

SCIENCE CAPSULES

Animal Models Show Role of Estrogen in Body Fat Accumulation with Age. Obesity is a significant and growing health problem in the U.S. Several recent studies have suggested that estrogen loss at menopause is associated with increased body fat in postmenopausal women. Increased fat mass occurring as abdominal visceral fat is associated with increased insulin resistance and a constellation of symptoms (hypertension, hyperlipidemia, atherosclerosis) known as syndrome X. Several new transgenic mouse models have been generated in which estrogen-related genes have been eliminated. These new models will permit exploration of how estrogen regulates body fat content. One strain of mice lacks the alpha form of the estrogen receptor, resulting in an increase in white adipose (fat) tissue with age. Another strain lacks the aromatase enzyme, which is involved in the biosynthesis of estrogen. Increased fat mass in both of these strains was associated with decreased spontaneous activity rather than overeating. These and other genetically modified mice provide powerful tools to study mechanisms by which estrogen influences age-dependent fat mass deposition.

Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, and Cooke PS: Increased adipose tissue in male and female estrogen receptor-_α knockout mice. Proceedings of the National Academy of Sciences USA 97: 12729-12734, 2000.

Jones MEE, Thorburn AW, Britt KL, Hewitt KN, Wreford NG, Proietto J, Oz, OK, Leury BJ, Robertson KM, Yao S, and Simpson ER: Aromatase-deficient (ArKO) mice have a phenotype of increased adiposity. Proceedings of the National Academy of Sciences USA 97: 12735-12740, 2000.

A Fly Model of Tau Neurodegeneration. One hallmark of Alzheimer's disease (AD) is abnormal collections of twisted filaments found inside nerve cells called neurofibrillary tangles. The chief component of these tangles is one form of a protein called *tau*. While *tau* gene mutations have not been linked to AD, *tau* mutations are associated with a group of dementias called hereditary frontotemporal dementia and parkinsonism, which are linked to chromosome 17 (FTDP-17). NIH-supported investigators have created a genetic model of *tau*-related neurodegenerative disease by introducing into fruit flies either a normal human *tau* gene or a mutant *tau* gene from FTDP-17. Fruit flies carrying mutant human *tau* mimic the *tau*-induced damage and symptoms seen in AD and FTDP-17, with the notable exception that neurodegeneration occurred without the neurofibrillary tangle formation seen in human disease and rodent models. If further research confirms that the neurodegeneration observed in the transgenic fruit flies is similar to that seen in human dementias, the fly model would be a useful tool to help researchers discover the molecular mechanisms that underlie *tau* neurotoxicity.

Wittman CW, Wszolek MF, Shulman JM, Salvaterra PM, Lewis J, Hutton M, and Feany M: Tauopathy in *Drosophila*: neurodegeneration without neurofibrillary tangles. Science (in press).

New Insights Into How a Gene Protects Our Health. p53 is a gene that plays a central role in protecting humans from cancer. Recent studies show that modifications of p53 influence its activity. Phosphorylation (addition of PO₃ groups) of p53 is intimately involved in cellular

responses to specific types of stress. Identification of specific phosphorylation sites on p53 and direct linkage to p53-mediated effects have historically not been very straightforward. Site-specific determination of phosphorylation often involves the use of radionuclides. Various stressors activate enzymes that modify p53 from its basal phosphorylated state to a stabilized and activated form capable of regulating cell growth, survival, or death. Sophisticated methods for measuring the fine structure of p53 by mass spectrometric analysis would be helpful in relating gene phosphorylation to biological activity. Recent studies have demonstrated the power of mass spectrometric analysis in relating the structural biology of the human p53 molecule to its tumor suppressor effects. Using a combination of several isolation techniques combined with mass spectrometric analysis, six specific phosphorylation sites were identified on p53 after expression in the presence of a phosphatase inhibitor, an enzyme that prevents phosphorylation. Mass spectrometric analysis uniquely revealed increased, site-specific phosphorylations on p53 after phosphatase inhibition which may be critical molecular events in defining p53 activity.

Merrick BA, Zhou W, Martin KJ, Jeyarajah S, Parker CE, Selkirk JK, Tomer KB, and Borchers CH: Site-specific phosphorylation of human p53 protein determined by mass spectrometry. *Biochemistry* 40: 4053-4066, 2001.

Cloning Mouse Genes to Study Skin Cancer. A genetically modified mouse was used to study the relationship between carcinogens and skin cancer. Traditional methods for the isolation of specific chromosomal regions from complex genomes are laborious and require the construction and screening of large libraries of clones. Transformation-associated recombination cloning allows entire genes and large chromosomal regions to be specifically, accurately, and quickly isolated. The gene in the transgenic mouse that is responsible for the skin tumors this mouse develops following exposure to carcinogens was isolated. The isolation of the gene (or a portion of the gene array) provides a tremendous opportunity to study the function of this gene in the etiology of carcinogenesis. Obtaining a molecular understanding of carcinogenesis will enhance the utility of this transgenic mouse model in identifying potential carcinogens and reducing human risk.

Humble MC, Kouprina N, Noskov, VN, Graves J, Garner E, Tennant RW, Resnick MA, Larionov V, and Cannon RE: Transformation-associated recombination cloning from the mouse genome: isolation of Tg.AC transgene with flanking DNAs. *Genomics* 70: 292-299, 2000.

Low Growth-Hormone Response to Pharmacological Challenge may be a Reliable Biological Marker in Childhood Depression. The search for specific biological markers for child depression includes examination of growth hormone (GH) regulation. Low GH response to infusion of growth hormone releasing hormone (GHRH) is one of the few biological markers that appear to be similar across child, adolescent, and adult depression. Animal research suggests that GH regulation is altered as a result of early stress or adverse social experiences, possibly conferring greater risk of depression. A group of NIH-funded researchers examined the stability of GH response to infusion by GHRH in depressed children. They conducted a test-retest study in a large sample of 82 depressed children, ages 7 to 15, compared with a matched

control group of 55 normal children. A subsample of depressed children also was retested after being taken off all medications following full clinical remission from depression. The GH response to GHRH was found to be significantly lower in the depressed group, compared with normal children, and test-retest reliability of GH response to GHRH was stable. Most importantly, GH response to GHRH remained low in children restudied during clinical remission from depression, indicating that it may be a biological trait marker for depression in children and adolescents as well as in adults. These findings may lead to a greater understanding of the mechanisms underlying GH regulation and its association with depression, as well as the development of new pharmacologic treatments.

Dahl RE, Birmaher B, Williamson DE, Dorn L, Perel J, Kaufman J, Brent DA, Axelson DA, and Ryan ND: Low growth hormone response to growth hormone-releasing hormone in child depression. *Biological Psychiatry* 48: 981-988, 2000.

Novel PET Ligands to Image the D4 Dopamine Receptor in Brain. The D4 receptor is a signal transduction component of neurons that responds to the chemical messenger dopamine and is found in brain regions thought to be involved in cognition and memory (frontal cortex, hippocampus, and thalamus). The finding that the atypical, antipsychotic drug clozapine binds with high affinity to the D4 receptor kindled interest in its potential as a target for developing antipsychotic drugs with minimal motor side effects. The ability to image D4 receptors in humans would aid in understanding the physiological role of this receptor and its potential involvement in cognitive impairments seen in schizophrenia and Alzheimer's disease. However, such in vivo studies have been hampered by a lack of receptor-specific radiolabeled compounds for PET (positron emission tomography) imaging in humans. Investigators now have identified a series of compounds that selectively target D4 receptors and are compatible with PET imaging technology. The D4 compounds will be radioactively tagged and tested in animals as potential candidates for PET imaging in humans. This research provides the groundwork for elucidating the biological role of D4 receptors in humans and its potential as a therapeutic target.

Huang Y, Kegeles LS, Bae S, Hwang D, Roth BL, Savage JE, and Laruelle M. Synthesis of potent and selective dopamine D4 antagonists as candidate radioligands. *Bioorganic and Medicinal Chemistry Letter*. 11: 1375-1377, 2001.

MRI Analysis Tools To Aid Developmental Neuropsychiatric Studies. Significant advances in brain imaging hold great promise for the study of normal and aberrant development. Magnetic resonance imaging (MRI) now provides exquisite images of brain anatomy containing a wealth of information. To fully utilize this information, sophisticated tools for characterizing complex anatomic structures are sorely needed. To meet this challenge, researchers developed an automated procedure for analyzing the morphology of the corpus callosum, as imaged with MRI. The corpus callosum is the large band of fibers that connects the two cerebral hemispheres, subserving communication between the two sides of the brain. Using sophisticated statistical algorithms, the researchers found that the complex shape of the corpus callosum was well characterized by eight factors related to the thickness, degree of arching or curvature, and

the bulbosity (shape) of its various anterior-to-posterior segments. Use of these algorithms to study the effects of age indicated a complex developmental trajectory. The corpus callosum first flattens in childhood and then increasingly bends in adulthood. The anterior-mid portions increase in thickness through childhood, then decrease in adulthood. Other associations with subject variables such as gender and IQ further support the sensitivity of these measures. Thus, this research provides a valuable tool for extracting information from MR images useful for studies of both normal development and childhood disorders.

Peterson BS, Feineigle PA, Staib LH and Gore JC: Automated measurement of latent morphological features in the human corpus callosum. Human Brain Mapping 12: 232-245, 2001.

Getting to the Right Place: A Novel Method to Sort Out Protein Localization. Brain cells (neurons) communicate by means of chemical messengers that are released by one neuron and received by another. Different kinds of protein molecules are involved in the release and the cellular response to these messengers, and particular proteins must get to specific locations within the neuron for normal cell-cell communication to occur. How does the cell know where to send these different protein molecules? Research suggests that the protein molecules themselves contain protein targeting signals (like address labels) that tell the cell where specific proteins ought to go, but the discovery of these signals has been limited by current in vitro (in test tubes) approaches. NIH-funded researchers have now developed a new, high-throughput method of identifying protein targeting signals using intact mammalian cells. Using a large set of randomized protein sequences and a machine to sort live cells based on cell surface fluorescence, the investigators have already identified new sequences important for targeting protein molecules to either the cell surface or a variety of intracellular compartments. This new approach will be extremely valuable in the rapid discovery of targeting signals for a wide variety of different proteins to a host of cellular locations, and will greatly aid our understanding of communication between neurons in both the normal and diseased brain.

Zerangue N, Malan M, Fried SR, Dazin PF, Jan YN, Jan LY, and Schwappach B. Analysis of endoplasmic reticulum trafficking signals by combinatorial screening in mammalian cells. Proceedings of the National Academy of Sciences USA 98: 2431-2436, 2001

Culturing Progenitor Cells from the Human Brain after Death. For the first time scientists have cultured neural progenitor cells from adult human brain tissue after death. These progenitor cells can multiply and give rise to brain cells, including nerve cells and supporting cells, but whether they have the versatility of stem cells to renew themselves many times and form all cell types remains to be seen. There are many hurdles to overcome before transplanting cadaver-derived cells might be a safe and effective therapy. A more immediate goal is to use these cells as a tool to look at the cellular and molecular events that underlie certain genetic diseases. Another long-term prospect is to use isolated progenitor cells to learn how to encourage the brain's own progenitor cells to respond to disease and injury.

Palmer TD, Schwartz PH, Taupin P, Kaspar B, Stein S, and Gage FH: Cell culture: progenitor cells from human brain after death. Nature 411: 42-43, 2001.

Turning Blood into Brain. New studies show, surprisingly, that bone marrow cells from adult mice, when injected into newborn mice, migrate to the brain and form cells that resemble nerve cells. Whether these cells act like nerve cells, what signals control the fate of these cells, and whether more than a tiny percentage of injected cells can make this transformation are among the many questions further research must answer before these findings might lead to useful therapies. An independent series of experiments demonstrated that injecting bone marrow cells following an experimental stroke improved the behavioral outcome in rats. How the cells act in these experiments is not clear, and the researchers speculate that the injected cells, instead of replacing lost cells directly, might help by releasing growth and survival chemicals to which brain cells are responsive.

Mezey E, Chandross KJ, Harta G, Maki RA, and McKercher SR: Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. *Science* 290: 1779-1782, 2000.

Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, and Chopp M: Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. *Stroke* 32: 1005-1011, 2001.

Highly Sensitive Solid State NMR. Many diseases are due to changes or abnormalities in the structure of a protein. For proteins that are soluble in water, x-ray crystallography provides a very powerful technique for solving structure. However, an important class of proteins associated with membranes of microorganisms, viruses, and cells, is very difficult to study using x-ray crystallography. A technology called solid-state nuclear magnetic resonance (NMR) can provide some structural information for these proteins, but still has technical difficulties. Using a newly developed device, it is now possible to increase the sensitivity by as much as 1,000 times. This increase promises to significantly extend the study of membrane protein structure.

Roasy M, Zeri AC, Astrof NS, Opella SJ, Herzfeld J, and Griffin RG: Sensitivity-enhanced NMR of biological solids: dynamic nuclear polarization of Y21M fd bacteriophage and purple membrane. *Journal of the American Chemical Society* 123: 1010-1011, 2001.

Next Generation Internet Implementation to Serve Visible Human Dataset. NIH is supporting a project to develop a Next Generation Internet (NGI) production system to deliver novel and useful educational tools and materials, which are based on the Visible Human (VH) Dataset. The tools include a comprehensive set of interactive 2D and 3D VH browsers that allow arbitrary 2D cutting and 3D visualizations of the Dataset. An interactive web-like navigation engine is being developed to create and visualize anatomic flythroughs under haptic control by the user. Flythroughs developed by expert anatomists in concert with clinicians will also be available. These visualization sequences will be fully labeled and linked to appropriate resources on the web. The system will allow for delivery of several simultaneous high quality digital streams, which will allow the creation of structured medical knowledge on demand using the VH Dataset. An experienced evaluation team will measure performance and educational effectiveness using emerging Advanced Distributed Learning principles. Networking experts will evaluate successes and failures of the NGI connectivity.

<http://www.nlm.nih.gov/research/visible/>

Remote Radiation Treatment Planning System. NIH is supporting the development, implementation, and evaluation of a system to provide remote radiation treatment planning. This application demonstrates the need for high bandwidth and quality of service to support interactive planning sessions; and for data privacy and security to protect patient privacy, confidentiality, and data integrity. Planning sessions provide a collaborative environment for radiation therapists at the planning site, oncologists at the care delivery site, and peer reviewers. The system utilizes video teleconferencing and allows for a shared view of the radiological images needed for radiation treatment planning. An evaluation phase will measure patient outcomes at the local care delivery site, process improvements at the remote treatment-planning site, and estimate cost impact on the treatment planning process.

<http://www.nlm.nih.gov/research/ngiinit.html>

Mammography for the Next Generation Internet. NIH is supporting a project to demonstrate the feasibility and benefits of a national breast imaging archive. The required network infrastructure will be provided using Next Generation Internet (NGI) technologies. The project goal is to provide immediate access to previous mammograms and thereby improve the performance of breast cancer screening. The imaging archive will support storage, retrieval, and distribution of breast images for clinical and research purposes and will ensure patient privacy and confidentiality with multilevel security embedded throughout the system. The system will: 1) support traditional breast screening through the maintenance and distribution of a digital record of prior breast examinations and relevant medical history for primary interpretation and expert consultation; 2) provide the opportunity to maintain and apply computer-aided diagnosis software at central, well-maintained computing resources to studies from all women; 3) provide unique tools for creating educational and training programs; and 4) create an unparalleled opportunity to study and understand many epidemiological issues in breast cancer through searches of a national breast screening database. NGI technologies will be used to securely transfer the large mammography data files in response to real-time queries. The project will demonstrate that the NGI technologies of quality of service, medical data privacy and security, and nomadic computing are necessary for the widespread deployment and optimal utilization of digital mammography.

<http://www.nlm.nih.gov/research/ngiinit.html>

Tribal Connections. NIH continues to support a groundbreaking effort to improve the Internet connectivity for selected American Indian reservations and communities and Alaska Native villages. The project began in the Pacific Northwest, has been extended to selected Indian tribes in the Pacific Southwest and, most recently, the Mid-Atlantic. Phase I evaluation is being completed at sites in the states of Alaska, Idaho, Montana, Oregon, and Washington. Phase II sites are being implemented in New Mexico (Pueblos of Taos and Jemez), Arizona/California (Colorado River Indian Tribes), Nevada (Shoshone-Paiute Tribes), and Maryland (American

Indian Cultural Center/Piscataway Indian Museum). By improving connectivity, NIH hopes to facilitate access of Native Americans living in rural, remote areas to health and biomedical information available over the Internet. The NIH project, in collaboration with the Regional Medical Library at the University of Washington in Seattle, and others, is using a community-based infrastructure development approach to help assure that Internet enhancements are responsive to local needs and conditions, and involve the local tribal and village leadership and health community. The project support at each site includes planning and technical assistance, training, and outreach in addition to provision of needed hardware, software, and telecommunications links. NIH is encouraging the involvement of other organizations, such as the Indian Health Service and State telecommunications departments, in order to make best use of scarce resources in a coordinated, sustainable way. Additionally, NIH has established an American Indian Powwow Initiative that includes participation of several NIH Institutes in select powwows in Maryland and Virginia. NIH has prepared a Native American Health page for inclusion on the MEDLINEplus consumer health web site, and is finalizing a special bookmark on "Connecting Native Americans to Health Information" for distribution at powwows and in tribal communities and villages.

<http://www.tribalconnections.org/>

Press N, Saheli R, Burroughs C, Wood FB, Rambo N, Fuller S, and Siegel E.: Tribal connections – results of an NLM outreach initiative. Bulletin of the Medical Library Association, (in press).

Internet and Web Performance Evaluation. NIH continues its research on evaluating the performance of the Internet involving biomedical institutions and users. The research began with a focus on the performance of the so-called "commodity Internet," then shifted to include high-bandwidth Internet connections, and now has expanded to include other dimensions of web evaluation. These include qualitative and quantitative measures of web usage and user satisfaction and impact. On April 17, 2001, NIH hosted a major symposium on "Evaluating Our Web Presence: Challenges, Metrics, Results," co-sponsored by CENDI (an interagency group of federal scientific and technical information managers). Over 140 persons attended from various NIH Institutes and other government agencies. A summary report is being prepared. The Internet is heavily used to support biomedical research and scientific collaboration, and thus the quality of Internet and web site performance is a major concern. This research has developed a set of methods and metrics for assessing Internet and web performance, and has applied these tools to evaluate the performance of selected Internet connections and web sites. Several NIH Institutes have taken the lead in piloting web evaluation methods. For example, one Institute has used a scientifically constructed randomized survey of MEDLINEplus users to gain a better understanding of user needs, perspectives, and satisfaction.

Wood FB, Cid VH, and Siegel ER: Evaluating internet end-to-end performance: overview of test methodology and results. Journal of the American Medical Association 5: 528-545, 1998.

Cid VH, Gill MJ, Aronson J, Wood FB, Siegel ER, and Lindberg DAB: Lindberg, Evaluating Internet End-to-End Performance Part II. Journal of the American Medical Informatics Association (under revision).

Rapid Identification and Characterization of Genetic Variations. Analyzing the entire human genome for variations in nucleotides, the building blocks of DNA, may be an efficient method to discover genes that play an important role in a variety of human functions. These types of genetic variations are known as gene-based single nucleotide polymorphisms (SNPs). NIH researchers have developed a new, highly efficient method to detect SNP markers. This new system uses computer-based tools that seek out candidate SNPs in publicly available genetic databases. These computer tools are then coupled with a highly specialized form of mass spectroscopy (MS), a technique in which substances are fragmented by a high-energy beam and charged electrically. The resulting spectra are analyzed using special software optimized for DNA. Use of this new system may hasten the discovery of genes that are involved in the development and modulation of cancer.

Buetow KH, Edmonson M, Macdonald R, Clifford R, Yip P, Kelley J, Little DP, Strausberg R, Koester H, Cantor CR, and Braun A: High-throughput development and characterization of a genomewide collection of gene-based single nucleotide polymorphism markers by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Proceedings of the National Institute of Sciences USA 98: 581-584, 2001.

New Database for Identification of Prostate Cancer Biomarkers. Tissue microarray analysis (TMA) is a technique through which very small tissue samples are placed into a recipient paraffin block for examination. This process ultimately allows the pathologist to review multiple cases on a single slide. However, in order for this method to be useful for the evaluation of possible biomarkers (indicators of disease potential or status), the pathological information must be linked to the clinical data. Investigators at the University of Michigan have created a multi-database model that links three resources: 1) their TMA database, 2) their TMA image database, and 3) the prostate pathology and clinical information database. This resource will enable more efficient testing of potential prostate cancer biomarkers.

Bova G, Parmigiani G, Epstein J, Wheeler T, Mucci N, and Rubin M: Web-based Tissue Microarray Visual Image Data Analysis: Initial Validation Testing through Prostate Cancer Gleason Grading. Human Pathology. (in Press).

Chaib H, Rubin M, Mucci N, Li L, Taylor J, Rhim J, and Macoska J: Activated in prostate cancer (AIPC): a PDZ domain-containing protein highly expressed in human primary prostate tumors. Cancer Research 61: 2390-2394, 2001.

Mucci NR, Akadas G, Manley S, and Rubin MA: Neuroendocrine expression in metastatic prostate cancer: evaluation of high throughput tissue microarrays to detect heterogeneous protein expression [published erratum appears in Human Pathology 31: 406-414, 2000.

Perrone EE, Theoharis C, Mucci NR, Hayasaka S, Taylor JM, Cooney KA, and Rubin MA: Tissue microarray assessment of prostate cancer tumor proliferation in African- American and white men. Journal of the National Cancer Institute 92: 937-939, 2000.

Rubin M, Mucci N, Figurski J, Fecko A, Pienta K, and Day M: e-cadherin expression in prostate cancer: a broad survey using high density tissue microarray technology. Human Pathology. (in press).

Shah R, Mucci N, Macoska JA, and Rubin MA: Postatrophic Hyperplasia of the Prostate Gland: Neoplastic Precursor or Innocent Bystander? American Journal of Pathology. (in press).

Development of Silk-Based Biomaterials for Bone Formation. Silks are a unique class of structural proteins in nature with a wide variety of functions. They serve as high strength netting to entrap insects, lifelines to support spiders, and protective membranes that can withstand environmental insult. Silkworm silks offer new options in the design of biomaterials and tissue engineering scaffolds because they are strong, resistant to compressive forces, stable in varying temperatures, insoluble in water, and flexible. Using a family of silk proteins to prepare silk-based scaffolds for bone formation, NIH scientists were able to stimulate the growth of human osteoblast-like cells (bone-forming cells) in laboratory studies. In particular, they found that silk modified with selective peptides important in influencing cell binding and inducing bone formation (mineralization) generated a positive response. Their study confirms that silks present opportunities for the design and development of protein scaffolds capable of inducing bone formation.

Sofia S, McCarthy, MB, Gronowicz G, and Kaplan D: Functionalized silk-based biomaterials for bone formation. *Journal of Biomedical Materials Research* 54: 139-148, 2001.

Infrared Lasers Used for the Removal of Carious Hard Tissue. The dental drill that is used to remove carious hard tissue has several disadvantages to it, including patient discomfort and unnecessary loss of healthy tissue. Infrared lasers, on the other hand, are better suited for the precise removal of carious hard tissue without discomfort. NIH scientists have made beneficial adjustments in the wavelength, the incident energy and the pulse duration of the laser system to allow for caries ablation and enamel surface modification.

Fried D, Ragadio J., Akrivou M, Featherstone JD, Murray MW, and Dickenson KM: Dental hard tissue modification and removal using sealed transverse excited atmospheric-pressure lasers operating at $\lambda=9.6$ and 10.6 microm. *Journal of Biomedical Optics*, (in press 2001).

New Cell Culture Process Offers Promise for Immunotherapy of Cancer. Dendritic cells occur normally in the blood and tissues of humans. They are an important part of the immune system and have a number of functions that have only been recognized over the past 20 years. Their main role is to enhance and control the interaction between antigens – such as molecules on a virus or a cancer cell – and the lymphocytes, the cells that mount the attack against the virus or cancer cell. Therefore, they are of great interest to investigators developing new treatments for cancer, infections, and autoimmune disease. Over the past 5 years, several research groups have been studying methods for large-scale generation of human dendritic cells that might be useful for new treatments. NIH researchers have developed a method to produce large numbers of dendritic cells from the cells circulating in the blood. After the 5-day process, the dendritic cells from a given cancer patient are stimulated with a specific cancer antigen, and then infused back into the same patient. This method is now being applied to several clinical trials, and early results demonstrate that some patients develop an immune response to their tumors. This process is currently being modified to increase the efficacy of the dendritic cells and to improve its practicality so that other centers can use it.

Wong ECC, Maher VE, Hines K, Lee J, Carter CS, Goletz T, Kopp W, Mackall CL, Berzofsky JA, and Read EJ: Development of a clinical-scale method for generation of dendritic cells from PBMC for use in cancer immunotherapy. Cytotherapy 3: 19-29, 2001.

A Stimulating Way to Donate Blood. Patients with very low white blood cell or granulocyte counts often develop severe bacterial or fungal infections. In most cases these infections can be treated effectively with antibiotics. In rare cases, antibiotics are not effective and white blood cell or granulocyte transfusions must be given. Granulocytes are collected from blood donors using a machine called a blood cell separator, but to collect enough white cells, donors must be given a drug to raise or “stimulate” their white blood cell count. A drug called Granulocyte Colony-Stimulating Factor (G-CSF) has been used to raise blood donor’s white blood cell counts. While G-CSF is very potent, many blood collection centers have been concerned that G-CSF is too toxic to give to blood donors. Researchers therefore measured symptoms in donors given G-CSF and found that G-CSF caused donors to experience mild symptoms for 1 or 2 days, but raised white blood cell counts 5- to 6-fold and the number of white cells collected 3- to 4-fold. It also was determined that G-CSF and the white cell collection process caused many minor changes in the donors’ blood chemistries and blood counts that lasted up to 28 days after the donation. These studies show that it is safe to give donors G-CSF but it is best to wait 28 days between donations.

Stroncek DF, Yau YY, Oblitas J, and Leitman SF: G-CSF plus dexamethasone administration produces greater granulocyte concentration yields while causing no more donor toxicity than G-CSF alone. Transfusion 41: 37-44, 2001.

A New Approach for Selecting Best Treatment Regimen When Using Therapeutic DNA Damaging Agents. Many therapeutic agents used in the treatment of diseases, such as cancer, kill cells by producing DNA damage. Radiation therapies, as well as many chemotherapeutic agents, damage DNA by ionization. The lethal events in such therapies are the formation of very chemically complex DNA double-strand breaks. A patient's innate cellular ability to repair these damages directly affects, and in many cases may determine, the success or failure of the agents used to treat their disease. This research investigates the potential for assessing an individual patient's tissues, or tumor, for repair of the actual damage produced by the DNA double-strand-break-inducing agents typically used therapeutically. This approach may become a useful tool for predicting patient sensitivity to therapeutic agents, and thus, help in the selection of more successful treatment regimens.

Pastwa E, Neumann RD, and Winters TA: *In vitro* repair of complex unligatable oxidatively induced DNA double-strand breaks by human cell extracts. Nucleic Acids Research 29: e78, 2001.

Developing Electronic Patient Records Systems for Public Health Surveillance and Clinical Care. The lack of accurate patient record-keeping systems in rural Africa is a critical issue, since without them, there are no reliable means of estimating rates of infectious diseases across populations, of prescribing therapies consistently, of tracking outpatient visits, or of managing

diseases like AIDS in any given country. Kenyan trainees supported by NIH's International Training Program in Medical Informatics have developed an electronic medical record system for outpatient information at the Mosoriot Health Center in Eldoret, Kenya that links health center data with public health research programs of Moi University. The new system provides much needed technology to improve the public health infrastructure and to enhance the capacity for epidemiologic research. It optimizes the relatively rudimentary infrastructure of the host institution and information technology skills of its staff, and is likely to be broadly transferable to other medical care facilities in Africa.

Hannan TJ, Rotich JK, Odero WW, Menya D, Esamai F, Einterz RM, Sidle J, Sidle J, Smith F, and Tierney WM: The mosoriot medical record system: design and initial implementation of an outpatient electronic record system in rural Kenya. International Journal of Medical Informatics 60: 21-28, 2000.

Non-invasive Technique to Detect Hypoglycemia in Patients with Diabetes. The importance of intensive control of blood glucose to dramatically reduce the devastating complications of diabetes was clearly demonstrated by two clinical trials: The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes. However, with the currently available treatments, tight glucose control remains unattainable for many people. Episodes of severe hypoglycemia, or low blood glucose, are the major obstacle to the achievement of normal blood glucose levels for many people. The frequency of severe hypoglycemia has been shown to increase with more intensive treatment and can result in significant morbidity and even mortality. Patients currently monitor blood glucose with finger pricks to obtain a blood sample. Increasing the frequency of glucose measurements makes it possible to detect a greater number of episodes of hypoglycemia. However, these techniques are associated with discomfort and frequently miss episodes of hypoglycemia, particularly those occurring at night during sleep. The GlucoWatch Biographer (Cygnus, Redwood City, CA) provides frequent, automatic and non-invasive glucose measurements for up to 12 hours after a 3 hour warming up period. The biographer, a watch-like device worn on the wrist, pulls glucose through the skin every 20 minutes and measures it with an electrochemical sensor. A recent study compared measurements taken with the GlucoWatch and blood glucose measurements to determine the optimal low-glucose alert level for the Gluco-Watch. Setting the alert level from 1.1 to 1.7 mmol/l above the glucose level of concern for hypoglycemia optimizes the trade-off between identifying episodes of true hypoglycemia and false alarms. In addition, the biographer can provide low-glucose alert levels that can be individualized to the patient's needs. This device, whose development was made possible by multi-disciplinary basic and clinical research, may become an important tool to help patients aggressively manage their diabetes while avoiding episodes of hypoglycemia.

Pitzer KR, Desai S, Dunn T, Edelman S, Jayalakshmi Y, Kennedy J, Tamada JA and Potts RO: Detection of hypoglycemia with the GlucoWatch Biographer. Diabetes Care 24: 881-885, 2001.

New Clinical Laboratory Test for Measuring Serum Cholesterol in Lipoprotein Fractions. Cholesterol is transported in the blood on various types of lipoprotein particles that differ in their density and in their role in the pathogenesis of heart disease. The measurement of cholesterol in

the different lipoprotein particles is useful in assessing the risk for heart disease and in monitoring the effectiveness of cholesterol-lowering therapies. A limitation of the current approach to the clinical laboratory analyses of lipoproteins is that it requires the performance of at least three separate tests. A new laboratory test was developed that simultaneously measures all of the major diagnostically important lipoprotein lipids, namely LDL-cholesterol, HDL-cholesterol and total triglycerides. Because the new test is relatively simple to perform, it can be used as a cost-effective screening test for the prevention of heart disease.

Sampson ML, Aubrey A, Csako G, and Remaley AT: Triple lipid screening test: A homogenous assay for HDL-cholesterol, total cholesterol, and triglycerides. *Clinical Chemistry* 47: 532-539, 2001.