SA, Butt W, Kumar VB, Franko MW, and Morley JE: Delivery across the blood-brain barrier of antisense directed against amyloid β : reversal of learning and memory deficits in mice overexpressing amyloid precursor protein. Journal of Pharmacology and Experimental Therapeutics 297: 1113-1121, 2001.

Neurotrophins and the Blood-brain Barrier. Neurotrophins are natural chemical signals that regulate survival of cells during development of the nervous system and in the adult brain. Animal studies show the promise of these chemicals for therapy of several brain disorders, but neurotrophins, like many large molecules, do not pass through the protective "blood-brain barrier" that isolates the brain from the general circulation. Now, two independent strategies in animals have circumvented the blood-brain barrier and invoked the beneficial effects of neurotrophins. One study administered adenosine, a smaller signaling molecule that penetrates the blood-brain barrier and mimics, indirectly, neurotrophins. The other approach linked the neurotrophin molecule to a chemical tag that directs cells of the barrier to actively transport it

into the brain. Enough neurotrophin reached the brain in this study to protect rats from an experimental stroke.

Lee FS and Chao MV: Activation of Trk neurotrophin receptors in the absence of neurotrophins. Proceedings of the National Academy of Sciences USA 98: 3555-3560, 2001.

Zhang Y and Pardidge W: Neuroprotection in transient focal brain ischemia after delayed intravenous administration of brain-derived neurotrophic factor conjugated to a blood-brain barrier drug targeting system. Stroke 32: 1378-1384, 2001.

Encouraging Nerve Cells to Grow with Integrins. Scientists have identified barriers to growth in the adult brain and spinal cord that are partly responsible for the failure of nerve cells to regenerate following damage. We know less about why adult nerve cells in the brain and spinal cord seem to have diminished intrinsic growth ability even in conditions that encourage growth. New findings show that the adult cells make less of proteins called integrins through which nerve cells interact with their surroundings. When researchers restored the embryonic levels of integrins in adult cells through genetic engineering, the cells showed dramatically improved growth ability in cell culture conditions designed to mimic the adult brain and spinal cord. Manipulating the intrinsic growth potential of adult nerve cells, combined with procedures to counteract growth inhibitors, may yield new approaches to repairing the damaged brain and spinal cord.

Condic ML: Adult neuronal regeneration induced by transgenic integrin expression. Journal of Neuroscience 21: 4782-4788, 2001.

Stretching Nerve Fibers to Help Them Grow. Scientists have learned how to encourage nerve fibers, or axons, to grow by mechanically stretching them. Researchers developed the idea by considering the ability of axons that are already connected to grow as the body grows. They devised a method of growing nerve cells on a material that can be naturally absorbed by the body and used a motorized device to slowly pull connected nerve cells, at a rate of 3.5 thousandths of a meter every 5 minutes. The axons elongated by a remarkable 1 centimeter in 10 days of stretch and formed bundles, like those that occur naturally, which might serve as a framework to encourage other nerve cells to grow across damaged areas. Adapting this procedure may someday allow transplanting bridges to help foster recovery from spinal cord injury and other damage to long nerve fibers, such as the optic nerve or the nerves of the body.

Smith DH, Wolf JA, and Meany DF: A new strategy to produce sustained growth of central nervous system axons: continuous mechanical tension. Tissue Engineering 7: 131-139, 2001.

Less Toxic Treatment for Patients with Chronic Granulomatous Disease. Chronic Granulomatous Disease (CGD) is an inherited immune deficiency characterized by a defect in a specific white blood cell, the phagocyte, which renders the affected individual susceptible to bacterial and fungal infections. CGD patients suffer from severe recurrent infections and have a

shortened life expectancy. While immune therapy and antibiotics are utilized as the first line of treatment to prevent infections in patients with CGD, transplantation of stem cells derived from the bone marrow of a matched donor has also been utilized for patients with chronic illness and debilitation. This treatment is suboptimal, however, as it requires toxic levels of radiation to eliminate immune cells in the patient's bone marrow prior to replacement with donor-matched cells. Recently, NIH scientists developed a new transplantation regimen for CGD patients that involves chemotherapy but does not require the use of radiation, and demonstrated its effectiveness as an alternative treatment for CGD. This advance should lead to increased life expectancy for chronically ill CGD patients who require transplantation.

Horwitz ME, Barrett AJ, Brown MR, Carter CS, Childs R, Gallin JI, Holland SM, Linton GF, Miller JA, Leitman SF, Read EJ, and Malech HL: Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. The New England Journal of Medicine 344: 881-888, 2001.

Structured Intermittent Therapy Can Control Simian Immunodeficiency Virus in Monkeys. Highly active antiretroviral therapy (HAART) involving treatment with a combination of several antiretroviral drugs (ARs), has dramatically improved the long-term prognosis for individuals infected with human immunodeficiency virus (HIV), resulting in reduced morbidity and mortality rates in the U.S. and other developed countries where HAART has become the standard treatment for HIV/AIDS. Unfortunately, patients on HAART, which is taken daily for the remainder of life, often suffer from toxic side effects characteristic of ARs. Several groups of investigators have attempted to alleviate these side effects by experimenting with structured treatment interruptions (STI), periods of drug treatment interspersed with periods when therapy is discontinued. Recently, NIH scientists demonstrated in monkeys infected with the simian immunodeficiency virus, the analog of HIV in humans, that implementing STI shortly after infection is as effective as continuous HAART treatment. This advance provides validation for the continued pursuit of STI regimens to treat humans with HIV/AIDS.

Lori F, Lewis MG, Xu J, Varga G, Zinn DE Jr, Crabbs C, Wagner W, Greenhouse J, Silvera P, Yalley-Ogunro J, Tinelli C, and Lisziewicz J: Control of SIV rebound through structured treatment interruptions during early infection. Science 290: 1591-1593, 2000.

Early Treatment of HIV-1 Leads to Augmented Immune Responses in the Chronic Phase of Infection. What makes HIV such an insidious infectious disease is that it attacks the immune system, which is the system the body uses to clear infection. HIV disables the immune system by infecting "helper T cells," the subset of immune system cells that play a central role in the immune response by signaling to other immune cells to perform their special functions. Studies involving patients who have been treated with highly active antiretroviral therapy (HAART) during the acute (early) stage of HIV infection, demonstrate that HAART can successfully control HIV virus replication, enabling the immune system to mount a strong response during this stage of infection. However, the impact of early HAART treatment on the long-term performance of the immune system remained undetermined. Recently, NIH scientists demonstrated in patients who had received early phase treatment, but subsequently discontinued

(and later restarted) the treatment, that the benefits of early HAART treatment on immune system function are maintained for at least 5 to 8 months. These findings provide a rationale to explore the development of therapies that strengthen immune response by augmenting helper T-cell function.

Rosenberg ES, Altfeld M, Poon SH, Phillips MN, Wilkes BM, Eldridge RL, Robbins GK, D'Aquila RT, Goulder PJR, and Walker BD: Immune control of HIV-1 after early treatment of acute infection. Nature 407: 523-526, 2000.

Higher Dose of Acyclovir Proves Effective Against Newborn Herpes Virus Infections.

Morbidity and mortality in neonatal herpes simplex virus (HSV) disease remain high despite treatment with acyclovir. Recently, NIH-supported scientists demonstrated that administration of high-dose acyclovir reduced mortality by 50 percent in newborns with disseminated herpes simplex virus, the most severe form of HSV disease. Although treatment side-effects are a consideration, this information will aid physicians in the management of neonatal HSV disease.

Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM, Gutierrez K, Shelton M, Weiner LB, Sleasman JW, Murguía de Sierra T, Weller S, Soong SJ, Kiell J, Lakeman FD, and Whitley RJ: Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 108: 230-238, 2001.

Successful Gene Therapy Prevents Kidney Rejection in a Large Animal Model. Major histocompatibility complex (MHC) molecules are present on the surface of almost every cell. Two individuals rarely share a matching set of MHC molecules, and in a solid organ transplant, graft rejection results when the recipient's immune system targets the mismatched MHC molecules. Graft recipients, therefore, must rely on potent immunosuppressive medications to control rejection. An alternative to lifelong immunosuppression is immune tolerance, that is, turning off the immune response to the grafts while leaving other protective immune responses intact. An NIH-supported researcher and colleagues have induced miniature swine to tolerate MHC-mismatched kidney transplants. Prior to transplantation, the researchers genetically modified the bone marrow of the recipient swine so that the marrow cells expressed the MHC genes of the kidney donor. With only a short course of immunosuppressive agents, treated animals maintained their transplants for up to three years. Control animals rejected their kidney transplants within two months. These results suggest that gene therapy has the potential to prevent graft rejection without long-term immunosuppression.

Sonntag KC, Emery DW, Yasumoto A, Haller G, Germana S, Sablinski T, Shimizu A, Yamada K, Shimada H, Arn S, Sachs DH, and LeGuern C: Tolerance to solid organ transplants through transfer of MHC class II genes. Journal of Clinical Investigation 107: 65-71, 2000.

Incentive to Work Helps to Keep Addicts Drug Free. An experimental program has been successful in helping drug-abusing women stay free of drugs by paying them a salary to attend a work/training program. In the Therapeutic Workplace, women in drug treatment are hired and paid to either perform assigned jobs or to participate in job training. To link salary to drug abstinence, patients are required to provide drug-free urine samples to gain daily access to the workplace. Program participation nearly doubled the patients' abstinence from opiates and

cocaine, as determined by urine samples collected three times a week during the six-month study. Over the course of the program, 59 percent of the urine samples from the workplace women were drug-free, compared to 33 percent of the samples from a control group of women. Forty percent of the Therapeutic Workplace participants had drug-free urine samples on at least 75 percent of testing occasions; in contrast, only 10 percent of the control participants did so. This project confirms the results of many years of previous research that demonstrate that reward-based treatment programs do result in decreased drug use. This program also exemplifies how research findings can be applied in real-world settings.

Silverman K, Svikis D, Robles E, Stitzer ML, and Bigelow GE: A reinforcement-based therapeutic workplace for the treatment of drug abuse: 6-month abstinence outcomes. Experimental and Clinical Psychopharmacology 9: 12-23, 2001.

The Consequences of Stroke Reduced in an Animal Model System. Therapy for acute ischemic (inadequate blood flow) stroke focuses on improving blood flow and minimizing biochemical and physiological responses that increase cell losses. Administration of hyperbaric oxygen, or oxygen at greater than atmospheric pressure, is one of the therapies that has been studied for this purpose. In an experimental rat model system, investigators demonstrated that by administering hyperbaric oxygen, the damaging effects of a stroke could be reduced. They proposed that the therapy prevents normally circulating white blood cells from becoming trapped in the area of the brain subject to reduced circulation during a stroke. When trapped, these cells break down and release toxic products that damage the vulnerable brain tissue. Further studies of the novel mechanism of action of hyperbaric oxygen may lead to improvements in our ability to reduce the consequences of a stroke.

Atochin DN, Fisher D, Demchenko IT, and Thom SR: Neutrophil sequestration and the effects of hyperbaric oxygen in a rat model of temporary middle cerebral artery occlusion. Undersea and Hyperbaric Medicine (in press 2001).

Labeling of Dietary Supplements May Differ from Actual Contents. Consumers of the dietary supplement ginseng believe that its use will increase the user's strength and energy. Ginseng-containing supplements are among the most popular medicines worldwide. However, because they can be prepared from a variety of plants, they are subject to botanical misidentification. With such a premise, one group of investigators examined 25 commercial products containing ginseng to determine if they contained the amount and type of ginseng consistent with their product labeling. The study showed that, although each product was appropriately labeled for the *type* of ginseng contained within, the *concentrations* of ginseng, as determined by analysis of marker of compounds, differed widely from that stated on the label. These results suggest that careful characterization and standardization of herbal products is a necessary step in the design and evaluation of studies using those products.

Harkey MR, Henderson GL, Gershwin ME, Stern JS, and Hackman RM: Variability in commercial ginseng products: an analysis of 25 preparations. American Journal of Clinical Nutrition 73: 1101-1106, 2001.

Botanicals Used in the Treatment of Menopausal Symptoms Possess Estrogenic Activity.

Women are increasingly using herbal remedies to treat menopausal symptoms, even though little is known about their efficacy or safety. Recent studies have begun to reveal underlying biochemical properties of some of these herbs. In a recent study, investigators evaluated eight of the botanical preparations most commonly purchased by women for the treatment of menopausal symptoms and found that three – red clover, hops, and chasteberry – showed significant estrogenic activity. This suggests that the three herbs might be popular remedies because they supplement the decreased estrogen in menopausal women. Additional studies are needed to determine whether the estrogen-like compounds work similarly to conventional estrogen replacement therapy or have different properties, and what effect those differences might have on the health of menopausal women.

Liu J, Burdette JE, Xu H, Gu C, van Breeman RB, Bhat KPL, Booth N, Constantinou AI, Pezzuto JM, Fong HHS, Farnsworth NR, and Bolton JL: Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. Journal of Agricultural Chemistry 49: 2472-2479, 2001.

Better Treatment for Blacks With Chronic Hepatitis C. Hepatitis C virus infects millions of people worldwide and in the U.S. Chronic hepatitis C is the most common cause of chronic liver disease and the most common indication for liver transplantation in this country. African-American patients have been reported to have a reduced rate of response to treatment with interferon, the most common therapy. This study showed that the impaired responsiveness of black patients to interferon monotherapy can be partially overcome by combining interferon with the drug ribavirin.

McHutchinson JG, Poynard T, Pianko S, Gordon SC, Reid AE, Dienstag J, Morgan T, Yao R, and Albrecht J: The impact of interferon plus ribavirin on response to therapy in black patients with chronic hepatitis C. Gastroenterology 119: 1317-1323, 2000.

Chemotherapy and Cognitive Function. Past research has shown that adult cancer survivors often have impaired memory and concentration after treatment with chemotherapy. Researchers reviewed previous research on this topic and concluded this area is understudied. In particular, they note that there has been no published research on the impact of various genetic factors on response to chemotherapy, and that the measures currently used to determine changes in cognitive functions are not sufficiently sensitive for standard-dose chemotherapy patients. Their review supports the need for additional research in the area.

Ahles TA: Cognitive effects of standard-dose chemotherapy in patients with cancer. Cancer Investigation (in press 2001).

Mechanism of HIV Drug Resistance. Soon after the introduction of the first anti-HIV drug zidovudine (AZT), mutations that confer resistance to the drug arose in some strains of the virus. It had been clear for some time that some of these mutations interfere with the incorporation of

AZT-like drugs into the virus's self-replication machinery. Recently, a second possible mechanism has been demonstrated – that the mutations actually cause the drug molecules to be excised (cut out) after they are incorporated into the virus. Scientists have now made an important discovery that provides new insights into how these mutations enhance the excision process, and how the mutations are able to target the excision specifically to AZT but not other drugs in the same class. Because the chemotherapeutic agents used to treat other microbial infections, as well as cancer, target similar molecular structures, this discovery may provide valuable clues to the mechanisms of drug resistance in a number of life-threatening diseases.

Boyer PL, Sarafianos SG, Arnold E, and Hughes SH: Selective excision of AZTMP by drug-resistant human immunodeficiency virus reverse transcriptase. Journal of Virology 75: 4832–4842, 2001.

Hsiou Y, Ding J, Das K, Clark AD Jr, Boyer PL, Lewi P, Janssen PAJ, Kleim JP, Rosner M, Hughes SH, and Arnold E: The lys103asn mutation of HIV-1 RT: a novel mechanism of drug resistance. Journal of Molecular Biology 309: 437-445, 2001.

Sarafianos SG, Das K, Tantillo C, Clark AD Jr, Ding J, Whitcomb JM, Boyer PL, Hughes SH, and Arnold E: Crystal structure of HIV-1 reverse transcriptase in complex with a polypurine tract RNA:DNA. European Molecular Biology Organization Journal 20: 1449-1461, 2001.

Interleukin 15 May Play A Role in Some Leukemias. Interleukin 15 (IL-15) is a protein that helps regulate the number of white blood cells in the body. High levels of IL-15 have been associated with childhood leukemias involving two types of white blood cells – T-cells and natural killer (NK) cells. Recently, researchers developed a mouse model that produced very high levels of IL-15. They found these mice first produced high levels of natural killer cells and CD8+ T cells; as the mice aged, they developed fatal leukemias. These results suggest that monitoring IL-15 levels in people with leukemia may be a way to track cancer progression or remission, or to better tailor chemotherapy to the individual patient.

Fehniger TA, Suzuki K, Ponnappan A, VanDeusen JB, Coopier MA, Florea SM, Freud AG, Robinson ML, Durbin J, And Caligiuri MA: Fatal leukemia in Interleukin 15 transgenic mice follows early expansions in natural killer and memory phenotype CD8+ T cells. Journal of Experimental Medicine 193: 219-231, 2001.

Melanoma and the p53 Gene. The gene p53 is often mutated in cancers but is functional in normal cells. Cells with functional p53 can be destroyed with radiation, while cells with mutated p53 often cannot. In some skin cancers (melanomas), p53 appears to be functional, but the cells do not respond to radiation. A recent study found that radiation leads to the removal of a phosphorus group on the p53 gene in normal skin cells, but not in skin cancer cells. If researchers could find a way to remove this phosphorus group in cancer cells, they may be able to make these cells respond to radiation therapy, thus increasing the effectiveness of the treatment.

Satyamoorthy K, Chehab NH, Waterman MJF, Lien MC, El-Dieiry WS, Herllyn M, and Halazonetis TD: Aberrant regulation and function of wild-type p53 in radioresistant melanoma cells. Cell Growth and Differentiation 11: 467-479, 2000.

Nephrectomy and Advanced Renal Cell Cancer. Prior studies have suggested a potential benefit of removal of the affected kidney (nephrectomy) in patients whose renal cell cancer had spread beyond the kidney (metastatic disease). In a recent study of 246 persons with metastatic renal cell cancer, patients were either given interferon-alpha therapy alone or received a nephrectomy followed by the same dose and schedule of interferon-alpha as those patients who did not undergo surgery. Results demonstrated that patients who underwent nephrectomy lived longer, and were more likely to be alive one year after treatment, than those who did not have a nephrectomy. These findings show that nephrectomy prior to adjuvant biologic therapy (interferon-alpha) improves the outcome in patients with metastatic kidney cancer. For patients who are fit enough to undergo nephrectomy and adjuvant interferon therapy, this two-phase treatment regimen may define a new standard of care and will serve as a reference for future clinical trials.

Flanigan RC, Blumenstein BA, Salmon S, and Crawford Ed: Cytoreduction nephrectomy in metastatic renal cancer: the results of southwest oncology group trial 8949. Proceedings of the American Society of Clinical Oncology 19: 2a, 2000.

Role for p38 Kinase Signaling in the Cellular Responses to Cytotoxic Agents. Cells have many mechanisms to prevent damage by toxic agents. Breakdown in these mechanisms can eventually lead to cancer. Researchers have uncovered two important functions of the enzyme p38 that offer insight into how cancer is initiated: 1) p38 activates the p53 gene, which normally responds to toxic agents by initiating the death of damaged cells. Without p38, p53 does not function properly. If researchers could find a way to block p38, they could protect normal cells from death after exposure to chemotherapy or radiation therapy. Tumor cells usually lack functional p53, so inhibition of p38 will protect normal cells but not tumor cells from chemotherapy-induced apoptosis (cell death). And, 2) p38 inhibits an enzyme called Cdc25B phosphatase, which helps initiate mitosis (cell division). When p38 is present, cell division is delayed, giving cells time to repair damage caused by toxins. Without p38, damaged cells will divide, which could lead to cancer. These results indicate that p38 may well be an important molecular target for experimental therapies.

Bulavin DV, Saito SI, Hollander MC, Sakaguchi K, Anderson CW, Appella E, and Fornace AJ Jr: Phosphorylation of human p53 by p38 kinase coordinates N-terminal phosphorylation and apoptosis in response to UV radiation. European Molecular Biology Organization Journal 18: 6845-6854, 1999.

Bulavin DV, Higashimoto Y, Popoff IJ, Gaarde WA, Basrur V, Potapova O, Appella E, and Fornace AJ Jr: Initiation of a G2/M checkpoint after UV radiation requires p38 kinase. Nature 411: 102-107, 2001.

Improved Outcomes for Children with a Deadly Form of Leukemia. Acute lymphoblastic leukemia (ALL) is the most common cancer in children. In about 15 percent of cases, children have a form of the disease known as T-cell ALL; these children tend to have poorer prognoses than children with other forms of the disease. Now, results from a clinical trial provide

convincing evidence of improved outcomes for children with T-cell ALL who receive high-dose methotrexate in addition to a multi-drug chemotherapy regimen. In this study, eighty-six percent of children who received high-dose methotrexate survived disease-free for at least three years, compared with 72 percent of children who received standard therapy. These are the best results for treatment for T-cell ALL published to date; the investigators anticipate that future trials attempting to improve outcome for children with T-cell ALL will build upon this treatment approach.

Asselin B, Shuster J, Amylon M, Halperin E, Hutchison R, Lipshultz S, and Amitta B: Improved event-free survival (EFS) with high dose methotrexate (HDM) in T-cell lymphoblastic leukemia (T-ALL) and advanced lymphoblastic lymphoma (T-NHL): A Pediatric Oncology Group (POG) study. Proceedings of the American Society of Clinical Oncology 20, Abstract Number 1464, 2001.

Low-fat, High-fiber Diet Does Not Reduce the Risk of Precursor to Colorectal Cancer.

Lifestyle factors, such as diet and physical activity, are thought to influence the development of colorectal cancer, the second leading cause of cancer death in the U.S. Researchers at the NIH conducted a nutritional intervention study to determine whether adults at high risk for colorectal cancer can reduce their risk through diet. This study, the Polyp Prevention Trial, looked at the effect of the levels of dietary fat and fiber, and the number of fruits and vegetables consumed each day, on the growth of new adenomatous polyps in persons with a prior history of polyps. Adenomatous polyps are precursors of most large-bowel cancers, and individuals whose polyps are removed often have a recurrence of polyps within 3 years. The study failed to show that a diet low in fat and high in fiber, fruit, and vegetables reduced the risk of recurrent colorectal adenomas. Additional studies are needed, however, since the study had some limitations. Furthermore, a low-fat, high fiber diet is still beneficial in preventing and managing heart disease and other medical conditions.

Schatzin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, and Cahill J: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. The New England Journal of Medicine 342: 1149-1155, 2000.

Combination Therapy Improves Outcomes for Patients with Stomach Cancer. Successful treatment of persons with gastric (stomach) cancer who have undergone surgery for their disease varies considerably, with only 5 to 40 percent of these patients considered cured of their cancer. A recent study of 603 patients with cancer of the stomach or gastroesophagus (GE) showed that both disease-free survival and overall survival were improved in patients who had surgery followed by chemotherapy and radiation treatment, as opposed to the standard treatment of surgery alone. On the basis of these findings, postoperative chemoradiation may now be considered a standard of care for high risk patients with resected locally advanced adenocarcinoma of the stomach and GE junction. The investigators did note that despite the success of this trial, caution is warranted because the tolerability of the combined treatment depended on extremely fastidious radiation quality control, including frequent adjustments to minimize serious toxicity.

Macdonald JS, Smalley S, Benedetti J, Estes N, Haller DG, Ajani JA, Gunderson LL, Jessup M, and Martenson JA: Postoperative combined radiation and chemotherapy improves disease-free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and G.E. junction. Results of Intergroup Study INT-0116 (SWOG 9008). Proceedings of the American Society of Clinical Oncology 19: A1, 2000.

Yeast Vaccine Stimulates the Immune System Against Cancer Cells. Researchers have developed a new anti-cancer vaccine using recombinant yeast – that is, yeast that has been engineered to produce specific antigens, or substances that activate the immune system. This vaccine, when administered to mice who were inoculated with lymphoma cells, was found to activate dendritic cells, which are specialized cells that are important to the immune response, and to boost immune function; the vaccine proved to protect the mice against the lymphoma cells. While this approach is still under study, the use of recombinant yeast in vaccines could provide a powerful strategy against cancer and a variety of other infectious diseases.

Stubbs AC, Martin KS, Coeshott C, Skaates SV, Kuritzkes DR, Bellgrau D, Franzusoff A, Duke RC, and Wilson CC: Whole recombinant yeast vaccine activates dendritic cells and elicits protective cell-mediated immunity. Nature Medicine 7: 625-629, 2001.

New Protein Promotes Corneal Wound Healing. In the cornea, wound healing occurs in ordered stages by a combination of processes. To prevent infection and restore visual clarity, the cornea must respond rapidly to injury. NIH researchers have found a new protein that promotes wound healing in the eyes of animal models. The protein, Thymosin beta 4, accelerates epithelial cell migration and decreases damaging inflammation. It enhances the tight connection between the cells, thereby preventing fluid loss and penetration by bacteria. This compound will have clinical use in repairing surgically treated eyes as well as injuries induced by trauma.

Sosne G, Chan CC, Thai K, Kennedy M, Szliter EA, Hazlett LD, and Kleinman HK: Thymosin beta 4 promotes corneal wound healing and modulates inflammatory mediators in vivo. Experimental Eye Research 72: 605-608, 2000.

Antigene Radiotherapy for Multidrug-resistance in Cancer Through Use of New Radiopharmaceuticals. Antigene radiotherapy is a new approach for targeting disease-related genes with special type of radioisotopes, so-called Auger-electron emitters that produce damage within an extremely short range. This approach is being applied to target and “knock out” the human multidrug-resistance gene (*MDR1*) that encodes a multidrug transporter, responsible for the increased resistance to anti-cancer drug therapies. The problem of multidrug-resistance is a major impediment in successful cancer chemotherapy. Short pieces of DNA carrying Auger-electron emitters were designed to target specifically a sequence within the *MDR1* gene. Experiments with cultured KB-V1 cancer cells showed that the designed radiopharmaceuticals can produce breaks in both DNA strands of the target sequence that should result in “knock out” of the *MDR1* gene.

Sedelnikova OA, Panyutin IG, Luu AN, Reed, MW T, Licht T, Gottesman MM, and Neumann RD: Targeting of the human *MDR1* gene by 125I-labeled triplex-forming oligonucleotides. Antisense and Nucleic Acid Drug Development 10: 443-452, 2000.

Sedelnikova OA, Luu AN, Karamychev VN, Panyutin IG, and Neumann RD: Development of DNA-based radiopharmaceuticals carrying auger-electron emitters for antigene radiotherapy. International Journal of Radiation Oncology, Biology, Physics 49: 391-396, 2001.

Workplace Issues Affect Nurse Workforce. Media reports on the nursing shortage, medical errors, and uneven quality of patient care have gained public attention. A recent survey of over 43,000 nurses in 5 countries found widespread discontent. In the US, more than 40 percent of responding nurses expressed dissatisfaction with their jobs, and 43 percent scored in the high burnout range for job-related stress. Across all five countries, 17 to 39 percent of nurses plan to leave their jobs within the next year. General concerns included poor workplace environment, adequacy of staffing, scheduling problems, provision of ancillary services, loss of nurse executive positions, and lack of management support, while areas of job satisfaction included good working relationships with physicians and satisfaction with current pay. These responses reflect long-term problems within the profession.

Aiken LH, Clarke SP, Sloane DM, Sochalski JA, Busse R, Clarke H, Giovannetti P, Hunt J, Rafferty AM, and Shamian J: Nurses' reports on hospital care in five countries. Health Affairs 20: 43-53, 2001.

Transitional Care Model. Many in the U.S. are attempting to improve the prenatal and maternal outcomes of death and disease complications. A model of delivering care by advanced practice nurses has been tested with other patient populations. The 170 women and 194 infants randomized into a treatment group, compared to those in the "usual care" group, had 2 versus 9 infant deaths, 11 fewer preterm births, 77 percent versus 33 percent of twin pregnancies carried to term and fewer prenatal and infant rehospitalizations. Compared to "usual care" mothers and infants, the improved outcomes among the mothers and infants in the new model of care saved 750 hospital days and about \$2.5 million. The new model of care has addressed an important health disparity for a vulnerable population subject to poor pregnancy outcomes.

Brooten D, Youngblut JM, Brown L, Finkler SA, Neff DF, and Madigan E: A randomized trial of nurse specialist home care for women with high-risk pregnancies: outcomes and costs. American Journal of Managed Care 7: 793-803, 2001.

Folate Levels Related to Restless Legs Syndrome in Pregnant Women. Researchers examined data from women before, during, and after pregnancy, to study the prevalence of restless legs syndrome (RLS), a sleep disturbance involving unpleasant sensation and movement in the legs. Of those women who became pregnant, 23 percent reported experiencing RLS during their third trimester. The RLS sufferers had significantly lower serum levels of folate. They also had more difficulty falling asleep and a more depressed mood state. These findings indicate a need to reconsider what normal values are for ferritin and folate during pregnancy, as

well as dietary recommendations for folate in pregnant women. Results may be better night time sleep, improved daytime mood, and higher quality of life among pregnant women with RLS.

Lee, KA, Zaffke ME, and Baratte-Beebe K: Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. Journal of Women's Health & Gender-Based Medicine 10: 335-341, 2001.

Comparing Costs of Birth Centers to Traditional Maternity Care. Maternity care is one of the most common health care services provided in the U.S., with total costs exceeding \$20 billion in 1992. Nurse researchers analyzed the total costs in a small rural community of low-risk maternity care for a freestanding birth center (FSBC), and compared those costs with those for the traditional medical model of care. While patient satisfaction was higher with the FSBC, and clinical outcomes were similar, the total costs were not significantly different, perhaps due to lower patient volumes at the FSBC.

Stone PW, Zwanziger J, Walker PH, and Buenting J: Economic analysis of two models of low-risk maternity care: A freestanding birth center compared to traditional care. Research in Nursing and Health 23: 279-289, 2000.

Expansion of Umbilical Cord Stem Cells for Transplantation. Studies of cell-based therapies to treat a number of diseases have found that the transplantation of umbilical cord cells can be a useful alternative to the transplantation of bone marrow. Cord blood stem cells have a number of important advantages over bone marrow: They are easier to obtain than stem cells from bone marrow; treatments using cord blood stem cells can be less costly than bone marrow transplants; and, perhaps most importantly, cord blood stem cells are a perfect match for the child from whom they are collected, thus eliminating the difficult process of finding a matching donor and minimizing the risks of rejection. This is especially significant for ethnic minority populations who tend to be under-represented in the National Marrow Donor Program. The number of stem cells from the cord and placenta is usually insufficient for successful transplantation of those recipients who have a large body mass. Scientists, therefore, seek to improve culture systems in order to “expand” umbilical cord blood stem cells – the higher the dose of cells, the faster the transplanted cells will engraft and the better the chance of cure. To this end, researchers developed a culture method to successfully expand a population of stem cells (called CD34⁺) from umbilical cord blood for as long as 14 days. Moreover, after transplantation to an immunodeficient strain of mouse, some of the cells differentiated into mature blood cells, while other cells retained their stem cell status. When the progeny of the stem cells were recovered from the animals, they were found to retain their multilineage differentiation potential for up to 28 additional days. When the cells were then re-transplanted to a secondary animal and harvested once again, the stem cell progeny of the transplanted cells could be maintained for up to 14 more days in culture. This series of experiments showed, for the first time, that umbilical cord stem cells can be maintained and expanded while retaining multilineage differentiation potential over an extended period of time. This knowledge could lead to the development of culture systems for clinically feasible expansion of cord stem cells, and to long-term engraftment of these cells in human clinical trials.

Lewis ID, Almeida-Porada G, Du J, Lemischka IR, Moore KA, Zanjani ED, and Verfaillie CM: Umbilical cord blood cells capable of engrafting in primary, secondary, and tertiary xenogeneic hosts are preserved after ex vivo culture in a noncontact system. Blood 97: 3441-3449, 2001.