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Baylor University Medical Center Proceedings (ISSN 0899-8280), a peer-reviewed journal, is published quarterly (January, April, July, and October). Proceedings is indexed in PubMed and CINAHL; the full text of articles is available both at www.BaylorHealth.edu/Proceedings and www.pubmedcentral.nih.gov. The journal’s mission is to communicate information about the research and clinical activities, continuing education, philosophy, and history of the Baylor Health Care System.

Funding for the journal is provided by the following:

• Baylor Health Care System Foundation
• Helen Buchanan and Stanley Joseph Seeger Endowment for Surgery

Funding is also provided by donations made by the medical staff and subscribers. These donations are acknowledged each year in the April or July issue. For more information on supporting Proceedings and Baylor Health Care System with charitable gifts and bequests, please call the Foundation at 214-820-3136. Donations can also be made online at http://give.baylorhealth.com/.

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<thead>
<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact Information (name, phone number, and e-mail address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult)</td>
<td>Rose Boehm, RRT, RCP, AE-C 214-820-9772 <a href="mailto:RoseB@BaylorHealth.edu">RoseB@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hematological malignancies, leukemia, multiple myeloma, non-Hodgkin's lymphoma; melanoma vaccine</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:cancer.trials@BaylorHealth.edu">cancer.trials@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Type 1 and type 2 diabetes, cardiovascular events</td>
<td>Kris Chionh 214-820-3416 <a href="mailto:kristen.chionh@BaylorHealth.edu">kristen.chionh@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Diabetes (Fort Worth)</td>
<td>Type 2</td>
<td>Theresa Cheyne, RN 817-922-2579 <a href="mailto:theresa.cheyne@BaylorHealth.edu">theresa.cheyne@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Crohn's disease</td>
<td>Dallas Clinical Trials Office 214-820-9626 <a href="mailto:jenniha@BaylorHealth.edu">jenniha@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Dallas)</td>
<td>Aortic aneurysms, coronary artery disease, hypertension, poor leg circulation, heart attack, heart disease, congestive heart failure, angina, carotid artery disease, familial hypercholesterolemia, surgical renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracotomy pain, stem cells, critical limb ischemia</td>
<td>Merielle Boatman 214-820-2273 <a href="mailto:MerielleH@BaylorHealth.edu">MerielleH@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Fort Worth)</td>
<td>Atrial fibrillation, carotid artery stenting</td>
<td>Deborah Devlin 817-922-2575 <a href="mailto:Deborah.Devlin@BaylorHealth.edu">Deborah.Devlin@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aneurysms; coronary artery disease; uncontrolled hypertension; intermittent claudication; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of AAA, TAA, and dissections with endografts; thoracic surgery leak repair; atrial fibrillation; carotid artery disease; heart failure; left atrial appendage and stroke; gene profiling</td>
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</tr>
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</tr>
</tbody>
</table>

Baylor Research Institute is dedicated to providing the support and tools needed for successful clinical research. To learn more about Baylor Research Institute, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BaylorHealth.edu.
Cancer care is expensive due to the high costs of treatment and preventable utilization of resources. Government, employer groups, and insurers are seeking cancer care delivery models that promote both cost-efficiency and quality care. Baylor University Medical Center at Dallas (BUMC), a large tertiary care hospital, in collaboration with Texas Oncology, a large private oncology practice, established two independent centers that function cooperatively within the Baylor Charles A. Sammons Cancer Center, the Oncology Evaluation and Treatment Center (OETC) and Infusion Center, to deliver urgent care and infusions after hours to oncology patients. Quality measures based on evidence-based care and cost-efficiency measures were implemented within these centers. Ability to meet predetermined goals for these measures will be a guide for implementing continuous quality and cost-efficiency interventions. During the first two quarters of operations, 2023 patients received care in the OETC (n = 423) and Infusion Center (n = 1600). The average time spent in the OETC was 48% less than the time spent in the BUMC emergency department (ED). Eighty-nine percent of the cancer center’s patients who received urgent care at BUMC were referred to the OETC for this care, instead of the BUMC ED. The hospital admission rate in the OETC was 59% lower than it was in the BUMC ED, a high-volume level I trauma center. The addition of the OETC and Infusion Center to the cancer center holds promise for providing continuous quality cancer care that is cost-efficient.

The ideal cancer care delivery model is coordinated to provide comprehensive multidisciplinary services (1). However, this type of care can be costly, not only with respect to the high cost of treatment, but also related to the preventable use of resources. Therefore, government, employer groups, and insurers are seeking models for the delivery of quality cancer care that is cost-efficient. Oncologists in private practice are in a unique position to take the lead in defining treatment and operational standards for the delivery of cancer care that is value based, with regards to cost and quality, through collaborations with hospitals and insurers. This article describes two independent centers—the Oncology Evaluation and Treatment Center (OETC) and the Infusion Center—that serve as a model for the delivery of continuous cancer quality care to promote cost-efficiency. The centers were established within the existing Baylor Charles A. Sammons Cancer Center through a joint collaboration of a hospital, Baylor University Medical Center at Dallas (BUMC), and Texas Oncology, a large statewide private oncology practice.

HISTORY OF THE BAYLOR CHARLES A. SAMMONS CANCER CENTER

The cancer center opened in 1976 and is an integral part of BUMC, a not-for-profit tertiary care hospital with 1025 beds whose medical staff is composed of physicians in private practice. The BUMC campus includes a large-volume emergency department (ED), designated as a Level I trauma center offering the most comprehensive level of service to patients. Promoting multidisciplinary interaction among physicians from Texas Oncology and other specialties housed at BUMC has been the main concept underlying the organization and development of a cancer center. The long-standing working relationship between BUMC and Texas Oncology dates back to 1972, when a small private practice called the Medical Oncology Group was developed to provide coverage and assistance with the growing number of oncology consults at BUMC (2). Currently, Texas Oncology leases space in the cancer center, further emphasizing the concept of collaboration between BUMC and Texas Oncology.

Since the opening of the Sammons Cancer Center in 1976, education and clinical and basic science cancer research has been an important part of the center’s activities (3). Along with the opening of the cancer center, a medical oncology fellowship program, funded in part by Texas Oncology and by BUMC, was established at BUMC the same year. In conjunction with the training program, cancer research at the cancer center is coordinated between BUMC and Texas Oncology. Texas Oncology is a part of the US Oncology Network. McKesson Specialty Health supports the US Oncology Network to advance the science of oncology by providing the infrastructure to support innovative clinical trials and clinical care operations, as
well as to provide the technological solutions to improve cancer clinical outcomes. The US Oncology Network is one of the nation’s largest networks of community-based oncology physicians, serving more than 850,000 cancer patients annually.

The new facility for outpatient services at the cancer center opened in 2011. BUMC opened the Baylor T. Boone Pickens Cancer Hospital in January 2012. Recognizing the need to further integrate oncology patient care at the cancer center to provide continuous quality care that promotes cost-efficiency, BUMC, in collaboration with Texas Oncology, opened the OETC and the Infusion Center in March 2012.

**ONCOLOGY EVALUATION AND TREATMENT CENTER AND INFUSION CENTER MODEL**

The OETC and the Infusion Center have a cooperative working relationship and are housed side by side in an outpatient facility located on the first floor of the cancer hospital. The OETC provides urgent care after office hours as well as scheduled procedures during office hours to adult oncology patients of all oncology physicians at BUMC, including Texas Oncology physicians. The procedures scheduled are diagnostic and therapeutic, such as thoracenteses, paracenteses, and lumbar punctures for the administration of intrathecal chemotherapy, as well as to maintain adherence to prescheduled clinical research testing, which may occur outside of normal office hours. All acute care can be provided at the OETC, with the exception of care required by patients who are transported by emergency medical services or care for patients with acute myocardial infarctions, cerebral vascular accidents, or trauma. Therefore, if necessary, OETC patients may be transferred to the BUMC ED, which is located in close proximity to the cancer hospital and is accessible by an indoor connector. The Infusion Center is open 24 hours a day 7 days a week to provide oncology patients access to blood product transfusions, as well as hydrating, chemotherapy, and biological therapy infusions. Thus, interruptions in cancer care can be prevented by administering infusions that are due on weekends and holidays in the Infusion Center, when private practice offices at the Sammons Cancer Center are closed.

The OETC and Infusion Center are staffed with a medical director under contract with BUMC, who is also a Texas Oncology physician, and a nurse manager employed by BUMC. BUMC owns and operates the OETC and the Infusion Center and owns the equipment therein, as well as employing the nursing staff within these two centers. Accordingly, BUMC bills facility and technical fees. Providers that evaluate and treat the patients in the OETC include Texas Oncology physicians and internal medicine physicians, all of whom have BUMC medical staff membership and admitting privileges, and these providers bill for the related professional fees. Patients are referred to the OETC by their oncology physicians. Patients in the OETC may be transferred for services provided in the Infusion Center 24 hours a day, and patients in the Infusion Center can be evaluated and treated after normal office hours by an OETC provider, if necessary.

To promote efficient patient care, providers staffing the OETC are able to access the Texas Oncology electronic medical record, iKnowMed, developed by the US Oncology Network, in addition to the BUMC electronic medical record, Eclipsys. Evidence-based medicine is used as a guide to deliver quality cancer supportive care in the OETC.

The most prevalent patient clinical problems evaluated and treated in the OETC are used to periodically select quality measures derived from the National Comprehensive Cancer Network Guidelines for Cancer Supportive Care (4). Adherence to clinical outcome-based quality of care measures for the OETC is measured on a quarterly basis (Table 1) (5–7). As an indirect measure of quality of care in the OETC, Press Ganey patient satisfaction scores will be collected and analyzed quarterly (8). The cost-efficiency measures were selected based on commonly accepted business practices, as well as a review of the literature (9, 10). These measures focus on health care utilization, staff, facility, and ancillary service costs required to evaluate and treat patients in the OETC, as well as the time that patients spend in the OETC. Adherence to these measures will be reported quarterly. Table 2 includes the current cost-efficiency measures for the OETC. The cost-efficiency measure, mean cost per visit,

<table>
<thead>
<tr>
<th>Table 1. Oncology Evaluation and Treatment Center quality measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult cancer supportive care</strong></td>
</tr>
<tr>
<td>Chemotherapy-related breakthrough nausea and vomiting</td>
</tr>
<tr>
<td>Palliative care consult</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td><strong>Quality measure</strong></td>
</tr>
<tr>
<td>Treat with an additional antiemetic agent from a different drug class</td>
</tr>
<tr>
<td>Obtain palliative care consult if pain is resistant to conventional interventions or if there is a high risk for poor pain control related to one or more of the following:</td>
</tr>
<tr>
<td>• Neuropathic pain</td>
</tr>
<tr>
<td>• Incident or breakthrough pain</td>
</tr>
<tr>
<td>• Associated psychological and family distress</td>
</tr>
<tr>
<td>• Rapid escalation of opioid dosage</td>
</tr>
<tr>
<td>• History of drug or alcohol abuse</td>
</tr>
<tr>
<td>• Impaired cognitive function</td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
</tr>
<tr>
<td>Hospital admissions for intractable nausea and vomiting</td>
</tr>
<tr>
<td>Hospital admissions for intractable pain</td>
</tr>
<tr>
<td><strong>Table 2. Cost-efficiency measures for the OETC</strong></td>
</tr>
<tr>
<td><strong>Cost-efficiency measure</strong></td>
</tr>
<tr>
<td>Mean cost per visit</td>
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</tbody>
</table>

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will be determined primarily based on nursing staff and provider hourly wages, drug and supply costs, and ancillary service costs, such as laboratory and radiology services. The cost per visit will be adjusted for severity of illness. Quality improvement and cost-efficiency interventions will be based on predetermined goals for adherence to the quality and cost measures listed in Tables 1 and 2.

Together, the OETC and Infusion Center provide patients with continuous supportive cancer care to 1) promote favorable clinical outcomes, 2) support the successful completion of clinical cancer research studies, and 3) reduce health care costs by decreasing preventable and expensive health care utilization. Within the OETC, health services research studies are being conducted to further advance our knowledge of the most cost-efficient ways to deliver quality cancer care (11). The Figure presents the model for the delivery of quality continuous cancer care to promote cost-efficiency that we developed by incorporating the OETC and Infusion Center within our existing cancer center infrastructure.

**INITIAL UTILIZATION RESULTS**

Between April and December 2012, the first two quarters of operations of the OETC and Infusion Centers, a total of 2023 oncology patients received care: 423 in the OETC and 1600 in the Infusion Center. During the first quarter, we identified visits to the BUMC ED if at least one cancer International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code was assigned for the care that was received during one of these visits (12). Health care delivery data for the first quarter of the OETC and Infusion Center operations are as follows. The average time spent in the OETC (3 hours and 48 minutes) was 48% lower than it was for the time spent for oncology patients in the BUMC ED (7 hours and 17 minutes). Ninety percent of the cancer center’s patients who received urgent care at BUMC were referred to the OETC for this care, instead of the BUMC ED. The hospital admission rate in the OETC was 34%, compared with 83% for the BUMC ED.

**DISCUSSION**

Comprehensive and coordinated oncology care is necessary to promote favorable clinical outcomes for oncology patients, but it is costly. In a recent study, it was projected that the total cost of cancer care would be $173 billion by 2020, which represents a 39% increase from 2010 (13). As a result, cost-containment efforts by insurers have become commonplace. These cost-containment efforts have resulted in lower reimbursement for drugs, as well as for evaluation and management services, which is occurring in the face of rising costs for the new technologies required for the treatment of cancer.

Coinciding with the decline in cancer care reimbursement from insurers over the last decade, the delivery of cancer care in the community setting decreased from 85% to 65% in 2012, correlating with a number of community-based oncologists entering into employment or management arrangements with institutionally based programs in 2011 (14). Thus, it is important for oncologists in community-based settings to be engaged in developing models that promote the cost-efficient delivery of quality cancer care due to the current trends in health care economics. To provide direction for addressing this issue, the Institute of Medicine recently convened a workshop where its participants determined that the medical home concept should be considered when redesigning models of care in oncology (15).

Because cancer is increasingly being viewed as a chronic disease, the concept of the patient-centered medical home (PCMH), a model that has been used mainly in the primary care setting, is a viable option for use in the delivery of cost-efficient and quality cancer care. In the medical home model, care is provided by a dedicated team of providers, and they are reimbursed with an upfront fee and higher reimbursement for episodes of care (15). An episode of care is a managed care concept in which a single payment for health care services is provided for a specific illness during a set time period (16). The National Committee for Quality Assurance (NCQA) developed the standards for the primary care PCMH program (17). The NCQA’s standards for the PCMH program require a physician-led care team to direct disease management and care coordination, to standardize care which is evidence-based, and to promote patient disease management education (17). Results
indicate that the use of the PCMH model has a positive effect on quality and cost, as well as satisfaction of the patient and the clinical team (17).

In 2010, Consultants in Medical Oncology and Hematology (CMOH), a community-based single-specialty practice in Philadelphia, became the first oncology practice recognized by the NCQA as a level three PCMH program (18). Achievement at this level requires the highest level of expertise related to patient communication, data tracking, care management, self-management support, electronic prescribing, test tracking, referral tracking, advanced electronic patient communications, and performance metrics reporting and improvement (18). As the result of CMOH implementing the PCMH model, ED visits decreased by 68%, chemotherapy-related hospital admissions decreased by 51%, and length of hospital stay decreased by 21% (14, 18). In addition, CMOH outpatient visits and chemotherapy outpatient visits per patient per year decreased by 22% and 12%, respectively (14, 18).

The US Oncology network launched its program, Innovent Oncology, in 2010 to improve the clinical management of oncology patients receiving chemotherapy (19). The program is supported by the US Oncology network and is offered at all of the Texas Oncology sites. This program creates a link between physicians and insurers by using evidence-based practice guidelines for the selection of chemotherapy, along with patient support services and advance care planning to promote favorable cost metrics and health care utilization patterns. The clinical and cost outcomes included in Innovent Oncology are chemotherapy-related hospitalizations and ED visits, length of hospital stay, chemotherapy costs, end-of-life care including hospice enrollment, death in a hospital, and chemotherapy administration within 2 to 4 weeks of death. Insurers make a single payment for each patient enrolled in Innovent Oncology, and they provide Innovent Oncology staff with access to program enrollment data to predict hospital and financial data to calculate the program’s clinical and cost outcomes. Initial results related to implementation of the program are encouraging. Physician adherence to the evidence-based practice guidelines for the selection of chemotherapy was 72%, which increased to over 80% for the most recent quarter (J. R. Hoverman, personal communication, September 12, 2012). In addition, there was a substantial decrease in the hospitalization costs for the first 100 patients enrolled in this program (19).

However, as important as CMOH and the Innovent Oncology program are in promoting the cost-efficient delivery of quality cancer care within the private oncology practice setting, we propose it is just as important to make interventions in the emergency and urgent care settings to prevent avoidable health care utilization. The need to develop interventions for reducing avoidable inpatient and outpatient visits at all points of care that are affordable, efficient, and of high quality is of further importance since it is projected that there will be a shortage of oncologists in the US by 2020 (13). This shortage in oncologists is due, in part, to the increase in the aging US population among whom the cancer incidence is higher (13). Through the combined efforts of an oncology group practice and hospital, the OETC and Infusion Center was incorporated within the cancer center, creating a model for the efficient delivery of continuous quality care to help prevent the avoidable use of costly health care resources.

Analysis of data from the first quarter of operations for the OETC and Infusion Center provides evidence that we are likely to achieve our goal of reducing preventable health care utilization in a cost-efficient manner. A total of 2023 oncology patients received care in the OETC and Infusion Center, and 90% of the cancer center’s patients who received urgent care at BUMC were referred to the OETC for this care, instead of the BUMC ED. The average time spent in the OETC was 48% lower than the time spent for oncology patients in the BUMC ED, as would be expected since the BUMC ED is a high-volume Level I trauma center. Moreover, the hospital admission rate in the OETC was 34%, which was more than 59% lower than it was for the BUMC ED. Similarly, the hospital admission rate in the OETC was almost 50% lower than what was recently reported for oncology patients in the ED using a statewide database in North Carolina (63.2%) (20). Furthermore, our new initiatives for conducting health service research within the OETC and Infusion Center hold promise for providing our care center and others with results that will assist in developing new methods for effectively organizing, managing, financing, and delivering quality cancer care.

An additional benefit related to establishing new models for cancer care delivery that promote favorable cost-efficiency and clinical outcomes is that more equitable medical insurance reimbursement contracts for both the payer and payee may be negotiated for this type of center. This type of center also has an infrastructure conducive to receiving bundled payments for a defined episode of care (21). The bundled payment functions as a tool of alignment between insurers and providers, which can eliminate some of the unintended financial incentives that can lead to fractured care. Using the episode of care model tied to bundled payments is a rapidly evolving movement by insurers to produce the best cost and clinical outcomes by decreasing unwanted variations in the delivery of health care (22).

Given the growing public awareness of the need to redesign the cancer delivery system, including government, physicians and hospitals, and employer groups and insurers, a new health care environment is developing that demands accountability for the cost and quality of care. Consequently, it is critical for oncologists to continue to take the lead in defining standards of care for specific disease states and to collaborate with hospitals and insurers when possible to develop systems for the delivery of high-quality and cost-efficient cancer care.

Acknowledgments

We thank Kevin Croy, vice president and assistant general counsel for the Baylor Health Care System, and JaNeene Jones, chief operating officer for the Baylor Health Care System and vice president for oncology services, for their critical review of the manuscript regarding the working relationship between Baylor University Medical Center and Texas Oncology at the Baylor Charles A. Sammons Cancer Center; J. Russell
Hoverman, MD, medical director for the US Oncology Innovent Oncology program, for his critical review of the manuscript and providing information regarding the status of Innovent Oncology; Dighton Packard, MD, chairman of the Department of Emergency Medicine at Baylor University Medical Center, for his critical review of the manuscript; Kimberly Hanna, RN, the nurse manager for the Oncology Evaluation and Treatment Center and Infusion Center, for her critical review of the manuscript; and Margaret Hinshaw, PhD, for her critical review of the manuscript along with completing its formatting and producing the tables and figure for the manuscript.

Thermoregulatory catheter–associated inferior vena cava thrombus

Joshua L. Gierman, MD, William P. Shutze Sr., MD, Gregory J. Pearl, MD, Michael L. Foreman, MD, Stephen E. Hohmann, MD, and William P. Shutze Jr.

The use of thermoregulatory catheters (TRCs) in critically ill patients has become increasingly popular. TRCs have been shown to be effective in regulating patient body temperature with improved outcomes. Critically ill patients, especially multitrauma patients and those with femoral catheters, are at high risk for deep vein thrombosis (DVT). Among patients for whom chemical DVT prophylaxis is not an option, inferior vena cava (IVC) filters are often placed prophylactically. The development of intravascular ultrasound (IVUS) has allowed placement of IVC filters at the bedside for patients who are too ill for transport to the operating room or cardiac catheterization lab. After encountering several patients with occult DVT of the IVC during bedside IVC filter placement, we performed a retrospective review to determine the incidence of DVT or pulmonary embolus (PE) in patients who had been treated with a TRC at Baylor University Medical Center at Dallas. Since 2008, IVC filters have been deployed at the bedside with the use of IVUS at Baylor University Medical Center. During that same time period, 83 patients had a TRC placed for either intravascular warming or cooling during their resuscitation. Forty-seven out of 83 patients who had a TRC placed survived their injuries. Ten of 47 patients (21%) were diagnosed with DVT or PE, and 6 of these 10 (60%) were found to have caval thrombus. We present this case series as evidence that undiagnosed IVC thrombus associated with TRCs may be higher than previously suspected, given that 5 out of 10 patients who had IVUS of their IVC for prophylactic IVC filter placement, as well as one patient diagnosed with PE, were found to have caval thrombus.

Within the last 15 years, the use of thermoregulatory catheters (TRCs) has gained popularity. They have been used to induce hypothermia to improve outcomes in cases of cardiopulmonary arrest and to reverse the harmful effects of hypothermia in the trauma patient by providing a means for rapid rewarming (1–3). Over the last 3 years at our institution, the trauma service has been utilizing the Alsius catheter and Coolguard Icy thermoregulatory system to aid in resuscitation of hypothermic patients as well as in the cooling of patients with fever and traumatic brain injury. During that same period of time, the vascular surgery service has been placing bedside inferior vena cava (IVC) filters in critically ill patients using intravascular ultrasound (IVUS) (4, 5). Some of the patients who had TRCs used during their hospital course also had IVC filters placed either for prophylaxis or after a diagnosis of deep venous thrombosis (DVT) or pulmonary embolus (PE). Surprisingly, caval thrombus was found in several of these patients undergoing placement of an IVC filter with IVUS. Currently, only one series has examined the risk of iliofemoral DVT (6), and only one case has been reported of vena cava thrombus associated with the use of a TRC (7). We performed a retrospective review to examine whether trauma patients who have been exposed to a TRC are at additional risk for iliocaval DVT in addition to the risk of DVT associated with femoral vein catheterization.

MATERIALS AND METHODS

Institutional review board approval was obtained for our study. Patient records were obtained from the trauma registry at Baylor University Medical Center at Dallas to identify patients who had TRCs placed beginning in 2008. Catheterization lab records were reviewed to identify patients receiving IVC filters during the same time period. The Student's t test was used for statistical comparison of age and injury severity score (ISS).

RESULTS

Since 2008, 83 trauma patients have had a TRC placed as part of their postinjury care: 47 of those patients, with an average age of 41 years and an ISS of 20.9, survived their initial injuries, and 32 patients had no diagnosis of DVT/PE, nor were they selected for prophylactic IVC filter placement. Fifteen of the 47 were referred for IVC filter placement. Five of these 15 patients were diagnosed with either DVT or PE prior to vascular referral. Four patients received an IVC filter; of them, three underwent filter placement under fluoroscopy, and the other patient who received a filter secondary to PE had it placed with IVUS guidance. This demonstrated a caval thrombus. The fifth patient was found to have a femoral DVT and was treated with anticoagulation.

Ten patients underwent prophylactic placement or attempted placement of an IVC filter at bedside with IVUS, four of whom were discovered to have IVC thrombus at the time of...
filter placement. A fifth patient was diagnosed with caval thrombus by IVUS, but had too extensive a thrombus to allow for IVC filter placement. He was treated with anticoagulation. The remaining five patients did not have caval thrombus detected by IVUS (Figure 1).

The average age for patients with DVT, PE, or vena cava thrombus was 28 years. This was less than the average age of the overall group (41) but was not statistically different ($P > 0.05$). The ISS of the patients in the DVT, PE, or vena cava thrombus subgroup was 33. This was much higher than in the overall group (ISS = 21) treated with TRCs who survived their initial injuries, and this difference reached statistical significance ($P = 0.039$).

DISCUSSION

TRCs have been shown to be an effective clinical tool, whether to improve outcomes when used for corporal cooling after cardiac arrest or to efficiently reverse hypothermia (1–3). However, there is little reported evidence addressing potential complications. Specifically, the potential to form venous thromboembolism (VTE) has only been reported in one study (6) and in a single case report (7).

The patient population examined in this study was at high risk for DVT/VTE. Because of their associated injuries, most of these patients could not receive chemical DVT prophylaxis. Critical illness with contraindications to chemoprophylaxis carries a 7% DVT risk (8). DVT/VTE associated with femoral vein catheters ranges from 10% to 25% (9, 10). In looking at our institutional experience with TRCs by the trauma service, we found that the overall rate of DVT/VTE formation was 21% (10/47). This is at the high end of the spectrum, but not out of line with what has been previously published. A previous study of DVT formation in patients with TRCs showed a 50% rate of DVT formation (6).

We found occult caval thrombus in 60% of patients ultimately diagnosed with DVT. Given the high incidence of occult caval DVT discovered at the time of prophylactic filter placement, we feel that the 21.3% rate of DVT (specifically caval DVT) in this study may be an underestimation. Only 10 of 47 patients underwent cavography or IVUS. The status of the IVC was not evaluated in 32 of the 47 patients in this series, and a significant number of caval DVT cases could have gone undetected.

We did find a higher ISS in patients with DVT/PE (33 vs. 21, $P = 0.039$) compared to the overall group. This could indicate that injury severity contributes to DVT formation. However, we feel that this possibly represents a selection bias, as the more critically ill patients are typically selected to receive prophylactic IVC filters. Only by studying every patient receiving a TRC can the true rate of DVT and caval DVT be determined and the effect of age and ISS be honestly assessed.

There are two points of concern regarding the DVT/VTE associated with these catheters. The first is the fact that half of the caval DVTs were found in asymptomatic patients. Therefore, the actual rate of DVT formation could be as high as 50% in our studied patient population (similar to the experience of Simosa et al). Since 60% of patients having prophylactic IVC filters placed were found to have IVC DVT, the use of TRCs may increase the incidence of DVT significantly higher than the baseline rates for critically ill patients who typically develop DVT in the lower extremity veins or in the femoral vein if a catheter has been placed there. The second point of concern is
that these proximal DVTs are much more dangerous, as they are associated with a higher mortality rate when compared with more distal DVTs (11). They are also less likely to be detected by surveillance, symptoms, or noninvasive imaging. The increased incidence of caval DVT with TRCs identified by our study is therefore quite worrisome.

Although there has not been a comparison of IVUS and venography for thrombotic occlusion, IVUS has been shown to be more sensitive than venography in detecting nonthrombotic lesions (12, 13). This increased sensitivity may translate to the diagnosis of thrombotic lesions as well. Caval DVT in patients from TRCs can be nonocclusive and attached to the wall of the IVC and may not be obvious on venography. However, IVUS readily identifies these clots (Figure 2). Notably, the three patients in our series who had fluoroscopy only when having their IVC filters placed could have had missed caval thrombus. We believe that the use of IVUS during the placement of IVC filters increased the sensitivity in identifying occult caval DVTs in asymptomatic patients. Therefore, we recommend the use of IVUS to detect occult DVT in patients with a history of femoral TRCs.

Impact of sham-controlled vertebroplasty trials on referral patterns at two academic medical centers

Sara S. Lindsey, MD, David F. Kallmes, MD, Michael J. Opatowsky, MD, Elizabeth A. Broyles, RN, and Kenneth F. Layton, MD

Debate persists regarding the merit of vertebroplasty following publication of blinded vertebroplasty trials in 2009, one of which was the Investigational Vertebroplasty Efficacy and Safety Trial (INVEST). This study was performed to determine whether referring physicians at two academic medical centers were aware of the trial results and to assess if this awareness prompted a change in their treatment of osteoporotic fractures. E-mail surveys were distributed to physicians within the Mayo Clinic and Baylor Health Care System (BHCS). Of 1390 surveys sent, 194 (14%) were returned. Results showed that 92 of 158 respondents (58%) reported familiarity with INVEST; 66 of 92 (72%) agreed that INVEST changed their understanding of vertebroplasty efficacy; and 64 of 92 (70%) agreed that INVEST diminished their enthusiasm to refer patients for vertebroplasty. However, 105 of 159 respondents (66%) felt vertebroplasty was an effective procedure in appropriate patients. Mayo physicians were more likely than BHCS physicians to be aware of INVEST (73% vs 67%, \( P < .0001 \)), respond that INVEST changed their understanding of the appropriate treatment for osteoporotic compression fractures (79% vs 57%, \( P = 0.026 \)), view vertebroplasty less favorably (45% vs 21%, \( P = 0.005 \)), and treat osteoporotic compression fractures with medical therapy/pain management alone (73% vs 48%, \( P = 0.003 \)). INVEST changed referring physicians’ understanding of the role of vertebroplasty and diminished their willingness to refer osteoporotic compression fracture patients; the impact varied by location.

The Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) (1) and a concurrent Australian vertebroplasty trial (2) were published in the *New England Journal of Medicine* in August 2009 and demonstrated equivalent efficacy for vertebroplasty and a sham intervention for improvement in pain and function in osteoporotic compression fracture patients. Despite extensive criticism (3–8), these studies created controversy regarding the benefit and appropriateness of vertebral augmentation. Historically, the literature has shown positive outcomes associated with thousands of vertebroplasty patients (9, 10). Follow-up vertebroplasty studies have ensued (11, 12), including a study from the Mayo Clinic, which documented a statistically significant decline in referral volumes before and after publication of the August 2009 sham-controlled studies (13). This study was performed to determine whether referring physicians at two academic medical centers, one of which (Mayo Clinic) was the lead site for INVEST, were aware of the INVEST trial results, whether their awareness of these results changed their understanding of the efficacy of vertebroplasty and/or their management decisions for patients suffering from painful osteoporotic fractures, and whether there were differences between the institutions regarding these research questions.

**METHODS**

Short e-mail surveys were distributed to physicians in a wide range of specialties (Table) that commonly encounter patients with osteoporotic compression fractures within the Mayo Clinic system (Rochester, MN) and the Baylor Health Care System (BHCS, Dallas–Fort Worth, TX). The survey was sent to all physicians with accessible e-mail addresses in these specialty areas, not only to individual physicians who had previously referred patients to interventional neuroradiology for vertebroplasty. Results were collected from September to November 2010 and were analyzed using Survey Monkey. Approval for this research was granted by the institutional review board of Baylor Research Institute.

The survey asked participants about their familiarity with the INVEST study, their understanding of the role of vertebroplasty for treatment of osteoporotic compression fractures, if the

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From the Department of Radiology, Baylor University Medical Center at Dallas (Lindsey, Opatowsky, Broyles, Layton); and the Mayo Clinic, Rochester, MN (Kallmes).

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INVEST results changed their understanding of the treatment for osteoporotic compression fractures or changed their referral patterns for vertebroplasty, and how they were currently treating patients with painful osteoporotic compression fractures. In addition to collecting information on respondents’ specialty, it asked whether they had seen at least one patient during the last 18 months with an osteoporotic vertebral compression fracture.

Statistical analysis of the data was performed with chi-square tests. Physicians were allowed to skip questions. Referring physicians were not queried regarding the Buchbinder et al trial (2) or any of the other vertebral augmentation trials in our survey. No incentives were offered for participation.

RESULTS

Surveys were distributed to 1390 clinicians with a collective response rate of 14% (194 participants). Overall, 92 of 158 respondents (58%) reported being familiar with INVEST (36 respondents did not answer this question), and 53 of these 92 respondents (58%) agreed and 13 (14%) strongly agreed that the results of INVEST had changed their understanding of the efficacy of vertebroplasty (Figure 1); 51 (55%) agreed and 13 (14%) strongly agreed that the study had diminished their enthusiasm to refer patients for vertebroplasty (Figure 2). Cumulatively, 105 respondents (66%) felt that vertebroplasty was an effective procedure in appropriate patients, 52 respondents (33%) felt that vertebroplasty was of limited efficacy, and 2 respondents (1.3%) felt that the potential benefits of vertebroplasty were outweighed by the risks of the procedure (Figure 3).

There was a statistically significant difference in the responses between clinicians in the two geographic locations, with Mayo physicians being more aware of the INVEST study (63 of 86 [73%] at Mayo vs 29 of 43 [67%] at BHCS; chi-square DF 1, \( P < 0.001 \)) and responding that INVEST had changed their understanding of the appropriate treatment for osteoporotic compression fractures (Figure 1; 49 of 62 [79%] at Mayo vs 17 of 30 [57%] at BHCS, chi-square DF 1, \( P = 0.026 \)). There was also a statistically significant difference between clinicians in the two locales in response to descriptions of their current understanding of vertebroplasty for treatment of osteoporotic compression fractures, with Mayo clinicians viewing vertebroplasty less favorably than BHCS physicians (Figure 3; 39 of 87 [45%] at Mayo vs 15 of 72 [21%] at BHCS, chi-square DF 2, \( P = 0.005 \)). A majority of respondents from both clinician groups indicated that the INVEST results had diminished their willingness to refer patients for vertebroplasty, although the difference between the two respondent groups was not statistically significant for this question (Figure 2; 45 of 62 [73%] at Mayo vs 19 of 30 [63%] at BHCS, chi-square DF 1, \( P = 0.366 \)). Mayo clinicians were also statistically significantly more likely than BHCS clinicians...
to treat osteoporotic compression fracture patients with medical therapy and pain management alone, rather than in combination with vertebroplasty (Figure 4; 57 of 78 [73%] at Mayo vs 28 of 58 [48%] at BHCS, chi-square DF 1, \(P = 0.003\)).

**DISCUSSION**

This survey suggests that INVEST negatively influenced clinicians’ perceptions of and referral patterns for vertebroplasty for treatment of painful osteoporotic compression fractures, similar to the findings reported by Luetmer and Kallmes (13). It also unveiled interesting geographic distinctions, as the survey results varied significantly by location. Though a percentage of physicians at both sites viewed vertebroplasty as an effective procedure in appropriate patients (55% at Mayo vs 79% at BHCS), the referral/utilization rates of vertebral augmentation were notably lower (27% at Mayo vs 52% at BHCS); the reason for this discrepancy is likely multifaceted but was not determined by this survey.

This study sampled a relatively small population of physicians and included inherent bias by limiting the survey to two predefined groups of physicians. The response rate was within the previously published range for e-mail–based surveys, which has been as low as 6% (14). Subgroup analysis by medical subspecialty was not performed due to the relatively small sample size. The Mayo Clinic physicians were likely more aware of the INVEST results since Mayo was the lead site in the original multicenter trial. Peer-to-peer education and interactive discussions were proactively performed at the Baylor University Medical Center campus to educate referring physicians about the INVEST data and to encourage continued patient referrals to interventional neuroradiology. Generalization of these two groups’ responses to the wider medical community may not be entirely representative. Additionally, extrapolation of this information to predict future trends in clinician demand and referral patterns for vertebroplasty is shortsighted without considering all of the subsequent and ongoing clinical trials investigating the efficacy of vertebroplasty.

Further research is needed to address the suggested flaws and confounding factors and to clarify the appropriate treatment of patients with osteoporotic compression fractures. The current ambiguity surrounding vertebroplasty should prompt physicians to enroll as many patients as possible into well-designed trials to help generate data.

**Acknowledgments**

The authors thank Sunni Barnes, PhD, director of survey research and clinical trials at BHCS.


**Figure 4.** Respondents’ approach to treating most of their patients with painful osteoporotic compression fractures. Difference between Mayo and Baylor respondents: \(\chi^2 (1, n = 136) = 8.73, P = 0.0031\).
High-intensity, occupation-specific training in a series of firefighters during phase II cardiac rehabilitation

Jenny Adams, PhD, Dunlei Cheng, PhD, and Rafic F. Berbarie, MD

Six male firefighters who were referred to phase II cardiac rehabilitation after coronary revascularization participated in a specialized regimen of high-intensity, occupation-specific training (HIOST) that simulated firefighting tasks. During each session, the electrocardiogram, heart rate, and blood pressure were monitored, and the patients were observed for adverse symptoms. No patient had to discontinue HIOST because of adverse arrhythmias or symptoms. For physicians who must make decisions about return to work, the information collected over multiple HIOST sessions might be more thorough and conclusive than the information gained during a single treadmill exercise stress test (the recommended evaluation method).

Firefighting is arduous and has one of the highest occupational fatality rates in the United States (1). Surprisingly, coronary heart disease (CHD), not injury, is the number one cause of on-duty deaths among firefighters (2). However, the vast majority of these firefighters were not previously diagnosed with CHD and had uncontrolled risk factors (3). Current recommendations state that firefighters with CHD should be restricted from performing strenuous emergency duties (4). To our knowledge, there are no data regarding firefighters’ exercise tolerance following successful revascularization of their CHD and hence no assessment of whether they are then able to perform simulated firefighting tasks.

The National Fire Protection Agency, which promotes codes and standards for fire safety worldwide, has proposed guidelines for veteran firefighters who may want to return to work in the presence of CHD. These guidelines include seven criteria, four of which are clinical observations that can be obtained from a patient history: 1) no angina, 2) no major coronary artery stenosis (>70% of lumen), 3) normal left ventricular ejection fraction, and 4) no persistent modifiable risk factor for plaque rupture (i.e., tobacco use, hypertension, total cholesterol >180 mg/dL, low-density lipoprotein cholesterol >100 mg/dL, or glycated hemoglobin >7%). The other three criteria involve observations made during an exercise stress test: 5) exercise tolerance >12 metabolic equivalents (METs), 6) no exercise-induced angina, and 7) no ischemia or ventricular arrhythmia during exercise (with imaging) (5). However, treadmill exercise stress tests are not always reliable predictors of performance in activities that require both strength and endurance (6), such as firefighting. Deciding whether a firefighter should return to work on the basis of the results from a single treadmill exercise stress test might be inadequate considering the unique specificity and intensity of the job.

In a prior study of the exercise tolerance of firefighters, we collected metabolic data on healthy subjects as they performed simulated firefighting tasks on an obstacle course (7). We then translated the study’s tasks, which required a mean level of 12 METs, into a telemetry-monitored program of high-intensity, occupation-specific training (HIOST) within the cardiac rehabilitation (CR) program at our institution. Our goal was to evaluate the firefighter-patient’s tolerance for performing strenuous occupational tasks in repeated sessions, with the resulting information assisting the physician’s decision about the patient’s physical potential for returning to work. Here, we report data from the first six patients with CHD to undergo this training.

PATIENT TRAINING

From June 2008 through May 2012, six male firefighters were referred to outpatient phase II CR in Dallas, Texas, following revascularization of CHD, and they consented to participate in CR 3 days per week. CR staff gave them the option of participating in HIOST or conventional CR; all selected the HIOST option. The hospital’s institutional review board approved the reporting of their data.

The patients’ demographic and clinical information is summarized in the Table. At enrollment, all six patients were on an antiplatelet regimen and were taking lipid-lowering drugs and beta-blockers. In addition, one was taking a nitrate and diuretic; another was taking ranolazine for angina.

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The patients were monitored by telemetry during exercise training. Resting heart rate and blood pressure measurements were taken before and after each session, and the patients performed warm-up and cool-down routines. A physician was in attendance during each session. No calculated target heart rate range was used to restrict exercise intensity. Training was symptom-limited; patients were monitored for hypertension (blood pressure >240/110 mm Hg), hypotension (systolic blood pressure decrease of ≥10 mm Hg), elevated rate-pressure product (≥36,000), ventricular arrhythmias, ST depression, angina, dizziness, pain, shortness of breath, and perceived exertion.

During HIOST, no calculated target heart rate range was used to restrict exercise intensity. Training was symptom-limited; patients were monitored for hypertension (blood pressure >240/110 mm Hg), hypotension (systolic blood pressure decrease of ≥10 mm Hg), elevated rate-pressure product (≥36,000), ventricular arrhythmias, ST depression, angina, dizziness, pain, shortness of breath, and perceived exertion.

The HIOST workouts were customized by incrementally increasing cardiovascular intensity and weight loads over the course of the CR program exercise sessions. The patients wore weighted vests (10 to 55 pounds) as they completed the following occupation-specific tasks (Figure):

- Carrying a weighted box ranging from 11.5 to 50 pounds (simulates carrying equipment)
- Climbing stairs carrying a 15- or 30-pound hose (simulates carrying a high-rise hose pack to an upper-story location)
- Dragging a 50-, 95-, or 165-pound dummy (simulates removing a victim from a fire scene)
- Using a stair-climbing machine (simulates walking up stairs)
- Pulling a 30- or 60-pound fire hose (simulates advancing a hose)
- Raising a pike pole weighing 5.5 to 15.4 pounds (simulates removing debris from a ceiling)
- Hitting a tire for 20 to 60 seconds with a 9-pound sledgehammer (simulates forcible entry)

The six patients participated in a total of 153 sessions; 36 consisted of supervised endurance training and 117 were HIOST. During each session, the peak exercise heart rate was determined from the electrocardiogram. Peak blood pressure was recorded a total of 73 times during HIOST, and the resulting rate-pressure product values were calculated (see the Table).

None of the patients had to stop training because of adverse arrhythmias or symptoms. Peak heart rates were likely blunted by beta-blocker therapy, but all six patients were able to perform firefighting tasks that mirrored the 12-MET activities from the prior study. During exercise, their peak blood pressures remained well below 240/110 mm Hg, the limit recommended by established guidelines (8), and their rate-pressure product values were below the 36,000 threshold (9).

**DISCUSSION**

The American College of Sports Medicine endorses using specificity of training for cardiac patients who desire to return to manual labor occupations (10). To our knowledge, this is the first report of firefighters’ ability to perform occupation-specific tasks following successful coronary revascularization.

The HIOST program has limitations. Because the CR setting lacks the danger and stress of actual fire suppression activities, the patients’ physiological responses during training may not reflect their responses on the job at a fire scene. In addition, the program cannot simulate many of the hazardous work conditions that firefighters must face, including exposure to smoke, carbon monoxide, fumes, and other chemicals (11); heat stress (12); and high noise levels (13).
Despite these limitations, HIOST allows patients to perform simulated firefighting tasks while their electrocardiogram, blood pressure, and heart rate are monitored in a clinical setting, providing information about exercise-induced angina, ischemia, and arrhythmias over multiple sessions. For physicians who must make decisions about return to work, these findings might be more thorough and conclusive than the information gained during a single treadmill exercise stress test.

Figure. Four of the occupation-specific activities performed by firefighters while wearing a weighted vest: (a) after climbing stairs with a hose pack, (b) dragging a dummy, (c) using a stair-climbing machine, and (d) hitting a tire with a sledgehammer.

Acknowledgments

Grant support was provided by the Harry S. Moss Heart Trust and the Baylor Health Care System Foundation, Dallas, Texas, through the Cardiovascular Research Review Committee and in cooperation with the Baylor Heart and Vascular Institute. The authors thank the committee for their continued support of cardiovascular rehabilitation research projects. Beverly Peters, MA, ELS, a freelance medical editor, assisted with manuscript development and preparation.


Morphological features of temporal arteritis

William C. Roberts, MD, Saleha Zafar, MD, and Jo Mi Ko, BA

Although it varies from center to center, the frequency of temporal artery biopsy in patients suspected of having temporal arteritis (TA) is relatively small. Most commonly, patients suspected of having TA are placed on prednisone for varying periods of time, and if symptoms disappear or lessen the diagnosis is made. During a recent 13-year period at Baylor University Medical Center at Dallas, 15 patients with TA had the diagnosis of TA confirmed by histological examination of a biopsy of one temporal artery. The length of the biopsied artery varied from 0.7 to 5.5 cm (mean 2.7). The 15 patients ranged in age from 68 to 94 years (mean 82, median 85), and 11 (73%) were women. In 13 of the 15 patients (87%), the lumen of the temporal artery was narrowed >95% in cross-sectional area by the panarteritis, and the temporal artery was associated with giant cells in 11 patients (73%). Large collections of erythrocytes were present in the inflamed arterial walls in 5 patients (33%). All 15 patients were treated with varying doses of prednisone with favorable response in each. Eight patients (53%) died from 1 to 105 months (mean 52, median 57) after biopsy of the temporal artery. We have neither positive nor negative evidence that the TA played a role in the patients’ death. Despite the present study and numerous others in the last 70 years, the cause of TA remains a mystery.

In 1932 and in 1934, Bayard T. Horton, a vascular specialist at the Mayo Clinic, and others (1, 2) reported two patients with headache, scalp tenderness, weight loss, fever, and night sweats, and histologic examination of one biopsied temporal artery disclosed granulomatous panarteritis. Thereafter, the condition was called temporal arteritis (TA) by some and Horton’s disease by others. In 1937, Horton and Magath (3) described visual loss, jaw claudication, and elevated erythrocyte sedimentation rates in several additional patients with the disease. According to Boes (4), Horton in 1942 was the first to give a patient with TA Kendall’s adrenocorticoid extract (nonpure), but apparently it had no effect on the patient’s disease. Shick and colleagues (5), in 1950, also at the Mayo Clinic, reported clinical improvement in two patients with TA using a pure form of cortisone. The present study summarizes findings in 15 patients with TA seen at Baylor University Medical Center at Dallas (BUMC) in the last 13 years and describes in detail the various histological features in the temporal artery in these patients.

METHODS

Cases coded as TA by the surgical pathology division of the Department of Pathology of BUMC from 1997 through 2012 were retrieved. Fifteen such cases having biopsy of one temporal artery were found. The paraffin blocks of the temporal artery in each patient were retrieved and recut. The resulting 6-micron-thick sections were stained by both the hematoxylin-eosin method and by the Movat method, and the sections were examined. The clinical records in each patient were retrieved and examined in the BUMC record room, and pertinent findings were tabulated in each patient. Finally, the Social Security Death Index was searched to determine how many of the 15 patients had died.

RESULTS

Pertinent findings in the 15 patients are summarized in Tables 1 and 2. The 15 patients ranged in age from 68 to 94 years (mean 82) at the time of the temporal artery biopsy; 11 were women and 4 were men. The age at biopsy in all 15 patients corresponded to the age at which symptoms and/or signs of TA appeared. The symptoms at the time of temporal artery biopsy are displayed for each patient in Table 1: headache in 12, visual disturbance in 10, mastication pain in 7, and temporal artery tenderness in 6. At the time of biopsy, the indirect systemic arterial pressure was ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic in 11 patients (73%). The body mass index was >25 kg/m² in 8 of the 15 patients, but in none was it ≥30 kg/m². Anemia (hematocrit <35%) was present in 8 (57%) of the 14 patients in which the result of this test was available. The platelet count was >250 mm³ in 9 of the 11 patients in whom it was performed. The erythrocyte sedimentation rates were elevated (>20 mm/hour) in all 10 patients where the results were available. The serum C-reactive protein was elevated in all 5 patients in which it was done. One patient (#2) had an aortic aneurysm, and one patient (#8) had had a stroke a few months before.
The length of the temporal artery biopsied ranged from 0.7 to 5.5 cm (mean 2.7 cm); sample images and descriptions appear in Figures 1 to 9.

In 13 of the 15 patients (87%), the lumen of the temporal artery was narrowed >95% in cross-sectional area. The temporal artery was associated with giant cells in 11 patients (73%). All 15 patients received prednisone (maximal dose 40–70 mg) for 0.25 to 73 months (mean 22), and all had symptomatic improvement, including 5 with loss or virtual loss of symptoms.

**DISCUSSION**

It might seem a bit inappropriate in 2013 to report a series of only 15 patients with biopsy-proven TA when others have reported such large series of patients with biopsy-proven TA (6–35). Gonzalez-Gay and colleagues (13, 19, 20, 25, 26, 28, 31), for example, in 7 articles from 1998 to 2011 described anywhere from 161 to 255 patients with biopsy-proven TA (called “giant cell arteritis” by the authors), but none contained a photomicrograph of a temporal artery. Indeed, of the 30 studies presented in Table 3 (6–35), only two included a photomicrograph of a temporal artery, and in both only hematoxylin-eosin–stained sections had been used. It is not possible to demonstrate the locations of the panarteritis, i.e., how much of the process involved the intima, media, and adventitia, without an elastic tissue stain that readily identifies the internal and external elastic membranes allowing clear demonstration of media, thus separating it from the intima and adventitia. We employed the Movat stain for this purpose in our study (36).

We prefer the phrase “temporal arteritis” to the phrase “giant cell arteritis” because giant cells are not seen in all TA patients having biopsies of the temporal arteries. Among our 15 patients, we found giant cells in only 11. Mahr and colleagues (37) suggested that finding giant cells in patients with TA is determined in part by the lengths of the temporal arteries examined. These authors also noted that finding giant cells in patients with TA is determined in part by the length of the temporal arteries examined. The length of the temporal arteries biopsied ranged from 0.7 to 5.5 cm (mean 2.7 cm); sample images and descriptions appear in Figures 1 to 9.

**Table 1. Clinical and laboratory findings in the 15 patients with temporal arteritis confirmed by biopsy and treated with prednisone**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of biopsy</th>
<th>Age at biopsy (years)</th>
<th>Sex</th>
<th>Interval from biopsy to death (mo)</th>
<th>Age at death (yr)</th>
<th>Age at symptom onset (yr)</th>
<th>Symptoms at time of biopsy</th>
<th>Temporal artery tenderness</th>
<th>BP s/d (mm Hg)</th>
<th>Hgb (g/dL)</th>
<th>HCT (%)</th>
<th>Platelet count (mm3)</th>
<th>ESR (mm/hr)</th>
<th>CRP (mg/dL)</th>
<th>BMI (kg/m2)</th>
<th>Mini- mal time on prednisone (mo)</th>
<th>Minimal dose of prednisone (mg)</th>
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<td>0</td>
<td>130/80</td>
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</tr>
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<td>75</td>
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<td>+</td>
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</tr>
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<td>32.0</td>
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<td>–</td>
<td>86</td>
<td>+ + + 0 + +</td>
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<td>150/55</td>
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<td>35.8</td>
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<td>32.5</td>
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<td>20.8</td>
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<td>60</td>
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<td>F</td>
<td>74</td>
<td>96</td>
<td>89</td>
<td>+ + + 0 + + +</td>
<td>+</td>
<td>220/80</td>
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<td>68</td>
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<td>32.0</td>
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<td>+ 0 + + + +</td>
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<td>–</td>
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<td>26.2</td>
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BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; CS, cigarette smokers; ESR, erythrocyte sedimentation rate; H, headache; HCT, hematocrit; Hgb, hemoglobin; LC, leg claudication; MP, mastication pain; PR, polymyalgia rheumatica; S/D, peak systole/end diastole; VD, visual disturbance; –, not done, not applicable, or no information.
Table 2. Morphological findings in the 15 patients with biopsy-proven temporal arteritis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Length (cm) of excised TA</th>
<th>Number of histological cross-sections</th>
<th>Maximal diameter (mm) of cross-sections</th>
<th>Cross-sectional narrowing</th>
<th>Collection of red blood cells in intima</th>
<th>Lymphocytes</th>
<th>Giant cells</th>
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<td>&gt;95%</td>
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<tr>
<td>3</td>
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<td>8</td>
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<td>&gt;95%</td>
<td>0</td>
<td>+++</td>
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<tr>
<td>4</td>
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<td>8</td>
<td>2</td>
<td>&gt;95%</td>
<td>+</td>
<td>+++</td>
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<td>5</td>
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<td>&gt;95%</td>
<td>+</td>
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<tr>
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<tr>
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<td>&gt;95%</td>
<td>0</td>
<td>+++</td>
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<tr>
<td>9</td>
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<td>&gt;95%</td>
<td>0</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>10</td>
<td>3.0</td>
<td>8</td>
<td>4</td>
<td>&gt;95%</td>
<td>0</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>11</td>
<td>0.7</td>
<td>2</td>
<td>2</td>
<td>&gt;95%</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
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<tr>
<td>15</td>
<td>3.0</td>
<td>7</td>
<td>3</td>
<td>51%–75%</td>
<td>0</td>
<td>+++</td>
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</table>

TA indicates temporal arteritis.

reports of temporal artery biopsies in 223 patients with TA and found that 164 (74%) of the reports mentioned the presence of giant cells. These authors also mentioned that a temporal artery length of at least 0.5 cm was sufficient for diagnosis of TA. Our smallest length among the patients was 0.7 cm. Among the four patients in whom we did not see giant cells, the lengths of the temporal artery biopsied were 0.7, 2.6, 3.0, and 3.5 cm; the latter three lengths were among the longest in the patients we studied.

Although the present study focuses on the histologic features of TA, one might reasonably ask if biopsy of this artery is a useful routine endeavor. A near universal observation in TA is a rapid, sometimes dramatic, diminution or loss of symptoms after corticosteroid therapy has been initiated. If there is not a quick symptomatic response, biopsy can then be performed. There appears to be little change in the histologic features of the TA before corticosteroid therapy and up to about 6 weeks after initiation of therapy (10). A report by Guevara et al described a positive biopsy after 6 months of prednisone treatment (38). If a patient with suspected TA has a negative biopsy of the temporal artery, is it useful then to biopsy the contralateral temporal artery? According to a study by Boyev and colleagues (18), biopsy of one temporal artery in a patient with TA provides a 97% chance that the same findings would be present in the contralateral temporal artery, so that the additional biopsy would rarely be useful diagnostically.

On occasion, TA resolves without corticosteroid therapy. Horton et al, in their original two patients, described temporary remissions with relapses (1), and they later described seven additional patients in whom remission occurred without drug therapy months after diagnosis (3). Patients have been described where headaches and local symptoms have disappeared simply by removal of a portion of the temporal artery for diagnostic purposes (39, 40).
Figure 2. Patient 2. (a) A Movat-stained section (×100) of temporal artery with severely narrowed lumen (within the green portion) of the intima with blood (red) within the intimal plaque and marked disruption of the internal elastic membrane (black). The adventitia is thickened by dense fibrous tissue (tan). (b) The same section stained by hematoxylin-eosin (×100). (c) A close up of a portion of the media showing numerous mononuclear cells (×400).

Figure 3. Patient 4. Movat-stained section (×40) of the temporal artery showing near-total occlusion of the lumen, blood (red) within the intimal plaque, disruption of the internal elastic membrane (black), and severely thickened adventitia by dense fibrous tissue (tan). The absence of much lumen and the marked thickening of the adventitia by dense fibrous tissue makes these arteries, by external palpation, quite firm and nodular.

Figure 4. Patient 6. Two views of Movat-stained sections of the temporal artery showing (a) virtual occlusion (×100) and (b) severe narrowing (×100). The internal elastic membrane (black) is interrupted and the quantity of fibrous tissue in the adventitia is considerably less than in previously illustrated cases.

Figure 5. Patient 8. (a) A Movat-stained section of the temporal artery showing near occlusion of the lumen by fibrous tissue and mucopolysaccharide material (green) and dense fibrous tissue causing considerable thickening of the adventitia. (b) Hematoxylin-eosin stain (×40) of another section of the same artery showing numerous inflammatory cells between the 8:00 and 11:00 positions. (c) Close-up (×400) of a portion of the inflammatory cells.
Figure 6. Patient 9. (a) View of a hematoxylin-eosin–stained section (×20) of the temporal artery with virtual total occlusion of its lumen. The darkened area represents collections of inflammatory cells. The adventitia is thickened by fibrous tissue. (b) A close-up (×400) of a minute portion of the inflammatory infiltrates. Granulomatous-type cells and a giant cell are visible.

Figure 7. Patient 9. (a) A Movat-stained section (×40) of three branches of a temporal artery with narrowing of each branch, marked disruption of the media in two of the branches, and dense fibrous tissue in the adventitia. (b) A close-up of a hematoxylin-eosin–stained section (×400) of a portion of the inflammatory cells in the media. (c) Another hematoxylin-eosin stained section (×400) showing giant cells among the collection of cells.

Figure 8. Patient 10. A Movat-stained section of the temporal artery showing (a) severe narrowing of the lumen (×100) and (b) less narrowing (×100). The amount of adventitial fibrous tissue is considerable. Inflammatory cells are present in the intima, media, and adventitia. The dark staining in the medial wall in part b represents calcific deposits.

Figure 9. Patient 13. (a) A Movat-stained section of the temporal artery (×40) with severe luminal narrowing. The lumen in all sections in temporal arteritis tends to be in the more central portion of the artery and not on the periphery, as it is in typical atherosclerosis. (b) A close-up hematoxylin-eosin–stained section (×400) shows several giant cells in the outer intima adjacent to the media. These cells are lined up perpendicular to the smooth muscle cells in the media.

Table 3. Reported studies of patients with temporal arteritis confirmed by biopsy of the temporal artery

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<th>First author, year of publication</th>
<th>Patients (n)</th>
<th>Biopsy-proven TA (n)</th>
<th>M/F</th>
<th>Age range (mean)</th>
<th>Length of study (yr)</th>
<th>Follow-up (yr)</th>
<th>Deaths attributed to TA</th>
<th>Mean ESR values (mm/hr)</th>
<th>Median hemoglobin values (g/dl)</th>
<th>Median platelet count (mm³)</th>
<th>Visual loss (n)</th>
<th>Received corticosteroids (n)</th>
<th>Maximal length of treatment (mo)</th>
<th>Patients that relapsed (n)</th>
<th>Temporal artery photo microscopy (n)</th>
<th>Giant cell histology (n)</th>
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<td>–</td>
<td>–</td>
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<td>–</td>
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<td>55</td>
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<td>56–92 (75)</td>
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<td>55–88</td>
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<td>11</td>
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<td>12</td>
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<td>(78.2)</td>
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</table>

ESR indicates erythrocyte sedimentation rate; F, female; M, male; TA, temporal arteritis; –, no information.


Quality of life of HIV/AIDS patients in a secondary health care facility, Ilorin, Nigeria

Shakirat I. Bello, MPharm, and Ibrahim K. Bello, MPharm

This study evaluated the quality of life (QoL) and associated factors for 160 HIV/AIDS patients in Sobi Specialist Hospital, Ilorin, Nigeria. The patients were assessed with the World Health Organization Quality of Life Questionnaire-Short Version. Frequency distribution, percentages, and means were employed for the statistical analysis of the results. The mean age of the HIV/AIDS patients was 38.0 years; 70% were females, 55% were literates, more than three quarters were married, and one third were businessmen/women. The overall mean scores for health-related QoL were 72 for the physical domain, 67 for the psychological domain, 65 for the environment domain, and 47 for the social domain. Significant differences were observed in all domains among patients who had received 12 months of antiretroviral therapy compared with those who had just begun therapy. Marital status, fewer pills, and longer duration of therapy appeared to predict better QoL in this study. The improved QoL in the physical, psychological, and environmental domains is suggestive of the interventions offered to the patients by the pharmacists in this setting.

The pandemic of HIV and AIDS has led to serious health and socioeconomic challenges for more than two decades (1). The epidemic has also facilitated the reemergence of disease conditions such as pulmonary tuberculosis, which cause physical and psychological damage and decreased quality of life (QoL) (2, 3). Based on an overall national prevalence of 4.1%, it is estimated that in 2012, 3.6 million Nigerians were living with HIV/AIDS, 2.5 million children were orphaned, and about 1000 new cases of HIV were discovered daily (4). With this alarming increase of the HIV/AIDS pandemic in developing countries and the limited accessibility and availability of highly active antiretroviral therapy (HAART), the majority of HIV/AIDS patients continue to suffer with the disease, with a serious impact on their QoL. (5). Many HIV patients battle numerous social problems such as stigma and depression, which affect their QoL in terms of their physical, mental, and social health (6). QoL is an indicator of not only how well an individual functions in daily life, but also how the individual’s perceptions of health status influence his or her life (7, 8).

In Nigeria, QoL has been found to be determined by education, income, family support, HIV serostatus, and patient age (9). Further, a study reported higher QoL scores in the physical, psychological, and environmental domains and a relatively lower score in the social domain among HIV patients in Nigeria (10). Mweemba et al (11) suggested that periodical assessment of QoL of people living with HIV/AIDS is imperative for holistic care, thereby ameliorating the symptoms of ill health. Such assessments are useful not only in documenting patients’ perceived burden of chronic disease, but also in evaluating treatment effects (12). This study was therefore conducted to assess QoL of HIV/AIDS patients in Sobi Specialist Hospital, Ilorin, Nigeria.

METHODS

The study site was the HIV/AIDS treatment center, Sobi Specialist Hospital, Ilorin, Kwara State. Sobi Specialist Hospital, Ilorin is a secondary health care facility established in April 1985 by the Kwara State Government, located in the north central part of Nigeria. The primary ethnic group of Kwara State is Yoruba, with Nupe, Bariba, and Fulani as minorities. The facility provides health services for citizens in Kogi, Niger, Osun, Oyo, and Ekiti States and other neighboring states in Nigeria. The hospital receives referrals of HIV-positive patients from surrounding private hospitals and primary health care centers. The center was funded by Friends in Global Health and supported by the Kwara State Government. As at June 2011, the clinic had registered 616 HIV/AIDS patients, of whom 554 were on HAART.

This cross-sectional study involved 160 patients selected from the population of 616 HIV/AIDS-positive patients receiving services and care from Sobi Specialist Hospital, Ilorin, during the period of April to October 2011. Included in the sample were known HIV/AIDS patients who were 18 years or older and regularly refilled their prescriptions in the pharmacy unit of the center. Newly diagnosed patients and children (less than 18 years) were excluded. At the time of drug refill, an information sheet describing the significance of the study was presented to the patients. Those who showed interest in participating were asked to sign informed consent forms. Ethical approval for the study was obtained from the ethics committee of Sobi Specialist Hospital. All data were analyzed using the SPSS version 20.
study was obtained from the Ethics and Research Committee of Kwara State Ministry of Health, Ilorin.

The patients were interviewed using a pretested structured questionnaire to obtain information on sociodemographic status and treatment variables. During the interview, all drug therapy problems encountered were identified, resolved, and prevented through pharmacist intervention in collaboration with other health care providers. Counseling, education, training, and information interventions on HIV/AIDS, drug adherence, good nutrition, safe drinking water, and malaria prevention were also offered to the patients on a monthly basis.

The English version of the World Health Organization Quality of Life Questionnaire-Short Version (WHOQoL-BREF) was used to assess the QoL of these patients. This questionnaire consists of 26 items in four domains. The physical health domain, with seven items, assesses the impact of disease on the activities of daily living, dependence on medication substances, fatigue, restricted mobility, presence of pain and discomfort, sleep and rest, a lack of energy and initiative, and perceived working capacity. The psychological well-being domain includes eight items that assess the patient's thoughts about body image and appearance, positive feelings, negative feelings, self-esteem and personal beliefs, higher cognitive functions, spirituality, anxiety, suicide, and depression. The third domain, social relationships, has three items that assess personal relationships, social contacts, social support, and sexual activity. The final domain, environment, with eight items, assesses areas such as freedom, quality of home environment, physical safety and security, financial status, involvement in recreational activity, health, and social care quality and accessibility. The English version of the instrument was translated to the Yoruba language (the main language understood by most patients); the translated version was validated prior to administration to participants.

The QoL of each patient was assessed monthly during drug refill at the main pharmacy of the hospital. The participants who could not read were interviewed, while literates completed the questionnaire under the supervision of the researchers. Participants selected the number on a 5-point Likert-type scale that best represented their opinion, based on their life over the previous 4 weeks. In the scale, 1 indicated low and negative perceptions, and 5 indicated high and positive perceptions, which denoted better QoL.

Negatively worded items were reverse scored, and all scores were checked for appropriate range (between 1 and 5). Descriptive statistics, including frequency, means, percentages, minimum values, and maximum values, were calculated. Each item contributed equally to the domain score. To transform scores so that they were equivalent to those used for the WHOQOL-100, two steps were used. First, scores were converted to a range between 4 and 20, comparable with the WHOQOL-100. Second, these scores were multiplied by 5 so that the scores were converted to a scale of 0 to 100, where 100 is the highest health-related QoL. Student’s t test was used to analyze the differences between the mean scores of QoL. P < 0.05 was set as the level of statistical significance.

A total of 160 eligible participants completed the questionnaires; most were married (76%) and female (70%). The mean age of the participants was 38.0 years (range 18–53 years). The modal age range was 31–40 years. Other participant demographics are shown in Table 1. Almost half of the patients were on HAART for over 12 months and employed self-reminder or alarm methods of medication-taking behavior (Table 2). A fixed-dose combination of a zidovudine-based regimen was most tolerated by the patients, and more than three quarters of the patients were taking two pills daily (Table 3).

HIV-seropositive married women had the highest QoL scores in all the domains compared to those with a different marital status (Table 4). Among the patients included in the present study, however, those on two pills per day of antiretroviral drugs had the best QoL in the four domains. There was no significant difference in the QoL of patients in the various domains when compared based on pill burden (Table 5).

When patients’ QoL was assessed with respect to duration of antiretroviral therapy, patients who had received treatment for over 12 months had higher QoL scores in the psychological and social domains; the difference was statistically significant for the psychological domain (Table 6). Table 7 reveals the overall QoL of the patients. The highest mean score was observed in the physical domain followed by the psychological and environmental domains, while the social domain had the lowest score.

| Table 1. Sociodemographic characteristics of 160 HIV/AIDS patients in Sobi Specialist Hospital, Ilorin |
|-----------------------------|-----------------------------|
| Variables                  | N (%)                      |
| Gender                     |                            |
| Females                    | 112 (70%)                  |
| Males                      | 48 (30%)                   |
| Age (years)                |                            |
| 18–30                      | 46 (29%)                   |
| 31–40                      | 67 (42%)                   |
| 41–50                      | 38 (24%)                   |
| >50                        | 9 (5%)                     |
| Marital status             |                            |
| Single                     | 19 (12%)                   |
| Married                    | 121 (76%)                  |
| Widowed                    | 12 (7%)                    |
| Divorced                   | 8 (5%)                     |
| Education                  |                            |
| None                       | 49 (31%)                   |
| Primary school             | 50 (31%)                   |
| Secondary school           | 38 (24%)                   |
| Tertiary                   | 23 (14%)                   |
| Occupation                 |                            |
| Businessmen/women          | 58 (37%)                   |
| Public servants            | 25 (16%)                   |
| Self-employed              | 34 (20%)                   |
| Students                   | 7 (4%)                     |
| Not employed               | 36 (23%)                   |
DISCUSSION

The present study showed the prevalence of HIV infection among all age groups but with the highest prevalence for those in their 30s followed by those 18 to 30 years. This is consistent with the findings of Bankole et al (13) and Khan et al (14), who reported that people within the age bracket of 15 to 24 years were vulnerable to HIV, while those in their 30s were most susceptible (15, 16). The demographic profile of the participants also showed the predominance of the female gender, which is consistent with other studies. Kelly et al (17) showed that 60% of those living with HIV/AIDS are women. In contrast, in the USA, 87% of the patients are men (18).

Patients who are more educated can better understand the disease state and the instructions given on drug usage, which invariably enhances their QoL. Almost one third of this study population had received no formal education. Patients on HAART for a longer duration, however, had higher QoL in this study. By this time, patients had perceived medications as part of their daily routine and had also developed coping strategies to overcome the adverse effects of HAART that might have affected their QoL. In line with this work was a study conducted by Mannheimer et al (19), who reported significant improvement in QoL after 1 to 4 months of treatment with antiretroviral therapy, and this improvement persisted at 12 months.

### Table 2. Treatment characteristics of 160 HIV/AIDS patients in Sobi Specialist Hospital, Ilorin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Therapy initiation period (months)</td>
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</tr>
<tr>
<td>3–5</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>6–8</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>9–12</td>
<td>60 (37%)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>67 (42%)</td>
</tr>
<tr>
<td>Patient’s medication-taking behavior</td>
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</tr>
<tr>
<td>Use of alarm/self-reminder</td>
<td>71 (44%)</td>
</tr>
<tr>
<td>Family/clinic counselor</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Daily routine</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>All of the above</td>
<td>68 (43%)</td>
</tr>
<tr>
<td>Drug allergies</td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>43 (27%)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>64 (40%)</td>
</tr>
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<td>Tetracycline</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>None</td>
<td>27 (17%)</td>
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### Table 3. Number of antiretroviral drugs taken per day by 160 HIV/AIDS patients

<table>
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<tr>
<th>Drugs</th>
<th>Pills per day (n)</th>
<th>N (%)</th>
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</thead>
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<td>Fixed-dose combination (AZT + 3TC + NVP)</td>
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<td>98 (61%)</td>
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<tr>
<td>Lose dose (AZT + 3TC + NVP)</td>
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<td>2 (1%)</td>
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<td>15 (9%)</td>
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<tr>
<td>Combined (FTC + TDF) + NVP</td>
<td>3</td>
<td>5 (4%)</td>
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<tr>
<td>Combined (FTC + TDF) + EFV</td>
<td>2</td>
<td>24 (15%)</td>
</tr>
<tr>
<td>Combined (FTC + TDF) + LPV/r</td>
<td>5</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Combined (AZT + 3TC) + LPV/r</td>
<td>6</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>3TC + ABC + NVP</td>
<td>6</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

### Table 5. Antiretroviral pill burden and quality of life scores of 160 HIV/AIDS patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>2 pills</th>
<th>4 pills</th>
<th>6 pills</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>73</td>
<td>72</td>
<td>71</td>
<td>0.022</td>
</tr>
<tr>
<td>Psychological</td>
<td>67</td>
<td>64</td>
<td>65</td>
<td>0.048</td>
</tr>
<tr>
<td>Social</td>
<td>47</td>
<td>44</td>
<td>43</td>
<td>0.242</td>
</tr>
<tr>
<td>Environmental</td>
<td>67</td>
<td>66</td>
<td>64</td>
<td>0.006</td>
</tr>
</tbody>
</table>

### Table 4. Marital status and quality of life scores of 160 HIV/AIDS patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>Single</th>
<th>Married</th>
<th>Divorced</th>
<th>Widowed</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>70</td>
<td>72</td>
<td>71</td>
<td>71</td>
<td>0.032</td>
</tr>
<tr>
<td>Psychological</td>
<td>66</td>
<td>69</td>
<td>66</td>
<td>67</td>
<td>0.355</td>
</tr>
<tr>
<td>Social</td>
<td>45</td>
<td>48</td>
<td>46</td>
<td>45</td>
<td>0.011</td>
</tr>
<tr>
<td>Environmental</td>
<td>64</td>
<td>65</td>
<td>62</td>
<td>61</td>
<td>0.428</td>
</tr>
</tbody>
</table>

### Table 6. Antiretroviral therapy duration and quality of life scores of 160 HIV/AIDS patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>3–5 mo</th>
<th>6–8 mo</th>
<th>9–11 mo</th>
<th>≥12 mo</th>
<th>P value</th>
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<tbody>
<tr>
<td>Physical</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>70</td>
<td>0.033</td>
</tr>
<tr>
<td>Psychological</td>
<td>62</td>
<td>60</td>
<td>64</td>
<td>68</td>
<td>&lt;0.017</td>
</tr>
<tr>
<td>Social</td>
<td>44</td>
<td>45</td>
<td>46</td>
<td>48</td>
<td>0.008</td>
</tr>
<tr>
<td>Environmental</td>
<td>64</td>
<td>64</td>
<td>65</td>
<td>63</td>
<td>0.453</td>
</tr>
</tbody>
</table>

### Table 7. Distribution of transformed quality of life scores obtained from WHOQoL-BREF questionnaire for 160 HIV/AIDS patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean scores (transformed 0–100)</th>
<th>Minimum domain</th>
<th>Maximum domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>72</td>
<td>43</td>
<td>80</td>
</tr>
<tr>
<td>Psychological</td>
<td>67</td>
<td>43</td>
<td>87</td>
</tr>
<tr>
<td>Social</td>
<td>47</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Environmental</td>
<td>65</td>
<td>47</td>
<td>80</td>
</tr>
</tbody>
</table>

WHOQoL-BREF indicates World Health Organization Quality of Life Questionnaire-Short Version.
In this study, patients on a lower pill regimen had better QoL. The explanation is probably related to fewer side effects, fewer tablets to swallow, and a smaller container (easy to convey and a pocket-friendly package). This study confirms the findings of Jack et al (20) that improvements in overall evaluations of QoL occurred for patients on a single daily dose.

The present study showed better QoL among married HIV/AIDS patients than for unmarried women. It is believed that the physical, emotional, and social support the married women received from their partners likely led to improved QoL. Evidence has shown that support from sources outside the family cannot compensate for what is missing in the family (21). Consistent with the present work was a study reported by Nojomi et al (22) that marital status had a significant effect on patients’ QoL. In contrast, Pedram et al (23) showed that marital status had no significant association with any domain of QoL.

Overall, however, the social domain showed the lowest score of the four QoL domains in this study. The social domain was affected by societal discrimination and stigmatization, as well as HIV/AIDS’ influences on patients’ sexual desire, personal relationships, and family life. In line with this study was that of Fatiregun et al (24) in Kogi State, Nigeria, who reported a significant association with any domain of QoL.

RECOMMENDATION

HIV/AIDS has affected many lives. Therefore, health care providers and other stakeholders should strengthen their efforts by addressing its social consequences to enhance QoL.

Timing and causes of death after injuries

Justin Sobrino, MD, and Shahid Shafi, MD, MPH

Currently, long-term outcomes are significant because health care system changes will likely lead to a single payment for each occurrence of care, including readmissions—the “bundled payment” system. Therefore, it is essential to understand the outcomes of trauma patients discharged alive from trauma centers. This article reviews the current knowledge base on the timing and causes of deaths after trauma. The trimodal mortality model (immediate deaths, early deaths, and late deaths) is utilized as the early research describing trimodal distribution is discussed. Also covered is the successive work as trauma systems matured, showing a shift toward a bimodal distribution with a decline in late deaths. Finally, studies of long-term outcomes are highlighted. Deaths occurring within minutes or a few hours of injury are largely unchanged, which underscores the enormity of injuries to the central nervous and cardiovascular systems. Late deaths caused by multiple organ failure and sepsis have declined considerably, however. Also, the causes of death in this patient population remain constant. Lastly, a considerable number of deaths after discharge may be due to nontraumatic causes.

Survival to discharge has long been the primary endpoint for research and quality improvement in trauma (1, 2). More recent studies have begun assessing long-term outcomes such as complications, costs, readmissions, and survival after discharge (3–11). We have recently shown that over a period of 1 year after the initial injury, about half of the deaths occur within the first 30 days but the rest occur afterward (12). It is important to understand the outcomes of trauma patients discharged alive from trauma centers. Baker et al and Trunkey defined timing of trauma deaths as a trimodal distribution in urban environments in the United States (13, 14). However, the development and maturation of region-alized trauma networks in the 1970s and 1980s have shifted the epidemiology of trauma patients and patterns of mortality. Subsequent research has shown a decline in deaths late after trauma, indicating that the trimodal concept may no longer be accurate in urban trauma environments (12, 15–18). A confounding factor is inconsistent time intervals chosen by researchers to define the timing of deaths (18–20). Herein, we review the existing knowledge on timing and causes of deaths after trauma. We use the trimodal mortality model to cover the early research describing the trimodal distribution, the subsequent work as trauma systems matured, and studies of long-term outcomes.

TIMING OF DEATHS

The first peak in the classic trimodal model of trauma mortality is immediate death occurring within minutes of the injury. These patients are declared dead on the scene or die shortly after arrival to the hospital. In most published reports, these include deaths at the scene, deaths occurring within 1 hour of arrival to the hospital, and all deaths in the emergency department. These deaths are generally a consequence of severe and likely nonsurvivable injuries. The seminal works of Baker et al and Trunkey in the 1970s showed that 64% and 53%, respectively, of trauma deaths occurred on the scene, with the patients not even transported to a hospital (13, 14). Figure 1 displays a summary of studies evaluating immediate deaths (12, 13, 15, 16, 18, 19, 21–24). This recognition led to rapid development of regionalized trauma systems in the United States, led by the work of Dr. Cowley in Maryland (25, 26). The primary purpose of regionalized integrated care was rapid transportation of patients from the scene to definitive care. It is interesting

Figure 1. Studies reviewing immediate deaths (12, 13, 15, 16, 18, 19, 21–24).

From the Institute for Health Care Research and Improvement, Baylor Health Care System, Dallas, Texas.

Corresponding author: Shahid Shafi, MD, MPH, Baylor Health Care System, 1600 W. College Street, Suite LL 10, Grapevine, TX 76052 (e-mail: shahid.shafi@baylorhealth.edu).
to note in Figure 1 that despite all the progress in emergency medical services and trauma systems, prehospital care, injury prevention, and automotive safety, the proportion of deaths occurring immediately after injury has remained unchanged over time, at 50% to 60%.

The second peak in the trimodal distribution is early deaths, defined as deaths within hours of arrival to the hospital. In most published reports, early deaths include deaths within 24 hours of arrival to a trauma center, excluding immediate deaths. These deaths are also a consequence of severe injuries, but the patients arrive at the hospital alive and are potentially treatable with prompt definitive care. Trunkey estimated this group to include approximately 30% of deaths (14). Figure 2 depicts a range of studies evaluating early deaths (12, 13, 15, 16, 19). Again, the proportion of deaths in this group has remained relatively unchanged over time, at 25% to 30% of all trauma deaths.

In Trunkey’s original description of the trimodal distribution, 20% of trauma deaths were “late deaths,” defined as those occurring days to weeks after the injury among patients who survived the initial insult (14). In most reports, this category includes deaths occurring after the first 24 hours and all other in-hospital deaths. Figure 3 displays studies evaluating late deaths (12, 13, 15, 16, 19, 22–24). In contrast to the first two categories, there has been a definite and dramatic drop in late deaths over time. In the most recent study by Gunst and colleagues, this group included only 9% of deaths (12).

Deaths among trauma patients after discharge have largely remained overlooked in the trauma literature. This is due in large part to the difficulty of follow-up in the trauma patient population. First, regionalized trauma networks often mean that patients are transported farther from home for their initial episode of care at designated trauma centers. Second, trauma patients are typically younger individuals who are more mobile in pursuit of work or education. However, several studies have shown that trauma patients have an increased risk of mortality after discharge. Follow-up methods have varied, but the most commonly used are trauma registries, hospital databases, and patient records from single institutions. Combined with a lack of communication between medical record systems, single-institution studies are likely to miss patients who pursue follow-up care closer to home at a different hospital. In order to capture higher percentages of the study population, particularly over longer periods of time, telephone interviews or mail surveys are commonly utilized. More recently, trauma researchers have employed vital statistics records and Social Security data as a means of capturing high percentages of patients while also obtaining cause-of-death data (27–29).

In a study of data from 1991 to 1993, Mullins et al reported an in-hospital mortality rate of 12.1 per 100,000 for trauma deaths. This increased to 14.1 per 100,000 when including patients who died within 30 days of discharge (30). Among injured Medicare patients discharged to home, the 30-day mortality ranged from 1.9% to 2.3% (31). In 2004, Clark and colleagues reported that among injured Medicare patients, 30-day mortality was 7.5% compared with 3.7% in-hospital mortality (6). In 2006, MacKenzie et al reported a case fatality rate for in-hospital deaths of 7.6%, which remained stable for 30 days but increased to 10.4% at 1 year (32). In 2008, Gorra et al reported 30-day mortality rates of 4.2% to 5.4% among injured Medicare patients discharged to a long-term care facility (31). A 2010 study by Clarke and colleagues reported a mortality rate of 3.6% at 30 days, 4.1% at 90 days, 5.5% at 1 year, and 8.1% over the entire study period (33). In 2011, Davidson et al demonstrated 9.8% mortality at 1 year and 16% 3-year cumulative mortality (34). The multiinstitutional prospective National Study on Costs and Outcomes of Trauma evaluated patients up to 1 year after discharge. In this study, MacKenzie et al reported an in-hospital mortality rate of 21.3%, but a further 2.6% were dead at 3 months, and an additional 2.2% were dead by 12 months (35). Similarly, in 2005, Wright and colleagues reported a 5-year mortality rate of 22.1% in trauma patients admitted to an intensive care unit during their initial hospitalization (36). In 2011, Timmers et al reported a 1-year mortality rate of 17%, which increased to 29% between 6 and 11 years (37). Finally, our recently published study utilizing Social Security data showed that almost half of the deaths in trauma patients occurred after discharge from the trauma center (27). All these studies are consistent in their findings that the risk of death among trauma patients remains elevated for months to years afterward.
CAUSES OF DEATH

Several studies have investigated the causes of death in trauma patients. Baker et al found that brain injury accounted for a majority of deaths, at 50% (13). Heart or aortic injury (17%), hemorrhage (12%), sepsis (10%), lung injury (6%), burn (3%), and liver injury (2%) accounted for the remainder. The majority of patients with major cardiac, vascular, or liver injury died of hemorrhage. Shackford and colleagues also found that head injury was the most common cause of death, and when combined with spinal cord injury, neurologic injuries were responsible for 49% of deaths (24). On autopsy, secondary brain injury, defined as diffuse cerebral edema; herniation; or cerebral necrosis due to hypoxia, hypotension, or cerebral edema that followed the primary injury was present in just over half of neurotrauma cases. Almost a third (31%) of victims died of hemorrhage in the chest, the abdomen, or both cavities. Other causes of death included asphyxia in 6%, cardiac arrest in 4%, sepsis in 3%, and pneumonia in 2%. The Table lists the most common causes of death for each time interval. Immediate and early deaths are considered together, given the similar etiologies.

In Trunkey and Lim’s initial case series in 1972, 45% of the patients in the immediate death category died of irreversible brain injury, such as lacerations of the brain, brain stem, or spinal cord, and 35% died due to hemorrhage resulting from injuries to the heart, aorta, liver, lungs, and pelvic fractures (21). Similarly, Meislin et al showed that for death within 1 hour of injury, 46% were neurologic injuries and 31% were due to circulatory collapse resulting from hemorrhage (19). Likewise, work from Sauaia et al showed that among those dead on the scene, 42% died from resulting from hemorrhage (18). Likewise, work from Sauaia et al showed that among those dead on the scene, 42% died from hemorrhage resulting from injuries to the brain, brain stem, or spinal cord, and 35% died due to hemorrhage accounted for the remainder. The majority of patients with major cardiac, vascular, or liver injury died of hemorrhage. Shackford and colleagues also found that head injury was the most common cause of death, and when combined with spinal cord injury, neurologic injuries were responsible for 49% of deaths (24). On autopsy, secondary brain injury, defined as diffuse cerebral edema; herniation; or cerebral necrosis due to hypoxia, hypotension, or cerebral edema that followed the primary injury was present in just over half of neurotrauma cases. Almost a third (31%) of victims died of hemorrhage in the chest, the abdomen, or both cavities. Other causes of death included asphyxia in 6%, cardiac arrest in 4%, sepsis in 3%, and pneumonia in 2%. The Table lists the most common causes of death for each time interval. Immediate and early deaths are considered together, given the similar etiologies.

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The cause of early trauma deaths is similar to that of immediate deaths and likely represents less catastrophic injuries or better prehospital care and shorter transport times to trauma centers. As described by Trunkey and Lim, the causes of death in this group include major internal hemorrhages of the head, respiratory system, or abdominal organs or multiple minor injuries resulting in severe blood loss (21). Sauaia et al reported that among trauma deaths within 48 hours of injury, exsanguination was the most common cause (51%) due to injuries to the liver, heart, or major blood vessels (7). This was particularly true for patients with penetrating injuries. Central nervous system injury was the second most common cause of death, including brain lacerations, contusions, and subdural hemorrhages (18). Meislin et al showed that neurologic injuries and circulatory collapse or hemorrhage accounted for over 80% of early deaths (19). Baker and colleagues showed that most of the deaths due to head injuries were within the first 2 days after injury (13).

Trunkey reported that 80% of late deaths in the hospital were due to infections or multiple organ failure (14). Similarly, Baker found that 78% of deaths after 7 days were due to sepsis and multiple organ failure (13). Cowley indicated that the most common causes of death in this group were overwhelming infection and irreversible head injuries (26). Sauaia et al reported that for deaths occurring after 1 week postinjury, organ failure claimed the majority of patients (61%) (18). More recently, Meislin et al reported that for the group dying within 24 to 48 hours, 45% died of neurologic injury, 42% of circulatory collapse or hemorrhage, and 9% of multiple organ failure (19). Similarly, for the group dying 2 days to 3 weeks after injury, 48% died of neurologic injury, 35% of circulatory collapse or hemorrhage, and 16% of multiple organ failure. These studies indicate that head injuries and hemorrhage remain important causes of death among patients who survive the first 24 hours, but multiple organ failure becomes more prominent with the passage of time.

Causes of death after discharge from trauma centers are less well studied. This is due, in part, to the difficulties of follow-up. Mullins evaluated cause-of-death codes reported on death certificates for injured patients who died of nontraumatic causes during their hospital stay and within 30 days after discharge (30). Of 1174 postdischarge deaths, 15% were due to neoplasms, 12% to cerebrovascular disease, 11% to cardiovascular disease, 11% to ischemic heart disease, 9% to chronic obstructive pulmonary disease, and 8% to acute myocardial infarction. Another 20% were due to a myriad of other causes. In a German study, Probst and colleagues described in-hospital and postdischarge causes of death for trauma patients (38). While in-hospital causes of death mirrored those previously discussed, postdischarge deaths included cardiovascular disease in 23%, a second major trauma in 19%, neurologic disease in 16%, suicide in 10%, and malignancies in 6%. Furthermore, trauma patients had increased mortality compared with the general population during the first year after injury. The mortality rates were more closely approximated during years 2 to 10 after injury. Claridge and colleagues classified deaths as trauma related in 33%, possibly related in 23%, and unrelated in 44% (33). Additionally, mortality after discharge was more likely trauma related in younger patients. The authors found that most deaths within the first year after injury were attributable to trauma, after which chronic diseases increased mortality. These studies indicate that postdischarge deaths among trauma patients are related to common chronic diseases within the population. However, the impact of injuries on the outcome of these chronic diseases remains unknown.

CONCLUSION

Three important conclusions can be drawn from this review. First, deaths occurring within minutes or a few hours of injury are largely unchanged, reflecting the devastating nature of injuries

<table>
<thead>
<tr>
<th>Immediate and early deaths</th>
<th>Late deaths</th>
<th>Postdischarge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain injury</td>
<td>Infection</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Multiple-organ failure</td>
<td>Second major trauma</td>
</tr>
<tr>
<td>Brain injury</td>
<td>Brain injury</td>
<td>Neurologic disease</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Hemorrhage</td>
<td>Malignancy</td>
</tr>
</tbody>
</table>

Table. Causes of death by timing category
to the central nervous and cardiovascular systems. Late deaths due to multiple organ failure and sepsis, however, have declined dramatically. Second, the causes of death in this patient population, i.e., those with severe head injuries and hemorrhage, remain persistent. Finally, a large number of deaths in trauma patients that occur after discharge may be related to nontraumatic causes. Reasons for the increased risk of death from nontraumatic causes after discharge need to be studied further.

Acknowledgment

The authors wish to thank Kelli R. Trungale, MLS, ELS, for editorial assistance.


Facts and principles learned at the 39th Annual Williamsburg Conference on Heart Disease

Mina M. Benjamin, MD, and William C. Roberts, MD

The December 2012 Williamsburg Conference on Heart Disease in Williamsburg, Virginia, was the 39th such annual conference to be held in that city. The conference has been directed by one of the authors (WCR) since 1972. The conference provides 16.5 hours of continuing medical education category one credit, and nearly all of the speakers are nationally and internationally recognized. It is one of the two longest-running cardiology courses. Its unique feature is that each presentation is 90 minutes, which allows the speakers time to discuss more than one topic and to answer questions from enrollees. This article summarizes the proceedings of the 2012 conference.

SOME FACTS AND PRINCIPLES LEARNED AFTER SPENDING 50 YEARS INVESTIGATING CORONARY HEART DISEASE

William C. Roberts, MD, Executive Director, Baylor Heart and Vascular Institute; Dean, A. Webb Roberts Center for Continuing Medical Education, Baylor University Medical Center, Dallas, Texas; and Editor in Chief, The American Journal of Cardiology and the Baylor University Medical Center Proceedings

Although the same blood flows through both arteries and veins, atherosclerosis affects only the arteries. The arterial system can be subdivided into various regions—coronary, carotid, cerebral, renal, peripheral (arm and leg), and aorta—and one region may cause symptoms of organ ischemia or discomfort and the other regions may be clinically silent. Nevertheless, when one region contains considerable amounts of atherosclerotic plaque such that it produces symptoms or discomfort in that region, necropsy studies have demonstrated that large quantities of atherosclerotic plaque also are present in the other regions. In other words, atherosclerosis is a systemic disease. To demonstrate this principle, detailed studies of the coronary arteries in patients with large abdominal aneurysms and/or aortas and one region may cause symptoms of organ ischemia or discomfort and the other regions may be clinically silent. Nevertheless, when one region contains considerable amounts of atherosclerotic plaque such that it produces symptoms or discomfort in that region, necropsy studies have demonstrated that large quantities of atherosclerotic plaque also are present in the other regions. In other words, atherosclerosis is a systemic disease. To demonstrate this principle, detailed studies of the coronary arteries in patients with large abdominal aneurysms and/or peripheral limb ischemia so severe that amputation was required disclosed atherosclerotic plaque in every 5-mm segment of each of the 4 major epicardial coronary arteries (right, left main, left anterior descending, left circumflex). The quantity was so severe that a large portion (about 33%) of the length of the four major coronary arteries had plaques that narrowed the lumens >75% in cross-sectional area (1, 2).

Multiple necropsy studies have shown that when any particular arterial region produces symptoms of organ ischemia (or discomfort in the case of abdominal aortic aneurysm), the atherosclerotic process in that region is diffuse and severe—i.e., there are no “skip areas” where a 5-mm-long arterial segment does not contain atherosclerotic plaque (3). Multiple necropsy studies of each 5-mm-long segment of the 4 major epicardial coronary arteries in a variety of coronary subsets (those with acute myocardial infarction, stable and unstable angina pectoris, healed myocardial infarction with and without chronic heart failure, and sudden coronary death) have demonstrated that about a third of the entire lengths of the 4 major coronary arteries is narrowed >75% in cross-sectional area by atherosclerotic plaque alone (3, 4).

There appears to be a common belief that atherosclerotic plaques consist mainly of lipid material. Several studies have examined the composition of atherosclerotic coronary plaques at necropsy in patients with fatal coronary heart disease (5–8). The studies traced out the various components of plaques from each 5-mm-long segment of each of the 4 major coronary arteries, and fibrous tissue was by far the dominant component of coronary plaques, comprising about 70%, while lipids comprised about 10%; calcium, about 10%; and miscellaneous, the other 10%. Fibrous tissue also was the dominant component of plaques in saphenous veins used for aortocoronary bypass grafts. That the predominant component of coronary plaques is fibrous tissue is probably advantageous for percutaneous coronary intervention (PCI) because that procedure works simply by cracking plaques and not by compressing them to the side.

Studying atherosclerosis at necropsy or after endarterectomy has convinced Roberts that the only real long-term therapy for the Western world’s number one disease is prevention. Although the Framingham investigators and others have convinced most physicians and the lay public that atherosclerosis is a multifactorial disease, Roberts is convinced that the disease has a...
single cause, namely cholesterol, and that the other so-called atherosclerotic risk factors are only contributory at most (9–13). As shown in Figure 1, most of the risk factors do not in themselves cause atherosclerosis.

There are in Roberts’ opinion 4 facts supporting the contention that atherosclerosis is a cholesterol problem: 1) Atherosclerosis is easily produced experimentally in herbivores (monkeys, rabbits) by giving them diets containing large quantities of cholesterol (egg yolks) or saturated fat (animal fat). Indeed, atherosclerosis is one of the easiest diseases to produce experimentally, but the recipient must be an herbivore. It is not possible to produce atherosclerosis in carnivores (tigers, lions, dogs, etc.). In contrast, it is not possible to produce atherosclerosis simply by raising a rabbit’s blood pressure or blowing cigarette smoke in its face for an entire lifetime. 2) Atherosclerotic plaques contain cholesterol. 3) Societies with high average cholesterol levels have higher event rates (heart attacks, etc.) than societies with much lower average cholesterol levels. 4) When serum cholesterol levels (especially the low-density lipoprotein cholesterol [LDL-C] level) are lowered (most readily, of course, by statin drugs), atherosclerotic events fall accordingly and the lower the level, the fewer the events (“less is more”). Although most humans consider themselves carnivores or at least omnivores, basically we humans have characteristics of herbivores (Table 1).

The Adult Treatment Panel of the National Cholesterol Education Program has provided guidelines for whom to treat with cholesterol-altering drugs. The latest (2004) guidelines are summarized in Table 2. The guidelines are aimed entirely at reducing the risk of atherosclerotic events. Lowering the LDL-C goal from <100 to <70 mg/dL is recommended by the committee only in patients who have already had an atherosclerotic event, who have diabetes mellitus, or who are at an extremely high risk of developing an atherosclerotic event (e.g., homozygous or heterogeneous familial hypercholesterolemia). Roberts’ guidelines, in contrast, are directed at preventing atherosclerotic plaques, and when they are prevented atherosclerotic risk is negated. The only requirement is an LDL-C <50 mg/dL.

Statins, at least in Roberts’ view, are the finest cardiovascular drug ever created (released in the USA in 1987) (14). Table 3 displays the equivalent doses of six statins, their average reductions in total cholesterol and LDL-C, and the additional LDL-C–lowering effect when ezetimibe is added to a statin (15).

---

**Table 1. The differences between carnivores and herbivores**

<table>
<thead>
<tr>
<th>Features</th>
<th>Carnivore</th>
<th>Herbivore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teeth</td>
<td>Sharp</td>
<td>Flat</td>
</tr>
<tr>
<td>Intestine</td>
<td>Short (3 × BL)</td>
<td>Long (12 × BL)</td>
</tr>
<tr>
<td>Fluids</td>
<td>Lap</td>
<td>Sip</td>
</tr>
<tr>
<td>Cooling</td>
<td>Pant</td>
<td>Sweat</td>
</tr>
<tr>
<td>Appendages</td>
<td>Claws</td>
<td>Hands or hoofs</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Self-made</td>
<td>Diet</td>
</tr>
</tbody>
</table>

BL indicates body length.

**Table 2. Drug treatment guidelines of the Adult Treatment Panel of the National Cholesterol Education Program (2004) to decrease risk**

<table>
<thead>
<tr>
<th>LDL (mg/dL)</th>
<th>Other RF</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;190</td>
<td>≤1</td>
<td>&lt;160</td>
</tr>
<tr>
<td>&gt;160</td>
<td>&gt;1</td>
<td>&lt;130</td>
</tr>
<tr>
<td>&gt;130</td>
<td>HA</td>
<td>&lt;100 (&lt;70)</td>
</tr>
</tbody>
</table>

HA indicates heart attack; LDL, low-density lipoprotein cholesterol; RF, risk factor.

**Table 3. Dosing of six statin drugs, their relative efficacy and effects on cholesterol, and the effect of adding ezetimibe**

<table>
<thead>
<tr>
<th>Equivalent dose (mg)</th>
<th>R (C)</th>
<th>A (L)</th>
<th>S (Z)</th>
<th>P (P)</th>
<th>L (M)</th>
<th>F (L)</th>
<th>↓ TC</th>
<th>↓ LDL</th>
<th>E (10 mg)</th>
<th>Total LDL ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>40</td>
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R indicates rosuvastatin (C, Crestor); A, atorvastatin (L, Lipitor); S, simvastatin (Z, Zocor); P, pravastatin (P, Pravachol); L, lovastatin (M, Mevacor); F, fluvastatin (L, Lescol); TC, total cholesterol; LDL, low-density lipoprotein cholesterol; E, ezetimibe.
ASSESSING THE BENEFIT OF THERAPY THAT RAISES HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

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All the major primary and secondary prevention statin studies have shown an average of 25% cardiovascular risk reduction at 5 years, which means that 75% of the cardiovascular events were not prevented during this time period. Statins act mainly on LDL-C, with much less effect on triglycerides or high-density lipoprotein cholesterol (HDL-C). Fibates act mainly on triglycerides, reducing it 30% to 35% with a slight increase in HDL-C and only a minor effect on LDL-C (16). In the FIELD study (17), fenofibrate did not significantly reduce coronary events in 9775 patients vs placebo. In the ACCORD trial (18), the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction (MI), or nonfatal stroke, compared with simvastatin alone in 5518 high-risk patients with diabetes mellitus. Niacin raises HDL-C by 30% to 35%, has a lesser effect on triglycerides than fibrates, and reduces LDL-C by 15% to 20%. Niacin also increases LDL particle size, from a small, dense pattern B to the larger nonatherogenic pattern A (19). In the Framingham study (20), LDL-C and HDL-C were independent risk factors of coronary heart disease (CHD). A patient with an LDL-C of 220 and HDL-C of 45 mg/dL had a similar risk to a patient with an LDL-C of 100 and HDL-C of 25 mg/dL. Statins had a maximal relative risk reduction in cardiovascular events of about 30% (21), niacin about 20% (22), and fibrates 23% (16). Although the National Cholesterol Education Program Adult Treatment Panel III guidelines (23) stated that low HDL-C is an independent risk factor for coronary artery disease (CAD) morbidity and mortality, the panel concluded that the risk reduction documented by controlled clinical trials is not sufficient to warrant setting a specific HDL-C goal.

Several surrogate marker studies (24–26) demonstrated slowing or even regression of arterial narrowing with niacin. The ARBITER 6-HALTS (26) trial was terminated early on the basis of a prespecified interim analysis showing superiority of niacin over ezetimibe for change in carotid thickness. Major adverse cardiac events occurred at a significantly lower incidence in the niacin (1.2%) vs the ezetimibe group (5.5%). In a metaanalysis of the 14 niacin studies including 2682 patients taking 1 to 3 g/day of niacin and 3934 controls, niacin decreased the rate of progression of atherosclerosis by 41% and decreased carotid intima thickness by 17 μm/year.

In the Coronary Drug Project (27), immediate-release niacin (3 g/day) reduced the incidence of CHD death/MI by 14%, nonfatal MI by 26%, and stroke/transient ischemic attacks by 21% after 5 years. There was also a 50% reduction in the need for coronary bypass surgery. In the VA-HIT study (28), gemfibrozil reduced CHD death/MI by 22% vs placebo after 5 years. These patients did not take statins, and the benefit was attributed to a decrease in triglycerides (∼31%) and an increase in HDL-C (+6%), as there was no significant change in LDL-C. It took 2 years in the VA-HIT trial for a considerable benefit to be evident with treatment, quite different from the time course seen with statins, where event reduction is seen as early as 2 weeks after institution of treatment.

Several single-center trials demonstrated the benefits of adding niacin to other cholesterol-lowering drugs. In the Familial Atherosclerosis Treatment Study (FATS) (29, 30), 126 men with known CHD were randomized to receive conventional therapy or lovastatin plus colestipol or niacin (4 g/day). All patients had a coronary angiogram at baseline. After 2.5 years, coronary narrowing in patients on conventional therapy progressed, while it regressed in the treatment group. Multivariate analysis showed that increasing HDL-C correlated independently with the regression of disease. The HDL Atherosclerosis Treatment Study (HATS) (31) was a 3-year trial of 160 patients with CHD whose HDL-C averaged 31 mg/dL and LDL-C, 125 mg/dL. Patients were administered either niacin (mean dose 2.4 g/day) plus simvastatin (mean dose 13 mg/day) or placebo for 3 years. In the group receiving niacin plus simvastatin, LDL-C levels decreased 42% and HDL-C increased 26%. The combination of niacin and simvastatin reduced CHD events by about 75%. There was a slight regression in coronary narrowing with simvastatin plus niacin but progression in all other groups. Both FATS and HATS were single-center studies with relatively small numbers of patients. Pooled data from 28 different lipid trials (32) showed that there was an aggregation of benefit from adding different cholesterol-altering medicines. Data from the 4S (33), CARE (34), WOSCOPS (35), and LIPID (36) trials demonstrated that a 1% decrease in LDL-C was associated with a 1% decrease in CHD events. A 1% increase in HDL-C was associated with a 3% decrease in events, as seen in HELSINKI (37), AFCAPS/TexCAPS (38), and VA-HIT.

The results from the Coronary Drug Project, VA-HIT, and HATS constituted the base for a large, multicenter trial assessing the outcomes for niacin. The AIM-HIGH (39) study was conducted mainly to investigate whether the residual risk associated with low levels of HDL-C in patients with established CHD (whose LDL-C therapy was optimized with statins ± ezetimibe) would be mitigated with extended-release niacin vs placebo. The patients were >45 years of age with CHD, cerebrovascular disease, or peripheral arterial disease and dyslipidemia (HDL-C <40 for men, <50 for women; triglycerides 150–400; LDL-C <180 mg/dL). A total of 3414 patients were randomized to receive extended-release niacin (1.5 to 2 g/day) or placebo. All patients received simvastatin (40 to 80 mg/day) plus ezetimibe (10 mg/day) (if needed) to maintain an LDL-C of 40 to 80 mg. (The placebo tablets had a small amount of niacin, 200 mg/2 g, to produce similar side effects as in the treatment group.) Patients on statins (94%) had a mean baseline LDL-C of 71 mg/dL. The trial was stopped after a mean follow-up period of 3 years due to a lack of efficacy. There was also an increased incidence of ischemic strokes in the niacin arm (n = 29) vs the placebo arm (n = 18). At study termination, HDL-C had increased from 35 to 42 mg/dL, LDL-C had decreased from 74 to 62 mg/dL, and triglycerides had decreased from 164 to 120 mg/dL. In both the Coronary Drug Project and VA-HIT, in the prestatin era, niacin and gemfibrozil increased HDL and lowered triglycerides.
and also decreased cardiovascular events, but baseline triglycerides and LDL-C were significantly higher than in AIM-HIGH. It appears that the addition of niacin did not work in this population, possibly because these patients had been well treated with statins and the HDL-C had increased to 38 mg/dL in the placebo arm, changes that might have minimized event rate differences between the treatment and placebo groups.

The HPS 2-THRIVE trial began in 2004 and is expected to be finished by 2013. It enrolled 25,000 patients with CAD or diabetes mellitus from the UK, Scandinavia, and China. Patients were randomized to simvastatin 40 mg or simvastatin plus extended-release niacin/laropiprant. The use of ezetimibe is allowed. There is no target LDL-C level or attempt to equalize LDL-C levels between groups.

COCAIN-ASSOCIATED MYOCARDIAL ISCHEMIA AND INFARCTION

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Five million Americans use cocaine daily, 1 million are addicted to it, and 5000 use it for the first time each day. Possible mechanisms of cocaine-induced myocardial ischemia include increased myocardial oxygen demand with severe CAD and decreased myocardial oxygen supply due to coronary arterial vasospasm (40) and/or coronary arterial thrombosis. α-Blockers abolish the coronary vasoconstrictor effect of cocaine, while β-blockers augment it (41). Cocaine-induced vasoconstriction is more pronounced in coronary arterial segments narrowed by atherosclerosis (42). The time course of cocaine-induced vasoconstriction parallels the blood concentration of cocaine following intranasal administration, after which a second “wave” of vasoconstriction parallels the increasing blood concentrations of cocaine’s major metabolites and occurs as the blood concentration of cocaine is decreasing (43). The deleterious effects of cocaine on myocardial oxygen supply and demand are exacerbated by concomitant cigarette smoking. This combination substantially increases the metabolic requirement of the heart for oxygen but simultaneously decreases the diameter of diseased coronary arterial segments (44). The combination of intranasal cocaine and intravenous ethanol causes an increase in the determinants of myocardial oxygen demand. The combination also causes a concomitant increase in epicardial coronary arterial diameter (45). Morphine can reverse cocaine-induced coronary arterial vasoconstriction (46). Sublingual nitroglycerin (47) 0.4 to 0.8 mg and intravenous verapamil (48) also reverse the coronary vasoconstrictive effect of cocaine, while intravenous labetalol has no effect (49). The mechanism of cocaine-induced vasospasm and its aggravating and relieving factors are summarized in Figure 2.

CORONARY ARTERY BYPASS GRAFTING—2012

L. David Hillis, MD

Coronary artery bypass grafting (CABG) is superior to medical therapy for eliminating angina pectoris (50). CABG, however, does not prevent MIs (51, 52). CABG is superior to medical therapy in improving survival only in patients with left main CAD, in those with 3-vessel CAD and left ventricular (LV) ejection fraction (EF) <50%, and in those with 2- or 3-vessel CAD with significant narrowing of the proximal left anterior descending coronary artery. In the VA COOPERATIVE study (53), the survival of patients with 1, 2, and 3-vessel CAD with a normal LVEF (medical therapy vs CABG) was 87% vs 82%, 82% vs 77%, and 68% vs 61% at 5, 7, and 11 years, respectively, while the survival of patients with 3-vessel CAD and LVEF <50% was (medical therapy [n = 97] vs CABG [n = 71]) 66% vs 83%, 52% vs 78%, and 38% vs 50% at 5, 7, and 11 years, respectively. In the STICH trial (54), a total of 1212 patients with an EF <35% and CAD amenable to CABG were randomly assigned to medical therapy alone (n = 602) or medical therapy plus CABG (n = 610). At 5 years, death from any cause was 41% in the medical therapy arm and 36% in the CABG group (insignificant), and the rate of hospitalization for heart failure was 54% vs 48%. Patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes. Compared with patients who have CABG, those who have PCI are more likely to require another revascularization procedure in the next 12 months (45), and rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (18% vs 12% for CABG), in large part because of an increased rate of repeat revascularization (13% vs 6%).

The determinants of peri-CABG mortality include age (peri-CABG mortality markedly increases above 70 years) (55), LV systolic function, comorbid conditions (chronic obstructive pulmonary disease, diabetes mellitus, azotemia, obesity), extra-cardiac vascular disease, left main CAD, previous thoracotomy (mortality of the first sternotomy 3% vs 7% for subsequent sternotomies), and gender (1.9% in men vs 4.5% in women in CASS [n = 6630] and 2.6% in men vs 5.3% in women in the Texas Heart Institute [n = 22,284] registry).

There was no significant difference in 30-day death, MI, stroke, or renal failure requiring dialysis between patients.
undergoing CABG off-pump or on-pump in a large trial involving 79 centers in 19 countries randomizing 4752 patients. Off-pump CABG reduced rates of transfusion, reoperation for perioperative bleeding, respiratory complications, and acute kidney injury but also resulted in an increased risk of early revascularization (56).

CARDIOPULMONARY RESUSCITATION AND PUBLIC-ACCESS DEFIBRILLATION

Richard L. Page, MD, George R. and Elaine Love Professor, Chair, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

The 2010 American Heart Association guidelines (57) place a strong emphasis on delivering high-quality chest compressions. Rescuers should push hard to a depth of at least 2 inches (5 cm) at a rate of at least 100 compressions per minute, allow full chest recoil, and minimize interruptions in chest compressions. Rescuers also should provide ventilation using a compression:ventilation ratio of 30:2. Longer periods of resuscitation are associated with better outcomes. Goldberger et al (58) studied 64,339 subjects with cardiac arrest in US hospitals. The median duration of resuscitation was 12 minutes in survivors vs 20 minutes in nonsurvivors. The survival to discharge was related to hospital duration of resuscitation.

The PAD trial (59) evaluated automated external defibrillator (AED) use vs conventional cardiopulmonary resuscitation (CPR) in 1000 US sites. There were more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of AEDs (30 survivors among 128 arrests) than there were in the units assigned to have volunteers trained only in CPR. Weisfeldt et al (60) reported 13,769 out-of-hospital arrests where 32% received CPR but no AED before paramedics arrived and 2.1% had an AED placed before paramedics arrived. The survival to hospital discharge was 9% with CPR only, 24% with AED application, and 38% with AED shock delivery. Page et al reported early results of the first use of the AEDs by a US airline between 1997 and 1999. Of 200 events (mean age 58 years), ventricular fibrillation (VF) was present in 16 patients. All VF episodes were recognized (sensitivity 100%) and shock delivered in 15 of 16. First shock success was 100%. Six of 15 patients receiving shocks for VF survived to hospital discharge (40%). Valenzuela et al (61) published a study where casino officers were trained in the use of AEDs. The first 148 patients were reported: 105 (71%) had VF and 59% survived to hospital discharge. There was a significant difference in survival between defibrillation used before and after 3 minutes of the arrest (26/35 [74%] vs 27/55 [49%]).

MANAGEMENT OF VALVULAR HEART DISEASE

Robert O. Bonow, MD, Goldberg Distinguished Professor of Cardiology, Director, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Only 0.3% of the guidelines for valvular heart disease are at evidence level A, i.e., based on high-quality randomized clinical trial or metaanalysis, while 70% are at evidence level C, i.e., based on expert consensus (62).

Mitral regurgitation (MR). The current guidelines for treatment of severe chronic primary (degenerative) MR recommend mitral valve surgery in symptomatic patients (class I), patients with LVEF <0.6 and LV end systolic dimension 50 to 55 mm (class I), asymptomatic patients with atrial fibrillation (class Ia), and asymptomatic patients with pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise (class Ia). Management of asymptomatic severe MR with preserved EF remains controversial.

The mortality of severe asymptomatic MR varies markedly among different studies. Maurice et al (63) studied 456 patients with MR (EF 70 ± 8%): the 5-year mortality rate with severe MR was 42%, while that of moderate MR was 33%. In contrast, Rosenhek et al reported 0% 5-year mortality in 132 patients with severe asymptomatic MR (64); Grigioni and coworkers (65) reported 14% 5-year mortality in 394 patients with severe MR who were followed for an average of 3.9 years; and Kang et al (66) reported 5% 7-year mortality among 286 patients with severe MR and preserved EF who were treated medically.

In a retrospective review of outcomes of 13,614 patients having elective surgery for MR between 2000 and 2003 in 575 North American centers (67), the hospital procedural volume was associated with higher frequency of valve repair, higher frequency of prosthetic valve usage in older patients, and lower adjusted operative mortality. There was variation among cardiologists as to the degree of knowledge and adherence to the guidelines about the timing of referral to surgery. In a survey in 2007, among 319 responders, LVEF was rated as extremely important in referral decisions by 71% of those who completed the surveys and moderately important by 26%. In asymptomatic patients, EF of 50% to 60% was correctly identified as a trigger for surgery by 57% of cardiologists, while only 16% of cardiologists correctly referred New York Heart Association (NYHA) class II patients with normal LV function (68).

Ischemic MR is managed differently from primary MR. Detection and quantification of ischemic MR provide major information for risk stratification and clinical decision making in the chronic post-MI phase (69). The mitral annulus clip is an evolving technique for treatment of functional MR. Treatment with the clip device in 51 severely symptomatic cardiac resynchronization therapy (CRT) nonresponders with functional MR was feasible, safe, and demonstrated improved functional class, increased LVEF, and reduced ventricular volumes in about 70% of these study patients (70).

Aortic stenosis (AS). The current guidelines do not recommend aortic valve replacement (AVR) in patients with severe asymptomatic AS. The producibility of symptoms or hypotension with exercise is currently a class IB indication, according to the American College of Cardiology and American Heart Association. In 123 adults with asymptomatic AS, event-free survival—with endpoints defined as death (n = 8) or aortic valve surgery (n = 48)—was 93%, 62%, and 26% at 1, 3, and 5 years, respectively (71). The likelihood of remaining alive without valve replacement at 2 years was only 21% for a jet velocity >4.0 m/s.
at entry, compared with 66% for a velocity of 3.0 to 4.0 m/s and 84% for a jet velocity <3.0 m/s. In another series of 128 patients with asymptomatic severe AS (72), event-free survival—with the endpoint defined as death (8 patients) or AVR necessitated by the development of symptoms (59 patients)—was 67%, 56%, and 33% at 1, 2, and 4 years, respectively. Rosenhek et al also reported a series of 116 asymptomatic patients (73) with very severe AS, defined by a peak aortic jet velocity ≥5.0 m/s. Event-free survival was 64%, 36%, 25%, 12%, and 3% at 1, 2, 3, 4, and 6 years, respectively. Patients with a peak aortic jet velocity ≥5.5 m/s had an event-free survival of 44%, 25%, 11%, and 4% at 1, 2, 3, and 4 years, respectively. Early elective valve replacement surgery should therefore be considered in these patients. The current guidelines recommend AVR in patients with a high likelihood for rapid progression (calcification) and/or very severe AS (maximum velocity >5 m/s, mean gradient >60 mm Hg, AV area <0.6 cm²) (class IA).

Exercise-stress echocardiography is very useful for risk stratification of true asymptomatic patients with AS (74). N-terminal beta natriuretic peptide (75) independently predicts symptomatic-free survival, and preoperative N-terminal beta natriuretic peptide independently predicts postoperative outcome with regard to survival, symptomatic status, and LV function. The STS score (76) is more suitable than the EuroSCORE (77) for estimating the perioperative mortality associated with AVR.

Transcatheter aortic valve implantation (TAVI) is an emerging technique with enormous potential (78). The PARTNER trial (79) investigators concluded that TAVI is superior to medical therapy in patients who are not fit for AVR and that TAVI is equivalent to surgical AVR in high-risk patients. In patients with severe AS and depressed LV systolic function, TAVI is associated with better LVEF recovery compared with surgical AVR (80). In 200 patients undergoing surgical AVR and 83 patients undergoing TAVI for severe AS (AV area ≤1 cm²) with LVEF ≤50%, patients who underwent TAVI had better recovery of LVEF compared with those who underwent surgical AVR (ALVEF, 14% vs 7%). Stroke and paravalvular regurgitation remain concerns with TAVI. The average hospital mortality for TAVI was 9% (13.0% for low-volume centers vs 6% for high-volume centers). The broad application of TAVI presents challenges for patient selection and the need for dedicated expert heart valve centers.

The goal in AS patients is to operate late enough in the natural history to justify the risk of intervention and early enough to prevent irreversible ventricular dysfunction, pulmonary hypertension, and/or chronic arrhythmias and sudden death.

OPERATIVE TREATMENT OF CARDIOVASCULAR DISEASE

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CABG remains the standard of care for patients with 3-vessel or left main CAD, since the use of CABG, as compared with PCI, results in lower rates of the combined endpoint of major adverse cardiac events or cerebrovascular events at 1 year (81). For patients with less severe CAD, symptom severity and non-invasive test results are used to stratify patients into one of two groups: those who will benefit from immediate revascularization and those in whom an initial trial of aggressive medical therapy alone may be safely attempted. In patients without the highest-risk CAD who require revascularization because of unacceptable symptoms or because of noninvasive test results indicating a high risk of failure of medical therapy, PCI with drug-eluting stents and CABG appear to result in similar rates of death and MI. Therefore, the choice depends largely upon how effectively the lesions can be treated with PCI and upon the patient’s feelings about the temporary disability and the slightly increased stroke risk associated with CABG vs the increased risk of repeat revascularization with PCI (82). Stroke predictors from prospective data collected on 4941 patients undergoing cardiac surgery included history of stroke and hypertension, older age, systolic hypertension, bronchodilator and diuretic use, high serum creatinine, surgical priority, great vessel repair, use of inotropic agents after cardiopulmonary bypass, and total CABG time (83).

Carotid endarterectomy (CEA). CEA currently remains the first choice of revascularization therapy for an asymptomatic carotid lesion in most centers (84). The Society for Vascular Surgery appointed a committee of experts to formulate evidence-based clinical guidelines for the management of carotid stenosis. In formulating clinical practice recommendations, the committee used systematic reviews to summarize the best available evidence and the GRADE scheme to grade the strength of recommendations (GRADE 1 for strong recommendations; GRADE 2 for weak recommendations) and rate the quality of evidence (high, moderate, low, and very low quality) (85). The following therapies had both GRADE 1 recommendation and high quality of evidence:

- Medical therapy for asymptomatic patients with <50% stenosis
- Medical therapy for asymptomatic patients with <60% stenosis
- CEA for symptomatic patients with ≥50% stenosis
- CEA for asymptomatic patients with ≥60% stenosis

Concomitant carotid and coronary artery surgery is safe and effective, particularly in preventing ipsilateral stroke, and neutralizes the impact of unilateral carotid stenosis on early and late stroke (86). In the US, patients who undergo carotid artery stenting and CABG have significantly decreased in-hospital stroke rates compared with patients undergoing CEA and CABG, but the in-hospital mortality is similar. Carotid artery stenting may provide a safer carotid revascularization option for patients who require CABG (87).

Surgical treatment of peripheral artery disease. Invasive therapy in peripheral artery disease is indicated for critical limb ischemia (ankle brachial index <0.4), not for claudication, unless it is disabling. The long-term results of the Bypass vs Angioplasty in Severe Ischemia of the Leg (BASIL) trial favor surgery rather than angioplasty if there is a good vein and the patient is fit (88).
Thoracic aortic aneurysms (TAA). Each year, 30,000 to 60,000 deaths occur due to TAA. Thus, in the USA, they are the 18th most common cause of death and the 15th most common cause of death in individuals >65 years of age. TAAs are increasing in incidence. TAA is a virulent condition but an indolent process, growing slowly at -0.1 cm per year. The use of an imaging technique to estimate true aortic size is confounded by its obliquity and asymmetry; thus, multiple imaging techniques may be required (89). Surgical intervention is indicated before TAAs reach 5.5 cm in diameter. A diameter of 5.0 cm may be the cut-off for patients with Marfan syndrome, a bicuspid aorta, or a family history of aortic dissection.

Aortic dissection occurs in a circadian and diurnal pattern, with predominance in winter months and early morning. Aortic dissections also occur around the time of extreme physical exertion or emotional distress. The frequency of aortic dissection or through-and-through rupture increases sharply when the ascending aortic diameter reaches 6.0 cm (34% lifetime risk of rupture or dissection) and 7.0 cm in descending thoracic aorta.

The Marfan syndrome. Marfan syndrome occurs due to a mutation of the fibrillin-1 gene. Patients with Marfan syndrome have a 50% risk of developing aortic dissection in their lifetime. About 5% of all TAAs are due to Marfan syndrome. TAAs in Marfan syndrome patients grow rapidly (>0.5 cm per year). A family history of aortic dissection may prompt earlier operative intervention at a diameter <5.0 cm. Pregnant patients with Marfan syndrome are at increased risk for aortic dissection if aortic diameter exceeds 4.0 cm.

Loeys-Deitz syndrome. Loeys-Deitz syndrome occurs due to mutations in the TGFBR1 and TGFBR2 genes. Patients have skeletal features of Marfan syndrome but with distinct cranial features, including craniosynostosis. Other features include hypertelorism, translucent skin and veins, arterial tortuosity, and aneurysms. Aortic repair should be done at aortic diameters <5.0 cm in patients with Loeys-Deitz syndrome.

Osteoarthritic syndrome. Osteoarthritic syndrome is an autosomal dominant disorder (SMAD3 mutations) responsible for 2% of familial TAA dissections. The main features of the disease include early onset of osteoarthritis (the usual reason for patients seeking medical attention), mild craniofacial abnormalities, and tortuositities throughout the arterial tree—mostly the intracranial, iliac, abdominal, and thoracic aorta—leading to aneurysms. Patients have a substantial mortality and a high risk of aortic rupture and dissection with mildly dilated aortas.

Penetrating atherosclerotic ulcers. Atherosclerotic lesions may ulcerate (penetrating the internal elastic lamina) and produce hematomas within the media (90% in the descending thoracic aorta). They appear as a mushroom-like outpouching of the aortic lumen with overhanging edges.

Pseudoaneurysm of the thoracic aorta. Pseudoaneurysms occur in the descending thoracic aorta due to deceleration or torsional trauma. They can also occur after aortic root or aortic valve surgery, catheter-based interventions, or penetrating trauma.

Takayasu’s aortitis. Takayasu’s aortitis (90), a chronic inflammatory vasculitis involving the ascending aorta and carotid, renal, and subclavian arteries, is rare (1–2 cases/million) and of unknown etiology. It affects women more than men (with a ratio of 9:1) and usually begins in the second or third decade of life. Takayasu’s aortitis produces intimal fibroproliferation that results in segmental stenosis, occlusion, dilatation, and aneurysm formation. It is the only aortitis that causes stenosis and occlusion. Takayasu’s aortitis is more prevalent in women of Asian descent, and 90% of the cases occur in patients <30 years of age. In its inflammatory stage, patients present with low-grade fever, tachycardia, pain adjacent to the inflamed arteries (carotodynia), and easy fatigability. Carotid and cervical bruises are often present. The systemic stage can be followed in 5 to 20 years by an occlusive stage. Neurologic symptoms are present in 80% of patients.

SEVERE BUT ASYMPTOMATIC AORTIC STENOSIS

Randolph P. Martin, MD

Severe AS is undertreated. More than 50% of patients with echocardiographic findings of severe AS are not referred for further evaluation for AVR. In the Euro Heart Survey (91), 36% of patients already had significant symptoms at the time of evaluation for AVR: 47% were NYHA class III/IV and 8% were NYHA class IV and had LV dysfunction at the time of surgery. Studies of severe asymptomatic AS suggest that a third of the patients will become symptomatic within 2 years. Within 4 to 5 years, two thirds have either had an AVR or died. The risk for sudden death is about 1% per year. Kang et al (92) showed a risk of sudden cardiac death of 1.7% per year in those with aortic velocity >5.0 m/sec.

The assessment of AS severity should be based on valve morphology: calcium, peak jet velocity, mean gradient, aortic valve area, LV EF, LV wall strain, LV wall fibrosis, and beta natriuretic peptide. These parameters should be integrated with presenting symptoms and response to exercise stress testing. The predictors of poor outcome in asymptomatic severe AS are a resting peak transvalvular velocity of 5.0 to 5.5 m/sec (73, 93), densely calcified aortic valve, valve area <0.75 cm² (94), mean gradient >50 mm Hg, abnormal LVEF, beta natriuretic peptide, and abnormal exercise test (defined as failure of systolic blood pressure to rise or a fall in systolic blood pressure, symptoms, or ST-segment depression with exercise). The echocardiographic predictors of poor outcome in AS also include the degree of valve calcium (95). The degree of valve calcium is not influenced by hemodynamic conditions, which is useful in low flow states. A computed tomography calcium score >1650 AU has 80% sensitivity and specificity for severe AS. Exercise stress testing can uncover symptoms in >40% of “asymptomatic severe AS” patients. Only 20% of patients who have positive stress tests are alive, symptom-free, without AVR at 24 months vs 85% with a negative test.

SYSTEMIC HYPERTENSION

William H. Frishman, MD, the Barbara and William Rosen- that Professor and Chairman, Department of Medicine, New York Medical College; Director of Medicine, Westchester Medical Center, Valhalla, New York

In older adults, hypertension is characterized by an elevated systolic blood pressure with normal or low diastolic blood
pressure, due to age-associated stiffening of the large arteries. Hypertension prevalence increases markedly with age; ~60% of the population has hypertension by age 60 and ~65% of men and ~75% of women have hypertension by 70 years (96). In the Framingham Study (97), hypertension eventually developed in >90% of subjects with normal blood pressure at age 55 years. Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg (98). Numerous randomized trials have shown substantial reductions in cardiovascular events in cohorts of patients 60 to 79 years old with antihypertensive drug therapy, though the effect on all-cause mortality has been modest. In HYPERTENSION, antihypertensive therapy reduced all-cause mortality in people ≥80 years old by 21% at 1.8-year follow-up. Those randomized to indapamide vs placebo had a 30% nonsignificant decrease in fatal/nonfatal stroke, 39% significant decrease in fatal stroke, 21% significant decrease in all-cause mortality, 23% insignificant decrease in cardiovascular death, and 64% significant decrease in heart failure.

Although the optimal blood pressure treatment goal in the elderly has not been determined, a therapeutic target <140/90 mm Hg in persons aged 65 to 79 years and a systolic blood pressure of 140 to 145 mm Hg, if tolerated, in persons aged ≥80 years is reasonable. The further lowering of diastolic blood pressure below 60 mm Hg may lead to coronary insufficiency and myocardial ischemic manifestations.

ALTERNATIVE MEDICINE FOR THE HEART
William H. Frishman, MD

About 50% of patients seek an alternative sort of medicine, which is defined as any practice that is put forward as having the healing effects of medicine, but is not based on evidence gathered by the scientific method. The placebo effects on blood pressure, arrhythmia (e.g., decrease in premature ventricular complexes), heart failure symptoms (increase in EF of 5% to 20%–30% of patients) and angina pectoris (about 50% of patients) have been noticed in every cardiovascular trial. Patients also develop common adverse effects to placebo drugs (99). No megavitamin, mineral, or nutraceutical has shown an evidence-based effect on cardiovascular disease. Most trials evaluating homeopathy have shown no benefit on cardiovascular diseases (100). Chelation therapy has theoretical benefits but had no effect on CAD in clinical trials (101). Neither masked prayer nor music, imagery, or touch therapy significantly improved clinical outcomes after elective catheterization or PCI (102). There are some conditions in which herbal medicines are used as cardiovascular treatments. Several adverse cardiovascular reactions have been observed with herbal medicines used for other indications. Also, several herbs have potential and documented interactions with warfarin (103).

HYPERTROPHIC CARDIOMYOPATHY AND PREVENTING SUDDEN DEATH IN THE YOUNG
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Age, magnitude of LV hypertrophy, EF, presence of atrial fibrillation, LV obstruction, apical aneurysm, and other cardiovascular risk factors all contribute to the outcome of patients with hypertrophic cardiomyopathy (HC). Morbidity in patients with HC includes sudden death, progressive heart failure, or the development of atrial fibrillation and stroke. The incidence of sudden death is proportional to the LV wall thickness; its incidence is only 0.2%/year in patients diagnosed after the age of 60 years. In a multicenter study of 670 low-risk HC patients, the incidence of sudden death was 0.6%/year. The Bethesda Conference recommended that athletes with an unequivocal diagnosis of HC should not participate in most competitive sports, with the possible exception of those of low intensity. This recommendation includes those athletes with or without symptoms and with or without LV outflow obstruction.

Drugs provide only a modest protection from sudden death in HC. A report of 506 patients showed that the implantable cardioverter defibrillator (ICD) intervened appropriately to abort ventricular tachycardia/fibrillation in 20% of patients over an average follow-up period of only 3.7 years, at a rate of about 4%/year in those patients implanted prophylactically, and often with considerable delays of up to 10 years (104). Appropriate device discharges for ventricular tachycardia/ventricular fibrillation occur with similar frequency in patients with 1, 2, or ≥3 noninvasive risk markers. In a study of 1101 patients with HC, the risk of progression to NYHA class III or IV or death specifically from heart failure or stroke was greater among patients with obstruction (relative risk: 4.4) (105). About 70% of HC patients have LV outflow obstruction either at rest (37%) or with provocation (33%).

Ommen and colleagues (106) evaluated 1337 consecutive HC patients: 289 patients had surgical myectomy; 228 had LV outflow obstruction without operation; and 820 had nonobstructive HC. Mean follow-up duration was 6 ± 6 years. Their 1-, 5-, and 10-year overall survival after myectomy was 98%, 96%, and 83%, respectively, which did not differ from that of patients with nonobstructive HC or from the general US population matched for age and gender. Compared with nonoperated obstructive HC patients, myectomy patients experienced superior survival free from all-cause mortality (98%, 96%, and 83% vs 90%, 79%, and 61%, respectively), HC-related mortality, and sudden cardiac death.

Different cardiology societies in the US and Europe recommend surgical myectomy as the gold standard in HC patients rather than alcohol septal ablation. Several issues remain with alcohol septal ablation: whether the outflow gradient/symptom relief is long-lasting; the relatively high rate of repeat procedures (25%); failure to obliterate the high gradients; and the fact that myectomy after failed ablations is difficult. The infarct/scar produced by ablation also may predispose patients to sudden death.

HEART FAILURE GUIDELINES
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April 2013  Facts and principles learned at the 39th Annual Williamsburg Conference on Heart Disease
There is a substantial variation among cardiologists in conformity with quality treatment measures for heart failure patients (107). Fonarow et al (108) reported 15,177 patients with reduced LVEF (≤35%) and chronic heart failure or post-MI. The mortality rate at 24 months was 22%. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, β-blocker use, anticoagulant therapy for atrial fibrillation, CRT, ICDs, and heart failure education for eligible patients were each independently associated with improved 24-month survival, whereas aldosterone antagonist use was not. Each 10% improvement in guideline-recommended composite care was associated with a 13% lower odds of 24-month mortality. The adjusted odds for mortality risk for patients with conformity to each measure was 38% lower than for those whose care did not conform for one or more measures.

The 2013 heart failure guidelines are expected to include changes in the areas of CRT, LV assist device, the role of reduced dietary sodium intake, and evidence-proven methods to reduce readmissions.

Cardiac resynchronization therapy. The REVERSE (109) trial was designed to determine if CRT ± ICD modified disease progression over 12 months in patients with asymptomatic and mildly symptomatic heart failure and ventricular dyssynchrony. Patients were in NYHA class II or I (previously symptomatic), normal sinus rhythm, QRS ≥ 120 ms, LVEF ≤ 40%, LV end diastolic diameter ≥ 55 mm, without bradycardia, with or without ICD indication, on optimal medical therapy. All patients received CRT and then were randomized to have the device either on or off. Beginning at 1 year in the US and 2 years in Europe, all patients with CRT ON underwent yearly follow-up over 5 years. The heart failure clinical composite response endpoint indicated 16% worsening with CRT-OFF compared with 21% worsening with CRT-ON. Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (−18.4 mL/m² vs −1.3 mL/m²) and other measures of LV remodeling. Time to first heart failure hospitalization was significantly delayed in CRT-ON (hazard ratio: 0.47). The investigators concluded that CRT produced sustained reverse remodeling accompanied by low mortality and need for heart failure hospitalization. The benefits of CRT persisted, indicating that CRT attenuates disease progression in mildly symptomatic heart failure patients with wide QRS over at least 5 years. REVERSE, however, was underpowered to show mortality benefit and there was no long-term comparator. The RAFT (110) and MADI CRT (111) trials also showed the benefit of CRT in mild to moderate heart failure with short follow-up periods.

Left ventricular assist device. Several clinical studies (112–115) have shown improved survival with LV assist devices compared to medical therapy for advanced heart failure. The LV assist devices have not been shown to be cost effective.

Salt restriction in systolic heart failure. Taylor et al (116) performed a Cochrane database review and identified 7 randomized controlled trials (3 in normotensives, 2 in hypertensives, 1 in a mixed population of normo- and hypertensives, and 1 in heart failure) with follow-up of at least 6 months comparing restricted dietary salt intake or advice to reduce salt intake to control/no intervention in adults, and reported mortality or cardiovascular disease morbidity data. All-cause mortality and cardiovascular mortality for both normotensives and hypertensives were not reduced compared with the control group. In heart failure patients, salt restriction significantly increased all-cause death. Dinicolantonio and colleagues (117) analyzed 6 randomized controlled trials comparing low-sodium diets (1.8 g/day) with a higher-sodium diet (2.8 g/d) in 2747 patients with systolic heart failure. The low-sodium diet significantly increased all-cause mortality, sudden death, death due to heart failure, and heart failure readmissions.

Heart failure readmission rates. Hernandez et al studied a population that included 30,136 patients from 225 hospitals (118). Patients who were discharged from hospitals with higher early follow-up rates had a lower risk of 30-day readmission. The proper planning for transition of care and early outpatient follow-up was the only evidence-proven method of decreasing readmission rates for heart failure patients.

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Our experience as a Health Volunteers Overseas–sponsored team in Huế, Vietnam

James I. Ewing, MD, Claude A. Denham, MD, Cynthia R. Osborne, MD, Nathan B. Green, DO, Josephine Divers, RN, and John E. Pippen Jr., MD

A group from Texas Oncology and Baylor Charles A. Sammons Cancer Center traveled to Huế, Vietnam, as part of Health Volunteers Overseas. From February 21 to March 6, 2012, five Baylor Sammons medical oncologists and an oncology nurse worked with a medical oncologist and a surgeon at the Huế College of Medicine and Pharmacy, suggesting approaches based on available resources. The two groups worked together to find optimal solutions for the patients. What stood out the most for the Baylor Sammons group was the Huế team’s remarkable work ethic, empathy for patients, and treatment resourcefulness. The Baylor Sammons group also identified several unmet needs that could potentially be addressed by future volunteers in Huế, including creation of an outpatient hospice program, establishment of breast cancer screening, modernization of the pathology department, instruction in and better utilization of pain management, better use of clinic space, and the teaching of oncology and English to medical students. There was a mutual exchange of knowledge between the two medical teams. The Baylor Sammons group not only taught but also learned how to take good care of patients with limited resources.

A group of health care professionals from Baylor Charles A. Sammons Cancer Center at Dallas traveled to Vietnam from February 21 to March 6, 2012, to work alongside local caregivers and introduce new concepts, teach new techniques, and identify needs that can be addressed on follow-up trips. The team from Baylor Dallas consisted of two experts in breast cancer (Drs. John Pippen and Cynthia Osborne), two general medical oncologists (Drs. Claude Denham and Nate Green), a former medical oncology fellow who now practices in Lincoln, Nebraska, a second-year oncology fellow (Dr. James Ewing), and an oncology nurse (Josie Divers, RN) (Figure 1). After a formal application was made to the Accreditation Council for Graduate Medical Education, Dr. Ewing received fellowship credit for the time spent in Vietnam.

Planning for the trip began when physicians of the Baylor Sammons Cancer Center and Texas Oncology were contacted by Health Volunteers Overseas (HVO), a not-for-profit organization dedicated to improving the availability and quality of health care in developing countries through the training and education of local health care providers. HVO works with numerous professional medical societies to develop training programs for a wide range of specialties. In its quarter century of existence, HVO has sent over 4000 volunteers to places around the world and has completed close to 8000 assignments.

The International Cancer Corps (ICC) of the American Society of Clinical Oncology (ASCO) began partnering with HVO in 2010, with the goal of having highly qualified health care professionals provide relevant, realistic training that focuses on oncologic diseases and health conditions relevant to the geographic area, so this knowledge can be disseminated to other health care providers in the area. The first ICC site chosen was Tegucigalpa, Honduras; the second, Addis Ababa, Ethiopia; and the third, Huế, Vietnam.

Huế is a city in central Vietnam that serves as the capital city of the Thua Thien-Huế province. It was once the ancient imperial capital of the Nguyễn Lords, who were rulers of what is now Southern and Central Vietnam. In the 1800s, still under the rule of the Nguyễn Lords, it became the capital of all of Vietnam. Due to its location near the border of North and South Vietnam,
this South Vietnamese city was a site of intense fighting in the Vietnam War, especially during the Tết Offensive of 1968. Now a peaceful large city bisected by the Sông Hương (Perfume) River (Figure 2), Huế is home to approximately 950,000 residents and the Huế College of Medicine and Pharmacy (Figure 3). The facility was founded in 1957 and has trained over 12,000 graduates in medicine, pharmacy, dentistry, and allied health professions. It has an annual enrollment of over 1000 students, with almost 4000 undergraduates studying various health-related fields on campus at any given time. The college serves the central area of Vietnam, whose population is approximately 20 million people.

Since Vietnam is a developing country, a large percentage of the patients served by the college have limited financial means, with the average monthly wage reported to be US $185 last year (1). Many of the patients travel 30 miles or more by bicycle or motorcycle to get to the clinic for an appointment with a doctor. Both the medical school and hospital are run by the government.

THE CLINIC

Working within the college’s oncology clinic were the Vietnamese hosts, Dr. Nguyen Van Cau, a medical oncologist, and Dr. Phung Phuong, a surgeon. Dr. Van Cau had one oncology fellow who helped with patient care. At least 10 nurses and other assistants also staffed the clinic. The clinic was an air-conditioned building built in the 1980s. The first floor housed the Gamma Knife center, and the upper floors housed the clinics and inpatient hospital rooms. The equipment was not new, but it was functional. Dr. Phuong, a surgeon by training, had dual roles, as he planned, mapped, and operated the Gamma Knife, in addition to operating and serving as a clinical professor at the medical school. Dr. Van Cau’s office (where most of the patients were seen) was located on the second floor, and this is where we spent most of our time. In addition to Dr. Van Cau’s office, there was a room for the nursing staff to meet and do charting, a room to prepare the chemotherapy, and another room storing medications. In the chemotherapy preparation room, there was a ventilation hood with a small hole cut in the back wall. A small fan took air from the hood and sent it outside. Most basic chemotherapy drugs and antiemetics were available.

The pathology department was on site as well. The department was small and simple, with processing and microscope work done in the same room. Several basic immunohistochemical stains were available for breast cancer, although Ki-67, an immunostain used as a measure of the proliferation index in breast tumor specimens, was not routinely used. The oncologists did not generally review the pathology themselves, but relied on written or verbal reports by the pathologists. The pathology reports did not always clearly establish orientation and distance of the tumor from surgical margins. This was one issue we addressed during our stay in Huế.

We were able to observe a number of patients undergo treatment during our visit, including a patient with a hepatoma who was being mapped prior to radiation therapy. Additionally, a patient with brain cancer was treated while we were there. The machine was old and was shut down one day by a water leak; however, the oncology team in the clinic did remarkably well with the tools they had available.

The gap in wealth in Vietnam is extreme. Those with connections to the communist leaders live quite well, with the rest of the population living in severe poverty. Most drugs and health care are subsidized by the Vietnamese government; however, there is an exception with trastuzumab for HER2-positive breast cancer. This drug is completely unsubsidized, but we did see one patient elect to add it to her adjuvant treatment, at a cost of over US $8000 per month. Obviously, not many in Vietnam can afford this treatment. Rituximab is partially subsidized by the government and is for patients who can afford the large copayments. Thus, during our trip we did see one patient with non-Hodgkin’s lymphoma treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), but most patients were treated with CHOP or CHOP-E (etoposide), regimens inferior to R-CHOP, for diffuse large B-cell lymphoma. Dr. Van Cau was able to order almost any chemotherapy drug on the World Health Organization (WHO) list.

The patients were treated in four rooms, each of which had five beds. As we went from room to room, the patients were quiet, well mannered, and did not ask a lot of questions. Both male and female patients were in the same rooms with no concern for privacy. If there were more patients than beds, the patients shared a bed, with one at each end (Figure 4). Each room had five to 10

Figure 2. Scenes from Huế, Vietnam: (a) flower vendors and (b) motorbikes.

Figure 3. Our first view of the Huế College of Medicine and Pharmacy.
tests were available. The subsidized cost to the patient was about outpatients. The quality of the images was quite good. Most lab ultrasound were locally available and performed quickly for the and radiology films in hand. Computed tomography images and their own records, and many would come in with their scans back to the patients. Patients seemed to be in charge of holding flurries of stamping a stack of documents, which were then passed among the physicians, who then made a declaration of when the discussion with the physician; rather, most discussions were brief visit, lasting less than 5 minutes. There was generally little to patients, it seemed that they only saw the doctor for a very be terminated. The patient already had four children, and her keep the baby, but her husband was adamant that the pregnancy presented with a left subareolar breast mass and a palpable axillary node. Dr. Van Cau, as well as the rest of us, encouraged her to involved a 34-year-old woman, 11 weeks pregnant, who pre- interesting and challenging mix of cases. One breast cancer case involved a 34-year-old woman, 11 weeks pregnant, who presented with a left subareolar breast mass and a palpable axillary node. Dr. Van Cau, as well as the rest of us, encouraged her to keep the baby, but her husband was adamant that the pregnancy be terminated. The patient already had four children, and her husband said he could not take care of another child. We also saw a 59-year-old Catholic nun who recently had a mastectomy for a T2N1M0 estrogen receptor–positive, HER2-negative breast cancer. After deciding chemotherapy was needed, she was treated with a combination of epirubicin and paclitaxel. This is the adjuvant chemotherapy regimen of choice for all breast cancer patients deemed to be in need of chemotherapy. The decision of whether or not to use adjuvant chemotherapy was hindered somewhat by the lack of availability of Ki-67 staining. Tests such as Oncotype DX were not used, largely due to cost.

Other types of cancer reflected what would be expected in a busy oncology clinic, with a tendency toward tobacco-related and gastric malignancies. Breast cancer and other malignancies seemed to present at a more advanced stage. This is likely related, at least in part, to the lack of screening or effective primary or secondary prevention programs. We were also surprised by the relative youth of the majority of the patients. Today, according to a 2010 WHO report, Vietnam is among the countries with the highest smoking rates in the world, with a prevalence of more than 45% in men aged 18 years or older (2). Several of the physicians we worked with were smokers themselves. Smoking among health care providers was found to have a prevalence >40%. Further efforts towards primary prevention are definitely needed. The high prevalence of smoking and cervical cancer relay the need for better primary prevention in Vietnam.

Several patients we saw showed the need for a linear accelerator, which has been used for over 50 years for external beam radiation treatments for cancer. There were several local recurrences of cancer that likely could have been prevented if standard radiation treatment was given either concurrently with or after chemotherapy. One such patient was a young woman with a painful vaginal recurrence of a rectal cancer. The cancer involved the posterior vaginal wall, and the tumor was exuding from the vagina and causing significant pain and bleeding. As stated earlier, the only radiation treatment available in the Hué Oncology Clinic is in the form of Gamma Knife radiosurgery. Access to other types of radiation treatments would have allowed treatment of a much wider range of cancers.

PALLIATIVE CARE

The lack of palliative care and hospice represents a great need for the people of Huế and is a topic we can explore much more with the medical staff on a subsequent trip. The use of long-acting narcotics was much more uneven between patients. Patients who were at the end stage of their cancer and experiencing a lot of pain could come back to the clinic and receive injections of morphine. Conversely, one of the clinic nurses could go out to the patient if he or she was nearby. Death was a topic not generally discussed with patients. When I asked one of the fellows if she ever told patients that cancer would end their life, the question was met with a surprised look and an emphatic “no, never!” The family was told to “be prepared for anything.” Unfortunately, the “anything” families are prepared for does not usually include death.

The differences in palliative care and hospice practices between our two countries were best represented by a patient we saw the first day while rounding on the inpatient service. The
patient was a 54-year-old man with a metastatic high-grade sarcoma. He had been diagnosed with a high-grade rhabdosarcoma of his leg 7 months previously. At the time of diagnosis, surgery was advised but the patient refused. Unfortunately, his malignancy progressed despite extensive anthracycline-based chemotherapy. He had been at the hospital since the time of diagnosis and his tumor had grown rapidly, extending from his right knee to above his hip in a circumferential manner. Moreover, he had severe pain and extensive pulmonary metastatic disease. We saw this patient once again several days later, during our next rounding. In talking with one of the fellows, we learned the patient had not been told his tumor would progress and eventually take his life. With help from the fellow in interpreting, we spoke with the patient, who was from a local village, about 30 km from Huế. He and his wife had four children; both of his sons lived with him. He worked in a shoe factory prior to his sarcoma diagnosis. His sister was staying with him to cook and take care of him in the hospital until he “gets better from his tumor.” At that time, his cancer had progressed while on chemotherapy and he was only on intravenous fluids and supportive medications. We found this patient had a real lack of insight and unrealistic expectations regarding his condition, but we were informed that often patients are not told they are going to die from their disease. We discussed through an interpreter with the patient about his diagnosis and how his tumor would continue to grow and likely ultimately take his life. He stated he definitely wanted to be home when he passed. Our conversation was relatively short by American standards, but the patient seemed to take the news well. He thanked us and smiled when we moved on with our rounds. When rounding the following day, we were told he was to be discharged that day to go home to be with family.

AN ONCOLOGY FELLOW’S PERSPECTIVE

In October 2011, I was asked by Dr. John Pippen, a member of the clinical faculty, if I would like to travel to Huế, Vietnam, to volunteer with a group from ASCO for 2 weeks. Dr. Pippen put together an incredible team for the trip. It took me all of two seconds to say, “Yes, let’s do this!”

During my first week, I was fortunate to locate the English-speaking club. On our third day I met a unique group of medical students who gathered weekly to practice their English skills. We reviewed core oncology and hematology skills, including how to evaluate a peripheral blood smear. During our time together, we talked extensively about the system of medicine in our two countries, medical training, oncology, and many other topics. I learned that in Vietnam all medical schools are run by the government. Due to the influence of their political system, every medical school has its own Communist Party committee. Typically, the dean or head of the department is appointed by the Communist Party committee.

In addition to learning medicine, medical students are taught Marx’s philosophy (during the first few years), Ho Chi Minh’s philosophy, as well as the history of the Communist Party. Upon completion of 6 years of medical school, graduates have several options. Most begin work as general doctors. Many engage in self-study or attend conferences to become specialists without a formalized system of training. For the more competitive 10% to 15% of new physicians, another option is to pursue postgraduate education through the academic track or the clinical track of study. The academic track is designed for those who will teach at a medical school or university. The clinical track is what Dr. Thi, a trainee with Dr. Van Cau, was doing. This program consisted of 3 years in residency training, similar to a US residency program. Admission to these postgraduate programs was highly competitive and required an entrance exam along with an interview.

From the students I learned that health care services in Vietnam are often paid for on a cash basis, despite a national health insurance program, known as “Bao Hiem Y Te.” The national plan has two types of health care insurance: obligatory and voluntary. Obligatory insurance is the plan for people who are currently working, and it is paid for by a combination of employer and employee contributions. Voluntary insurance is for those not belonging to the obligatory section, such as students or those out of work. This insurance still may require a fee, but it is much less. All children under 6 years of age have free medical insurance in Vietnam; however, access to medical services varies greatly based on geography and socioeconomic factors.

I was told by some that patients who pay cash usually receive more attention and better care; however, we saw no evidence of this in our experience in the clinic. I met with the English club several times on my trip. I continue to correspond with one of the fourth-year medical students whose goal is to pursue a career in oncology. Overall it was an incredibly rewarding opportunity for me as an oncology fellow, and I believe that many of the lessons and experiences we shared with our Vietnamese colleagues will be integrated into their everyday practice. I think that we were able to learn much from the resourcefulness and ingenuity of Dr. Van Cao and his team, and I am looking forward to a future return trip to the site.

TRAVEL-RELATED ISSUES FOR THE VOLUNTEER

Several minor obstacles, other than just the lengthy air travel, must be overcome to successfully navigate Vietnam. In addition to a valid passport, a tourist visa must be obtained. For a stay longer than 4 weeks, visitors require a different class of visa. Since there are a limited number of Vietnamese consulates in the US, it is easiest to employ a travel service to obtain the tourist visa, which is valid for one entry into Vietnam. The total expense for the visa is around $300. In-country travel is inexpensive, owing to the strength of the dollar relative to the Vietnamese currency. In addition to completion of the necessary paperwork, travel to a developing country requires some advance medical preparations. Vietnam is an area known to be endemic for malaria, so DEET-containing insect repellent is recommended. If traveling outside of urban areas, malaria prophylaxis is advised. Other common-sense travel precautions should be followed, including drinking bottled water, avoiding salad items that may have been washed with tap water, and using sufficient sunscreen, a huge task even for a well-practiced group from Texas.
IDENTIFICATION OF NEEDS

There are opportunities to make a positive impact on subsequent trips to the Huế College of Medicine and Pharmacy. Below is a partial list of opportunities.

1. Modernization of the pathology department. In breast and other cancers, the orientation of the specimens was not always known, and on some specimens it appeared as if cancer was at the margins. The Ki-67 tumor marker test needs to be added to the breast cancer immunohistochemical analysis panel to better gauge the proliferative status of a tumor. A visiting pathologist could go a long way in making sure basic protocols are in place to improve their diagnostic capabilities.

2. Instruction in the use of long-acting oral pain medicines and further instruction on WHO’s pain relief ladder. In addition to managing the pain of cancer patients, managing the side effects of narcotic medications is another area that could be taught.

3. An outpatient hospice. This hospice could be organized by first utilizing the current clinic nursing staff. A discussion with the chief administrators may be helpful in creating a cadre of palliative care nurses to visit patients in their homes. Economic issues may be problematic, but motorbike transportation is relatively inexpensive, and Huế is easy to traverse for an experienced cyclist.

4. More efficient use of space in the clinic. Putting six chairs in each of the rooms may prove more helpful than five cots. Chairs would be more comfortable than cots and would allow more patients to be treated in a shorter amount of time.

5. Mammography and breast conservation training. Again, acquisition of a linear accelerator would make this a possibility and could potentially cut down on the number of local recurrences seen in the cancer patients. Purchase of a new machine, however, may be problematic in a developing nation. Better surgical techniques would include the addition of more accurate sentinel node assessments.

6. Teaching medical students. In Huế, we had the privilege of lecturing to the students, all of whom were respectful and attentive. With many of them interested in oncology, there is great opportunity for volunteers to help with improvement in oncology education and screening. A series of basic lectures in medical oncology would likely be well received.

7. English as a second language. The students wanted to learn better English. Evening practice sessions with team members and students, accompanied by an excellent local beer, would be a good way to facilitate this process.

PARTING THOUGHTS

Our trip to Vietnam really opened our eyes to what others in the world must contend with in their medical practices. Even though we were able to teach them a great deal, they taught us about how to take good care of patients with limited resources. We were able to experience, on a limited level, what people in Vietnam experience on a daily basis. All was not work on our trip, however, as we took some time to see some of the sites of Vietnam. We stopped in Hô Chi Minh City (formerly Saigon) and saw the tunnels of Cù Chi, a vast network used by the Viet Cong guerrillas during the Vietnam War. They were the Viet Cong’s base of operations for the Tết Offensive in 1968 and now an important part of their history.

We also took a day trip to Tây Ninh, about 90 km northwest of Hô Chi Minh City. There we saw the Cao Đài Temple (Figure 5). The Cao Đài faith, indigenous to Vietnam, includes the teachings of the major world religions. It was quite interesting to see how the Vietnamese integrated so many diverse faiths. When our trip came to an end, we were thanked profusely by our hosts, including a presentation of flowers (Figure 6). We all learned much on our journey and hope to make it again soon.


Most physicians are aware of the history of the Flexner Report, published in 1910. It gave a detailed report card of the nation’s medical schools, prepared by Abraham Flexner with funding from the Carnegie Foundation. This report revolutionized medical education in America and will be the subject of a future review article. Why do few physicians know about the work and findings of the Committee on the Cost of Medical Care (CCMC)?

During the 1920s, the rising cost of physician and hospital care became a concern to many. At a national economic conference in 1925 in Washington, DC, a committee was self-organized to address this issue and became known as the CCMC. This effort received funding of $1 million from eight foundations, and its activities were directed by a staff of employees. The Carnegie Foundation and Milbank Memorial Fund were the largest contributors. The committee included 15 physicians in private practice and was chaired by Ray Lyman Wilbur, MD, of Stanford University. He was a well-known figure with conservative Republican credentials, and he soon became secretary of the interior under President Hoover. Dr. Stewart R. Roberts of Atlanta was one of the doctors on the panel. He was on the Emory faculty at the time and had been president of the Fulton County Medical Society and was active in the Southern Medical Association. He was later president of the American Heart Association. He was well published and well respected and was considered to be Georgia’s first cardiologist.

The CCMC and its staff issued 15 separate reports over 5 years, which were published and available as pamphlets. The final report with all its recommendations was printed in book form (Figure). This was the first time that many economic aspects of medical care in the US were documented. Among its many findings, the CCMC estimated that health care consumed 4% of the gross domestic product. Spending for physician services was the largest category, accounting for 29.8¢ of each dollar. Hospital care consumed 23.4¢, medications 18.2¢, dental care 12.2¢, nursing care 5.5¢, “cultists” 3.4¢, public health 3.3¢, and other 4.2¢. The average gross income of physicians in 1929 was $9000 per year at a time when the average family income was $1700 per year. An overhead of 40% was typical for a physician in practice, and 10% to 20% of fees were uncollected. Despite much charity care by physicians, hospitals, and health departments, in the lowest-income groups about half received no medical care at all. It was estimated that if medical care was organized economically, all the usual needed care for the entire country could be provided for $20 to $40 per person per year (excluding capital costs). The most quoted statement from the report indicated the basic problem in medical care was “not the system, but the lack of a system” to organize care.

The most common physician practice then was the solo private general practitioner. The CCMC also documented other styles of practice, such as industrial medicine, group practice with or without hospital employment, capitated models, public health system practice, and university-sponsored student health care. These nontraditional types of practice needed to grow. The final report supported expansion of group practice and formation of the “community medical center” as the most effective means of providing care. More national spending on overall medical care was required to meet all the needs, especially to provide for those who had no medical care. Preventive care was thought best provided through public health facilities. The most controversial recommendation of the CCMC was for national health insurance, either voluntary or compulsory through taxation.

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Notable was the fact that eight physicians dissented and wrote a minority report. They supported continued experimentation with such models and new proposals but strongly felt that the independent practicing physician should be in charge of any programs or changes. They objected to competition based on price as “unprofessional.” This group felt that even voluntary health insurance would lead to a compulsory national health insurance, as was in place in many European countries. Georgia’s Dr. Roberts supported the work of the committee and signed the final report.

Two of the nonphysician committee members felt that the report did not go far enough or make strong enough recommendations for national health insurance. They stated that the purpose of the committee had not been fulfilled. Edgar Sydenstricker and Walton Hamilton were these two.

Little time passed before the editor of the Journal of the American Medical Association, Dr. Morris Fishbein, penned a blistering denouncement of the work of the CCMC on December 3, 1932, stating it was “incitement to revolution,” “socialist,” and “communist.” The American Medical Association (AMA), in its 1933 House of Delegates, took a position of opposition to any further government involvement with medical care. Franklin Roosevelt had been elected president in the depth of the Depression, and the winter of 1933 was the nadir of despair. Any changes in the health care system took a back seat to more pressing matters. The famous “First Hundred Days” dealt with banking reforms, help with mortgage foreclosures, and many regulations for businesses in an effort to stabilize a critically damaged economy and put people to work, even if it was “make-work.” The Civilian Conservation Corps, Works Progress Administration, and Public Works Administration were funded with unheralded deficit spending. In many respects, the report of the CCMC was a tiny blip on any graphic of the crisis.

Within 2 years, Roosevelt appointed an Economic Security Committee in June 1934, which included several of his cabinet members, and called an Economic Security Conference in Washington in November 1934 under the leadership of Frances Perkins, secretary of labor, and Harry Hopkins, director of federal relief programs. Roosevelt asked for unemployment insurance, old age pensions, and proposals on medical care insurance. He spoke in November and advocated medical efforts “whether soon or at some point later,” indicating ambivalence about the health care proposals. A technical staff had been drafting proposals on all these areas since Roosevelt’s first speech in July 1934 on the subject, including national health insurance models. During the November conference, an invited Medical Advisory Committee attended and expressed their reservations about the program.

This group then met separately in January 1935, ostensibly to give their approval. The meeting was chaired by Edgar Sydenstricker, one of the main dissenters of the CCMC. Dr. Walter Bierring, president of the AMA, was among the panel members. The prior work of the CCMC was discussed and provided the statistical basis for many recommendations. The charge of the advisory group was to respond to the proposed changes for potential legislation. The minutes of these meetings, available online through the Social Security historical archives, provide interesting insight into medical issues of the time. The advisory committee allowed the recommendation for national health insurance to survive, but there was much internal opposition. Harvey Cushing, the prominent Boston neurosurgeon, was on the advisory committee and spoke outside the committee in opposition. Other physicians on the committee were opposed. Dr. Stewart Roberts appears to have been in support and stated that the medical community was “on trial” and would “regret its actions” if it did not move forward to include medical care with other aspects of Social Security legislation. He apparently felt that the committee members and their work was maligned by the position of the AMA.

With leaks from the committee and the impression that health insurance was coming soon, the AMA called an emergency House of Delegates meeting in February 1935 and vehemently opposed any efforts at national health care insurance or government regulation of medicine. The AMA assumed from the committee structure and technical work that a health care proposal was sure to follow. This strong stance by the House of Delegates generated many telegrams from local physicians and state and county medical societies to the White House. It can be safely assumed that the physicians of the day were mostly held in high regard locally and nationally. What impact did this vocal opposition really have on the final decisions? Harry Hopkins continued to favor inclusion of medical assistance, but Frances Perkins advised against it, fearing that the whole Social Security bill would go down. Roosevelt showed caution and held his cards. Whether the medical opposition led to its exclusion or whether Roosevelt was reluctant from the beginning to include national health care in his bold social initiative is the subject of much debate among historians. Roosevelt was known for skillfully making each side feel he agreed with them. The final report of the Medical Advisory Committee did not materialize in 1935 and was not published until many years later. The Senate finance committee gave the Economic Security Bill a beating but ultimately let it through by a small margin, with Senator Thomas Pryor Gore of Oklahoma famously explaining his view that “the dole ruins the soul.” Although some public health funding was given, comprehensive national health programs were excluded from the final bill approved by Congress in June 1935.

Many of the proposals advocated in the 1930s still retain their fire as public debate and divided opinions on the Affordable Care Act of 2010 loom large.


After much debate, national health insurance was excluded from the Economic Security Bill of 1935, which passed during the first administration of President Roosevelt. As Dr. Thomas B. Gore points out in an adjacent article, my paternal grandfather, Stewart R. Roberts, MD (1) (Figure 1), was involved in this debate and took a rather contrary position as a physician.

Roberts was a member of two pertinent groups in this national debate, the Committee on the Cost of Medical Care (CCMC), organized in 1925, and the Medical Advisory Board, organized in 1934. He appears to have been strongly supportive of national health insurance and found himself in direct opposition to the American Medical Association (AMA) under the leadership of Dr. Morris Fishbein, who viewed such a plan as socialist, if not communist.

The CCMC final report in 1932 highlighted the disconnect between lay reformers, who generally wanted national health insurance, and physicians, who generally opposed that level of governmental involvement. Some physicians, however, including Roberts, went against the majority view within the medical profession. In his 1999 book, ...And the Pursuit of National Health, Jaap Kooijman described the circumstance:

The polarization within the medical profession reappeared, however, with a statement by Dr. Stewart Roberts, who bitterly criticized the obstinate position of the AMA. When in 1932 he had signed the CCMC majority report [written by lay members and physicians, advocating national health insurance], Roberts had been, as he claimed, condemned by the editorials in the Journal of the American Medical Association. The medical profession’s obstruction had to stop, Roberts argued: “Now this American Medical Association, we doctors of America, are on trial in this room this afternoon. If we obstruct and reason and dally, we are going to receive the contempt of the American people, and will rightly deserve it” (2).

The Medical Advisory Board, organized in 1934 and composed of 11 physicians, appeared to favor the expansion of existing public health services, as an alternative to a national health insurance plan. The “round robin” letter generated by the board (Figure 2) recommended that “experiments in voluntary insurance” be done first, before establishing compulsory health insurance. Roberts was the only board member who did not evidently support this cautious position.

My paternal grandfather disliked Roosevelt, but I thought it was because the USA was being drawn into a Second World War in Europe (through the lend-lease program, etc.), an inevitability which my grandfather, an isolationist, like Charles Lindbergh, opposed. The attack on Pearl Harbor, which occurred after my grandfather’s death in 1941, would certainly have changed this view.

What did not occur to me until Dr. Gore shared his research was that my grandfather probably disliked Roosevelt more for excluding a national health insurance plan in his Economic Security Bill of 1935. I am grateful to Dr. Gore for reminding us of these national deliberations, which occurred some 80 years before the Affordable Care Act of 2010. It proves again that there is nothing new under the sun (Ecclesiastes 1:9).

Figure 2. Round robin letter from the Medical Advisory Board in 1935 with recommendations concerning national health.
Lymphoma is a rare neoplasm in the breast. In this location, it may be primary or secondary, depending on whether there is lymphoma elsewhere in the body. The most common presentation of breast lymphoma is a painless palpable mass, indistinguishable from that of breast carcinoma, although the treatment regimens for these two neoplasms differ vastly. Knowledge of the varied mammographic and sonographic presentations of breast lymphoma should prompt more frequent recognition of this unusual malignant entity. Proper diagnosis of this neoplasm is of the utmost importance to guide appropriate treatment planning and prevent unnecessary and potentially harmful surgery. We describe secondary breast lymphoma in a woman who had been diagnosed and treated for non-Hodgkin’s lymphoma several years earlier.

CASE REPORT

A 49-year-old white woman presented for a bilateral diagnostic mammogram in February 2009 with complaints of a painless, palpable lump in the medial right breast. She had non-Hodgkin’s lymphoma of unknown histologic subtype diagnosed and treated into remission at age 40 (2003). Approximately 1 month before presentation, a computed tomography (CT) scan demonstrated a mass within the right breast. Routine craniocaudal and mediolateral oblique views of both breasts demonstrated scattered fibroglandular densities within the breast parenchyma (Figure 1). An additional spot tangential view of the right breast over the patient’s palpable area of concern (Figure 2a) demonstrated a 5 cm gently lobulated, ovoid mass at the 3 o’clock position, located approximately 7 cm from the nipple (yellow circles, Figure 1). A right breast sonogram (Figure 2b) demonstrated a 4 × 2 × 1 cm well-circumscribed, hypoechoic ovoid mass at the 3 o’clock position, 8 cm from the nipple, corresponding to the patient’s palpable area of concern. An 0.8 cm ovoid mass at the 11 o’clock position, 8 cm from the nipple, corresponded to an intramammary lymph node (blue circle, Figure 1). In addition, sonographic evaluation of the right axilla demonstrated a 2.7 cm lymph node with a thickened cortex.

A percutaneous, ultrasound-guided core needle biopsy of the ovoid mass within the right breast was consistent with a grade I (low-grade) follicular B-cell lymphoma (Figure 3). The B lymphoid cells stained positive for CD20 and CD79a, and follicular structures demonstrated a 10% positive reaction for BCL-2. A positron emission tomography (PET) scan 2 months later for restaging purposes demonstrated a hypermetabolic ovoid mass within the medial right breast, corresponding to the biopsied lesion at the patient’s palpable area of concern (red circles, Figures 4 and 5). Additional hypermetabolic foci identified at various locations above and below the diaphragm were compatible with recurrent or residual lymphoma (Figure 4). The enlarged right axillary node previously identified on the right breast sonogram showed intense hypermetabolic activity on PET scan.

The patient was treated with cyclophosphamide, vincristine, prednisone, and rituximab, and a follow-up PET scan (not shown) performed 1 month following the patient’s last round of chemotherapy demonstrated interval resolution of all hypermetabolic foci previously identified, compatible with a complete response to therapy.

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therapeutic response to chemotherapy.

DISCUSSION

Breast involvement by lymphoma constitutes ≤0.5% of all mammary malignancies (1–5). The rarity of lymphoma in the breast may be attributed to its relative paucity of lymphoid tissue. Lymphomas demonstrate a bimodal age distribution, with peaks in the fourth and seventh decades of life (4, 5). Most breast lymphomas are of the non-Hodgkin’s B-cell type, with diffuse large B-cell lymphoma constituting the most prevalent subtype (6).

Intramammary masses, most of which are round or oval in shape with circumscribed or gently lobulated margins, are the most common mammographic finding. Calcific deposits and spiculated margins are uniformly absent, and architectural distortion is rare (1, 4). High-grade lymphomas have been reported to manifest more frequently as diffuse breast enlargement, whereas low- to intermediate-grade neoplasms preferentially display a more nodular pattern (4, 7). Sonographically, breast lymphoma appears as a hypoechoic to almost anechoic round or oval-shaped mass with relatively well-defined margins with or without posterior acoustic enhancement (4, 6). In addition, a pseudocystic serpentine mass appearance has been documented on sonographic evaluation of two breast lymphoma cases in a study by Gal-Gombos et al (8).

Although few studies have described the magnetic resonance imaging (MRI) characteristics of breast lymphoma, certain features have been elucidated to date. Surov et al (4) and Yang et al (5) characterized these lesions as hyperintense compared with surrounding breast parenchyma on T2-weighted images and isointense on T1-weighted images. Global intense heterogeneous or homogeneous contrast enhancement was identified after the administration of intravenous gadolinium. Kinetic analysis of contrast enhancement demonstrated rapid initial signal increase, which plateaued or rapidly washed out (type 2 or type 3 kinetic curves), the findings of which are characteristic for malignancy.

In an attempt to differentiate between primary and secondary breast lymphoma, a few distinguishing characteristics may be helpful, though they are not pathognomonic in and of themselves. In contrast to primary disease, masses in secondary breast lymphoma often demonstrate smaller diameters upon initial presentation. Sabaté et al (7) indicated that the average diameter of a mass in secondary breast lymphoma measured 2.8 cm compared with an average of 4.6 cm for primary breast lymphoma. This finding may be partially explained by the fact that the duration of symptoms prior to clinical and radiologic examination may be shorter in patients in whom lymphomatous disease is known. Likewise, the number of intramammary masses has been reported to be higher in secondary than in primary breast lymphoma (4), in keeping with the overall extent of primary versus secondary lymphomatous disease. Parenchymal breast involvement in association with bilateral axillary lymph node enlargement may...
be suggestive of lymphoma, particularly secondary breast lymphoma, although widespread metastatic breast carcinoma could also have a similar presentation (7).

Treatment of breast lymphoma remains somewhat controversial; however, certain guidelines have been elucidated. In a study by Fruchart et al (1), all patients undergoing mastectomy, either alone or in association with chemotherapy, died of their lymphoma. It has been postulated that this may have resulted from delay of appropriate systemic treatment. Correct diagnosis with tissue sampling is therefore of the utmost importance to prevent the morbidity and mortality associated with unnecessary surgery. Alternatively, multiple studies (1, 7) have suggested a treatment regimen consisting of combination chemotherapy with or without concurrent radiotherapy.


Figure 5. Axial images from (a) PET scan and (b) localization CT demonstrate an ovoid hypermetabolic mass within the medial right breast (red circles). This lesion corresponds to the ovoid soft tissue density in this location and to the dense ovoid mass seen on prior mammography and sonography (see Figures 1–4).
Inflammatory breast carcinoma
Kelli Y. Ha, MD, Shannon B. Glass, MD, and Louba Laurie, MD

Inflammatory breast carcinoma is a rare form of invasive breast cancer often characterized by erythema, warmth, and a classic “peau de orange” or “orange peel” appearance of the affected breast. The average age of onset is within the fourth and fifth decades. Lesions are usually detected and evaluated with mammography, sonography, and recently, breast magnetic resonance imaging. We present the case of a 49-year-old woman with inflammatory breast carcinoma in her left breast and describe the imaging appearance of this aggressive lesion on the modalities listed above. Because this lesion may be misdiagnosed as infection (i.e., mastitis) or as the sequelae of a dermatologic disorder, proper characterization of inflammatory breast carcinoma is of the utmost clinical and radiologic importance.

CASE REPORT
A 49-year-old woman presented with a history of a palpable mass within her left breast, which had been present for 2 years. Routine digital mammographic imaging of the right breast (not shown) did not demonstrate any abnormality. Within the upper outer aspect of the left breast at the palpable area of concern, a region of asymmetry, partially obscured by coarse trabecular thickening, was seen in addition to marked axillary lymphadenopathy (Figure 1). Diffuse cutaneous thickening was also demonstrated within the left breast. Sonography demonstrated a large heterogeneous mass at the palpable area of concern, in the 2:00 position, 10 cm from the nipple, measuring approximately 4.6 × 4.5 × 4.4 cm (Figure 2). Left axillary lymphadenopathy, measuring up to 4.4 cm in the long axis, was also observed. The patient underwent surgical biopsy, and the histology proved consistent with inflammatory breast carcinoma (IBC). She was subsequently treated with a neoadjuvant chemotherapy regimen consisting of six cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide. Mastectomy was then performed.

DISCUSSION
IBC is an infrequent form of invasive breast cancer that often presents with a rapid onset of diffuse erythema, warmth, edema, and/or peau d’orange changes of the breast. In addition, these changes are accompanied by breast tenderness and/or pain, palpable mass or masses, and diffuse rapid breast enlargement in conjunction with cutaneous thickening and dermal ridging. In the absence of clinical symptoms and abnormal laboratory values, i.e., fever, chills, and/or an elevated white blood cell count, one should immediately consider a diagnosis of IBC. This disease entity accounts for 1% to 6% of all breast cancers in the United States, with the average age of onset between 45 and 54 years (1–3). Similar to other types of breast carcinoma, IBC can occur in men, but usually at an older age (median age at diagnosis 66.5 years) than in women. IBC cases in men constitute between 0.6% and 1.4% of all newly diagnosed breast cancers (4).

Pathologic diagnosis of this clinical entity is generally based upon the presence of tumor emboli within dilated lymphatic vessels and a surrounding lymphocytic reaction in the dermis (2, 5; Figure 3). Although infiltration of dermal lymphatics confirms a diagnosis of IBC, the disease may only be evident clinically, and punch biopsies may be negative. In such cases, patients are treated for IBC based upon clinical data. While IBC is relatively uncommon compared with other malignancies, it remains aggressive, with a tendency to metastasize early (3). Therefore, information about this malignancy is of interest and importance to both radiologists and clinicians alike.

On mammography, IBC demonstrates a pattern of diffuse “inflammatory change,” to include cutaneous and trabecular thickening, increased parenchymal density, breast distortion, and nipple retraction. Changes on mammography are secondary to dermal lymphatic infiltration and obstruction by tumor, rather than a true inflammatory process. Because of the increased parenchymal density, which is often seen throughout the affected breast, a focal mass lesion or group of suspicious calcifications is less often seen mammographically (2, 6). Additional associated mammographic findings, albeit observed less consistently, include axillary lymphadenopathy and nipple retraction. Of particular note, the contralateral breast should be carefully inspected for developing asymmetry and trabecular and/or cutaneous thickening, given the possibility of cancer spread or a simultaneous lesion in the contralateral breast, which occurs in approximately 1% to 5% of patients with primary IBC (5).

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IBC may be divided into two clinical subgroups, first described by Taylor and Meltzer in 1938. The primary form is seen in patients with IBC characteristics that are evident from the onset, while the secondary form is described in those whose clinical features appear subsequent to appropriate treatment of a primary noninflammatory breast carcinoma (7). Given that our current patient presented without a known history of previously treated breast carcinoma, her disease was characterized as a primary lesion.

Sonographic evaluation of IBC is helpful in demonstrating lymphatic dilatation in association with tumor emboli, as well as depiction of hypoechoic shadowing masses, cutaneous thickening, skin/pectoral muscle invasion, and axillary lymphadenopathy. Sonography is notably a better modality for depicting these characteristics and should be used in conjunction with mammography and physical examination for diagnosis whenever possible.

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Sentinel node biopsy is ultimately used for the diagnosis of axillary involvement, as skin punch biopsy or ultrasound-guided core needle biopsy of suspicious masses is for IBC (3).

Recently, breast magnetic resonance imaging (MRI) has become a primary modality for the depiction of IBC disease entities, either in conjunction with or in replacement of standard mammography. MRI can be obtained in place of mammography if mammography would be too painful or uncomfortable for the patient or if compression is inadequate secondary to tumor bulk. Although patients are usually evaluated initially with mammography, MRI is useful for determining the extent of disease and may be helpful in monitoring treatment response in some cases.

Global skin thickening, enhancing masses, breast enlargement, breast/chest wall edema, and/or tumor infiltration is often obscured on mammography. However, these entities are well characterized on MRI, leading to a higher detection rate of primary breast parenchymal lesions/masses using this modality. Multiple enhancing breast masses are more often described

Figure 1. Routine digital mammographic imaging of the left breast: (a) craniocaudal view, (b) mediolateral view. Both views demonstrate a region of asymmetry (arrow), which corresponds to the palpable area of concern in the upper outer quadrant. Diffuse cutaneous and trabecular thickening is also identified about the surface of the left breast, which gives the appearance of increased breast density.

Figure 2. Sonographic image of the left breast demonstrates a large heterogeneous, predominantly hypoechoic mass at the 2:00 position of the left breast, 10 cm from the nipple, measuring approximately 4.6 × 4.5 × 4.4 cm.

on MRI than a single index breast lesion in IBC (1). Primary tumors in IBC often demonstrate low signal intensity on T1WI and heterogeneous iso- or high signal intensity on T2WI. Increased signal intensity and enhancement of the thickened skin are also consistently reported attributes of IBC (2).

Inflammatory breast carcinoma is not the only disease process that presents with mammographic or physical signs of breast tissue inflammation. In fact, the differential for these findings remains vast, and correlation with patient history in conjunction with physical and radiologic examination findings remains crucial in these situations. Inflammation of the breast tissue may be seen after surgery and postradiation therapy, as well as from trauma, infection (i.e., mastitis), and various dermatologic disorders. Breast edema may be secondary to other systemic conditions such as superior vena cava syndrome, congestive heart failure, and lymphoma. In patients who present with inflammatory signs that continue despite proper antibiotic treatment, biopsy is indicated to definitively exclude a diagnosis of IBC (3).

Goldfarb and Pippen recently reviewed treatment of IBC at Baylor University Medical Center at Dallas (8). As they noted, the recommended therapy is induction chemotherapy with an anthracycline-based regimen with or without the addition of taxanes, followed by mastectomy with axillary lymph node dissection in those who respond well. Preoperative trastuzumab may be considered for patients with HER2-positive disease. Any remaining cycles of planned chemotherapy can be completed after surgery, and patients with hormone receptor–positive disease may begin endocrine therapy after surgery as well. Postsurgical radiotherapy of the chest wall and regional axillary nodes should follow completion of the chemotherapy regimens.

The current case describes a patient who presented for her first mammogram with an advanced inflammatory breast carcinoma, undoubtedly neglected for some time given initial palpation 2 years prior. This case highlights the importance of mammography in screening for breast carcinoma and of seeking proper and timely evaluation upon palpation of a new breast mass. It is unique given the extensive inflammatory change that was denied evaluation until a late and advanced stage. Although IBC can easily be mistaken for an infection or other disease process as discussed previously, failure to improve with antibiotics/treatment should remain a “red flag” for the relatively rare diagnosis of IBC.

Plasmablastic lymphoma following transplantation

Michael J. Van Vrancken, MD, MPH, Latoya Keglovits, MD, and John Krause, MD

Posttransplant lymphoproliferative disorder is a serious complication following solid organ as well as hematopoietic stem cell transplantation due to prolonged immunosuppressive therapy. Plasmablastic lymphoma, although classically associated with HIV infection, has since been described in transplant patients as a variant of posttransplant lymphoproliferative disorder with varying clinical presentations. Here we add two additional cases to the literature: one following lung transplantation and one following pancreatic transplantation. In addition, the demographic, therapeutic, and immunophenotypic characteristics from prior reported cases are summarized.

Plasmablastic lymphoma was first described in 1997 as an oral mucosal lesion associated with HIV-positive individuals as a subtype of diffuse large cell lymphoma (1, 2). Since its initial description, it has now become well established as an entity seen in HIV-negative individuals as well, albeit rarely (3). In 2003, the first case of plasmablastic lymphoma in a posttransplant lymphoproliferative disorder (PTLD) was reported as a cutaneous leg ulcer (4). Since this original description, several additional cases have been reported following various solid organ and bone marrow transplantations. We present two cases of plasmablastic lymphoma, one following lung transplantation with subsequent immunosuppressive therapy (previously reported in the context of unusual clinical findings) (5) and another following pancreatic transplantation.

CASE 1

A 67-year-old man with idiopathic pulmonary fibrosis diagnosed at age 63 (2008) underwent sequential bilateral lung transplantation in October 2011. The patient had a complicated clinical course thereafter with repeated episodes of respiratory failure requiring reintubation and eventual tracheostomy. He subsequently developed bilateral pulmonary infiltrates and was placed on antibiotics. Biopsy showed acute lung injury, and the patient was placed on high-dose steroids for presumed acute rejection. The patient’s respiratory status continued to decline, and he developed worsening pulmonary infiltrates. Repeat biopsy again showed acute lung injury with organization. He was again treated with high-dose corticosteroids as well as a 10-day trial of antithymocyte globulin (Atgam) for possible rejection. The patient began to recover clinically, and at the time of his discharge 45 days later, he was breathing room air and his tracheostomy site was healing. To modulate his posttransplant immune function, the patient was treated with tacrolimus, prednisone, and azathioprine.

In February 2012, the patient presented with facial swelling, numbness, right lower lip swelling, and mild erythema within...
the inner lip with corresponding numbness. He had macrocytic anemia with normal folate and vitamin B12 levels. Brain magnetic resonance imaging revealed multifocal patchy regions of marrow signal abnormality involving the calvaria, skull base, and visualized upper cervical spine. He had elevated copies of Epstein-Barr virus (EBV).

Histologic analysis of a bone marrow biopsy specimen disclosed scattered cellular sheets of a plasmacytoid infiltrate composed of medium- to large-sized cells with an abundant amount of basophilic cytoplasm, eccentrically located nuclei with a clock-faced chromatin, and a perinuclear hof. Many malignant cells displayed a large central nucleolus with finely dispersed immature chromatin consistent with a “plasmablast”-type morphology (Figures 1 and 2). Occasional cells showed bi- and trinucleated forms, and mitotic activity was increased with many atypical figures seen.

Immunophenotypically, these cells were characterized by strong immunohistochemical staining to CD138 with patchy membranous positivity seen with CD56. CD30 and CD20 were negative in the plasmacytoid cells. Most malignant infiltrates were negative for both kappa and lambda in situ hybridization with rare scattered cells showing positivity. Additionally, most cells stained positively for EBV early RNA (EBER) by in situ hybridization (Figure 2).

After a diagnosis of posttransplant plasmablastic lymphoma was made, the patient was started on a cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone/...
prednisolone (CHOP) chemotherapy regimen. After 1 cycle of treatment, the patient elected to receive palliative care only.

CASE 2

In 2008, a 45-year-old woman received a pancreas transplant for brittle diabetes mellitus type I. Over the next year, the patient was hospitalized multiple times with abdominal pain, which was attributed to pancreatitis. In May 2009, the patient was hospitalized for abdominal pain, again with a failed pancreatic transplant. She underwent a planned pancreatectomy. During the procedure, a 16-cm loop of small bowel was identified wrapping around a 6.0 × 5.0 × 4.0 cm soft tissue mass within the abdomen, and it was resected.

Histomorphologically, the mass was composed of large round to oval-shaped cells with finely dispersed immature chromatin and prominent nucleoli consistent with a “blast”-type morphology (Figure 3). Immunohistochemically, the cells had a positive stain for CD138 and CD56 and were positive for EBER by in situ hybridization, confirming the diagnosis of plasmablastic lymphoma. Postoperatively, the patient had a complicated course and died 7 days following the procedure due to overwhelming gram-negative sepsis.

DISCUSSION

PTLD is a heterogenous disease seen in patients who have undergone solid organ or hematopoietic stem-cell transplantation. It was first described in 1968 in association with renal transplantation. In patients who have received a transplant, the risk of lymphoma is increased 20% to 120% compared with the general population (6). Additionally, several risk factors have been shown to increase the risk of PTLD, including immunosuppression (6–8), EBV (9–12), genetic susceptibility (13), and a host of other miscellaneous factors including Caucasian race (14), hepatitis C, cytomegalovirus, and human herpes virus-8 infection (15–17). PTLD is classified into four categories based on immunophenotype, morphology, and molecular criteria. These include early lesions, polymorphic, monomorphic, and classical Hodgkin lymphoma (18).

Traditionally, plasmablastic lymphomas have been described in HIV-positive individuals, typically occurring in the mucosa of the oral cavity. The lesion is characterized morphologically by blastic cells with a plasma cell immunophenotype. In recent years, this entity has also been described in individuals who have previously undergone a transplantation procedure, including kidney, heart, heart/lung, liver/small bowel, and bone marrow (Table 1) (4, 19–24). To our knowledge, the present report is the first describing plasmablastic lymphoma following pancreatic transplantation.

Morphologically, PTLD plasmablastic lymphoma is characterized by larger immature cells with abundant cytoplasm, nucleoli, and an open chromatin pattern. Immunophenotypically (Table 2), previously reported cases have been predominately positive for CD138 and VS38 and usually display either a kappa or lambda restriction. B-cell markers, such as CD20

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<td>0/2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

κ indicates kappa; λ, lambda; EBER, Epstein-Barr virus early RNA; EMA, epithelial membrane antigen; LCA, leukocyte common antigen; HHV-8, human herpes virus-8.
and CD79a, are typically negative, and the proliferative index (Ki-67) is invariably high, usually above 80%. The preponderance of reports demonstrates positivity for EBER through in situ hybridization, with one other case demonstrating an EBV and human herpesvirus-8 coinfection (20). The role of EBV in the development of PTLDs (including plasmablastic lymphoma) is well established. EBV preferentially infects B cells, where its genome can lay dormant as an episome (25). In healthy immunocompetent individuals, activated T cells play an important role in controlling the proliferation and elimination of infected B cells. Due to immunosuppressive therapy severely impairing T-cell activity, immunosuppressed patients are at risk for uncontrolled proliferation of the infected B cells.

The treatment for PTLD has many modalities with varying degrees of effectiveness. Antiviral therapies, particularly ganciclovir, have been used as prophylactic agents to prevent EBV-related PTLD, although the data are not definitive. Donor-derived EBV-specific cytotoxic T-cell lymphocyte infusions (adoptive immunotherapy) have also been shown to play a role in PTLD prophylaxis in both adult and pediatric populations (26, 27). Treatment modalities of diagnosed PTLD have included reduced immunosuppression as well as CHOP-based chemotherapy with or without rituximab. A recent study looking at treatment options for PTLD plasmablastic lymphoma by Zimmermann et al found that immunosuppression with systemic chemotherapy (CHOP–21) achieved a more lasting and complete remission than immunosuppression with local therapy (24).

Acute flaccid paralysis following chemotherapy has a wide differential diagnosis, including drug toxicity, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), and malignant nerve infiltration. We present a case of recurrent acute quadriparesis due to AIDP following chemotherapy for non-Hodgkin lymphoma, which resolved each time following administration of intravenous immunoglobulin. Although many chemotherapeutic agents can cause neurologic side effects, such as peripheral neuropathy, drug toxicity as a cause is a diagnosis of exclusion.

CASE PRESENTATION

A 62-year-old man with recently diagnosed stage IV diffuse large B-cell lymphoma presented for his first cycle of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The diagnosis had been confirmed by pleural and testicular biopsies. Pretreatment positron emission tomography (PET) scan had revealed diffuse nodal activity and extranodal involvement in the pleura, testicles, and bones (Figure 1a). The patient had been otherwise healthy.

He tolerated his first cycle of R-CHOP chemotherapy with no issues. Two days after completing the R-CHOP cycle, he began to notice bilateral lower-extremity weakness, which began at his feet and gradually moved upwards to his hip girdle muscles. The weakness gradually worsened to the point where he needed to use his hands to push off and stand from a seated position. Shortly thereafter, he noted bilateral arm weakness and became unable to stand due to the inability to push off with his arms. He also developed numbness in all four extremities from his mid forearms distally and the knees down. Throughout this time, he retained bowel and bladder function. His severe weakness and footdrop prompted a trip to the emergency department, and he was admitted for workup.

Examination at this time revealed mild upper-extremity weakness proximally with moderate to severe upper-extremity distal weakness. He had profound lower-extremity weakness, distal worse than proximal. While lying supine, he could move his legs minimally from side to side but was unable to lift them against gravity. He was unable to move his feet at all. Deep tendon reflexes at the knees were markedly diminished bilaterally, and ankle reflexes were completely absent. The Babinski sign was negative.

Due to concern for Guillain Barré syndrome, lumbar puncture and electromyography with nerve conduction studies were ordered. Cerebrospinal fluid from the lumbar puncture exhibited albuminocytologic dissociation with an elevated protein (77 g/dL) and a cell count of 1 cell per microliter. Electromyogram revealed diffusely abnormal motor nerve conduction with low amplitude; slow, dispersed compound muscle action potentials; and conduction block in the median, ulnar, tibial, and peroneal nerves. HIV and hepatitis studies were negative. He was diagnosed with AIDP, and IVIG was initiated at 400 mg/kg/day for 5 days.

Shortly after being given the first dose of IVIG, his strength began to improve. Upon awakening the following morning, he was able to raise both knees and his left arm against gravity. By that afternoon, he was able to stand and walk a few steps with a wheeled walker and assistance. Upon completion of the 5-day course of IVIG, the numbness in his forearms and hands had resolved completely. He was discharged to the inpatient rehabilitation unit, where he continued to recover. At discharge after just 4 days of rehabilitation, he was able to ambulate without the assistance of a cane.

During his second R-CHOP cycle, the vincristine dose was halved. Afterwards he experienced a brief episode of tingling and mild weakness in his hands and feet, which resolved completely after 48 hours. Follow-up PET scan prior to cycle 3 demonstrated complete radiologic remission (Figure 1b) with...
no sign of lymphomatous involvement of the nerves. Full-dose vincristine was given with his third R-CHOP cycle. After 5 days, he noted complete loss of sensation in his fingers and feet. His symptoms resolved over the next few days and were attributed to vincristine. As such, vincristine was withheld during his fourth cycle. Five days following this fourth cycle, he experienced severe weakness in his legs bilaterally in addition to numbness in his hands and feet, similar to his initial episode of AIDP. A repeat electromyogram once again demonstrated findings consistent with polyradiculoneuropathy. Lumbar puncture demonstrated protein of 98 g/dL with 1 total nucleated cell per microliter. A complete serum and cerebrospinal fluid paraneoplastic panel and cerebrospinal fluid cytology sent at that time were negative. He was treated again with a 5-day course of IVIG (400 mg/kg/day) with complete resolution of symptoms.

**DISCUSSION**

The differential diagnosis in our patient’s acute ascending weakness included autoimmune AIDP secondary to his underlying lymphoproliferative malignancy, vincristine or rituximab neurotoxicity, and direct lymphomatous involvement of the peripheral nerves. The weakness was not likely due to vincristine or rituximab, as the symptoms developed after the first dose. Furthermore, vincristine toxicity was unlikely as he had a severe recurrence of weakness following his fourth cycle when vincristine was withheld. His malignancy responded extraordinarily to R-CHOP, as his testicles decreased to normal size a few days after his first cycle. Ultimately, his recurrent neurologic symptoms were attributed to AIDP from the underlying lymphoma, as his miraculous rapid improvement with IVIG did not fit with drug toxicity or direct lymphomatous nerve infiltration.

Non-Hodgkin lymphoma is the most common cause of lymphomatous neuropathy syndromes (1). Although AIDP is most classically associated with Hodgkin lymphoma (2, 3), non-Hodgkin lymphoma can also cause a clinical picture of AIDP with evidence of demyelination on electromyography and needle conduction studies. R-CHOP, a frequently used regimen in the treatment of non-Hodgkin lymphoma, has been linked to the development of AIDP (4, 5), particularly rituximab (6) and vincristine (7–10). AIDP, the major variant of the group of neurologic disorders commonly referred to by the eponym “Guillain Barré syndrome,” is believed to be due to autoimmune attack on the myelin of peripheral nerves, leading to electrical conduction slowing and muscular weakness. It is often preceded by an upper respiratory or gastrointestinal tract infection, most commonly due to *Campylobacter jejuni*, Epstein-Barr virus, or cytomegalovirus (11). Other systemic illnesses associated with AIDP include HIV, viral hepatitis, sarcoidosis, and systemic lupus erythematosus (2).

The diagnosis is multifaceted. Clinical findings include progressive symmetric muscle weakness and diminished or absent deep tendon reflexes. Lumbar puncture with analysis of cerebrospinal fluid typically reveals normal cell count with elevated protein, also known as albuminocytologic dissociation. Electromyography with needle conduction study is helpful in the diagnosis of AIDP, typically revealing slowing of nerve conduction with conduction block or abnormal dispersion, prolonged distal latencies, and delayed F waves (12).

Treatment consists of supportive care and disease-modifying therapy. Up to 30% of patients require mechanical ventilation due to weakness of muscles of respiration or inability to swallow.
and protect the airway. Plasmapheresis and IVIG are the main therapies for AIDP. Plasmapheresis removes circulating autoantibodies in the blood, while IVIG may neutralize autoantibodies (13) and prevent complement-mediated nerve damage (14).


Avocations

A red fox from Alaska. Copyright © Jed Rosenthal, MD. Dr. Rosenthal is a cardiologist in Dallas, Texas (e-mail: jedr2@sbcglobal.net).
Endolymphatic sac tumor and otalgia

Mehrzad Zarghouni, MD, Michael L. Kershen, MD, Lauren Skaggs, MD, Amol Bhatki, MD, Steven C. Gilbert, MD, Conan E. Gomez, MD, and Michael J. Opatowsky, MD

Otalgia is a common complaint seen by general practitioners, but its etiology is vast. Rarely, otalgia could be secondary to a neoplasm. We describe a case of otalgia and ear discharge in which the imaging revealed a rare neoplasm, an endolymphatic sac tumor, which contributed to the patient’s symptoms. The primary diagnosis was made via characteristic imaging features that were later confirmed by histology.

Endolymphatic sac tumor is an uncommon neoplasm arising from the endolymphatic sac or endolymphatic duct. This tumor is generally classified as a papillary adenoma. We report a case of endolymphatic sac tumor in which the patient presented with otalgia and ear discharge.

CASE DISCUSSION

A 49-year-old woman presented with recent onset of left ear pain and discharge. The patient had a remote history of left ear tumor resection as a child; however, the type of tumor was not known with certainty at the time of the current evaluation. A noncontrast head computed tomography (CT) as part of the initial examination revealed an expansile mass destroying much of the temporal bone (Figures 1a–1b, white arrows). Given the absence of parenchymal brain edema, an indolent slow-growing tumor was suspected. Unenhanced and gadolinium-enhanced magnetic resonance imaging (MRI) showed a large, heterogeneous, and avidly enhancing mass centered on the left mastoid and petrous bones (Figures 1c–1f, white arrows). A fluid-fluid level within the dependent portion of the mass on the T2 axial image (Figure 1c, yellow arrow) was present. Areas of T1 bright hyperintensity were suggestive of hemorrhage (Figure 1d, yellow arrow). An endolymphatic sac tumor was ultimately confirmed by histologic correlation following operative resection. The patient was discharged postoperatively without adverse neurological deficits.

DISCUSSION

The most common clinical presentation of endolymphatic sac tumor is sensorineural hearing loss (1). Tinnitus, vertigo, and facial nerve palsy can also occur. While these tumors are generally benign, they can be lethal. Late recurrence is possible, although there is generally a very favorable prognosis following complete resection. This tumor may be associated with the neurocutaneous syndrome von Hippel-Lindau
disease (2, 3). In contrast to its sporadic form in which hearing loss is inevitable, in von Hippel-Lindau disease these tumors are generally small, which allows for hearing preservation (2, 3).

The best diagnostic clues on imaging for an endolymphatic sac tumor include its characteristic location in addition to central calcified deposits and bone spicules on CT along with intratumoral high signal intensity on noncontrast T1 MRI evaluation (1–3). This is seen in conjunction with avid enhancement on gadolinium-enhanced T1-weighted MRI sequences.

Inguinal lymphadenopathy as the initial presentation of sarcoidosis

Jim George, MD, Reese Graves, MD, and Robert Meador Jr., MD

Sarcoidosis is a multisystem disease of unknown etiology characterized by granuloma formation. Despite pulmonary involvement in most patients, sarcoidosis can have a varied presentation. Lymph node involvement is rarely found in isolation. Even rarer are cases of sarcoidosis presenting with peripheral edema. We describe a case of sarcoidosis presenting with isolated unilateral peripheral edema.

CASE PRESENTATION

A 50-year-old African American woman with iron deficiency anemia secondary to menorrhagia and uterine fibroids was admitted for symptomatic anemia, requiring blood transfusions. The patient reported worsening right groin swelling and right leg swelling over the last 10 years with progressive pain with activity. A brother had lymphoma.

On admission, she was afebrile and normotensive. Her right leg was 1.5 times larger in circumference than her left leg with nonpitting edema and a negative Homan’s sign. A 7 × 4 cm nodular mass was palpable in her right groin. There was no associated erythema or tenderness to palpation. Her white blood cell count was 4.6 K/uL, hemoglobin 6.5 g/dL, and platelets 331 K/uL. She had a positive antineutrophil antibody result with a 1:320 titer, an angiotensin-converting enzyme level of 25 mg/L, a vitamin D level of 52.9 ng/mL, an erythrocyte sedimentation rate of 47 mm/hr, a C-reactive protein level of 4.8 mg/dL, a complement 3 (C3) level of 147 g/L, and a complement 4 (C4) level of 48.4 g/L. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed right deep pelvic and inguinal bulky adenopathy, with an 8.1 × 5.3 cm right pelvic sidewall mass, multiple enlarged right inguinal lymph nodes measuring 6 cm, and a large left uterine mass, measuring 8 cm (Figure 1). No abnormalities were noted in the chest or abdomen. A dilatation and curettage with endometrial biopsy was completed. An ultrasound-guided core needle biopsy was performed to further evaluate her inguinal mass. Her endometrial biopsy showed numerous myometrial tissue fragments and acute and chronic inflammation with squamous metaplasia, all suggestive of underlying submucosal leiomyoma and atrophy. The tissue sample was negative for granulomas, atypia, or malignancy. The ultrasound-guided core needle biopsy of the large right inguinal lymph node showed noncaseating granulomatous inflammation with special stains negative for acid-fast bacilli and fungi (Figure 2). Flow cytometric analysis showed no evidence of a malignant hematolymphoid process.

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The patient was started on prednisone 40 mg daily and discharged home. She experienced an initial yet short-lived improvement in her right groin and lower extremity swelling. Attempts to taper the prednisone dose below 20 mg daily resulted in worsening right lower leg lymphedema. Multiple ultrasounds of her right lower extremity were done to rule out deep venous thrombosis, all of which were negative.

A repeat CT scan of her chest, abdomen, and pelvis 5 months after her initial diagnosis suggested progressive sarcoidosis with increasing pelvic and inguinal lymphadenopathy, new low-density areas within the spleen, and multiple subcentimeter scattered pulmonary nodules. One month later, she died. The cause of death was not known.

DISCUSSION

Three main mechanisms of sarcoidosis causing asymmetric peripheral edema have been described. The first is lymphatic obstruction due to peripheral lymphadenopathy. Our patient’s edema illustrated this mechanism and, to our knowledge, is only the sixth case reported to date. Of these cases, four (including ours) were described in black patients, one in an Indian patient, and one in an Asian patient (1–5). This distribution is consistent with findings from a US study that demonstrated that extrathoracic lymph node involvement is more common in black patients than in white patients (6). The location of the obstructing lymph nodes was inguinal in three cases and retroperitoneal in two (1–5). In these cases, systemic steroid treatment resulted in prompt resolution of the lymphadenopathy and associated edema within 2 months.

A second mechanism by which sarcoidosis can cause peripheral edema is by direct infiltration into surrounding tissues. Two cases displaying this mechanism have been reported. One involved a 39-year-old black man (7). He had known sarcoidosis with pulmonary and skin involvement and presented with asymmetric lower-extremity edema. A CT scan revealed “diffuse, infiltrative masses involving the subcutaneous tissues of the right leg” (7). His symptoms abated within 1 month following systemic steroids. A second case involved a 59-year-old woman with cutaneous nodules, bilateral lower-extremity edema, and ulceration (8). Her symptoms improved with prednisolone but recurred when doses were decreased below 15 mg.

A third mechanism is tenosynovitis, producing distal peripheral edema. In one case series, five patients presented with lower-extremity pitting edema localized to the dorsal foot and ankle associated with acute sarcoidosis (9). Magnetic resonance imaging showed extensive tenosynovitis. As with previous cases, all responded quickly to systemic steroid treatment.

Acknowledgments

The authors thank Paul Bannister, MD, from the Department of Pathology at Baylor Medical Center at Garland, for providing histology images.

Levamisole-induced vasculitis

Raghad Abdul-Karim, MD, Caitriona Ryan, MD, Christina Rangel, and Michael Emmett, MD

Levamisole-contaminated cocaine is an increasingly reported cause of a syndrome characterized by vasculitic skin lesions and immunologic abnormalities. With approximately 70% of cocaine in the United States now contaminated with levamisole, the incidence of this syndrome is likely to increase. We report two cases of this syndrome and review its clinical presentation, course, and prognosis.

DESCRIPTION

The first patient, an African American woman, presented with recurrent necrotizing vasculitis of her ears (Figure 1) and was found to have positive serology for cytoplasmic antineutrophil cytoplasmic antibody, human neutrophil elastase antibody, and anticardiolipin antibody. The second patient was an African American woman with widespread necrotizing vasculitis of her ears, nose, cheeks, and about 30% of her body surface area (Figure 2). She also had necrotizing pneumonia. Serologic findings were similar to those of the first case. She did not improve despite maximum supportive management and died. The Table shows the major laboratory and clinical features of the cases.

DISCUSSION

Levamisole-induced vasculitis was first described in the 1970s. This syndrome produces a characteristic clinical presentation of vasculitis in association with a variable pattern of immunologic disturbances. In a case series of five children treated with levamisole for nephrotic syndrome, all five developed necrosis of their ears, with variable involvement of their cheeks and extremities (1). Levamisole was originally marketed as an anthelmintic agent but was also found to have major immunomodulatory properties. It induced interferon synthesis and synergized the effect of steroids and other immunosuppressants. It was used in cancer therapy, to treat various immunological renal diseases, and to treat a number of skin diseases, including Behçet’s disease. However, the drug was withdrawn from the human market in 1999 because of serious side effects including leukopenia, agranulocytosis, and skin vasculitis (2). It is still available as a veterinarian deworming drug.

Relevant to this manuscript, levamisole has also been recognized as an adulterant in illicit cocaine since 2003 (3). A 2009 national survey found that approximately 70% of cocaine in the USA is contaminated with levamisole (2, 3). Levamisole is added to cocaine because it potentiates its stimulant effects by inhibiting both monoamine oxidase and catechol-O-methyltransferase activity, thereby prolonging the action of catecholamines in the neuronal synapse and increasing the reuptake-inhibition

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effect of cocaine. Levamisole metabolites also have a stimulatory effect. Very importantly, levamisole reacts as cocaine in the “bleach test,” a quick, widely utilized street test for cocaine purity. Therefore, it adds bulk to illicit cocaine without reducing the native drug’s apparent purity, as occurs with other bulking agents such as sugar or lidocaine (2). Both snorting and smoking levamisole-contaminated cocaine have been associated with the vasculitic syndrome (4).

Levamisole-induced syndrome has a characteristic presentation (2, 4). The distinctive vasculopathic purpura typically involves the ears, but purpura can also be observed on the nose, cheeks, extremities, and diffusely. Cutaneous lesions tend to be stellate with a bright erythematous border and necrotic center. This lesion usually resolves spontaneously within a few weeks of drug discontinuation and recurs with subsequent contaminated cocaine abuse.

The half-life of levamisole is 5.6 hours, and only 3% to 5% of the drug is found in urine within 48 hours of last use. Leukopenia can occur in 50% to 60% of cases (3) and can first develop after as long as 12 months of continuous use (5). Agranulocytosis has also been reported in patients with cocaine/levamisole abuse (6).

The syndrome has a very interesting spectrum of autoantibody findings. High-titer perinuclear antineutrophil antibodies (p-ANCA) are almost always found (86%–100%), and about 50% of the cases also have cytoplasmic antineutrophil antibodies (c-ANCA) (4–10). However, the specific antigens responsible for generating these positive ANCA fluorescent patterns are not yet clearly defined. Antibodies against proteinase-3 (anti-PR3), the autoantibody most commonly associated with a c-ANCA pattern, are present in about 50% of these patients, while antibodies against myeloperoxidase (anti-MPO), the antibody most often responsible for a p-ANCA pattern, are found in almost every case (3, 10).

In addition, antiphospholipid antibodies and antinuclear antibodies are also often present. The Mayo group has reported another antibody in these patients that is directed against human neutrophil elastase. Anti–human neutrophil elastase (anti-HNE) is also present in most patients with cocaine-induced midline destructive lesions, but not in patients with classic ANCA vasculitis (4, 9). Both PR3 and HNE belong to the same family of serine proteases, and cross-reactivity between these antibodies/antigens may occur. These two cocaine abuse–associated syndromes are distinctly different. Cocaine-induced midline destructive lesions may be caused by the cocaine itself and do not generate the distinctive skin involvement that occurs with the levamisole-related condition (11). Conversely, the levamisole-related vasculitis does not usually cause destructive damage to the nose, sinuses, and palate.

The histology of cutaneous lesions typically shows thrombotic vasculitis or leukocytoclastic vasculitis with or without vascular occlusion (2–4). The natural history of levamisole-induced vasculitis is spontaneous resolution without treatment when the levamisole is withdrawn. Immunologic abnormalities generally resolve within 2 to 14 months of withdrawal of the levamisole (2). However, some severe cases may not improve, as in our second patient, who had a fulminant form of vasculitis.

Table. Characteristics of the two cases of levamisole-induced vasculitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Race</td>
<td>African American</td>
<td>African American</td>
</tr>
<tr>
<td>Urine cocaine screen</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>4.5</td>
<td>13.8</td>
</tr>
<tr>
<td>Serum levamisole</td>
<td>Negative</td>
<td>Not checked</td>
</tr>
<tr>
<td>Antinuclear antibody titer</td>
<td>1:12,560</td>
<td>1:640</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody (indirect immuno-fluorescence)</td>
<td>p-ANCA, 1:2,560</td>
<td>p-ANCA, 1:10,240</td>
</tr>
<tr>
<td>Antibodies against neutrophil cytoplasmic antigens (ELISA capture)</td>
<td>Anti-HNE, positive</td>
<td>Anti-HNE, positive</td>
</tr>
<tr>
<td>Antibodies against neutrophil cytoplasmic antigens (ELISA capture)</td>
<td>Anti-PR3, positive</td>
<td>Anti-PR3, positive</td>
</tr>
<tr>
<td>Antibodies against neutrophil cytoplasmic antigens (ELISA capture)</td>
<td>Anti-MPO, negative</td>
<td>Anti-MPO, positive</td>
</tr>
<tr>
<td>IgM anticardiolipin antibody (normal 0.0–12.4 U/mL)</td>
<td>21.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Skin findings</td>
<td>Markedly tender, black discoloration and necrosis of the helices and anthesises of both ears; a large, necrotic, indurated, inflammatory plaque on her nose; a 5.0-cm-diameter punched-out ulcer on her left lateral shin; an indurated livedoid plaque on her left upper arm; nailfold infarcts</td>
<td>Extensive black discoloration and necrosis of the ears, eyelashes, forehead, and bilateral cheeks; digital necrosis of both hands and feet; rapidly progressive areas of epidermal detachment, necrosis, and bulla formation of the trunk and upper and lower limbs</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>Gangrenous necrosis with acute inflammation and fibrosis</td>
<td>Leukocytoclastic vasculitis with fibrinoid necrosis of the blood vessel walls and sub-epidermal bullae formation</td>
</tr>
<tr>
<td>Treatment</td>
<td>Short course of high-dose prednisone</td>
<td>Mechanical ventilation; steroid tapering induced worsening of her respiratory status and skin lesions</td>
</tr>
<tr>
<td>Outcome</td>
<td>Spontaneous resolution of skin lesions</td>
<td>Deep eschars of the face with extensive destruction of nasal and ear cartilages; death after 60 days in the hospital</td>
</tr>
</tbody>
</table>

ESR indicates erythrocyte sedimentation rate; CRP, C-reactive protein; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; anti-PR3, anti-proteinase 3 antibody; anti-MPO, anti-myeloperoxidase antibody; ELISA, enzyme-linked immunosorbent assay.
and a fatal outcome. Although steroids have been used for treatment of this syndrome, it is unclear if they provide any benefit. The side effects may be harmful, especially since most reported cases had no internal organ involvement (3, 4).

Here we describe a case of a 22-year-old woman who presented with acute liver failure and Kayser-Fleischer rings suggesting the diagnosis of Wilson’s disease.

A 22-year-old woman with no known past medical history presented to an emergency department with a 3-week history of fatigue, decreased appetite, and jaundice. Her initial laboratory workup indicated acute liver injury with a total bilirubin level of 12.1 mg/dL (reference range, 0.2–1.0); alkaline phosphatase of 45 U/L (reference range, 50–136); aspartate aminotransferase of 111 U/L (reference range, 15–37); alanine aminotransferase of 27 U/L (reference range, 12–78); ceruloplasmin of 19 mg/dL (reference range, 20–60); and prothrombin time of 29.11 seconds (reference range, 9.0–12.0).

Additionally, she was found to have concurrent acute kidney injury and a Coombs-negative hemolytic anemia.

The patient underwent a laparoscopic cholecystectomy at an outside hospital that revealed the presence of ascites and a nodular liver with an otherwise normal gallbladder. The patient quickly decompensated into acute liver failure during her postoperative course, and physical examination revealed the presence of Kayser-Fleischer (KF) rings (Figure).

The presence of KF rings and jaundice with abnormal liver function tests, including low ceruloplasmin and alkaline phosphatase, suggested the diagnosis of Wilson’s disease. The patient was transferred to Baylor University Medical Center at Dallas, where she underwent evaluation for orthotopic liver transplantation, which was successfully performed on hospital day 4. Elevated hepatic copper (2145 mcg/g; reference range, 10–35) on dry weight liver biopsy was consistent with the diagnosis of Wilson’s disease. Mutation analysis indicated that the patient was homozygous for the pathogenic mutation 3201 C>A in exon 14, resulting in the amino acid change His1069Gln.

DISCUSSION

Wilson’s disease is an autosomal recessive mutation of the ATP7B gene, whose protein both traffics excess copper into the bile canaliculus for excretion and binds copper to apoceruloplasmin, forming holoceruloplasmin. Oxidative damage ensues when uncomplexed copper begins to accumulate in hepatocytes. Liver injury can present in various forms ranging from asymptomatic abnormal liver function tests to acute and chronic liver failure. With ongoing hepatic damage, uncomplexed copper is released from the liver and deposited in other organs, including the lenticular nucleus of the basal ganglia, resulting in Parkinson-like symptoms; the proximal renal tubule, resulting in Fanconi’s syndrome; and the red blood cells, resulting in a Coombs-negative hemolytic anemia. Other organs affected include the heart, pancreas,

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The eye is uniquely affected, as copper accumulates in Descemet’s membrane of the corneal limbus, resulting in KF rings (Figure), and in the lens, resulting in sunflower cataracts. The observation of the characteristic brown-gold-yellow KF ring at the margin of the cornea and sclera generally requires a slit-lamp examination, but some rings can be seen under normal light. Each of these ocular findings resolves over time following transplant (1, 2).

Ascites with elevated protein content as the presenting sign of constrictive pericardial disease

Betsy Ann George, MD, Gregory dePrisco, MD, James Ford Trotter, MD, Albert Carl Henry III, MD, and Robert Craig Stoler, MD

Two men, one 63 and one 52 years old, presented with ascites. Analysis of the ascitic fluid in both patients revealed a high protein content and an elevated serum-ascites gradient. Various studies showed the cause of the ascites to be constrictive pericardial disease. Total excision of their parietal pericardia relieved their symptoms, decreased their cardiac filling pressures, and increased their cardiac indices. These cases highlight the importance of suspecting pericardial constriction as an etiology for high-protein-count ascites.

We describe two patients who presented with high-protein-count ascites as the initial sign of constrictive pericardial disease. These cases highlight the importance of early recognition of a cardiac etiology for ascites, as prompt treatment with a total pericardiectomy significantly improved the patients’ quality of life.

DESCRIPTION OF CASES

Pertinent clinical features in each of the two patients prior to surgery are summarized in Table 1. The two patients had evidence of ascites for 6 and 60 months, respectively. Both received multiple therapeutic paracenteses and escalating doses of diuretics for refractory ascites. The first patient had no attributable hepatic cause for his ascites, but the second had a history of heavy alcohol use prior to its cessation at age 47. Despite receiving a Denver shunt, the second patient continued to have intractable ascites so was referred for possible transjugular intrahepatic portosystemic shunt and liver transplantation. Both patients had no previous cardiothoracic surgery, pericarditis, radiation treatment, or collagen vascular diseases. Neither patient had cardiopulmonary symptoms. Physical examination in these patients revealed normal blood pressure and heart rate, distended jugular veins, clear lungs, and no precordial murmurs or abnormal heart sounds. Their abdomens had clear evidence of ascites. Laboratory tests in the first patient were normal. The second patient had renal insufficiency and mildly elevated bilirubin. Analysis of their ascitic fluid revealed an elevated total protein content and a high serum-ascites albumin gradient.

The patients were then referred to cardiology for evaluation of a cardiac cause of the ascites. Transthoracic echocardiograms in both patients revealed a bright, thickened parietal pericardium, “septal bounce,” exaggerated respiratory variation across the tricuspid and mitral valves, a dilated inferior vena cava, expiratory hepatic vein diastolic flow reversal, normal tissue Doppler velocities, and no pericardial effusion (Figure 1). Cardiac catheterization pressure waveforms in each showed equalization of the elevated diastolic pressures and discordance of right and left ventricular systolic pressures (Figure 2). Cardiac magnetic resonance imaging scans disclosed marked thickening of the parietal pericardium (Figure 3).

Both patients underwent total excision of their parietal pericardia with resolution of their ascites and elevated cardiac filling pressures. Hemodynamics before and after pericardiectomy are shown in Table 2. The parietal pericardium in each was severely thickened by dense fibrous tissue (Figure 4).

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DISCUSSION

Constrictive pericardial disease is a rare cause of recurrent ascites. Both of our patients had high-protein-count ascites with an elevated serum-ascites albumin gradient, a finding well described in previous reports of constrictive pericarditis (1–3). A serum-ascites albumin gradient ≥1.1 g/dL and an ascites fluid total protein <2.5 g/dL (1).

A common finding in our cases was jugular venous distention, a sign not usually seen in patients with hepatic cirrhosis. Previous case series indicate that about 80% of patients with constrictive pericardial disease present with elevated jugular venous pressures. Neither of our patients had dyspnea or orthopnea. As many as half of the patients who undergo a pericardiectomy lack cardiopulmonary symptoms (4). Therefore, a high index of suspicion is required to diagnose this entity, especially in patients with elevated-protein-count ascites, jugular venous distention, and no cardiopulmonary symptoms.

The echocardiograms in our two patients were quite specific for constrictive pericardial disease. However, a transthoracic echocardiogram typically has low sensitivity in detection of this entity, and a constrictive pericardium may easily be overlooked. Thus, a physician should not be reassured with a negative echocardiogram if there is a high concern for this disease. Constrictive disease differs from restrictive disease by having normal tissue Doppler velocities on echocardiogram and discordance of right and left ventricular systolic pressures on cardiac catheterization.

Constrictive pericardial disease can lead to significant morbidity. Both patients suffered from the sequelae of ascites with repeated therapeutic paracenteses and escalating doses of diuretics before the proper diagnosis was made.

Pericardiectomy is the treatment of choice for patients with symptomatic chronic constrictive pericardial disease. The early hospital mortality is about 7% (5). The most common cause of death in the perioperative period is low-output heart failure (6). The long-term survival curves after pericardiectomy differ according to the etiology of the constrictive pericarditis and the type of surgery. Idiopathic/viral and postsurgical constrictive pericardial disease have the best 10-year survival rates after pericardiectomy of about 67% and 56%, respectively, while postradiation pericarditis has the worst at 11% (5). Also, total pericardiectomy has a better survival rate than partial pericardiectomy (7).

Acknowledgments

We gratefully acknowledge William Clifford Roberts, MD, for editorial assistance with the report and Jong Mi Ko, BA, for the photography of the surgical specimens.


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Table 2. Hemodynamics before and after pericardiectomy

<table>
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<tr>
<th>Measurement</th>
<th>Case 1</th>
<th>Case 2</th>
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<td>Mean right atrial pressure (mm Hg)</td>
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<td>Right ventricular pressure (mm Hg)</td>
<td>35/19</td>
<td>28/15</td>
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<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
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<td>41/19</td>
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<td>Central venous pressure (mm Hg)</td>
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<td>Cardiac index (L/min/m²)</td>
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*Intraoperatively.*
Described herein are two brothers, both with a congenitally bicuspid aortic valve—one of which was stenotic and one of which functioned normally—and one with associated aortic isthmic coarctation. Summarized also are previously reported families with more than one member with a congenitally bicuspid aortic valve.

The occurrence of a congenitally bicuspid aortic valve (BAV) in more than one family member has been described in several published reports (1–7). Of the 47 family members in whom the BAV was confirmed at the time of aortic valve replacement or at necropsy, the valve was stenotic in at least 27 of them, and none had associated aortic isthmic coarctation. In this report we describe two brothers with a congenitally BAV—stenotic in one and functionally normal in the other—and aortic coarctation in one of them (Figure).

**PATIENT DESCRIPTIONS**

**Case 1**

A 16-year-old white boy had been well until about a month before hospitalization when he had an episode of severe dizziness followed by progressive breathlessness. He was hospitalized for “pneumonia” but never had any microorganisms cultured from sputum. When the chest radiograph cleared, cardiac catheterization disclosed the following pressures in mm Hg: pulmonary artery wedge a wave 34, v 32, and mean 32; pulmonary trunk 55/38; right ventricle 57/29; left ventricle 133/36 and aorta 77/66, yielding a peak systolic pressure gradient of 56 mm Hg; and mean systolic gradient 39 mm Hg. The calculated aortic valve area was 0.6 cm$^2$, and the cardiac output was 4.6 L/min/m$^2$. A cardiac operation was performed, and he died 2 weeks later.

**Case 2**

This 21-year-old white man had been well until he was found dead in the bathroom at home, shortly after taking an amphetamine. He apparently never had evidence of cardiac dysfunction. Necropsy disclosed the pericardial sac to be filled with blood (550 mL). The ascending aorta was a 5-cm long tear without dissection with a through-and-through perforation.

Figure 1. Diagram showing the cardiovascular features of each of the two patients. Both had congenitally bicuspid aortic valves. In case 1, the valve was severely stenotic, and there was no coarctation of the aorta. In case 2, the valve functioned normally, and there was a severe coarctation of the aorta. A indicates anterior aortic valve cusp; I, innominate artery; L, left; LCC, left common carotid; LMCA, left main coronary artery; LS, left subclavian; P, posterior aortic valve cusp; R, right aortic valve cusp; RCA, right coronary artery.

The ascending aorta was quite dilated. At the aortic isthmus (that portion of aorta just distal to the origin of the left subclavian artery), a severe coarctation was found. The aortic valve was congenitally bicuspid but the cusps were very pliable and noncalcified. Thus, the aortic valve function was considered to have been normal. A fibrous, nonstenotic ring was located in the left ventricular outflow tract about 1 cm below the base of the aortic valve cusps. The mitral valve was normal. The left main coronary artery ostium was located about 1 cm cephalad to the sinotubular junction.

From the Baylor Heart and Vascular Institute (Zafar, Roberts) and the Departments of Internal Medicine (Division of Cardiology) and Pathology (Roberts), Baylor University Medical Center at Dallas.

**Corresponding author:** William C. Roberts, MD, Baylor Heart and Vascular Institute, 621 North Hall Street, Dallas, TX 75226 (e-mail: wc.roberts@BaylorHealth.edu).
Table. Previously published reports of patients with a familial congenitally bicuspid aortic valve with aortic valve replacement or necropsy

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<th>Year of publication</th>
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<th>Patient age (yrs) at death</th>
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DISCUSSION

The Table lists previously published reports (1–7) describing a BAV in more than one family member with study of the valve at either aortic valve replacement or at necropsy. In the 18 families, 47 members had a congenitally BAV: 11 families had 2 members, 5 families had 3 members, and 2 families had 5 members with a BAV. Of the involved family members, 3 were fathers, 8 were mothers, 20 were sons, 8 were daughters, and the remaining were siblings or other relatives. Of the 47 family members, 30 (64%) were male and 17 (36%) were female. Twenty-three family members had aortic valve replacement; their ages ranged from 16 to 93 years (mean 47). Sixteen family members had died, 9 after aortic valve replacement. In the 18 families, all with BAVs were male in 3 families, all were female in 1 family, and both males and females were represented in 14 families.

In addition to the studies where the bicuspid structure of the aortic valve was confirmed morphologically, an echocardiographic study (8) described 11 families in whom 28 members had a BAV, 3 (11%) of whom had associated coarctation of the aorta.

A 21-year-old woman was transferred from another hospital in her 23rd week of pregnancy. She had had an audible precordial murmur the day of her birth and had had pneumonia three times in the first few years of life. Otherwise, she was asymptomatic during childhood and adolescence. Aside from being small (4’11” tall and 85 lbs before becoming pregnant), she had developed normally. When she was transferred, she was asymptomatic and on no medication.

Pertinent physical findings were a regular pulse at 96 beats/min; a blood pressure of 116/60 mm Hg; normal neck veins; brisk, full, symmetrical arterial pulses in the arms and legs with no radial-femoral delay; a loud and palpable second heart sound along the upper and mid left sternal border; and a small apical impulse just outside the left mid-clavicular line. A harsh, grade 4/6, systolic ejection murmur, heard over the entire chest and back and in the neck, was loudest at the cardiac base and of equal intensity on the right and left sides. A decrescendo diastolic murmur was maximal in the third left intercostal space. There was no gallop, ejection click, cyanosis, or clubbing.

The admission electrocardiogram showed normal sinus rhythm, left axis deviation of the QRS complex, and no septal Q waves in leads I, aVL, V5, or V6, but Q waves were present in leads II, III, aVF, and V1 (Figure 1). The history, physical examination, chest radiograph (Figure 2), and electrocardiogram provided some, albeit incomplete, insight into the patient’s congenital cardiac malformations and the consequent pathophysiology. A systolic murmur heard the day from the Sections of Cardiology, Departments of Medicine, Louisiana State University Health Sciences Center and the Interim Louisiana State University Public Hospital, New Orleans.

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great arteries functions as long and as well as a morphologic left patient with isolated congenitally corrected transposition of the great arteries, i.e., the systemic ventricle, in a (2). Such patients have lived into their 70s (3). Whether the through the heart is normal if there are no other malformations rects” the atrioventricular discordance, and the path of the blood valve into the aorta. Thus, ventriculoarterial discordance “cor-
rects” the atrioventricular discordance, and the path of the blood through the heart is normal if there are no other malformations (2). Such patients have lived into their 70s (3). Whether the morphologic right ventricle, i.e., the systemic ventricle, in a patient with isolated congenitally corrected transposition of the great arteries functions as long and as well as a morphologic left ventricle does in a normal person has been affirmed by some experts (4) and denied by others (5). The vast majority of patients with congenitally corrected transposition of the great arteries, however, have associated cardiac malformations. Three of these occur frequently enough to be considered part of the anomaly: ventricular septal defect in approximately two thirds of patients (2); left ventricular (pulmonary ventricular) outflow tract obstruction, which can be valvular and/or subvalvular, in one half (1); and anatomic abnormalities of the tricuspid (systemic atrioventricular) valve in 90%, many of which are not clinically significant and the most common of which is Ebstein’s anomaly (2). Other malformations seen in patients with congenitally corrected transposition of the great arteries include atrial septal defect; subaortic obstruction, which is often associated with coarctation of the aorta; aortic valve atresia with hypoplasia of the morphologic right ventricle; and pulmonary atresia with hypoplasia of the morphologic left ventricle.

Because of malalignment of the atrial septum with the inlet ventricular septum, the atrioventricular conduction system is abnormal (2), and up to 75% of patients with congenitally corrected transposition of the great arteries eventually have atrioventricular block ranging from first degree to third degree (1). Wolff-Parkinson-White type ventricular preexcitation may occur, as it does in other persons with Ebstein’s anomaly of the tricuspid valve, and some, but not all, supraventricular arrhythmias in congenitally corrected transposition of the great arteries are associated with a left-sided accessory pathway (1). Because the morphologic left ventricle and the left bundle branch lie to the right of the morphologic right ventricle in congenitally corrected transposition of the great arteries, initial septal depolarization is from right to left and often inferosuperiorly as well, as seen in Figure 1.

As is often the case, especially with congenital heart disease, the echocardiogram and Doppler examination added important diagnostic information to that obtained by history, physical, chest radiograph, and electrocardiogram. In this patient, echo-Doppler confirmed congenitally corrected transposition of the great arteries, a nonrestrictive ventricular septal defect, and pulmonic valvar and subvalvar stenosis with a 75 mm Hg peak systolic pressure gradient between the pulmonary ventricle (morphologic left ventricle) and the pulmonary artery. Because her systemic arterial systolic pressure at the time was 105 mm Hg and the ventricular septal defect was nonrestrictive, her pulmonary arterial systolic pressure was approximately 30 mm Hg. The echo-Doppler also revealed a restrictive patent ductus arteriosus, which explained the full, brisk pulses and the decrescendo diastolic murmur. The systolic component of the continuous murmur of the patent ductus was obscured by the louder murmur of pulmonic stenosis. Both ventricles had normal systolic function, and both atrioventricular valves were completely competent.

The patient stayed on the obstetrical service throughout the remainder of her pregnancy. She entered active labor at 34 weeks of gestation and under epidural anesthesia delivered a 2425 g daughter with Apgar scores of 8 and 9. Bilateral tubal ligation
was then performed. Mother and daughter were doing well at discharge on postoperative day 4.

Two questions remain. First, why, with such a complex congenital cardiac malformation, was this woman asymptomatic after the first years of life and able to have a successful pregnancy? It was because the severe malformations were balanced in such a way that the circulatory system was quite adequate. Pulmonic stenosis prevented early severe heart failure or subsequent Eisenmenger reaction from the nonrestrictive ventricular septal defect. At the same time, there was sufficient blood flow through the pulmonic valve and the restrictive ductus to prevent cyanosis and allow normal activity and a successful pregnancy. Thus far she has avoided two common accompaniments of congenitally corrected transposition of the great arteries, i.e., tricuspid (systemic atrioventricular) valvular regurgitation and atrioventricular block.

Second, should the patient undergo operative repair? An article from the Mayo Clinic points out that most persons with congenitally corrected transposition of the great arteries eventually undergo cardiac surgery and that for many, the operation comes too late for optimal results (6). Those statements are difficult to refute. On the other hand, in this patient, so-called complete repair would require extensive complicated surgery, which is difficult to recommend to an asymptomatic patient. In addition, few institutions have a Gordon Danielson, one of the paper’s authors and one of the foremost congenital cardiac surgeons of his or any other day. Most importantly, the patient prefers not to undergo an operation as long as she feels well.

Persistent giant U wave inversion with anoxic brain injury

Matthew N. Peters, MD, Morgan J. Katz, MD, Lucius A. Howell, MD, John C. Moscona, MD, Thomas A. Turnage, MD, and Patrice Delafontaine, MD

CASE PRESENTATION

A 29-year-old Caucasian man with previous anoxic brain injury presented to our facility with a 3-day history of nausea and vomiting. According to his mother, he had overdosed on alprazolam in an apparent suicide at the age of 17 and was in a coma for several days. During the subsequent year, he had daily seizures and was started on levetiracetam, eventually becoming seizure free. Current medications (all of which were administered via percutaneous endoscopic gastrostomy tube) included twice-daily levetiracetam, daily 20 mg citalopram, and daily 40 mg esomeprazole. Initial vital signs were all within normal limits. His blood pressure was 100/70 mm Hg. He was nonverbal. Complete blood count, complete metabolic profile, and thyroid studies were within normal limits. A chest radiograph revealed no evidence of acute cardiopulmonary processes, and an abdominal radiograph revealed a nonobstructive bowel gas pattern. An initial electrocardiogram (ECG) demonstrated deep, symmetric T wave inversions in the inferior and lateral leads followed by large negative deflections, of varying amplitude, most prominent in the lateral precordial leads (Figure). Three sets of cardiac troponins separated by 6 hours each were <0.05 g/dL. A transthoracic echocardiogram showed a normal left ventricular ejection fraction, normal intracardiac chamber sizes,

Various electrocardiographic changes have been reported in the setting of acute neurological events, among them large, upright U waves. In contrast, the occurrence of inverted U waves is strongly suggestive of cardiovascular disease, most commonly hypertension, coronary artery disease, or valvular abnormalities. Presented herein is the case of a 29-year-old man with previous anoxic brain injury (but without apparent cardiovascular disease) whose electrocardiogram demonstrated persistent giant inverted U waves.

Figure. Electrocardiogram revealing deeply inverted U waves, most notable in the lateral precordial leads, V3–V5.
and no regional wall motion abnormalities. Repeat ECGs over the subsequent 36 hours revealed a similar pattern. An ECG when he was 26 years old (9 years following the anoxic brain injury) appeared almost identical. After 24 hours of intravenous fluid administration and cessation of tube feedings, the patient demonstrated marked clinical improvement and 12 hours later was discharged.

**DISCUSSION**

The T wave and U wave are thought to represent the terminal component of ventricular repolarization. While the mechanism of U wave genesis remains uncertain, the clinical specificity of a negative U wave (defined as any discrete negative deflection >0.05 mV within the T-P segment) for heart disease is high (1). Occurring in only 1% of all hospital ECGs, the presence of an inverted U wave suggests the presence of coronary artery disease, valvular heart disease, or hypertension (2). Historically, the correlation of negative U waves with acute myocardial infarction has been felt to be important, given the ability of negative U waves to precede typical ECG changes of acute myocardial infarction by several hours (1). When combined with the presence of T wave inversion, a negative U wave has specificity for coronary artery disease as high as 88% (1). In the presence of myocardial ischemia, U wave vectors are typically directed away from the akinetic or dyskinetic myocardial segment (1). It is difficult to assess whether or not U wave vectors would have similar orientation in the presence of ischemia without wall motion abnormalities because these two entities usually occur in tandem and subsequent revascularization typically leads to the complete disappearance of inverted U waves (1). While association with ischemic heart disease has been regarded as the most clinically important cause of negative U waves, the most common cause (according to a 1982 study of 488 patients with negative U waves) has been found to be hypertension (39.5%), followed by coronary artery disease (33.2%) and valvular heart disease (15.4%). Other less common causes of negative U waves include congenital heart disease (2.5%), hyperthyroidism (1.4%), primary cardiomyopathy (0.8%), and in 7.2%, no manifestations of heart disease (2).

Association between ECG changes and acute neurological events is well known, with causes including subarachnoid hemorrhage, subdural hematoma, neoplasm, infection, epilepsy, and cerebrovascular accident (3). Associated ECG changes include prolonged QT interval, deep, symmetrical T wave inversions, pathologic Q waves, and tall, upright U waves. Cardiac insult related to an acute neurological event is thought to be related to alterations in the autonomic nervous system. Specifically, release of norepinephrine from sympathetic nerve terminals causes widespread opening of calcium channels within the myocardi um and subsequent calcium ion influx (4). Consequently, ECG changes do not typically persist past the acute setting.

We believe that the occurrence of persistent giant negative U waves in the absence of apparent cardiac disease is a unique clinical finding and likely somehow related to our patient’s previous anoxic brain injury. The possibility of artifact was also considered but deemed unlikely given the fact that multiple ECGs obtained during the patient’s hospitalization as well as an ECG obtained from 3 years prior appeared nearly identical. The actual mechanism of these findings is uncertain. His current medications have not been reported to produce any such abnormalities. Coronary artery disease cannot be completely excluded as an etiology (since coronary arteriography was not performed), but we think it very unlikely in a 29-year-old person without other evidence of heart disease. It is possible that the changes may be related to ongoing autonomic nervous system dysfunction, especially in light of his hypotension, although this explanation is purely speculative at the present time.

The milk-alkali syndrome was a common cause of hypercalcemia, metabolic alkalosis, and renal failure in the early 20th century. It was caused by the ingestion of large quantities of milk and absorbable alkali to treat peptic ulcer disease. The syndrome virtually vanished after introduction of histamine-2 blockers and proton pump inhibitors. More recently, a similar condition called the calcium-alkali syndrome has emerged as a common cause of hypercalcemia and alkalosis. It is usually caused by the ingestion of large amounts of calcium carbonate salts to prevent or treat osteoporosis and dyspepsia. We describe a 78-year-old woman who presented with weakness, malaise, and confusion. She was found to have hypercalcemia, acute renal failure, and metabolic alkalosis. Upon further questioning, she reported use of large amounts of calcium carbonate tablets to treat recent heartburn symptoms. Calcium supplements were discontinued, and she was treated with intravenous normal saline. After 5 days, the calcium and bicarbonate levels normalized and renal function returned to baseline. In this article, we review the pathogenesis of the calcium-alkali syndrome as well as the differences between the traditional and modern syndromes.

CASE REPORT

A 78-year-old Caucasian woman presented to the emergency department after falling and injuring her right arm. She complained of general malaise, weakness, and dizziness for several days. She denied fevers, chills, weight changes, bone pains, dyspnea, chest pains, palpitations, or urinary symptoms. Her past medical history was significant for chronic obstructive pulmonary disease, hypertension, atrial fibrillation, and chronic kidney disease with a baseline creatinine of 1.3 mg/dL. Her regular medications included verapamil 180 mg twice daily, ramipril 5 mg daily, warfarin 5 mg daily, ibandronate 2.5 mg daily, and calcium with vitamin D over-the-counter supplements. The patient lived in an independent living facility. She had a previous 15 pack-year history of tobacco use but quit 17 years ago. She denied any alcohol or recreational drug use.

On initial examination, her blood pressure was 215/90 mm Hg, pulse 100 beats/minute, respiratory rate 20 breaths/minute, and temperature 97°F. She was alert and oriented to person, place, and time; however, she was irritable, drowsy, and slow to answer questions. She had dry mucous membranes and poor skin turgor. Her chest was clear to auscultation bilaterally. On precordial examination, no murmurs were heard. Her abdomen was soft, nontender, and nondistended. Her extremities had full range of motion and normal strength.

Initial laboratory results included hemoglobin, 16.2 g/dL; hematocrit, 48.2%; sodium, 138 mEq/L; potassium, 4.2 mEq/L; chloride, 96 mEq/L; bicarbonate, 32 mEq/L; blood urea nitrogen, 35 mg/dL; creatinine, 2.9 mg/dL; calcium, 14.4 mg/dL; albumin, 4.0 g/dL; ionized calcium, 1.52 mmol/L; phosphorus, 5.2 mg/dL; intact parathyroid hormone, 21.0 pg/dL; thyroid-stimulating hormone, 2.66 microIU/L; free thyroxine, 1.26 ng/dL; and 25-hydroxy-vitamin D, 11.0 pg/dL. Serum and urine protein electrophoreses did not reveal any monoclonal proteins.

Her chest radiograph was normal. Renal sonography showed bilateral increased echogenicity and cortical thinning, consistent with chronic renal disease.

Upon further questioning, the patient reported that she had ingested about one bottle (>50 tablets) of calcium carbonate tablets (500 mg) over the previous 3 days to treat heartburn.

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symptoms. During this time she also continued taking her regular calcium and vitamin D supplements. The diagnosis of calcium-alkali syndrome was made.

Intravenous normal saline was administered, and all calcium and vitamin D supplements were discontinued. On day 2, the patient was more lucid, awake, and able to readily communicate. Calcium and creatinine levels dropped to 12.8 mg/dL and 2.7 mg/dL, respectively. On day 5, the calcium and bicarbonate levels were normal at 9.6 mg/dL and 27 mEq/L. The creatinine and blood urea nitrogen were at her baseline values of 1.3 mg/dL and 16 mg/dL, respectively.

The patient was educated on the proper use and dosing of all over-the-counter medications, including calcium and vitamin D supplements. She was discharged home on the fifth day of hospitalization.

**DISCUSSION**

The calcium-alkali syndrome is the third leading cause of hypercalcemia in hospitalized patients after primary hyperparathyroidism and malignant neoplasms (4). The current version of this syndrome has several biochemical and epidemiological differences from the traditional milk-alkali syndromes described in the early to mid 1900s. The historic conditions were more common in middle-aged men with peptic ulcer disease and were due to the hourly ingestion of sodium bicarbonate, magnesium carbonate, and bismuth subcarbonate ("Sippy Powder") together with cream and milk. In 1949, Burnett et al described a chronic, more persistent variant of this disorder (5). The introduction of histamine-2 receptor blockers (in 1976) and proton pump inhibitors (in 1989) to block acid secretion, as well as treatments directed at eradicating *Helicobacter pylori*, virtually eliminated the classic acute and chronic forms of the milk-alkali syndrome. Over the last several decades, the "modern" version was recognized. This form more commonly affects postmenopausal women who ingest large amounts of calcium supplements, sometimes together with vitamin D and occasionally with thiazide diuretics to prevent or treat osteoporosis (6–8). It has also occurred in transplant patients taking high doses of calcium carbonate to prevent osteoporosis related to chronic steroid use (6). The use of calcium-containing antacids to treat dyspepsia also may occur, as was the case in the current report. It has been suggested that the modern syndrome be called the calcium-alkali syndrome because it is due to ingestion of soluble calcium salts instead of milk, cream, and the other alkali sources listed above (3).

The calcium-alkali syndrome, similar to the traditional version, is characterized by hypercalcemia, metabolic alkalosis, and renal injury. However, serum phosphorus levels were usually high in the historic forms due to the high phosphorus load from cream and milk and the development of acute and chronic renal injury. The current calcium-alkali syndrome more typically presents with a normal or even low serum phosphorus concentration resulting from the dietary phosphate-binding properties of calcium carbonate (6–8).

Although serum vitamin D is usually suppressed in patients with calcium-alkali syndrome, it may be normal or even increased if vitamin D supplements have contributed to the disorder (8). Serum parathyroid hormone levels, which would be expected to be low, are sometimes normal. This may be due to renal insufficiency or related to a rapid fall in serum calcium soon after initiation of aggressive intravenous saline infusion (7).

The pathogenesis of calcium-alkali syndrome involves the interplay of multiple organ systems, including bone, intestines, and the kidney. The ingestion of large amounts of calcium-containing compounds increases intestinal absorption of calcium and causes hypercalcemia. Hypercalcemia will constrict the renal arterioles, reduce the glomerular filtration rate, and decrease renal calcium excretion (9). Calcium-sensing receptors (CaSRs) are located in many tissues throughout the body, including the renal tubules, the intestines, and the parathyroid and thyroid glands. When high calcium levels activate the CaSRs in the thick ascending loop of Henle, sodium chloride reabsorption at this site is inhibited, causing diuresis and increasing renal calcium excretion (i.e., a loop diuretic-like effect). This effect also contributes to volume depletion and metabolic alkalosis (10). CaSRs are also present on the luminal membrane of the distal convoluted tubules, and activation of these receptors (by high renal tubule calcium concentrations) increases calcium reabsorption via TRPV5 channels (10). In addition, CaSRs are found on the luminal membranes of the collecting duct cells, and their activation reduces expression of aquaporin 2 water channels. This reduces renal tubule water reabsorption and causes the excretion of dilute urine (10). The net effect is a salt and water diuresis with variable impact on renal calcium excretion. Metabolic alkalosis helps to perpetuate this cycle by increasing the affinity of the CaSRs to calcium, which enhances the natriuresis. An alkaline pH also stimulates the activity of an important calcium selective receptor called the transient receptor potential vanilloid member 5 (TRPV5); this enhances calcium reabsorption and leads to worsening hypercalcemia (10, 11). To the extent hypercalcemia suppresses serum parathyroid hormone, renal bicarbonate reabsorption is promoted. Additionally, hypercalcemia may generate nausea and vomiting, which worsens the volume depletion and alkalosis (9).

The diagnosis of calcium-alkali syndrome should be considered when a patient presents with acute renal injury, metabolic alkalosis, hypercalcemia, and a history of excessive calcium (+ vitamin D) intake. Generally, the first and most important treatment for calcium-alkali syndrome is extracellular volume expansion with intravenous saline. This will helpfully improve renal function and increase renal calcium and bicarbonate excretion. It is also essential to identify all calcium salt and vitamin D–containing medications that the patient is taking and to provide education about appropriate dosing. It may be difficult to determine the appropriate dose of calcium salts for a given patient. The syndrome has been reported after ingestion of doses as low as 1 g of elemental calcium daily (11). However, most reported cases of the syndrome document ingestion of at least 4 g of elemental calcium per day. Although a daily intake of 2 g of calcium is considered safe for the general population, smaller doses of 1.2 to 1.5 g daily should be used when patients...
have risk factors that increase their likelihood of developing the calcium-alkali syndrome (3, 8, 9). For example, the elderly and patients with chronic kidney disease are more susceptible because they will have a lower glomerular filtration rate and decreased calcium clearance (9, 11). Additionally, the skeleton of elderly subjects does not buffer calcium loads as well as that of younger subjects (9).

Thiazide diuretic use may also predispose to the development of this condition by enhancing renal tubule calcium absorption and by promoting volume depletion and alkalosis. Furthermore, any medications that reduce glomerular filtration rate, such as nonsteroidal antiinflammatory drugs and angiotensin-converting enzyme inhibitors, can contribute to the development of the syndrome (9).

Since the introduction of recombinant tissue plasminogen activator and thrombolysis, acute ischemic stroke has become a treatable disorder if the patient presents within the 4.5-hour time window. Typically, sporadic stroke is caused by atherosclerotic disease involving large or small cerebral arteries or secondary to a cardioembolic source often associated with atrial fibrillation. In the over-65-year age group, more rare causes of stroke, such as antiphospholipid syndromes, are unusual; such stroke etiologies are mostly seen in a younger age group (<55 years). Here we describe acute ischemic stroke in three patients >65 years with hepatitis C-associated antiphospholipid antibodies. We suggest that screening for antiphospholipid disorders in the older patient might be warranted, with potential implications for therapeutic management and secondary stroke prevention.

The risk factors for ischemic stroke have been well categorized by major epidemiological studies, such as the Framingham population-based study established in the 1950s. Such epidemiological studies particularly highlight modifiable risk factors of ischemic stroke such as hypertension, diabetes mellitus, smoking, alcohol usage, and dyslipidemia. The contribution of other risk factors for ischemic stroke, such as hypercoagulable states, is typically found in persons <55 years old (1). The typical antiphospholipid patient with acute ischemic stroke is a young woman of childbearing age with recurrent miscarriages (2). The etiology of stroke is customarily defined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, with the presumption that the main attributable stroke risk factors are derived in the general stroke population from the presence of atherosclerotic vascular disease (3). The occurrence of other modifiable risk factors in the multifactorial etiology of acute ischemic stroke is an area of active study. In this report, we present three patients >65 years where we found an association between hepatitis C and the occurrence of antiphospholipid antibodies more typically found in younger patients.

CASE REPORTS

In all patients, coagulation screens were performed, including factor 8, homocysteine, antiphospholipid, factor V Leiden, antithrombin III, Russell viper venom assay, and protein C and S. Only the antiphospholipid screen was found to be abnormal in our patients. The Table summarizes patient demographic data and results of the antiphospholipid screens.

Case 1

Six months prior to his third hospital admission, a 72-year-old right-handed African American man presented with a past medical history of hyperlipidemia and a 2-day history of left leg weakness, dizziness, and left-sided facial numbness with a National Institutes of Health Stroke Scale (NIHSS) score of 3. Evaluation for acute stroke with diffusion-weighted magnetic resonance imaging (MRI) demonstrated a subacute lesion in the right posterior internal capsule. The extended symptom time course precluded use of recombinant tissue plasminogen activator (rt-PA) or another neurovascular intervention. The patient was admitted to address secondary stroke prevention and was found to have a cholesterol of 142 mg/dL; high-density lipoprotein cholesterol of 9 mg/dL; low-density lipoprotein cholesterol of 71 mg/dL; triglycerides of 639 mg/dL; cardiac ejection fraction of ~60%; regular cardiac rhythm; and no persistent foramen ovale or pulmonary hypertension. In addition, blood cultures showed no growth, and cerebral computed tomographic angiography showed minimal atherosclerotic disease in the carotid bulbs with a hypoplastic left vertebral artery. A diagnosis of small vessel stroke was made and the patient was encouraged to be more compliant with his hypertension regime and adopt a heart and stroke–healthy diet together with smoking cessation. Secondary prevention therapy included lisinopril, aspirin, and atorvastatin. An albumin-immunoglobulin protein gap was noted, and the patient was subsequently screened and diagnosed with hepatitis C; he was referred to gastroenterology for further evaluation.

Approximately 5 months later, the patient presented with sudden onset of right facial numbness, slurred speech, and right
arm and leg weakness. These symptoms were confirmed on physical examination. Presentation to the emergency room was outside the 4.5-hour window, and thrombolysis with rt-PA was not administered. Diffusion-weighted MRI was positive for a diffusion lesion in the right parietal area. The patient's final admission was due to statin-induced rhabdomyolysis and an associated pancreatitis. During this admission, the patient was noted to be in atrial fibrillation, his stroke was presumed to have a cardioembolic etiology. A diffusion-weighted MRI after administration of rt-PA showed a small ischemic area in the right posterior parietal cortical area. The patient was discharged on warfarin with a therapeutic INR goal of 2 to 3.

Over the next 6 months, the patient's warfarin regime was difficult to maintain within goal despite patient adherence. The patient then presented with a further acute ischemic stroke episode with increased left-sided weakness and problems with gait and balance over a 3- to 4-day period. MRI demonstrated a new lesion in the left cerebellar hemisphere, together with a lesion in the right parieto-occipital region and a further lesion on the left frontal area. The patient's INR at the time of presentation was 1.7, and a diagnosis of cardioembolic stroke secondary to chronic atrial fibrillation was again made. The patient's warfarin regime was discontinued, and he was started on dabigatran.

Approximately 2 months after this admission, the patient presented with a generalized tonic-clonic seizure, and epilepsy secondary to ischemic stroke structural damage was diagnosed. The patient was started on antiepileptic drugs and at that time was also noted to have an albumin-immunoglobulin protein gap. Screens for hepatitis and HIV were performed with the patient's consent. The hepatitis C screen returned positive, and a full gastroenterology workup was performed. As part of an extended workup for etiological factors associated with the patient's stroke, antiphospholipid screening was performed. Antiphosphatidylcholine IgG returned elevated at 48. The patient was continued on dabigatran, with the introduction of aspirin 81 mg daily as part of his secondary stroke prevention regime.

**Case 3**

A 65-year-old right-handed Caucasian man with a history of hypertension, dyslipidemia, posttraumatic stress disorder, and hepatitis C contracted during service in Vietnam was admitted with significant left-sided weakness affecting the face, arm, and leg. The patient initially presented at an out-of-state hospital and was not treated with rt-PA. Computed tomography and MRI showed ischemic lesions in the right parietal area. The patient underwent angiographic evaluation and a stent placement in April 2013

**Hepatitis C and recurrent treatment-resistant acute ischemic stroke**

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**Table 1. Patient demographics and antiphospholipid screen in the three described male patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>treated 147/74</td>
<td>treated 140/90</td>
<td>189/100</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>3</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>142</td>
<td>141</td>
<td>146</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>71</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>9</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>639</td>
<td>57</td>
<td>219</td>
</tr>
<tr>
<td>Smoker</td>
<td>1–3 packs/day</td>
<td>1–2 packs/day</td>
<td>N/A</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>&lt;4.5</td>
<td>&lt;3.5</td>
<td>10.7</td>
</tr>
<tr>
<td>IgM anticardiolipin antibody</td>
<td>13</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>IgG anticardiolipin antibody</td>
<td>21</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>IgA anticardiolipin antibody</td>
<td>31</td>
<td>10</td>
<td>&lt;9</td>
</tr>
<tr>
<td>IgM β-2 glycoprotein (GPI IgM units)</td>
<td>&lt;9</td>
<td>&lt;9</td>
<td>9</td>
</tr>
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<td>IgA β-2 glycoprotein (GPI IgA units)</td>
<td>18</td>
<td>&lt;9</td>
<td>10</td>
</tr>
<tr>
<td>IgM phosphatidylcholine (0–25 MPS IgM)*</td>
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<td>6</td>
<td>23</td>
</tr>
<tr>
<td>IgG phosphatidylcholine (0–11 GPS IgG)*</td>
<td>7</td>
<td>48</td>
<td>24</td>
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<tr>
<td>IgA phosphatidylcholine (0–20 APS IgA)*</td>
<td>21</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

*Units indicate the value showing absence (versus low, moderate, or high positivity).

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.
the right M1 branch of the middle cerebral artery for a critical large vessel stenosis. The stroke was believed to be caused by large vessel disease, and the patient was continued on aspirin 325 mg and clopidogrel 75 mg once daily for secondary stroke prevention. The patient was found to have elevated anticardiolipin antibody at IgG 20, anticardiolipin antibody at IgM 13, and antiphosphatidylcholine at IgG 24.

**DISCUSSION**

We present a single-center observational case series of hepatitis C and antiphospholipid antibody positivity in the older stroke patient population (>65 years) that altered therapeutic management from antiplatelet therapy to warfarin in two cases and from warfarin to dabigatran in one case. Screening for antiphospholipid antibodies is not part of the usual clinical workup for modifiable stroke risk factors in those >65 years, although it is well described as an independent risk factor for acute ischemic stroke in those <55 years. We suggest that in patients with hepatitis C and acute ischemic stroke, such screening may have a higher yield than in the <55-year demographic.

There are limited references reporting hepatitis C–associated antiphospholipid antibodies and stroke, and most consist of incidental case reports (4–6). One case report described a 43-year-old woman with ischemic stroke, while a further case report described a 54-year-old man with chronic hepatitis C and antiphospholipid-positive serology and ischemic stroke. Of interest, the treatment of hepatitis C with interferon appeared to contribute to the patient’s remission from further ischemic stroke events (6). The only case-control patient series came from a Romanian publication, where 58 patients (age range 46–77 years, mean 62 years; 39 women and 19 men) were found to have a higher prevalence ($P < 0.001$) of antiphospholipid antibodies in the hepatitis C–positive group with stroke compared to age- and sex-matched controls (5).

The presence of antiphospholipid antibodies is known to contribute to the development of acute ischemic stroke. Our small observational case series suggests that no particular type of stroke is favored, since we had patients with both small- and large-vessel disease together with cardioembolic stroke. The additional risk of antiphospholipid-positive serology should suggest optimization of antiplatelet therapy and possibly extension of therapy to anticoagulation with warfarin or direct thrombin inhibitors such as dabigatran. The control of hepatitis C virus expression through interferon therapy is a further therapeutic consideration in these patients and may reduce the risk of stroke (5). Our patients were all noted to have an elevated albumin-immunoglobulin protein gap, suggesting that there is an abnormal immune response to hepatitis C. The infection of vascular endothelial cells by hepatitis C may result in the exposure of previously nonimmunogenic antigens to immunocompetent cells, promoting endothelial dysfunction and potential stroke. However, dysregulation of hepatic synthetic function following hepatitis C infection may also be an important etiologic consideration.

Diagnosis and management of delayed hemoperitoneum following therapeutic paracentesis

Morgan J. Katz, MD, Matthew N. Peters, MD, John D. Wysocki, MD, and Chayan Chakraborti, MD

Abdominal paracentesis is a frequently employed diagnostic and therapeutic procedure for patients with refractory ascites, typically in patients with cirrhosis. It is generally regarded as a safe procedure with significant complications occurring in <1% of cases. Most hemorrhagic complications are due to abdominal wall trauma, during which clear evidence of active bleeding is usually visualized during the procedure. Delayed hemoperitoneum is a rare complication of large-volume paracentesis in which clinical evidence of active bleeding is typically absent until substantial blood loss has taken place (often several days to a week later), leading to an exceedingly high mortality rate. Herein we describe a case of delayed hemoperitoneum in a 55-year-old man with heart failure. This case emphasizes the importance of identifying patients who are at high risk for delayed hemoperitoneum as well as the need to closely monitor complete blood counts in the days following a large-volume paracentesis.

CASE DESCRIPTION

A 55-year-old man presented with a 2-week history of worsening dyspnea and abdominal distention. He had atrial fibrillation, chronic heart failure (last known ejection fraction 25%), and chronic kidney disease. He reported nonadherence to his furosemide for 3 weeks. He had a massively tense and protruding abdominal wall and 3/4+ pitting lower extremity edema to his knees bilaterally. His international normalized ratio was 2.3 (on warfarin), serum creatinine 2.33 mg/dL (baseline: 2.0–3.0 mg/dL), and albumin 2.3 g/dL. Abdominal ultrasound revealed hepatomegaly without cirrhosis. Two doses of 80 mg intravenous furosemide led to minimal reduction of his abdominal ascites. A paracentesis under ultrasound guidance was performed in the left lower quadrant and yielded 5 L of clear, transudative fluid. No evidence of hematoma was noted, and the procedure provided immediate symptomatic relief.

Three days later the patient began complaining of mild, diffuse abdominal discomfort. Over the previous 3 days his hemoglobin level had dropped from 8.4 to 6.9 g/dL. No evidence of gastrointestinal or genitourinary blood loss was noted. The patient, a Jehovah’s Witness, refused transfusion of any blood products and in the next 2 days his hemoglobin declined to 2.9 g/dL. A repeat diagnostic paracentesis was performed and showed 10 mL of blood-tinged fluid. The following day a tagged red blood cell scan indicated evidence of increased activity near the duodenum and gastric antrum (Figure 1). An urgent upper endoscopy demonstrated no evidence of active upper gastrointestinal bleeding but did demonstrate a bluish hue on the posterior stomach wall, suggestive of a possible intraperitoneal or retroperitoneal bleed. Subsequent noncontrast computed tomography (CT) of the abdomen and pelvis showed likely hemoperitoneum localized to the mid-lower abdominal wall (Figure 2). An urgent epigastric and gastroduodenal angiogram did not reveal any evidence of active bleeding.

The patient continued to refuse blood transfusion and was treated supportively with intravenous fluid and albumin infusions. Slight improvements in serum creatinine (3.6 mg/dL) and hemoglobin (4.1 g/dL) were noted. The patient refused any further intervention and was discharged to home hospice; he died 3 days later, 11 days after the initial paracentesis.

DISCUSSION

Large-volume paracentesis (>4 L) is a common bedside procedure utilized in patients with refractory abdominal ascites with...
poor response to diuretic therapy. The procedure is typically regarded as safe and carries a hemorrhagic complication rate of <1% (1, 2) (further reduced with ultrasound guidance and a left lower quadrant approach [3, 4]). When hemorrhagic complications occur, they are typically due to abdominal wall vessel puncture, with visible bleeding during the procedure (2). Consequently, many patients are discharged soon after the procedure and without close follow-up.

Delayed hemoperitoneum is a rare hemorrhagic complication of large-volume paracentesis. The proposed mechanism is the large volume fluid removal, which results in a rapid drop in intraperitoneal pressure. This promotes a transient pressure gradient in the splanchnic circulation, promoting dilation and rupture of friable mesenteric varices (1, 5, 6). Due to slow venous bleeding rates, patients are often initially asymptomatic. The most commonly reported symptom is vague abdominal pain (1), which may be overlooked in patients with chronic ascites. Peritoneal signs typically do not occur until late stages (if at all), and any clinical signs of bleed may be absent until substantial blood loss has taken place as long as several days to a week later (1, 5). Consequently, patients have been known to present in hemorrhagic shock, and mortality rates are reported to exceed 70% (5).

Given the rare occurrence of delayed hemoperitoneum, clinicians must be made aware of high-risk patient groups. Previously established risk factors include advanced cirrhosis with refractory ascites, history of previous large-volume paracentesis, and the appearance of retrograde mesenteric venous flow on ultrasound (due to the occurrence of large mesenteric collaterals, which are predisposed to rupture) (5). Additionally, an association between postparacentesis hemorrhagic complications and chronic kidney disease has also been noted (likely due to platelet dysfunction) (6). Surprisingly, no associations between coagulopathy and hemorrhagic complications of paracentesis have been shown, so there are currently no guidelines for either preprocedural coagulation parameters that contraindicate paracentesis or the prophylactic administration of fresh frozen plasma or platelets (3, 5).

Previously described cases of delayed hemoperitoneum have not demonstrated evidence of intraprocedural abdominal wall trauma or other complications; thus, it is critical to recognize potential warning signs (1, 6). Complete blood counts should be closely monitored for a minimum of several days in high-risk groups, and once a notable drop in hemoglobin is detected, a diagnostic paracentesis should be performed to assess the presence of visible blood (5). If blood is detected on diagnostic paracentesis, an abdominal CT scan or ultrasound should be performed to evaluate for abdominal wall hematoma. In the absence of apparent hematoma formation, angiography should be strongly considered (5, 6).

Initial management should focus on identification of a bleeding source with interim supportive management. Coagulopathies should be corrected, and patients should be fluid resuscitated with normal saline and packed red blood cells as needed (6). In the event of patient blood transfusion refusal (as in our case), albumin or artificial colloid solution should be given. Previously described successful interventions include portocaval shunting and embolization or surgical ligation of bleeding vessels (2, 5). Unfortunately, angiographic visualization of bleeding vessels is often difficult, and in the setting of hemodynamic instability, laparotomy may be needed for adequate visualization of the bleeding site (5).

The most important preventative measure in delayed hemoperitoneum is daily monitoring of complete blood counts for a minimum of several days to ensure rapid detection and minimize blood loss (1, 5). Patients with underlying renal dysfunction may benefit from prophylactic transfusion of fresh frozen plasma or desmopressin acetate—a target of future studies (6). Finally, patients with risk factors for hemoperitoneum may benefit from either a lower-volume paracentesis, slower drainage of ascites, or concurrent administration of albumin to guard against rapid changes in the intraperitoneal pressure gradient (1).

![Figure 2. CT of the abdomen and pelvis without contrast reveals hemoperitoneum (arrows) localized to the lower left and middle quadrant.](image-url)
Baylor, Scott & White sign agreement of intent to join forces, create new health system

The boards of Baylor Health Care System (BHCS) and Scott & White Healthcare signed an agreement of intent to combine the strengths of their two health systems to create a $7.7 billion organization with the vision and resources to offer its patients continued exceptional care while creating a model system for an industry undergoing fundamental transformation. The alliance reflects a vision to create a new health system engineered to meet the demands of health care reform, the changing needs of patients and payers, and the extraordinary advances in clinical care. With approval of the agreement of intent, the organizations have entered a period of exclusive negotiations and due diligence. The next stage in the transaction—a definitive agreement—is anticipated to be complete in 2013.

The new system, named Baylor Scott & White Health, would include the organizations’ combined 42 hospitals, more than 350 patient care sites, more than 4000 active physicians, 34,000 employees, and the Scott & White Health Plan. It would be the largest not-for-profit health system in Texas and one of the largest in the United States. It would be governed by a single board with equal representation from both founding members.

“Baylor has a century-long tradition of quality, innovation, and service. And in this time of great change in the health care industry, Baylor is looking forward and preparing to once again lead by joining forces with Scott & White to create this new model of care,” said Joel Allison, president and CEO, BHCS. "Scott & White is a perfect partner for us as it is nationally known for its high-quality, efficient care. Our proposed new organization reflects many months of discussion between our two like-minded systems on how we could work together to continue to meet the needs of the communities we serve in this dramatically changing environment. The new organization will continue to honor and carry forward Baylor’s 100-plus-year legacy as a Christian ministry of healing.”

“Our new organization will not only prepare us for health care reform but will help drive and shape what health care delivery in this country will become,” said Robert Pryor, MD, president and CEO, Scott & White Healthcare. “Scott & White has been recognized as a national leader for our strong physician-led population health model. Our shared vision with Baylor is to build upon our unique approach and create an innovative health care delivery model enhanced by medical education and research.”

Both organizations are affiliated with Texas A&M Health Sciences Center and have extensive investments in medical education and research. Baylor Scott & White Health will have the ability to expand training opportunities for the next generation of health care professionals by integrating education programs at both organizations.

Some details of the agreement of intent:

- **Unified board:** A unified board of trustees will comprise 14 individuals, with an equal number of representatives from each institution. Drayton McLane Jr., the chair of the Scott & White board of trustees, will serve as chair of the new organization’s board. Jim Turner, the chair of the BHCS board of trustees, will serve as chair-elect of the new organization’s board.

- **Leadership:** The new organization will be led by a single executive leadership team. Joel Allison will serve as chief executive officer of the new company. Dr. Robert Pryor will serve as president and chief operating officer of the new organization.

- **Operations:** The new system will have two operating divisions, which will consolidate over time. The Scott & White division will be headquartered in Temple, and the Baylor division will be headquartered in Dallas.

- **Brands:** The new organization will be called Baylor Scott & White Health. Both Baylor and Scott & White will retain their individual brand names.

- **Foundations:** The foundations will remain separate.

- **Medical staffs:** The medical staffs will remain independent.

“This partnership is the right thing for Baylor. It’s the right thing for Scott & White. And, it’s the right thing for our communities,” said Drayton McLane Jr., chair of the Scott & White board of trustees. “Both health systems are well-organized, well-run, best-in-class organizations. We can learn from each other, and I think this only benefits the patients we serve by allowing us to deliver better quality care and increased access to care.”

For patients, the new organization will ultimately mean

- Greater, more convenient access to high-quality care through an extensive network of physicians, advanced practice professionals, medical centers and hospitals throughout North and Central Texas

- Increased coordination of patient care

- Improved patient outcomes, by combining the expertise of primary care physicians and medical specialists and adopting the best practices of both organizations

- The ability to attract, retain, and train the very best national and international talent

- Greater access to world-class primary and pediatric care and centers of excellence in cardiology, oncology, transplant, rehabilitative medicine, and other specialties

“Together, our two health systems will cover two geographically diverse areas that are nearly contiguous and highly complementary,” said Jim Turner, chair of the BHCS board of trustees. “We strongly believe our neighboring geographies will allow us to be well positioned to lead the transformation of health care in Texas and beyond.”

**Introducing the Baylor Charles A. Sammons Cancer Center Network**

For the past 2 years, Baylor medical centers throughout North Texas have been working to achieve the distinction of using the Baylor Sammons Cancer Center name for their oncology programs by meeting or exceeding the stringent criteria established by BHCS. In addition to the...
RECENT GRANTS

- **JC virus and human colorectal neoplasia**
  Principal investigator: C. Richard Boland, MD
  Sponsor: National Cancer Institute
  Funding: $267,374
  Award period: 2/1/2013–8/1/2013

- **Glycemia reduction approaches in diabetes: a comparative effectiveness study**
  Principal investigator: Priscilla Hollander, MD
  Sponsor: George Washington University/National Institute of Diabetes and Digestive and Kidney Diseases
  Funding: $186,241
  Award period: 1/1/2013–7/31/2013

- **Molecular mechanisms of pDC interactions**
  Principal investigator: Yong-Jun Liu, MD
  Sponsor: MD Anderson Cancer Center/National Cancer Institute
  Funding: $313,600
  Award period: 9/1/2012–8/31/2013

- **Expanding the impact of the Baylor Health Care system delirium research program**
  Principal investigator: Andrew Masica, MD
  Sponsor: The Discovery Foundation
  Funding: $36,080
  Award period: 12/4/2012–6/15/2015

- **The high value healthcare collaborative: engaging patients to meet the triple aim**
  Principal investigator: Andrew Masica, MD
  Sponsor: Dartmouth College/Centers for Medicare and Medicaid Services
  Funding: $176,952
  Award period: 7/1/2012–6/30/2013

- **Enhancing clinical effectiveness research with natural language processing EMR**
  Principal investigator: Andrew Masica, MD
  Sponsor: Kaiser Foundation Research Institute
  Funding: $209,336
  Award period: 9/30/2012–9/29/2013

- **Vaccination with IL-15 dendritic cells to generate melanoma-specific protective memory T cells**
  Principal investigator: A. Karolina Palucka, MD
  Sponsor: National Cancer Institute
  Funding: $230,897
  Award period: 2/1/2013–1/31/2014

- **Role of mucosal DC subsets in the control of influenza A virus immunity**
  Principal investigator: A. Karolina Palucka, MD
  Sponsor: Mt. Sinai School of Medicine/National Institute of Allergy and Infectious Diseases
  Funding: $74,000
  Award period: 7/15/2012–6/30/2013

- **MIRA—Cellular therapy for cancer (C1)**
  Principal investigator: A. Karolina Palucka, MD
  Sponsor: Baylor College of Medicine/Cancer Prevention and Research Institute of Texas
  Funding: $46,303
  Award period: 7/1/2012–6/30/2013

- **MIRA—Cellular therapy for cancer (C2)**
  Principal investigator: A. Karolina Palucka, MD
  Sponsor: Baylor College of Medicine/Cancer Prevention and Research Institute of Texas
  Funding: $102,612
  Award period: 7/1/2012–6/30/2013

- **North Texas Hepatitis B Consortium: clinical site for the Hepatitis B network**
  Principal investigator: Robert Perrillo, MD
  Sponsor: UT Southwestern Medical Center
  Funding: $114,527
  Award period: 6/1/2012–5/31/2013

- **Role and function of prohibitin in intestinal inflammation**
  Principal investigator: Arianne L. Theiss, MD
  Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases
  Funding: $146,459
  Award period: 2/1/2013–1/31/2014

- **A novel replication competent flavivirus-based HIV vaccine platform, i.e. RepliVax, as a priming component for improving antibody response**
  Principal investigator: Gerard Zurawski, MD
  Sponsor: Centre Hospitalier UV/Gates Foundation
  Funding: $92,222
  Award period: 9/6/2012–8/31/2015

Original Baylor Charles A. Sammons Cancer Center at Dallas, six other BHCS facilities are now Sammons Cancer Centers:
- Baylor Charles A. Sammons Cancer Center at Fort Worth
- Baylor Charles A. Sammons Cancer Center at Irving
- Baylor Charles A. Sammons Cancer Center at Garland
- Baylor Charles A. Sammons Cancer Center at Grapevine
- Baylor Charles A. Sammons Cancer Center at Plano
- Baylor Charles A. Sammons Cancer Center at Waxahachie

The cancer programs at the two newest hospitals in the health care system—Baylor Medical Center at Carrollton and Baylor Medical Center at McKinney—are well on their way to achieving accreditation and designation.

Each BHCS institution that wanted to join the network had to submit a request to BHCS oncology leadership showing its readiness. To qualify, they had to be accredited by the Commission on Cancer of the American College of Surgeons as an approved cancer program. They also had to demonstrate active participation in a number of areas, including BHCS oncology strategic initiatives; oncology safety and health care improvement projects; oncology educational efforts in nursing, medicine, or other ancillary education related to oncology; and research initiatives, either within the facility or by supporting other Baylor facilities and their oncology research by making clinical trials available to patients, regardless of the location of the trials. After a determination that all criteria have been met, the Baylor facility has the distinction of using the Baylor Charles A. Sammons Cancer Center name.

Patients will be the major beneficiaries of the Baylor Sammons Cancer Center network. When initially deciding upon a treatment center, they will have the assurance that any institution carrying the Baylor Sammons brand will offer quality cancer care. By receiving care at a Baylor Charles A. Sammons Cancer Center, patients can be treated close to home for most of their cancer care needs.

Vikas Aurora, MD, hematologist and medical oncologist on the medical staff as well as the chairman of the Cancer Committee at Baylor Grapevine, is excited about the growth of the program. “We are working to be at the forefront
of community cancer care by integrating physician and nurse enthusiasm with administrative support,” he said. “It takes time and resources to fuel growth but we have it here, with the strong support of Baylor Health Care System.”

Rather than having to “reinvent the wheel” at each site to develop new treatment options or patient outreach programs, physician leaders from each institution can come to thequarterly BHCS Oncology Council to share ideas and best practices with colleagues at their sister facilities. A program that has been developed and perfected at one center can be used as a model at other sites. Cooperation among cancer centers can bring the strength of numbers to bear on conducting new clinical trials that make innovative treatment options available to patients.

- **Ultragenyx announces in-licensing of clinical-stage product from Baylor Research Institute**

Ultragenyx Pharmaceutical Inc., a biotechnology company focused on the development of treatments for rare and ultra-rare genetic disorders, announced on January 10, 2013, that it has in-licensed rights for triheptanoin, a promising treatment for long-chain fatty acid oxidation disorders, from Baylor Research Institute (BRI), the research arm of BHCS.

“It is gratifying to see the fruits of everyone’s labor as this agreement moves forward,” said Dr. Raphael Schiffmann, director of BRI’s Institute of Metabolic Disease. “Staff have put a lot of time and effort into the study of triheptanoin and its use for fat oxidation and glycogen storage diseases, among others. Triheptanoin has a potential benefit for these disorders and others with an underlying energy deficit, many of which do not have adequate therapy. We are confident that Ultragenyx will advance triheptanoin therapy for the benefit of these patients in the US and abroad.”

- **Baylor Medical Center at Garland donates mobile clinic to local charity**

Less than a month after opening its doors in October 2012, the Avenue F Family Health Center, one of the first charity care clinics in Collin County, was quickly running out of space. That’s when leaders at Baylor Medical Center at Garland stepped in with a solution, donating a fully functioning mobile clinic on wheels. The vehicle had been unused for a number of years. “We are thrilled to be able to help Avenue F Family Health Center with this donation. It truly is a win-win situation for everyone involved. The mobile clinic van will allow the organization to reach more patients in need within the community and continue to honor Baylor’s mission to serve all people through exemplary healthcare,” said Tom Trenary, president, Baylor Medical Center at Garland.

The Avenue F Family Health Center serves patients who are uninsured and live in the 75074 and 75075 zip codes of Plano, with a particular focus on the Douglass and East Plano communities. The clinic is open 5 days a week but visits with the physician are currently available only on Mondays and Wednesdays. Avenue F Church of Christ serves as the current location of the clinic and founding institution of AFFECT, Inc. The mobile clinic van will be parked on the church campus and used as the interim home of the clinic until a permanent physical space is

### PHILANTHROPY NOTES

- **Baylor Foundation launches $250 million campaign**

BHCS Foundation formally launched the first comprehensive campaign in Baylor’s history with an event at the AT&T Performing Arts Center’s Wyly Theatre on February 27. The $250 million fundraising effort—Campaign 2015: Baylor Makes Us All Better—marks Baylor’s most ambitious fundraising effort to date and is designed to strengthen every aspect of Baylor, from patient-centered programs and capital needs to innovative research and medical education.

The simple phrase, “Baylor Makes Us All Better,” was the impetus for a bold vision: take BHCS to national preeminence in areas of health care that have the power to transform lives and the communities we serve. To date, more than $160 million has been raised toward the $250 million goal, including transformational gifts from the men and women of Sammons Enterprises, Inc., Annette C. and Harold C. Simmons, and T. Boone Pickens.

“We are grateful for the support our community has already shown and encouraged by the momentum we have,” said Rowland K. Robinson, Foundation president. “We are proud that we have made it two thirds to our goal, but we have not yet met our challenge.”

Completely donor-driven, this comprehensive campaign focuses on four priorities—capital, education, research, and programmatic initiatives at Baylor—and offers significant opportunity to redefine health care, both locally and nationally. Donors can determine where they wish to make an impact and give to the area for which they have the greatest passion. With increased community support, we can develop innovative models of care, utilize advanced medical technology, engage in game-changing research, and train more physicians to care for future generations.

While Baylor has already earned national recognition for safety, quality, leadership, and bedside care, sustaining this level of excellence requires more than stewardship; it requires investment and innovation.

“With your partnership and support, we can maintain Baylor’s steadfast commitment to excellence and secure the future of health care for our community,” said Joel Allison, president and chief executive officer of BHCS.

For more information, visit Give.BaylorHealth.com.

### UPCOMING CME PROGRAMS

The A. Webb Roberts Center for Continuing Education of Baylor Health Care System is offering the following programs:

- **Urology Update 2013 with Clinical Cases in Oncology**, April 5–6, 2013, at BUMC
- **Wound Care: The Next Generation**, April 27, 2013, at BUMC
- **Fourth Annual Latest Advances in Ischemic and Hemorrhagic Stroke Therapy Conference**, May 18, 2013, at Westin Galleria Dallas
- **40th Annual Williamsburg Conference on Heart Disease**, December 8–10, 2013, at the Williamsburg Conference Center, Williamsburg, Virginia

For more information, call 214-820-2317 or visit www.cmebaylor.org.
located and built. Once that goal is achieved, the mobile unit will travel around Plano and Dallas to help meet the needs of uninsured and underinsured individuals in those communities.

■ **Five Baylor hospitals chosen to pioneer state project to improve breastfeeding rates**

Despite the benefits of breastfeeding, Texas has one of the lowest breastfeeding rates in the US, with only 13.7% of Texas mothers exclusively breastfeeding for 6 months. Five BHCS hospitals—Baylor All Saints Medical Center, Baylor Medical Center at Carrollton, Baylor Medical Center at McKinney, Baylor Regional Medical Center at Grapevine, and Baylor University Medical Center at Dallas—were recently chosen to join a pioneering group of hospitals hoping to reverse this trend. They are among 20 hospitals/facilities in North Texas selected to be part of the “Texas Ten Step Star Achiever Breastfeeding Learning Collaborative,” a 5-year quality improvement project designed to improve facility environments to better support a mother’s choice to breastfeed. What distinguishes this new project is collaboration. What these hospitals learn will be shared among other participants, helping more mothers across the state become more successful in exclusively breastfeeding their babies.

■ **Baylor Irving awarded advanced certification for primary stroke centers**

The Joint Commission, in conjunction with the American Heart Association/American Stroke Association, has awarded Baylor Medical Center at Irving Advanced Certification for Primary Stroke Centers. This certification demonstrates that the program meets critical elements of performance to achieve long-term success in improving outcomes for stroke patients.

“This designation has given us the opportunity to highlight the quality stroke care we provide for our patients,” said Cindy Schamp, president, Baylor Irving. “In collaboration with the emergency department physicians on our medical staff and our staff, we remain poised and ready to serve the residents who present in our hospital with signs and symptoms of stroke.”
When it comes to the depiction of the medical world on the motion picture screen or on television, you can count me out. The errors and inconsistencies that pop up there are more than this observer can tolerate. A story set in the 1930s or 1940s meticulously observes the clothing, furniture, and even automobile models of the period. Then, when a senior physician appears, he is not wearing a long white laboratory coat appropriate to his position but, rather, a short white jacket, more properly worn by medical students and junior house officers. We are shown a scene in an examining room or operating suite, and there on the x-ray view box is the chest film of the patient—inserted backwards. (And no, Virginia, the story is not about an outbreak of situs inversus.)

On the popular series ER, we witnessed junior residents in the emergency room performing all kinds of sophisticated diagnostic and therapeutic procedures short of open heart surgery. Then there was Dr. House, showing up week after week badly in need of a shave, a haircut, and, possibly, delousing judging from his appearance. The only thing more distasteful than that was his personality. When he strode with impunity into an isolation unit, alarms should have gone off rather than the welling up of stirring background music. How this character became an icon simply baffles me.

Complaining about such misrepresentations as these might be called nitpicking. They are clearly in the realm of fiction. There is another example of malpractice in the world of make-believe that, unlike the other transgressions, extends into the real world. What I refer to is the practice of attempting to auscult the chest through one or more layers of clothing. Aside from seeing this on TV and in films, I had noticed it occurring every once in a while in real life, most often in the setting of a busy outpatient clinic with doctors pressed to rush patients through that particular gantlet.

The presence of any layers of clothing lying between the stethoscope head and the patient’s skin is bound to muffle any findings—normal or otherwise—that might be present. Faint heart murmurs and gallops as well as fine rales in the lungs might well be lost to detection. Appreciation of the splitting of the heart sounds, present in most patients, even those without heart disease, might be reduced as well. Such failures in auditory perception might lead to serious failures in diagnosing heart or lung pathology and following up with appropriate diagnostic technologies. Conversely, a patient with dramatic symptoms unsupported by history or physical findings may prompt a physician, uncertain of his bedside skills, to order a number of expensive tests that might only increase the patient’s fears as well as his medical bill.

Such considerations got me to wondering how widespread this deviation from good clinical practice had become. To get some idea of this, I began tabulating all representations of chest auscultation in the public media, almost exclusively television, and noting whether proper technique was being demonstrated (SKINS) or the improper technique of listening to the chest through one or more layers of apparel (CLOTHES). All these examples were placed in the category of either professional representations (doctors and nurses on newscasts and in documentaries) or commercials (actors in dramas, pharmaceutical advertisements, or health care facility promotions). I also made note of the sex of the subject being examined. (Would the reluctance about representing free frontal nudity of women on television work against their being included among the SKINS?) Instances in which the clothing remained in place but with the stethoscope inserted under it to make contact with the skin were registered as SKINS. It took about 2 years to collect the 100 cases I wished to accumulate for analysis.

It turned out that of the 100 individuals portrayed, 71 appeared in the professional category and 29 in the commercial category. Among the latter, only 16% were SKINS, not terribly surprising considering the source. I turned my attention to the professional group. Here 37% were SKINS. Surprisingly, gender did not have a hand in this distribution: among men the proportion of SKINS was 36% and among women the finding was 42%. In both groups, however, the number of correctly performed examinations was depressingly low.

Recent studies evaluating skills in performing physical examinations by medical students, housestaff, and even medical school faculty have uniformly shown a 20% to 80% error rate in recognizing actual or simulated findings (1–5). Such deficiencies

From the Department of Medicine (retired), University of Medicine and Dentistry of New Jersey, Newark.

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can only be exacerbated by improper auscultatory technique such as that described here. For those of us too easily prone to become overwrought or even incensed at certain troubling realities, our friends and colleagues may properly caution, “Keep your shirt on.” But when our patients’ bodies are trying to tell us through an examination of the heart and lungs, for example, what may or may not be troubling them and when such findings are so clearly obfuscated by faulty technique, perhaps we should be swayed by a different kind of advice. Recall the sultry Swedish blonde in that classic Noxzema shaving cream commercial who urged us to “Take it off. Take it all off.”

### Reader comments

**Dear Dr. Roberts:**

Thank you for including the image of mine, Vespers, in the January edition of the *BUMC Proceedings* in the Avocations “department.” It is an honor to have an image of mine presented.

This issue is another wonderful publication. Dr. O’Brien’s article, “My Surgical Heroes,” included many surgeons that I know and hold in the same high esteem: Dr. Sparkman and Dr. Bookatz, both of whom were examples to me of excellent physicians. I met Dr. Bookatz as a medical student during my rotation through surgery at Parkland as a junior and senior medical student at Southwestern Medical School in 1963 and 1964. I later met Dr. Sparkman when I joined the surgical staff at Baylor in 1971 as a member of his surgical department. Dr. Sparkman influenced not only the residents that he trained but also the staff members of his department. He set an example for perfection and extracted the utmost from those who strove to practice medicine up to the standards he set. My own surgical heroes include Dr. Owen Wangensteen and Dr. Walton Lillehei, under whom I trained at the University of Minnesota in 1954–1955.

Your article, “Facts and ideas from anywhere,” is an exciting compendium of revelations concerning so many aspects of medicine and helps one focus on the timeline of medical thought and practice. It is a marvel the way you can accumulate and present such a wide spectrum of ideas.

—Jay Hoppenstein, MD

**Dallas, Texas**

**Dear Dr. Roberts:**

I keep a stack of “to-read” magazines and journals on my coffee table for times of leisure reading, and any unread *Baylor Proceedings* is always at the top.

Last Saturday, with a fire going in the den fireplace and our cat beside me in our chair (the cat thinks it is her chair), I opened up the new January issue of the *Proceedings* and, as I always do, read it cover to cover. Your “Facts and ideas from anywhere” is the first thing I always read, and the section on hydrophobia was really fascinating—so much so I gave it to my wife, who also read it and enjoyed it as well. You have an easy-to-read writing style for this section that is unmatched.

The other articles were excellent as well—important and right to the point. The ECG in hypothermia even prompted me to add this to our Internet-based disease surveillance program. The ECG stood out particularly well on that great paper you use.

Please keep up the good work and keep those *Proceedings* coming for their place at the top of the stack!

—Vincent E. Friedewald, MD, FACC

Spicewood, Texas

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In memoriam

George E. Hurt Jr., MD
Department of Urology, Baylor University Medical Center at Dallas

George Ellison Hurt Jr., MD, died on November 11, 2012, after a long illness. He was born on December 21, 1932, in Dallas and spent most of his life there, graduating from Highland Park High School, Southern Methodist University, and the University of Texas Southwestern Medical School. Graduating first in his medical school class, he received the Ho Din award for the graduating student deemed most outstanding by his peers and the faculty. Dr. Hurt completed his internship at Denver General Hospital and his general surgery and urology residencies at Parkland Memorial Hospital in Dallas. He then enjoyed a thriving private urology practice at Baylor University Medical Center for 41 years, with partners Drs. Alexander, King, Fuqua, and Ware. He was a member of the Combined Examination Committee of the American Board of Urology and the American Urological Association and served as president of both the National Society for Pediatric Urology and the South Central Section of the American Urological Association, in addition to holding many other leadership and service positions. Beyond his practice at Baylor, he founded the urology clinic for spina bifida patients at Texas Scottish Rite Hospital and directed it for 40 years. He was also associate clinical professor of urology at UT Southwestern, a member of medical advisory committees at Parkland Memorial Hospital, and director of the pediatric urology service at Children’s Medical Center. He was internationally regarded as a surgeon, educator, and innovator in urology and was the recipient of numerous community and humanitarian awards. Tributes to Dr. Hurt appear on p. 194 of this issue.

Harold C. Urschel Jr., MD
Department of Thoracic Surgery, Baylor University Medical Center at Dallas

Harold Clifton Urschel Jr. died on November 12, 2012, at the age of 82. He was interviewed in Proceedings (2003;16(3):315–333), and the introduction to his interview by Dr. Roberts appears below. Tributes to Dr. Urschel appear on p. 196 of this issue.

Hal Urschel was born in Toledo, Ohio, in 1930 and grew up primarily in Bowling Green, 20 miles away. After public schools, he went to Princeton University on a football scholarship and graduated cum laude in 1951. The Princeton team was undefeated during his freshman and senior years. He also had a scholarship to Harvard University School of Medicine, where he again graduated cum laude in 1955. His internship, residency, and chief residency in general, vascular, cardiac, and thoracic surgery were at the Massachusetts General Hospital in Boston. After serving in the US Navy as chief of experimental surgery at the National Naval Medical Research Center in Bethesda, Maryland, he and his young family moved to Dallas. In addition to his practice at Baylor University Medical Center at Dallas, Dr. Urschel taught extensively and was clinical professor of cardiovascular and thoracic surgery at the University of Texas Southwestern Medical School. He published over 300 articles in medical journals or chapters in books and was an editor of and major contributor to seven books. He was visiting professor at a number of medical centers in the USA and abroad and was an honorary member of the thoracic surgery faculty of the University of Toronto and the Harvard Medical School. He served as president of five major surgical societies: the Society of Thoracic Surgeons, American College of Chest Physicians, International Academy of Chest Physicians, Southern Thoracic Surgical Association, and Texas Surgical Society. He received a number of honors for his achievements, including two honorary doctorates. He and his lovely and brilliant wife, Betsey, were the proud parents of five children, all of whom are graduates of Princeton University.

Elgin Willis Ware Jr., MD
Department of Urology, Baylor University Medical Center at Dallas

Dr. Elgin Willis Ware Jr. died on November 20, 2012, at the age of 88. He recently established a lectureship in medical history at Baylor, and the introduction to the lecture provided by Dr. Michael Emmett appears below. A tribute to Dr. Ware appears on p. 199 of this issue.

Dr. Elgin Ware, a long-time urologist at Baylor University Medical Center at Dallas and chief of urology from 1986 to 1987, spent his entire life in Dallas: he graduated from Highland Park High School, Southern Methodist University, and the University of Texas Southwestern Medical School before completing an internship at Baylor Hospital and a urology residency at Parkland Hospital. After completing his training, Elgin entered the practice of urology and quickly became a leader at the local, state, and national level. He was the president of the Dallas County Medical Society in 1976, was a delegate of the Texas Medical Association (TMA) for many years, and served as a trustee of the TMA from 1980 to 1990. He was elected president of the American Association of Clinical Urologists in 1978. Beyond the hospital, he served as a member of the Highland Park School Board for 14 years, worked as a volunteer and then director of the Stewpot, a downtown Dallas soup kitchen, and initiated a medical clinic to provide care to the indigent. Finally, Elgin had a profound interest in medical history. He chaired the History of Medicine Committee of the TMA from 1989 to 2001. In 1995, he established the Elgin W. Ware Jr. TMA collection of prints and drawings at the Blanton Museum of Art on the University of Texas campus to educate the public about the profound connections between medicine, art, and print making from the renaissance to the present. He also coestablished, with Robert Mickey, the History of Medicine Photography Gallery at the TMA. The Elgin W. Ware Jr., MD, Lectureship in Medical History at Baylor is one of three lecture series he endowed.
Tributes to George E. Hurt Jr., MD

BOB ALLISON, MD

Happy, with apologies to Rodgers and Hammerstein’s Sound of Music, “How do you hold a ‘sunbeam’ in your hand?”

I met George Hurt poolside at a Phi Chi rush party, September 1953, just prior to entry into the freshman class at Southwestern Medical School. We pledged Phi Beta Pi. He organized our anatomy table—six students to a cadaver in the shacks on Oak Lawn Avenue. It was a macabre scene: 18 bodies and 100+ students in a relatively small space with no air-conditioning! This was Dr. Hal Weathersby’s first year at Southwestern.

George was one of the smartest people I’ve ever known, if not the smartest. He was academically number one in our medical school class. He was five average points ahead of the next classmate. The next 20 guys were within two average points of each other. He was the obvious choice for the Ho Din award of the class. We had a great time in medical school, playing widow whist or ping-pong at lunch the first 2 years. Ann and George married after our freshman year. Happy drove a yellow cab that summer. Catherine was born our senior year. We topped off the fourth year by wearing our tuxes with short pants with long white socks to the spring formal at the Dallas Country Club.

George completed his urology training at Parkland Memorial Hospital with Dr. Harry Spence. He joined the firm of Alexander, King, Fuqua, and Ware in Dallas. Happy did a lot of things for a lot of people, most of which he took little or no credit for. George founded the urology clinic for spina bifida patients at Texas Scottish Rite Hospital and served as director of the clinic for 40 years.

He really helped a lot of friends and acquaintances down on their luck as well as visiting national and international professors and others. I once sent one of the principals of Texas Instruments to see Happy as a work-in without calling ahead; George questioned my judgment. I told him it did not make any difference. He treated all patients the same, rich or poor, famous or infamous.

George was honored as a Distinguished Alumnus at both Highland Park High School and Southern Methodist University. His senior year in high school, he was recognized as the best all-around athlete, lettering in football, basketball, and baseball.

Happy always had time for his children: coaching Y teams, going horseback riding, skiing, going on hunting and fishing trips and multiple trips in and out of the USA.

I can never adequately express my admiration for the care Ann provided Happy during the years of his very protracted illness.

I may not be able to hold a sunbeam in my fingers, but I can in my heart.

CATHERINE HURT SCHEIHING

You can read about my father’s many honors and accolades, but the true essence of this amazing man was much more than a title. Daddy was a brilliant man with the heart of a child. That translated into incredible adventures for us, his kids. He was always laughing and thinking of crazy fun stuff. The list of our activities—like helicopter rides, horses in our front yard, river rafting, and so much more—reads like an adventure series.

Family road trips in the station wagon were a vacation staple. The Hurts traveled to both coasts, more than once, plus a couple of times to Canada, south into Mexico, and everywhere in between. Daddy was happiest behind the wheel, in control, going 80 miles an hour, faster if Mother wasn’t looking.

Every winter there were road trips to Colorado. He was the most beautiful skier I have ever seen. You could spot him from far away gliding like an angel down the black slopes. He proudly skied until his late 60s, finally qualifying for a free senior lift pass. Most of the time you could find Daddy on the bunny slopes, always helping whomever was the youngest at that time—since you never knew when another Hurt kid would enter this world.

One summer Daddy called one of his famous family meetings. With great joy, we felt certain that all the begging for a swimming pool had come to fruition. Instead we were stunned to find out that instead of a pool, we were getting a new baby brother. Hello Gregory, good-bye swimming pool.

All of these multiple car trips made for terrific memories, tremendous family times, outrageous laughter, singing, story telling, and catching Daddy’s contagious thirst for learning and seeing all there was to our wonderful nation. On one trip after many battlefield visits and historical sites, Daddy instilled such a powerful reverence for our country that Doug and I are saluting in every photo from that trip.

Daddy also traveled around the globe. For many of the years, Mama stayed home with “the baby,” whoever that was at the time. Daddy almost always took one or two or even three of us with him on his travels. Eventually even Mama joined in on the adventures. Once Daddy crossed the border leaving Texas, his cowboy hat was on his head and his boots on his feet. He was so proud to be a Texan.

Carolyn went with him to Red China as it first began to open its borders to Americans. He took the boys to Africa; all of
us went to Europe, many times. We went to Israel, too. Other travels included India, Saudi Arabia, South America, Australia, and countless other places.

The language barrier was never a problem for Daddy. He had his own universal language. Daddy would smile from ear to ear and give a Tootsie Pop. In Kazakhstan, on the far eastern side of what was then the Soviet Union, Daddy was the first American most of the people there had ever seen. They were terribly afraid of him at first, but Daddy’s sincerity, smile, and Tootsie Pop language won their hearts.

Once I witnessed this myself. We were driving through Yugoslavia just when Eastern Europe had begun to allow a few people in. We were on a one-lane road barely passing ox-pulled carts. We saw a group of children and their mothers in the field harvesting their wheat with scythes. Daddy stopped the car, hopped out, gave a loud whistle, and the curious folks walked over. When the mothers saw his smile and the Tootsie Pops Daddy was holding high in the air, they gave a nod and the children rushed forward laughing and smiling. Tootsie Pops for everyone!

Daddy was magical with children. He was the kind of person that sat on a bench at a park and before you knew it, little children had gathered around him. He took our entire neighborhood on bike rides; I’m talking 20 to 25 kids on bikes and one adult, Daddy. The youngest would be sitting in the front basket hood on bike rides; I’m talking 20 to 25 kids on bikes and one adult, Daddy. The youngest would be sitting in the front basket of his bike. Our doorbell would ring, and when we answered we were in for an amazing show. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle. The Hurt kids would go to the front porch and whistle.

Daddy coached every sport offered at the YMCA to every age group imaginable. He loved every second of it. I remember when he first started coaching Ellison’s soccer team. None of the parents even knew the rules of soccer at the time, so volunteers were few. Daddy went into coaching soccer full steam ahead, just like all the other sports. He just loved being with his kids and their friends.

At my wedding, the overwhelming memory most people have is that we had an ice cream Sundae bar. Why? Because my dad said, “I don’t like to eat cake without ice cream.” Dad proved that a human could live on coffee, Diet Dr. Pepper, and Bluebell ice cream.

Daddy really lived. He burned the candle at both ends. Daddy worked long, hard hours, but when he got home, he would go to the front porch and whistle. The Hurt kids would come running, along with a few other neighbors. Once Daddy was home, he was all ours. The fun had arrived!

One year in high school, the school phone book came out. There was an ad in it that read simply, “No phone calls after 9:00 pm. Dad.” I was mortified and went straight home and demanded to know if he had put that ad in the phone book. Daddy looked at me puzzled. His answer, “How did you know?”

Daddy liked to go to bed by 9:00 pm. That rarely happened, but that was always his plan. He was up and gone by 4:30, 5:00 at the latest. His rounds were done by 6:00 am and surgery started. By mid morning he was in the office seeing patients.

Every Tuesday afternoon was Daddy’s time off. Instead of taking the time off, this was his day to work at the Texas Scottish Rite Hospital and later the hospital’s Spina Bifida Clinic that he founded. It was a labor of love. He loved on all those special kids, and they loved him back. Those donated afternoons gave him countless wealth in his heart. He showed us how to be generous with our time in helping others.

So many people I know and have met have wonderful stories about how Daddy saved their life or changed their life for the better. He was a true physician. He cared tremendously about his patients. The time and concern he gave each one was genuine.

Daddy loved people—all people, every kind of person imaginable. He had the uncanny gift to make each person feel as if he or she mattered. Indeed, each person did matter to Daddy.

Daddy loved his children and grandchildren. Most of all he loved Mama. It was a joy to see Daddy come home and grab Mama in a bear hug and tell her he loved her. Then Mama would shake her head and say, “Oh Happy!” It made us all laugh.

Daddy was passionate about many things. He showed us by the way he lived that love of family mattered. He showed us to love the Lord with all your heart. He showed us that love of country and the great state of Texas should be ingrained. Do your best. Never stop trying. Do what is right. Forgive. Find the best in all people. Friends are a blessing and a joy.

Daddy told us often that family is enormously important. You stick together. Family is whom you can count on. Never let anything come between us brothers and sisters. I guess somehow that got through to us. My younger brothers and sister and I have muddled through all these years, sticking together and loving each other as Daddy taught us. I can’t say it was always easy; we are so different. But to this day we remain very close. I am proud to have passed that belief on to my own children, who are each other’s best friends.

The stories about Daddy are countless, incredible, crazy, hilarious, and all true. I imagine all those who knew him have their own encyclopedia of hair-raising tales about or including Happy Hurt. I know I do. If I told even a small amount, we’d be laughing, we’d be crying. And we would still be here when the sun came up. I know that Daddy would say to each of you here: You matter so much to me. I love you. Now go out and love others. Laugh and take a handful of Tootsie Pops with you to share.

WILLIAM C. ROBERTS, MD

I was fortunate at Southern Methodist University to be a classmate and fraternity brother of George Hurt. I knew no one when arriving in Dallas, but George and his friends rapidly took me in. A trip to Mexico with George and several others and then a visit to his family’s ranch remain vivid in my mind all the years since. The more I learned about George, the more I was awed by him. I heard that he had never made less than an A through college either, going to medical school after 3 years. George, I believe, could walk out of a class and quote the lecture he had just heard, and read a page and recite it. He certainly had one of the most brilliant minds that I have encountered. Additionally, George was a wonderful athlete. You name the sport and he was good at it. And all the time he was friendly, fun, humble, and modest. His nickname “Happy” was most appropriate. George, you were special and you will be missed.
**Tributes to Harold C. Urschel Jr., MD**

**AMANDA URSCHEL GOLDSTEIN**

I am Hal's fourth child and first girl (in the whole generation on both sides, as he would always say). Dad was one of my very favorite people in this world, my biggest inspiration. He was a man of excellence, a man of great faith, and a man who made it his mission to serve others. His devotion to his family and friends proved paramount. Dad loved to learn and even more to teach. Humor was his modus operandi. We are so lucky to have had him so long and so great until the end! When he died, he was 82 and still working full-time, still on the cutting edge. In fact, he had just finished a weekend in Los Angeles, coordinating research on the use of stem cells to treat heart failure.

While it is so sad and shocking for those of us left behind, we take great comfort in knowing that he went the way he told us he had hoped to go—instantly and traveling while working on what he loved most. What a blessing for him. The Lord was especially nice to take him the day before the election.

As many of you know from his fabulous stories, Dad grew up in Bowling Green, Ohio, as Tubby. Having witnessed his dad dying from a heart attack when he was just 13 years old, Dad was determined to find a way to prevent that for others by committing himself to study heart surgery. At home, he quickly took over as the head of the household to help his mom raise his younger brother, Bill, and his sister, Ann, who had Down’s syndrome. They counted completely on their friends for food and the basics of life. I believe this is why he cherished every friend, more than most do. His faith carried him through those days and proved to be the foundation of his life.

We always joke that nobody had more best friends than Dad—but it was true! He constantly called to check in, remembered something significant, or thanked us for a simple deed. Every little gesture was noticed and appreciated. He was a man who managed dozens of tasks simultaneously, yet when you called, it seemed as if he had nothing else on his mind but you. He was so proud of his family. He would send out e-mails to hundreds of people describing his grandkids’ accomplishments—with excessive exaggeration.

He always fought for and supported those in need. In fact, he had a special gift with those in need and took care of so many for years.

Dad approached life with humor. He was perpetually telling jokes, many of which can’t be repeated. One of his favorites was: When I die, I want to go peacefully in my sleep like my grandfather did, not screaming like the other passengers in the back of his car. Then he’d laugh and laugh—usually with tears streaming down his face.

Dad loved sports and loved to win. He loved football, particularly the St. Mark’s Lions, the Princeton Tigers, and the Dallas Cowboys. He believed sports taught one more about life than anything else. And he believed that coaches are the most influential people in one’s life, next to one’s parents. As we watched the Cowboys this past Sunday, as he did faithfully, we could hear him cheering along with us. In high school, we had to be the captain of every sport we played. If a coach didn’t put his kid or grandkid in the game, you could hear Dad yelling across the field to put his kid in, with a few choice expletives added.

Many of you know that Dad could out-cuss anyone—whether at home, in the OR, or at Grandparents’ Day. Nurses would tally his f-bombs in the OR, and he clearly set records. And then, after each operation, he would grade them on how they performed in the surgery. He left owing Liam (his youngest grandson) 9 minutes for bad language. On Liam’s timeout chart the penalty was 1 minute for each bad word. Grandpa would cuss and laugh, and Liam would say, “Grandpa, you are up to 9 minutes already!”

Dad always amazed us with the latest technology and medical advances. He always had the latest camera and took so many pictures that it was painful. He’d bark to us, “Smile, and like it!” Then we were lucky enough to be forced to sit and watch the unedited versions of countless family movies over the holidays.

Growing up in the Urschel family was always entertaining. We always had breakfast/dinner together. Often Dad would come home to eat, then go back to work. He would serenade us on his ukulele with his two favorite songs: *Take Me Out to the Ballgame* and *Mr. Moon*.

Dad also often embarrassed us. We were known as the family that showed up to church on Christmas morning in our pajamas and thought that was normal. Dad and Mom, out of sheer enthusiasm, belted out hymns during the service, as if they were competing to see who could sing the loudest. My friend would come pick me up early on Sunday mornings and hope she didn’t arrive as Dad was out getting the paper—naked. Other times, he would lecture and then force my friends to eat their vegetables at our dinner table.

Dad could roar louder than most. It didn’t take me long to realize, though, that if you just gave it right back to him, he would respect you. My kids would just smile as Dad yelled,
and he would soon break and start laughing himself. While he seemed like a big, burly grizzly bear, he was really a big, snuggly teddy bear. He would pull out the yellow legal pad every few months and call me in to go over everything I had done wrong. I would just smile and say, “Yes, Sir.” Nobody was ever good enough for his daughters. In fact, no boy was allowed on our property when we lived at home.

Dad loved St. Mark’s, Harvard Medical School, and especially Princeton. Our Christmas presents were always Princeton glasses, blankets, doormats, and trash cans. He bled orange and black. And he played the Tigertones in his car until the very end.

PawPaw also loved to hunt and fish. He cherished sharing the outdoors with us and enjoying things as simple as watching a cardinal in a tree. He would give us guns for Christmas or birthday presents and we’d go to the shooting range for family outings over the holidays—again a little different than most.

Dad traveled the world and wanted everyone else to. He and Mom would pack all seven of us in the station wagon and drive to Colorado in the summer. We would laugh too much in the back seat and get screamed at, only to make us laugh harder and get in more trouble. We always had to stop at the Big Tex Steak House in Amarillo so all four boys in the family could eat the 72-oz steak, appetizer, baked potato, roll, and a dessert in less than an hour, so we could get it free. They succeeded every time, of course. Once Brad and Hal could drive, we started taking two cars. Mom would quiz us on vocabulary words over the CB radio, only to get bashed by the truckers using that same channel. We were known for our eating contests at the hotel buffets and our tanning contests on the beach.

Dad always wanted the best and nothing less. Dad often preached to us that “learning is fun!” His excitement about learning was clearly contagious. He lived every single minute of his life. He worked at night and then would fall asleep sitting up, mid meal, or mid conversation the next day. He would come in our rooms at 7:00 AM on weekends, raise the curtains, and say, “Wake up. You are wasting your day!” Dad never settled for the status quo or mediocrity. Do everything to perfection, regardless of what you were doing. Marry the best, as he did, and marry for good breeding genes. Fight for what is right and refuse to lose.

Our stories with Dad are endless, just as our love for him is. The love he doled out will last forever more. Dad was our biggest fan and our biggest inspiration. What an example. What a gift to this world! I challenge you: Be the friend he was, laugh for the American Heart Association when he sustained his cardiac arrest.

I was asked by Hal and Betsey to join them on a trip to Israel a couple of months ago, where Hal was going to teach the lead surgeons how to do his thoracic outlet procedure. I almost did not go because of commitments back at Baylor but I am so glad I did. It was truly a trip to remember. Zoe and I arrived in Tel Aviv and were picked up at the airport. We had just brought carry-on bags—we travel light—but we had to wait for the Urschels’ checked bags. The physician greeting us announced, “OK, we need 6 camels for the Urschels and one mule for the Ramsays.” Hal operated at the Rabin Medical Center,

Michael Ramsay, MD

Hal was described to me recently as an icon of cardiothoracic surgery by Dr. Mike Mack—what a fitting description of a great physician and man. We celebrate the life of a truly amazing individual who has contributed so much to medicine, research, and mankind. I knew Hal as a great family person; in the operating room as a world-class surgeon; and in research as a cutting-edge physician-scientist.

I first met Hal and Betsey when Zoe and I arrived in Dallas at Baylor 36 years ago at a cardiac surgery meeting at the Petroleum Club that he and his good friend Denton Cooley were hosting. Hal gave many talks—an invited speaker around the world—scientific as well as “after dinner.” He was never at a loss for words and could ad lib on any topic. He would also give great introductions to renowned individuals like Denton Cooley, but somewhere he would often include the sentence, “I taught him everything he knows—but not everything I know!” Hal published extensively, and this included the authoritative tome on thoracic surgery that he edited with Joel Cooper.

Family first—always—Betsey, Hal, Brad, Locke, Amanda, and Susanna. He was always supporting the young. He would call my children and tell them in no uncertain terms which schools to go to—no discussion! Tara, my daughter, came to me one day and said, “Dad, Hal Urschel just called. I am going to Williams College!”

In the operating room, it was not for the weak, faint-hearted, or incompetent. Hal was intolerant of incompetence, complacency, and particularly less than 110% commitment. He was very fast to unleash expletives but always had patients’ best interest at heart. At the peak, he, Drs. Donovan Campbell, Maruf Razzuk, and Guy Prater were a world-leading team in cardiovascular and thoracic surgery and in bringing new innovations to the patient. Hal had the personality to make things happen. He did not pull punches and was very direct in his commentary. He awarded grades to everyone after a surgery, and F minus was frequently given; he set the bar high. Later Hal kept his prominence with his unique transaxillary approach to cure thoracic outlet syndrome, which he continued to this day.

Hal was the epitome of the clinical scientist, bringing research from the bench to the bedside. As he slowed down his surgery practice, he increased his drive to make major advances in cardiovascular research. He was the Baylor Chair in Cardiovascular Research. He was the Baylor Chair in Cardiovascular and Thoracic Research and Clinical Excellence. With Cara East, Baron Hamman, Greg Pearl, Jeff Schussler, and the team, he led a stem cell program where bone marrow cells were taken, prepared, and injected back into damaged heart muscle to grow back into healthy heart cells. Hal was the “behind-the-scenes” mantra, always striving to make the field and the patients better. He was preparing his presentation on this work for the American Heart Association when he sustained his cardiac arrest.

I was asked by Hal and Betsey to join them on a trip to Israel a couple of months ago, where Hal was going to teach the lead surgeons how to do his thoracic outlet procedure. I almost did not go because of commitments back at Baylor but I am so glad I did. It was truly a trip to remember. Zoe and I arrived in Tel Aviv and were picked up at the airport. We had just brought carry-on bags—we travel light—but we had to wait for the Urschels’ checked bags. The physician greeting us announced, “OK, we need 6 camels for the Urschels and one mule for the Ramsays.” Hal operated at the Rabin Medical Center,
teaching the whole cardiothoracic surgical team. Then we went to Jerusalem—escorted by Dr. Dan Meyer's sister, Devorah, who runs the YMCA there, and her husband, Robert Buerger, the CBS reporter who you will hear every morning on KRLD reporting on latest events in the Middle East. In Jerusalem we visited Calvary and the site of Christ's crucifixion. Hal confided to me there that it would not be too much longer before he would join him. I wondered if God realized what he was taking on. I am sure he did! At least he surely does now!

Hal will be remembered for his strong personality, his drive, and his impatience with anyone who was preventing progress, but also for his compassion, family first, and inspiration for the young. He was committed to making Baylor Health Care System great. He was at Baylor for 50 years and loved it and did everything he could to make it thrive in the forefront of medicine. In his pursuit of excellence, Hal would say: “Excellence is a result of caring more than others think is wise, dreaming more than others think is practical, risking more than others think is safe, and expecting more than others think is possible.”

It does not seem that long ago that Hal joined a team climbing Mt. Everest. He would often say:

Life is short
And the art long
The occasion instant
The experiment perilous
The decision difficult.

Hal, your life was too short, but you lived it to the full. We love you and Betsey—you will never be forgotten.
Tribute to Elgin W. Ware Jr., MD

STEVE FROST, MD

The city of Dallas, and for that matter, the state of Texas, has lost a legend. Elgin W. Ware Jr., MD, passed away recently. And with his passing, we've lost a truly great physician. His contributions to medicine were multiple. I first met him as a resident here at Baylor, where he would patiently teach surgical technique but also “the art” of medicine. I was fortunate to later join him in private practice where his partners all called him “the Squire” because he was such a gentleman to all we came in contact with and always had a story to share.

He was born, educated, and trained in Dallas and joined the urology group at Baylor in 1953, where he practiced until 2003. He held many leadership positions, including chief of urology at Baylor, president of the American Association of Clinical Urologists, president of the Texas Medical Association 50 Year Club, president of the Texas Urological Society, and president of the Dallas County Medical Society, among others. When he retired from the practice of medicine, he became the medical director of the Stewpot Medical Clinic, caring for the homeless of Dallas. He was also very interested in the history of medicine.

In an article in Texas Medicine in 2008, he reflected on a comment from a colleague that his generation was the greatest generation in medicine. He first noted, “Beginning after World War II, this ‘greatest generation’ witnessed and indeed was involved in a veritable explosion of knowledge in all areas of medicine, discoveries and advances far too many to enumerate.” Yet, what had set the generation apart probably had more to do with the art of medicine, “nothing more or less than a sincere and compassionate care and caring for the patient.” He hoped that for the younger generations, “their claim to greatness might be marked not only by those scientific advances, but more importantly, by an awareness and a continuation of their long heritage of those qualities that are a vital component of the Art of Medicine”—an art he practiced so well.

Good job, Squire! You will be missed!
Making Rounds with Oscar: The Extraordinary Gift of an Ordinary Cat by David Dosa

Reviewed by James Marroquin, MD

In a 2007 issue of the New England Journal of Medicine, amid the usual fare of the latest and greatest in biomedical research, there appeared a short piece about a cat named Oscar (1). Living as a pet in a nursing home dementia unit, Oscar demonstrated an uncanny ability to predict which of its residents were about to die. The furry creature’s presence at a person’s bedside invariably signaled that life’s end was near. The story generated a good deal of interest, earning the feline 15 minutes of fame. Now, years later, a book entitled Making Rounds with Oscar chronicles a doctor’s discovery of the animal’s special gift.

The author, David Dosa, is a geriatrician at the Steere House Nursing Center in Rhode Island where Oscar lives. He begins the book by explaining why he made the unusual choice to specialize in care for the elderly. I call his career decision unusual because gerontology remains among the least popular fields of practice for medical students to enter. Geriatric fellowship training programs at even the most prestigious institutions are sometimes unable to find willing candidates. Why is this the case at a time when our aging population needs more practitioners equipped to care for its elderly members? In a fee-for-service system that pays physicians for performing procedures and seeing a high volume of patients, the time-intensive nature of geriatric medicine makes it a specialty with some of the lowest reimbursement for the greatest amount of work. And while many young people enter medicine hoping to someday be the celebrated bearers of miracle cures, geriatric care focuses on helping individuals adapt to the inevitable failings and limitations that come with age.

But Dosa does not lament or even mention what he has foregone in money, power, and prestige. The fulfillment he derives from his vocation among the elderly does not seem to leave much room for feelings of martyrdom or envy. It is a fulfillment, he says, that comes from bearing witness to the stories of his patients as they live the last of their days. These stories form the heart of the book, and Oscar’s tale serves as an ideal vehicle for sharing them.

When a trustworthy nurse at the Steere House tells Dosa about the cat’s extraordinary talent, he is at first skeptical and sets about investigating the matter. One by one, he interviews the families of the patients Oscar accompanied in their final hours. Since all of them suffered from dementia, a revealing portrait of this devastating illness emerges. Dementia is characterized by deterioration in cognition, resulting in behavioral problems and difficulty performing the basic activities of daily life. Alzheimer’s, defined by the accumulation of certain proteins in the brain, is the most common form of dementia, accounting for 60% to 70% of cases. Dr. Dosa’s clinical expertise and the poignant narratives of patients and families dealing with this disease combine to make the book a valuable educational resource. In fact, the afterword contains some explicit guidance for those doing the admirable and arduous work of caring for people with intellectual disabilities.

But beyond being useful, Making Rounds with Oscar’s depiction of dementia speaks profoundly to the nature of personhood and the practice of modern medicine. Since at least the time of John Locke, philosophers have reflected upon the idea of personal identity. As an individual changes, what remains constant and defining, allowing him or her to be considered to be the same person over time? For the loved one of somebody with dementia, this can be much more than a matter for idle speculation. When the essential qualities and traits of your parent, spouse, or sibling are no longer present in their diminished state, who is it exactly that you are caring for and relating to? The son of one Steere House patient implicitly responds to this question by remarking, “I said good-bye to my mother a long time ago. Now I’ve just fallen in love with this little lady!” Other characters in the book do not share such a sanguine approach to what has been lost. When one day, after 63 years together, the wife of a man named Frank Rubenstein no longer recognizes him, he never again returns to the nursing home to see her. Though Rubenstein continues to call daily to check on his wife’s status, he cannot bear to see the fear and suspicion on her face when she encounters him as a stranger entering her room. But even as dementia surrounds a self in isolating darkness, creative acts of engagement can sometimes reconnect us, if only briefly, to the person we once knew. For example, Jean Ferretti, the wife of the pioneering musical composer and Steere House patient Ercolino Ferretti, reports to Dosa that “one of the things I found most interesting about my husband’s disease was that even toward the end of his life he responded to music. Here was this man who could no longer do much of anything. Sometimes he would get agitated. If you put on a jazz record, though, he would just sit there contentedly for hours.” As dementia transforms these individuals’ relationships with their affected loved ones, what does not and cannot change are the covenantal bonds they share with them. No matter how faintly these victims of...
dementia resemble who they once were, to their family they are still father, mother, husband, wife, sister, and brother.

Closely related to the issue of personal identity is the question of what makes human beings valuable and worthy of care. The residents of the Steere House dementia unit have lost capacities that many people see as essential for a meaningful life. In their impaired state, they can no longer contribute anything to society. Given these realities, is the tremendous work required to care for them warranted? Based on a certain utilitarian calculus, the answer to this question is no. But if all people are considered to have intrinsic dignity and worth, then a radically different response is demanded. For instance, in the Christian tradition, the Gospel is most manifest when people embody Jesus’ special love for those who can offer nothing in return.

But we must not confuse our sacred call to care for people with dementia with the automatic, reflexive use of all available technologies in efforts to extend their lives. When a medical intervention is more likely to be burdensome than beneficial, the more loving course of action may be to aim for comfort rather than the prolongation of life at all costs. This is illustrated in a heartrending story about a frail, debilitated Steere House resident named Saul Strahan. When Strahan develops a severe infection, Dosa discusses his grave condition with Strahan’s daughter and recommends against sending her father to the hospital’s intensive care unit (ICU) for aggressive and likely futile treatment. He suggests instead that Strahan remain in the familiar surroundings of the nursing home with a focus on providing him a peaceful death as the infection worsens. Viewing this approach as giving up on her dad, she insists that “everything be done,” even if there is very little chance of his recovery. Dosa later finds Saul Strahan in the ICU on life support—a breathing tube down his throat, a central line in his neck, and a dialysis machine at his bedside about to be used as a substitute for his failing kidneys. Dosa is saddened, but not surprised to soon thereafter learn of his patient’s death.

All available medical technology had been utilized on this man’s behalf. But amid the heroic efforts to save his life, nobody was really present with him during his lonely transition into the unknown. This tragic irony reflects many patients’ and practitioners’ conflicted experience of contemporary medicine. The past century witnessed the emergence of biomedical innovations our ancestors could have scarcely imagined. We can administer vaccines and antibiotics to prevent and eliminate previously fatal infections. We can replace insulin and other vital hormones when our bodies’ production of them is insufficient. We can open obstructed arteries during heart attacks and strokes, halting lethal damage to our hearts and brains. We can cure certain cancers with surgery, radiation, and chemotherapy. This growing, seemingly limitless capacity to triumph over afflictions before which humans had hitherto been helpless has radically altered our expectations of health care. For the first 23 centuries of Western medical practice (dating from the time of Hippocrates), clinicians’ primary role was to accompany and guide their patients through the experience of illness. In contrast, now that efficacious interventions are available, achieving desirable results is what matters. Yet positive outcomes are not always possible. Indeed, despite modern medicine’s numerous successes, death is still the ultimate outcome for us all. And as the focus has turned to most efficiently fixing patients’ problems, the healing, pastoral aspect of care that once constituted the heart of medicine has been neglected, to the frustration of patients and physicians alike. The simple example of a cat lying lovingly at a dying person’s side calls health care practitioners back to the sacred role of being a compassionate presence.


The reviewer, James Marroquin, MD, completed his residency at Baylor University Medical Center at Dallas and now is an internist in Austin, Texas. He can be reached at jamesmarroquin@gmail.com.
Facts and ideas from anywhere

US HEALTH

An expert panel appointed by the US Institute of Medicine reported their findings in January 2013 (1, 2). We in the US live shorter lives than any of 16 peer nations, including Australia, Canada, Japan, and 13 European countries (Figure 1). Swiss men live nearly 4 years longer than American men, and Japanese women live >5 years longer than American women. Americans get their health care in a less coordinated system than in any of the 16 other nations, and we in the US pay more for it. The cost of care in the US in 2011 was $2.7 trillion, or $8680 for each American. The closest among the other 16 nations was Switzerland, which spent $5489 per person. Americans are more reckless than those in the other 16 countries. Only Italians wear seatbelts less often. Nowhere else do motorcyclists go without helmets as often. Americans die more often in traffic accidents linked to alcohol consumption, and they own far more guns (89 per 100 people compared with 46 per 100 people in Switzerland, the peer group country with the next highest rate of gun ownership).

Far fewer Americans than in the past use tobacco, and only the Swedes now smoke fewer cigarettes than Americans. This is a reversal of the situation in the 1950s, when Americans smoked the most. Nevertheless, in 2003, smoking accounted for 1 in 5 deaths among Americans >50 years of age. But, smoking-related deaths are expected to decline further in the USA with the drop in the number of smokers and the rise in countries like France, where 46% of adults smoke.

The panel pointed out, of course, that what we eat is a major factor in the lower US lifespan. Americans eat, on average, 3770 calories a day. That’s 1100 more calories than the average adult male needs, and 1700 more calories than an average woman should consume. Between 1999 and 2001, Australians, Belgians, and Italians ate more but, by 2007, Americans were well ahead of anyone else. The average Swede consumes 17% fewer calories daily than the average American.

GLOBAL OBESITY

Overweight and obese people now outnumber the malnourished by nearly 2 to 1. According to the World Health Organization (WHO), in 2010, 80% of American adult men and 77% of women were overweight (3). Obesity costs at least $150 billion a year in American health care spending. But obesity is spreading rapidly in other parts of the world. Saudi Arabia and other Arab states and many Pacific Island nations are fatter than in the USA. Most of the adult population of Samoa is obese; in 2008, 46% of Egyptian women were obese. Mexican women are heavier than US women, and Mexican men will soon eclipse US men in poundage. These changes in part reflect advances in public health. In 1900, pneumonia, tuberculosis, and childhood diarrhea were the leading killers of Americans. Now, the top causes of death are noninfectious diseases, mainly atherosclerosis, hypertension, and cancer. In 2008, 63% of deaths around the world were caused by noncommunicable diseases and 80% of them occurred in low- and middle-income countries.

Many countries are trying to come to grips with this major shift in public health. Japanese companies require employees to undergo annual physicals that include waistline measurements.
Measurements of over 33.5 inches in men and over 35.4 inches in women count against the company. If too many fail the test, the firm has to increase its contribution to public health care for the elderly. Several countries tax soft drinks and other sugared beverages. Mexican legislators introduced a bill in December 2012 that would add a 20% tax to the cost of such drinks. In 2011, the average Mexican adult consumed 728 servings of Coca-Cola; the average American, 403 servings. The China Health Ministry has asked Dr. Kenneth Cooper of Dallas, founder and chairman of Cooper Aerobics, to explore the introduction of Fitness Gram Testing among its schoolchildren. Cooper indicated that Ross Perot contributed $2 million to help pay for a computer system to aggregate the results. Ten years ago there was hardly any obesity in China, according to Cooper. WHO estimates that 45% of Chinese men and 32% of Chinese women are now overweight or obese. The fast-food chains are rapidly expanding in China. Yum Brands, which owns Pizza Hut, KFC, and Taco Bell restaurants, has 38,000 restaurants globally, including 740 Pizza Huts and 4,043 KFC establishments in China.

Business groups complain that taxes, regulations, and unfair trade practices hurt their international competitiveness. Now, we can add body weight to that list. The Organization for Economic Cooperation and Development (OECD) in 2012 updated an obesity epidemic watch among its 34 country members (usually described as the wealthier developed countries) and found that the average rate of obesity across the OECD was 17% (4); in the USA, 34%; in Korea, 4%; in Germany, nearly 15%; in the UK, 23%; and in Mexico, 30%. In 19 of the 34 OECD countries, most of the population is now either obese or overweight. In the US and in Texas, more than two thirds of the population is either obese or overweight (Figure 2). Texas comptroller Susan Combs has estimated that obesity costs Texas employers nearly $10 billion in 2009.

BODY WEIGHT AND LEADERSHIP ABILITY

New research suggests that extra pounds or enlarged waistlines affect an executive’s perceived leadership ability as well as stamina on the job (5). Leadership experts and executive recruiters say that staying trim is now virtually required for anyone on track for the CEO corner office. Executives with larger waistlines and higher body mass indexes tend to be perceived as less effective both in performance and interpersonal relationships. While weight remains a taboo conversation topic in the workplace, heavy executives are judged to be less capable because of assumptions about how weight affects health and stamina. A business school professor recently stated that he could not name a single overweight Fortune 500 CEO.

SODA CONSUMPTION

In the USA, soda consumption is declining (6). Per capita consumption of carbonated soft drinks in 2005 was over 50 gallons, and by 2012, 42 gallons. Soda companies raised prices in 2011 and again in 2012 and volumes kept falling. The sugary bubbles are simply unhealthy. Sodas’ traditional target market, namely youth, is often now turning to water, energy drinks, and coffee instead. This of course is good news unless you happen to be an investor in Coca-Cola, PepsiCo, or Dr. Pepper/Snapple, which I avoid.

US MILK CONSUMPTION

In 1975, the US milk consumption per capita was 28.6 gallons and by 2011 it had fallen to 20.2 gallons (7). This decline is good news. Cows are the biggest source of our cholesterol, including their muscle, milk, butter, and cheese, and also our biggest source of saturated fat.

RELATION OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR TO SERUM PROSTATE-SPECIFIC ANTIGEN

A recent piece in the Mayo Clinic Proceedings (8) involving 1672 men found that for every 1-hour increase in sedentary behavior, the participants were 16% more likely to have an elevated prostate-specific antigen (PSA) concentration, and for every 1-hour increase in light physical activity, participants were 18% less likely to have an elevated PSA concentration. We men sit on our prostate gland. Get up and keep moving.

FASTING VS NONFASTING MEASUREMENTS OF BLOOD LIPIDS

Current guidelines recommend that total lipids and lipid subclass levels be measured with a patient in a fasting state.
and high-density lipoprotein cholesterol differed little among intervals. The mean triglyceride levels showed variations of up to 10% variation among groups of patients with differing fasting intervals. The mean calculated low-density lipoprotein cholesterol levels showed up to 10% variation among groups of patients with differing fasting intervals. The mean triglyceride levels showed variations of up to 20%.

MORE ON TATTOOS

Tattoos have become increasingly popular in recent years. In the USA, in 2012, an estimated 21% of adults had tattoos, up from 14% in 2008. The process of tattooing exposes the recipient to risks of infections, some of which are serious and difficult to treat. Historically, as LeBlanc and colleagues (10) emphasize, the control of tattoo-associated dermatologic infections has focused on ensuring safe tattooing practices and preventing contamination of ink used in the tattoo parlors—a regulatory task overseen by state and local authorities. In 2012, several outbreaks of nontuberculous microbacterial infections associated with contaminated tattoo ink raised questions about the adequacy of prevention efforts implemented at the tattoo-parlor level. The Food and Drug Administration (FDA) began reaching out to health care providers, public health officials, consumers, and the tattoo industry to develop more effective measures for tattoo ink-related public health problems. Some reports of tattoo-related nontuberculous microbacterial infections suggested that tap water or distilled water used to dilute inks at tattoo parlors was a likely source of contamination. Findings from more recent outbreaks suggested that the inks were contaminated before distribution.

Under the Federal Food, Drug, and Cosmetic Act, tattoo inks are considered to be cosmetics, whereas the pigments used in the inks are color additives that require premarketing approval. This law requires that cosmetics and their ingredients not be adulterated or misbranded, which means, among other things, that they cannot contain poisonous or deleterious substances or unproved color additives, be manufactured or held in unsanitary conditions, or be falsely labeled. Furthermore, cosmetic manufacturers are supposed to ensure the safety of a product before marketing it. But, the FDA does not have the authority to require premarketing submission of safety data from manufacturers, distributors, or marketers of cosmetic products, with the exception of most color additives (dyes, pigments, or other substances used to impart color). The FDA, however, can conduct investigations, request that a manufacturer recall volatile products, issue advisory letters, and request that the Department of Justice conduct seizures, enjoin a firm or person from manufacturing or distributing products, or file criminal charges against a firm or responsible persons on behalf of the FDA.

It is particularly important to increase awareness about certain types of tattoo ink–related infections because of several features of nontuberculous microbacteria. They may be difficult to diagnose and treat. It can take up to 6 weeks to identify the organism. A special culture medium and a skin biopsy may be required. Antibiotic choices are limited by the susceptibility profile of the organism, and prolonged treatment may be necessary to clear the infection. Moreover, complications such as co-infections with pathogens such as methicillin-resistant Staphylococcus aureus may pose additional challenges. Beware of tattoos.

RENAI SYMPATHETIC DENERVATION FOR DRUG-RESISTANT HYPERTENSION

Esler and colleagues (11) for the Symplicity HTN-2 investigators indicate that among the 7 billion people residing on Planet Earth, nearly 1 billion adults have high blood pressure. Despite the availability of numerous effective antihypertensive medicines, hypertension remains uncontrolled for various reasons, including inadequate treatment. Among hypertensive patients receiving treatment, the estimated proportion of patients with blood pressure uncontrolled (>140/90 mm Hg) ranges from 45% to 85% in Europe and North America. Furthermore, a subset of patients who receive a prescribed pharmaceutical regimen of ≥3 drugs, including a diuretic, continue to have uncontrolled or resistant hypertension. In the US, estimates of resistant hypertension prevalence range from 10% to 30% of adults receiving drug treatment for hypertension. These numbers reflect a serious health challenge because every 20/10 mm Hg increase in blood pressure leads to a doubling of cardiovascular mortality.

The sympathetic nervous system plays an important role in hypertension. Catheterization-based renal denervation is a minimally invasive procedure involving the application of radiofrequency energy in short bursts along the length of the main renal arteries to ablate the renal nerves that lie within and just beyond the artery’s adventitia.

The Symplicity HTN-2 trial randomized patients with resistant hypertension to either renal denervation or to no renal denervation, with both groups maintained for 6 months on antihypertensive medications. The primary endpoint, change in office-based systolic blood pressure at 6-month follow-up, demonstrated a significant difference in systolic blood pressure between the treatment and control groups. Patients in the control group then had the option to receive the renal denervation procedure. The 1-year results of this second trial, which included 6-month outcomes for the control group who were treated with renal denervation, resulted in a significant drop in blood pressure similar to that observed in patients receiving immediate denervation. Thus, renal denervation appears to provide a safe and sustained reduction of blood pressure to 1 year in patients with previous resistant hypertension.

WHY PATIENTS VISIT DOCTORS

St. Sauver and colleagues (12) from the Mayo Clinic analyzed medical records of 142,377 patients in the county
in which the Mayo Clinic is located to learn of the various conditions that prompted patients to visit their physicians during a 5-year period (2005–2009). Fifty-three percent of the patients were female. The 20 most common conditions among these individuals were as follows: skin disorders, 43%; osteoarthritis and joint disorders, 34%; back problems, 24%; disorders of lipid metabolism, 22%; upper respiratory disease (excluding asthma), 22%; anxiety, depression, and bipolar disorders, 20%; chronic neurologic disorders, 20%; hypertension, 18%; headaches, including migraine, 14%; diabetes mellitus, 14%; arrhythmias, 13%; esophageal disorders, 10%; asthma, 9%; thyroid disorders, 9%; iron deficiency and other anemias, 9%; bowel disorders, 9%; cancer, 8%; biliary and liver disorders, 8%; obstructive pulmonary disorders, 8%; and coronary heart disease, 8%. Ten of the 15 most prevalent disease groups were more common in women in almost all age groups, whereas disorders of lipid metabolism, hypertension, and diabetes were more common in men. The prevalence of 7 of the 10 most common groups increased with advancing age. Prevalence also varied across ethnic groups (whites, blacks, and Asians).

**BEDBugs AND SniffING DOGS**

Canines trained to detect bedbugs did big business in Dallas during the summer of 2012 (13), and that infestation may be back this summer. Bedbugs are resilient and can travel on everything. As someone said, “It’s basically a hitchhiker. It goes on suitcases and people spread it to other people. And once they make their way into a home, getting rid of them can cost several thousand dollars.” Apparently there is a pheromone in the bedbugs that dogs can smell. Dogs are about 97% accurate in finding the bugs, while humans are only about 30% accurate.

**GRAPHOLOGY**

I have kept a visitor’s book in my office for years and request a signature and address from all those willing to provide it. A number of years ago, while visiting The Greenbrier in West Virginia, I took a class on graphology. The teacher talked about letters leaning to the left or right, whether or not the long letters touched the top line or the lower letters went below the lower line, and whether or not there were lively movements in the top one and flamboyant swirls in the lower ones and what they meant. She recommended that potential spouses before marriage have a couple of paragraphs of their handwriting analyzed by a graphologist.

Sherlock Holmes asked Dr. Watson in *The Sign of Four*, “What do you make of this fellow’s scribble?” (14). “Look at his long letters,” he said. “They hardly arise above the common herd. That d might be an a, and that t an e. Men of character always differentiate their long letters, however illegibly they may write. There is vacillation in his k’s and self-esteem in his capitals.”

**THE LEAST HEART-HEALTHY STATE IN THE USA**

The official state meal of Oklahoma—designated by the legislature in 1988—includes barbecue pork, chicken-fried steak, sausage, biscuit and gravy, fried okra and squash, strawberries, black-eyed peas, grits, corn, cornbread, and pecan pie. A survey by the Centers for Disease Control and Prevention (CDC), published in 2012, indicates that only 1% of adults in Oklahoma are free from risk factors for or behaviors increasing the risk for heart disease—the highest rate for any state in the nation (15). Oklahomans also are less likely to report eating 5 or more servings of fruits and vegetables a day, and they are the most likely to be overweight.

**DROWSY DRIVING**

According to a study by the CDC, one in 24 motorists admitted to falling asleep behind the wheel in the past month (16, 17). The problem is more common in men than women and in drivers aged 25 to 34 compared to older drivers. According to Angie Wheaton, the lead author of the CDC study, approximately 2.5% of all fatal motor vehicle crashes (around 730 in 2009) involved drowsy drivers, as did 2% of crashes that resulted in nonfatal injuries (around 30,000 in 2009). They also found that around 4% of respondents fell asleep while driving in the previous year. The government estimated that approximately 3% of fatal traffic crashes involve drowsy drivers, but some studies have put that estimate as high as 33%. Brief moments of nodding off can be extremely dangerous, particularly when traveling 60 miles per hour. A single second translates to moving 90 feet, the length of 2 school buses. According to Dr. Kingman Strohl, a pulmonologist in Cleveland, a typical driver makes about 1000 decisions a minute. If a person has not slept for 18 consecutive hours, his or her impairment on those decision-making tasks is similar to that of someone above the legal alcohol limit. Everyone knows about driving and alcohol drinking, but there is much less emphasis on the importance of sleep before driving.

**FALLING TELEVISIONS**

According to Kim Painter, falling TV sets have killed >200 children since 2000 (18). The Consumer Products Safety Commission showed that 29 people in the US, most of them children, were killed by falling TVs in 2011 alone, and 18,000 people a year in the US, most of them children, are treated for injuries from falling TVs. That is happening despite the widespread switch to lighter flat-screens. Safety experts say the switch may actually be making the problem worse, because consumers often take old, heavy sets out of their family rooms and put them atop unstable bedroom dressers and playroom shelves. Children climb up on furniture to turn the TV on and there goes the heavy television as well as the piece of furniture. The 50- to 100-pound TVs can crush a child. The TVs often are on shelves never designed to hold the heavy weight. Flat-screen TVs also fall on kids because parents do not install them in the safest way. Let’s secure these TVs, and if anchoring is not an option, place the TV on a low sturdy base and remove any items from the top that might attract children.

**GUNS**

The US has about 315 million people and about 290 million guns. Germany has about 80 million people and 5.5 million
guns (19). Germany has recently initiated a large registry that details every legal gun owner in the country, along with information about all of their firearms. The new gun database, which went into service January 1, 2013, allows law enforcement officials to scroll through lists of owners and their guns in seconds on their computers. And the gun owners did not resist the establishment of this registry. Many gun advocates in Germany say that if cars can be registered and regulated, so can weapons. It’s not quite that way in the USA, but the US has about 50 times as many guns as are present in Germany.

In the US it is easy to acquire any number of weapons and unlimited amounts of ammunition. Those who pass laws make it possible. The National Rifle Association traditionally muzzles any congressional attempts at gun control laws. Surely there is a relation between the number of people killed with guns and the number of guns available.

**VIRGINIA TECH, FORT HOOD, AURORA, SANDY HOOK . . .**

Using news accounts and records from the Federal Bureau of Investigation (FBI) from 2006 through 2010, the most recent years for which complete records were available, *USA Today* identified 156 murders that met the FBI definition of mass killings, in which 4 or more people are killed by the attacker (20). The attacks killed 774 people, including at least 161 children aged 12 or younger. Mass killers, in other words, target Americans once every 2 weeks on average, in attacks that range from robberies to horrific public shooting sprees like the massacre in Newtown, Connecticut. The *USA Today* review did not include murders in 2011 or 2012, both of which were marked by a series of high-profile public shootings. The 2006 to 2010 killings offer a portrait of mass murder that in many ways belies the stereotype of a lone gunman targeting strangers: lone gunmen, such as the one who terrorized Sandy Hook Elementary School, account for fewer than half of the nation’s mass killers. About one quarter of mass murderers involved 2 or more killers. A third of mass killings did not involve guns. Mass murderers tend to be older than other killers, an average of nearly 32 years of age. Like all killers, they are overwhelmingly men. The mass killings during those 5 years accounted for about 1% of all murders during that time in the USA.

**DALLAS CRIME**

Despite increases in some major areas—rape, robbery, and murder—overall reported crime in Dallas dropped nearly 11% in 2012 compared to 2011, a record ninth consecutive year. The drop is in line with what is happening nationally and was driven by significant decreases in every area of property crime, which had about 7600 fewer offenses in 2012 than the previous year. Twenty percent more thieves were arrested in 2012 than in 2011 through the help of a task force that targets rings that buy and sell stolen property. Police Chief David Brown indicated that the longer a thief is in jail, the better the stats are going to be. Murders in Dallas in 2012 numbered 151, an increase from 133 the previous year. In comparison, Chicago had 506 murders in 2012, nearly twice as many killed than US troops in Afghanistan.

**MILITARY SUICIDES**

Suicides in the US military surged to a record 349 in 2012, far exceeding American combat deaths in Afghanistan (n = 295 Americans), and up from 301 in 2001 (23). Defense Secretary Leon Panetta and others have called the problem an epidemic. The problem appears to reflect severe strains on military personnel burdened with more than a decade of combat in Afghanistan and Iraq, complicated by anxiety over being forced out of a shrinking workforce. The 349 total in 2012 was the highest since the Pentagon began tracking suicides in 2001. The army, by far the largest of the military services, had the highest number of suicides among active-duty troops in 2012 at 182. The Marine Corps had the highest percentage increase—a 50% jump to 48. The Air Force had 59, and the Navy, 60 suicides, an increase in each of about 15% over the previous year.

**GENDERCIDE**

There are too many examples of global violence against women. Beverly Hill, who is founder and president of the Gendercide Awareness Project, calls it gendercide—the elimination of females, both young and old, through sex-selective abortion, infanticide, gross neglect, and in the case of older women (particularly widows), lack of access to food and shelter (24). The United Nations Population Fund, which tracks this problem, has estimated that 117 million women are missing in the world because of these practices. “Missing,” as Ms. Hill indicates, equals death. That’s more deaths than World War I and World War II combined. She indicates that it is no exaggeration to say that gendercide is an atrocity as colossal as any the world has seen. East Asia, South Asia, West Asia, the Middle East, Africa, and Southeastern Europe are all ravaged by gendercide. Every year, according to Ms. Hill, we lose 2 million baby girls to sex-selective abortion and infanticide alone. That equates to 4 girls every minute.

The United Nations reports that China has the greatest sex imbalance in the world, with 10% of its female population eliminated; India and Afghanistan follow with 7%. These sex imbalances lead to a host of social problems. Contrary to popular belief, the status of women does not improve when females are in short supply. In fact, just the opposite occurs. Sex trafficking increases, as does the buying and selling of brides. Aging bachelors, unable to find women of appropriate age, marry ever younger girls. These child brides leave school and begin bearing children. Maternal death rates are high. Ms. Hill goes on to indicate that there is a strong correlation between sex imbalance and crime. Sex ratios apparently are the best predictors of murder rates in India—better predictors than poverty, illiteracy, or urbanization. Crime spiked in the Chinese regions where sex-selective technology first became available. And finally, Ms. Hill writes: “Gendercide proceeds from the belief that female life is disposable. Gendercide devastates the hopes of women everywhere. It is unworthy of us as human beings. It is time to end this slaughter.”
WOMEN IN CONGRESS
Of the 100 US Senators, 20 (20%) are women and of the 435 House Representatives, 78 (18%) are women; both of these are records (25).

FIBRONACCI NUMBERS
By definition, the first 2 numbers of the Fibronacci sequence are 0 and 1. Each subsequent number is the sum of the previous two (26). The Fibronacci sequence is:

0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, etc.

The ratio of any two consecutive numbers eventually approaches the “golden ratio” of 0.618.

\[ \frac{1}{11/22/33/55/88/1313/2121/3434/5555/8989/144} \]

\[ 1.00, 0.6670, 0.600, 0.6250, 0.6150, 0.6190, 0.6180, 0.6180, 0.6180 \]

The sequence made its first appearance in the West in the book Liber Abaci (1202) by Leonardo of Pisa, also known as Fibronacci. (The sequence first appeared in Indian literature centuries before.) The Fibronacci sequence is important in nature: it describes the branching in trees, the arrangement of leaves on a stem, the fruitlets of a pineapple, the flowering of an artichoke, the uncurling of a fern, and the arrangement of a pine cone. Fibronacci numbers are truly fascinating. They have many implications for mathematicians.

PUBLIC HIGH SCHOOL GRADUATION RATES
The percentage of students at public high schools who graduate on time has reached its highest level in nearly 40 years (27). The public high school graduation rate, i.e., students earning a diploma within 4 years of starting high school, reached 78% for the class of 2010, the highest rate since 1974. Graduation rates improved for every race and ethnicity in 2010. The student graduation rates were as follows: Asians, 93%; Whites, 83%; Hispanics, 74%; American Indians and Alaskan natives, 69%; African Americans, 66%. In 2010, 38 states had higher graduation rates, while rates for the other 12 states were flat.

SMART DEVICES WINNING
Using a cellphone during class used to mean possible confiscation and perhaps detention for students (28). Now, a growing number of schools are turning to the smart phones students bring to school as an instructional device that can augment classroom learning. Teachers ask students to use their smart phones to look up vocabulary words, take photos of an assignment written on the board, or text themselves homework reminders. Teachers use countless apps to better connect students with coursework on a platform they are familiar with. The Verizon Foundation chose 12 schools in 2012 and 24 in 2013 to receive up to $50,000 in grant funding to bring laptops, tablets, and mobile phones to class. The focus is on science, math, and technology studies. The apps offer an easy way to do research, solve problems quickly, and motivate students.

IQ
The average American in 1900 had an IQ that by today’s standards would measure about 67 (29). Since the traditional definition of mental retardation was an IQ < 70, that leads to the remarkable conclusion that most Americans at the beginning of the 20th century would today be considered “intellectually disabled.” The trend of rising intelligence is known as the Flynn effect, named for James R. Flynn, the New Zealander who pioneered this area of research. The average American IQ has been rising steadily by 3 points a decade. Spaniards gained 19 points over 28 years, and the Dutch, 20 points over 30 years. Kenyan children gained nearly 1 point a year. These figures are from Flynn’s new book entitled Are We Getting Smarter? It’s an uplifting tale, a reminder that human capacity is on the upswing. The country that tops the IQ charts is Singapore, at 108. Singaporeans have great respect for learning and an outstanding school system. Flynn argues that IQ is rising because in industrialized societies we give our brains a constant mental workout, much greater than when we were mostly living on isolated farms. Modern TV shows and other entertainment can be cognitively demanding, and video games require more thought than Solitaire. It appears that talent is universal but opportunity is not. Our public school budgets are being slashed. According to Nicholas Kristof, some 61 million children in the world still don’t attend primary school. The cost of a single F-35 fighter could pay for more than 4 years of the Reading Is Fundamental program in the entire USA.

DEGREES AND INCOMES OF US ETHNIC GROUPS
As reported by Siegel (30), in 2010, the percentages of Americans aged 25 and older with at least a bachelor’s degree were as follows: all US, 28%; Asians, 49%; Whites, 31%; Blacks, 18%; and Hispanics, 13%. The median household income in the US in 2010 was as follows: all US, $49,800; Asians, $66,000; Whites, $54,000; Hispanics, $40,000; and Blacks, $33,300.

TWO INTERESTING HERBIVORES
My friend, Dr. Vince Friedewald in Austin, sent me the following information on camels and kangaroos (31). Camels can live where food and water are scarce. They have an amazing ability to conserve water. When dehydrated, a camel can drink as much as 120 liters (32 gallons) in 15 minutes. To conserve water, camels can regulate their body temperature so that they hardly sweat, their kidneys can concentrate the urine, and they store a lot of water in their erythrocytes, which have the ability to swell to over twice their normal size without bursting. The camel’s hump functions as a reservoir of adipose tissue that can metabolize to provide emergency energy. As the fat is depleted, the hump wilts and flops to one side. The fatty humps also help keep the animal cool, as fat conducts the sun’s heat relatively slowly and their woolly covering provides extra insulation. Thus, camels can go for weeks with little or no water or food.

Kangaroos in Australia have the ability to cross vast distances in search of food and water, keys to their survival. Capable of an 8-meter (25-foot) single bound across level ground, the red kangaroo is one of the world’s greatest long jumpers. Thanks to large feet and strong legs, it can travel at over 50 kilometers (30 miles) per hour for hours. While a kangaroo’s hind legs are big and powerful, they can’t work independently of each other,
and so kangaroos have to hop on two feet. The hind leg tendons are strong and elastic. With every hop, elastic energy is recaptured in the tendons ready for the next jump. The kangaroos use their long tail for balance and counterbalance. It swings up as the animal leaves the ground and down as the legs swing back with every bounce to help propel the kangaroo. A kangaroo’s big toes are in the center of the other toes, not to one side like in humans, and are thus in line with their leg bones, enabling them to push off with great force. The kangaroo has a pouch to carry the newborn for about 10 months after birth. To win the Olympics a human has to jump further than a kangaroo (to nearly 9 meters). The best jumper of all is the snow leopard, who can leap 15 meters.

**THE AVALANCHE OF UNFUNDED DEBT**

Mortimer B. Zuckerman, the editor of *U.S. News & World Report* and the publisher of *The New York Daily News*, in a December 2012 column paints the picture well (32, 33): “A sound in the mountain range. . . . It’s the sound made by an avalanche, the trillions of dollars of debt that’s heading our way, gathering speed and mass. For most people, it’s out of earshot.” Liabilities are not set out by our government in accordance with well-established norms of the private sector, where our overhang of liabilities would set off alarm bells in the markets, with boards of directors in emergency sessions. We have gone from being the world’s largest creditor nation, with no foreign debt at the end of World War II, to the world’s largest debtor, with half of our public debt held by foreign countries. During the last 4 years alone, our national debt has grown by more than $5 trillion to over $16 trillion. Although the Federal Reserve is keeping borrowing rates historically low, the cost of paying interest on the debt for fiscal year 2012 was just under $360,000,000,000!

Despite our huge annual deficit, the greatest fiscal challenge to the US government, opines Zuckerman, is its total liabilities. Our federal balance sheet, he indicates, does not include the unfunded obligations of Medicare, Social Security, and the future retirement benefits of federal employees. The estimated unfunded total of these commitments is more than $87 trillion, or 550% of our gross domestic product. And the debt per household is more than 10 times the median family income! The real annual accrued expense of Medicare and Social Security is $7 trillion. The government’s balance sheet does not include any of these obligations but focuses on the current year deficits and the accumulated national debt. The annual budget deficit, however, is only about one fifth of the more accurate figure! Zuckerman argues that if Americans saw our financial statements in the same way that public companies report their pension liabilities, these liabilities would require borrowing on a scale that would not only bankrupt the programs themselves but would bankrupt the entire government. Zuckerman adds that the Social Security programs and other mandatory programs are not subject to an annual spending limit. Today, <40% of our budget is actually decided by Congress and the president, down from 62% 40 years ago. Our liabilities are so huge and are multiplying so fast that eventually they cannot be honored. Today, all payroll taxes for Social Security and Medicare are spent in the year that they are collected, leaving no leftovers for the unfunded obligations!

And this does not take into account other risks such as the fact that the Federal Housing Authority confronts a $16.3 billion net deficit after its latest audit that may force a taxpayer bailout for the first time in its 78-year history. And, by 2016, the Disability Insurance Trust Fund will be fully depleted.

**US TAX RATES**

Taking into account all taxes on earnings and consumer spending—including federal, state, and local income taxes, Social Security and Medicare payroll taxes, excise taxes, and state and local sales taxes—the US average effective tax rate is around 40%. High tax rates—on labor, income, and consumption, as indicated by Prescott and Ohanian (34)—reduce the incentive to work by making consumption more expensive relative to leisure. The incentive to produce goods for the market is particularly depressed when the tax revenue is returned to households either as government transfers or transfers in kind—such as public schooling, police and fire protection, food stamps, and health care—that substitute for private consumption. In the 1950s, when European tax rates were low, many Western Europeans, including the French and Germans, worked more hours per capita than did Americans. Over time, tax rates that affect earnings and consumption rose substantially in Western Europe and have accounted for much of the nearly 30% decline in work hours in several European countries—to 1000 per adult per year today from around 1400 in the 1950s. The average American today works just over 1300 hours per year, the same as Japan, which has the same tax rate essentially as does America.

**OBAMACARE’S INDEPENDENT PAYMENT ADVISORY BOARD**

The Independent Payment Advisory Board (IPAB) is a government-appointed panel to help slow the growth of Medicare spending (35). The 15-person IPAB will propose Medicare cuts if the growth in the program’s spending exceeds inflationary targets. Some fear that their decisions will lead to rationing. The law, however, gives the panel no authority to ration care or cut benefits for Medicare recipients. It can’t touch reimbursement to hospitals until 2020. Instead, it is expected to find savings by eliminating fraud and reducing payments to private insurance companies that work with Medicare and prescription drug providers. And, it can only do that if the government is projected to spend more than it’s supposed to. Each spring, the Office of the Actuary of the Centers for Medicare and Medicaid Services forecasts how much the programs will cost 2 years in the future. On April 30, 2013, the panel will issue its per capita estimates for 2015. The actuary also will release a spending target, based on predictions about the pace of health care inflation. If the increase in expected Medicare costs exceeds the spending target, the IPAB steps in to propose cuts. It will take a 60% Senate vote to reject its recommendations, and then legislators must find alternate cuts that achieve the same savings. The law allows them to debate the IPAB's proposal for 30 hours maximum, making it filibuster proof.

How will the White House recruit the board members? So far no IPAB members have been appointed, even though the
board is supposed to get to work by April 2013. The law requires the panel to be made up of prominent physicians, economists, hospital executives, and insurance industry representatives. Candidates are subject to Senate approval, which means that they must endure potentially hostile public hearings. Board members willing to go through all that must also agree to serve for 6 years, full time; they have to quit their current jobs because of conflict of interest concerns. The annual salary for each board member is $165,300. And, the life of an IPAB member may be rather dull since its powers kick in only if spending is surging. It’s no wonder that Obama has yet to announce his candidates. If there is no IPAB in place by the time its services are needed, the law allows the secretary of the US Department of Health and Human Services to do its job until the panel is up and running. I can’t imagine who would want to be one of the 15 on that panel!

WATER

When the headline of the Dallas Morning News reads “The word on water: Conserve,” we have a problem (36). The state is running out of water, as shown in Figure 3. The projected Texas population in the next 50 years is expected to grow from 25 million to about 46 million (54%↑) and the projected need for additional water from 3.62 to 8.33 million acre-feet per year (43%↑). Get ready. Life with limited water will not be the same. Quick showers, low-flush toilets, and irrigation restrictions will be the norm. San Antonio, Texas, apparently is already in the swing of water conservation, and we must follow in Dallas.

Projected water demand and existing supplies

<table>
<thead>
<tr>
<th>Millions of acre-feet per year</th>
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<tr>
<td>25</td>
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<tr>
<td>15</td>
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<tr>
<td>10</td>
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</tbody>
</table>

2020 2030 2040 2050 2060

Demand
Supply

SOURCE: Texas Water Development Board

Wett

Figure 3. The supply and demand for water in Texas. Reprinted with permission from The Dallas Morning News.

US OIL BOOM

It’s really unbelievable, at least to me. The US oil output is surging so fast that the USA could soon overtake Saudi Arabia as the world’s biggest producer (37). Driven by high prices and new drilling methods, US production of crude and other liquid hydrocarbons rose approximately 7% in 2012 to an average of just under 11 million barrels per day. This is the fourth straight year of crude increases and the biggest single year since 1951. The Energy Department forecast that US production of crude and other liquid hydrocarbons, which include biofuels, will average 11.4 million barrels per day in 2013. That would be a record for the US and just below Saudi Arabia’s output of 11.6 million barrels per day. The production is forecast to reach 13 to 15 million barrels per day in the US by 2020, helping to make North America “the new Middle East.” I used to think that making the US “energy independent” was a joke, but it is great to see that it isn’t.

BALLPOINT PEN

We all use them. Peter Pesic summarized the book Ballpoint written by Hungarian author György Muldova (38, 39). The Hungarians are astonishingly creative. Eleven won the Nobel Prize during the 20th century, far more per capita than from other nations. There were other Hungarian geniuses, including mathematician John Von Neumann and physicists Leo Szilard and Edward Teller. Talented students flourished in some Budapest schools until the 1920s when the government began limiting university admissions to those “who are completely reputable in respect of their national allegiance,” effectively excluding Jews, who thereafter emigrated when they could.

One of the Jewish beneficiaries of those Budapest schools was László Biró (1899–1985), a journalist and artist in the 1930s who noted that the ink used for newspapers dried relatively quickly compared with the ink for fountain pens. Handwritten papers had to be carefully blotted or set aside until the ink dried. Biró tried using quick-drying ink in a fountain pen, but the fluid was too thick to flow down to the nib and simply clogged the reservoir. He solved the problem of how to deliver thick, quick-drying ink to a paper surface without requiring the ink to flow by closing the end of the pen instead of using a nib, leaving an opening with just enough room for a tiny metal ball that would spin against the ink in the reservoir, distributing it to the paper. Through much trial and error and with the help of an early backer and business partner, Endor Goy (1896–1991), Biró developed a working ballpoint pen. The two men signed a contract to produce and market the pen in 1938. Biró kept refining the pen and experimenting with recipes for the ink paste essential for his concept while fleeing dangers in Europe and finally settling in Argentina. Though Biró faced the hardships of wartime immigration, he soon started up a pen-manufacturing operation in Argentina. Biró’s story is relatively well known in much of the English-speaking world. “Biró” is synonymous with ballpoint pen. In Argentina, the pen is known as a “Birome,” and Biró’s birthday, September 29, is celebrated as “Inventor’s Day” in Argentina. Thus, the ballpoint took its place alongside the zipper, the pencil, and the paperclip devised by inventors who long struggled to produce objects we now take for granted.
EPIE AND POPO

These were their nicknames. They were identical twins, Esther Pauline Friedman Lederer and Pauline Esther Friedman Phillips, aka Abigail Van Buren, born in Sioux City, Iowa, on July 4, 1918. They shared a joint wedding and honeymoon trip. Esther was the first to become a columnist, taking over the Chicago Sun-Times’ “Ann Landers” column in 1955. Pauline, living in California, started a replacement advice column for the San Francisco Chronicle, “Dear Abby,” in 1956. She created her own byline, combining a biblical wise woman with the eighth president of the US. Within 2 years, both columns were in a combined 400 newspapers. Pauline’s “Dear Abby” column at its peak appeared in 1400 papers. Life magazine in 1958 said the sisters were “the most widely read and most quoted women in the world.” For a long time they did not speak to each other, but their differences were eventually patched up. Mother and daughter started sharing the byline in 2000, and Jeanne Phillips took over in 2002. Amazing (40).

SPORTS

Stan Musial: Years ago I was invited to give a talk in St. Louis by the son-in-law of Stan Musial, a physician, who brought me a baseball signed by Stan-the-Man. It is one of my favorite sport collectibles. When I was growing up, Musial was one of my baseball heroes. He played 22 years in the Major Leagues, all with St. Louis, in 3026 games. He had 10,972 at-bats and only struck out just over 600 times (41). He had 3630 hits, scored 1942 runs, had 6134 total bases, and hit 475 home runs. He won the National League batting title 7 times and participated in 24 all-star games. And all the time he was a great guy. He contributed to his community generously. He was 6 feet tall and weighed 175 pounds. Those also are my dimensions, but Musial had a much better eye for the ball.

Stacy Lewis: She is the first American to be named Player of the Year on the Ladies Professional Golf Association tour since 1994 (42). She had severe scoliosis and wore a back brace 18 hours a day for 7 years as a child. She had a steel rod with 5 screws installed in her spine just after getting her high school diploma. She didn’t know at that time whether she could play golf again, but she certainly did.

Johnny Manziel: As a red-shirt freshman, “Johnny Football” won the Heisman Trophy Award for 2012 and shortly after doing so set the Cotton Bowl record for total offense with 516 yards (43, 44). Seven other college football players have played in the Cotton Bowl after receiving the Heisman Award, but none came close to doing what Johnny Manziel did in the January 2013 classic.

Golf: The average professional golfer takes 15,000 steps during an 18-hole round, walks 7 miles, and burns 2000 calories. The numbers when using a cart are unclear.

BODY WEIGHT IN THE NATIONAL FOOTBALL LEAGUE

Fran Tarkenton, a National Football League quarterback from 1961 to 1978 and member of the Pro Football Hall of Fame, in a recent piece in The Wall Street Journal discussed body weight of professional football players when he played and subsequently (45). When Tarkenton entered pro football in 1961, every member of his offensive line weighed <250 pounds. During his last year, 1978, the biggest lineman on his team weighed 260 pounds. No Super Bowl–winning team had a 300 pounder on its roster until the 1982 Washington Redskins. Now, it is unusual for a team to have fewer than ten 300 pounders. This year’s Super Bowl teams, the San Francisco 49ers and the Baltimore Ravens, had twenty-four 300 pounders between them.

Have players gotten bigger thanks to genetics, diet, and nutrition? Or is there something else going on? Shortly after retiring from football, Tarkenton learned from an owner of one of the biggest gym chains in the country that muscles can only get so big by weightlifting regimes alone. Huge muscles come from performance-enhancing drugs, which Tarkenton indicated were just starting to enter professional football during his time. The National Football League does not talk about steroids or human growth hormone, but these drugs make players bigger, faster, and stronger, and they are used widely in football. Why do so many former players look like miniature versions of themselves after they retire?

In their most recent collective-bargaining agreement, signed in 2011, the National Football League and the Player’s Union agreed to start testing players for human growth hormone. Yet, two seasons later there still isn’t any testing! (In contrast, Major League Baseball in recent years worked out a testing regime that includes human growth hormone.) At the college football level, meanwhile, testing looks almost exclusively for recreational drugs, with practically no attention to performance-enhancing ones.

Although everyone claims to care about player safety at all levels of the game, the use of performance-enhancing drugs, which have made current players bigger and stronger than ever, causes collisions to be more violent and players therefore to suffer worse injuries. These violent encounters on the field not only affect the safety of the players during games but they clearly affect long-term health—dementia, Alzheimer’s disease, depression, suicide, and early death.

William Clifford Roberts, MD
1 February 2013


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AMERICAN JOURNAL OF CARDIOLOGY
Necropsy findings early after transcatheter aortic valve implantation for aortic stenosis
Roberts WC, Stoler RG, Grayburn PA, Hebeier RF Jr, Ko JM, Brown DL, Brinkman WT, Mack MJ, Guileyard JM

Although transcatheter aortic valve implantation has been available for 10 years, reports of cardiovascular morphologic studies after the procedure are virtually nonexistent. The investigators describe such findings in 2 patients, both 86 years of age, who died early (hours or several days) after transcatheter aortic valve implantation. Although the prosthesis in each was seated well, and each of the 3 calcified cusps of the native aortic valves was well compressed to the wall of the aorta, thus providing a good bioprosthetic orifice, the ostium of the dominant right coronary artery in each was obliterated by the native right aortic valve cusp. Atherosclerotic plaques in the common iliac artery led to a major complication in 1 patient, who later died of hemorrhagic stroke. The other patient developed fatal cardiac tamponade secondary to perforation of the right ventricular wall by a pacemaker catheter.

AMERICAN JOURNAL OF NEURORADIOLOGY
Interobserver variability in retreatment decisions of recurrent and residual aneurysms
McDonald JS, Carter RE, Layton KF, Mocco J, Madigan JB, Tawk RG, Hanel RA, Roy SS, Cloft HJ, Klunder AM, Suh SH, Kallmes DF

Background and purpose: The degree of variation in retreatment decisions for residual or recurrent aneurysms among endovascular therapists remains poorly defined. We performed a multicenter study to determine what reader and patient variables contribute to this variation.

Materials and methods: Seven endovascular therapists (4 neuroradiologists, 3 neurosurgeons) independently reviewed 66 cases of patients treated with endovascular coil embolization for ruptured or unruptured aneurysm. Cases were rated on a 5-point scale recommending for whether to retreat and a recommended retreatment type. Reader agreement was assessed by intraclass correlation coefficient and by identifying cases with a “clinically meaningful difference” (a difference in score that would result in a difference in treatment). Variables that affect reader agreement and retreatment decisions were examined by using the Wilcoxon signed-rank test, Pearson χ2 test, and linear regression.

Results: Overall interobserver variability for decision to retreat was moderate (ICC = 0.50; 95% CI, 0.40–0.61). Clinically meaningful differences between at least 2 readers were present in 61% of cases and were significantly more common among neuroradiologists than neurosurgeons (P = .0007). Neurosurgeons were more likely to recommend “definitely retreat” than neuroradiologists (P < .0001). Previously ruptured aneurysms, larger remnant size, and younger patients were associated with more retreat recommendations. Interobserver variability regarding retreatment type was fair overall 0.25 (95% CI, 0.14–0.41), but poor for experienced readers 0.14 (95% CI, 0–0.34).

Conclusions: There is a large amount of interobserver variability regarding the decision to retreat an aneurysm and the type of retreatment. This variability must be reduced to increase consistency in these subjective outcome measurements.

BREAST CANCER RESEARCH AND TREATMENT
Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer
Blum JL, Barrios CH, Feldman N, Verma S, McKenna EF, Lee LF, Scott N, Gralow J

We assessed the efficacy and safety of capecitabine across treatment lines, and the impact of patient and disease characteristics on outcomes using data from phase II/III trials. Individual patient data were pooled from seven Roche/Genentech-led trials conducted from 1996 to 2008 where single-agent capecitabine was the test or control regimen for metastatic breast cancer (MBC). Data were analyzed from 805 patients: 268 in the first-line metastatic setting and 537 in the second-line or later setting. Baseline characteristics were balanced across treatment lines. Patients receiving second-line or later versus first-line capecitabine had lower objective response rates (ORR: 19.0 vs. 25.0%, respectively, odds ratio 0.70; 95% CI: 0.5–1.0) and significantly shorter progression-free survival (PFS: median 112.0 days [3.7 months] vs. 150.0 days [4.9 months]; P < 0.0001) and overall survival (OS: median 396.0 days [13.0 months] vs. 666.0 days [21.9 months]; P < 0.0001). In multivariate analysis by backward elimination, significantly improved ORR (P = 0.0036), PFS (P < 0.0001) and OS (P < 0.0001) with capecitabine were demonstrated in patients with estrogen receptor (ER) and/or progesterone receptor (PgR)-positive versus both ER and PgR-negative tumors. Hand-foot syndrome (HFS) was the most common adverse event (AE) in 63% of patients. Overall, 7% of patients discontinued and two patients (<1%) died from treatment-related AEs. Significantly improved survival was observed in patients developing capcitabine-related HFS (P < 0.0001 PFS/OS) or diarrhea (P = 0.004 OS; P = 0.0045 PFS) versus patients without these events. In this pooled analysis of individual patient data, first-line capecitabine was associated with improved ORR, PFS, and OS versus second or later lines. Multivariate analyses identified greater ORR, PFS, and OS with capecitabine in patients with ER and/or PgR-positive versus ER/PgR-negative tumors. Safety was in line with previous phase III trials in MBC.
Safety and tolerability of the T-cell depletion protocol coupled with anakinra and etanercept for clinical islet cell transplantation


Background: Islet cell transplantation (ICT) is a promising approach to cure patients with type 1 diabetes. We have implemented a new immunosuppression protocol with antithymoglobulin plus anti-inflammatory agents of anakinra and etanercept for induction and tacrolimus plus mycophenolate mofetil for maintenance [T-cell depletion (TCD-AI) protocol], resulting in successful single-donor ICT.

Methods: Eight islet recipients with type 1 diabetes reported adverse events (AEs) monthly. AEs were compared between three groups: first infusion with the TCD-AI protocol (TCD-AI-1st) and first and second infusion with the Edmonton-type protocol (Edmonton-1st and Edmonton-2nd).

Results: The incidence of symptomatic AEs within the initial three months in the TCD-AI-1st group was less than in the Edmonton-1st and Edmonton-2nd groups, with a marginally significant difference (mean ± SE: 5.5 ± 0.3, 7.5 ± 0.5, and 8.3 ± 1.3, respectively; P = 0.07). A significant reduction in liver enzyme elevation after ICT was found in the TCD-AI-1st group compared with the Edmonton-1st and Edmonton-2nd groups (P < 0.05). Because of AEs, all patients in the Edmonton protocol eventually converted to the TCD-AI protocol, whereas all patients tolerated the TCD-AI protocol.

Conclusions: TCD-AI protocol can be tolerated for successful ICT, although this study includes small cohort, and large population trial should be taken.

Stimulation of adult resident cardiac progenitor cells by durable myocardial expression of thymosin beta 4 with ultrasound-targeted microbubble delivery

Chen S, Shimoda M, Chen J, Grayburn PA


It has been proposed that thymosin beta 4 (TB4)-protein delivery stimulates differentiation of resident adult WT1-positive cardiac progenitor cells, but with very low efficiency. We determined whether gene therapy with human TB4 stimulates proliferation of resident adult cardiac progenitor cells in normal rat heart. Ultrasound-targeted microbubble destruction (UTMD) was used to deliver the human TB4 gene under a piggybac transposon plasmid to normal rat heart. The rat hearts were assayed by quantitative reverse transcription-PCR and immunohistochemistry with a confocal microscope at 1, 2, 3, 4 and 12 weeks after UTMD. Exogenous TB4 stimulation resulted in the presence of WT1-positive cardiac progenitor cells from epicardium to endocardium. TB4 stimulated angiogenesis and arteriogenesis. One month after TB4 gene therapy by UTMD, the percentage of NKK2.5-positive cardiomyocytes was 5.5 ± 1.0% and NKX2.5 mRNA was 24-fold higher than in the control groups (P < 0.001). Similar results were found for ISL-1, BrDu, Ki-67, PHH3 and aurora B (P < 0.001). Cardiac-specific delivery of exogenous human TB4 gene efficiently stimulates proliferation and differentiation of resident WT1-positive adult cardiac progenitor cells into three intact cardiac cell lineages—vascular endothelial cells, coronary artery smooth muscle cells and cardiac muscle cells in normal adult rat heart.

A pilot study of prasugrel followed by post-procedural maintenance with clopidogrel in patients receiving percutaneous coronary intervention

Benjamin MM, Filardo G, Donsky MS, Schussler JM


Background: Dual anti-platelet therapy including clopidogrel or prasugrel is standard of care for patients receiving stents. Prasugrel has quicker onset so it can be loaded later than clopidogrel with greater efficacy. However, prasugrel is much more expensive than clopidogrel.

Objectives: To describe the incidence of 30-day death from cardiovascular causes, myocardial infarction, unstable angina requiring intervention, and minor and major bleeding in patients loaded with 60 mg of prasugrel prior to percutaneous coronary intervention (PCI) and then continued on 75 mg of clopidogrel daily after the procedure.

Methods: We reviewed sequential medical records of 102 patients (mean age: 67.8, male 68.6%, smokers: 22.6%, BMI: 29.5%, hypertension: 90.2%, DM: 33.3%, average ejection fraction: 49.7%) who underwent PCI (3.9% STEMI, 12.7% NSTEMI, 35.3% unstable angina and 48.1% electively) at Baylor University Medical Center between October 2009 and December 2011 who were loaded with prasugrel 60 mg prior to procedure, and then continued on 75 mg clopidogrel daily.

Results: None of the patients died or experienced a myocardial infarction (MI) within 30 days of the procedure. Three patients experienced unstable angina requiring intervention but none had in-stent thrombosis or restenosis on repeat angiography. None of the patients experienced a major bleeding event. One patient developed a gastrointestinal bleed which did not require blood transfusion and the bleeding resolved on discontinuation of the clopidogrel.

Conclusion: In this retrospective pilot study, a strategy of loading patients needing PCI with prasugrel 60 mg immediately prior to coronary intervention, then continuation of anti-platelet therapy with 75 mg clopidogrel daily was safe and effective.

Decisional involvement in Magnet®, magnet-aspiring, and non-magnet hospitals

Houston S, Leveille M, Luquire R, Fike A, Ogola GO, Chando S


Background: Empowered decision making can help establish innovative work cultures.

Objective: This study used the Decisional Involvement Scale to determine differences in actual and preferred decisional involvement among staff RNs and administrators in Magnet®, Magnet-aspiring, and non-Magnet hospitals.
Methods: Two facilities were Magnet designated, 3 were Magnet aspiring, and 9 were non-Magnet. A total of 5000 staff RNs and administrators were asked to participate in the nonexperimental descriptive survey.

Results: The difference observed in actual global scale score by Magnet status was statistically significant ($P = .01$). Respondents in Magnet hospitals had the highest actual global scale score on average, followed by Magnet-aspiring, then non-Magnet.

Conclusions: Decisional involvement is higher among Magnet-designated than non-Magnet facilities.

MICROBIAL PATHOGENESIS

Dendritic cells and vaccine design for sexually-transmitted diseases


Dendritic cells (DCs) are major antigen presenting cells (APCs) that can initiate and control host immune responses toward either immunity or tolerance. These features of DCs, as immune orchestrators, are well characterized by their tissue localizations as well as by their subset-dependent functional specialties and plasticity. Thus, the level of protective immunity to invading microbial pathogens can be dependent on the subsets of DCs taking up microbial antigens and their functional plasticity in response to microbial products, host cellular components and the cytokine milieu in the microenvironment. Vaccines are the most efficient and cost-effective preventive medicine against infectious diseases. However, major challenges still remain for the diseases caused by sexually-transmitted pathogens, including HIV, HPV, HSV and Chlamydia. We surmise that the establishment of protective immunity in the female genital mucosa will bring significant benefit for the protection against sexually-transmitted diseases. Recent progresses made in DC biology suggest that vaccines designed to target proper DC subsets may permit us to establish protective immunity in the female genital mucosa against sexually-transmitted pathogens.

TRANSPLANTATION

Sirolimus and cardiovascular disease risk in liver transplantation


Background: Two adverse effects of sirolimus are hypertriglyceridemia and hypercholesterolemia. These elevated levels often lead clinicians to discontinue the sirolimus from concerns of an increased cardiovascular disease (CVD) risk; however, evidence suggests that sirolimus might be cardioprotective. There are no published reports of sirolimus CVD in liver transplantation.

Methods: We reviewed all 1812 liver recipients who underwent transplantation from 1998 to 2010, identifying a cohort using sirolimus as part of the initial immunosuppression (SRL Cohort) and a control group of the remaining patients from this period where SRL was never given (Non-SRL Control). A prospectively maintained database identified all episodes of myocardial infarction (MI), congestive heart failure (CHF), abdominal aortic aneurysm (AAA), and cerebrovascular accident and tracked triglyceride, high-density and low-density lipoproteins, and total cholesterol levels. A Framingham Risk Model calculated the predicted 10-year risk of CVD for both groups.

Results: The SRL Cohort (n = 406) is older, more predominantly male, with more pretransplantation hypertension and diabetes and post-transplantation hypertension compared to Non-SRL Controls (n = 1005). The SRL Cohort has significantly higher triglyceride, low-density lipoprotein, and cholesterol levels at 6 months and 1 year. There is no difference in MI incidence in the SRL Cohort (1.0% vs. 1.2%) and no difference in AAA, cerebrovascular accident, and CHF. The Framingham Risk Model predicts that the SRL Cohort should have almost double the 10-year risk of CVD compared to the Non-SRL Control (11% vs. 6%).

Conclusions: Sirolimus causes hypertriglyceridemia and hypercholesterolemia, but it does not increase the incidence of MI or other CVDs. Considering the SRL Cohort has more cardiac risk factors and nearly double 10-year predicted CVD risk, the fact that the CVD incidence is similar suggests that sirolimus is in fact cardioprotective.
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Note: See also Oncology for research on colon cancer.

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145. Brouwer ES, West SL, Kluckman M, Wallace D, Masica AL, Ewen E, 
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care using data from a vendor-based electronic health record. Pharma-

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Schneeweiss S. The incident user design in comparative effectiveness 

Electronic health record use to classify patients with newly diagnosed ver-
sus preexisting type 2 diabetes: infrastructure for comparative effectiveness

April 2013 2012 publications of the Baylor Health Care System medical and scientific staff
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Note: See also Transplantation.


METABOLIC DISEASES


NEPHROLOGY


NEUROLOGY/NEUROSURGERY


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OTOLARYNGOLOGY


PATHOLOGY


PHYSICAL MEDICINE AND REHABILITATION


PULMONOLOGY/SLEEP MEDICINE


**RADIOLOGY**

Note: See also Oncology and other departments in which radiologists were first authors or coauthors.


**RHEUMATOLOGY**


**SURGERY**

Note: Most surgery articles are subclassified by specialty, even if general surgeons were first authors or coauthors.


**TRANSPLANTATION (ORGAN AND PANCREATIC CELLS)**


472. Itoh T, Takita M, Sorelle JA, Shimoda M, Sugimoto K, Chujo D, Qin H, Naziruddin B, Levy MF, Matsumoto S. Correlation of released HMGB1 levels with the degree of islet damage in mice and humans and with the outcomes of islet transplantation in mice. *Cell Transplant* 2012 Apr 26 [Epub ahead of print].


INTERVIEWS


EDITORIALS, BOOK REVIEWS, AND MISCELLANEOUS


519. Mack MJ. If this were my last speech, what would I say? *Ann Thorac Surg* 2012;94(4):1044–1052.


Note: This list (finalized on February 11, 2013) was based on submissions from medical and allied health staff and on PubMed searches. Although the list is representative of the year’s publications, some articles and book chapters were undoubtedly missed, since only a small percentage of researchers respond to the request for publications. Staff are encouraged to submit their publications each year. For more information or to submit publications for this list, please contact Cynthia Orticio (cynthiao@BaylorHealth.edu).
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