Epilepsy
Administering inhaled nitric oxide (NO) during surgery helps protect liver transplant patients from organ failure by minimizing reperfusion injury, according to UAB pathologist Rakesh Patel, PhD, coauthor of the paper published in the *Journal of Clinical Investigation*. The study also showed NO administration decreased hospital length of stays, and improved blood-clotting and liver-enzyme activity in post-transplant tests. Results from this small study are preliminary and must be confirmed through larger clinical trials, which will be conducted at UAB in conjunction with Seattle-based University of Washington and the US Department of Veterans Affairs Puget Sound Health Care System. This study has important implications for other solid organ transplants as well.

**UAB Hospital** again is the only hospital in the Birmingham area to earn a National Research Corporation (NRC) Consumer Choice Award. The award means UAB Hospital is among the nation’s 225 top hospitals in terms of consumer perceptions of quality and image. In what NRC calls “the nation’s most comprehensive consumer assessment of the health care industry,” consumers named 3200 hospitals in 190 markets throughout the contiguous United States. The annual survey represented 450,000 consumers in 200,000 households. “We are extremely proud to receive this recognition. We strive day and night to provide the highest quality of care possible to the patients who trust us with their health. This is another important recognition for our professionals in their efforts to provide excellent care,” said Michael R. Waldrum, MD, UAB Hospital chief executive officer. “This acknowledgement is especially meaningful in that it comes directly from the people utilizing our services.”

To help meet the demand for physicians with clinical experience in hospice and palliative medicine to work in hospices and hospital-based palliative care programs, the American Academy of Hospice and Palliative Medicine (AAHPM) offers a focused clinical experience at selected hospice and palliative care sites for physicians who desire training in palliative medicine but who are unable to complete an entire fellowship. AAHPM has designated the UAB Center for Palliative Care (including both the Veterans Affairs and UAB clinical sites) as one of eight national training sites for its Clinical Scholars Program. For more information: [www.ahpm.org/education/clinicaltraining.htm](http://www.ahpm.org/education/clinicaltraining.htm).
At UAB’s Level IV comprehensive epilepsy center — the highest designation given by the National Association of Epilepsy Centers — patients receive expert, broad-based care, support, and education for seizure conditions and related comorbidities, as well as the socioeconomic issues so often associated with epilepsy, says Professor and Director R. Edward Faught Jr, MD.

The UAB Epilepsy Center began as an Epilepsy Foundation-sponsored clinic in 1980. In 1983 the medical center added an inpatient seizure monitoring unit and in 1985 established the epilepsy surgical treatment program. A year later the epilepsy program grew into a multidisciplinary center drawing on faculty from the departments of neurology, pediatric neurology, neurosurgery, neuropsychology, and others. The center’s core faculty now includes five adult neurologists, four pediatric neurologists, two neurosurgeons, two doctors of pharmacy, and a large staff of research nurses and research assistants.

“We have the necessary technology and treatment techniques to provide our patients with state-of-the-art care. As a comprehensive epilepsy center, our mission also is to address the full scope of our patients’ needs, which can include psychosocial issues,” Faught says. “People with epilepsy often have trouble finding or holding a job, yet do not always qualify for Social Security disability benefits. Through connections with social services, the Epilepsy Foundation, and drug assistance programs, we can help patients find employment or seek disability and assist with obtaining medications, which many people with epilepsy cannot afford.”

Center physicians are adept at identifying conditions that coexist with epilepsy and provide treatment or specialist referral, Faught says. “We have, for example, a dedicated clinic for women with epilepsy to meet the special needs of patients of childbearing age. Women receive counseling and education about issues related to birth control, pregnancy, and child care.”

**Drug Development**

With one of the largest clinical trials programs in the Southeast, the UAB epilepsy program has been at the forefront of antiepileptic drug (AED) development since the 1980s, when the National Institutes of Health began emphasizing the need for novel, effective medications. “Prior to 1993 no drugs for epilepsy had been introduced for more than 20 years. Since then 15 new medications have become available,” Faught says. “UAB participated in trials of 12 of those medications and was the leading center for patient enrollment for 5 of the new drugs.”

AED development continues, and UAB currently has three medications in clinical trials. “The drugs under investigation are designed primarily for patients who have not achieved complete seizure control with other medications,” Faught says. “The latest generation of drugs can potentially offer benefits beyond seizure control. Many recently developed AEDs have other effects on the nervous system and have some efficacy for treating conditions such as migraine and mood disorders, both of which are common among epilepsy patients.”

Faught is principal investigator for UAB’s AED development trials, which include a multicenter randomized placebo-controlled trial of ganaxolone, one of a new class of anticonvulsants that modulate GABA$_\text{A}$ receptors.

Investigators are evaluating the drug’s efficacy and safety as an add-on therapy in patients of both genders with uncontrolled
partial-onset seizures and in women with catamenial epilepsy — a condition in which seizure activity increases around the time of ovulation or menstruation.

“Ganaxolone is chemically similar to progesterone, which suppresses seizures. The drug avoids the negative hormonal effects of progesterone and may be particularly useful in women whose seizure frequency is linked to their menstrual cycle.”

Faught notes the primary benefit of newer AEDs is fewer negative side effects. “We need more options,” he says, “as current drugs leave up to 30% of patients with inadequate seizure control.”

Patients with difficult-to-diagnose epilepsy or who have medically uncontrolled seizures undergo evaluation at UAB Hospital’s Penfield Epilepsy Service — the center’s inpatient monitoring unit. Epileptologists use the eight-bed unit for long-term (usually 3-5 days) electroencephalogram (EEG) recording of brain waves and videotaping of seizure activity.

“Inpatient evaluation helps us confirm diagnoses of epilepsy, classify individuals’ seizure type, and determine the site of seizure focus, which is crucial for epilepsy surgery evaluation,” Faught says. “Intensive studies help us direct patients to the most appropriate treatments.”

The service evaluates about 50 adult patients per month. Epileptologists assess younger patients at Children’s Hospital of Alabama’s four-bed inpatient unit.

NEUROIMAGING

UAB has a long history of investing in emerging imaging tools and was well positioned to take advantage of the technological boom that began in the 1990s and continues today, says Epilepsy Center Co-Director Robert C. Knowlton, MD, MSPH, who also directs the inpatient seizure monitoring unit and the Health Services Foundation Magnetoencephalography (MEG) Laboratory. UAB’s imaging capabilities are expanding as new technologies become available. Imaging tools currently include:

- Combined EEG and functional MRI (fMRI)
- Ictal single photon emission computed tomography
- Position emission tomography

Only a handful of US epilepsy centers offer all these capabilities, Knowlton says. “The EEG-fMRI is the latest advance in imaging, and we have begun studies to compare its efficacy in presurgical brain mapping with other technologies. EEG-fMRI simultaneously records and correlates scalp EEG events, which reflect electrical brain changes, with fMRI data that show associated hemodynamic changes,” he says. “EEG-fMRI identifies functional abnormal brain areas with high spatial resolution — information other noninvasive imaging tools cannot capture.”

Multiple, complementary imaging technologies allow epileptologists and neurosurgeons to better select surgical candidates. “Many imaging tools are so new that we are still studying their clinical impact,” Knowlton says. “It is clear, however, that advanced neuroimaging capabilities are increasing the pool of surgical candidates; these technologies allow us to locate seizure foci we could not identify in the past and give surgeons much more information to guide procedures.”

Faught notes, “Surgical treatment is the best chance for patients with intractable epilepsy to achieve complete seizure control. Both physicians and patients often view epilepsy surgery as a treatment of last resort, which is a major misconception. Surgery is an effective, standard treatment that has been available for half a century,” he says. “People with medically refractory epilepsy should be evaluated for surgery early, ideally when trials of no more than two medications have failed to completely control seizures. Too many epilepsy patients live with uncontrolled seizures. Earlier evaluation can mean decades of improved quality of life for patients who might otherwise try and fail multiple medications.”

Knowlton agrees. “I think there is sometimes a mistaken view that patients who are having limited seizures have achieved adequate control, but the bottom line is that epilepsy is not effectively treated until a person is seizure free.”

After a patient undergoes comprehensive evaluation of their seizure condition, all experts involved — neurologists, neurosurgeons, neuropsychologists, and nurses — discuss the case and provide a joint recommendation for optimal care. “Bringing together all data to make the best decision for the patient is one of the primary functions of a comprehensive epilepsy center,” Faught says.

PEDIATRIC EPILEPSY SURGERY

Up to 40% of people with epilepsy will not achieve complete seizure control with medication, says UAB pediatric neurosurgeon Jeffrey P. Blount, MD. “These individuals tend to be patients with structural abnormalities in the brain, and children are disproportionately represented in this group.”

Functional imaging advances allow surgeons to precisely map seizure foci and remove these areas with low risk to the patient, Blount says. “Cortical dysplasias, the most common congenital brain abnormality, are the major cause of medically refractile pediatric epilepsy.” He notes cortical dysplasias — malformations of cortical development that lead to disorganization of the cerebral cortex — went unrecognized as distinct pathological entities until the 1980s and are still widely missed outside of epilepsy centers.

Temporal lobectomy is the most common surgical intervention among adults with epilepsy. Children with seizure conditions are much less likely to undergo lobectomy, Blount says, as cortical dysplasias arise in the neocortex. “Cortical dysplasias can look and act like normal tissue and require refined invasive monitoring to identify accurately,” he says.

“Localization of the seizure focus and determination of surgical candidacy rests on mapping the semiology of the seizure and on test concordance, which is achieved when different modalities implicate the same region and spread pattern in the brain,” says Blount.

Once epileptologists and neurosurgeons identify the most likely region of
seizure origin, they perform a two-step procedure: Surgeons place grids directly on the brain surface, where they remain for several days and let surgeons observe electrical activity and seizure spread. Based on grid monitoring, surgeons can better define the chances of ending or attenuating seizures with surgery. If substantial improvement through surgery is highly probable, the operation proceeds.

“If grid findings show seizures involve eloquent areas, we must carefully consider the risks of introducing neurological deficits,” he says. “This is an individualized, prolonged decision-making process involving the family, the surgeon, and the epileptologist. Surgery is only considered when it could provide sufficient seizure control to warrant the possible introduction of a neurological deficit. Families whose children have severe, frequent seizures sometimes are willing to trade the unpredictability of epilepsy for a fixed deficit.”

A significant number of pediatric patients at UAB and Children’s Hospital undergo functional hemispherectomies. “We no longer remove half the brain as was done with anatomical hemispherectomy,” he says. “Advanced techniques allow us to leave a larger portion of tissue in place, which maintains spinal fluid dynamics and avoids hemosiderosis — the major complication of anatomical hemispherectomy.”

Blount also performs corpus callosotomy for children who have tonic or atonic drop events. “Sectioning the major fiber tract that links the left and right brain decreases spread of epileptic discharge,” he says. “This is not a curative operation but is highly effective for eliminating drop events, which cause serious injuries.”

Implantable vagus nerve stimulators also are an option for children who have drop events and for those with medically refractile multifocal epilepsy.

Virtually all epilepsy surgical series show that between 70% and 80% of people with epilepsy had seizures begin in childhood, Blount says, noting that after a child has failed two medications, it is time to consider surgical evaluation.

Although seizure freedom is the ideal goal for all pediatric surgeries, Blount says that improved seizure control can make substantial, favorable differences in children’s lives. Frequent seizures significantly impair children’s cognitive development, limiting their potential to grow into productive adults. Eliminating or reducing seizures also improves learning ability and can dramatically increase self-esteem and social skills.

“Carefully designed surgical intervention can make a tremendous difference in the lives of children who may be seizing 50 to 100 times a day with devastating effects,” he says. “Reducing seizure frequency can change the lives of these children and their families, but surgery is still grossly underutilized in the pediatric population. The overwhelming majority of our pediatric surgery patients experience significant improvements. Surgery should be considered very early in the course of treatment — not years later when cognitive deficits are irreversible.”

**ADULT EPILEPSY SURGERY**

All adults with epilepsy who are not seizure free with medical therapy should be assessed for surgery, says UAB neurosurgeon Kristen Riley, MD. “The average time for referral for surgical evaluation is 14 years. Although only 10% to 15% of adults with medically refractile epilepsy are surgical candidates, a significant number with localized epilepsy could have been seizure free years ago through surgery,” she says, noting that adults with temporal lobe epilepsy whose imaging studies show concordant data indicating a well-localized seizure focus have an 85% chance of achieving seizure freedom with surgery.

“If there were an anticonvulsant with an 85% cure rate, it would be widely used,” she says. “The only way to identify surgical candidates is through an evaluation including inpatient EEG monitoring, noninvasive imaging studies, and occasionally invasive monitoring. Invasive monitoring with grids is becoming more common as imaging techniques improve,” says Riley. “We want to work with referring physicians to evaluate their epilepsy patients for surgery as early as possible in the course of their condition.”

**GENETICS OF EPILEPSY**

UAB is 1 of 13 centers in the nation that will participate in the Epilepsy Phenome/Genome Project (EPGP), a 5-year, $15 million study investigating the complex genetic factors that underlie both common and rare forms of epilepsy. The EPGP, which is funded by the National Institute of Neurological Disorders and Stroke, is recruiting more than 3700 epilepsy patients and 3000 controls, including 1500 sibling pairs with epilepsy and 750 patients with rare epilepsies and their families.

“During the first phase project investigators will collect information about phenotypic features in a rigorous, consistent fashion,” explains Knowlton, who is principal investigator for the UAB site of the EPGP. Family and medical histories, EEGs, imaging studies, treatment response information, and blood or saliva samples will be amassed and archived in a central data repository. Later phases will involve whole genome scans of genetic material and investigation of potential connections between participants’ DNA sequences and phenotypic characteristics.

UAB, one of the initial four epilepsy centers that began recruitment this fall (others begin activities in 2008), will enroll 300 patients. Candidates are individual aged 4 weeks to 50 years with generalized or localized epilepsy who have a sibling who can participate and patients with infantile spasms, Lennox-Gastaut syndrome, polymicrogyria, and periventricular heterotopia who have parents who can donate DNA.

“The project’s ultimate goal is to identify new molecular targets for drug development, individualize therapy by revealing mechanisms of treatment response, and eventually, prevent the disease in people at risk,” Knowlton says.
Bone Marrow Transplantation and Cell Therapy Program

UAB’s Program Offers Cutting-edge Care

UAB’s 1-year survival rates for matched unrelated donor bone marrow transplants are the highest among major transplant centers in the region, out-ranking centers such as M.D. Anderson Cancer Center, Emory University, and Vanderbilt University.

The National Marrow Donor Program (NMDP), which locates almost all donors for matched unrelated bone marrow transplants performed in the United States, analyzes each center’s case mix to produce expected 1-year survival rates and reports the actual outcomes of all transplants it facilitates. For patients undergoing transplant during the last 5-year period analyzed (2000-2004), UAB’s predicted 1-year survival was 51.8%. Actual survival was 57.8%, exceeding the rate of the center with the next highest actual survival rate by more than 5%.

The success of UAB’s Bone Marrow Transplantation and Cell Therapy Program (BMT&CT) is due largely to a single-staff model of care, says Director William P. Vaughan, MD, MBA, who instituted the system when he established UAB’s program in 1991. “Under the single-staff model, a patient is cared for by the same team of physicians and nurses at every visit, whether inpatient or outpatient,” he says. These physicians and nurses deliver inpatient, outpatient, and emergency care in a single location at UAB Hospital, 24 hours a day, 365 days a year. “Patients also benefit from a highly structured set of transplant procedures and a stable faculty and staff, some of whom have been with the program since its inception.”

Allogeneic bone marrow transplantation has curative potential for various leukemias and lymphomas and a number of other malignant and nonmalignant disorders. However, there is only a one in four chance that a sibling will be a good human leukocyte antigen match. Less than 25% of patients needing a transplant will have a suitably matched family member. Although the NMDP has more than 4 million registered volunteer donors, and the BMT&CT can access European registries, Vaughan says that suitable unrelated volunteer donors, particularly those from minority populations, always are in short supply.

Expanded Transplant Eligibility

UAB’s BMT&CT program is at the forefront of research that is expanding transplant eligibility in older patients and individuals with significant comorbidities. UAB research has produced a pharmacokinetic-directed dosing strategy for intravenous busulfan-based preparative regimens for treatment of advanced, aggressive non-Hodgkin’s lymphoma. “This strategy has virtually eliminated busulfan-related mortality without compromising efficacy and has resulted in excellent long-term relapse-free survival [50% at 4 years] in otherwise incurable patients with advanced, aggressive non-Hodgkin’s lymphoma,” he says.

BMT&CT scientists are studying strategies to maximize benefits and minimize risks of allogeneic grafts. Investigators are the first in the nation to receive a Food and Drug Administration investigational device exemption to standardize T-cell content of all graft products. “Lower T-cell content of marrow products results in less graft-versus-host disease. Standardizing content allows us to do rigorous clinical trials to identify the other determinants of good and bad outcome,” Vaughan says.

BMT&CT faculty and staff maintain a close relationship with referring physicians and offer a dedicated line for gathering information and arranging patient evaluations. “Our goal is providing compassionate and uncompromisingly expert care to ensure the best possible outcomes,” he says.

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### Matched Unrelated Donor BMT Outcomes

<table>
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Sites 1-5 (listed in alphabetical order): Emory University; H. Lee Moffitt Cancer Center and Research Institute; M.D. Anderson Cancer Center; Shands Cancer Center; and Vanderbilt University. Source: NMDP
UAB recently opened the first Tuberous Sclerosis Clinic in the Southeast, offering comprehensive, lifelong patient services and genetic counseling to children and adults with tuberous sclerosis complex (TSC).

TSC is a genetic disorder caused by mutations in TSC1 or TSC2, the two involved genes thus far identified. TSC is inherited as a dominant trait, although two thirds of cases are due to new mutations. “Given the complicated nature of TSC genetics, all families who have an affected relative should discuss their unique risk to have either TSC or a child with TSC,” says Bruce R. Korf, MD, PhD, chair of the UAB Department of Genetics, who codirects the clinic with neurologist Martina Bebin, MD, MPA.

Symptoms of TSC can range from mild and often unnoticed to very severe. Its signature hamartoma formations can manifest in many organ systems, but the majority of patients with severe, early complications are diagnosed after a seizure episode. “Most morbidity and mortality are associated with benign tumor growth in the brain or kidney, but many patients can have fairly normal life spans,” Korf says.

“The Tuberous Sclerosis clinic provides initial evaluation and annual follow-ups, comprehensive day-to-day care, and regular monitoring of currently silent giant cell astrocytomas, which can block cerebrospinal fluid flow, or renal angiomyolipomas that can become a life-threatening surgical emergency,” Korf says. “Our clinic involves experts in genetics, neurology, epilepsy, dermatology, and genetic counseling, and can readily coordinate access to consultants in endocrinology, pulmonology, nephrology, neuropsychology, neurosurgery, ophthalmology, and others, all of whom are familiar with the medical concerns of TSC patients and their families.”

Korf, Bebin, dermatologist Amy J. Theos, MD, and genetic counselor Christina Barger, MS, staff the monthly clinic. Patients and family members, often part of the highly structured Tuberous Sclerosis Alliance (TSA), have welcomed the clinic. Bebin says, “They feel secure knowing their overall management conforms to the latest guidelines and that new scientific developments will be quickly available.” The TSA helps fund a network of US clinics. UAB plans to apply for inclusion in 2008, which will allow the clinic to participate in a recently created natural history database and offer patients access to clinical trials.

TSC has an estimated incidence of 1 in 6000 births and occurs equally in both sexes and all ethnic groups. It is a clinical diagnosis, based on an algorithm that seeks to identify multiple major features or a combination of a single major plus multiple minor features. Major features may include:
- facial angiofibromas or forehead plaque
- nontraumatic ungual or periungual fibroma
- hypomelanotic macules
- shagreen patch
- multiple retinal nodular hamartomas
- cortical tuber
- subependymal nodule
- subependymal giant cell astrocytoma
- cardiac rhabdomyoma
- lymphangioleiomyomatosis
- renal angiomyolipoma

A. and B. MRIs show multiple cortical tubers within the brain parenchyma and a subependymal giant cell astrocytoma within the lateral ventricle.

C. CT scan shows calcified nodule in a tuberous sclerosis patient
Behavioral Genetics Clinic

Multidisciplinary Specialists Available

The UAB Behavioral Genetics Clinic, which opened in 2007, combines the skills of experts in genetics, child neurology, and developmental pediatrics to provide a single medical home for children and adults who have complicated genetic disorders that feature problematic behavior and developmental delay as integral components.

The behavioral aspects of these disorders can be overwhelming for families, and problems may increase as patients mature and potentially become physically imposing to aging parents. A team approach to treatment and counseling offers practical, coordinated assistance, says UAB pediatric neurologist Alan K. Percy, MD, clinic director. Percy, associate director of the UAB Civitan International Research Center, is recognized as a leading authority on Rett syndrome and other inherited childhood neurodegenerative disorders.

The Behavioral Genetics Clinic, one of the multidisciplinary UAB Civitan-Sparks Clinics, offers comprehensive diagnosis, evaluation, and treatment of children and adults with mental retardation and developmental disabilities. Clinics provide full-service clinical programs, including dental care.

The Behavioral Genetics Clinic meets monthly, primarily seeing patients with a defined diagnosis of Angelman, Prader-Willi, velocardiofacial (DiGeorge), or Williams syndromes, but is not limited to patients with these conditions. Most are aged 1 to 10 years and are seen once or twice a year. Clinic faculty and staff also see adolescents and adults. Families consult with a team of specialists that includes Percy, geneticist Edward J. Lose, MD, a registered nurse, developmental psychologist, nutritionist, and social worker. Patients also have access to consulting psychiatrists, cardiologists, speech and language pathologists, and occupational therapists.

“We saw the need for a clinic that evaluates problematic situations, provides directed management, and offers hands-on help with issues that often involve nutritional problems,” Percy says.

“The clinic is of extra value when a patient develops symptoms of a complication expected at a particular developmental stage — such as hypertension resulting in renal disease in Williams syndrome or orthopaedic problems associated with excessive weight in Prader-Willi syndrome,” he says.

Lose, Percy, and geneticist Nathaniel H. Robin, MD, developed the clinic.

“When I saw these patients in my 13-year community pediatrics practice I often had to make appointments with multiple specialists plus ancillary care providers,” Lose says. “These specialists and others are available in the new clinic and all have experience managing behavioral genetic conditions. Our goal is not only to treat illness, but also to help these patients participate as fully as possible in all aspects of life.”

“Because these genetic conditions are rare, many families feel isolated, but this clinic draws a large enough population from all the disorders so patients and their families feel part of a larger community,” he says.

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Rosiglitazone (Avandia)

Diabetes Drug Is at Center of Heated Debate

Last May The New England Journal of Medicine (NEJM) published a meta-analysis of the diabetes drug rosiglitazone (Avandia) that ignited a media firestorm (2007;356:2457-2471). Nissen and Wolisiki concluded that the thiazolidinedione (TZD) rosiglitazone was associated with a 43% increased risk of myocardial infarction (MI) and a 64% increased risk of cardiovascular death. The Food and Drug Administration (FDA) issued an alert and required black box warnings on TZD products.

In August the FDA strengthened the warnings on TZDs, stating the drugs are not recommended for patients with symptomatic heart failure and are contraindicated in those with New York Heart Association class III or IV heart failure.

The original NEJM article and accompanying editorial sparked heated debate, multiple reanalyses of available data, and publication of interim results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabete trial, which proved to be inconclusive.

TZD’s cardiovascular impact is important to the 16 million Americans with diabetes as heart disease is the most common cause of death among this population. The FDA approved rosiglitazone in 1999 based on clinical trials showing the drug reduced blood sugar levels in type 2 diabetes.

Physicians are in a difficult position,” says UAB endocrinologist Fernando Ovalle, MD. “Rosiglitazone is a mainstay of diabetes treatment. It lowers blood sugar as well as insulin and sulfonylurea; improves insulin sensitivity; improves pancreatic beta-cell function and prolongs its lifespan; and is effective in patients who may not respond well to metformin, the first-line treatment.”

Nissen’s and Wolisiki’s meta-analysis combined 42 studies with a variety of trial designs and protocols, none of which specifically targeted MI or ischemic events. “Avandia shows little or no suggestion of increased cardiovascular risks in trials that compare it with metformin or sulfonylurea,” Ovalle says.

“The NEJM analysis artificially inflated the risk estimate. Two recent large, prospective, randomized, controlled trials — including ADOPT and an interim analysis of the RECORD study — did not demonstrate evidence of such a risk; in addition, a more recent meta-analysis published in The Lancet provides further reassurance” (2007; 370:1129-1136).

Ovalle warns against removing the drugs from treatment regimens without careful consideration. “Risks, benefits, and side effects vary by individual. Those without major heart disease should continue taking Avandia until further studies establish the drug’s precise risks,” he says. If a patient insists on switching, Ovalle advises opting for the TZD pioglitazone. For those who decline TZDs he recommends sulfonylurea or metformin — both have long safety records. “For some people, the only alternative to Avandia is insulin. Many of these patients will never achieve the same degree of glycemic control they enjoyed with a TZD, and suboptimal control results in significant increases in neuropathy, kidney disease, eye disease, and other microvascular complications,” he says.

“Physicians can reassure patients that the link between MI and Avandia has not been proven,” Ovalle says. Ongoing studies with cardiovascular-related end points may help resolve the issue. Until that information is available, clinicians can maintain a balanced and informed perspective and closely monitor their patients for cardiovascular risk factors.
Diabetes is a documented risk factor for cardiovascular disease, including heart failure (HF), and the prognosis of patients with HF is worse in the presence of diabetes. Some research suggests diabetes-associated increased mortality in HF may be worse in women than in men.

A new study published in *Heart* confirms the additive consequences of diabetes in women with HF (Heart. 2007; 93:1584-1590). The findings from that study also suggest diabetes-associated increased mortality and hospitalization in HF is primarily observed in older women. This is important as most HF patients are older adults, and HF is the number one reason for hospital admission in this population.

Ali Ahmed, MD, MPH, director of UAB’s Geriatric Heart Failure Clinic and Research Program, led the multicenter research team investigating diabetes’ effect on the natural history of HF. Ahmed designed a propensity-matched study of HF patients participating in the National Heart, Lung, and Blood Institute-funded Digitalis Investigation Group trial.

To reduce possible confounding effects of baseline variables, Ahmed and colleagues used propensity scores to match patients. Propensity matching created a cohort of patients (with and without diabetes) who were well balanced in all measured baseline covariates. No previous studies evaluating diabetes’ effect on HF outcomes have applied this technique.

Evaluation of more than 4000 matched HF patients demonstrated a complex, interactive relationship among sex, diabetes, and age. “The extent to which poorer outcomes are due directly to diabetes or are due to diabetes-associated comorbidities has not been well understood,” he says.

Examination of the effects of diabetes on mortality and hospitalization rates in HF patients revealed clear differences between men and women. HF patients of both sexes with diabetes have higher absolute risk values for mortality and hospitalization. Yet in women the effects of diabetes on mortality and hospitalization were significantly worse than in men. In men, for example, diabetes was associated with a 5% absolute increase in mortality; in women diabetes was linked to a 14% increase.

When investigators examined age-related effects of diabetes on mortality and hospitalization in groups of patients <65 years and >65 years, older women suffered the most consequences. Diabetes was associated with a 19% absolute increase in mortality among older women compared with a 4% increase in older men. In younger men the absolute increase in mortality was 6%, versus 8% in younger women.

In the next 20 years the number of elderly women with HF is projected to double. “Because the prevalence of diabetes also increases with age, the numbers of older women with HF and diabetes will rise,” he says.

Ahmed advocates improving diabetes diagnosis and management in these patients. “Preventing diabetes in elderly women with heart failure and preventing heart failure in elderly women with diabetes are key components for optimizing outcomes for patients with both diseases,” he says.
Atrial fibrillation (AF) affects more than 2 million Americans and is increasing in frequency. AF causes hemodynamic compromise, heart failure, a two-to-seven times increased risk of ischemic stroke, and higher overall mortality.

Antiarrhythmic drugs and anticoagulation remain front-line therapy for patients with highly symptomatic AF, but these approaches carry potentially serious adverse effects and failure rates of approximately 50% at 1 year and 84% at 2 years. Class I drugs block sodium and/or potassium channels and class III drugs primarily block potassium channels thereby prolonging ventricular repolarization. For people with symptomatic AF refractory to or intolerant of at least one class I or III antiarrhythmic drug, nonpharmacologic therapies increasingly are viable options.

“Current recommendations now place ablation of AF earlier in the treatment course,” says cardiac electrophysiologist G. Neal Kay, MD. The UAB Section of Cardiac Electrophysiology and the Division of Cardiac and Thoracic Surgery offer percutaneous and surgical ablation procedures.

“The Cox-Maze III operation is the gold standard, with a success rate of approximately 95%. The procedure is not widely used because it is technically challenging, time-consuming, and requires cardiopulmonary bypass,” Kay says. It involves an extensive cut-and-sew incision pattern to create a linear conduction barrier in the atrial wall and to isolate the pulmonary veins, pulmonary antrum, or both, the most common origins of electrical triggers that cause AF.

“We have modified the Cox-Maze III by simplifying the pattern of atrial lesions and combining cut-and-sew techniques with radiofrequency ablation and cryoablation,” says UAB cardiac surgeon David C. McGiffin, MD. “We decrease stroke risk by oversewing the left atrial appendage, which is where clots tend to form. We achieve a success rate equal to that of the traditional Maze III but have minimized the risk of the operation and shortened recovery time,” he says.

Candidates for surgical ablation are those with indications for concomitant cardiac surgery, such as mitral valve replacement, repair of coronary bypass, or repair of congenital heart defects.

The vast majority of patients with AF do not require cardiac surgery but may be candidates for catheter ablation. “We perform about 500 catheter ablations for atrial fibrillation a year,” Kay says. “The technique has an 80% long-term success rate, although approximately 25% of patients require a repeat procedure.” Using catheters that irrigate radiofrequency delivery with a saline-cooling system and electroanatomic mapping systems that sync with imaging to supply a three-dimensional picture of the catheter’s location and the ablation site have improved success and lowered risk for adverse events.

Kay and McGiffin are involved in several clinical trials for patients with AF, including a study of catheter cryoablation using a cryoballoon and a trial comparing catheter ablation with drug therapy. “This 125-center study proposes that catheter ablation is superior to antiarrhythmic drugs for reducing total mortality and incidence of stroke and other adverse events. It will be a landmark trial that shapes therapy and policy in years to come,” Kay says.
More than 80 million Americans suffer from venous diseases, which produce significant morbidity and economic costs. Venous thrombosis, for example, affects 1 in 20 people over a lifetime, with an annual incidence of 2 million cases and 60,000 cases of pulmonary embolism (PE) — the third leading cause of in-hospital deaths in the United States.

“Venous disease can be far more serious than just an unsightly embarrassment,” says UAB vascular surgeon Marc A. Passman, MD. “Symptoms can include burning, pain, swelling, and chronic skin changes in lower extremities. Venous insufficiency can affect mobility, independence, and quality of life, and venous thrombosis can cause fatal pulmonary embolism.”

In Alabama and surrounding states venous diseases affect more than 1 million individuals, and regional centers providing health care for the full spectrum of venous disease are few. To address these gaps, the UAB Vein Program offers outpatient care and hospital inpatient services to provide coordinated and comprehensive treatment for venous diseases.

Passman and fellow vascular surgeons William D. Jordan Jr, MD, chief of the Section of Vascular Surgery and Endovascular Therapy; Mark A. Patterson, MD; and Steven M. Taylor, MD; provide care for severe venous thrombotic problems; offer advanced surgical options for chronic venous insufficiency (CVI); and perform catheter-based endovenous procedures and complex venous reconstruction. Vascular medicine specialist Bart R. Combs, MD, focuses on evaluation and management of venous thrombotic disease, including venous thrombosis risk assessment and prevention, evaluation of hypercoagulable states, and medical management of anticoagulation and venous insufficiency.

“In a single setting, the UAB Vein Program identifies, evaluates, and treats the broad range of venous disease, from improving the appearance of varicose veins to surgical interventions for serious deep venous thrombosis [DVT] complications,” says UAB Vein Program Director Passman.

UAB Vein Program physicians’ extensive history treating arterial vascular problems such as aortic aneurysm, peripheral arterial disease, and carotid occlusive disease has culminated in a uniquely experienced approach for the most serious forms of venous disease with the most appropriate techniques, ranging from conventional medical therapies and minimally invasive outpatient procedures to cutting-edge surgical interventions.

VARICOSE VEINS AND TELANGIECTASIAS

More than 24 million Americans have varicose veins or spider veins, which can be a cosmetic issue for some and a medically symptomatic condition for others. These venous conditions can lead to more serious problems including spontaneous rupture, thrombophlebitis, and ulceration. Studies have found spider veins, varicose veins, superficial venous reflux, and superficial thrombophlebitis affect more women than men, but men experience higher rates of deep venous reflux and trophic skin changes (Am J Epidemiol. 2003;158:448-456).

UAB Vein Program physicians diagnose and individualize treatment for venous problems after a thorough evaluation of medical symptoms, history, comorbidities, and imaging. The program offers a variety of treatment options, including conventional medical therapies, minimally invasive procedures, and cutting-edge surgical interventions.

From Spider Veins to Life-threatening Illnesses

Vein Program Treats Full Range of Venous Conditions

A. Ultrasound-guided needle access of the saphenous vein for endovenous ablation
B. Transillumination of varicose veins for powered phlebectomy (Trivex)
C. Before and after combined endovenous ablation and Trivex
and patient concerns; clinical examination; and noninvasive testing with venous duplex ultrasound. “We offer outpatient sclerotherapy, endovenous laser treatment, ambulatory phlebectomy, and endoscopic transilluminated powered phlebectomy [Trivex] to help eliminate the unsightly appearance of veins and improve symptoms,” Taylor says. “Most are relatively simple hour-long outpatient procedures with minimal risk of scarring and postoperative infection. Recovery is rapid after such procedures, which produce excellent clinical and aesthetic outcomes.”

**CVI, Venous Ulcers**

“Compression techniques for venous stasis ulcers are cost-effective and clinically proven for the majority of venous ulcers. However, large surface area ulcers or conditions coupled with arterial insufficiency may require adjunctive techniques, including surgery,” Patterson says.

Endovenous techniques to treat superficial reflux and endoscopic techniques including Trivex, subfascial endoscopic perforator surgery (SEPS), perforator ablation, and complex venous reconstruction may benefit patients with CVI-related ulcers by locating and ligation dysfunctional veins. “Eliminating areas of treatable venous reflux with appropriate techniques can promote rapid healing of venous ulcers,” Patterson says. Studies indicate SEPS reduces morbidity, has a low recurrence rate of 3%, and facilitates healing that is up to four times faster than conventional treatment (Seminars Vasc Surg. 2005;18:41-48).

**Evaluating DVT**

“Preventing DVT and pulmonary embolism in high-risk patients saves lives,” Combs says. US health care costs for DVT exceed $1.5 billion per year. Death occurs within 1 month of diagnosis in 6% of people who present with DVT, and in about 12% of patients diagnosed with DVT and PE (Circulation. 2003;107[Suppl 23]:14-18). “We diagnose DVT with ultrasound and individualize treatment options, which include medical therapy with anticoaguants or thrombolytics and thrombectomy,” he says.

Prophylaxis in patients with a significant risk for PE is critical, especially in high-risk situations. “Prolonged sitting, bedrest, or traveling; hypertension; smoking; complex surgery; lower body trauma; obesity; MI; stroke; congestive heart failure; hormonal changes [including hormone therapy]; family history of DVT or pulmonary embolism; advanced age; and rare coagulation disorders all contribute to increased DVT risk,” Combs says. He advises that patients with these risk factors receive appropriate preventive therapies when in high-risk situations. Formal DVT risk assessment is available through the UAB Vein Program.

Suspected DVT requires rapid evaluation for proper diagnosis and treatment to prevent life-threatening complications of PE. Up to half of those diagnosed with DVT have no painful symptoms. “Anticoagulation is traditional therapy for DVT, and newer anticoagulants are available,” Jordan says. “Thrombolytics are an established component of clot management, and we are exploring a potentially expanded role for these drugs. Traditionally reserved for patients with highly symptomatic or severe extremity venous disease, thrombolytics and catheter thrombectomy are emerging as important tools in preserving venous valve function and will hopefully prevent some severe problems of postphlebetic venous insufficiency.”

**IVC Filters**

Patients at risk for PE or with the diagnosis of DVT who cannot tolerate anticoaguants or antithrombotic therapy may be candidates for inferior vena cava (IVC) filters. Using a variety of imaging options and minimally invasive techniques, IVC filters are placed to prevent clot migration to the lungs.

“Prophylactic use of permanent or retrievable filters may be appropriate in certain illnesses or injuries that result in prolonged immobility, when risks of thromboembolism are increased and anticoagulation is contraindicated,” Passman says. When critically ill patients who are at significant risk for venous thromboembolism cannot tolerate transport, he performs bedside vena cava filter placement using transabdominal duplex ultrasound or intra-vascular ultrasound. Passman has extensive experience placing bedside filters for prophylaxis in high-risk DVT patients. A Vanderbilt University study showed the bedside approach with ultrasound placement performed by trained vascular surgeons is a safe, cost-effective, and convenient alternative, with success rates comparable to standard techniques with contrast venography (Ann Vasc Surgery. 2005;19[2]:229-234). “Retrievable filters are not a replacement for permanent filters but should be considered in carefully selected patients who require temporary venous thromboembolism prophylaxis,” he says. “Ongoing studies will better define the most appropriate design, materials, and surgical procedures for implanting and retrieving vena cava filters.”

**Patient Awareness**

Passman promotes patient education through the UAB Vein Program and is cochair of the American Venous Forum’s (AVF) National Venous Screening Program that annually provides free screening and risk assessment for participants. Results of the AVF’s first national screening found a high rate of positive findings for venous disease. Investigators identified 77% of participants (most were 60 years or older and overweight) as high risk or very high risk for developing DVT if placed in high-risk situations. Signs of CVI were frequent; one in three people had varicose veins and one in five had a CVI clinical classification score ≥3, indicating skin changes due to venous disease and healed or active ulcers (J Vasc Surg. 2007;45:142-148).

“We encourage the public and health care providers to seek information regarding venous disease for this often misunderstood, underappreciated, and potentially life-threatening medical problem,” Passman says.

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Understanding Metastasis

Stopping Process Could Make Cancer a Chronic Disease

Metastasis remains the major cause of morbidity and mortality among cancer patients, but researchers are starting to untangle the complex processes of cancer cell dissemination. Recent findings regarding intrinsic and extrinsic molecular mechanisms that determine how, when, and where cancers metastasize have important implications for disease management, though translating advances will take years.

Cancer biologist Danny R. Welch, PhD, who heads the National Foundation for Cancer Research Center for Metastasis Research at UAB, has focused his laboratory’s efforts on metastasis suppressors — a class of proteins that block metastasis without inhibiting primary tumor formation. “When cancer cells migrate to a secondary location, a few proliferate and colonize and some lie dormant. A subset of suppressors keep disseminated cells inactive,” he says.

Investigators have identified more than 20 metastasis suppressors, but little is known about how they work. “Metastasis suppressors exhibit diverse mechanisms of action and act on different steps of the metastatic cascade,” Welch says. Breast cancer metastasis suppressor 1 (BRMS1), for example, suppresses breast, melanoma, bladder, and ovarian cancer cells. It inhibits transcription of osteopontin, a tumor-metastasis activator, by abrogating NF-κB, a nuclear transcription factor that regulates multiple tumorigenic and metastatic processes.

The KISS1 gene suppresses melanoma, ovarian, and breast cancer by altering tumor cells’ interaction with the microenvironment at the secondary site. “The exact mechanisms remain a mystery although recent studies provide clues,” Welch says.

Genes, such as KISS1, that stop colonization — the final step in the metastatic cascade — have the most translational potential (J Natl Cancer Inst. 2007;99:309-321). “Therapeutic intervention at any point except the endpoint is virtually fruitless. Even with early diagnosis of a primary tumor, cancer cells may be sitting in a distant site as occult micrometastases,” Welch says.

“Modulation of KISS1 protein function may enable us to hold disseminated cells in a dormant state for extended periods, making cancer a chronic disease.” Investigators have restored suppressor gene expression in metastatic cells and found that the cells did not colonize. Some epidemiological studies suggest the genes may predict a patient’s tendency for metastasis and survival.

Welch’s laboratory also strives to explain how tumor cells invade bones, the most common metastatic site for breast and prostate cancers. He and his colleagues have demonstrated that breast carcinoma cells enter the bone and manipulate normal homeostasis by killing osteoblasts. The process may explain why patients receiving bisphosphonates fail to build bone despite inhibiting osteoclast-mediated bone resorption. Welch aims to repair the defects caused by osteoblast loss by genetically engineering preosteoblastic mesenchymal stem cells that home in on regions of bone damage and replace lost osteoblasts.

Welch notes the hope behind metastasis research is that clinicians will one day exploit molecular targets scientists are now uncovering to effectively treat metastatic disease. “Although translation to the clinic is years ahead, emerging knowledge of metastatic suppressor gene function will provide new targets for novel drugs and therapies that halt metastasis.”

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Emerging Research May Improve Prostate Cancer Treatment

ABSTRACT
Discoveries related to the effects of leptin levels, insulin resistance, chronic inflammation, and resveratrol on prostate cancer offer hope for prevention. Minimally invasive surgery shortens recovery.

CME OBJECTIVE
The reader will learn about ongoing research on factors that affect prostate cancer growth and emerging diagnostic and therapeutic options.

Christopher L. Amling, MD, no conflicts of interest

Exploring obesity and chronic inflammation as potential risk factors may lead UAB clinical investigators to design novel strategies for prevention and treatment of prostate cancer, the second leading cause of cancer deaths in American men.

“Genetics and environment are critical factors in determining prostate cancer risk and are particularly important in regions like Alabama because African American men are much more likely than whites to die from prostate cancer,” explains urologic oncologic surgeon Christopher L. Amling, MD, director of UAB’s Division of Urology.

Alabama residents have elevated rates of obesity and a regional diet that is higher than the national average in saturated fat. Emerging research suggests these factors are associated with several potential mechanisms that promote prostate cancer. Amling’s work indicates hormone production from adipocytes increases leptin levels, which may stimulate prostate growth and angiogenesis. Increased saturated fat intake may lead to greater risks of lesions associated with chronic inflammation, and insulin resistance may be linked with prostate cancer progression.

Studies show increased body mass index (BMI) predicts increased cancer death rates for multiple cancers, including prostate cancer, Amling says. He led a multicenter analysis of more than 3000 men undergoing radical prostatectomy and found obesity is associated with higher grade cancer and higher recurrence rates following radical prostatectomy (J Clin Oncol. 2004;22[3]:439-445).

Another tool in prostate cancer prevention may be around the corner at UAB’s Department of Pharmacology and Toxicology, where Coral A. Lamar-tiniere, PhD, studies the antioxidant resveratrol, shown to reduce by 87% the risk of developing prostate cancer in male mice (Carcinogenesis. 2007;28:1946-1953). A 2006 study found resveratrol enabled mice fed a high-fat diet to live normal, active lives despite becoming obese (Nature. 2006;444:337-342). The compound, found in red wine, grapes, and berries, is in clinical trials and may represent a multifactorial approach to preventing prostate cancer and the long-term effects of a high-fat diet.

EARLY WARNING SIGNS
Amling studies the potential importance of chronic inflammation leading to cellular hyperproliferation (proliferative inflammatory atrophy, or PIA) hold in the initiation of prostate cancer. “PIA precedes prostatic intraepithelial neoplasia, abnormal cells detected with needle biopsy that are strongly associated with prostate cancer,” he says. “Learning to identify and treat PIA could potentially

Model for development and progression of prostate cancer.
prevent abnormal cells from becoming cancerous and replicating in the prostate.”

Amling also is exploring the possibility that prostate cancer may have an infectious etiology, and that the effects of infection, inflammation, or dietary and environmental factors may predispose cells to PIA. “Sexually transmitted diseases and prostatitis significantly increase relative risk for prostate cancer. Genetic and histologic changes may lead to defects in cellular defense against infection and oxidative stress, affecting disease initiation and development.”

### Screening Ethics

“Prostate cancer is being diagnosed in younger men, not because of an increased incidence in that population, but because more men in their 50s are getting screened,” Amling says.

Controversy has surrounded prostate specific antigen (PSA) screening for decades, as evidence regarding the benefit of early screening on long-term health outcomes remains inconclusive. Treatment that eliminates prostate cancer may introduce serious sexual or urinary side effects. Autopsy data indicate nearly 70% of 80-year-old men have prostate cancer, yet the malignancy accounts for just 3% of mortality among US men.

“PSA screening is sensitive but not specific,” Amling cautions. “PSA levels are clinically useful in guiding treatment decisions but can rise with benign prostatic hyperplasia, leading to unnecessary biopsies. Genetic testing for the PCA3 gene may provide a better screening model. The PCA3 gene, which is a noncoding segment of mRNA located on chromosome 9, is overexpressed in prostate cancer cells compared with normal cells. A simple urine test after prostate massage can identify PCA3, and unlike PSA, the test is not confounded by age, prostate volume, prostate trauma, or 5-alpha-reductase inhibitors.”

The PCA3 test is not yet approved by the Food and Drug Administration and, like PSA methods, cannot identify which cancers are likely to metastasize. However, research unveiled in an online issue of Oncogene in July 2007 shows a genetic variation within tumor cells may indicate if patients have a potentially fatal form of prostate cancer. Such findings could stratify the patients most likely to benefit from aggressive intervention. Clinical investigators found patients with prostate cancer often have a fusion of TMPRSS2 and ERG genes, yet the small numbers of patients who carry two copies of this fusion (known as 2+Edel) have a 25% rate of survival at 8 years, compared with 90% cause-specific survival among prostate cancer survivors with no alterations in the same DNA region. (Published Online: July 16, 2007 [doi:10/1038/sj.onc.1210640]).

“African American men and men who have a family history of prostate cancer should begin digital rectal exams and PSA screening at age 40,” Amling says. “Screening should begin between ages 45 and 50 in other men, particularly in those who have difficulty voiding, hematuria, or signs and symptoms of metastatic cancer.

“If an elevated PSA or abnormal digital exam leads to a diagnosis of prostate cancer, we initiate a treatment plan calculating individual risks and benefits,” he says. “Comprehensive plans range from watchful waiting to UAB’s state-of-the-art protocols for hormone therapy, chemotherapy, radiotherapy, or minimally invasive prostatectomy.”

### Radical Prostatectomy

When tumors are confined to the prostate, radical prostatectomy is likely to be curative, particularly in the hands of highly skilled surgeons. Experience is key to successful radical prostatectomy outcomes; doctors who have performed more than 250 surgeries to remove a cancerous prostate are more successful than less experienced surgeons, and prostate cancer is far less likely to relapse in men treated by experienced surgeons, according to a recent Memorial Sloan-Kettering Cancer Center study (J Natl Cancer Inst. 2007;99:1171-1177).

Amling performs open and laparoscopic radical prostatectomy using the da Vinci robotic surgical system for minimally invasive prostatectomy. “The robotic alternative offers the benefits of standard laparoscopic approaches and also provides a stereoscopic three-dimensional view with 10-fold magnification of tissue planes and neurovascular bundles,” Amling says.

Traditional open procedures require lower midline incisions and longer recovery times, but newer nerve-sparing retropubic techniques are associated with postsurgical potency rates as high as 86% from 2 to 18 months after surgery when performed by surgeons who have extensive experience with the technique. (J Urol. 2000;163[6]:1802-1807).

“The da Vinci system offers a minimally invasive approach to prostate cancer surgery that allows men to recover more quickly. Long-term studies comparing this approach to open radical prostatectomy are not yet available, but preliminary findings suggest recurrence rates and return of potency and continence are at least equivalent to traditional procedures,” he says.

The decision to undergo prostate surgery often is complicated by patients’ fears of impotence and incontinence. “Potency is largely determined by age and preoperative erectile function. About 80% of men in their 40s regain potency after nerve-sparing prostatectomy. When patients are in their 50s, that number falls to 70%, and 50% of patients older than 60 years remain potent after prostatectomy,” he says.

A majority of men now achieve full continence after prostatectomy. “More than 90% of men can expect postsurgical continence, usually within a few weeks to months after surgery,” Amling says. Meanwhile, he leads UAB’s urologic oncology research team, searching for markers of aggressive disease, devising approaches to prevent and screen for prostate cancer, and refining treatment strategies.
Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease involving innate and acquired immune systems that occurs worldwide, predominantly in young women. Women are 10 times more likely to develop SLE than men, and African Americans and Hispanics may experience higher incidences or more severe cases of SLE. “Lupus can affect any organ in the body, and because initial symptoms are often nonspecific and may present with different manifestations during disease progression, diagnosis is sometimes elusive,” says W. Winn Chatham, MD, director of UAB’s Multidisciplinary Lupus Clinic.

“Lupus is frequently associated with reduced quality of life and shortens life expectancy in patients with significant internal organ involvement,” he says. “Nearly 90% of patients with lupus experience excessive fatigue, arthralgia, and skin rashes, and 10% to 20% live with visceral organ complications such as nephritis or central nervous system complications ranging from stroke syndromes to psychosis.”

The diagnosis of lupus is still based on a composite clinical assessment of the patient’s history and physical and laboratory findings. The American College of Rheumatology (ACR) established SLE criteria for research classification purposes, not as absolute criteria for diagnosis. “Optimal outcomes are more likely if we initiate treatment at the earliest signs, rather than waiting until four ACR criteria have accrued,” Chatham says. “When applying criteria to patients, it is important to exclude non-SLE related causes of manifestations in ACR criteria.”

Several manifestations not included in ACR criteria are common in people with SLE. One study of 600 patients treated at a single center found 42% suffered from fever and constitutional symptoms, 22% had Raynaud’s phenomenon, 18% experienced alopecia, and 13% had cutaneous vasculitis (Semin Arthritis Rheum. 2004;33:217-230).

“Clinicians who avoid diagnosing SLE in patients with two or three criteria may fail to treat people with early stage disease. Such patients may progress to more serious disease that could have been prevented with earlier intervention,” says Chatham, who notes sicca symptoms and xerostomia and intolerance to sulfa drugs are common presenting features in SLE patients.

“A family history of any autoimmune disorder can be an important clue to early SLE diagnosis,” he says. “Patients with autoimmune disorders appear to have certain genetic variants that predispose their immune systems to abnormal reactions to environmental stimuli.”
Different sets of genes can produce similar clinical phenotypes in patients with SLE. Clinical investigators researching genetic susceptibility and environmental factors continue to discover genetic associations among autoimmune disorders, particularly linking genetic variants associated with SLE with those found in patients with rheumatoid arthritis (RA).

In one study, researchers found the same variant of the STAT4 gene was strongly linked with lupus in three independent collections of patients and controls. Those who carry two copies of the disease-risk variant form of the STAT4 gene have a 60% increased risk for RA and more than double the risk for lupus compared with controls (New Engl J Med. 2007;357[10]:13-22).

“We do not know how the disease associated variant of the STAT4 gene increases risk for developing RA or lupus, but knowing STAT4 plays a fundamental role in autoimmune diseases could speed development of targeted immunotherapies,” he says.

Recent SLE research suggests its pathogenesis may be one of poor housekeeping among certain cells. “In patients with lupus, apoptosis is triggered by ultraviolet light and viral infections, but the body fails to appropriately process, clear, and dispose of the products of cellular apoptosis. Deficiencies in C-reactive protein, mannoside binding lectins, or complement proteins can inhibit normal processing of apoptotic material. This apoptotic debris may then become antigenic, engendering formation of autoantibodies that play a role in triggering lupus flares,” Chatham says.

TREATMENT

“Fatigue is the most debilitating symptom of SLE and remains a problem current systemic therapies do not adequately address,” says Chatham, who advises at least 1 hour of rest a day for SLE patients. “We must find ways to prevent premature cardiovascular complications, the major cause of long-term morbidity and mortality in people with SLE, he says. Controlling hypertension is critical to avoid premature cardiovascular morbidity and renal function decline in patients with lupus nephritis.”

Patient education, rest, and suppression of inflammation are primary treatment goals. Nonsteroidal anti-inflammatory drugs, corticosteroids, or methotrexate may reduce inflammation and pain; other pharmacologic therapies include immunomodulators. “Antimalarials are usually well tolerated, improve fatigue, skin and joint manifestations, and have a favorable impact on long-term cardiovascular morbidity, but they may be ineffective in severe manifestations. The selective immune modulator leflunomide targets lymphocyte proliferation and is useful for managing articular complications,” he says.

With prompt, broad, inhibitory effects on immune cells, corticosteroids are ideal for lupus flares, but undesirable side effects require careful monitoring and limit long-term use of high doses. “If patients need corticosteroids to suppress inflammation and preserve organ function, tapering to the lowest possible dose or transitioning to alternate day dosing may help prevent osteoporosis and other catastrophic effects.”

Immunosuppressive drugs, such as cyclophosphamide, azathioprine, and mycophenolate mofetil, are traditional approaches to SLE. The drugs are steroid sparing, but may induce cytopenia or gastrointestinal toxicity. “Azathioprine has traditionally been effective for renal, cutaneous, serosal, and neurological complications of SLE, but dosing is limited by broad myelosuppression. Mycophenolate mofetil is a newer immunosuppressant that selectively targets lymphocytes, has minimal effects on patients with neutropenia, and may be better tolerated than azathioprine,” he says.

“We are working with even more selective, less toxic treatments developed for SLE. Biologic reagents in current UAB clinical trials include the monoclonal antibodies rituximab and epratuzumab, which target B cells; CTLA4-Ig fusion protein; belimumab and TACI-Ig, which target B-cell survival factors; and rhuanti-IFNα, a monoclonal reagent with specificity for interferon-α. The latter is of particular interest given its demonstrated high expression in SLE and its putative role in causing fatigue, he says.

“Encouraging patients with lupus to enroll in patient registries, clinical trials, and genetic studies will help us better understand the multiple genes and underlying factors involved in SLE susceptibility,” Chatham says. “When we can intervene earlier in the disease, we can potentially delay or avoid SLE progression and its devastating effects.”
Autism was once considered an uncommon occurrence, but now the Centers for Disease Control and Prevention estimate that 1 in 150 US children has autism or an autism spectrum disorder (ASD), with boys being three to five times more likely than girls to have the condition. With such prevalence, primary care physicians will likely see multiple patients who have an ASD. Clinicians face considerable challenges in diagnosing and treating autism and other pervasive developmental disorders, which have a diverse range of syndrome expression. Psychiatrists estimate that only 50% of children are diagnosed before kindergarten. Yet early intervention is crucial as it can produce dramatic improvements in patients’ and families’ lives.

ASDs include classic autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). The more severe ASDs — Rett syndrome and childhood disintegrative disorder — are quite rare. Important differences exist, but all are characterized by some degree of dysfunction in communication, reciprocal social interaction, and behavior patterns. Children with autism also may have unusual responses to sounds, lights, or the way objects look.

Increasing Incidence

The number of autism cases has increased rapidly in the last decade, but reasons for that growth are unclear. “Prevalence has not necessarily increased,” says UAB child and adolescent psychiatrist Latamia M. White, MD, “but awareness has, and we are using a much improved diagnostic classification.” The developmental disorder currently has no cure, and its etiology remains undetermined. Twin studies have shown a strong genetic link. If an identical twin has the disorder, the chance that the co-twin will have it is between 70% and 90%, and siblings of ASD patients have 10 times the risk of the general population (Lancet. 2003;362:1133-1141). “Heritability accounts for most of the risk, but genetic factors do not fully explain it. Rather than a single mechanism, a cluster of factors is probably at work, and environmental agents may play a part. Evidence of reported connections to immunizations is anecdotal, but those associations merit scientific research before we rule them out,” White says. About 10% of autism cases are due to single-gene disorders or chromosomal abnormalities.

Early Identification Crucial

Autism spectrum disorders can be reliably detected in children ≥3 years, and in those as young as 18 months. Studies suggest that earlier diagnoses — some in children aged 1 year — may be possible in the next 5 years. Recently, researchers identified the disorder at 14 months, the earliest autism
Early diagnosis facilitates timely interventions that significantly improve outcomes and lessen family stress. “Research shows that children’s prognoses are much better when they are diagnosed and treated within the first 24 months of life,” White says.

A new clinical report from the American Academy of Pediatrics (AAP) recommends universal formal ASD screening for children aged 18 and 24 months whether or not there are concerns (www.pediatrics.org/cgi/doi/10.1542/peds.2007-2361. Accessed November 14, 2007). When concerns arise, a comprehensive evaluation by a multidisciplinary team is indicated. Although finding time for screening in a busy practice is challenging, it is crucial to do so, White says. For every 1000 patients they see, primary care physicians will have five or six children with an ASD. “Most pediatricians recognize developmental red flags, and parents, who often are the first to notice something is ‘not quite right,’ will mention problems,” she says. According to the AAP report, absolute indications for immediate evaluation include: no babbling or pointing or other gesture by 12 months; no single words by 16 months; no two-word spontaneous phrases by 24 months; and loss of language or social skills at any age.

“Several instruments are available that quickly gather information within medical settings about a child’s social and communicative behaviors.” She recommends the Checklist of Autism in Toddlers (CHAT), (www.depts.washington.edu/dataproj/chat/html), the Parental Evaluation of Developmental Status (www.pedstest.com/index.php), and the Child Development Review (www.childdevrev.com).

Asperger syndrome and high-functioning autism screening tools include the Autism Spectrum Screening Questionnaire (J Autism Dev Disord. 1999;29[2]:129-141) and the Childhood Asperger Syndrome Test (www.autismresearchcentre.com/tests/cast_test.asp). White often sees children who are diagnosed late. “Physicians frequently find the word ‘autism’ hard to introduce to parents in an office visit. A pediatrician might take a wait-and-see approach when parents come to them with concerns about speech, for example, but well-intentioned efforts to postpone identifying the disability deprive children of essential specialized attention. First time parents, having no reference point, may not notice delays, putting these children at higher risk for late recognition. If there is a developmental abnormality or something unusual is noted on the CHAT rating scale,” she says, “take a better-safe-than-sorry approach. Refer them for an initial evaluation with a speech or behavioral specialist. Do not lose the opportunity for critical early intervention.”

**Differential Diagnosis**

Delayed or abnormal speech often is the first indicator of an ASD. Also present may be an impaired reciprocal social interaction and the absence of affect sharing, eye contact, social referencing, interest in peers, simple pretend play, and orienting to name. Clinicians also should ask parents about prenatal development, sleep, diet, coordination problems, sensory hypersensitivities, allergies, immune deficiencies, and exposure to toxins.

Differentiating among classic autism, Asperger syndrome, PDD-NOS, and other developmental disorders can be complicated. Diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR outline the specifics. In autistic disorder, the apparent onset of symptoms is usually within the first 2 to 3 years of life.
life. In addition to language delay, parents notice stereotyped movements. In Asperger syndrome, early development is normal. The child may have unusual interests they pursue with intense focus. Poor peer relationships and lack of empathy surface as the child reaches school age. In PDD-NOS social deficits are less severe than in classic autism. Individuals may have early or late age of onset, impaired reciprocal social interaction or communication skills, and stereotyped behavior and interests.

A clinic such as the UAB Autism Clinic can provide extensive assessment and referrals to specialists. Because symptom presentation varies, diagnostic evaluations at the UAB clinic include information from audiology, optometry, speech and language, occupational therapy, social work, and neurology. Specialists can give families verbal and written information and resources for developing a comprehensive treatment program.

Autism requires a multidisciplinary treatment model that includes the participation of parents, speech, behavioral, and occupational therapists, school personnel, a psychiatrist, psychologist, and social worker. A core physician tailors treatment to address the individual’s specific needs. Initial therapy should be consistent, intensive (at least 25 hours a week), and must involve family, White says.

Intervention should begin in highly structured situations and over time can be generalized to more naturalistic ones. Therapeutic targets may include improved verbal and nonverbal communication, enhanced social skills, and replacement of maladaptive behaviors with developmentally appropriate behaviors. Working on fine and gross motor skills and development of academic and organization skills also are goals. Occupational therapists focus on sensory integration problems.

Parental involvement has emerged as a major factor in treatment success. Educated parents can reinforce therapy at home. “The more information they have the easier it is to navigate the complexities of the disorder,” White says. “The news can be devastating, particularly when a child is initially diagnosed. It is helpful for clinicians to offer parents resources, such as books or Web sites.

National organizations, such as the Autism Society of America, and parent-run organizations such as Autism Speaks, coordinate support groups that help parents and families cope.

PHARMACOLOGIC INTERVENTION

The Food and Drug Administration has approved risperidone for treatment of autism spectrum symptoms. Studies have shown it is a safe and effective long-term medication that decreases self-injury, aggression, agitation, stereotypy, and hyperactivity (Eng J Med. 2002;347:314-321) and (J Am Acad Child Adolesc Psychiatry. 2005;44:1137-1144). The medication can cause weight gain. White is recruiting participants for a multicenter study of aripiprazole, another atypical antipsychotic drug, which causes little or no weight gain. Such antipsychotics can reduce aggression, self-injurious behavior, and tantrums. Selective serotonin reuptake inhibitors, neuroleptics, tricyclic antidepressants, lithium and mood stabilizers, and anxiolytics may have varied efficacy. “Autism patients must be monitored carefully, as they may not have typical responses to medications. Clinicians also must be aware of potential drug-to-drug interactions,” she says.

Some families choose to add complementary and alternative remedies. “As long as it will not be harmful, and the family can use the method consistently for a year, I tell them it is worth a try,” White says. “Some families use gluten-free or casein-free diets and swear their child does much better.” Pet therapy, eliminating fluorescent light, and swimming help some patients. White cautions that parents should try a single method at a time to determine its effectiveness. “Above all, primary care physicians should maintain an open-minded, balanced perspective on treatment and work collaboratively to educate parents to achieve an approach that works for that family. If there is any question about an observed behavior, refer the child for an evaluation to take advantage of early interventions, which are becoming more sophisticated and effective,” White says. Research aimed at finding a cause and a cure for autism continues. Meanwhile, early diagnosis and intervention are the most effective tools for improving outcomes for children with ASDs.

RESOURCES

BOOKS:
Jessica Kingsley Publishers:

Future Horizons: www.futurehorizons-autism.com

Tony Atwood: www.tonyattwood.com.au

WEB SITES:

www.autism-alabama.org
www.autism-pdd.net/links/alabama.html
www.iser.com/AL.html
www.cdc.gov/ncbddd/autism/index.htm
www.autism-society.org
www.autismspeaks.org/index2.php
www.nimh.nih.gov/publicat/autism.cfm
www.aspennj.org
www.patientcenters.com/autism
www.autism.org
www.autism.com/dan/index.htm
www.aspergers.com

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Migraine and Cardiovascular Disease Risk

**ABSTRACT**
While migraine may be linked to cardiovascular disease (CVD) in a small subset of patients, the mechanisms remain unclear. What is clear is that migraine headaches are undertreated.

**CME OBJECTIVE**
The reader will better understand the risk of CVD in people with migraine and better understand the appropriate therapeutic approach to acute and chronic migraine. John F. Rothrock, MD, no conflicts of interest.

The International Headache Society (IHS) has identified and classified 130 different types of headache. Migraine, the second most common neurological disorder in the United States, is a significant public health issue, affecting 12% of adults and causing 157 million missed work days annually with a cost burden of $12 billion (J Occup Environ Med. 2007;49:368-374). A flurry of research now suggests that, in addition to its debilitating nature, migraine also may lead to significant health consequences.

**CARDIOVASCULAR DISEASE RISK**

“A number of studies show the risk of ischemic stroke in migraine is increased about two- to threefold relative to gender- and age-matched nonmigraineurs. There is not much question about that,” says UAB neurologist John F. Rothrock, MD, editor of Headache.

In one comprehensive analysis of studies on migraine and cerebrovascular disease, investigators found that women who experienced migraine with aura (MA) had the highest risk of stroke (BMJ. 2005;330:63-65). Kurth and colleagues’ analysis of prospective data from the Women’s Health Study (WHS) found women aged >45 years with MA had 1.5-fold increase in risk of ischemic or hemorrhagic stroke and 1.7-fold increase in risk of ischemic stroke (Neurology. 2005;64:1020-1026).

In an additional analysis of WHS data, Kurth et al found women with MA had an increased risk of both intracerebral and subarachnoid hemorrhage (Stroke. 2007;38:458). He notes that the total number of strokes in this population was very small. “Stroke remains a rare complication of migraine,” Rothrock says.

**CORONARY HEART DISEASE**
The relationship between migraine and coronary heart disease (CHD) is less clear, although early evidence seems to indicate increased risk in male and female migraineurs (Neurology. 2004;63:2233-2239) and (Headache. 2004;44:[suppl. 1] S5-12). Kurth and colleagues again analyzed WHS data and found that MA, but not migraine without aura, was linked in women to increased risk of CHD, including angina, myocardial infarction (MI), and coronary revascularization procedures (JAMA. 2006;296:283-291).

In another observational study, Kurth and colleagues found the associations between migraine and major CVD, ischemic stroke, and MI in men to be compatible with findings from the WHS. In the prospective cohort of more than 20,000 men, Kurth found a 24% increased risk of major CVD and a 42% increased risk of MI (Arch Inter Med. 2007;167:795-801).

While the association between migraine (particularly MA) and CVD seems clear, the exact mechanisms underlying the increased risk are undetermined. One question to ask, says Rothrock, is what factors beyond migraine alone may increase stroke risk. “Risk of stroke appears to be higher for women with migraine with aura,” he says. “Oral contraceptive use and smoking likely add to that risk” (Stroke. 2007;38:2438-2445). The IHS recommends female migraineurs who use oral contraceptives stop smoking and have regular checkups for cardiovascular risk factors.
“Even so, very few migraineurs are at high risk for CVD, and in the concern over this relative handful, one should not lose sight of the millions of Americans who suffer debilitating migraines that affect the quality of their daily life,” Rothrock says.

Migraine Inadequately Treated

Migraine headaches are highly co-morbid with depression, interfere with daily activities, often necessitate bed rest, impair cognitive ability, and may reduce work or school productivity by half or more. Effective medications are available but are underused. Too often migraineurs resort to emergency department care, waiting hours for treatment, even though the longer an acute migraine attack lasts, the harder it is to treat. “Emergency physicians may order brain scans or other unnecessary tests and prescribe a nonspecific drug or no medication at all for the acute migraine,” Rothrock says. “Often the patient leaves the ED no better, and even if there is improvement, chances are good the migraine will recur at home.”

Triptans, specifically injectable sumatriptan (Imitrex), are the most effective prescription medications for acute migraine. Treatment with a triptan within 20 minutes of onset is 90% effective in alleviating the attack (Ann Neurol. 2000;47:614-624). “These drugs, particularly injectable Imitrex, are underutilized,” Rothrock says. Health care providers cite concerns about the cardiovascular safety of triptan therapy, despite the 2004 American Headache Society consensus statement that acknowledged there is no evidence of an increased risk of cardiovascular morbidity or mortality with triptan use in the indicated population or even the population for whom the drugs are contraindicated (Headache. 2004;44:414-425). After an exhaustive search of the relevant published literature, investigators found: (1) most data on triptans and cardiovascular morbidity were derived from patients without known coronary artery disease; (2) chest symptoms occurring during use were generally nonserious and were not explained by ischemia; (3) the incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice was extremely low; and (4) the cardiovascular risk-benefit profile of triptans favored their use in the absence of contraindications.

Why the disconnect? “Educating patients in the use of injectable Imitrex use is time consuming, and uninformed patients understandably are concerned about side effects, such as chest pressure and neck squeezing, which lead them to think they are having a heart attack,” Rothrock says.

Oral triptans, which are prescribed more often than injectable Imitrex, are inconsistently effective when used for moderate to severe headache. They are more effective if used early in an attack. Rothrock suggests primary care physicians become familiar with two or three oral triptans, instruct patients how to use them optimally (ie, take the tablet at the beginning of an attack), and provide a rescue medication for more severe headaches. “Specifically,” Rothrock says, “physicians should teach their migraine patients how to best use injectable Imitrex and explain its side effects.”

Chronic Migraine

One in 50 Americans has chronic migraine, and each year that number increases. The IHS recently introduced diagnostic criteria for chronic migraine: Individuals have chronic migraine if they (1) have had at least five previous migraine attacks; and (2) currently have at least 15 days of headache per month, at least 8 days of which involve migraine headache or headache that responds to a triptan or ergotamine. This population has the most profound clinical need for prophylactic therapy, but only recently has the research focus shifted from episodic to chronic migraine.

Two drugs receiving the most attention are botulinum toxin type A (BoNTA) and topiramate (Topamax). While BoNTA does not appear to be effective for episodic migraine or tension headache, preliminary data from large scale multicenter clinical trials suggest it may suppress chronic migraine. A national trial is underway to evaluate BoNTA’s safety and effectiveness. “Early data look promising, with results in responders lasting 3 to 6 months at the cost of no or few side effects,” Rothrock says.

Topiramate is Food and Drug Administration-approved for the prevention of episodic migraine, and several studies published in 2007 have shown the medication is effective in reducing migraine or migrainous headache days in those with chronic migraine (Headache. 2007;47[1]:139) and (Cephalalgia. 2007;27[7]:814-823).

Rothrock and colleagues are recruiting for several clinical trials, including a study of a migraine drug that works through a different mechanism from that of currently available prophylactic medications, and an investigation of the anticonvulsant levetiracetam (Keppra) as a rescue medication for migraine that is refractory to self-administered therapy.

While migraine may be linked to CVD in a small subset of patients, and further study may be necessary to delineate that relationship, millions of Americans suffer daily from chronic headache. “These people are miserable and cannot fully participate in their lives. Relieving their pain is the most important migraine-related public health issue facing clinicians and researchers,” Rothrock says.
New Therapies for Viral Hepatitis

UAB Liver Center Trials for HCV

Hepatitis C virus (HCV) infects an estimated 4 million Americans. Eighty percent of these individuals develop chronic disease, making it the leading cause of liver transplantation.

The cornerstone of care for chronic hepatitis C is the combination of peg-interferon alfa-2a/b and ribavirin, which is effective for up to 90% of patients with genotype 2 or 3 HCV and between 40% and 50% of those with genotype 1. HCV has at least six distinct genotypes, which play a significant role in therapeutic decisions.

“Up to 15% of HCV patients cannot tolerate labor-intensive interferon therapy, which is notorious for adverse side effects. Ribavirin adds to that burden, and poor adherence is common,” says UAB hepatologist Michael B. Fallon, MD.

Treatment with combination pegylated interferon and ribavirin may be required for a year or longer. The UAB Liver Center’s clinical trials group is dedicated to finding novel approaches to fine-tune and shorten treatment duration. “Shorter regimens are better tolerated and more likely to result in adherence — a key factor in positive treatment outcomes,” Fallon says. Several clinical trials are underway examining novel small molecules and alternative doses of ribavirin and pegylated interferon. “We are using the latest agents combined with new approaches for patients who are refractory to standard treatment or who have complicating comorbidities, such as HIV or end-stage renal disease,” he says.

Multicenter studies at UAB are assessing the safety and efficacy of various pegylated interferon and ribavirin combinations. Investigators are recruiting patients for a trial evaluating higher doses of peginterferon alfa-2a (Pegasys) or higher ribavirin doses in individuals with genotype 1 to achieve an improved virological response.

A second study compares efficacy and safety of albumin interferon alfa-2b and ribavirin to the current standard of care in treatment naïve patients. Early studies have shown albumin interferon alfa 2b induces antiviral responses in this population and those refractory to a peginterferon and ribavirin combination. This combination will extend time between doses, increasing regimen convenience.

The Liver Center is enrolling patients in a trial evaluating daily consensus interferon (Infergen) and ribavirin in partial responders or nonresponders to previous interferon therapy. This study is open to HCV monoinfected and HIV coinfected patients.

Liver Center investigators are considering new trials to discover medications for hard-to-treat populations, such as nonresponders and patients with thrombocytopenia, insulin resistance, and HIV. Treatment options for patients with hepatitis B also are a research interest.

Comprehensive Care
Clinical and translational research are key components of UAB’s Liver Center, which offers patients comprehensive care, education, support, and serves as a resource for physicians with patients diagnosed with HCV and other liver diseases.

Current translational research at the Liver Center is limited to the pathogenesis of pulmonary vascular complications of chronic liver disease. In the near future efforts will expand hepatitis C research and will eventually encompass all aspects of liver disease.
Fundoplication for GERD

Provides Freedom From Reflux for Selected Patients

Acid suppression remains the therapeutic mainstay for gastroesophageal reflux disease (GERD). Highly effective antireflux agents, particularly proton pump inhibitors, provide symptomatic control and esophageal healing for the vast majority of patients. Yet for a select population — individuals with severe reflux and those who are intolerant of or refractory to medications — antireflux surgery can relieve painful symptoms, prevent, and sometimes reverse esophageal damage as well as the laryngeal and pulmonary complications associated with GERD.

“Fundoplication is an option for patients whose symptoms impair their quality of life, such as those with GERD-related dysphagia that interferes with eating and individuals who have nocturnal regurgitation of acid or food, which can cause heartburn, chest pain, coughing, choking, and sleep disturbances,” says UAB’s Chief of the Section of Gastrointestinal Surgery Mary T. Hawn, MD. “Although there is no evidence fundoplication prevents esophageal malignancy, the procedure eliminates symptoms without the need for medications in 90% of carefully selected patients.”

Only 5% to 10% of patients have refractory or severe enough GERD to warrant surgical evaluation for fundoplication. “Because antireflux drugs are so effective, the diagnosis of GERD should be reconsidered in nonresponsive patients. We must also define anatomy with a barium swallow study and/or flexible endoscopy, which can reveal strictures and other abnormalities of the esophagus or stomach,” Hawn says.

Motility can assess esophageal function and a 24-hour pH probe can measure the amount of acid refluxed into the esophagus and determine if symptoms are associated with those acid reflux events.

When presurgical studies show patients are likely to benefit from antireflux surgery, Hawn typically performs a laparoscopic Nissen fundoplication (360º wrap). During the procedure the fundus of the stomach is completely wrapped around the esophagus to create a mechanical barrier against gastric refluxate. Hiatal hernias, which are common in patients with GERD, are repaired during the same procedure.

“Partial wraps are not as durable as complete fundoplication. Wraps in obese patients also tend to break down, and I advise these individuals to lose weight prior to surgery,” she says. “Weight loss may even cure reflux or bring symptoms under control.”

Recent data show laparoscopic fundoplication is effective and durable, with 90% of patients symptom free 10 years after surgery (Surg Endosc. 2006;20:159-165). Hawn says surgeons have experimented with general endoscopic therapies including radiofrequency ablation and injection of polymer fillers to strengthen the esophageal sphincter. These techniques have proven ineffective, providing minimal improvement in reflux control.

Up to 20% of patients develop new conditions after surgery — typically dysphagia and gas-bloat syndrome. “People with uncontrolled GERD often are willing to accept such complications rather than continue to suffer with chronic, painful reflux,” she says. “Physicians should consider fundoplication for patients with severe or medically refractory GERD. In addition, patients who have extra-esophageal symptoms such as hoarseness and coughing should undergo endoscopic evaluation to uncover conditions that could lead to GERD-related injuries.”
Pregabalin (Lyrica) for Postsurgical Pain

Pilot Study Underway at UAB

A key area in acute pain research focuses on new analgesics or combinations to reduce the need for opioids and their unwelcome side effects.

UAB investigators have joined the search with a new study of the gabapentinoid pregabalin (Lyrica), a nonnarcotic that is Food and Drug Administration-approved for diabetic peripheral neuropathy, postherpetic neuralgia, partial onset seizures in epilepsy, and since June 2007, for fibromyalgia.

“Gabapentin’s exact mechanism of action is unclear, but it appears to attenuate the hyperexcitability of the dorsal horn neurons, reducing pain sensation,” he says. “Pregabalin works through the same pathways, and preliminary studies indicate equivalent efficacy with fewer dose-related adverse effects,” says study coinvestigator and anesthesiologist Aimee H. Walsh, MD, who is medical director of UAB’s Pain Treatment Clinic.

Volgas and Walsh are evaluating pregabalin’s effectiveness in postoperative pain management for patients who have sustained an orthopaedic fracture, including pelvic fractures, that requires operative fixation. Only patients who undergo a single surgical episode will meet the inclusion criteria.

The need for opioids varies by patient, but the drugs often are required for weeks after surgical repair, either due to incision pain, rehabilitation, or fracture-related nerve injury. “Opioids do not alleviate true neurogenic pain associated with fractures,” Volgas says.

Pregabalin, as part of a multimodal approach to managing acute postoperative pain, may lessen such nerve pain and reduce opioid usage, thereby avoiding side effects (sedation, respiratory depression, concentration problems) and potential for addiction.

Volgas and Walsh plan to enroll 100 patients aged 19 to 70 years for the pilot study that started in May. Prior to surgery investigators randomize patients to placebo or pregabalin, and participants receive narcotic pain medication as determined by the attending physician. On postoperative day one, patients are given oral oxycodone as needed with Demerol for breakthrough pain. In addition, they receive pregabalin (either 75 mg or 150 mg twice a day) or placebo. On discharge, participants are given hydrocodone and pregabalin or placebo. Investigators will follow patients for 3 months.

The primary end points are the amount of narcotic used during hospitalization and the outpatient period. Other end points include pain scores, the time and frequency of use of rescue analgesics, quality of life parameters, and adverse events.

“We anticipate better pain control with fewer opioid-related adverse effects in the groups receiving pregabalin. This drug could be an effective adjunct to pain management in patients, such as elderly individuals, who are at risk for becoming overnarcotized,” Volgas says.
Total Ankle Arthroplasty

New Protheses Offer Good Results

Advanced surgical techniques coupled with new ankle implant designs make total ankle arthroplasty an acceptable option for end-stage joint disease. UAB orthopaedic surgeon John S. Gould, MD, has refined the surgical technique to achieve favorable outcomes. His colleague John S. Kirchner, MD, also performs the procedure.

“Our goal is relieving pain, maintaining ankle motion and function, minimizing stress on surrounding structures, and preventing development of progressive arthritis in surrounding joints,” Gould says.

Ankle joint arthritis is most often seen in patients with severe posttraumatic arthritis, rheumatoid arthritis, or osteoarthritis. Symptoms and signs may include swelling, stiffness, increased pain with weight-bearing activity, decreased range of motion, visible ankle joint deformity, a limp, or instability secondary to pain.

According to Gould, other treatments for ankle arthritis include ankle supports and braces that limit or completely block motion or axially unload pressure on joint surfaces. Some devices both unload the joint and block motion.


Prostheses

Unfavorable long-term results and high complication rates once limited use of ankle joint replacement. The new generation of prostheses has improved outcomes, however, and UAB surgeons commonly use the LP Agility Total Ankle Replacement, Salto Talaris Ankle, and In-Bone Ankle implants.

“The LP Agility dual anchor system addresses the cause of first generation implant failure, which was often due to loosening of the prosthesis resulting from poor bone fixation and improper alignment during installation,” Gould says.

The Salto Talaris Ankle anatomic design provides stability with a hollow fixation plug and three bone cuts to resurface the talus with minimal bone removal. “Bone preservation increases longevity and provides more options if revision surgery is required,” he says.

“The Salto’s customized components offer precision alignment of the tibial and talar components, reducing stress on the joint, minimizing loosening and wear, and promoting reproducible results.”

New designs facilitate earlier mobilization and improved overall prosthetic longevity. Older Agility implants had an average 70% 10-year survivorship. New models should be more durable,” he says.

“Ideal arthroplasty candidates are aged 50 years or older, with postinjury or post-multiple-sprain arthritis or those who have experienced a prosthesis failure. Patients who have ankle fusions with adjacent arthritic surrounding joints also are candidates,” Gould says. “In the past, technical aspects of ankle replacement limited its usefulness, but current implants are carefully detailed, with precision equipment for insertion, which enables us to achieve excellent, reproducible results.”

FOR MORE INFORMATION

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Glaucoma affects an estimated 3 million adults in the United States and remains one of the leading causes of blindness. Treatment options are currently aimed at lowering intraocular pressure (IOP) to prevent ocular nerve damage. Medical or surgical therapy can limit this damage by improving aqueous outflow or reducing aqueous production.

Although existing glaucoma treatment can control elevated IOP and slow disease progression, a cure is still elusive. Glaucoma therapies continue to improve, but further progress is dependent on identifying advances that produce durable results, says Jason C. Swanner, MD, assistant professor of ophthalmology.

Monotherapy with topical medications such as prostaglandin analogues, which increase aqueous fluid outflow, is one of several first-line treatments for glaucoma. However, multidrug regimens—carbonic anhydrase inhibitors plus a beta blocker, for example—often are necessary to achieve therapeutic goals, Swanner says.

Current glaucoma research includes clinical trials examining memantine, a drug used to treat Parkinson’s disease and Alzheimer’s disease. Researchers in UAB’s Department of Ophthalmology are studying the drug’s effect on the optic nerve. Results of these phase 3 trials will not be available for some time, but investigators are optimistic that memantine may offer some protection to the optic nerve.

Surgical intervention for glaucoma may be appropriate when patients do not achieve target IOP with successive medical therapies. Advances in surgery include selective laser trabeculoplasty (SLT), which improves fluid drainage while avoiding the ocular scarring associated with traditional argon laser trabeculoplasty (ALT).

A clinical trial underway at UAB compares the effectiveness of the SOLX Gold shunt, an investigational aqueous implant, with the Ahmed Glaucoma Valve. Both devices increase aqueous outflow to lower IOP. Although currently approved shunts may not reduce IOP as effectively as SLT or ALT, they lower the risk of scarring. Candidates for the SOLX trial are individuals with primary open-angle glaucoma who have not responded adequately to medication and conventional first-line surgical interventions.

The SOLX Gold shunt is in phase 3 trials throughout the United States, Canada, and Israel. UAB is 1 of 11 participating centers. “The SOLX implant is different because it creates a new fluid pathway by connecting the anterior ocular chamber and the suprachoroidal space,” Swanner says. “The SOLX shunt remains permanently in the suprachoroidal space and may prevent the scarring associated with other surgical methods.”

In addition to its innovative placement, the shunt is made of 24-karat gold and contains multiple channels that can be opened to provide additional flow routes from the anterior chamber to the suprachoroidal space. This new method of IOP control allows postsurgical adjustment to achieve target pressures.

“If the SOLX shunt effectively lowers IOP, its novel aspects represent promising advances that could optimize outcomes for patients in the near future,” Swanner says.
Reynolds Historical Library Celebrates 50th Year

Holdings Include 13,000 Rare Medical Texts

The pale, leather-bound first edition of Andreas Vesalius’s *De Humani Corporis Fabrica Librorum Epitome* (On the Workings of the Human Body) rests inconspicuously on a shelf in the Reynolds Historical Library. This groundbreaking volume of human anatomy — published in 1543, dedicated to Holy Roman Emperor Charles V, and believed to be illustrated by Titian’s pupil Jan Stephen van Calcar — is surrounded by thousands of other rare works of medical literature of immense historical value.

In addition to *De Fabrica*, UAB’s collection contains many other volumes related to the famous Flemish-born anatomist, including his later works, books by his teacher, and volumes by his pupils and other anatomists of the period, many of whom embraced his ideas.

“Vesalius was the first to emphasize human dissection and an understanding of the body as a structure filled with organs arranged in three-dimensional space,” explains Associate Director for Historical Collections Michael A. Flannery. “Before Vesalius, most ideas on human anatomy came from the first-century physician Galen, who based his teachings primarily on animal dissection.”

The library boasts other major works that laid the groundwork for modern medicine: a 1628 printed volume by William Harvey, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings), a text that offered the first proof that the heart pumps blood through the body and a selection of works by the celebrated 16th century surgeon Ambrose Paré, who developed many surgical methods based on ideas introduced in *De Fabrica*.

Other important works include one-of-a-kind incunabula, extremely rare handwritten books produced before 1501. The library holds more than 30 incunabula, including Arnold of Villanova’s *Brevarium Practicae Medicinae* (1485) and A Commentary on the Ninth Book of the Al’ Mansuri written by Tolbiel ben Samuel in the early 15th century.

“We hold one of only five original copies of the first medical book ever published in America — *The English Physician* by Nicholas Culpeper [1708],” says Flannery, who edited a reprint with an introduction and details on the brews and concoctions used for medical treatment in the early days of the North American colonies.

The Reynolds Library also holds a collection of the correspondence of famous health care figures. Among these handwritten treasures are letters written by Louis Pasteur, Florence Nightingale, Oliver Wendell Holmes Sr, Sir William Osler, and George and Martha Washington.

Laying the Foundation

On February 2, 1958, eminent radiologist Lawrence Reynolds, MD, (1889-1961) officially dedicated his collection of more than 5000 rare books and letters to UAB to form the core of the Reynolds Historical Library, which is now recognized as having one of the finest and most valuable collections of medical literature in the world.

Reynolds was born in the small Alabama town of Ozark. “His love of books began in his youth, when he read to his physician father, who lost his sight in old age,” Flannery says. “In his later years, Reynolds spent much time and money amassing exceptional works of medical literature.”

Although Reynolds was an Alabama native, his career took him away from the state permanently, and with
a number of institutions seeking to acquire his valuable collection, its donation to UAB was by no means certain.

Reynolds completed his undergraduate education at the University of Alabama. He received his MD degree from John's Hopkins Medical School in 1916 and was the first radiology resident at Johns Hopkins Hospital. After 2 years of World War I military service in France, he spent 3 years as a roentgenologist at Harvard Medical School and Peter Bent Brigham Hospital in Boston. Reynolds joined Harper Hospital in Detroit, Michigan in 1922 and remained there until his death.

Wayne State University, the University of Michigan, Yale University, and others lobbied for the collection, but ultimately, Flannery says, “Reynolds’ Alabama roots motivated him to return something of great value to his native state.”

THE COLLECTION GROWS

Flannery notes that since Reynolds’ original contribution to UAB, the library’s holdings have expanded to include almost 13,000 works. A major area of concentration is Civil War medicine, a collection that began with substantial support and expertise from former UAB Department of Surgery Chair Arnold G. Diethelm, MD, an ardent champion of the library.

“The medical and surgical history of the Civil War is laid out in published memoirs of Union and Confederate physicians and soldiers, original copies of official medical handbooks and guides, and a massive three-volume set of *The Medical and Surgical History of the War of Rebellion* [1870-1888] — the most comprehensive summary of Civil War medicine available,” Flannery says. More recent acquisitions include books related to diseases common to the South — malaria and cholera, for example.

UAB Historical Collections

The university’s commitment to the medical humanities has continued, with the library and related areas growing to become “a more powerful resource for medical history and research than anything Lawrence Reynolds could have imagined 50 years ago,” Flannery says.

In 1996 the Reynolds Historical Library evolved into the UAB Historical Collections, which encompasses three distinct entities — the Reynolds Library, the Alabama Museum of the Health Sciences, and the UAB Archives. The museum holds instruments, specimens, and models that represent the practice of medicine around the world for the past 700 years and intricately carved male and female ivory figurines, or anatomical manikins, each with removable upper trunks that expose the viscera. “The figurines were most likely made during the 17th and 18th centuries to show internal differences between the sexes,” Flannery says. The UAB Archives is a repository for original documents pertaining to UAB as well as materials related to the history of health sciences in Alabama.

Flannery credits much of this growth to strong supporters who include Diethelm; former UAB presidents S. Richardson Hill Jr, MD, and Charles A. McCallum Jr, DMD, MD; founder of UAB’s Division of Rheumatology Howard L. Holley, MD; School of Medicine Dean Emeritus and UAB Distinguished Professor James A. Pittman, MD; and former Reynolds Library Associates Chair Wayne H. Finley, MD.

“This collection is more than just a window into history — it represents a constellation of medical humanities supporting activities that enrich our understanding of all of medicine,” says Flannery, who recalls the official 1958 dedication inscribed on the entrance of the library:

*Each time one of you reaps from the great minds of the past the desire for finer achievements in your profession and nobler development of your own character, the Reynolds Library will have been rededicated.*

(Top) Hans von Gersdorff illustrates an early amputation in *Feldbuch der Wundartzney* (1517 folio)

(Bottom) Woodcut of human skeleton from *Hortus Sanitatis* (1497)

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EMERGENCY MEDICINE

Jarred J. Thomas, MD, has accepted an appointment as assistant professor of emergency medicine and director of the future Emergency Department Chest Pain Evaluation Unit, which will focus on rapid evaluation and care of patients with acute chest pain. Thomas received his MD degree from the University of South Alabama College of Medicine, where he completed an internship in medicine. He subsequently did an emergency medicine residency at UAB, serving as chief resident, and a cardiovascular emergencies fellowship at the University of Virginia. His clinical and research interests include acute coronary syndromes, myocardial infarction, and risk stratification.

NEUROLOGY

John R. Rinker II, MD, has accepted an appointment as assistant professor of neurology. A graduate of the Medical College of Georgia in Augusta, Rinker completed an internship in internal medicine and a residency in neurology at Barnes-Jewish Hospital in St. Louis. He held a postdoctoral fellowship and recently completed the K30 Mentored Training Program in Clinical Investigation at Washington University in St. Louis School of Medicine. His research interests center on the study of biomarkers for disability outcomes in multiple sclerosis (MS); ethnic differences in MS, specifically in disability outcomes and immune function; and immunological differences among clinical subtypes of MS.

NEURORADIOLOGY

Joseph C. Sullivan III, MD, has accepted an appointment as assistant professor of radiology in the Division of Neuroradiology. His interests include all forms of imaging of the brain, head, neck, and spine, with a particular interest in magnetic resonance imaging and computed tomography of the spine. Sullivan pursued graduate studies in biology at the University of South Alabama before earning his MD degree from St. George’s University School of Medicine in Grenada. He served as an intern in general surgery at Wake Forest University Baptist Medical Center before completing a residency in diagnostic radiology at the University of South Alabama, serving as chief resident. He completed a fellowship in neuroradiology and comes to UAB from the Medical College of Georgia, where he was twice voted teacher of the year.
OBSTETRICS AND GYNECOLOGY

Todd R. Jenkins, MD, has accepted an appointment as associate professor of obstetrics and gynecology and as director of the Division of Women’s Reproductive Health Care. Jenkins’ clinical and research interests include hysteroscopic and laparoscopic surgery, robotic surgery, general gynecology, and instruction of medical students, residents, and practicing physicians in minimally invasive gynecology.

A graduate of UAB School of Medicine, Jenkins completed an internship at University of Cincinnati Hospital and a residency at UAB in obstetrics and gynecology. He began practice in the PrimeCare Group at The Kirklin Clinic before accepting a position at the University of California, Irvine (UCI), where he served as director of women’s ambulatory care for the UCI Family Health System. In 2002, he joined Carolinas Medical Center in Charlotte, North Carolina as director of ambulatory services and director of the Gynecology Division. He returns to UAB after completing an American Association of Gynecologic Laparoscopists and Society of Reproductive Surgeons fellowship in gynecologic endoscopy at the Chattanooga Women’s Laser Center with world-renowned laparoscopist C. Y. Liu, MD.

ORTHOPAEDIC SURGERY

Joseph G. Khoury, MD, has accepted an appointment as assistant professor of surgery in the Division of Orthopaedics. His clinical and research interests include adolescent and infantile scoliosis, deformities of the lower limb, and pediatric foot and ankle care. A graduate of the University of Iowa College of Medicine in Iowa City, Khoury completed an internship and residency at the University of Iowa Hospitals and Clinics and a fellowship at Children’s Orthopaedics of Atlanta. He comes to UAB from the Shriners Hospitals for Children in Erie, Pennsylvania, where he served as assistant chief of staff, vice president of the medical executive committee, and physician director of the myelodysplasia program.

RADIATION ONCOLOGY

M. Christian Dobelbower, MD, PhD, has accepted an appointment as assistant professor of radiation oncology. His clinical interests include the study and treatment of gastrointestinal malignancies and head and neck cancers as well as image-guided radiotherapy and radiosurgery. Dobelbower earned his PhD in nuclear engineering from Ohio State University where he also worked as research associate in the nuclear engineering program. He earned his MD degree at the Medical College of Ohio, and completed an internship at Mercy Health Partners in Toledo, Ohio, and a residency in radiation oncology at UAB.
Cancer Center Director Named

Edward E. Partridge, MD, is the new director of the UAB Comprehensive Cancer Center. A graduate of the UAB School of Medicine, Partridge completed his obstetrics and gynecology residency at UAB, serving as chief resident. He also completed cancer fellowships at UAB and with the American Cancer Society.

He is a principal investigator for the Deep South Network for Cancer Control, a community-based participatory research network and is the principal investigator for the Morehouse School of Medicine/Tuskegee University/UAB Comprehensive Cancer Center Partnership, a grant that joins research efforts of UAB investigators with those of researchers at historically black colleges and universities to enhance cancer health disparity research.

He has a distinguished academic record, with more than 130 peer-reviewed publications, and is a leader in Alabama medicine. He currently chairs the Board of the Mid South Division of the American Cancer Society and serves on the National Board of Directors of the American Cancer Society.

New Radiology Chair Appointed

Reginald F. Munden, DMD, MD, a national leader in diagnostic imaging, has been named the new chair of UAB Department of Radiology, effective February 2008. Munden currently serves as interim chair of diagnostic radiology in the division of diagnostic imaging at M.D. Anderson Cancer Center. He began his career as a dentist, earning his doctorate in medical dentistry from the College of Dental Medicine at the Medical University of South Carolina (MUSC). After 3 years in private practice and 2 years on the faculty of the College of Dental Medicine, Munden returned to MUSC to earn his medical degree and complete a diagnostic radiology residency. He then served as a clinical thoracic fellow in radiology at Brigham and Women’s Hospital, Harvard Medical School.

Munden joined the University of Texas Houston Medical School before joining M.D. Anderson in 1997. He was named section chief in thoracic imaging in 1998 and associate division head for translational and clinical research in 2005 prior to being appointed interim department chair. He is the author or coauthor of more than 100 academic writings.
UAB Insight CME Self-assessment Test

Fall 2007 (ED0779)

The following questions can be used to obtain continuing medical education credit; this process takes about an hour. To apply for 1 AMA PRA Category 1 Credit™ toward the AMA Physician’s Recognition Award, read the articles marked on the inside cover with a CME box and then check the correct answer(s).

Complete the required information and fax to 205.975.6902. Or, you may submit your self-assessment, evaluation responses online at www.uab.edu/cme or at www.uabhealth.org/insight.

CME Self-assessment Questions:

1. Obesity is associated with higher grade prostate cancer and a higher recurrence rate following radical prostatectomy.
   - True
   - False

2. Check all the factors that may promote prostate cancer:
   - Diet high in saturated fat
   - Insulin resistance
   - Prostatitis
   - Resveratrol
   - Sexually transmitted diseases

3. A clinical diagnosis of lupus requires the presence of four American College of Rheumatology criteria before starting therapy.
   - True
   - False

4. Premature cardiovascular complications are the major cause of mortality and morbidity in SLE.
   - True
   - False

5. Autism spectrum disorders can be reliably detected in children ≥3 years, and in those as young as 18 months.
   - True
   - False

6. Delayed or abnormal speech development often is the first indicator of an autism spectrum disorder.
   - True
   - False

7. Treatment for autistic disorder will not benefit patients until they are aged 4 years.
   - True
   - False

8. Risk of stroke remains a rare complication of migraine.
   - True
   - False

9. Injectable Imitrex should only be given in a hospital setting.
   - True
   - False

10. Evaluation questions: Circle 1 if you strongly DISagree, 2 if you DISagree, 3 if you have no opinion, 4 if you agree.

   The content was objective and balanced.
   1 2 3 4

   The content was evidence-based.
   1 2 3 4

   The type of evidence was identified.
   1 2 3 4

   The source of evidence was identified.
   1 2 3 4

   There was no inappropriate commercial bias toward products of any company.
   1 2 3 4

   Please provide any specific feedback about articles, or suggestions for future articles, here:

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Attn: UAB Division of CME
JNWB 406, 500 22nd St S
Birmingham, AL 35233
FAX: 205.975.6902

NAME (print or type):
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Upon successful completion of this self-assessment test, a certificate will be faxed to you within 2 weeks from date of receipt.
UAB Health System Consultation and Referral Information

UAB Health System consultations, physician services, patient referral
1.800.UAB.MIST (1.800.822.6478)
934.MIST in Birmingham

UAB Health System Physician Online Resource Center
www.uabhealth.org/4docs

UAB physicians via e-mail
mist@uabmc.edu

UAB Continuing Medical Education
www.uab.edu/cme

UAB Insight
www.uabhealth.org/insight
CME OPPORTUNITIES

Reynolds Historical Library Lecture Series
All Lectures are held in the Ireland Room on the third floor of Lister Hill Library of the Health Sciences, 1700 University Blvd, Birmingham, Alabama.

www.uab.edu/reynolds/lecture.htm

December 14, 2007: Hughes Evans, MD, PhD, UAB School of Medicine Senior Associate Dean for Academic Affairs — Lecture opening the exhibit “Changing the Face of Medicine;” 3 PM.

January 9, 2008: Diann Jordan, PhD, professor of biology, Alabama State University — “Sisters in Science: Conversations with Black Women Scientists on Race, Gender, and the Passion for Science;” noon.

February 8, 2008: Annual Reynolds Historical Lecture and Reynolds Library 50th Anniversary Celebration — Stephen J. Greenberg, PhD, National Library of Medicine, History of Medicine Division — “Real Books: What They Are and Why We Still Need Them;” 4 PM.


Medical Alumni Weekend 2008
February 8-9, 2008: Birmingham Hilton Perimeter (1.800.HILTONS for reservations). For details, contact Medical Alumni Office, 205.934.4463 or office@alabamamedicalalumni.org.

Alumni weekend activities include the Reynolds Historical Lecture. Saturday morning’s scientific program focuses on “Pain Management” introduced by UAB Chief of Anesthesiology Keith A. (Tony) Jones, MD. The annual Alumni Luncheon and the Pittman Lecture at 12:30 PM feature Norman E. McSwain Jr, MD, director of Trauma, Department of Surgery, Tulane University School of Medicine. He will speak on the Hurricane Katrina aftermath. Alumni reception and class dinners on Saturday night will be at the Country Club of Birmingham.

Calendar of Sponsored CME Events
www.cme.erep.uab.edu/aboutUs/calendar.html

ONLINE CME COURSES

Patient Adherence to Pharmacological Therapy
www.alabamacme.uab.edu/courses/Patient_Adherence/ID0371A.asp

Ophthalmology Cases for Primary Care Physicians: A Case of Red Eye; sponsored by the Division of Continuing Medical Education; 0.25 AMA PRA Category 1 Credit™.
www.cme.erep.uab.edu/onlineCourses/Ophthalmology_Cases/default.html

Chronic Obstructive Pulmonary Disease Co-Sponsored by the University of Alabama School of Medicine Division of Continuing Medical Education and The Alabama Quality Assurance Foundation; certified for 1 AMA PRA Category 1 Credit™.
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