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Clinical research studies enrolling patients through Baylor Research Institute

Currently, Baylor Research Institute is conducting more than 800 research projects. Studies open to enrollment are listed in the Table. To learn more about a study or to enroll patients, please call or e-mail the contact person listed.

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<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
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</thead>
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<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></td>
<td>Idiopathic pulmonary fibrosis</td>
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<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, neuropathy, cardiovascular events, inhaled insulin</td>
<td>Kris Chionh 214-820-3416 <a href="mailto:kristen.chionh@BaylorHealth.edu">kristen.chionh@BaylorHealth.edu</a></td>
</tr>
<tr>
<td></td>
<td>Pancreatic islet transplantation</td>
<td>Kerri Purcell, RN 817-922-4640 <a href="mailto:kerrip@BaylorHealth.edu">kerrip@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>
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<tr>
<td>Gastroenterology</td>
<td>Coon’s disease</td>
<td>Dallas Clinical Trials Office 214-820-9626 <a href="mailto:jenniha@BaylorHealth.edu">jenniha@BaylorHealth.edu</a></td>
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<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, anginga, 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>
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<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>
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<td>Heart and vascular disease (Plano)</td>
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<td>Natalie Settele, PA-C 469-814-4712 <a href="mailto:natalie.settele@BaylorHealth.edu">natalie.settele@BaylorHealth.edu</a></td>
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<tr>
<td>Hepatology</td>
<td>Liver disease</td>
<td>Michelle Acker 214-820-6624 <a href="mailto:Michelle.Acker@BaylorHealth.edu">Michelle.Acker@BaylorHealth.edu</a></td>
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<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>Bryan King, LVN 214-823-2533 <a href="mailto:bryan.king@ntidc.org">bryan.king@ntidc.org</a></td>
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<td></td>
<td>Hepatitis C, hepatitis B</td>
<td>Cheryl Sandbach, RN 214-820-6267 <a href="mailto:Cheryl@BaylorHealth.edu">Cheryl@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Nephrology</td>
<td>Homocysteine and kidney disease, dialysis fistulas, urine/protein disorders in cancer patients</td>
<td>Dallas Clinical Trials Office 214-820-9626 <a href="mailto:jenniha@BaylorHealth.edu">jenniha@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Neurology</td>
<td>Stroke</td>
<td>Dion Graybeal, MD 214-820-4561 <a href="mailto:Dion.Graybeal@BaylorHealth.edu">Dion.Graybeal@BaylorHealth.edu</a></td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Annette Oaki, MD 214-820-4655 <a href="mailto:annette.oaki@BaylorHealth.edu">annette.oaki@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Cerebral aneurysms</td>
<td>Kennith Layton, MD 214-827-1600 <a href="mailto:KennethL@BaylorHealth.edu">KennethL@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Rheumatology (9900 N. Central Expressway)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis</td>
<td>John J. Cusht, MD 214-987-1253 <a href="mailto:johnn.j.Cusht@BaylorHealth.edu">johnn.j.Cusht@BaylorHealth.edu</a></td>
</tr>
<tr>
<td></td>
<td>Kathyrn Dao, MD</td>
<td>KathrynDao, MD 214-987-1249 <a href="mailto:KathyrnDao@BaylorHealth.edu">KathyrnDao@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Spine</td>
<td>Vertebral compression fractures</td>
<td>Kennith Layton, MD 214-827-1600 <a href="mailto:KennethL@BaylorHealth.edu">KennethL@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Transplantation</td>
<td>Bone marrow, blood stem cells</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:grace.townsend@BaylorHealth.edu">grace.townsend@BaylorHealth.edu</a></td>
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<tr>
<td></td>
<td>Solid organs</td>
<td>Michelle Acker 214-820-6624 <a href="mailto:Michelle.Acker@BaylorHealth.edu">Michelle.Acker@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Weight management</td>
<td>Obesity</td>
<td>Kris Chionh 214-820-3416 <a href="mailto:kristen.chionh@BaylorHealth.edu">kristen.chionh@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Women’s health (Fort Worth)</td>
<td>Endometriosis and endometrial ablation</td>
<td>Theresa Cheyne, RN 817-922-2579 <a href="mailto:theresa.cheyne@BaylorHealth.edu">theresa.cheyne@BaylorHealth.edu</a></td>
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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.
Results of an educational program to promote the use of pooled instead of single-donor platelet transfusions

Micah Burch, MD, Reva Schneider, MD, Ayman Barakat, MD, Laith Abushahin, MD, Ying Cao, MD, James Ewing, MD, and Marvin J. Stone, MD

Transfusion of platelets is commonly indicated in the inpatient oncology setting. These platelets are obtained either through apheresis from a single donor or pooled from the whole blood of several donors. The amount of transfused platelets, infection risk, incidence of alloimmunization, and increases in posttransfusion platelet count are similar for these two platelet products. Although single-donor platelets are preferred over pooled platelets in some instances, single-donor platelets are often given regularly, despite a higher cost and more limited donor supply. Oncology fellows at Baylor University Medical Center at Dallas initiated an education campaign regarding the indications for pooled and single-donor platelet transfusions. The quality improvement campaign included seminars led by oncology fellows for nursing personnel and resident housestaff on the two oncology floors, as well as electronic correspondence to attending physicians. The number of pooled and single-donor platelet transfusions on the two floors was recorded for the 3 months after the education campaign (July-September 2011) and compared with the corresponding data from the previous year. Over the 3-month study period after the education campaign, the average percentage of pooled platelets transfused increased to 34.1% from 13.1% for the prior year. Given this increase, the estimated cost benefit over the 3-month study period was $45,000.

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METHODS

This study was approved by the institutional review board at BUMC. The number of pooled, SDP, and total platelet transfusions given on the inpatient oncology floors (6 and 9 Roberts) was recorded by the BUMC blood bank. The study period included the 3 months following the education intervention (July–September 2011). The period of July to September 2010 was used as a control. The education campaign included presentations given by oncology fellows to nursing personnel on 6 and 9 Roberts as well as internal medicine housestaff. In addition, flyers were posted on 6 and 9 Roberts, and electronic correspondence was sent to attending physicians commonly rotating on those floors. The education campaign initially began in April 2011 but was delayed due to a shortage of pooled platelet products during that time. The primary education campaign took place in a 2-week period prior to the study period. Educational material encouraged the use of pooled platelets rather than SDP, exposures and thus reduce the risks of infection and alloimmunization. However, studies have not shown a benefit with using SDP versus pooled random-donor platelets for prevention of alloimmunization, provided platelets are leukocyte reduced (2). SDP that are HLA matched are indicated for patients with a known history of alloimmunization (3). Also, current testing for viral transmission has greatly reduced the incidence of transfusion-related viral infections (4). The risk of bacterial infections with platelet transfusions is increased due to platelet storage at 22°C rather than the 4°C required by red cells. This allows for more rapid growth of bacterial contamination of platelet products, which is usually caused by contamination by skin flora at the time of blood collection. While one study reported a decreased risk of infections with SDP versus pooled platelet transfusion (5), this risk should now be mitigated, as each product routinely undergoes rapid bacterial culture testing prior to transfusion (6).

From the Department of Oncology, the Baylor Charles A. Sammons Cancer Center at Dallas and Baylor University Medical Center at Dallas.

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except when histocompatible donors were needed for patients with a known history of alloimmunization.

The percentage of pooled platelet transfusions for July, August, and September 2010 (preintervention) was calculated, as well as the percentage over the same months in 2011 (postintervention). To compare the 2 years, a two-sample test for proportions was used. A cost-benefit analysis was performed by multiplying the total number of platelets transfused during the study period by the percentage of pooled platelets transfused during the control period from the previous year. This number was then subtracted from the actual number of pooled platelets transfused during the study period to give the estimated number of SDP saved. SDP saved was then multiplied by $275 (the approximate cost difference between SDP and pooled platelets) to determine the cost benefit.

RESULTS

The absolute numbers of pooled and SDP transfused on 6 and 9 Roberts are shown in the Table. A total of 1197 platelet units were transfused during the 6 months studied. Of these, 312 were pooled and 885 were SDP; 788 were transfused on 6 Roberts and 409 were transfused on 9 Roberts. During the control period, 443 units of platelets were transfused on oncology floors, and 55 (12.4%) were pooled platelets (confidence interval [CI] 9.7%–15.8%). During the study period, 754 units of pooled platelets were transfused, and 257 (34.1%) were pooled platelets (confidence interval [CI] 30.7%–37.5%). The absolute difference in percentage of pooled platelets transfused between 2010 and 2011 was 21.7% (CI 17.1%–26.2%), which was statistically significant (P < 0.001). The increase in pooled platelets transfused was seen on both 6 and 9 Roberts. There was no increase in platelet transfusion reactions or adverse events related to transfusion during the study period months.

The cost-benefit analysis revealed that approximately 94 units of pooled platelets would have been transfused during the study period had transfusions continued at the control rate of 12.4%. When this number was subtracted from the actual number of pooled platelets transfused during the study period, 164 units of SDP were saved. When multiplied by the average cost difference between DP and pooled platelets, the cost benefit was approximately $45,000 during the study period.

DISCUSSION

A large proportion of platelets transfused at BUMC are given to oncology patients. Our experience revealed that transfusion of SDP rather than pooled platelets was occurring at a high rate on oncology floors at BUMC. This was likely occurring due to a number of factors, including a previous system in which there was a significant cost benefit for apheresis platelets due to expenses related to bacterial testing of each platelet concentrate in a unit of pooled platelets. This cost benefit, however, has been abrogated by the ability to test the whole pooled unit of platelets only once. Currently, at BUMC, each unit of SDP costs the hospital $550, compared with $275 for pooled platelets. A cost-effectiveness study showed that the estimated cost per quality-adjusted life year of using SDP as opposed to pooled platelet therapy in stem cell transplant patients ranged from $168,700 to $519,822 (7).

In addition to cost, another factor that may have played a role in the culture of SDP use over pooled platelet use at BUMC was the belief among medical personnel that pooled platelets would result in a higher incidence of alloimmunization due to more donor exposures. However, no studies have shown a benefit to using leukoreduced SDP compared with leukoreduced pooled random-donor platelets to reduce alloimmunization (2). All platelet products at BUMC are universally leukoreduced.

Another factor influencing the increased use of SDP over pooled platelets was likely fear of increased infection with pooled platelets. Certainly, there is an increased risk of bacterial contamination of platelets due to storage at 22°C rather than 4°C. Ness et al found an increased risk of septic platelet transfusion reactions in pooled platelet products versus SDP (5). However, this retrospective observational study was performed prior to the mandate by the American Association of Blood Banks and College of American Pathologists for universal bacterial testing of all blood products (8, 9). Other more recent data show an equivalent low risk of bacterial contamination with pooled platelets and SDP when screening bacterial cultures are used (10). Concern over an increased risk of viral transmission with pooled platelets is not as strong as it once was, given the advent of routine nucleic acid testing of blood for HIV, human T-cell lymphotrophic virus, hepatitis C, and hepatitis B (4).

<table>
<thead>
<tr>
<th>Table. Pooled and single-donor platelets transfused on 6 and 9 Roberts</th>
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<tr>
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</tr>
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</table>
Some variability in our data set warrants further analysis. The increased overall number of platelets transfused during our study period compared to the control period was likely due to the transition of bone marrow transplant patients onto 6 and 9 Roberts in spring 2011. In addition, the higher percentage of pooled platelets given during the study period may be attributable to a previous educational campaign launched in April 2011. This campaign was delayed when there was a shortage of pooled platelet products in that month.

Despite an effective campaign to decrease the amount of SDP transfused on oncology floors at BUMC, most platelet products are still SDP. This is likely due to the ingrained culture and habits of using SDP at BUMC. Further increases in pooled platelet use are still warranted, however, as an appropriate goal for pooled platelet use should be closer to 90%. This could be attained through more extensive and personalized education for attending physicians, as our education campaign only included electronic correspondence for this group. Individualized feedback related to platelet-prescribing history for attending physicians and comparison to their peers may be a way to improve these practices. In summary, pooled platelets are as safe and effective as single-donor platelets and also have cost-benefit advantages. Therefore, continued efforts to promote the use of pooled platelets are worthwhile.

Lessons learned from study of depression in cardiovascular patients in an acute-care heart and vascular hospital

Michael Davis, ThM, J. Michael Brennan, MD, MBA, Nancy Vish, RN, PhD, FACHE, NEA-BC, Jenny Adams, PhD, Mary Muldoon, RN-BC, CEPS, Tara Renbarger, BSN, RN-BC, and John Garner, MD

Depression is highly prevalent in patients with cardiovascular disease, but questions about the effectiveness of screening and intervention remain unanswered. To evaluate the effects of proactive intervention at an acute-care heart and vascular hospital, patients who reported depressive symptoms on admission were randomized to an active, counseling-based depression intervention plus standard care (referral to a primary or psychiatric care physician) or to standard care alone. Despite early termination of patient enrollment because of lower-than-expected recruitment rates, the project had a positive impact. By involving and educating staff, the investigators raised awareness and improved the process of identifying and helping depressed patients. The lessons in study design and execution gained from this experience will help ensure success in future studies of this condition.

In 2008, the American Heart Association issued a science advisory recommending routine depression screening for patients with coronary heart disease. Soon after, Ziegelstein et al issued rebuttals labeling the recommendation “premature” and called on the American Heart Association to rescind the advisory owing to a lack of rigorously evaluated evidence demonstrating clear plans to benefit patients through reasonable use of resources (1). The risk of depression in cardiovascular patients and the worsened outcomes that result are clear, but screening remains controversial, as does the question of what intervention, if any, is a reasonable response to patients identified as depressed. A 2006 study by Rieckmann et al demonstrated a 1% improvement in medication adherence for each point of improvement in the Beck Depression Inventory (BDI) score (2), but studies showing improvement in other outcome measures are lacking. Investigators also have yet to identify a reproducible and reliable intervention that can improve depression scores and/or outcome measures in this particular population. With the goal of improving screening at a single high-volume acute-care cardiovascular hospital, a novel study was undertaken to compare depression screening tools in a population self-identified to be at risk and to evaluate via randomized trial the potential efficacy of a counseling-based intervention for those identified with severe symptoms.

METHODS

To evaluate current screening methods, study personnel completed a random chart audit that examined the admission database, a form filled out by patients upon admission. As shown in Figure 1, the section of the form serving as the depression-screening tool asks two questions: Are you feeling hopeless or worthless? If yes, are you having thoughts of suicide or harming yourself? A review of 340 charts at the cardiovascular hospital over a 3-month period in the fall of 2008 revealed that 4.4% of the population (15 patients) had noted signs of depression on their admission database. Of those 15 patients, only 1 was referred to counseling (via the office of the chaplain). The feelings of hopelessness and worthlessness expressed by the other 14 patients were not acted upon further, presenting an opportunity for improvement. At the time, the chart review was undertaken solely to evaluate the magnitude of the problem, so no further attempt was made to interpret the demographic characteristics of the patients who reported depressive symptoms. In retrospect, this oversight represented a missed opportunity to learn more about this group.

A high-profile suicide at another facility further increased interest in intervention for at-risk patients, prompting development of a protocol to evaluate tools for identifying depressed patients and providing support in the cardiac acute-care setting.

Depression associated with cardiovascular disease can be multifaceted, making assessment and intervention more complicated. When a patient answers yes to the current question about feeling hopeless or worthless, it is unclear whether those feelings are due to depressive symptomatology. Patients with cardiovascular disease often feel fatigued for weeks and lack the energy to conduct routine activities, mimicking key symptoms of depression even when full criteria are not met.

The 16-question Quick Inventory of Depression Symptomatology (QIDS) questionnaire is a tool that enables staff to measure the severity of a patient’s depression (3). Although...
validated in multiple population subgroups, it had not been validated in the specific population of cardiovascular acute-care patients.

The objective of the pilot study was to clarify the association between the newer QIDS tool and the industry-standard Beck Depression Inventory revision 2 (BDI-II) and to classify the unique features of cardiovascular inpatients and their depressive symptomatology. Power calculations assuming prevalence of depression consistent with the audit described above determined that an enrollment of 120 patients would be needed for statistical significance. Prior to any screening or enrollment, all protocols were approved by the hospital’s institutional review board.

Inclusion criteria were admission to a single acute-care unit within the cardiovascular hospital, an affirmative answer to feelings of hopelessness or worthlessness on the admission screening form, and duration of stay sufficient for completion of all necessary study procedures. Exclusion criteria included preexistent psychiatric medications for depression or psychosis, a QIDS score >14 (risk exceeding that acceptable for this pilot study), inability to consent, and active suicidal or homicidal thoughts.

Enrolled patients were randomized to one of two groups in a 1:1 ratio (Figure 2). The control group received the standard referral to their primary care physician or a mental health provider. Those randomized to the intervention group received referral to a physician or mental health provider, a 15- to 30-minute counseling session, a depression workbook, activity chart, and three follow-up calls over the course of 3 months. Both groups were asked to complete the BDI-II, a suicidality assessment (if they had not already done so) and a brief demographic questionnaire. Those who chose not to enroll were given a supportive visit, encouragement to follow up with a physician or mental health provider, an activity chart, and a depression workbook.

At the end of 3 months, participants in both groups were to be reassessed and asked to complete the QIDS, the BDI-II, the suicidality assessment, and the demographic questionnaire. All participants were also to be asked whether they followed up with a physician or mental health professional to address depression. The results from the two groups were to be compared to determine 1) which domains of depressive symptoms measured by the QIDS and the BDI-II reliably reflected depression in cardiovascular patients and 2) whether the intervention was significantly beneficial in this population.

**RESULTS**

During initial enrollment (February 2011 to February 2012), 126 cardiovascular patients noted feelings of hopelessness or worthlessness on the admission database and were screened for inclusion. Enrollment did not occur at the anticipated rate. Of 126 patients screened, only 8 were enrolled, and 6 of the 8 dropped out of or withdrew from the study.

Obstacles to successful completion of the study included the complexity of the study design, insufficient dedicated research time for the primary investigator, difficulty in scoring the QIDS, and the rapid flow of patients in the acute-care setting.

The study’s ambitious and complex design—comparing the results from the two depression-screening tools and measuring whether or not patients followed up with a primary care or mental health provider—resulted in too many end goals for the small patient population. Likewise, scoring the QIDS was complicated; incorrect scoring occurred often and in some cases led to incorrect referrals. It was clear that if the QIDS were not used routinely, the tool itself would present an educational barrier to those trying to administer it.

The rapid flow of patients in the acute-care setting also impeded enrollment. In many cases, eligible patients had stays as short as 4 to 5 hours, making an enrollment process that took upwards of 90 minutes infeasible. Compounding this problem further, it was generally the case that patients could only be enrolled preprocedure because the lingering effects of anesthetic or sedative agents prohibited consent thereafter. Patients who stayed longer were easier to engage, but maintaining their privacy was a challenge. To be accurate, depression screening must
be done in private, but having staff members ask family or visitors to step out during this time is an awkward proposition.

To help overcome these enrollment obstacles, the institutional review board allowed the inclusion of patients on two additional floors in February 2012; nevertheless, the team was not able to increase the rate of enrollment. Administrative matters (i.e., team member transitions, new study and support personnel, and divided roles of the research investigators) further hampered successful enrollment.

DISCUSSION

The hospital’s research council learned much from this experience, such as recognizing that the end goals were too numerous and that a study of this magnitude requires a research coordinator and a part-time chaplain/counselor to fulfill all the duties of the principal investigator. After the initial year of the study, enrollment was ended because the rate was insufficient to achieve the study goals. A new protocol was approved and will be implemented before the end of 2012.

Despite the inability to achieve the more mathematical goals of the project, a profound impact on depression was nonetheless produced. When the project was begun, many patients reporting hopelessness, worthlessness, or even suicidality were not seen or offered any support. Since April 2009, however, over 1100 patients have received follow-up. This number includes not only depressed patients but also suicidal patients who have been identified and helped with appropriate interventions, up to and including protective custody orders for those with immediate intent toward self-harm. In one such case, after further screening indicated that no true intent was evident, the protective order was removed and the patient was appropriately counseled about end-of-life options such as palliative care and hospice. Though enrollment into the study proper failed to demonstrate improvements as intended, the very screening process for the study dramatically improved identification of patients at risk for depression, their transition to appropriate follow-up, and in several cases, the ultimate outcome of their situation.

This research project, in its development and even in its failure to achieve its targeted endpoints, demonstrated an ongoing need to improve the routine screening and intervention process for depressed inpatient populations. Ziegelstein et al raised concerns about screening being imprecise (1), and the current admission screen fits that description. The first question—Are you feeling hopeless or worthless?—identifies specific depressive symptoms but does not effectively measure their timing or severity, two key elements in the diagnosis of depression.

None of the screening tools used in the study were ideal. Although the QIDS indicates timing and severity of depression, its time-consuming administration and scoring difficulty were prohibitive. The BDI-II, used only for validating the QIDS in the cardiovascular inpatient setting, was easier to score but was never considered for routine use because it was expensive and time-consuming to administer.

The Patient Health Questionnaire (PHQ), recommended by the American Heart Association, facilitates a self-rated, two-step approach to assessment. The first two questions (PHQ-2) serve as a basic screen; if the patient scores above threshold, the remaining seven questions are also asked (PHQ-9). In a study published in 2010, investigators used this approach in a large inpatient cardiac setting and found that the PHQ was highly desirable for depression screening (4). The instrument offers the benefits of simple scoring, quick administration, public domain access, and easy transition from the short version (PHQ-2) to the more specific full instrument (PHQ-9).

The ideal screen would be normalized for patients in a cardiovascular inpatient setting, a feature lacking in currently available instruments. Indeed, the inadequacy of our current screening is illustrated by the fact that patients who express feelings of hopelessness or worthlessness on the morning of admission often indicate no such feelings after their procedure (e.g., after percutaneous coronary intervention). Furthermore, even statistically reliable instruments may have limitations in this population. The QIDS, for example, includes questions about sleep patterns and energy level, indicators of depression that are also intimately related to cardiovascular illness. Likewise, none...
Texas, instituted a two-step intervention for all postpartum parallel projects. Baylor All Saints Medical Center in Fort Worth, sensitive aspects of their care. and decrease staff reservations about engaging patients in these and consistent manner could help further streamline the process ensure that staff members pursue patient privacy in an appropriate and consistent manner could help further streamline the process and decrease staff reservations about engaging patients in these sensitive aspects of their care.

Work within Baylor Health Care System also continues in parallel projects. Baylor All Saints Medical Center in Fort Worth, Texas, instituted a two-step intervention for all postpartum

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<thead>
<tr>
<th>Name of tool</th>
<th>Format</th>
<th>Comments</th>
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<td>Current tool used by Baylor Health Care System</td>
<td>Two questions (initial question about depressive symptoms)</td>
<td>No reference to time or severity, critical to diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)</td>
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<tr>
<td>Quick Inventory of Depressive Symptomatology (QIDS)</td>
<td>Sixteen questions, covering all DSM-IV depression domains</td>
<td>Reflects the DSM-IV. Harder to administer and score in a short-stay setting. Concerns exist about inpatient reliability.</td>
</tr>
<tr>
<td>Patient Health Questionnaire (PHQ)</td>
<td>Two-question initial screen (PHQ-2), extensible to the full nine-question version for follow-up (PHQ-9)</td>
<td>Easy and quick to administer. Reflects the DSM-IV. Statistically reliable.</td>
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<td>Ideal future tool that is appropriate for inpatient settings</td>
<td>To be determined</td>
<td>Goals: Easy to administer. Reflective of the inpatient cardiovascular setting. Statistically reliable.</td>
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Table. Comparison of depression-screen approaches used

of the screening tools reflect chronic pain, recent bereavement, or substance use, among other situational aspects of the patient history. Yet, these factors may also figure prominently in the cardiovascular profile (5).

As a result of the lessons learned from the initial protocol, the new research protocol features a simpler goal: to compare the current depression-screening questions to the PHQ-2 (for basic screening) and PHQ-9 (for follow-up screening). There is no intervention arm in the new protocol, and the hypothesis is straightforward: the PHQ will generate referrals more accurately than the current screen. The team hopes that revising the admission database questions will better identify depressed patients and improve the rate of follow-up, thereby improving depression-screening outcomes and overall patient outcomes. The Table compares the formats and features of the current screen, the QIDS, the PHQ, and an ideal future tool yet to be developed.

Further recommendations include involving a dedicated study coordinator with experience in behavioral research to optimize efficiency of study execution. A study-specific script to ensure that staff members pursue patient privacy in an appropriate and consistent manner could help further streamline the process and decrease staff reservations about engaging patients in these sensitive aspects of their care.

Work within Baylor Health Care System also continues in parallel projects. Baylor All Saints Medical Center in Fort Worth, Texas, instituted a two-step intervention for all postpartum

patients prior to discharge consisting of mandatory nurse-patient counseling (in which a nurse discusses postpartum depression and its signs and symptoms) and a take-home brochure about the condition. The outcomes of this intervention were presented at the 2007 Nursing Quality Summit and served as an inspiration for the present project.

In conclusion, the field of depression research among cardiovascular patients remains in a primal stage of development. No study need engage ambitious and far-reaching goals to make major contributions in this field. Each step brings us closer to an effective program of screening and intervention and truly has the power to help save lives. Our work in this matter will begin anew to help take these smaller steps forward, and we hope our experience will help other centers to develop plans, tools, and techniques to do the same.

Acknowledgments

The authors thank Betsy George, MD, for stepping in as the primary study physician after Dr. Garner’s departure; Rebecca Morton, RN, Niamat Chandani, RN, BSN, CVN, and Sherry Keithly, RN-BC, for assisting with project design, screening potential participants, and administering the QIDS; Sandra DeJong, BSN, RN-BC, for project design and document review; and Beverly Peters, MA, ELS, for editorial assistance. David W. Morris, PhD, Assistant Professor, Department of Psychiatry, University of Texas Southwestern Medical Center, participated in the assessment design process, and Jackie Gollan, PhD, Associate Professor in Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, allowed us the use of the Activity Chart and helped with intervention design. This project was funded by the Plough Metz Cardiovascular Fund of the Cardiovascular Research Review Committee in cooperation with the Baylor Heart and Vascular Institute.

Depression and cardiovascular disease: association, causation, and the right thing to do

The link between depression and cardiovascular disease is well known and is associated with poorer overall outcomes (1). Unfortunately, whether depression is a causative agent, a byproduct of the cardiovascular disease state, or a confounding comorbidity in this scenario has not been clearly delineated (2). For example, depression has been shown to be an independent risk factor for death after acute myocardial infarction, but does not have a significant effect on mortality until nearly 12 months after the acute event, and this does not seem related to recurrent cardiovascular events (3, 4).

Given the strong association, there is interest in screening for depression in this high-risk cohort. Unfortunately, the tools used for screening these populations are flawed and may be confounded by the cardiac condition for which the patients are being treated (5). In addition, while the association is strong, treating depression in the setting of cardiovascular disease does not improve mortality, although it does improve well-being (6).

Davis et al attempted an ambitious study to try to validate a newer screening tool that may be more useful in the evaluation of cardiovascular patients for depression (7). Given the high prevalence of depression and depressive symptoms in this cohort of patients, it would make sense that screening would have a high yield and would allow meaningful intervention from a psychosocial perspective. They were not able to come to any concrete conclusions, mostly due to flaws in the design of the study.

Despite the flaws in the study, several interesting pieces of information emerged. In the retrospective portion of the study, almost 1 in 20 patients revealed signs of hopelessness or suicidality in the routine intake questionnaire. Given the high volume of patients passing through our hospital, this is a large number of people in whom there is another potentially life-threatening (or certainly quality-of-life impacting) concern that we can positively impact.

The investigators also learned several practical lessons about designing and carrying out research protocols. These included issues related to allocating appropriate manpower for a trial and limiting the complexity of the study so that it allows for focused endpoints. While they were unable to prove the validity of their hypothesis, along the way they were able to positively impact several patients, and based on this study they are planning another research protocol that has a higher chance of coming to more definitive conclusions.

In conclusion, while the trial itself did not ultimately achieve its original goal, we can appreciate three vital things. First, we acknowledge that in cardiology, as with the practice of medicine in general, we only have two opportunities: to make people live longer and to make them feel better. While the final word on screening for depression in cardiovascular patients may be that we only have the opportunity for the latter, this does not make it a less worthwhile pursuit. Second, while it is far less common for negative trials to be published than for trials where there is a statistically significant outcome, these trials may be very educational. The importance of these trials is often underestimated, as without them we are doomed to repeat similar mistakes (8). Lastly, we recognize the compassionate people who work in a hospital system that devotes time and resources to answer questions about the most vulnerable of our patients, if only in order to help them feel better. This is commendable and should be encouraged.

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Intestinal perforation caused by insertion of a nasogastric tube late after gastric bypass

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A 57-year-old woman, who had undergone Roux-en-Y gastric bypass surgery 9 years earlier, was admitted to the intensive care unit because of pneumonia. Despite antibiotic therapy, she died 40 days later, apparently because of sepsis and organ failure related to the pneumonia. However, the patient’s family requested an autopsy, which revealed that her death was due to perforation of the Roux limb of her gastric bypass, which had resulted in severe peritonitis. The perforation was caused by a nasogastric tube inserted for enteral nutrition. We discuss ways nasogastric tubes might be inserted more safely after gastric bypass, the response of Baylor University Medical Center at Dallas to this complication, and the role of autopsy in improving the quality of hospital care.

In 2005, it was estimated that approximately 1 million people in the United States had undergone Roux-en-Y gastric bypass (RYGB) for treatment of severe obesity (1). When RYGB functions well for a number of years, it may be overlooked or forgotten when a patient is admitted to a hospital for a nongastrointestinal problem. Some of these patients, especially those admitted in intensive care units (ICUs), will receive nasogastric or orogastric tubes for enteral nutrition (2), often according to hospital protocol under the direction of nutrition services and nursing staff.

This article describes a case where insertion of a nasogastric tube caused intestinal perforation in a patient who had previously undergone RYGB. Like most of the nasogastric tubes used for enteral nutrition or for removal of gastric contents by suction, the tube that caused intestinal perforation in our patient was made of polyvinylchloride (PVC). Such tubes are flexible, but they are stiff enough to permit advancement through the nose or mouth into the stomach or duodenum.

CASE REPORT

A 57-year-old woman was brought to the emergency department with a 3-day history of productive cough and confusion. She had been on chronic immunosuppression with adalimumab and methotrexate for rheumatoid arthritis and was started on prednisone about 1 month earlier for Hashimoto’s encephalopathy. She had had RYGB 9 years earlier for severe obesity. A chest radiograph showed an infiltrate in the right middle and upper lobe. While in the emergency department, she developed severe respiratory distress, and an endotracheal tube was inserted. A 16 Fr (5.3 mm) PVC orogastric tube was also inserted, presumably for routine gastric decompression to prevent aspiration. A subsequent radiograph was interpreted by a radiologist as showing that the tube was “apparently in the stomach.” (A retrospective review of the film showed that the proximal aperture of the tube was below the gastroesophageal junction and that the tip was in the upper part of the Roux limb; Figure 1a.) She was then admitted to the ICU with a preliminary diagnosis of healthcare–associated pneumonia and started on broad-spectrum intravenous antibiotics.

Sputum staining showed gram-negative rods, and the cultures grew *Escherichia coli* and methicillin-sensitive *Staphylococcus aureus*. Blood cultures were negative. The patient was hemodynamically stable on hospital day 2, and the nutrition service recommended enteral tube feedings. On hospital day 3, tube feedings were started using the orogastric tube that had been inserted in the emergency department.

On hospital day 15, the patient removed her endotracheal and orogastric tubes. She developed hypoxemia shortly thereafter and the endotracheal tube was replaced. A new 16 Fr PVC nasogastric tube was also inserted, and a portable abdominal radiograph was interpreted as showing that the tip of the tube was in the stomach. (A retrospective review of this film showed that the proximal radiolucent side hole of the tube was located near the gastroesophageal junction [Figure 1b]; the distal 8 cm of tube containing smaller holes was presumably located in the gastric pouch and Roux limb.) Tube feedings were resumed. Over the next 2 weeks, the patient remained in the ICU and slowly improved.

On hospital day 28, the nasogastric tube could not be aspirated or flushed; it was therefore removed and a new 16 Fr PVC tube was inserted. Three portable supine abdominal radiographs were utilized during this tube insertion. The first and second radiographs revealed that the tip of the tube had not passed the...
apparent esophagogastric junction, and the radiologist recom-
mended advancement of the tube after each of the two films.
After the second advancement, a third film was interpreted as
follows: “Nasogastric tube courses into the stomach with the
proximal side hole visualized well below the gastroesophageal
junction.” Retrospective review of the final abdominal radio-
graph taken on day 28 showed that the inserted nasogastric
tube took a diff erent course within the abdominal cavity than
the orogastric tube that was inserted on day 1 and that it devi-
ated leftward and extended about 20 cm beyond the assumed
location of the gastrojejunostomy (Figure 1c). There was no
evidence of free air in the peritoneal cavity on the three supine
abdominal radiographs taken on day 28.

After interpretation of the third radiograph on day 28,
Oxepa® tube feeding was instituted (35 to 50 mL/hour). Ap-
proximately 12 liters of tube feedings were infused through
the tube during the next 11 days. “Gastric residual volumes”
were zero on multiple occasions. Bowel sounds were present,
and initially the abdomen was recorded to be nondistended.
However, the patient’s clinical condition gradually worsened
with hypotension, hypoxemia, fever, leukocytosis, renal failure
requiring dialysis, and diarrhea. Fecal fluid tested negative for
Clostridium diffi  cile toxin. On day 39, the abdomen was noted
to be distended and firm. After a family meeting on day 39, the
decision was made to withdraw life support measures, including
continuous venovenous hemodialysis, vasopressors, mechanical
ventilation, and nasogastric feeding. The nasogastric tube was
therefore withdrawn. The patient expired about an hour after
the vasopressors were stopped. The clinical diagnosis at the time
of death was pneumonia, sepsis, and multiorgan failure. Subse-
dent to her death, the patient’s family requested an autopsy.

Autopsy

Examination of the lungs revealed intraalveolar fibrosis and
organizing diffuse alveolar damage consistent with resolving
pneumonia. There was no evidence of aspiration of foreign
material.

Examination of the abdominal cavity revealed adhesed loops
of small intestine encased in approximately 1600 mL of puru-
lent fluid within a loculated area in the left upper quadrant. A
well-demarcated 4- to 5-mm circular perforation was visible
on the external surface of one of the loops of small intestine
(Figure 2). Further dissection revealed that the small intestinal
perforation was in the jejunal Roux limb 14 cm distal to the
gastrojejunostomy, immediately proximal to a hairpin turn of
the jejunum (Figure 3). This hairpin turn of jejunum was caused
by adhesions between two loops of the jejunal Roux limb. Mi-
croscopic refractile material was entrapped in the serosal infl am-
matory infiltrate, consistent with food or pill particles.

The round and sharply circumscribed transmural perfora-
tion was not associated with histological evidence of peptic ulcer,
vasculitis, or transmural ischemic necrosis of the surrounding
bowel wall. The pathological fi ndings were most compatible
with perforation from an inserted nasogastric tube (which
had been withdrawn just prior to death). Subsequent review

Figure 2. View at autopsy of formalin-ﬁxed external surface of loops of small intestine bound together by adhesions and containing a 5 mm small intestinal perforation.
of radiographs (Figure 1) also led to the conclusion that the perforation was the result of insertion of the nasogastric tube on day 28.

The pathologist concluded that the immediate cause of death was purulent peritonitis and sepsis due to perforation of the Roux limb of a gastric bypass procedure that had been performed years earlier. As stated above, the perforation was caused by a nasogastric tube inserted for nutritional support. The pneumonia that precipitated her admission to the hospital was resolving at the time of death.

**DISCUSSION**

The fact that this patient had had an RYGB procedure 9 years prior to her admission was noted in the past surgical history, but was not mentioned in daily progress notes, nursing notes, or nutrition service notes during her 40-day hospital stay. A review of the hospital records revealed no evidence that the radiologists who interpreted nasogastric tube positions were made aware of the previous RYGB.

When this complication was discussed at a clinical case conference, it became clear that physicians, nurses, and dietitians at our hospital did not know of any possible increased risks of nasogastric tube insertion in patients who previously had an RYGB. Moreover, in reviewing medical and nutritional publications, we found no case reports or guidelines stating that insertion of any type of nasogastric tube was dangerous in patients who had a remote history of RYGB. However, a search of Internet discussion boards on bariatric surgery revealed that some patients who have undergone RYGB fear complications from nasogastric tubes or have been cautioned by their surgeon not to receive a nasogastric tube (3, 4). Wikipedia has an article on nasogastric intubation that states that “use of an NG tube is also contraindicated in patients who have had gastric bypass surgery” (5). This statement appears to have been added in July 2008, about a year before our patient was admitted with pneumonia.

Our single case does not prove that patients with RYGB have a higher risk of complications from nasogastric tube insertion than patients who have not had RYGB. However, we believe that the complication experienced by our patient, when combined with knowledge of RYGB anatomy and pathophysiology, logically suggests that insertion of nasogastric tubes after RYGB may be more dangerous.

Nasogastric or orogastric tubes are designed for intubation of an anatomically normal stomach, which is large, highly distensible, and can hold an air volume of >1600 mL with little or no increase in intragastric pressure (6). A standard PVC nasogastric tube in our hospital is 122 cm in length, and its distal 8 cm contains multiple side holes through which fluids can be aspirated or infused. The entirety of the distal 8 cm of the tube can easily fit within a normal stomach. If excess tube length is inserted, the tube can coil within the normal stomach.
with little risk of causing significant damage. In contrast, the volume of the gastric pouch following RYGB is only about 30 mL, and its height is only about 4 cm (7, 8). There is no room for tube coiling, and it is unlikely that all of the holes in the distal 8 cm could be within the gastric pouch at the same time. Either some proximal holes of the tube would be in the lower esophagus, or some of the distal holes would have traversed the gastrojejunal anastomosis and be located in the Roux limb.

In the normal stomach, there are no recognized anatomic sites that are highly vulnerable to injury by a nasogastric tube, whereas in patients with RYGB there are several vulnerable sites. One of these is the narrow Anastomosis between the gastric pouch and jejunum. This gastrojejunal anastomosis is usually about 10 mm in diameter, only about twice the diameter of a 16 Fr tube (5.3 mm), and it is often poorly vascularized, making it susceptible to ulceration and injury (9, 10). Another location prone to injury is the blind loop of the Roux limb, which has no direct exit (Figure 4) (11). The wall of this blind loop is much thinner than the stomach wall. Still another vulnerable area is the proximal Roux limb, also known as the alimentary limb, which carries ingested food through the upper intestine. Like the blind loop, its wall is thin. Moreover, due to the operation that creates an RYGB, or due to anastomotic leaks in the early postoperative period, or due to previous unrelated abdominal surgical procedures, serosal adhesions may develop and produce kinks in the Roux limb. In our patient, fibrous serosal adhesions caused a hairpin turn 14 cm below the gastrojejunalostomy, and this prevented the inserted tube from moving distally within the jejunum, facilitating perforation when the tube was advanced.

Despite the possible increased risk of perforation, in several clinical situations use of a nasogastric tube is therapeutically essential in RYGB patients—most notably in those who have intestinal obstruction or prolonged ileus. Moreover, our single case report does not justify a ban on the use of PVC nasogastric tubes for nutritional support in patients who have previously received RYGB. However, our case does suggest that extra caution be employed when intubating patients who have had an RYGB.

Based on our experience with this case, we have several suggestions. The nurse or physician inserting the tube and the radiologist should know if the patient has previously had an RYGB, and they should have knowledge of bypass anatomy and the vulnerable sites noted above. They should not advance a PVC tube against resistance. They should recognize the substantial variation in distances between the nares and the upper part of the small intestine in people with an intact stomach (ranging from 51 to 74 cm) (12) and how these distances are altered by RYGB.

In adult patients with normal gastric anatomy, the length of tube, measuring from the nose, that has to be inserted so that the tip of the tube would lie in the body of the stomach can be estimated by using the formula \((\text{NEX} – 50)/2 + 50\), where NEX is nose to earlobe to xiphoid length in centimeters (13). This calculated length of tube can be inserted and then proper position can be verified using a radiograph. For many patients this calculated distance for initial insertion is about 58 cm, and presumably for this reason the PVC nasogastric tubes in our hospital are ink marked at 58 cm from the tip of the tube. Although this is probably an entirely safe length of tube to blindly insert in patients with normal gastric anatomy, in our opinion it is 10 to 15 cm longer than should be initially inserted into a patient who has previously had RYGB.

The final position of the tube, following adjustments based on radiography, should probably have the proximal side hole of the tube just below the estimated location of the lower esophageal sphincter. If the tube is not inserted far enough, nutrient solutions will be infused into the esophagus through the proximal holes of the tube, with risk of aspiration. (This problem could be mitigated somewhat by using a nasogastric tube with a single opening in the most distal part of the tube, although this might reduce efficacy of suctioning.) If too much tube is inserted, the end of the tube will move far down in the Roux limb, which has an unpredictable course.

The risk of perforation with PVC tubes could probably be reduced by using fluoroscopic guidance, which allows visualization of the tip of the tube as the tube is advanced. Using
polyurethane or silicone nasogastric tubes, which are softer and more flexible than PVC tubes, would further reduce the risk. These tubes are more difficult to insert, a problem that can be mitigated by use of a guide wire if needed (14).

Hospital response

Following autopsy, a conference was held between Baylor physicians and the patient's family. The autopsy results were fully explained, and the family was told that death of the patient was caused by perforation of the small intestine during insertion of a nasogastric tube.

This complication was discussed extensively at a special case conference. It was decided that prior bariatric surgery would be added to the list of conditions in which a physician, rather than a nurse, would insert nasogastric tubes. The revised Baylor policy for nasogastric/orogastric tube insertion is as follows: “In patients with altered physiology of the nares, oropharynx, esophagus, or stomach, such as occurs with bariatric surgery, other gastric surgery, nasal deformity or surgery, esophageal varices, or chronic epistaxis, nurses will not insert nasogastric or orogastric tubes, but consult with the physician to perform the procedure.” Two years after the new policy, one of the authors of this report interviewed 10 Baylor nurses from different floors and ICUs, and 9 of them were aware of the requirement for a physician to insert gastric tubes in patients who have had a gastric bypass. It was pointed out that this policy is also conveyed to newly hired nursing staff during their orientation.

The authors also requested the medical safety officer of Baylor University Medical Center at Dallas to consider adding a requirement that a radiologist who interprets the position of gastric tubes be informed when patients have previously received bariatric surgery.

The role of autopsy in this case

This case illustrates, once again, the value of a traditional hospital autopsy for discovery of clinically unanticipated findings and how such information may lead to useful modifications of hospital policies and procedures and provide the family with the true cause of death.

Autopsies on patients who die in the hospital are mainly done at the request of the patient’s family or physicians in order to clarify the cause of death, to assess clinical care, and occasionally for other purposes (15). The average hospital autopsy rate declined in the United States from 16.9% in 1972 to 4.3% in 2007 (16, 17). At the present time, autopsy rates remain near 20% in only a few hospitals, including Brigham and Women’s Hospital (personal communication, Gayle Winters, MD, August 23, 2012), Mayo Clinic (personal communication, Joseph J. Maleszewski, MD, August 23, 2012), and The Johns Hopkins Hospital (18). At Mayo Clinic, a concerted effort is under way to raise the autopsy rate from 25% to 50% (personal communication, Joseph J. Maleszewski, MD, August 23, 2012). At Baylor University Medical Center at Dallas, autopsy rates from 2006 to 2011 were relatively constant and averaged 4.4%. In our opinion, with rates this low, it is impossible to accurately calculate the frequency of therapeutic complications and misdiagnoses, and the quality of teaching programs and health care improvement programs is compromised.


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Intestinal perforation caused by insertion of a nasogastric tube late after gastric bypass

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Hodgkin lymphoma transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma

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Transformation to a large cell lymphoma may occur during the course of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in approximately 5% of the cases. This is known as Richter’s transformation. A much less frequent transformation to Hodgkin lymphoma may occur. We report a case of CLL/SLL in which a transformation to Hodgkin lymphoma occurred, and we review previously published reports of this transformation. Transformation to Hodgkin lymphoma in CLL/SLL has a poor outcome compared to de novo cases of Hodgkin lymphoma.

CASE REPORT

A 44-year-old man was well until September 2011, when he presented with massive lymphadenopathy and a white cell count of over 300 K/μL (Figure 1). He was subsequently diagnosed with CLL/SLL by morphology and flow cytometry. He underwent plasmapheresis and was started on rituximab and bendamustine. He showed a good response to chemotherapy and by February 2012 had only minimal residual disease. He completed eight cycles of chemotherapy up to May 2012. He then started having watery diarrhea and became febrile (up to 105°F). He was admitted to Baylor Regional Medical Center at Grapevine in May 2012 for evaluation and treatment of his symptoms. Blood cultures were negative. His stool culture was positive for *Giardia lamblia*. He was then treated with metronidazole, nitazoxanide, and octreotide with control of the diarrhea. However, he remained febrile. An abdominal computed axial tomography study showed hepatosplenomegaly and mild lymphadenopathy. A complete blood count revealed pancytopenia. Additionally, his lactate dehydrogenase level was normal.

A bone marrow biopsy showed two small focal areas containing atypical cells suspicious for involvement by Hodgkin lymphoma. There was no evidence of residual CLL/SLL. To establish a definitive diagnosis, an additional bone marrow biopsy was performed a week later and showed several atypical cellular areas containing Reed-Sternberg–like cells (Figure 2). Immunohistochemical stains revealed the large cells to be positive for CD30 and CD15 (Figure 3) and negative for Oct2 and Bob.1. An in situ stain for Epstein-Barr virus was also positive in these cells (Figure 4). These findings supported the diagnosis of Hodgkin lymphoma. There was no morphologic or
flow cytometric evidence of residual bone marrow involvement by CLL/SLL. The patient underwent treatment with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine). Unfortunately, he died from his disease in September 2012, about 4.5 months after the diagnosis of Hodgkin lymphoma.

**DISCUSSION**

The largest series of Hodgkin transformation in CLL/SLL has been reported from M. D. Anderson Cancer Center (3). Among their series of 4121 patients with CLL/SLL, only 18 patients (0.4%) transformed to Hodgkin lymphoma. Only a handful of other cases of Hodgkin transformation of CLL/SLL have been reported (3–10). Two types of Hodgkin transformation of CLL/SLL have been described. Type 1 is characterized by Hodgkin-Reed Sternberg (H-RS) cells scattered in a background of CLL cells (6, 11). In the type 2 transformation, H-RS cells are present in a typical polymorphous, inflammatory background separate from CLL cells (9–11). Our case fits the type 2 pattern. In the type 1 transformation, histologic and immunophenotypic findings suggest that the H-RS cells represent histologic progression of the underlying CLL cells, especially when the H-RS cells express B cell markers (12). Although in the type 2 transformation, two different disease types are considered to be present, the two lesions may be related. It is unknown whether the two types of Hodgkin transformation in CLL/SLL are associated with distinct clinical and prognostic features. The H-RS cells and the CLL cells seem to have a clonal relationship using single-cell polymerase chain reaction analysis and DNA sequencing (12).

In the M. D. Anderson series, the median overall survival was 0.8 years (range 0.03–6.7+). The median failure-free survival duration was 0.4 years. Fourteen of the 18 patients were treated with chemotherapy. Nine patients received Hodgkin lymphoma-type therapy, including five patients who received ABVD (doxorubicin, bleomycin, vincristine, and dacarbazine), three patients who received CVPP (cyclophosphamide, vincristine, procarbazine, and prednisone), and one patient who received CVPP/ABVD. Five other patients received other cytotoxic regimens with or without rituximab. All patients died from disease recurrence or progressive disease without responding to therapy. Most of the other papers report an equally poor response. Although the number of patients in the M. D. Anderson series was small (although it is still the largest series reported), the authors suggested that newer, more effective intensified combined-modality regimens may be more effective.
One paper reported a partially successful treatment (5). This patient was treated with lomustine, mitoxantrone, and vinblastine and achieved a complete response but relapsed and died 2 years and 2 months after the diagnosis of Hodgkin disease. Another short correspondence from 2000 described three cases of patients with CLL who subsequently developed Hodgkin disease and had a good response with complete remission (13). Two patients were treated with intensive chemotherapy (Stanford V regimen) followed by radiotherapy, and one patient received three courses of MOPP (mechlor-ethamine, vincristine, procarbazine, prednisone)/ABVD (14). The authors also stated that such an outcome was rare. One piece of information that is not consistently available in the papers is the stage of Hodgkin lymphoma at the time of diagnosis, which may have some influence on the outcome. Our case was stage IV. An association with Epstein-Barr virus (also present in our case) has been noted; it is important to determine whether this virus is present and, if so, antiviral therapy might be incorporated in combination with chemotherapy (6, 14).

Although Hodgkin lymphoma transformation is infrequent in CLL/SLL, the prognosis is unfavorable. It will be important to evaluate any newer innovative regimens developed for Hodgkin lymphoma.

T-cell prolymphocytic leukemia

Robbie L. Graham, MD, Barry Cooper, MD, and John R. Krause, MD

T-cell prolymphocytic leukemia is a rare and unusual malignancy characterized by the proliferation of small- to medium-sized prolymphocytes of postthymic origin with distinctive clinical, morphologic, immunophenotypic, and cytogenetic features. Involvement of the peripheral blood, bone marrow, lymph nodes, liver, spleen, and skin can occur. The clinical course is typically very aggressive with poor response to conventional chemotherapy and short survival rates, and the only potential long-term curative treatment is hematopoietic stem cell transplantation. We report the case of a man with de novo T-cell prolymphocytic leukemia and discuss the distinctive clinical, morphologic, immunophenotypic, and cytogenetic features of this entity.

Prolymphocytic leukemia (PLL) is a rare lymphocytic disorder characterized by marked lymphocytosis and splenomegaly and represents only 2% of all mature lymphocytic leukemias in adults over the age of 30. PLL is clearly defined into subtypes as B-cell prolymphocytic leukemia (B-PLL) and T-cell prolymphocytic leukemia (T-PLL), with T-PLL representing approximately 20% of the cases (1). While these subtypes have their similarities, T-cell and B-cell PLL are two distinct diseases with different clinical and laboratory features. T-PLL is more rare and more rapidly progressive and aggressive than B-PLL (2). T-PLL is generally resistant to conventional chemotherapy, and historically the median survival has been about 7 months, while that for B-CLL is 30 to 50 months (3–5). We report a case of de novo T-PLL and discuss the typical clinical, morphologic, immunophenotypic, and cytogenetic features of this entity.

CASE PRESENTATION

A 75-year-old African American man was hospitalized at Baylor University Medical Center at Dallas in May 2012 after a recent fall and a 4-month history of progressive weakness. An evaluation by an oncologist 18 months earlier had disclosed a white cell count of 47,000 K/uL, hematocrit of 44%, and platelet count of 165,000 K/uL. A differential count at that time revealed many convoluted, atypical lymphocytes comprising 91% of the circulating mononuclear cells. Peripheral blood flow cytometry confirmed a T-PLL with lymphocytes expressing CD2, CD3, CD4, CD5, CD7, CD26, and CD52. This population was negative for CD1a, CD8, and TdT. The clonal T-cell receptor beta gene rearrangement assays were positive. Cytogenetics confirmed a complex karyotype including an inversion of chromosome 14 and isochromosomes 8q. Fluorescence in situ hybridization also revealed 11q22 deletion and 17p13 loss. The patient was lost to follow up, and he did not return for marrow assessment or to discuss treatment options.

On this admission, he was lethargic and appeared chronically ill. Medications included amlodipine, rosuvastatin, and ranitidine. There was no peripheral lymphadenopathy. Auscultation of the chest revealed diffuse rhonchi, normal heart sounds, and a 2/6 systolic murmur. His spleen was palpable 7.0 cm below the costal margin. His hematocrit was 29% and his white blood cell count was 476,000 K/uL with 96% lymphocytes and 3% neutrophils. Many atypical large lymphocytes with slightly convoluted nuclei containing prominent nucleoli and copious nongranular cytoplasm were present (Figure 1a). The platelet count was 47,000 K/uL. Blood cultures on admission were positive for coagulase-negative Staphylococcus. Uric acid was 7.9 mg/dL, and lactate dehydrogenase was markedly elevated at 2369 u/L (reference range 185–249). Creatinine was 1.6 mg/dL, and liver function studies were normal. A computed tomography scan of the chest revealed mediastinal lymphadenopathy, and an abdominal sonogram confirmed the splenomegaly.

On the second hospital day, a bone marrow biopsy (Figure 1b) along with flow cytometry and cytogenetics confirmed T-PLL. During his hospitalization he was treated with a 7-day course of 2-chlorodeoxyadenosine at 0.1 mg/kg intravenously daily by continuous infusion. He was maintained on broad-spectrum antibiotics but developed renal insufficiency and recurrent gastrointestinal bleeding secondary to a benign esophageal ulcer documented on endoscopy. His white blood cell count only marginally improved with his chemotherapy, with a white count of 199,000 K/uL after 6 days of chemotherapy. At that time...
intensive care was withheld, comfort care measures were instituted, and the patient died on the 10th hospital day.

**DISCUSSION**

T-PLL, a rare hematological malignancy, was first described in 1973. It represents ~2% of mature lymphocytic leukemias (1, 6, 7). T-PLL primarily affects older adults with an average age at presentation of 65 years with a slight male predominance (8). Most patients present with hepatosplenomegaly (splenomegaly in 82% to 92%) and generalized lymphadenopathy (1). Other common findings include skin lesions (27%) and pleural serous effusions (14%) (7).

The peripheral blood commonly exhibits anemia and thrombocytopenia with a marked lymphocytosis and lymphocyte counts frequently >100,000 K/uL (7). A distinctive hematologic aspect is a rapidly rising white blood cell count with a doubling time of weeks to months (9). The key morphologic feature in the diagnosis of T-PLL is a population of prolymphocytes in the peripheral blood. The typical morphology consists of prolymphocytes of medium size with condensed nuclear chromatin, a single prominent nucleolus, and intensely basophilic nongranular cytoplasm with cytoplasmic protrusions or "blebs." The nuclei can be round, oval, or irregular (10, 11). In 25% of cases, the cell size is smaller and the nucleolus may not be visible by light microscopy (small cell variant) (12). In 5% the nuclear outline is markedly irregular and can even be cerebriform, mimicking Sézary cells (13). Both of these variants are otherwise similar to typical T-PLL, including immunophenotype and cytogenetics, and thus it is justified that all three are grouped together in a single category (11).

The bone marrow is diffusely infiltrated by prolymphocytes in most cases with variable residual hematopoiesis. Reticulin fibrosis is almost always present (10, 11). When the spleen is involved, histology finds a dense red pulp infiltrate with invasion into the splenic capsule, blood vessels, and extension into the atrophied white pulp. In lymph nodes, the involvement is diffuse with paracortical expansion by T prolymphocytes, sometimes with sparing of follicles (14). Multiple prominent high endothelial venules are often infiltrated by neoplastic cells (10). Skin involvement differs from that seen in mycosis fungoides and Sézary syndrome, with dermal infiltrates primarily around the appendages and without epidermotropism (7, 15).

**Figure 1.** Morphology of T-cell prolymphocytic leukemia. (a) Peripheral blood stained with Wright's stain (original magnification under oil 1000×). (b) Bone marrow stained with hematoxylin and eosin (original magnification 400×).

Immunophenotypically, T prolymphocytes are mature postthymic peripheral T cells that do not express TdT and the cortical thymic marker CD1a. The cells are positive for CD2, CD3, and CD5 and have strong CD7 staining. This strong CD7 intensity is in contrast to other mature T-cell malignancies, where this marker may be weak or negative. The membrane expression of CD3 may be weak or even negative in occasional cases, but T-cell receptor-beta/gamma chain genes are always rearranged. CD52 is usually expressed at high density in T prolymphocytes and can be used as a target of therapy by the monoclonal antibody alemtuzumab (8, 16). In 65% of patients, the cells are CD4+ or CD8+, and in 13% they are CD4+, CD8-. In 21% the T prolymphocytes coexpress CD4 and CD8, which is a feature almost unique to T-PLL. The distinctive coexpression of CD4 and CD8 together with the weak CD3 membrane expression and the strong CD7 expression suggest that the T-PLL cell may be at an intermediate stage of differentiation between a cortical thymocyte and a circulating mature T cell (7). The most specific markers for T-PLL by immunophenotyping are CD26 and TCL-1 protein expression, which are not detected in the other mature T-cell leukemias (11). The overexpression of the oncogene TCL1 is useful for detecting residual T-PLL in bone marrow sections after therapy (9).

T-PLL is characterized by complex chromosomal abnormalities, which suggests that chromosomal aberrations might occur progressively during the course of the disease, thus explaining the aggressive nature of this condition. Recurrent changes mainly affect chromosomes 14, 8, 11, and X (17). The most common characteristic chromosome abnormality, seen in 80% of cases, is inversion of chromosome 14 with breakpoints in the long arm at q11 and q32 (inv (14)(q11;q32)). Reciprocal tandem translocations between the two chromosomes 14 occur in 10% (t14;14)(q11;q32) (17, 18). These two rearrangements involve the 14q11 and 14q32.1 loci, where the genes coding for TCRγ and the protooncogene TCL-1 are localized, respectively. The rearrangements result in juxtaposition of these two genes and lead to expression and activation of TCL-1 (19). About 20% of patients have the translocation t(X;14)(q28;q11), which results in rearrangement of the MTCP1 gene (20). Both TCL-1 and MTCP-1 have oncogenic properties, as both can induce a T-cell leukemia (CD4+/CD8−) in transgenic mice (19, 21, 22). Abnormalities involving both arms of chromosome 8 are frequent, t(8:8)(p11-12;q12) as well as trisomy 8q, with both being seen in 70% to 80% of cases. Other alterations seen in T-PLL include deletions of 12p13 and 11q22, with the latter being the locus for the ataxia telangiectasia mutated gene. Abnormalities of chromosome 6 and 17 and deletion of the TP53 gene are also not uncommonly encountered (10).

T-PLL is aggressive and often resistant to therapy. The overall prognosis is poor, with a median survival of approximately 7 months in patients treated with conventional regimens.
Recently the average survival has been extended to >2 years following the introduction of newer therapies (11). The initial treatment of choice for most patients is the monoclonal antibody alemtuzumab (anti-CD52); the best responses have been seen with this agent, but responses are still transient and further disease progression is inevitable (3, 23). Purine analogues also have activity in this disease (24, 25). Both autologous and allogeneic stem cell transplants in patients who achieve remission have been used and are associated with more durable outcomes (26). Because of the severe immunosuppression associated with alemtuzumab, the purine analogue 2-chlorodeoxycadenosine was selected for the reported patient’s treatment.

Breast fibromatosis mimicking breast carcinoma

Kelli Y. Ha, MD, Patricia DeLeon, DO, and Raynal Hamilton, MD

Fibromatosis arising from the breast, also referred to as desmoid tumor, aggressive fibromatosis, or low-grade fibrosarcoma, is a rare benign entity, accounting for only 0.2% of all breast tumors. Associations with familial multicentric fibromatosis and trauma, including that resulting from surgical intervention, have been reported. Awareness of this lesion is important, as the diagnosis has often been confused with that of breast carcinoma. We present the case of a 30-year-old white woman who presented with a palpable mass within the medial portion of her right breast. She reported breast carcinoma in both her paternal grandmother and maternal aunt. Subsequent mammographic and sonographic evaluation demonstrated an irregular solid mass within the posteromedial portion of the right breast. Ultrasound-guided core needle biopsy revealed low-grade myofibroblastic proliferation consistent with breast fibromatosis. The lesion was surgically resected via wide local excision. Follow-up mammograms performed 1 and 2 years after resection demonstrated no radiographic evidence of recurrence.

CASE REPORT
A 30-year-old white woman presented to Baylor University Medical Center at Dallas (BUMC) with a palpable mass in the medial portion of her right breast. Past medical history disclosed migraine headaches. Breast carcinoma had occurred in her paternal grandmother at age 58 and maternal aunt at age 52. She reported the onset of menarche at age 11 and had never been pregnant.

Bilateral diagnostic mammogram at BUMC demonstrated an ill-defined 2-cm mass at the 3 o’clock position at the palpable area of concern within the right breast. Associated distortion and tenting of the underlying pectoralis muscle were also noted (Figures 1 and 2). Subsequent sonographic evaluation of the right breast demonstrated a 1.9 × 1.6 cm irregular hypoechoic lesion extending to the pectoralis muscle at the 3 o’clock position of the right breast, 9 cm from the nipple (Figure 3).

The patient underwent a sonographic-guided core needle biopsy of the lesion, which demonstrated a low-grade myofibroblastic proliferation consistent with breast fibromatosis (Figure 4). The patient subsequently underwent wide local excision of the lesion from the right breast and subsequent bilateral mammoplasty. Follow-up mammograms performed at 1 and 2 years following the excision demonstrated no evidence of lesion recurrence.

DISCUSSION
Fibromatosis arising from the breast, also referred to as desmoid tumor, low-grade fibrosarcoma, or aggressive fibromatosis, is a rare benign entity characterized histologically by low-grade spindle cell proliferations composed of interlacing fibroblastic bundles and fascicles with varying degrees of...
collagen. The lesions are noted to have irregular, finger-like margins, with spindle cells infiltrating and surrounding normal breast parenchyma. Grossly, the lesion appears as a rubbery, poorly vascularized grayish-white mass (1–3). Although cellular atypia may be present, the spindle cells are typically uniform with a low mitotic index (1, 4). The histopathologic differential diagnosis includes scar formation, fibrosarcoma, and fibromatosis-like metaplastic spindle cell tumor (4).

Fibromatosis is a benign entity without metastatic potential but carries a significant risk for local recurrence (5). It accounts for only 0.2% of all breast tumors and 0.3% of all solid tumors (4). The calculated lesion occurrence at BUMC is also 0.2% of all breast tumors. Between January 1, 2009, and March 31, 2011, there were four documented cases of breast fibromatosis among the 2174 breast tumors biopsied. The patients ranged in age from 13 to 83 years. Most cases occurred in young, premenopausal women, but cases have also been reported in men (3, 4, 6).

The etiology of this lesion is not well understood, but an association with Gardner’s syndrome was initially delineated in 1964 in the first reported case of breast fibromatosis (3, 7). Since then, few cases of breast fibromatosis have been associated with Gardner’s syndrome. Additional associations include familial multicentric fibromatosis, silicone and saline breast implants, and incidental and surgical trauma (1, 4).

Although some reports have suggested an association with sex steroid hormones, a 2000 study by Devouassoux-Shisheboran et al refuted this association. Of the 33 reported cases of breast fibromatosis in their study, only one case demonstrated estrogen receptor (ER) and progesterone receptor (PR) positivity within a tumor localized to the chest wall (8). Similarly, a case study performed by Reis-Filho et al assessed the immunohistochemical expression of ER and PR in one patient who developed simultaneous mammary fibromatosis and abdominal fibromatosis. While cells from the abdominal desmoid tumor specimen demonstrated immunoreactivity for both receptors, the cells from the primary breast tumor were deemed negative (9).

Clinically, desmoid tumors of the breast present as firm, painless, movable masses, and skin retraction and/or dimpling may be present. Nipple retraction is often seen in tumors that are close to the nipple. Nipple discharge and palpable lymphadenopathy are not associated with breast fibromatosis. Desmoid tumors are often irregularly shaped, high-density lesions with spiculated margins that closely mimic breast carcinoma on mammography. Rarely do these tumors demonstrate calcific deposition. Sonographically, breast fibromatosis presents as a poorly defined, hypoechoic mass with posterior acoustic shadowing and an echogenic rim, findings that make it indistinguishable from breast cancer (3–5, 10). Desmoid tumors are heterogeneous on magnetic resonance imaging and may be hypointense to isointense on T1-weighted images and...
hypointense to hyperintense on T2-weighted images. Moderate to strong enhancement is noted following the administration of intravenous contrast (10, 11). Mutations of alterations in the adenomatous polyposis coli and beta-catenin pathway are implicated in the development of sporadic and familial adenomatous polyposis–associated breast fibromatosis (4).

Management of desmoid tumors includes wide local surgical excision despite high local recurrence rates ranging from 24% to 77% over the course of 10 years. Radiation therapy is used in patients with unresectable tumors or lesions that would require extensive surgical resection, to include amputation or major chest or abdominal wall resection. Medical therapy for breast fibromatosis includes three major classes of drugs: hormonal agents, antiinflammatory agents, and cytotoxic agents (2).


Avocations

Preying on the unsuspecting
Exploiting genetic vagaries
Camouflaged insidious foe
Roosting in the helix
Perfidious mutant of the self
Pillages parent’s nest

Laying primordial daughter cells
Spreading evil seed
Evaiving achromatic soldiers
Crosse sanguineous moats
Despised mother of all thieves
Steals innocent smiles

Trusting lives to my care
Daunting expectations
See the fugitive in their eyes
And I surmise
Can’t pretend to be them
Yet they become part of me

—AMANULLAH KHAN, MD, PhD

Dr. Khan (e-mail: aman1963@gmail.com) is an oncologist on the medical staff of Baylor Medical Center at McKinney. In addition to publishing over 100 research articles, he is an award-winning poet who has written poems in three languages.
Synovial metastasis from lung cancer
Harold R. Levine, MD, Eric Tingle, MD, Brett Carter, MD, and Dee Dockery, MD

Intraarticular masses are infrequently encountered in clinical practice; however, the differential diagnosis can be broad. Neoplasia, both benign and malignant, and proliferative processes are the most common etiologies. We present a case of metastatic disease in the synovium in a patient with a history of lung cancer. Lung carcinoma is the most common primary malignancy to metastasize to synovial tissue, and the knee joint is the most common joint to be affected.

In this report, we discuss the differential considerations for intraarticular masses and the clinical presentation of metastatic synovial disease. We discuss some findings that are classic for specific entities; however, many radiologic findings concerning synovial pathology are nonspecific. As the differential considerations for intraarticular masses are vast, clinical history is often as necessary as radiologic findings to elucidate the correct diagnosis.

CASE PRESENTATION
A 61-year-old man who underwent a left pneumonectomy for cancer 4 months before presentation complained of knee pain with swelling since the operation. The knee joint was aspirated, and the fluid demonstrated inflammatory white blood cells but was negative for microorganisms. A diagnosis of rheumatoid arthritis had been made in the past, but the knee pain had never been of this character or intensity. The patient was unable to bear weight or straighten his leg in the emergency room. On examination, he was afebrile, normotensive, and tachycardic, with underlying atrial fibrillation and a ventricular rate of 90 to 127 beats per minute. The knee was edematous, erythematous, and warm with a range of motion of <90°. His leukocyte count was 23,600 cells/mL.

Conventional gadolinium-enhanced magnetic resonance (MR) imaging of the left knee revealed diffuse enlargement of the knee joint space secondary to multilobulated and heterogenous mass-like structures (Figures 1–4). These structures demonstrated heterogeneously increased T2 hyperintense and intermediate T1 intensity characteristics. Most of the joint space was replaced by hyperenhancing synovium. Enlarged lymph nodes were seen in the popliteal fossa. At that time, differential considerations included severe inflammatory arthritis and synovial chondromatosis rather than unusual metastasis. Surgical pathology showed a diagnosis of synovial metastasis from primary large-cell lung carcinoma.

DISCUSSION
Approximately 48 cases of synovial metastasis have been reported. Adenocarcinoma has been the most common type of synovial metastasis encountered. Despite the highly vascular nature of synovial tissue, neoplastic masses in articular spaces are much less frequently encountered than mass lesions secondary to infectious and inflammatory arthritides. If intraarticular masses are discovered when they are still small, the tissue of origin such as synovium or cartilage may be delineated. However, commonly both cell types are involved, and the type can be impossible to decipher when the mass is as large, as in the case presented. Primary lung cancer is the most common cancer to metastasize to articular surfaces.

We present the first reported case of poorly differentiated large-cell lung carcinoma metastatic to the knee joint. Large-cell lung cancer comprises about 5% to 10% of all lung cancers. It is a diagnosis of exclusion, as it is often the diagnosis in which a lung malignancy does not show characteristics of small cell, squamous cell, or adenocarcinoma. Most cases with synovial metastasis, specifically of the knee joint, from a lung primary demonstrated adenocarcinoma features histopathologically, followed by squamous cell carcinoma features. Unfortunately, all synovial metastasis carries with it a dreadful prognosis. Average survival after discovery is 5 months.

While the mechanism of spread that causes synovial metastasis remains unproven, two theories have been postulated: hematogenous versus direct invasion from a metastatic osseous lesion. In our case, hematogenous spread is favored, as there is no evidence of osseous disease in the adjacent bone.

The main differential considerations for intraarticular masses include both benign and malignant etiologies. While innumerable intraarticular processes can mimic masses, the few that should be considered in the same discussion as synovial
metastasis include granulomatous septic arthritis (particularly tuberculous and fungal), proliferative articular processes like pigmented villonodular synovitis, rheumatoid arthritis, and deposition disease such as gout or pseudogout. Malignant etiologies that should be a differential consideration include synovial sarcoma and synovial chondrosarcoma.

Concerning the benign entities, septic arthritis, particularly in immunocompromised or diabetic patients, may have an insidious or acute course. Infectious arthritides tend to produce more joint fluid than a metastatic process. More periarticular

osseous erosions are expected in septic arthritis. Enhancement characteristics are not a helpful discriminator, as both entities can demonstrate avid or patchy enhancement. Rheumatoid arthritis can also have an appearance similar to that of synovial metastasis, as the pannus or hypertrophic synovium can appear T1 hypointense and T2 hyperintense. Again, marginal erosions, diffuse joint space narrowing, and periarticular osteopenia are usually seen in rheumatoid arthritis, none of which are expected in synovial metastatic disease. Pigmented villonodular synovitis is a benign proliferative synovial process that is most commonly monoarticular. While joint space and subchondral bone are commonly preserved early in the disease,
MR imaging shows a characteristic low signal for the intraarticular masses on all sequences secondary to blood products, as these lesions have a high tendency to bleed. Usually only mild enhancement is demonstrated; however, the pansequence hypointensity is a helpful discriminator. Crystal deposition disease manifests in intraarticular mass lesions as well, but classically signal characteristics demonstrate an intermediate T1 signal and hypointense T2 signal. More aggressive-appearing marginal erosions with overhanging edges are also expected in gout and pseudogout, whereas synovial metastasis does not usually result in a destructive or degenerative pattern in the subchondral bone.

After an extensive literature search, this case appears to be first documented large-cell lung carcinoma metastasis to the synovium. While the differential considerations for intraarticular masses are vast, certain MR characteristics, in conjunction with a thorough history, can help raise suspicion for the diagnosis. Existing reports do not suggest an increased risk for metastasis to the synovium in patients with an underlying history of rheumatoid arthritis, as was present in our patient. One could conjecture that synovial tissue is more hyperemic than normal tissue in chronic inflammatory arthritides like rheumatoid arthritis, which may portend to an increased risk of hematogenous spread of tumor. However, further research is needed to see if a true association exists.

Percutaneous tattoo pigment simulating calcific deposits in axillary lymph nodes

Amy R. Yactor, MD, Michael N. Michell, MD, Meghan S. Koch, DO, Tyler G. Leete, MD, Zeeshan A. Shah, MD, and Brett W. Carter, MD

The isolated finding of calcific deposits within axillary lymph nodes on mammography suggests a broad range of differential diagnoses, from benign causes such as granulomatous reaction secondary to previous histoplasmosis infection to malignancies such as breast cancer and metastatic disease from extramammary primary malignancies. Therefore, the isolated finding of intranodal calcium may warrant biopsy for a definitive diagnosis when a benign etiology is not apparent. We present a patient with isolated axillary lymph node densities on mammography and chest computed tomography, which were subsequently proven to represent deposition of tattoo pigment.

CASE DESCRIPTION

A 30-year-old woman presented for a diagnostic mammogram with a palpable lump in her right breast. She was 9 weeks postpartum and otherwise healthy. In the palpable region of concern, prominent lactational changes were seen without any apparent mammographic abnormality. Normal-sized bilateral axillary lymph nodes with punctate hyperdensities were identified, simulating the appearance of intranodal calcium (Figure 1). A chest computed tomography (CT) scan confirmed hyperdense foci within bilateral axillary lymph nodes (Figure 2). The patient underwent left axillary lymph node excisional biopsy. Histology demonstrated subcapsular and paracortical deposits of dark-colored pigment and multiple histiocytes containing internal black pigment granules (Figure 3). There was no evidence of malignancy. Although no tattoos were present on her anterior chest, many multicolor tattoos were present on her back (Figure 4).

DISCUSSION

Dermal tattooing provokes predictable body responses, including initial sloughing of the overlying epidermis, variable dermal inflammation, and gradual assimilation of pigment into macrophages. Much of the pigment is eventually carried into regional draining lymph nodes (1). The composition of tattoo pigments is highly variable, but most consist of various metallic ions including aluminum and titanium (2). If sufficient quantities of pigment reach lymph nodes, punctate hyperdensities mimicking intranodal calcific deposits can be seen radiographically.

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Axillary lymph node calcium due to metastatic ovarian cancer and papillary thyroid carcinoma has also been reported (8, 9). Lymph node calcific deposits may also be seen in the setting of treated lymphoma (4, 5). The broad differential diagnosis of axillary intranodal calcific deposits seen on radiologic examinations emphasizes the importance of histologic examination when a benign etiology is not apparent.

An additional clinical situation where intranodal tattoo pigment is an important diagnostic consideration is with sentinel lymph nodes of melanoma patients. Intraoperatively, a darkly pigmented lymph node is concerning for metastatic disease but may represent a draining lymph node containing tattoo pigment if a dermal tattoo is present in the area of the primary melanoma (10). Histologic examination is warranted for definitive diagnosis.

Combined congenitally bicuspid aortic valve and mitral valve prolapse causing pure regurgitation

William C. Roberts, MD, Saleha Zafar, MD, Jong Mi Ko, Melissa M. Carry, MD, and Robert F. Hebeler, MD

Described herein is a patient with a purely regurgitant congenitally bicuspid aortic valve and a purely regurgitant prolapsing mitral valve. Although it is well established that the bicuspid aortic valve is a congenital anomaly, it is less well appreciated that mitral valve prolapse is almost certainly also a congenital anomaly. The two occurring in the same patient provides support that mitral valve prolapse is also a congenital anomaly.

It is well appreciated that the bicuspid aortic valve (BAV) is usually of congenital origin. It is less well appreciated that mitral valve prolapse (MVP) is usually of congenital origin. Most patients with a congenitally BAV (unless complicated by superimposed infective endocarditis) have a structurally normal mitral valve. It is most unusual for a patient with a congenitally BAV, particularly one that is purely regurgitant, to have associated MVP. Such was the case, however, in the patient described herein.

CASE DESCRIPTION

A 64-year-old white man with a doctorate, who was born in June 1947, had been well until November 2011, when he had the first of several episodes of syncope. During hospitalization for acute appendicitis, an electrocardiogram disclosed the presence of atrial fibrillation. Another syncopal episode and the appearance of exertional and nocturnal dyspnea in 2012 prompted a visit to a cardiologist. His body mass index was 30 kg/m². A grade 2/6 basal precordial systolic murmur and a grade 4/6 blowing apical systolic murmur with radiation into the left axilla were heard. The initial electrocardiogram showed supraventricular tachycardia with a ventricular rate of...
Figure 2. (a) Photomicrograph of a portion of the posterior mitral valve leaflet and attached chordae tendineae (CT). The leaflet and chordal thickening is the result of superimposed fibrous tissue on both atrial (A) and ventricular (V) aspects of the leaflet and surrounding the chordae. The leaflet itself consists primarily of the fibrosa element; the spongiosa element is minimal. These histological features are characteristic of mitral valve prolapse. Elastic von Gieson stain, ×40. (b) A color-coded replica with green representing the ventricular aspect, yellow representing the atrial aspect, and red representing the mitral valve leaflet.

Figure 3. (a) Photomicrograph of a portion of the mitral leaflet and chordae tendineae (CT) with superimposed fibrous tissue on the atrial (A) aspect and on the ventricular (V) aspect. The underlying normal leaflet and chordae tendineae are outlined by a black-staining elastic membrane. It is likely that the chordae had ruptured in the distant past and later the portion closest to the leaflet was covered by fibrous tissue. Elastic von Gieson stain, ×40. (b) A color-coded replica with green representing the ventricular aspect, yellow representing the atrial aspect, and red representing the leaflet and chordae.
140 beats a minute. An echocardiogram showed MVP with a flail P2 portion of the posterior leaflet and severe mitral regurgitation. The aortic valve was bicuspid, and moderate aortic regurgitation was present. The left ventricular cavity was of normal size, and its ejection fraction was 60%. Cardiac catheterization disclosed the following pressures in mm Hg: left ventricle, 136/33; aorta, 139/70; pulmonary artery wedge, a wave 23, v wave 38, mean 11; pulmonary artery, 34/13; right ventricle, 39/14; and right atrium, a wave 14, v wave 13, mean 11. The cardiac index was 2.9 L/min/m2. Coronary angiogram disclosed no luminal narrowing; the right coronary was the dominant artery. Left ventricular cavity size and contractility were normal. The aortic regurgitation was graded 2+/4+.

Five days later the purely regurgitant aortic valve was replaced with a #29 Mosaic porcine xenograft. The mitral valve was repaired by resecting P2, replacing two chordae, and inserting a #37 ATS annuloplasty ring (Figures 1–3). Additionally, a Maze procedure was performed. Seven days postoperatively, because of the development of complete atrioventricular disassociation, a dual-chamber pacemaker was inserted. Electrocardiogram in July 2012 disclosed sinus rhythm (75 beats a minute) and complete left bundle branch block. When seen on September 11, 2012, 3 months after the valve operation, the patient was asymptomatic and “feeling great.”

DISCUSSION
The occurrence of both a congenitally BAV and MVP in the same patient suggests that both conditions are of congenital origin. That the BAV is a congenital anomaly is well accepted, but that MVP is also likely a congenital anomaly—at least some of the leaflet and chordal tissue is congenitally deficient—is less well appreciated.

Iqbal and colleagues (1) in 1980 appear to have been the first to report MVP associated with a congenital BAV. They described two patients, one a 39-year-old man who underwent mitral and aortic valve replacement for combined mitral and aortic regurgitation and the other, a 23-year-old man with mitral regurgitation and a normally functioning congenitally BAV.

Chisholm (2) in 1981 found a congenitally BAV in 8 of 257 black patients with MVP. None of his 8 patients had either mitral or aortic dysfunction severe enough to warrant operative intervention. All 8 patients had evidence of trace aortic regurgitation, and none had evidence of aortic stenosis. None apparently had significant mitral regurgitation. The cardiac size in all 8 patients was normal.

In 1994 Fernicola and Roberts (3) described 11 patients who underwent aortic valve replacement for a dysfunctioning congenitally BAV and mitral replacement for a purely regurgitant mitral valve. In 2012 Roberts and colleagues (4) described another 16 patients at another institution who had aortic valve replacement for a dysfunctioning congenitally BAV and simultaneous mitral valve operation for a dysfunctioning mitral valve. The Table summarizes the findings in the combined studies by Fernicola and Roberts (3) and by Roberts et al (4). Of their 28 patients, the BAV was stenotic in 19 (68%) and purely regurgitant in 9 (32%); the mitral valve was stenotic in 6 (21%) and purely regurgitant in 22 (79%). Of the 19 patients with stenotic BAVs, at least 4 (21%) had MVP; of the 9 patients with a purely regurgitant BAV, only 1 (11%) had MVP, as did the patient described herein.

Massive bloody pericardial effusion as an initial manifestation of chronic kidney disease

Poorya Fazel, MD, Ravi C. Vallabhan, MD, and William C. Roberts, MD

We describe a 35-year-old man with a massive bloody pericardial effusion, which was his initial manifestation of chronic kidney disease. Pericardiocentesis and hemodialysis restored cardiac function and relieved the associated massive anasarca.

A 35-year-old Latin American immigrant man, a known alcohol, cocaine, and tobacco abuser, presented with a 2-week history of progressive dyspnea, dark stools, and epigastric discomfort. He was anasarca and oliguric. On precordial examination, the cardiac sounds were faint and no murmurs were noted. There was evidence of a large quantity of fluid in the abdominal, pericardial, and pleural cavities. Chest radiograph confirmed the large pleural effusions and the enlarged cardiac silhouette (Figure 1). Electrocardiogram showed low voltage and an ectopic atrial tachycardia (Figure 2). An echocardiogram confirmed the massive pericardial effusion (Figure 3). Results of pertinent laboratory values are shown in the Table. Pericardiocentesis yielded 1300 mL of bloody fluid having a hematocrit of 11%. Cultures for bacteria, fungi, and acid-fast organisms were negative. No neoplastic cells were identified by cytology examination. Another 525 mL was drained from the pericardial sac over the next 48 hours. Renal sonogram confirmed small echogenic kidneys with kidney length equal to 6.3 cm and 6.8 cm (normal 10–12 cm), respectively. This finding was consistent with chronic kidney disease. The patient received hemodialysis, and repeat echocardiogram afterwards showed only a small residual pericardial effusion (Figure 3c, 3d). He was discharged in stable condition to return to Mexico and establish outpatient care.

Pericardial effusion is a known clinical manifestation of chronic kidney disease. With the advent of advanced renal replacement therapy, the incidence of hemodynamically significant effusions has decreased (1–3). The above described patient presented with symptoms related to a massive pericardial effusion (with pretamponade) as the initial indication of chronic renal failure. The presentation of an effusion as the initial indication of underlying undiagnosed chronic kidney disease is unique. By volume, his pericardial effusion is one of the largest reported and probably the largest of recent memory at Baylor University Medical Center at Dallas.

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Table. Laboratory values

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Figure 1. Chest radiograph revealing a large pleural effusion and a large “cardiac” silhouette.
Figure 2. Electrocardiogram demonstrating low voltage and an ectopic atrial tachycardia with a nonspecific intraventricular conduction delay.

Figure 3. Echocardiographic images demonstrating a large pericardial effusion (asterisk) in (a) a parasternal short-axis view and (b) an apical four-chamber view. (c and d) Confirmation of small residual pericardial effusion immediately after pericardiocentesis (arrow) in the same echocardiographic views.

Primary *Streptococcus pneumoniae* pericarditis

Matthew N. Peters, MD, Kathleen S. Hesterman, BA, Morgan J. Katz, MD, Meredith B. Barnes, MD, Ryan R. Brown, MD, Vikram S. Nijjar, MD, Mohannad B. Bisharat, MD, and Anand M. Irimpen, MD

Although commonly fatal, bacterial pericarditis is often not diagnosed antemortem due to its infrequent occurrence and fulminant course. Historically, *Streptococcus pneumoniae* has been the most common cause of bacterial pericarditis. Over the past 70 years, however, it has become largely eliminated and now occurs almost exclusively in immunocompromised individuals with a preceding primary site of infection. Herein, we present a case of primary *S. pneumoniae* pericarditis that developed over the course of 3 to 4 weeks in an immunocompetent 45-year-old man. The patient, who developed cardiac tamponade shortly after admission, experienced a rapid resolution of symptoms following pericardial drainage and initiation of antibiotics.

Bacterial pericarditis requires prompt recognition due to its fulminant and often fatal course. While currently considered quite rare, many cases of bacterial pericarditis are likely undetected, as reflected by the large percentage of cases that are not identified until after death. Formerly *Streptococcus pneumoniae* was the most common cause of bacterial pericarditis. However, the combined introduction of antibiotics and the pneumococcal conjugate vaccine within the last 70 years has nearly wiped it out entirely, with most cases now occurring almost exclusively in immunocompromised patients with a preceding primary infection. Presented herein is an immunocompetent patient who developed symptoms of primary pericarditis over a period of 3 to 4 weeks before rapidly deteriorating and developing cardiac tamponade shortly after admission.

**CASE DESCRIPTION**

A 45-year-old African American man with no prior medical or surgical history experienced the onset of chest pain and dyspnea, which had progressively worsened over 3 to 4 weeks. The pain was sharp and was exacerbated by exertion or lying flat and was somewhat relieved by leaning forward. The patient denied fever, chills, or recent illness. He was born in Guyana and moved to the United States at the age of 12 and reported being homeless for the previous 3 months. He also stated that he was vegan and had lost a significant amount of weight over the past several months due to a lack of available dietary options.

His temperature was 98.2°F; blood pressure, 121/74 mm Hg; heart rate, 82 beats/minute; respiratory rate, 19 breaths/minute; and oxygen saturation, 99% on room air. He had diffuse abdominal tenderness. The precordial examination was completely normal. His lung fields were clear and he had no subcutaneous edema. No jugular venous distention, Kussmaul’s sign, pulsus paradoxus, or ascites were noted. Initial laboratory studies are noted in the Table. An electrocardiogram showed diffuse ST segment elevation, most prominent in the anterior precordial leads, with reciprocal ST segment depression in lead AVR and diffuse PR depression (Figure 1). A bedside transthoracic echocardiogram demonstrated a left ventricular ejection fraction >55% but a moderate-sized circumferential pericardial effusion (Figure 2). Chest radiograph revealed an enlarged cardiac silhouette but no other abnormalities. A diagnosis of pericarditis and pericardial effusion was made. He was treated initially with ibuprofen 600 mg every 8 hours and colchicine 0.6 mg every 12 hours.

Diagnostic workup included negative blood and sputum cultures, negative HIV and hepatitis panels, and negative serum antinuclear antibody, adenosine deaminase, and anti-double-stranded DNA tests. PPD revealed a maximal induration of 6 mm. Upon further questioning, the patient revealed that he may have had a Bacillus Calmette-Guerin vaccination while living in Guyana. Three sets of sputum smears and cultures for acid-fast bacilli were negative. Computed tomography of the chest and abdomen with contrast revealed a moderate pericardial effusion, a mildly thickened pericardium (without calcification), and a minimal amount of perihepatic ascitic fluid (the likely cause of the patient's abdominal tenderness).

By hospital day 5, the patient's symptoms had worsened. Examination revealed a blood pressure of 112/72 mm Hg, distant heart sounds, jugular venous distention, and new-onset lower extremity edema. Repeat electrocardiogram showed no signs of electrical alternans but, due to suspicion for cardiac tamponade, the patient urgently underwent right heart catheterization, which revealed equalization of intracardiac pressures (Table) and blunting of the descent on right atrial tracings (Figure 3). Emergent pericardiocentesis was performed and drained 450 cc
of bloody fluid, after which intracardiac pressures normalized (Table) and jugular venous distention disappeared.

Analysis of the pericardial fluid was limited by the large amount of blood and thrombus present, and no cell count could be performed. Cytological analysis, fungal culture, acid-fast bacilli, and adenosine deaminase studies of the pericardial fluid were all found to be negative. The initial Gram stain revealed the presence of gram-positive cocci in pairs. Antibiotic therapy was initiated (vancomycin 1 g intravenously every 12 hours and ceftriaxone 2 g intravenously every 24 hours), and ibuprofen and colchicine were discontinued. Despite initial improvement immediately following the procedure, the patient rapidly experienced recurrence of chest pain and shortness of breath.

On postprocedure day 2, repeat transthoracic echocardiogram revealed the recurrence of a moderate-sized pericardial effusion. Accordingly, a pericardial window was placed and an additional 150 mL of serosanguinous fluid was withdrawn. Postoperatively, two Jackson-Pratt drains were inserted and drained an additional 25 mL of serosanguinous fluid over a course of 2 days before being removed. All repeat pericardial fluid studies were negative and pericardial biopsy revealed only inflammatory exudate.

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Table. Chronological laboratory and hemodynamic findings

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<th>Variable</th>
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*Before pericardiocentesis.
†After pericardiocentesis.

Figure 1. Admission electrocardiogram demonstrating diffuse ST segment elevation, most prominent in the anterior precordial leads with reciprocal ST segment depression in lead AVR.
The following day, culture from the initial pericardial fluid revealed heavy growth of *Streptococcus pneumoniae*. The antibiotic regimen was changed to 500 mg of oral penicillin V potassium every 6 hours. A subsequent workup for underlying immunodeficiency included tests for serum gamma globulin levels, serum C3 and C4, as well as total and alternative complement activity, and all were within normal limits. The patient had no further symptoms and was discharged on a 14-day course of oral penicillin. In the 6 months following discharge, the patient has had no recurrence of his symptoms.

**DISCUSSION**

The list of etiologies of pericarditis in developed countries is extensive and varied. Possible causes include autoimmune disorders, underlying neoplasms, and bacterial infections, including tuberculosis. Often no specific cause of acute pericarditis is identified. In these cases the pericarditis is considered idiopathic, possibly due to an undetected underlying virus. In immunocompetent individuals, 80% to 90% of all cases of pericarditis are designated idiopathic (1–3). In contrast, bacterial infection is an infrequent cause of acute pericarditis in the United States, accounting for <1% of all cases (1, 4, 5). While idiopathic pericarditis typically is benign and usually resolves with nonsteroidal antiinflammatory therapy, bacterial pericarditis often has a fulminant course, requiring both immediate antibiotic administration and surgical drainage, with mortality approaching 100% if it is not promptly recognized and treated (6). With appropriate emergent treatment, mortality has been demonstrated to decrease to 20% (6, 7). Unfortunately, an antemortem diagnosis is made in only 10% to 20% of cases of bacterial pericarditis, and even in those patients in whom a diagnosis is made, there is an average delay of 21 days until treatment is initiated (8, 9).

**Figure 2.** Parasternal short-axis view of a transthoracic echocardiogram revealing a large echo-free space, suggesting an extensive circumferential pericardial effusion (see arrow and white bar). RV indicates right ventricle; LV, left ventricle.

**Figure 3.** Right heart catheterization tracing of the right atrium showing blunting of the y descent consistent with cardiac tamponade. The mean right atrial pressure was measured at 18 mm Hg.
There are several possible reasons why the clinical recognition of bacterial pericarditis is challenging. One major factor is the absence of classical physical findings such as a pericardial friction rub and pulsus paradoxus, which are reportedly present in only 30% of cases (9). Another important factor is a low level of clinical suspicion, since the condition is encountered infrequently. Bacterial pericarditis has never been common, but its incidence has declined drastically over the past 70 years. This decline strongly correlates with the near abolition of \textit{S. pneumoniae} as the infecting agent. Following the introduction of antibiotics into clinical practice in the 1940s, the incidence of \textit{S. pneumoniae} as an etiology has declined from 51% to 9% (10). Additionally, the implementation of the pneumococcal conjugate vaccine into standard childhood immunization schedules in 2000 has diminished the incidence of all pneumococcal infections (11). In fact, <25 cases of \textit{S. pneumoniae} pericarditis have been reported in English publications since 1980 (11). These various factors may also play a role in the change in patient population experiencing \textit{S. pneumoniae} pericarditis. Prior to 1943, \textit{S. pneumoniae} pericarditis mainly occurred in children and young adults, usually in the setting of a concurrent pneumonia (8). More recently, the average age of affected patients has increased to 49, and the condition now occurs mainly in patients with underlying chronic disease (10). This change in demographics may also reflect the increase in the use of immunosuppressive agents and the increase in invasive procedures such as renal dialysis and thoracic surgery (10).

There are several reasons why we believe the present case to be unique. To our knowledge, ours is only the eighth case ever reported of primary pericarditis (without signs of underlying infection elsewhere) (11–14). The mechanism of pericardial involvement is believed to occur either via contiguous spread from a surrounding area, usually pneumonia (93%), or via hematogenous spread from an underlying infection elsewhere in the body, such as osteomyelitis, otitis media, mediastinitis, impetigo, or meningitis (10, 15). It has even been suggested that pneumococcal pericarditis is rarely, if ever, truly primary and that most cases are due to a small discrete area of pneumonia that is radiologically silent or to another occult infection (12, 13). Of the seven previously reported \textit{S. pneumoniae} cases of primary pericarditis, five occurred either in patients under 1 year of age or patients with underlying major medical conditions such as hypogammaglobulinemia, alcoholism, and diabetes (9, 13). In one of the other two cases, reported in 1924, the diagnosis was questionable due to the lack of sophisticated imaging techniques and the subsequent development of pleural empyema during hospitalization (14). The remaining case, reported by Keersmaekers et al from Belgium in 2002, is remarkably similar to our patient in that it involved an immunocompetent individual who presented without fever or leukocytosis (6). The main difference is that their patient had positive blood cultures in addition to a positive pericardial fluid (6). Finally, we believe that our patient was unusual because his symptoms developed gradually over a 3- to 4-week period, rather than presenting with the relatively fulminant picture usually associated with this disorder. Typically, individuals with bacterial pericarditis are hospitalized within 3 days of symptom onset (regardless of bacterial etiology) (16).

High-intensity cardiac rehabilitation training of a police officer for his return to work and sports after coronary artery bypass grafting

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

A 39-year-old male police officer with coronary artery disease enrolled in our cardiac rehabilitation (CR) program after coronary artery bypass grafting. He wanted to return not only to his job but also to playing ice hockey and outdoor soccer, and his responses to a self-assessment scale confirmed that he identified strongly as an athlete. On the basis of this unique profile, the CR staff designed an occupation- and sport-specific exercise program that was symptom limited and enabled the patient to train safely, but earlier and at a higher intensity than is typically allowed in conventional CR programs. The exercises were selected to replicate the various combinations of muscular strength, agility, and cardiovascular endurance required by the patient’s police work and two competitive team sports. He completed the high-intensity training with no clinically significant adverse symptoms.

CARDIAC REHABILITATION EXERCISE TRAINING

During all 18 exercise training sessions, the patient’s blood pressure was measured before and after exercise, and he performed warm-up and cool-down routines. His heart rate and rhythm were continuously monitored by telemetry, and peak blood pressure measurements were taken while he performed various training exercises. A physician was present in the rehabilitation room at all times. The first two sessions consisted of supervised endurance training (treadmill walking and recumbent biking), during which the nurse on duty confirmed that

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The patient’s vital signs were responding appropriately to exercise and that he had no adverse physiological symptoms that would require cessation of training.

The remaining 16 sessions consisted of gradually increasing high-intensity exercise that was specifically designed to simulate the tasks and MET requirements of the patient’s police work and two strenuous sports, as summarized below:

- **Police work—8 to 10.5 METs** (6, 8). Involves chasing suspects on foot (often over or around obstacles) and overpowering and restraining combative individuals. Exercises included sprinting over hurdles, resistance training, grappling, boxing, and striking dummies.

- **Outdoor soccer—10 METs** (6). Requires sprinting, quickly changing directions, heading and dribbling the ball while running, and kicking the ball long distances. Exercises included core training with medicine balls, forcefully kicking a dummy, dribbling a soccer ball through cones, multidirectional sprinting, resistance speed sprinting, and agility drills.

- **Ice hockey—8 METs** (6). Involves continuous skating and squatting movements. Exercises included repetitive squat slide training on the slide board, plyometric step-ups, and core training.

The 75-minute sessions were designed so that the patient moved from one exercise to another, ensuring that he trained each day to meet the physical demands of all three goal activities.

Peak heart rates during conventional CR training are commonly restricted, either by a fixed value (typically 150 beats/min [9]) or by a calculated limit such as the percent maximal heart rate, defined as 64% to 94% of age-predicted heart rate (10). In part because the patient in this case was taking a beta-blocking agent, which slows the heart rate, we used symptom-limited training, meaning that no heart rate limit was used to restrict exercise intensity. Using this approach allowed our staff to train him at higher intensities than would normally be used in conventional CR.

During high-intensity exercise training, the patient’s blood pressure and chronotropic responses (means, 112/62 to 147/58 mm Hg and 79 to 141 beats/min, respectively) were within safe ranges and likely blunted by beta-blocking medications. Peak blood pressure measurements were well below 240/110 mm Hg, the recommended maximum (9). In addition to monitoring the patient’s heart rate and blood pressure, the CR staff watched for unusual arrhythmias, ST depression, angina, dizziness, pain, dyspnea, and perceived exertion. The patient had no adverse events that required the discontinuation of any exercise session.

**DISCUSSION**

The 39-year-old police officer–athlete began high-intensity training 15 days after cardiac surgery and after only two sessions of supervised endurance training—far sooner than the 4 weeks of supervised endurance training recommended by the American College of Sports Medicine (5). With only 16 sessions available for this patient’s high-intensity training, it was essential for our staff to have a well-planned and carefully executed exercise prescription to adequately prepare him for a safe return to work and sports (Figure).

One purpose of CR is to return patients to a normal and productive life after a cardiac event, and rebuilding their self-confidence is an integral part of that process. After coronary artery bypass grafting, patients may fear the intensity of physical training that would be required for their return to strenuous activities. One of this patient’s most important goals was to regain confidence that a fellow officer could depend on him in perilous situations. By testing his reaction to heavy exertion in a safe and monitored CR setting, he demonstrated that he could perform capably and reliably on the job. After training at high physical intensities in our CR program, he not only returned to work as a police officer but also resumed playing ice hockey 6 weeks after surgery. He resumed playing outdoor soccer during the next scheduled season.

![Figure. The patient (a) back at work as a police officer and once again playing (b) outdoor soccer and (c) ice hockey after high-intensity cardiac rehabilitation training following coronary artery bypass grafting.](image-url)
Although many cardiac patients reach their goals by participating in conventional CR exercise training, others may want to return to more physically demanding sports and jobs. The patient in this report was the first police officer–athlete to undergo combined occupation- and sport-specific training in our CR program; indeed, we believe his case is the first of its kind to be described. He performed high-intensity exercises that are not usually attempted by CR patients, particularly after sternotomy. More than a year after graduating from the program, he is still on the job and playing competitive team sports with no negative cardiovascular symptoms.

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 Cardiovascular Research Review Committee for their continued support of cardiovascular rehabilitation research projects. They also thank the patient for graciously allowing his story and photographs to be published. Beverly Peters, MA, ELS, a freelance medical editor, assisted with manuscript development and preparation.


Labor complicated by mitral stenosis

Erica N. Grant, MD, Koriand’r C. Williams, PhD, and Beverly J. Perez, DO

A case where a 28-year-old woman presented in labor complicated by mitral stenosis is described. Mitral stenosis is the most commonly encountered valvular lesion in pregnancy.

CASE DESCRIPTION

A 28-year-old woman from Mexico, G2 P1001 at 36 weeks' gestation, presented to labor and delivery with uterine contractions. The patient denied having any significant medical and/or surgical history. She was mildly tachycardic, and both legs were edematous. Cervical examination disclosed 3 cm dilatation, 80% effacement, and –3 station.

Nine hours after admission, she began complaining of dyspnea with contractions. She revealed being diagnosed with a “heart murmur” at age 18, receiving monthly “injections” with subsequent resolution of the problem, and being discharged by a cardiologist 8 years prior. Repeat physical examination was significant for persistent tachycardia, bilateral crackles at lung bases, leg edema, and jugular vein distention. Her brain natriuretic peptide was 1754 mg/dL, and a portable chest radiograph revealed marked cardiomegaly and mild congestive failure. She was given 20 mg of furosemide as an intravenous bolus. A transthoracic echocardiogram disclosed a moderately dilated left atrium, right atrium, and ventricle; a flattened ventricular septum consistent with right ventricular pressure overload; global left ventricular hypokinesis; a left ventricle ejection fraction of 25% to 30%; and moderately reduced right ventricular systolic function. The mitral valve was thickened and calcified with an area of 1.3 cm², peak velocity of 2.5 m/s, and mean diastolic gradient of 18 mm Hg.

Twelve hours into admission, the patient requested pain relief, which was achieved with a slow, controlled, low-concentration epidural. In preparation for placement of the epidural, we used standard monitors, an arterial line (to closely monitor blood pressures), and a central line (to facilitate placement of a pulmonary artery catheter, which we later placed). She had an assisted vaginal delivery and was taken to the cardiac intensive care unit for escalation of care. There she was started on esmolol and furosemide intravenous infusions, was discharged on day 9, and returned 2 months later for mitral balloon valvuloplasty without further incidence.

DISCUSSION

Mitral stenosis (MS) is the most commonly encountered valvular lesion in pregnancy (1), with the leading cause being attributed to rheumatic heart disease (2). Patients with MS do not tolerate the physiologic changes of pregnancy well, and it is not uncommon for MS to become unmasked for the first time during pregnancy (1). During pregnancy, associated pulmonary hypertension can be exacerbated due to the various hemodynamic changes that occur during gestation, and it carries a substantial health risk to both mother and fetus (3).

When a pregnant woman presents with MS, the mode of delivery is a major determinant of anesthetic management, with vaginal delivery being preferred over cesarean delivery (4, 5). In our case, the patient presented in active labor and after discussion among perinatology, cardiology, and anesthesiology, she was allowed to continue labor, which was quite successful.


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A passing motorist found a 28-year-old man on a cold January day outside of his wrecked automobile in a water-filled ditch. The state police noted that the victim was confused but able to answer simple questions, and his Glasgow Coma Score was 5 when he arrived at our emergency department.

The electrocardiogram recorded in the emergency department showed atrial fibrillation with a controlled ventricular response, a huge J wave, nonspecific ST-T wave changes, and a long Q–T interval (Figure 1). These are typical changes of hypothermia (1, 2)—the patient’s rectal temperature was 28.3°C or 82.9°F—and disappear as core temperature returns to normal (Figure 2).

J waves, so called because of their location at the junction of the QRS complex and the ST segment, are common (3, 4), may be large in early repolarization, and reach their greatest size in hypothermia, when they are called Osborn waves. Atrial fibrillation is common in patients with core temperatures of 32° to 22°C, and the lower the temperature, the higher the incidence of atrial fibrillation (5, 6). The patient is fortunate that he did not drown and that the motorist spotted him next to the secluded road. More time in the water would have resulted in an even lower core temperature, and ventricular fibrillation occurs between 30° and 15°C, and the lower the temperature, the higher the incidence of ventricular fibrillation (5).

Hypothermia is caused by exposure to cold and the inability to protect against it for any number of reasons, which is often an altered mental state produced by psychosis, stroke, stroke.

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**Figure 1.** Electrocardiogram recorded in the emergency department. See text for explication.

**Electrocardiographic Report**

**Electrocardiogram in a man who drove off the road**

D. Luke Glancy, MD, and Rehan Z. Ali, MD
severe hypothyroidism or, most commonly, alcoholic stupor. This young man apparently had consumed a large amount of beer on the night he drove off the road, and his social history, low serum albumin (2.2 g/dL; reference, 3.4–5.0), and elevated aspartate aminotransferase and alanine aminotransferase levels (160 U/L and 80 U/L, respectively; references, <45 and <46) suggest long-standing excess alcohol consumption with alcoholic liver disease.

Motor vehicle accidents often result in orthopedic injuries, and our patient had a left transverse posterior wall acetabulum fracture, left second and third metatarsal base fractures, right subtalar dislocation, and bilateral knee collateral ligament disruption. He also had an open wound of his left leg and a small right pneumothorax. His mental state returned to normal with time and rewarming. After reduction of the subtalar dislocation and open reduction and internal fixation of the left transverse posterior wall acetabulum fracture, he was transferred on the 17th hospital day to a rehabilitation unit.


Figure 2. Five days after the electrocardiogram shown in Figure 1 was recorded, the electrocardiogram was normal except for sinus tachycardia and minor T-wave change, i.e., TV₁ taller than TV₆.
A 60-year-old man had his aortic valve replaced and a HeartMate II ventricular assist device (VAD) inserted; 18 months later, he received a heart transplant. The explanted heart had a grossly fibrotic appearance on the ventricular side, with scar tissue extending onto the cusps. VAD therapy can lead to both acute and chronic changes in the valves, which may be clinically significant.

A 60-year-old man with known severe aortic stenosis presented with dyspnea. He had had multiple recent hospitalizations for systolic (low output) heart failure exacerbations. After several days of critical care support, he underwent aortic valve replacement with a 23-mm Carpentier-Edwards valve and implantation of a HeartMate II ventricular assist device (VAD). Due to the severity of systolic dysfunction, the chances of ventricular performance recovery with valve correction alone were thought to be poor, and the VAD was inserted at the time of valve replacement.

After 18 months of mechanical circulatory support, the patient went on to receive a heart transplant. The aortic valve bioprosthesis of the explanted heart had minimal changes on the aortic side but a grossly fibrotic appearance on the ventricular side. There was scar tissue extending onto the cusps (Figure).

**DISCUSSION**

With the prevalence of VAD therapy consistently increasing, the phenomenon of heart valve alterations in this setting is being recognized. Both acute and chronic changes have been noted in bioprosthetic as well as native valves in the setting of VAD therapy (1, 2). Gross examination of explanted bioprostheses in the aortic valve position has disclosed endocardial fibrosis of the sewing rings and fibrous tissue extending onto the cusps with significant fusion (1). Histological examination of the aortic bioprosthesis after several weeks of VAD therapy revealed recent thrombus on the aortic surface and aggregates of macrophages on both surfaces of the cusps (1).

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**Figure.** (a) Transaortic and (b) left ventricular outflow views of the bioprosthetic aortic valve of the explanted heart after 18 months of left ventricular assist device therapy.
The structural remodeling of the left ventricular outflow tract during VAD therapy is related, in large part, to mechanical stress on the tissue leading to inflammation, deterioration, and fibrosis (3). This process could be clinically significant as a potential source of emboli or as nidus for infection. Additionally, in the setting of bridge-to-recovery therapy, left ventricular outflow obstruction could limit parallel flow and elevate left ventricular end diastolic pressures, thereby limiting myocardial recovery (2).


Acknowledgment of reviewers for BUMC Proceedings, volumes 22–25

Our thanks to those who reviewed and critiqued manuscripts submitted to Baylor University Medical Center Proceedings for publication in volumes 22 through 25. Reviewing scientific papers is an often unrecognized, arduous, and time-consuming task. We are grateful to our editorial board members and to the following additional reviewers for contributing their valuable comments and suggestions.

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Endovascular treatment of stent fracture and pseudoaneurysm formation in arteriovenous fistula dialysis access

L. Michael Kershen, MD, and Daniel A. Marichal, MD

Arteriovenous fistulae (AVF) and grafts (AVG) for hemodialysis access generally provide good long-term solutions for the patient with end-stage renal disease. However, complications of both AVGs and AVFs are common and require a multimodality approach to maintain their patency and continued use. Commonly encountered problems include stenosis, thrombosis, aneurysm or pseudoaneurysm formation, rupture, and infection. Each needs to be addressed on a case-by-case basis. Outflow stenosis, often occurring within the cephalic arch in patients with a brachiocephalic fistula, may occur alone or be discovered in conjunction with other access problems. Pseudoaneurysm of the venous end generally arises from traumatic weakening of the vessel wall, often from repetitive venipuncture. More rare is the fracture of a previously placed stent. We present a case of stent fracture complicated by pseudoaneurysm formation with concomitant stenosis of the cephalic arch treated successfully with single-procedure placement of endovascular stent grafts.

CASE DESCRIPTION

A 49-year-old man with end-stage renal disease (ESRD) with a left upper extremity brachiocephalic fistula presented with marked swelling of his left upper extremity. Ten months previously, he underwent placement of a stent graft (Fluency, Bard Peripheral, Tempe, AZ) for access site extravasation not amenable to conservative management. The left upper extremity was evaluated with sonography prior to the procedure and demonstrated a large pseudoaneurysm and associated hematoma (Figure 1). The patient could not extend his elbow, and the decision was made to access the left cephalic vein via a right groin approach from the right common femoral vein.

After ultrasound-guided access using a standard Seldinger technique and placement of a vascular sheath, a 0.035-inch guidewire and 5F selective catheter were negotiated into the superior vena cava and into the left subclavian vein. Exchange was then made over an Amplatz guidewire (Boston Scientific, Natick, MA) for a 90 cm, 8F vascular sheath that was advanced into the left subclavian vein. Venography of the left cephalic vein was performed, confirming extravasation into a pseudoaneurysm (Figure 2). An 8 mm × 15 cm Viabahn (WL Gore, Flagstaff, AZ) stent graft was advanced, and the pseudoaneurysm and fractured stent were covered. Repeat venogram under a digital subtraction technique demonstrated stagnant blood flow due to poor venous outflow; therefore, the stent graft was extended to the level of the cephalic arch using an additional 8 mm × 5 cm Viabahn stent graft. The stent grafts were postdilated with an 8 mm × 40 mm Dorado balloon (Bard Peripheral, Tempe, AZ). Postangiographic imaging demonstrated successful occlusion of the bleeding pseudoaneurysm with no extravasation and robust venous outflow (Figure 3).

DISCUSSION

Stent grafts have offered interventionalists an additional weapon in their arsenal for treating commonly encountered arteriovenous access complications from an endovascular approach and might offer improved long-term patency compared with treatment with percutaneous transluminal angioplasty (PTA) alone (1). The use of the stent graft to maintain circuit patency is considered off label. The only use of stent grafts approved by the Food and Drug Administration is for vessel rupture after PTA, although stent grafts have been used for a host of other problems routinely for many years (1–3). A study by Dolmatch et al highlighted the versatility of covered stent use in the treatment of dysfunctional access: they treated a myriad of...
problems with the Fluency stent graft with a high rate of technical success and a low rate of complications (3). Cephalic arch stenosis is a commonly encountered problem with brachiocephalic fistulae, reported to develop in up to 77% of cases. A retrospective study by Shawyer et al demonstrated the effective treatment of cephalic outflow stenoses with the Viabahn-covered stent graft, showing improved rates of access patency compared with the previously reported data for bare metal stents (4). Failure to address problems in the venous outflow as in our case can lead to early failure of corrective procedures performed for arteriovenous access problems elsewhere.

Rare but increasingly reported are stent fractures, a known complication of stent placement elsewhere in the body. Cases of fractured stents placed for the treatment of coronary artery disease (5), peripheral vascular diseases (6), and chronic mesenteric ischemia (7) have been reported. Factors thought to contribute to stent fracture include placement in motion-prone segments, compressive forces, stretching of the stent during placement, and the presence of overlapping stents (5–7). Stent fractures have been classified in one system as type I to IV, with type I reflecting a single strut fracture; type II, multiple strut fractures; type III, multiple strut fractures resulting in complete transverse fracture; and type IV, a complete transverse fracture with stent separation (7). In our reported case, a type IV fracture was clearly evident on fluoroscopy, given the above parameters.

Pseudoaneurysms commonly arise at sites of cannulation through weakening of the vessel wall, although the development of pseudoaneurysms appears multifactorial, with high pressures from arterial flow and venous outflow stenosis being implicated. The presence of pseudoaneurysm is problematic and can lead to an increased risk of rupture with potential exsanguination, compromised viability of the overlying skin, limitations in the territory available for cannulation, infection, and cosmetic concerns. Indeed, the National Kidney Foundation guidelines recommend treatment when a pseudoaneurysm limits cannulation availability or when viability of the overlying skin becomes compromised (8). Historically, surgical revision was required, although now there are numerous case reports of successful exclusion of the pseudoaneurysm via the placement of stent grafts (9) with or without thrombin injection (10). Following placement of a stent graft, issues relative to cannulation territory may remain, and indeed it has been suggested that access through a stent graft should be avoided given potential complications and the lack of long-term safety data (11). These issues remain unresolved at present, and theoretical drawbacks of endovascular treatment must be carefully considered when either surgical revision or access abandonment appear to be the only options. The access in this case was salvaged by endovascular management and remained patent and usable at 10-month follow-up, despite necessary cannulation through the stent grafts.

I just received the July 2012 issue, one of the very best, and I want to congratulate you. The quality of the journal keeps going up and up, a real treat! Incidentally, Charles S. Roberts’ critique of “G.O.D.’s” (good old Denton’s) book was excellent. Please convey my congratulations. “Facts and ideas from anywhere” was as always enjoyable and informative, especially the piece on the major personality types. Again, many thanks for including me on your mailing list.

—Peter Alivizatos, MD
Athens, Greece

Thank you for including my photograph of the Margaret Hunt Hill Bridge at dawn in the October issue of Baylor University Medical Center Proceedings. It is a great honor to have a work of mine included in this outstanding medical journal.

The October issue is fresh and exciting to read. Among the many articles and papers I liked, I was fascinated by your “Facts and Ideas from Anywhere.” Your interview with Dr. Barry was informative and, at times, quite humorous. The Proceedings has become my favorite medical journal.

—Jay Hoppenstein, MD
Dallas, Texas

Writing medical articles

Dr. Bill Roberts has written and edited more medical manuscripts than almost anyone. In a recent issue of The American Journal of Cardiology, which he has edited since 1982 (in addition to editing Baylor University Medical Center Proceedings), Bill has provided a valuable and fascinating treatise on preparing manuscripts for publication in medical journals (1). It tackles the subject in a soup-to-nuts, tour de force fashion beginning with formulating an answerable question and then advising about each of the nascent article’s sections (introduction, materials and methods, results, discussion, figures, tables, and references). Along the way, Roberts’ article is filled with down-to-earth and practical advice on what to write first, selecting the title, considering the pros and cons of abbreviations, and proofing the manuscript with or without a time interval after completion (“cold eye” and “hot eye”). There are segments on getting the manuscript accepted (“Think Like a Lawyer and Cover the Flanks”) and clarity and conciseness in writing. A list of classic references on writing, words, and editing is provided, and discussion of the editing process adds further dimension to the overall topic. An informative section on impact factor and the Eigenfactor™ in medical journals is included. The importance of using alkaline paper in journal preservation is emphasized. The final portion of the manuscript deals with writing versus editing. Dr. Roberts has done a huge amount of both and concludes that editing is much easier, largely because writing involves creating something that did not exist before.

Anyone who prepares articles for publication in medical journals will benefit from reading this amazing short-course-in-doing-everything article. Dr. Roberts has done all of us a tremendous favor by transmitting some of the breadth and depth of his enormous knowledge in a most enjoyable manner.

—Marvin J. Stone, MD, MACP
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Note: Readers interested in obtaining an electronic or print copy of this article may contact Cindy Orticio at cynthiao@baylorhealth.edu.
Persistent bilateral proatlantal type II artery

Mehrzad Zarghouni, MD, and Daniel Marichal, MD

Vascular anomalies and variants are common in patients undergoing imaging studies, and patients with these anomalies are generally asymptomatic. Remnants of fetal carotid-basilar circulation are rarely identified. We report a rare case of persistent type 2 bilateral proatlantal arteries, in which the patient presented with dizziness.

A 62-year-old man presented with headache, dizziness, and a remote parietal cortical infarction. Magnetic resonance angiography (MRA) of the head and neck was subsequently obtained. The MRA images revealed bilateral persistent type 2 proatlantal arteries (Figure 1b, short white arrows) originating from the bilateral external carotid arteries (Figure 1a, long white arrows) and eventually contributing to and forming the verteobasilar circulation (Figure 1a, 1b, yellow arrows). Moreover, the V1 and V2 segments of the bilateral vertebral arteries were atretic. The patient’s presenting symptoms were not attributed to this vascular variant, and he was discharged home with resolution of the presenting symptoms.

DISCUSSION

Anomalous communications between the carotid and verteobasilar system arise from fetal remnants of four carotid and verteobasilar system anastomoses that once played a vital role in supplying the posterior circulation of the embryo (1–3). Such anastomoses begin to form at the 4- to 5-mm embryo stage and disappear at the 7- to 12-mm embryo stage (1–4). The first anastomosis to involute is the otic artery, followed by the hypoglossal artery that originates from the internal carotid artery at the C1 to C3 level and enters the hypoglossal canal prior to joining the basilar system. The type 1 variant arises from the internal carotid artery, while the type 2 variant originates from the external carotid artery prior to joining the verteobasilar system (3).

Very seldom there is bilateral presence of such variance. As such, persistent bilateral type 2 proatlantal artery is extremely rare, and only a handful of reported cases exist in the literature. As in our case, such variants are commonly associated with other vascular anomalies such as vertebral artery aplasia or hypoplasia and have an increased incidence of intracranial aneurysm formation (3). Although patients with proatlantal arteries are generally asymptomatic, they remain at increased risk of posterior circulation hemorrhage secondary to altered hemodynamics, as well as ischemia in the setting of occlusion of these variant arteries (3).


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Figure 1. (a and b) Magnetic resonance images reveal bilateral proatlantal type 2 arteries (long white arrows) originating from the external carotid arteries forming the vertebral arteries (short white arrows) forming the basilar artery (yellow arrow). (c and d) Magnetic resonance angiogram images demonstrate a persistent trigeminal artery (long white arrow) originating from the cavernous segment of the left internal carotid artery (short white arrow) before joining the basilar artery (yellow arrow).
Subependymomas are rare, slow-growing benign neoplasms. Although most are asymptomatic, they can present with symptoms related to increased intracranial pressure and hydrocephalus. We describe a 47-year-old man with worsening headaches who was found to have a subependymoma, with a focus on the imaging findings, differential diagnoses, pathology, and treatment.

CASE REPORT

A 47-year-old man, who previously had undergone gastric bypass for morbid obesity, presented to his neurologist complaining of headaches for 3 years, with major worsening of their frequency and severity for 2 weeks. The headaches now involved his entire head and were only transiently relieved with over-the-counter analgesics.

Magnetic resonance imaging (MRI) of his brain was obtained and revealed an extraxial mass in the inferior fourth ventricle extending through the foramen magnum and impressing upon the pontomedullary junction and medulla with posterior compression of the cerebellar tonsils. The mass had similar signal intensity to brain parenchyma on T1-weighted images and showed scattered heterogeneous enhancement (Figure 1). The T2-weighted images revealed increased signal intensity relative to brain parenchyma and lack of adjacent edema (Figure 2). A gradient echo sequence showed scattered foci of hypointensity indicating \( T_2^* \) susceptibility favoring the presence of calcific deposits and/or blood (Figure 3).

The patient underwent a craniotomy with complete resection of the fourth ventricular mass (Figure 4). Histologic evaluation of the lesion confirmed the diagnosis of subependymoma (Figure 5). The patient was subsequently discharged from the hospital after an uneventful postoperative course.

DISCUSSION

Subependymomas account for about 1% of all intracranial neoplasms (1). They are slow growing and well circumscribed. While they usually arise in the fourth ventricle in adults (60%), they have also been described in the lateral and third ventricles as well as in the spinal cord (2). Imaging characteristics commonly include a well-defined solid or less frequently mixed solid and cystic intraventricular mass. The solid component is isodense on computed tomography, isointense on T1-weighted images, and hyperintense on T2-weighted images. Peritumoral edema is usually not present. Lesions are typically 1 to 2 cm in diameter; however, tumors >5 cm have been described (2). Enhancement characteristics are variable: they are most often absent, but mild to moderate and even intense enhancement has been described. Calcific deposits can be seen with larger tumors and are frequently a constituent of fourth ventricular subependymomas. Hemorrhage is rare (2–4). The differential diagnosis of a subependymoma is an ependymoma, choroid plexus papilloma, central neurocytoma, subependymal giant cell astrocytoma, hemangioblastoma, cavernous malformation, and metastasis. In an individual of this age, and in the location of this mass with the given MRI features outlined above, the
diagnosis of exclusion was a subependymoma with a less likely consideration being an ependymoma.

On gross examination, subependymomas have a white to gray color, are well circumscribed with a firm texture, and are usually avascular with an attachment to the ventricular wall by a narrow pedicle. These lesions are thought to arise from subependymal glial cells, although other considerations include astrocytes from the subependymal plate, ependymal cells, and mixed ependymal and astrocytic cells (2, 5). On histological examination, clusters of nuclei on a fibrillary background are seen. Immunohistochemical staining for glial fibrillary acidic protein is highly positive. Mitotic activity is typically minimal or absent, corresponding to a World Health Organization grade 1 lesion (2, 5).

The treatment of choice for subependymomas is complete surgical resection, which yields an excellent prognosis with rare recurrences (2, 6). A complete surgical resection is more commonly possible with lesions located in the lateral ventricles,
with fourth ventricular locations often treated with subtotal resections. There is little documented additional benefit from chemotherapy or radiotherapy (2, 6).


**Vibrio vulnificus** necrotizing fasciitis preceding herpes zoster

Kelli Y. Ha, MD, and Stephen K. Tyring, MD, PhD

A 74-year-old white man presented with unilateral radicular pain extending across the left side of his chest and back. A diagnosis of postherpetic neuralgia, a sequela of herpes zoster, was made. Herpes zoster represents a reactivation of the varicella zoster virus that lies dormant in patients with past chickenpox. Risk factors for the disease include advanced age, stress, immunodeficiency, and immunosuppression. Treatment of herpes zoster entails traditional antiviral medications, while prevention may be achieved with a new prophylactic vaccine.

Herpes zoster (HZ), also known as varicella zoster or more colloquially as “shingles,” is a neurodermal disease characterized by unilateral radicular pain, tingling, pruritus, and a characteristic vesicular rash set on an erythematous base. The rash entails a reactivation of the latent varicella zoster virus (VZV) that lies dormant in cranial or sensory nerve ganglia. The most commonly affected dermatomes lie in the cranial and thoracic regions of the body. Approximately 98% of the population remains susceptible to HZ, as the virus lies quiescent in individuals previously afflicted with chickenpox. Because of such widespread susceptibility, it is important to identify the risk factors that may predispose one to HZ.

**CASE REPORT**

A 74-year-old white man presented with a 10-month history of unilateral radicular pain extending across the left side of his chest and back in the region of the T5 dermatome; he rated this pain as a “10” on a 0- to 10-point scale. The patient revealed that his HZ outbreak had been preceded by necrotizing fasciitis, which resulted in several hemorrhagic bullae located along the left upper extremity (C6, C7, and C8) (Figure 1). The infection was induced by a puncture wound that arose while the patient was fishing in the Gulf of Mexico. He was hospitalized for 1 week and treated with cefotaxime, ciprofl oxacin, and minocycline. Approximately 7 days following his discharge from the hospital, the hemorrhagic bullae had begun to resolve and painful vesicles in the adjacent T5 dermatome began to emerge. The patient was subsequently diagnosed with HZ and treated with famciclovir. Previously, he had type 2 diabetes mellitus treated with rosiglitazone.

Examination revealed a hypopigmented scar that closely followed the course of pain along the indicated dermatome (Figure 2). Swelling and soreness were noted under the patient’s left arm, making any voluntary movement of the arm extremely painful. Though the patient did not have a history of shingles, he affirmed that his son, grandson, and brother had all been afflicted with the malady at various times. The patient remembered having had chickenpox as a child.

**DISCUSSION**

Although most of the population remains susceptible to HZ after recovering from a bout of chickenpox, the lifetime risk is estimated at approximately 15% (1). This incidence, however, rises dramatically with age, affecting up to 50% of those ≥85 years. Advanced age represents the most potent risk factor for the development of HZ and its associated sequelae. Among these sequelae are postherpetic neuralgia (PHN), ophthalmic zoster, Ramsay-Hunt syndrome, bacterial super-infection, scarring, meningoencephalitis, pneumonitis, and...
PHN is the most serious complication and is characterized by chronic HZ-associated pain that lingers for months to years after the erythematous rash has disappeared (1). The increased risk of HZ among the elderly may result from a general waning of cellular immunity that occurs with advanced age. Alternatively, a prolonged length of time since primary varicella exposure may contribute to a heightened risk for HZ (3). The age at which the most dramatic rise in HZ incidence occurs is about 60 years. Patients with HIV/AIDS, certain cancers, organ transplants, and those receiving immunosuppressive treatments have also been shown to have a heightened risk for HZ (4).

Aside from aging and immunosuppression, a number of additional risk factors may contribute to the prevalence of HZ. Stress, both psychological and mechanical, appears to play an important role in the attainment of the disease. Trauma, surgery, and/or injury to a specified region of the body may induce or predispose one to an outbreak of HZ. Nerve stimulation from mechanical trauma may precipitate HZ in the affected dermatome by triggering reactivation of the virus in the dorsal root ganglion (4).

*Vibrio* species may affect humans through three clinically distinct illnesses: gastroenteritis, wound infection, and primary septicemia. Infection may arise when chafed skin or minor abrasions are exposed to seawater or during the preparation of seafood (5). Alternatively, penetrating injury by fish fin spines or ingestion of uncooked seafood may ultimately result in soft tissue infections and lethal septicemia. Injury to the distal extremities caused by fish fin spines is frequently sustained by fishermen and those who handle live seafood (6).

*Vibrio vulnificus* is a naturally occurring, Gram-negative, halophilic bacterium found in both estuarine and marine environments throughout the world. Its presence is especially prevalent within the warm coastal waters of the Gulf of Mexico, South America, Asia, and Australia. Infection with *V. vulnificus* may lead to the development of necrotizing fasciitis and primary septicemia, two complications that are most prevalent in immunocompromised patients with underlying hepatic disease, diabetes mellitus, chronic renal insufficiency, and adrenal insufficiency (7). Our case report highlights the development of necrotizing fasciitis in a diabetic patient who acquired a puncture wound while fishing in the Gulf of Mexico. The trauma induced by the wound and its subsequent necrotizing fasciitis may have provided an adequate degree of stress to provoke the development of HZ and its associated PHN.

Although many of the predisposing factors to HZ are acquired throughout one’s lifetime, others may be inherent. A recent study proposed that a distinct polymorphism in the promoter region of the interleukin-10 (IL-10) gene may be responsible for this genetic susceptibility, as IL-10 is a cytokine that aids in downregulating cellular immunity (8). In addition, an individual’s ethnicity may play a role in the attainment of HZ. Previous studies (4, 9–11) have demonstrated a lower prevalence of HZ in black individuals as compared to white individuals. Hypothesized reasons for these disparities include differences in VZV immunity, age of varicella onset, and exposure to varicella over one’s lifetime (12).

The clinical course of HZ often begins with a prodrome characterized by pain, paresthesias, general malaise, fever, and lymphadenopathy. Prodromal symptoms may last 1 to 3 days and occur in approximately 80% of HZ patients. Following the viral prodrome, a distinctive unilateral eruption of herpetiform vesicles occurs in one or more affected dermatoes. The HZ rash begins as erythema, followed by water-clear vesicles at 12 to 24 hours, confluent vesicles at 48 to 96 hours, and pustules at 72 hours. New crops of vesicles continue to emerge for 1 to 7 days. The cranial and thoracic regions of the body are most frequently affected (13), with <1% of patients exhibiting bilateral nerve involvement (14). Some patients may not develop the characteristic HZ rash, a condition termed “zoster sine herpette,” which may further complicate the diagnosis (15).

Early identification of HZ is crucial in the treatment and prevention of the virus’s numerous complications. Diagnosis of HZ is often made by clinical observation alone. Three antiviral drugs, acyclovir, famciclovir, and valacyclovir, are currently available for the treatment of HZ and appear to be more effective than treatment with corticosteroids alone (15). Though acyclovir is significantly less expensive, famciclovir and valacyclovir are preferred due to more convenient dosing regimens (5 times daily versus 3 times daily, respectively). One study demonstrated that famciclovir could reduce acute HZ pain by 1 to 2 days and PHN pain by 60 days if given within 72 hours of an outbreak (16). Famciclovir has since been shown to be equivalent to valacyclovir in regards to rash healing time and reduction of pain caused by PHN (17).

A new vaccine that was approved by the Food and Drug Administration in May 2006 may be the best option for those at risk for HZ. In October 2006, the Centers for Disease Control and Prevention recommended Zostavax as part of a routine vaccination for senior citizens aged ≥60 years. A study highlighting the efficacy of Zostavax revealed that cases of HZ were reduced by half in those who received the vaccine versus placebo. Participants who were vaccinated but still acquired HZ were 66% less likely to develop PHN than those given a placebo (18).
Hence, the new HZ vaccine may reduce the incidence of HZ and its potential complications in patients with a heightened risk of developing the disease.

Identification of designer drug 2C-E (4-ethyl-2, 5-dimethoxy-phenethylamine) in urine following a drug overdose

Michael J. Van Vrancken, MD, MPH, Raul Benavides, MD, and Frank H. Wians Jr., PhD, MT(ASCP)

In recent years, access to information regarding acquisition and synthesis of newer designer drugs has been at an all-time high due largely to the Internet. As these drugs have become more prevalent, laboratory techniques have been developed and refined to identify and screen for this burgeoning population of drugs. This provides a unique opportunity for learning about many of these methods. Laboratory testing techniques and instrumentation are obscure to many health care professionals, yet their results are crucial. Here, we present a case of an overdose of an uncommon designer drug (2C-E) and discuss the basics of liquid chromatography and mass spectrometry, two important techniques used in isolating and identifying the drug. Although often overlooked and taken for granted, these techniques can play a pivotal role in the diagnosis and subsequent management of select patients.

The drug scene is constantly changing and evolving. Traditionally, drugs of abuse are associated with popular street drugs such as marijuana, heroin, cocaine, and methamphetamine. In the 1990s, several other drugs were added to this list, including the so-called “club drugs”: ecstasy, ketamine, and gamma hydroxybutyric acid. In more recent years, “designer drugs” have emerged, which are either chemically altered natural substances or completely synthetic molecular structures that have psychotropic effects. Due to the widespread use of the Internet, information regarding synthesis and access to novel compounds is more accessible than ever. This poses new challenges to the medical community in terms of treatment as well as identification of the abused substance, especially in patients unable to communicate. Here we present a case of a fatal overdose of the designer drug known as 2C-E (4-ethyl-2, 5-dimethoxy-β-phenethylamine), a phenethylamine derivative. Although previously published, the prior case report focused on radiographic findings (1). In the present article, we focus on how 2C-E is detected in the urine using basic chromatography and mass spectrometry principles.

**DISCUSSION**

The 2C family of designer drugs is a large group of chemicals classified as ring-substituted phenethylamines, most of which were first synthesized in the 1970s by the chemist Alexander Shulgin (2). They are characterized by methoxy groups at positions 2 and 5 of the benzene ring. Within the 2C family, there are differences in the substitution of the fourth position on the benzene ring. For instance, at position 4, 2C-I substitutes iodine while 2C-B substitutes bromine. For 2C-E in particular, an ethyl group is substituted at position 4 (Figure 1). A full list of 2C compounds published by Shulgin is provided in Table 2.

Pharmacologically, 2C-E (and the 2C family) shows strong efficacy for the 5-HT2C receptor, accounting for its hallucinogenic effects (3). Accounts from users typically report a dosage range from 10 to 30 mg (2). Although little is known of the pharmacokinetics of the drug, it seemingly takes effect within seconds of insufflation, with a slightly delayed action if taken according to the patient’s friend, he had ingested a drug known as 2C-E, but was not aware of any other drug or alcohol use. The patient had prescriptions for various psychiatric medications including sertraline, clonazepam, gabapentin, and zolpidem.

In the emergency department, his clinical status remained unchanged. An initial urine toxicology screen was positive for marijuana metabolites and benzodiazepines. A head computed tomography scan was negative, and electroencephalography showed diffuse slowing. The patient’s initial laboratory studies are shown in Table 1.

On admission, the patient had acute kidney failure and leukocytosis, and he subsequently developed a right lower lobe pneumonia, which resolved with antibiotics. Although the patient remained obtunded, his brain stem reflexes remained intact throughout his hospitalization. After discussing the patient’s prognosis in detail, the family decided to withdraw life-supporting therapy. The patient died about 2 weeks after his initial admission. Subsequent specialized urine drug screens were positive for the compound known as 2C-E.

CASE REPORT

A 26-year-old white man with known polysubstance abuse and psychiatric problems was found unresponsive at a friend’s house. Initial emergency responders intubated the patient and treated him with naloxone with no change in clinical status.

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The drug displays a marked dosage effect, and hallucinogenic activity typically lasts for 4 to 8 hours (2). Metabolism of 2C-E appears to have several pathways, although the main ones appear to be via hepatic oxidative deamination and/or O-demethylation (4–6).

The clinical presentation of users of the 2C group can be varied. At lower doses, the drugs act as a stimulant (2). However, at higher doses (>10 mg), there is a marked hallucinogenic and psychoactive effect. Deaths have also been reported following the usage of 2C compounds including, but not limited to, 2C-T-7 (7) and 2C-I (8).

For diagnosis, an analytic method for detection and quantification is required for clinical chemistry and forensic toxicology. Many different techniques have been developed to screen for these newer designer drugs, including capillary electrophoresis–mass spectrometry (9–12), capillary electrophoresis coupled with a diode array detector (13), gas chromatography–mass spectrometry (14, 15), and liquid chromatography–mass spectrometry (LC-MS) (16). In more recent years, LC-MS in tandem (LC-MS/MS) has become the detection test of choice due to its ability to separate and identify small molecules with similar structures in one run (17).

In order to understand LC-MS/MS, it is easiest to break it up into its separate analytic components. The liquid chromatography phase, specifically high-performance liquid chromatography, separates chemicals by running a solvent
spectrometers identify the molecules present in a sample based on ionized and given either a positive or a negative charge. Mass spectrometry is useful for identifying unknown chemicals in the sample. This is where coupling of liquid chromatography (mobile phase) containing the chemicals of interest through a column (stationary phase). The chemical (2C-E) binds to the column through hydrophobic interactions. As can be expected, different molecules elute through the column at different times due to differences in molecular structure and hydrophobic interactions. This technique is very good at separating chemicals (even molecules with very similar masses); however, it does not necessarily identify the compound, especially if there are many unknown chemicals in the sample. This is where grouping of mass spectrometry is useful.

In typical non-tandem mass spectrometry, these unknown compounds enter the mass spectrometer, where they are initially ionized and given either a positive or a negative charge. Mass spectrometers identify the molecules present in a sample based on their mass-to-charge ratio (m/z). The molecules then move into the quadrapole chamber, which consists of four parallel magnetic rods arranged in a square formation (Figure 2) (18). The rods are calibrated in such a way that only the ions of a specific mass-to-charge ratio (m/z) that matches the analytes of interest. Because only ions matching the selected m/z are transmitted, the resultant chromatogram and mass spectra are clean and easy to interpret. However, because the two analytes of interest have identical m/z, the mass spectrometer is unable to differentiate between them. Reprinted with permission from Hill et al, 2011 (18).

Figure 2. Schematic of a quadrapole mass spectrometer. The quadrapole is set to transmit only ions with a specific mass-to-charge ratio (m/z) that matches the analytes of interest. Because only ions matching the selected m/z are transmitted, the resultant chromatogram and mass spectra are clean and easy to interpret. However, because the two analytes of interest have identical m/z, the mass spectrometer is unable to differentiate between them. Reprinted with permission from Hill et al, 2011 (18).

Figure 3. Schematic of a mass spectrometer in tandem. Q1 is set to only transmit ions with a specific mass-to-charge ratio (m/z) that matches the analytes of interest. The collision cell, q2, produces fragments from these transmitted ions, while Q3 constantly scans across the entire m/z range, allowing all fragments produced in q2 to reach the detector. The recording of all fragments results in a complex chromatogram and mass spectra but has allowed for the unique identification of each analyte at the appropriate sampled time point, indicated in blue and yellow. Reprinted with permission from Hill et al, 2011 (18).


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A dozen Baylor facilities earn Joint Commission “Top Performer” status

Twelve Baylor Health Care System (BHCS) facilities stretching from Denton to Tarrant to Ellis County earned Top Performer status from The Joint Commission, the leading accreditor of health care organizations in America:

- Baylor Grapevine was recognized for achieving excellence in performance on its accountability measures during 2011 for conditions including heart attack, heart failure, pneumonia, and surgical care
- Baylor Plano was recognized for heart failure, pneumonia, and surgical care
- Baylor Carrollton was recognized for heart attack, pneumonia, and surgical care
- Baylor Waxahachie was recognized for heart failure, pneumonia, and surgical care
- Baylor Jack and Jane Hamilton Heart and Vascular Hospital was recognized for heart attack, heart failure, and surgical care
- The Heart Hospital Baylor Plano was recognized for heart attack, heart failure, and surgical care
- Baylor Orthopedic and Spine Hospital at Arlington, Baylor Medical Center at Uptown, North Central Surgical Center, Baylor Surgical Hospital at Fort Worth, Baylor Medical Center at Frisco, and Baylor Medical Center at Trophy Club were recognized for surgical care

The 12 facilities met two criteria. First, each achieved performance of 95% or above on a single composite score that included all the accountability measures for which it reported data to The Joint Commission, including measures that had <30 eligible cases or patients. Second, the facilities met a 95% performance threshold for every accountability measure for which they reported data. Of nearly 3400 hospitals reporting data to The Joint Commission, only 620 (about 18%) were top performers in at least one category.

“Making the Top Performers list is no easy feat,” commented Joint Commission President Mark R. Chassin, MD, FACP, MPP, MPH. “I salute these organizations for their hard work in attaining excellence. By consistently using evidence-based treatments, their patients are getting better hospital care.”

Baylor Dallas earns Consumer Choice award

For the 17th consecutive year, Baylor University Medical Center at Dallas (BUMC) has earned the Consumer Choice Award for Best Overall Quality and Best Image/Reputation from the National Consumer Choice Award for Best Overall Quality and Best Image/Reputation from the National Research Corporation. The Consumer Choice Award is given to the hospitals that consumers have selected as having the highest quality and image in 300 markets throughout the United States. Award winners are determined by gauging consumer perceptions on multiple quality and image ratings collected through the company’s Market Insights/Ticker survey. Of the 3200 hospitals named by consumers in the study, the winning facilities rank highest in their core-based statistical areas, as defined by the US Census Bureau. The 2012/2013 study surveyed more than 250,000 households representing 450,000 consumers in the contiguous 48 states and the District of Columbia.

American Heart Association recognizes Baylor Grapevine for quality heart and stroke care

Baylor Regional Medical Center at Grapevine recently received two national awards—the Get With The Guidelines®—Heart Failure Gold Quality Achievement Award from the American Heart Association/American College of Cardiology and the Get With The Guidelines®—Stroke Gold Plus Quality Achievement Award from the American Heart Association/American Stroke Association. The heart failure award signifies that Baylor Grapevine reached an aggressive goal of treating heart failure patients according to the guidelines of care. As a result, heart failure patients are started on aggressive risk-reduction therapies if needed, including cholesterol-lowering drugs.

ACCOLADES

Physiatrist Amy J. Wilson, MD, medical director for BIR, was named in the top 1% of US physical medicine and rehabilitation doctors by U.S. News & World Report. She also was recently chosen by D Magazine for its “Best Doctors in Dallas” issue.

Becker’s Hospital Review recently named Nancy Vish, RN, PhD, NEA-BC, FACHE, president and chief nursing officer at Baylor Jack and Jane Hamilton Heart and Vascular Hospital, one of the “120 Women Hospital and Health System Leaders to Know.”

Andrew Masica, MD, MSCI, vice president of clinical innovation for BHCS, was the Dallas—Fort Worth Hospital Council’s choice for 2012 Young Healthcare Executive of the Year. The award honors youthful North Texas professionals who demonstrate the key abilities of successful health care leaders.

The BHCS Public Relations team took top honors for Best Online Newsroom in Ragan’s Health Care Communication News’ inaugural Health Care PR & Marketing Awards competition. In addition, Baylor’s Sammons Says blog received an honorable mention in the Best Blog category.

BHCS’s Conflict of Interest Management Program was honored with a Best Practice Award from the Health Ethics Trust. Baylor is one of only three health care systems to receive this top award.

Three BHCS hospitals were Press Ganey 2012 Summit Award winners. Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Baylor Regional Medical Center at Plano, and The Heart Hospital Baylor Plano won awards for inpatient satisfaction. The Heart Hospital Baylor Plano also received a Summit Award for emergency department satisfaction. The Summit Award, one of Press Ganey’s most prestigious awards, honors hospitals that sustain an overall patient satisfaction rank above the 95th percentile for at least the past 3 consecutive years. Only 100 organizations receive the award in each category.

The American Medical Group Association honored HealthTexas Provider Network (HTPN) for its initiative, “Transforming Healthcare Delivery Through Patient-Centered, Value-Based, Quality Care.” HTPN was one of only three top medical groups to be recognized by the association as an Acclaim Award honoree and was the only group to receive this honor for 2 consecutive years.
beta-blockers, ACE inhibitors, aspirin, diuretics, and anticoagulants while in the hospital. Before discharge, they also receive education on managing their heart failure and overall health. To receive the stroke award, Baylor Grapevine developed a comprehensive system for rapid diagnosis and treatment of stroke patients admitted to the emergency department. This includes always being equipped to provide brain imaging scans, having neurologists available to conduct patient evaluations, and using clot-busting medications when appropriate.

Baylor Grapevine has also been recognized as a recipient of the association’s Target: Stroke Honor Roll for improving stroke care.

**New medical documentary series features three heroic patients and their fight to beat cancer**

The Baylor Charles A. Sammons Cancer Center, Baylor T. Boone Pickens Cancer Hospital, and three Baylor patients were the subject of a three-part, inspirational documentary, *Dallas Hope*, which aired on November 8, 15, and 17, 2012, on WFAA Channel 8. Episodes can now be viewed at www.DallasHope.com.

Viewers watched as Michelle Berndt, a 30-year-old mother of two and Mrs. Texas pageant contestant, fought breast cancer. Meanwhile, 25-year-old leukemia patient Cherysse Daniels held out hope that her brother was a stem cell match, so she could get the bone marrow transplant she needed to survive. Finally, 78-year-old Bill the “Bull” Bradford, no stranger to a challenge, faced one of his most formidable opponents, terminal lymphoma. Will the clinical trial he enrolled in help him beat the odds?

“We couldn’t be prouder of this show and all the people at Baylor who care for these brave patients during such a difficult time,” said Alan Miller, MD, PhD, chief of oncology for BHCS. “Cancer may be a devastating disease, but it also brings out the best in people. That really shines through in each episode.”

Award-winning filmmaker Tony Martinez, who directed the documentary, agreed. “I’ve worked on documentaries about sports figures and World War II, but this is definitely one of the most moving projects I’ve ever been a part of. I think everyone who tunes in will be captivated.”

**Baylor Surgical Hospital at Fort Worth announces new facility**

Baylor Surgical Hospital at Fort Worth announced the purchase of 5.3 acres of land with plans to construct a new replacement hospital to be located on Park Place Avenue in Fort Worth, Texas. The new facility will replace its current facility, located at 750 12th Avenue in Fort Worth. The three-story, 77,000-square-foot, acute care replacement hospital is expected to break ground in May 2013 with an estimated completion in August 2014. The new facility will feature 30 inpatient beds, 14 operating rooms, a 24-hour emergency room for minor emergencies, an imaging suite, convenient parking, wireless Internet access, flat screen monitors in each patient room, and an uncommon commitment to patient safety and satisfaction.

**Department of Education grant supports traumatic brain injury rehabilitation research at Baylor Institute for Rehabilitation**

Baylor Institute for Rehabilitation (BIR) has received a $2.2 million grant extending for another 5 years the institute’s designation as a National Institute on Disability and Rehabilitation Research model system site for traumatic brain injury (TBI). BIR has held the designation since 2002. The status and funding will help the institute—in collaboration with the University of Texas Southwestern Medical School in Dallas and John Peter Smith Hospital in Fort Worth—continue to generate valuable new knowledge about how to improve the functional outcomes of patients with TBI.

The latest grant will involve two novel research projects. The first will measure variations in clinical practices and patient outcomes across several rehabilitation centers nationwide, as well as develop a list of evidence-based guidelines for best practices in TBI rehabilitation. The second will identify patients with TBI who will benefit from certain medications in their recovery. Dr. Shahid Shafi, a surgeon on the medical staff at Baylor Regional Medical Center at Grapevine and a clinical scholar at the BHCS Institute for...
Health Care Research and Improvement, is the principal investigator on this grant. BIR treats more than 200 patients with brain injury annually and, among the 16 model system facilities, enrolled the fifth most patients in the associated studies. The TBI program is led by physiatrist Randi Dubiel, DO, who specializes in brain injury. The program incorporates a designated team of neuropsychologists and neuro-certified physical and occupational therapists, speech therapists, and nurses.

**Baylor supports Hurricane Sandy relief efforts**

BHCS’s Faith in Action Initiatives is responding to the needs of those on the East Coast impacted by Hurricane Sandy. As in many other disaster situations, it helps fulfill local, national, and worldwide health and disaster needs. In response to Hurricane Sandy’s devastation, Faith in Action Initiatives sent a pallet of medical and disaster relief goods from its warehouse to the New England Baptist Convention headquarters in Northboro, Maryland.

**Baylor offers emotional support to help children understand concepts of serious adult illness**

Baylor is the first North Texas health care provider to offer child life services in an adult medical setting. BHCS pioneered these services at BUMC and, in August 2012, added a child life specialist to the supportive and palliative care team at Baylor All Saints Medical Center at Fort Worth. The Baylor program flips the typical child life specialist role from helping a child understand his own illness to helping a child understand a significant adult’s illness. Services differ in every situation but can include the following:

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### PHILANTHROPY NOTES

- **T. Boone Pickens invests $10 million in Baylor**
  
  In September 2012, BHCS Foundation announced that legendary oil and gas entrepreneur and philanthropist T. Boone Pickens pledged $10 million in support of Baylor initiatives. In recognition of this gift, and in a move that links the innovative business leader with a leading cancer program, Baylor honored Boone by naming its new cancer hospital the Baylor T. Boone Pickens Cancer Hospital.
  
  “No matter what industry you’re in, from energy to healthcare, it takes bold people who have vision, a commitment to excellence and a passion for efficiency to reach new levels of success,” said Boone. “Baylor brings that attitude and commitment to providing health care to all North Texans, whether it is advanced prevention, screening, diagnosis, or treatment.”

- **2012 Celebrating Women luncheon brought hope and Rob Lowe to Baylor’s fight against breast cancer**
  
  BHCS Foundation hosted its 13th annual Celebrating Women luncheon in October at the Hilton Anatole hotel in Dallas. Celebrating Women has raised more than $19 million over the past 13 years to benefit BHCS’s breast cancer initiatives.

  The keynote address, delivered by award-winning actor and best-selling author Rob Lowe, was heard by more than 1350 luncheon attendees. After losing his mother, grandmother, and great-grandmother to breast cancer, Rob has been a passionate advocate for research and early detection.

  “There is so much hope in today’s war on cancer. To talk to the doctors on the cutting edge is to come away with an optimism and excitement that is extraordinary,” said Rob. “Everyone in this room is a living example of how far we’ve come; walking miracles of medicine, faith, and perseverance. There is little doubt that as more lives are saved, even better news is just around the corner. If we didn’t believe that, we wouldn’t be here.”

- **Grand Rounds® Golf Tournament raises money for medical education**
  
  At the 11th annual Grand Rounds® Golf Tournament, 200 golfers helped BHCS Foundation raise a record $305,000 in support of medical education for both undergraduate medical students and graduate physicians at BUMC. The event, presented by Bank of Texas, was held October 1, 2012, at Northwood Club in Dallas.

  Following the day’s rounds, players enjoyed a VIP reception and a golf talk with guest speaker Tom Kite. Tom, winner of the 1992 US Open at Pebble Beach, shared stories from the road and answered questions regarding his experiences at the Ryder Cup and his thoughts on the trajectory of the game of golf for the future.

  Baylor University Medical Center at Dallas currently trains 240 residents and fellows in 37 specialty and subspecialty programs. With donor support, BHCS Foundation plans to fund 28 residents and fellows at a cost of more than $1.9 million this fiscal year.

- **Baylor emergency services receives $1.2 million gift for new software**
  
  BHCS is working to create more efficiency in the emergency departments across the entire system. One key step in this process is the implementation of MEDHOST software, which is an electronic health record system that tracks process times and helps staff identify areas for improvement.

  The efficient, easy-to-use software is specifically designed for emergency departments. And, thanks to a $1.2 million gift from EmCare, Inc., BHCS now has the resources to better customize MEDHOST to fit Baylor’s unique needs. The goal is to have MEDHOST software installed in most of Baylor’s emergency department facilities by 2013.
• Helping parents anticipate and respond to children’s reactions to hospital visits to see an ill parent or adult, to a new or progressive diagnosis, and to changes in the adult’s physical abilities and appearance.
• Helping parents find age-appropriate explanations for the adult’s medical condition. “One young boy thought his father was sick with ‘amnesia’ because the 7-year-old had seen a TV show in which the character was groggy and forgetful,” recalled Cinda McDonald, MEd, a child life specialist at BUMC. “We used a teaching doll when we discussed his father’s true diagnosis with the boy, allowing us to explain the father’s condition in a manner the 7-year-old would understand.”
• Meeting with children to answer questions and help them understand and manage their thoughts and feelings about their loved one’s medical condition. Several sessions with a child life specialist helped two children recreate the scene of a car accident in which their father was seriously injured. Although the children were at the accident scene, they could not process the event. “These sessions in which we recreated the accident scene with toy miniatures helped the children to unravel what had happened, eventually allowing them to talk about what it was like to be there at the accident and address their questions,” said Cinda.
• Beginning discussion with children about end-of-life issues, anticipated death, or a traumatic event.
• Assisting children with memory-making/legacy activities in the event of anticipated or unexpected death.

Dr. Robert Fine, clinical director of palliative care at Baylor, explained, “Adult hospitals have historically given little attention to the children of seriously ill adult patients—patients who face many challenges, not the least of which is helping their children understand what is going on. I’ve seen how the guidance provided by our child life specialists not only helps the children of seriously ill adults, but lessens the emotional suffering of the adult patient as well.”
I would like to thank all of you for the great honor and privilege of serving as your president this year. It is a tremendous honor to be included in the list of presidents of this great organization.

In 1979, Willie Nelson sang a song entitled “My Heroes Have Always Been Cowboys.” I have changed this somewhat to my heroes have always been surgeons and educators. In this address, I briefly discuss the nature of heroes, introduce you to my wonderful family, and look at my surgical heroes from medical school, surgical training at Baylor University Medical Center at Dallas, and M. D. Anderson Hospital in Houston, Texas. Then, I review how two of the progenitors of my heroes laid the groundwork for my surgical heroes. In a brief conclusion, I look at today’s heroes.

THE NATURE OF HEROES
A hero has been defined in several ways:
• A mythological or legendary figure, often of divine descent, endowed with great strength or ability (e.g., Superman)
• An illustrious warrior (e.g., Audie Murphy)
• A man admired for his achievements and noble qualities (e.g., Abraham Lincoln)
• One who shows great courage (e.g., Ephraim McDowell, who on Christmas morning 1809 did the first ovariotomy on Jane Todd Crawford in Danville, Kentucky)
• The principal male character in a literary or dramatic work (e.g., Hamlet)
• The central figure in an event, era, or movement (e.g., Martin Luther King)
• An object of extreme admiration and devotion; an idol (e.g., Babe Ruth)

Benjamin Disraeli said, “There are men whose phrases are oracles: who condense in a sentence the secrets of life, who blurt out an aphorism that forms a character, or illustrates an existence.” Such are my heroes.

FAMILY HEROES
My first heroes are Esther and Jack O’Brien, my parents. My three brothers, three sisters, and I were raised in a warm and nurturing atmosphere where scholarship was encouraged, as was a strong work ethic. I cannot tell you how many times I heard my mother say, “If it is worth doing, it is worth doing well.”

All of my brothers and sisters have been very successful in their own right, and I have drawn inspiration from them through the years. We get together every 2 years. Four years ago, we met with our spouses in San Antonio (Figure 1). Two years ago, we had a general family meeting, which included all of our children and grandchildren, almost 60 participants (Figure 2).

Another of my heroes is my lovely wife, Sarah, to whom I’ve been married since medical school (Figure 3). Sarah is the light and the love of my life. She gave up a career as an intensive care unit nurse to raise our three wonderful children. She is now very involved with our nine grandchildren, a role in which she is very competitive. Her avocation is studying Egyptology; she is quite an expert in that discipline. She also has a great sense of humor, thus explaining the longevity of our marriage.

SURGICAL HEROES
I was fortunate to have great teachers throughout grade school, high school, and university. When I attended medical

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Presented as the presidential address at the 190th meeting of the Texas Surgical Society, October 13, 2012, San Antonio, Texas.
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school at St. Louis University, I met my first surgical hero, Dr. C. Rollins Hanlon (Figure 4). My first clinical rotation as a junior student was on pediatric surgery. I had the opportunity to be one of the many trainees who scrubbed on some of Dr. Hanlon’s cases. Dr. Hanlon had been a resident of Dr. Alfred Blalock of The Johns Hopkins Hospital. He was a gentleman and a scholar and an excellent surgeon. It was wonderful to hear him teach the residents. When I was a senior student on the surgical service at the Cochran Memorial Veterans Administration Hospital in St. Louis, Dr. Hanlon would meet with us for an hour each Thursday. We were given the subject to be discussed in advance, which sent all of us scurrying to our surgical textbooks. Dr. Hanlon would come to the session, impeccably dressed as always, and we would discuss the assigned topic. Dr. Hanlon never asked about what was in the book other than general information, but he would encourage us to think about the clinical entity and the reason for doing what we proposed. How I wanted to be like that man!

I did my general surgery training at Baylor University Medical Center at Dallas and had the great experience of training under Dr. Robert S. Sparkman (Figure 5). He was another gentleman and scholar. He too was an excellent surgeon and had a gift for teaching. He was an excellent historian, particularly in the field of surgical history. When Dr. Sparkman operated, he would make the incision and cover one edge with a sterile towel while he clamped the bleeding vessels on the opposite side with mosquito hemostats. After these vessels were ligated, we would remove the towel from the other edge of the incision and would find very few vessels that required ligation. One day I had the temerity to ask Dr. Sparkman why we didn’t cover both edges of the incision with towels, proceed with the procedure, and remove the towels a bit later. Perhaps, that would decrease the number of vessels we tied. You would have thought that I had stabbed the man in the heart. I learned to ask questions about other facets of surgical problems.

Each resident in our program has a technique or procedure named after him or her. During my senior resident year, I diagnosed a woman with gallstone ileus: air in the biliary tree, intermittent small bowel obstruction with air fluid levels, and two radiopaque gallstones in the right lower quadrant. That Saturday morning with Dr. Sparkman as my staff, we made a laparotomy incision, ran the small bowel, and found only the two stones. Dr. Sparkman had his ubiquitous camera with him, and as we could see the stones through the bowel wall he asked me to hold up that segment containing the stones so he could get a photograph. I held the bowel up. Dr. Sparkman requested that I hold it up higher, then higher, and at that point I realized I had separated the bowel from the mesentery. After achieving hemostasis we had to do a small bowel resection rather than an enterotomy to remove the stones. This is the O’Brien procedure. It is mentioned only to be condemned except in very special circumstances.

These first two surgical heroes, Dr. Hanlon and Dr. Sparkman, had something in common: they both trained under Dr. Mont Reid at the University of Cincinnati. Dr. Reid was the 16th of the 17 resident surgeons (chief residents) trained by Dr. William Stewart Halsted at Johns Hopkins University (Figure 6). Dr. Sparkman did his residency under Dr. Reid and was called to the army for World War II. As he left the housestaff quarters at Cincinnati General Hospital, he left some caricatures that he had drawn of Dr. Reid on the door (Figure 7). As the next occupant
of that room, Dr. Hanlon found them and kept them for many years. Dr. Hanlon and Dr. Sparkman became lifelong friends.

I was exposed to many wonderful surgeons during my training at Baylor. One surgeon who had great influence on me was Dr. Allan Bookatz. Dr. Bookatz trained at the Cleveland Clinic and came to Dallas to practice. On July 1, 1969, the first day of my internship, I reported for duty in the surgeon’s lounge at Baylor. I noticed that I had been scheduled to assist Dr. Bookatz with a hemorrhoidectomy. While I waited to identify Dr. Bookatz and introduced myself, three of the senior residents came up to me and said that Dr. Bookatz could be quite hard on the housestaff, so be strong and survive. Well, that certainly set the tenor for the day! After I met Dr. Bookatz, I tried to help him while afflicted with the usual “first day of internship” brain fog. I found him to be an excellent teacher and technical surgeon.

As I progressed through my training, if I did not perform to his exacting standards, he would say, “Do not get in the habit of doing less than perfect work, just because you can get away with it. Do everything as perfectly as you can because you will have complications with your best efforts—and many times that if you do not aspire to perfection.” He would then add, “Practice does not make perfect; perfect practice makes perfect.” He agreed with Guy de Chauliac (1300–1370), who said, “A blind man works on wood the same way as a surgeon on the body, when he is ignorant of anatomy.”

During my first 2 years of training, I accompanied Dr. Bookatz to gross anatomy lab at the Baylor College of Dentistry twice a week, as a teaching (actually learning) assistant. This was a great experience for me and well worth the effort. When working with Dr. Bookatz, I often remembered my mother’s admonition: “If it’s worth doing, it’s worth doing well.”

At the completion of my 5 years of surgical residency, I was one of six fortunate young men who obtained a surgical oncology fellowship at the M. D. Anderson Hospital and Tumor Institute in Houston, Texas. I had the opportunity to work with Dr. Richard Martin, the most focused surgeon with whom I worked. There was no idle chit chat, only discussion of the tumor stage and the reason for doing the procedure. His hands always worked with purpose with no extraneous motions. I tried to emulate him in my surgical technique. Dr. Charles McBride was the melanoma expert at M. D. Anderson. From him I learned much about melanomas and that you could tie any vessel in the body with 4-0 silk with the possible exception of the aorta. Dr. Ted Copeland, an honorary member of the Texas Surgical Society, was the newest member of the surgical team and brought a new perspective and hyperalimentation to the surgical services.

The head and neck service at that time was one of the greatest collections of head and neck surgeons ever assembled. Drs. Richard Jesse, Alando Ballantyne, Oscar Guillamondegui, Robert Byers, Helmuth Goepfert, and Don Gard were superb. Dr. Goepfert was the first otolaryngologist on the head and neck service. All five of the head and neck surgeons...
were president of the Head and Neck Society at some time. Don Gard was the plastic surgeon at a time when we did not have the wonderful flaps with which we reconstruct patients today. He taught us how to cover vital structures with what tissues were available in the local/regional area.

TEACHERS AS HEROES

In an address before the Michael DeBakey International Surgical Society in 1995, Dr. C Rollins Hanlon addressed the nature of teachers and why we commemorate certain teachers:

- Teachers must be able to instruct pupils and inculcate a desire for learning
- Teachers are exemplars who are imitated by their students
- Certain teachers are commemorated because they developed “schools” or philosophies of surgery
- Teachers have personal characteristics that help form attitudes and virtues in their pupils (1).

Halsted

The first progenitor of my personal surgical heroes is William Stewart Halsted, who was such a teacher (Figure 9). He was born in New York City on September 23, 1852, and died in Baltimore, Maryland, on September 7, 1922. He was one of the original “Big Four” at The Johns Hopkins Hospital. William Welch, a pathologist, was hired to organize the clinical services. He hired William Osler and Howard Kelly from the University of Pennsylvania to head the departments of medicine and gynecology, respectively. Welch initially wanted to hire Professor William Macewen from the University of Glasgow in Scotland. They were unable to come to terms, and Welch influenced the administration to hire Halsted in spite of his known drug problem (2, 3).

Halsted had lived a privileged life. His parents were wealthy import merchants. He was tutored at home until age 10. He went to a school in Monson, Massachusetts. After an unpleasant experience, he transferred to Phillips Academy in Andover, Massachusetts, where he graduated. He went to a private school for a year to prep for the Yale entrance exam. He went to Yale in 1874, where he majored in sports, not academics. He was described as trim and athletically built and was very strong for his size, 5′6″, weighing 160 pounds. While a senior at Yale, he purchased Gray’s Anatomy and Davenport Physiology. He became interested in academics at this point. He started medical school in 1874 at the College of Physicians and Surgeons. He studied under Drs. Henry Sands and John Dalton and spent much of his time in the anatomy and physiology labs. Dr. Dalton introduced Halsted to animal experimentation to prove or disprove a theory (3). Halsted made the experimental model a major endeavor at Johns Hopkins later in his career.

Medical school at this time was 3 years in duration. During Halsted’s second year, he decided to take the exam for a Bellevue Hospital internship. He thought that he would find out what the exam was like so that in his third year he could retake the exam and get the internship. He scored the fifth highest on the exam and was an intern at Bellevue the same year he completed his third year in medical school. While at Bellevue in 1877 he became interested in Listerism, or antisepsis. He spent the next year as house surgeon at New York Hospital, where he learned basic surgical techniques and devised the TPR chart (temperature, pulse, and respiration) (4)—to which one of his residents, Harvey Cushing, added the blood pressure, forming the present-day clinical ward and anesthesia chart. During this year he met William Welch, the pathologist. In the fall of 1878, Halsted left for 2 years of study in Europe. And what 2 years those were!

Halsted visited the famous surgical clinics of Billroth in Vienna, Austria, Volkman in Halle, Germany, and many others. Under these surgeons he studied surgical techniques and the German language. During this time he did not ignore the basic sciences and studied anatomy with Zuckerkandl and learned under other famous clinicians such as the dermatologist Kaposi and pathologists Chiari and Huber (4). He returned to the United States in 1880. He practiced in New York until 1889, when he was hired as the chief of surgery at The Johns Hopkins University Dispensary (the outpatient clinic). Later he was named professor of surgery and chief of surgery of Johns Hopkins Hospital.

Halsted’s legacy is measured primarily by the 17 resident surgeons who trained under him during his 33 years as chief at Hopkins. Joseph Colt Bloodgood wrote up the experience of breast cancer treatment with the radical mastectomy. Harvey Cushing, the renowned neurosurgeon, was instrumental in setting up the Hunterian Laboratory of Experimental Medicine and was very active in teaching medical students and residents (4). Cushing left Johns Hopkins in 1912 to go to the Peter Bent Brigham Hospital in Boston, where he started the second Halstedian surgical training program. In 1899, when Halsted had an attack of acute cholecystitis with common duct stones, he asked his seventh resident surgeon, Richard Follis, who was in practice to do his surgery. Follis was ably assisted by Mont Reid, who was a junior resident. George Heuer, the 13th resident surgeon, and Mont Reid, the 16th resident surgeon, were sent to Cincinnati to start the third Halstedian training program in 1922. Heuer left in 1932 to go to New York Hospital–Cornell to head up the surgical program. Walter Dandy, the 15th of Halsted’s resident surgeons, was an innovative neurosurgeon who did the first pneumoencephalography, pneumoventriculography (5), and clipped the first intracranial aneurysm. Halsted requested that Heuer and Reid come back to Hopkins to

Figure 9. William Stewart Halsted, MD. Portrait by Stocksdale.
do his second common duct procedure, from which he never recovered.

Halsted left surgical principles to use in operating. These include asepsis, gentle handling of tissues, absolute hemostasis by the individual ligation of vessels, leave no dead tissue in the wound, and accurate approximation of the wound in proper layers without dead space or tension. He also insisted that his residents know anatomy. Halsted chose his resident surgeons due to their ability to teach, not because of technical prowess, and many became professors of surgery. Of the 238 surgeons trained in the Halsted tradition—i.e., either by Halsted himself or in programs established by his chief residents—99 were in private practice, and 139 were in full-time university work (Table) (6).

Halsted’s legacy also includes technical procedures for repair of inguinal hernias, radical mastectomy, improved biliary tract surgery, thyroid and parathyroid surgery, bowel anastomosis (Halsted and Franklin Mall, an anatomist, did anastomosis experiments that showed that the submucosal layer was the strongest layer and should be included in anastomosis) (2), vascular surgery, the use of fine silk ligatures rather than the coarse chromic catgut that had been previously used, and the use of latex gloves in the operating room.

Halsted left us a wonderful aphorism about patients and surgeons: “The only weapon with which the unconscious patient can immediately retaliate upon the incompetent surgeon is hemorrhage” (7). Certainly Halsted fulfilled the four criteria given by Dr. Hanlon as reasons why we commemorate certain teachers.

Hunter

My last hero and another progenitor of surgical teachers is John Hunter (Figure 10). He was born in East Kilbride, Scotland, on February 13, 1728, according to the parish register. However, he celebrated his birthday on February 14, and that is the day on which the Hunterian Oration is given at the Royal College of Surgeons in London in odd-numbered years.

Hunter was the 10th of 10 children. Three of the children died in childhood, four died of tuberculosis in the “prime of life” between ages 20 and 35, and three outlived the parents: John, William, and Dorothea. John Hunter was born in the family home, Long Calderwood, a structure that has been carefully maintained and is a national monument. John Hunter was described as a willful child and would throw temper tantrums if he did not get his way (8). His father was 65 years old and quite ill when he was born, so discipline was left to his mother, who spared the rod. His early education was given at home by his mother and older siblings. He was sent to grammar school, which he quit at age 13. Two important circumstances occurred in that year: his father died and all instruction in school was given in Latin. John had to contribute to the work in maintaining the house and farmland and saw no use in learning Latin (8). It was his desire to learn from nature, and he thus became an excellent observer.

John’s older sister Janet married “Amen” Buchanan of Glasgow (8, 9). He was called Amen due to his work and singing in the Presbyterian Church. He also owned a cabinet-making shop, where John went to work learning woodworking skills. John was always known as someone who was good with his hands and was very clever technically. After a day’s work in the shop, John would accompany his brother-in-law Buchanan to the local pub. After a night of drinking, John would walk drunken Amen home. John saw no future in Glasgow so he petitioned his brother William to come to London. On receiving an affirmative response he traveled to London on horseback, covering the 400 miles in 2 weeks. He arrived in September of 1748 at age 20. He received a rather cool welcome from his brother William, who had changed greatly. William had served an apprenticeship under Dr. William Cullen in Hamilton, Scotland. This is a small town near East Kilbride, their hometown. He went to Edinburgh, Scotland, to study anatomy and then moved to London in 1840. He trained under Dr. William Smellie and Dr. James Douglas (of pouch of Douglas fame). These men were excellent anatomists and were male midwives, or accoucheurs. They were instrumental in starting the specialty of obstetrics.

William had learned to speak with a London accent and was thought of as a social climber. He wore a wig and the fancy clothing of the day. John, on the other hand, had not changed at all. He was still rude, crude, and rather socially unacceptable. He was 5′2″
tall, with carrot-red hair spewing in all directions. He had broad shoulders, a short neck, and spoke with a strong Scottish brogue. He was very prone to cursing and foul language (throughout his lifetime). He was not given to conversation or small talk; in his youth, he drank heavily and fraternized with the lower classes of society. He was said to have had poor table manners.

William did not know what to do with John. After considering sending him to the army, he decided he needed an assistant for his anatomy school. He took John to his anatomy lab, where he gave him a cadaver arm and a few dissection instructions. John was to dissect the arm. When William returned, he found that John had done an excellent job. Maybe he would work out! Perhaps his woodworking training contributed to his dissecting abilities. William gave him another cadaver arm to dissect; this one had the vessels injected with wax of different colors. Again, the result was an excellent specimen. As John had shown an aptitude for dissection, William hired him as his assistant for his anatomy course, which began 2 weeks later.

William was a gifted speaker who spoke plainly with a charming delivery and included clever anecdotes in his lectures. His courses were popular, often attended by up to 100 attendees, including pupils and townspeople who came to hear the lectures. Later John was asked to give some of the lectures because William would be out at night for deliveries. It has been stated that John dreaded lecturing and that he took 20 to 30 drops of Laudanum (tincture of opium) in a glass of port prior to his lectures. He never lifted his eyes from his manuscript and droned on with his Scottish brogue. The Hunterian Orator of 1979, George Qvist, took issue with this characterization. After examining the notes of the students who attended John Hunter’s lectures, Qvist felt that John Hunter was very organized and lucid except for his archaic language (10).

Through William’s influence, John followed William Cheselden at the Chelsea Hospital during the summers of 1749 and 1750. Cheselden had a series of strokes that incapacitated him, and John then went to follow Percivall Pott at St. Bartholomew’s Hospital in the summer of 1751. Hunter was able to attend rounds with these teachers only during the summer because the anatomy courses were given from fall through spring each year during cold weather so the cadavers would not decompose so rapidly.

William Cheselden was the top surgeon in London at the time John followed him. He had made his reputation by “cutting for the stone,” removing bladder stones via a lateral, transperineal approach. The average time of a procedure was 2 minutes. Cheselden would get physically sick prior to operating due to his concern for the pain that he was going to inflict on the patient (11).

Percivall Pott was an excellent surgeon and anatomist and became the top surgeon in London after Cheselden’s misfortune. He gave lectures to the pupils who followed him, which was quite uncommon at this time. In addition to teaching anatomy and surgery, Pott encouraged his pupils to allow nature to take its course to aid in the healing of the patient (8). Pott also described “soot wart” on the scrotums of chimney sweeps. This was skin carcinoma induced by environmental coal soot (8).

John studied and taught anatomy for 12 years at William Hunter’s anatomy school, from 1748 until 1760. Among his duties was procuring bodies from the “resurrectionists” (grave robbers) for the “Paris method.” William Hunter had studied anatomy in Paris in 1743 to 1744. Here, each pupil had his own cadaver to dissect. Afterwards, he went to study in Leiden, Netherlands, where there was only one or two bodies for the entire class. Many pupils did not get an opportunity to do any of the dissection. William decided that he wanted to use the Paris method in his teaching. Unfortunately, this required a large number of bodies, which were obtained from the resurrectionists. Families would often place a mortsafe (iron bars) over the burial place in an attempt to prevent the grave robbers from doing their nefarious activity.

When John was teaching in the anatomy school, he also became a pupil at St. George’s Hospital in 1754. In 1755 William, desiring to make a gentleman of his brother, sent John to St. Mary’s Hall at Oxford University. John lasted only 2 months before coming home. He stated, “They were trying to make an old woman of me” and wanted him to learn Latin (12). In 1756 he became house surgeon at St. George’s Hospital for 5 months, once again having to quit, returning to the anatomy school to teach.

In 1759 John developed a pulmonary complaint. Having seen four of his brothers and sisters die of tuberculosis, he was very concerned. He quit the anatomy school in 1760 and took Hippocrates’ recommendation: he who would be a surgeon should go to war. John volunteered for the army and was sent to Belle-Isle, a small island off of the west coast of France. After the English army captured the island, he began studying wounds and the effects of not traumatizing them. He noted that inflammation was an effect of disease and not a disease itself. He also studied the effect of velocity on missile wounds. He met Lieutenant Robert Home, who was the regimental surgeon for General John Burgoyne. Burgoyne was one of the English generals who fought in the American Revolutionary War in 1776. Lieutenant Home invited John to come over to visit when he returned to London.

After Belle-Isle, the army was transferred to Portugal to help defend the Portuguese from attacks by the Spanish. While John Hunter was there, he studied a broad plain outside of Lisbon. There he noticed the remnants of sea creatures in the soil and postulated that perhaps at one time this land had been underwater. This sparked his interest in geology.

At the end of the Seven Years War, at the age of 35, John returned to London. William had hired a new assistant for his anatomy school and had no work for John. John found it very difficult to live on his half-pay army pension of 10 shillings per day.

In the general scheme of things at this time, physicians and internists received the most respect. Surgeons were on the second rung, and dentists were little respected (8). John joined a reputable, ethical dentist named James Spence (8) in order to make a living. He threw himself into his work with his typical scientific fervor and began a scientific study of teeth. Part one dealt with the development and nature of teeth and was published
in 1771. In this work he separated the molars or grinders into bicuspids and molars, thus giving the bicuspids their name (8). Part two of his work was published 7 years later in 1778 on the pathology of teeth. These studies are still quite germane today. Hunter also worked on tooth transplantation. He noticed that if a tooth was loose or had been knocked out traumatically, it could be wired in place and would sometimes reestablish its solid attachment to the bone (9). When rich people learned of this, they would pay a poor person to have his or her teeth removed, and then they would ask the dentist to implant that tooth in their mouths (8). They found that this did not work; however, they were able to transplant disease in this manner.

On return to London, John went to visit his army friend, Lieutenant Robert Home. He met his family and was particularly enamored of his daughter Anne. She was described as the brightest star in the family constellation. She was 23 years old and quite the opposite of John. She was tall and thin with blonde hair and blue eyes. She had a beauty at once ethereal and sensuous (11). She was well educated and talented. She played the harpsichord, composed music, and wrote poetry. She fit effortlessly into London's high society. Robert Burns thought so much of her poetry that he added two of her poems to his diary—the only verse besides his own he ever preserved there (11).

That same year, 1764, John Hunter's scientific work began in earnest. Three years later in 1767 he was elected fellow of the Royal Society (9, 11), 3 months before his brother William, who had been in London longer than he. He also began his study of venereal disease. It has been reported that John injected himself with material from an infected patient whom he thought had only gonorrhea (8, 11). Unfortunately, the inoculum also contained the spirochetes of syphilis. He made accurate observations regarding the development of the disease: the hard Hunterian chancre, the development of buboes in the groins, and the rash of secondary syphilis (9). While his observations were correct, his conclusions were incorrect in thinking that the disease he documented was caused only by one organism rather than a combination of two. In an article in 2003 in the *Scottish Medical Journal*, Roy Humble concluded that John Hunter most likely hired a poor person to serve as the subject for this experiment (13). This obviously was not against the law at that time.

William Hunter moved into his new home and anatomy school on Great Windmill Street, and John moved into William's old home on Jermyn Street in 1768. That same year John received a diploma from the Company of Surgeons. This was unexpected, as one of the criteria for admittance to the Company of Surgeons was to have studied Latin. Hunter was also elected surgeon at St. George’s Hospital at this time.

On July 22, 1771, after 7 years of engagement, Anne and John were married at St. James Church, Piccadilly, on Jermyn Street. He was 43 and she, 29. John and Anne settled into a close married life.

John Hunter's day began before 6:00 AM because morning sunlight was best for his dissection work (11). He would go to the dissecting room in a tan surgical gown. He dissected and then lectured to his students. Breakfast was taken at 9:00. At 9:30 AM he began seeing patients in his home office. He saw the poor patients first and let the wealthy wait. Hunter stated that the rich had nothing to do when they went home; the poor had to work. To patients he was most kind and patient unless he perceived malingering. He never took a fee from a nonbeneficed clergyman or a poor person. He had the patients state a fee commensurate with their situation (11).

At 12:30 sharp, his coach would arrive and he would make house calls and then go to St. George's Hospital for rounds or surgery. He was usually finished before 4:00 PM. Dinner was served exactly at 4:00 PM at his insistence, whether he was present or not. After dinner he would retire to his study, where he would rest for an hour and then begin to work on his correspondence, some 3000 to 4000 letters per year. He would also review the notes that he made that day (11). At any one time, Hunter would have 30 to 50 active studies or investigations. As thoughts occurred to him during the day, he would write them down on any scrap or piece of paper that was handy and place them in his pocket. In the evening he would withdraw these notes and with the help of his pupils and amanuensis, he would have them put into the proper fascicles, one book for each study. He rewrote what he had previously written if he felt his new ideas were better. He went to bed after midnight.

Hunter's character was described as kindly and generous, though outwardly rude and repelling. There is abundant testimony of the kindness of his disposition, his fondness for animals, his aversion to operations, his thoughtful and self-sacrificing attention to his patients, and especially his zeal to help forward struggling practitioners. Pecuniary means he valued no further than they enabled him to promote his research (14).

Hunter was always broke. He spent his money on specimens for his collection, his wife's entertaining, land and homes, and employees. At any one time he had up to 50 people in his employment. He often borrowed money to make ends meet. At that time he was one of the leading surgeons in London and was making approximately £6000 per year, worth about £360,000 or $540,000 per year in 2012. Money was never a driving force in Hunter's life.

While Hunter is described as being uneducated, at least in the classical sense, he wrote his own works for publication and then asked students and friends to edit them into pleasing prose. Some authors have questioned whether a classical education would have stifled his naturally inquiring mind. As befitting his brilliance, John Hunter was a humble man. His publications were signed only with three words: "John Hunter, Surgeon." His political opinions were as conservative as his scientific theories were radical: "I wish that all the rascals who are dissatisfied with their country would be good enough to leave it."

During his work Hunter dissected many tiny things and described the three parts of a bee's tongue and the hearts of earthworms. He also dissected many large things such as elephants, giraffes, and whales. In several works Hunter is described as using glasses (8), but most works do not mention sources of magnification. Magnification has been known since Egyptian times; glasses were invented at the end of the 13th century and microscopes around the end of the 16th century.
By his own testimony in a court case, John Hunter had dissected some several thousand bodies during his work in anatomy, autopsies, and surgery. Hunter felt that things that rely only on beliefs rather than knowledge (such as religion) arise rather from a weakness of the mind than a weakness in the system. When his favorite pupil, Edward Jenner, wrote to him about a problem that he was thinking about, Hunter wrote back to him, “I think your solution is just, but why think? Why not try the experiment?”

John Hunter developed a school of surgery, the philosophy of which was that surgery should be governed by scientific principles based on reasoning, observation, and experimentation. He encouraged his pupils to be reluctant surgeons, to operate only when necessary and when it was an operation that they themselves would undergo (11). He wanted to develop hypotheses, test by rigorous observation, study the results, and develop principles from his studies. He wanted to use the scientific method. Contrary to many of the surgeons teaching in his era, he would change his mind when the facts demanded it.

When John Hunter taught at his home anatomy school on Leicester Square, he had changed little. His course on anatomy and surgery said little about doing procedures but much about anatomy and physiology. In contrast to William Hunter’s anatomy courses, which often had as many as 100 attendees, John never had more than 30, but the nature of the students had changed markedly. There were pupils, but the others in attendance were practicing surgeons in London. All of these men went on to become London’s leading surgeons of the future. His students included William Shippen Jr., John Morgan, and Philip Syng Physick of Philadelphia. Shippen and Morgan opened the first maternity hospital in the United States, and Physick brought Hunter’s method of teaching to the States (8). Other devotees of John Hunter were Astley Cooper of St. Thomas and Guy’s Hospitals, William Blizard of The London Hospital, Henry Cline of St. Thomas Hospital, and Edward Jenner of Berkeley, England (of smallpox vaccination fame).

Hunter felt that if the students knew the form (anatomy) and the function (physiology), they would become good doctors (14). He incorporated these disciplines into his treatment of patients. Perhaps his greatest lesson was the application of principles derived from animal studies to the treatment of human disease, equipping his students to operate on organs formerly considered inoperable. For this he is called the father of scientific surgery.

Some of John Hunter’s notable contributions to science and surgery are his work on transplantation, ligation of aneurysms, and the demonstration of the development of collateral circulation after ligation. He tried to revive a comatose person with electricity, and he attempted to resuscitate a hanged person using a bellows from the fireplace. He was the first to do artificial insemination in humans in a patient with hypospadias, he skin grafted the traumatized leg of a young boy, and he demonstrated that bone growth occurred from the ends of the bone rather than the mid portion of the shaft. He was also the first to describe the absorptive function of the lacteals of the small intestine and the first to make a systematic study of teeth, and he described the descent of the testis into the scrotum guided by the gubernaculum testis. He also did the study on venereal diseases and expressed his opinion that wounds should be handled gently rather than dilated as recommended by Paré. Of the treatment of cancer, he stated that leaving the least part was equal to leaving the whole.

At this time at the St. George’s Hospital, there were four surgeons who shared the students’ fees; however, three fourths of the students followed John Hunter. Hunter would often state, “I am but a pygmy in knowledge, yet I feel as a giant when compared with those men.” Unfortunately he would say this in a loud voice such that the other men could hear him, engendering much animosity. Due to the uneven workload, Hunter suggested to the hospital board that the students’ fees be paid directly to the surgeon whom the pupils were following rather than shared in four equal parts. Hunter also suggested that the surgeons give lectures to the students as Percivall Pott had done during his training.

When John Hunter was incapacitated with chest pain, the three other surgeons had onerous regulations passed by the St. George’s Hospital board to retaliate against Hunter. The surgeons hoped that John Hunter would quit or at least become so ill that he could not fulfill his obligations. These regulations included having to visit postoperative patients twice a week, attend to patients’ dressing changes personally, attend staff meetings each Friday afternoon, and operate only on Monday, Wednesday, or Friday with the exception of emergencies. When a patient died, the surgeon had to do the autopsy and do an illustrative operation on the corpse for the students’ benefit. Weekly lectures by the surgeons in rotation were mandated, as suggested by John Hunter. Hunter wrote to the board accepting the new duties.

The regulation that ultimately led to John Hunter’s death was that to qualify for admittance as pupils to St. George’s Hospital, the students had to be certified as having been bred to the profession. Two young Scotsman applied without certification, noting that they had not served an apprenticeship or studied at a medical school. John Hunter advocated for them at the hospital board meeting on October 16, 1793. In a heated exchange, Hunter grabbed his chest, staggered from the room, and died (8).

John Hunter initially had chest pain in 1772. These pains were diagnosed as angina pectoris by Edward Jenner (11). Angina had been described by William Heberden 4 years earlier. His second attack occurred 3 years later. After that the attacks came more frequently and took less to precipitate them. He stated, “My life is at the mercy of any rogue who chooses to annoy me.” His mercurial temper did not help.

Hunter’s autopsy was done by his brother-in-law, Everard Home. Home found two white fibrotic areas in the ventricles, severe coronary artery disease, calcific aortic and mitral valvular disease, and a small increase of pericardial fluid. Hunter was buried in the crypt of St. Martin-in-the-Fields Anglican Church on October 22, 1793. Sixty-six years later, Francis Buckland, a natural scientist, noticed that the crypt of St. Martin’s was to be cleared and the coffins removed. For 1 week, Buckland
searched through 3260 coffins. The next to the last coffin was Hunter’s. The coffin was removed and he was buried in Westminster Abbey with honors 2 months later. While visiting the Abbey, Sarah and I obtained a copy of the marker of Hunter’s tomb (Figure 11). The plaque reads, “The Royal College of Surgeons of England has placed this tablet on the grave of Hunter to record admiration of his genius as a gifted interpreter of the divine power and wisdom at work in the laws of organic life, and its grateful veneration for his services to mankind as the ‘founder of scientific surgery.’”

In his commemoration of surgical teachers, Hanlon stated:

Hunter was a consistent and expert user of the experimental method in the study of living processes, and it is upon this fact that his fame essentially and ultimately rests. It was by impressing this method on his pupils and successors that his service to science and surgery has had their most extended and their richest effects. . . . Hunter’s contribution in founding a tradition of scientific surgery was reflected in the career of William Stewart Halsted, whose individual surgical contributions were significant. Both men made an impressive impact on the lives and the surgical philosophy of their pupils (1).

HEROES OF TODAY

Who are my heroes of today?
• Our patients who entrust us to help them with invasive procedures and from whom we must continue to learn. We must never forget, as Russell John Howard stated, that the most important person in the operating theater is the patient.
• Our students and residents who help stimulate us to continue to learn and learn from us as we once learned from our heroes
• Our nurses and the other medical professionals who are part of the treatment team
• Our colleagues who stay the course in the rough winds of political perfidy

I close with one of Dr. Sparkman’s favorite quotations:

We are like dwarfs seated on the shoulders of giants if we see more and farther than they, it is not due to our own clear eyes or tall bodies; but because we are raised on high and upborn by their gigantic bigness.

—Bernard de Chartres, 12th-century French philosopher

I would like to thank the society for your attention and for the honor and privilege of being your president. Thank you.

HYDROPHOBIA

Few diseases bring as much gut-wrenching ancient fear as rabies. Infection from the bite of a slavering animal means death unless the individual is vaccinated early. The husband-and-wife team of Bill Wasik, a writer, and Monica Murphy, a veterinarian, have written a well-researched tale of the war against the world’s most diabolical virus (1). The rabies virus is the most fatal one in the world. It kills nearly 100% of its hosts in most species. The virus is shaped like a bullet, a cylindrical shell of glycoprotein and lipids that carries in its rounded tip a malevolent payload of helical RNA. On entering a living thing, it eschews the bloodstream. Instead, unlike almost any other virus, rabies courses through the nervous system, creeping upstream at 1 or 2 cm per day (on average) through the axoplasm, the transmission lines that conduct electrical impulses to and from the brain. Once inside the brain, the virus works slowly but fatally to warp the mind, suppressing the rational and stimulating the animal. Aggression rises to fever pitch; inhibitions melt away; salivation increases. The infected creature now has only days to live, and these will likely be spent on the attack, foaming at the mouth, chasing and lunging and biting in the throes of madness because the demon, as Wasik and Murphy write, that possesses him seeks more hosts. The rabid bite is the visible symbol of the animal infecting the human.

Wasik and Murphy write that about 60% of our diseases are zoonotic, that is, they originate in the nonhuman animal population: swine flu, AIDS, West Nile, Ebola, rabies. Nothing, they write, has made humans sicker than our association with nonhuman animals. Not only our emerging diseases today but the major killers throughout the ages—smallpox, tuberculosis, malaria, and influenza—evolved from similar diseases in nonhuman animals. This is what Jared Diamond has called “the lethal gift of livestock,” a major shaper of human destiny. Yet until the 20th century, humans had no idea that so many of their illnesses derived from nonhuman hosts. There was the Black Death or bubonic plague, which spreads to humans via fleas living on the backs of rats and other rodents. Scholars blamed nearly everything else, from demonic forces in bad air to astronomical happenings and even human malefactors. For centuries, rabies was the only illness in which the animalistic transfer, or more like a transformation, was evident. A mad animal bit; a bad man appeared; each would die a terrible death. The madness could lurk within any mammal, even in—especially in—the most domesticated and loyal of all, the dog. As the lone visible instance of animal-to-human infection, rabies has always shaded into something more supernatural: into bestial metamorphoses, into monstrous hybridities. As Susan Sonntag wrote, “That infection transforms people into madden animals.”

During the 20th century, after Pasteur’s invention of a rabies vaccine provided a near-foolproof means of preventing its fatality in humans, our fascination with rabies seemed only to swell. The vaccine itself became as mythologized as the bug, such that even today many Americans believe that treatment requires some 20 or 30 shots, delivered with a foot-long syringe into the stomach. (In fact, today’s vaccine entails four shots into the arm that are not particularly deep.) Even as vaccination of dogs in the USA was reducing the infection rate in that species to negligible levels, a generation of children learned to scrutinize their pet pooches for the slightest sign of madness.

Every year about 55,000 persons, according to the World Health Organization, die of rabies. Few of these deaths, however, occur in the USA or Western Europe. The deaths are mainly in Asia and Africa, from countries where vaccination is too expensive or too difficult to procure.

The sequence of horrors faced by a typical rabies patient today is hardly different from those experienced by the man who was probably the most eminent rabies victim in history: Charles Lennox, fourth Duke of Richmond, who for 2 years leading up to his death in 1819 served as governor-general of Canada, the top post in what was then still a colonial government. The duke was a lover of dogs. Ironically, it was not a dog but rather a fox, the ostensibly tame pet of a soldier whose garrison the duke had occasion to inspect in Quebec, whose jaws were to blame for his demise. When the fox tangled with the duke’s own dog, Lennox naturally stepped in to separate the two. The mad fox seized this chance to insult the visiting dignitary, chomping down hard on the base of his thumb. After a bite, the rabies virus binds quickly into the peripheral nerves but then makes its course with almost...
impossible sloth, usually requiring at least 3 weeks and often as long as 3 months to arrive at and penetrate the brain. On rare occasions, a full year, or even 5 years, can elapse before the onset of symptoms. During this time, the wound will heal and the victim may even forget about his scrape with a snarling beast. But healed or not, as the virus enters the brain, the wound will usually return with some odd sensation occurring at the site, such as stabbing pain or numbness, burning or unnatural cold, tingling or itching, or even a tremor. At roughly the same time these soon-to-be-doomed patients typically display general signs of influenza, with fever and perhaps a sore throat or nausea. In the case of the Duke of Richmond, symptoms began with shoulder pains and a sore throat and then progressed the following day to insomnia and fatigue.

All this is merely prelude to its most notable symptom in humans, unique to rabies among all diseases: a terrifying condition called *hydrophobia*, a fear of water, though the word “fear” does not do justice to the eerie and fully physical manner in which it manifests. Present the hydrophobic patient with a cup of water, and, desperately though he wants to drink it, his entire body rebels against the consummation of this act. The outstretched arm jerks away just as it is about to bring the water to the parched lips. Other times the entire body convulses at the thought. Just beholding the water can make the diaphragm involuntarily contract, causing patients to gag and retch. During the course of his illness, the Duke of Richmond finally lost all desire to drink any liquids. He could not even accept his customary shave, so repelled was he by the water in the basin. They tried to put him in a boat but he jumped back to the shore. Taken to the closest house, he begged to be moved further inland. The sound of running water became unbearable to him.

Fever spikes high during the final phase of the disease. The mouth salivaizes profusely. Tears stream from the eyes. Goose-bumps break out on the skin. Cries of agony can produce the impression of an almost animal bark. In the throes of their convulsions, patients have even been known to bite. They also hallucinate. Not uncommonly, male patients succumb to an even more lurid sort of abandon. The virus’s action on the limbic system of the brain can cause them to exhibit hypersexual behavior: increased desire, involuntary erections, and even orgasms, sometimes occurring at a rate of once per hour. Some cases have reported up to 30 ejaculations in a single day. And yet, despite all the horrors of hydrophobia, the attacks often subside, for a time allowing sufferers periods of poignant lucidity. They are given the opportunity to fully contemplate what their condition portends. Before his death, the duke dictated a lengthy letter to his oldest daughter, giving instruction that his beloved dog be handed over to her.

Lewis Pasteur and his assistants, to develop their vaccine, had to corral dogs at the apex of their madness and extract deadly slather from their snarling jaws. Pasteur once performed this trick with a glass tube held in his mouth as two assistants with gloved hands penned down a rabid bulldog.

Diagnosing rabies for veterinarians today is a gruesome affair. Vets do not use a blood test for rabies in animals. It is not a pinprick and wait-and-see affair. Only a sampling from the brain will suffice. Therefore, the animal must be killed with its head removed and shipped off to authorities for study.

Despite a thorough investigation using all the tools of the Pasteur laboratory, no combination of methods and media available to Pasteur and his assistants would yield a microbial cause for rabies. Even as Pasteur’s team discovered that the infectious principle for rabies resided in both the central nervous system and the salivary glands, they failed to culture a pathogen from either location. Thanks largely to the work of Pasteur himself, it was by this time a basic tenet of medical science that infectious diseases are caused by specific demonstrable microorganisms. Robert Koch’s famous “postulates,” first articulated in 1880, had made clear the relation between microorganisms and disease, defining a disease-causing microbe as one that appears exclusively in diseased individuals; that can be isolated and cultured from a disease host; that will cause disease when next introduced into a susceptible host; and that can be subsequently recovered from the experimental host and shown to be identical in culture to the microbe originally isolated. For rabies, not a single one of these conditions had been met. Koch’s precepts have often been summed up with the phrase “one disease, one microbe,” and Pasteur concurred with this view, but his vision saw a third term in this equation: one vaccine. He believed every disease-causing microbe, once isolated, could be attenuated so as to safely confer immunity on a potential host. But it was hard to see how this equation could hold true unless a pathogen could be isolated, identified, trapped under glass, and then tamed.

Pasteur referred to the unseen—apparently unseizable—agent of rabies as a virus. The word *virus* had until that point been associated with a darkly mysterious etiology. Rabies behaved as though it were a microbiotic contagion, and so Pasteur maintained absolute faith that it was one, even though he could neither culture it in broth nor observe it under the microscope. The word *virus* conveyed his uncertainty about rabies’ specific form and characteristics. It was not until 1898 that a virus was scientifically defined as a microbe that is invisible under the light microscope and can pass through a filter designed to trap bacteria; it was not until 1903 that it was experimentally demonstrated that the agent of rabies fit within that category.

Despite the confounding invincibility of rabies, despite the fact that it seemed to violate the scientific principles of the day to do so, Pasteur persevered in his work on the vaccine. He concluded early on that trying to cultivate the agent of rabies using existing laboratory methods would be fruitless. Instead, he refocused his attention and that of his assistants on inducing immunity in animals and eventually humans, to what would remain an obscure, intangible foe.

There occurred in 1880 in Paris a surge of rabies such that the Pasteur laboratory had no trouble obtaining infectious material. They got it from kennels of the National Veterinary School and from private veterinary offices around the city. Because rabies could not be cultured on a plate or in a vial, it had to be maintained in living tissue. In the 1880s, this meant within the corporeal cells of a living afflicted animal. The maintenance of rabid animals within the modest rooms and basement of the Pasteur laboratory was a microcosm of the entire edifice of biology, the germ theory of disease, and modern microbiology.
Pasteur laboratory was discomforting to the personnel. There was the ever-present risk of contracting rabies.

To create and test a vaccine against rabies, the Pasteur team first had to develop a strain of rabies that behaved more reliably than the natural infection. The crude method of one animal’s biting another, followed by an anxious wait over weeks or longer to see whether infection had been transmitted, was unsatisfactory. The technique involved the dangerous collection of saliva from a raging animal. They soon found that rabies could be as readily communicated with material from the affected animal’s brain stem as with its saliva. Thus, they were able to improve the infection rate and shorten the incubation period by administering chloroform anesthesia to the recipient animal, trepanning a hole in its skull, and then inoculating the rabid nervous tissue into the dura mater. The trepanation technique allowed successful transfer of the rabies to the healthy animal in every case attempted. Signs of disease were apparent in the inoculated animal in <2 weeks, and death occurred within a month. Canine rabies was thereby passed to a rabbit and from one rabbit to another rabbit, and from that rabbit to still another rabbit, and so on in successive passages. The incubation period became reliably shorter. Once 21 passages had been made, brain to brain, one rabbit to another, the incubation period had decreased to 8 days and there it became fixed. The shortened incubation period was associated with increased virulence.

The next step would be attenuation: the deliberate weakening of the virus to induce immunity without causing disease. If the infection inhabited the brain before protective immunity had taken hold, the patient’s death from rabies would be as certain as ever. Pasteur created his highly immunogenic but determinately safe rabies vaccine strain through a two-stage process: a first stage to hone the virulence of the virus and a second to deliberately blunt it. Both stages relied on manipulation of postmortem nervous tissue from rabid animals. Soon they were able to demonstrate the powerful effectiveness of their attenuated-virulent strain as a vaccine.

The first patient to receive the Pasteur vaccine was Joseph Meister, a 9-year-old boy who had received 14 penetrating wounds to his legs and hand by a vicious dog while walking to school. After receiving approval from two prominent pediatricians (Louis Pasteur had never been trained as a physician nor did he have a medical license), Meister received his first injection on July 6, 1885, 60 hours after the bites of July 4. He received, in a syringe, portions of the spinal cord from a rabbit dead of rabies on June 21, 1885. The cord had been kept in a flask of dry air for 15 days. The full 10-day treatment consisted of 13 inoculations, all delivering postmortem spinal tissue from a rabid rabbit. Each successive injection would contain a section of cord that had been exposed to air for a shorter time than the one before it so that as the series proceeded the vaccine would become less attenuated. On July 16, Meister received his final inoculation, the most virulent tissue of all: rabid spinal cord from a dog that had been infected with a strain of rabies virus maximally strengthened by serial passage in the rabbit and harvested only 1 day prior to injection.

The boy remained free of rabies symptoms. Pasteur’s modest laboratory was immediately transformed into a clinic and dispensary. People terrified of rabies arrived in droves to receive inoculations. By December 1885, 80 courses of treatment had been completed or were in progress in Pasteur’s bustling lab.

In December 1885, four children from New Jersey bitten by rabid dogs were en route to Paris to receive Pasteur’s now internationally famous cure. These four children also were cured, and that announcement led to a profound change in the way Americans thought about science and medicine. It reversed the assumption that older doctors and older medicines were better than new ones. It created a new expectation that medicine can and should change, that progress was to be expected, that the new advances would come from laboratory experiments on animals, and that specific injections would be a major tool of the new medicine. By the year 1900, there were at least six clinics in the USA devoted to administering rabies vaccines. Pasteur had a fundraising campaign in several countries to expand his laboratory, which in 1888 became known as the Institut Pasteur.

US DRUG SHORTAGES

An editorial by Sharmila Devi (2) in Lancet suggests that severe shortages of drugs, such as sterile injectables, in the USA will continue for several more years. Around 280 drugs, almost all manufactured in the USA, remain in short supply because of several factors: a dwindling number of makers of some drugs, deteriorating conditions in factories, and low prices for generics, leading to a lack of investment to upgrade plants. According to Devi, the shortages have led to delays in surgery and cancer treatments, left patients in pain, and forced hospitals to prescribe less effective substitutes. The US Food and Drug Administration (FDA) is at the forefront of an increasingly complex battle to ensure that the US retains access to critical drugs. President Obama issued an executive order in October 2011 requiring drug companies to report to the FDA when critical supplies were threatened. New legislation that would make it mandatory for companies to notify the FDA of supply problems and give the agency extra powers languishes in Congress.

SHORTENING MEDICAL TRAINING

Currently, it takes an average of 14 years of college, medical school, residency, and fellowship to train a subspecialty physician. Emanuel and Fuchs (3) from the University of Pennsylvania and Stanford University suggest that this period could easily be reduced to 10 years, or by approximately 30%. The time wasted by some of our most highly educated and talented people is improper. Future efforts to reduce the Medicare budget will likely be accompanied by a reduction in the federal government’s support of graduate medical education. Streamlining residencies will save money for academic health centers because they would have to spend less on training that now is compensated by federal support. Additionally, shortening the length of training would benefit medical students and trainees. With one less year of medical school they would have lower debts. The average medical student graduates today with $160,000 in debt.
Changing the structure of training might force medical leaders to eliminate unnecessary and repetitious material.

This shortening is already occurring. According to Emanuel and Fuchs, >30 medical schools now operate 6- or 7-year medical programs in which premedical training is reduced from the typical 4 years of college to 2 or 3 years. Most medical schools in the UK and Europe have 6 years of medical school training after graduation from high school.

Why is medical school 4 years in length? The answer probably has to do with the Flexner Report’s recommendation in 1910 for 2 years of premedical science training followed by 2 years of clinical training. Yet, most physicians could be trained in significantly less time. Since 1997, the University of Pennsylvania has had only 1.5 years of preclinical science training. Duke University medical students focus on the basics in the first year, complete core clerkships during the second year, and devote the third and fourth years to research and electives.

The important patient care skills can be obtained in <2 years of clinical training. Harvard Medical School requires students to complete only 15 months of clinical rotations. Eliminating one-half year of preclinical and one-half year of clinical training can be done without adversely affecting academic performance. Clinical training of 1.5 years still gives students sufficient exposure to a wide range of specialties. Texas Tech School of Medicine and two Canadian medical schools now offer 3-year medical school programs.

It is also possible to reduce residency training by 1 year. For internal medicine, pediatrics, and similar 3-year residencies, the third year is not essential to ensure competency. Many trainees already are permitted to short-track into subspecialty fellowships, reducing their residency from 3 to 2 years. Shortening training in an era of workweek limits will force hospitals to reengineer programs to ensure residents’ clinical competence.

Many surgical training programs include a year of research. The most important factor, however, in becoming a competent surgeon is high volume—performing specific procedures multiple times. A research year, of course, does not add to surgical volume and usually does not improve surgical skills.

REDUCING HEALTH CARE COSTS

One way is to shift health care responsibility away from physicians and hospitals to each of us. Most of us know what good health habits are. The challenge is to do them so that we stay healthy. The top of the list in my view is to maintain an ideal body weight. Doing so tends to keep the blood pressure and blood glucose down so our chances of developing hypertension and diabetes mellitus decrease considerably. Exercise keeps us more mentally alert as well as providing us with more energy and pep. There is nothing better than good home scales: weighing every day and not letting those pounds accumulate. Learning to use a blood pressure cuff at home and recording the number is useful. Daily flossing of our teeth yields healthy gums and decreases dental expenses. The health care system in the USA is broken, and each of us needs to do our part to keep illness away.

MILK ALTERNATIVES

In recent times I have switched from skim milk to milk substitutes, including soy, almond, coconut, flax, or rice. Sales of these nondairy milk beverages reached $1.3 billion in 2011, a jump of more than 10% from 2009 (4). These milk substitutes have fewer calories, less fat, and less protein than whole milk. One cup of whole milk has approximately 150 calories, nearly 8 grams of fat, and 8 grams of protein. Soy milk, in contrast, has 90 calories, 3.5 grams of fat, and 6 grams of protein. Flax milk has no protein, and almond, rice, and coconut milk have only 1 gram. These milk substitutes last much longer in the refrigerator than regular milk. The alternative milks can be expensive, however, sometimes $5 to $6 for a gallon compared with about $3.50 for regular milk.

COFFEE DRINKING AND MORTALITY

Freedman and colleagues (5) from Rockville, Maryland, and Washington, DC, examined the association of coffee drinking with subsequent total and cause-specific mortality among 229,119 men and 173,141 women in the National Institutes of Health–AARP Diet and Health Study. All were 50 to 71 years of age at baseline. Participants with cancer, heart disease, and stroke were excluded. Coffee consumption was assessed once at baseline. During 5,148,760 person-years of follow up between 1995 and 2008, a total of 33,731 men and 18,784 women died. The risk of death was increased among coffee drinkers. Coffee drinkers, however, were also more likely to smoke, and after adjustment for tobacco-smoking status and other potential confounders, there was a significant inverse association between coffee consumption and mortality. Adjusted hazard ratios for death among men who drank coffee as compared with those who did not were as follows: 0.99 for drinking <1 cup per day, 0.94 for 1 cup, 0.90 for 2 or 3 cups, 0.88 for 4 or 5 cups, and 0.90 for ≥6 cups of coffee per day. The respective hazard ratios among women were 1.01, 0.95, 0.87, 0.84, and 0.85. Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes mellitus, and infections, but not for deaths due to cancer. Thus, coffee consumption was associated with less total and cause-specific mortality. Thank goodness!

SITTING TIME AND MORTALITY RISKS

Investigators from Sydney, Australia, examined questionnaire data in New South Wales from 220,497 individuals aged 45 or older. During 621,695 person-years of follow-up (mean follow-up 2.8 years), 5405 deaths were registered (6). All-cause mortality hazard ratios were 1.02, 1.15, and 1.40 for 4 to <8 hours, 8 to <11 hours, and ≥11 hours per day of sitting, respectively, compared with <4 hours per day adjusting for physical activity and other confounders. The association between sitting and all-cause mortality was consistent across the sexes, age groups, body mass index categories, and physical activity levels, and for healthy participants as well as participants with preexisting cardiovascular disease or diabetes mellitus. Thus, prolonged sitting is a risk factor for all-cause mortality, independent of physical activity! Get up and move.
SEVERE OBESITY

Severe obesity is usually defined as a body mass index $\geq 40$ kg/m², or roughly 100 or more pounds overweight. In 2010, 6.6% of US adults, roughly 15.5 million people, had a body mass index $\geq 40$ (7). Severe obesity is approximately 50% higher among women than men and is twice as high among blacks as Hispanics and whites. The percentage of severely obese under age 40 is similar to those who are over age 40 years. It is difficult to be healthy if one weighs too much.

HOSPITAL CALORIES

Mayor Michael Bloomberg, in my view, has done much for the health of New York City dwellers. His latest health campaign is aimed at banishing sugary and fatty foods from both public and private hospitals (8). In recent years the city’s 15 public hospitals have cut calories in patients’ meals and restricted the sale of sugary drinks and unhealthy snacks at vending machines. Now the city is tackling hospital cafeteria food, and the Healthy Hospital Food Initiative is expanding its reach to 16 private hospitals. The hospital cafeteria crackdown will ban deep fryers, make leafy green salads a mandatory option, and allow only healthy snacks to be stocked near the cafeteria entrance and at cash registers. At least half of all sandwiches and salads must be made or served with whole grains. Half-sized sandwich portions must be available for sale. Most hospitals have already overhauled their vending machines by allowing only two types of 12-oz high-calorie beverages at each vending machine, and most also have swapped out most baked goods for snacks such as granola bars and nuts. Mayor Bloomberg has a strong podium, and he is using it well.

SMOKING AND THE FEDERAL CIGARETTE TAX

The Federal Cigarette Tax jumped from $0.39 to $1.01 per pack on April 1, 2009, to finance expanded health care for children (9). The change has brought in more than $30 billion in new revenue. The tax increase lifted prices 22% overnight, more than all state and local tax hikes combined over the past 10 years when adjusted for inflation. Tobacco companies have raised their prices to make money off of fewer customers. Consumer spending on tobacco rose from $80 billion in 2008 to $98 billion in 2011 in inflation-adjusted dollars, even though the amount of tobacco purchased fell 11%. Higher taxes accounted for about half that spending increase. Today, taxes and fees make up 55% of Marlboro’s retail price.

The tax hike helped restart a long-term decline in smoking that had stalled in recent years. The federal tax hike helped push tobacco use down 19% in 2011, the lowest level on record according to surveys from the Centers for Disease Control and Prevention. Overall, about 3 million fewer people smoked in 2011 than in 2009, despite a larger population. The tax is hardest on families who make <$50,000 a year, and this group accounts for two thirds of smokers. Teen smoking immediately fell about 12% when the tax hike took effect. Higher taxes, however, are not the only reason smoking has fallen dramatically among adults since the early 1980s and among teens since the mid 1990s. Health concerns, smoke-free buildings, and marketing restrictions have played a role.

Even smokers who do not quit smoke less. In the 1990s, one of every 20 high school students smoked 10 or more cigarettes a day; today, one in 71 students smoke that much. The elderly and Hispanics cut smoking most dramatically, each down more than 15% from 2008 to 2011. More women than men have quit smoking. Least affected were middle-aged men, down just 1%. About 1 million adults on Medicaid quit smoking.

50TH ANNIVERSARY OF THE CORONARY CARE UNIT CONCEPT

In 1937, my father had an acute myocardial infarction (AMI) at age 57 and was hospitalized at Emory University Hospital for 1 month. He then was placed in bed at home for another 2 months. From months 4 through 6, his movements were limited to the house and its immediate environs, and then from months 7 to 12 he was able to get out into the community. His partners paid him for a full year while he was resting from the heart attack. In 1939, just 2 years later, Mallory and associates (10) from Boston, Massachusetts, asked the simple question: How long does it take to heal an AMI? They found that it takes 2 months to heal a large AMI and about 6 weeks to heal a small AMI. Thus, my father was out of work 10 months unnecessarily. In 1941, at age 61, he had a second AMI. As a cardiologist himself, he decided this time that he would stay home, and a few days later that is where he died.

When I interned in medicine at Boston City Hospital in 1958, the site where Mallory et al demonstrated the length of time it takes to heal an AMI, patients with AMI were placed in the general ward, and the mortality rate during the hospitalization was approximately 35%.

In a beautiful piece by Dr. W. Bruce Fye, cardiologist and renowned medical historian, the history of the coronary care unit (CCU) is beautifully presented (11). The concept of the CCU, as Fye writes, was first described in North America in an abstract in Circulation in October 1961 by Los Angeles cardiologist Morris Wilburne, who outlined a technology-inspired extension of the intensive care unit model that had been developed during the previous decade. There was a crucial difference, as Fye describes. The intensive care unit was a place to care for acutely ill patients with a broad range of surgical and medical problems. The CCU, in contrast, was conceived as a program of care that targeted a specific group of patients: those at risk of sudden death in the context of an AMI. Such patients were admitted to a special space staffed by nurses trained to use new electronic technologies for the rapid diagnosis and treatment of life-threatening arrhythmias and to perform cardiopulmonary resuscitation. On October 14, 1961, almost the same day that Circulation published Wilburne’s abstract, Lancet published Desmond Julian’s long article, “Treatment of cardiac arrest and acute myocardial ischemia and infarction” (12). Julian called closed-chest massage an “outstanding advance” and recommended combining it with artificial respiration and transthoracic defibrillation. In his beautiful article, Fye published Wilburne’s abstract in full and described early CCUs developed in a number of US hospitals. The CCU
rapidly decreased mortality rates during AMI, which are now about 5%. This is a gem of an article.

FREDERICK NOVY AND THE RAT VIRUS
Frederick Novy (1864–1957), a US physician, medical researcher, and influential microbiologist of the early 20th century, devised culture techniques to visualize anaerobic bacteria, parasites, and spirochetes (13). In 1909, he began investigating the cause of unexplained deaths in his laboratory rats. In 1918, the test tubes he had been using for these experiments vanished from his laboratory. His dream of finding a virus as the likely cause of the mysterious deaths of his rats apparently was lost. Novy retired in 1935. Thirty-three years later, in 1951, a box containing the test tubes was discovered by chance during clean up in preparation for a laboratory move. Novy’s curiosity had not waned with time. Notified of the find and 16 years into his retirement, he returned to his laboratory at the age of 88 to continue the experiments he had begun >40 years earlier. He completed his investigations in 1953 and published his findings. A virus was indeed the unidentified organism that had swiftly killed his laboratory rats in 1909.

WARREN BUFFETT’S PHILANTHROPIC HERO
At the Forbes 400 Summit on Philanthropy, which was held at the iconic main branch of the New York Public Library, Warren Buffett, worth $50 billion, brought a well-worn hardcover copy of I Remember, the 1940 autobiography of Abraham Flexner (14). Buffett stated, “Abraham Flexner probably influenced philanthropy as much as any individual in the country . . . not in terms of the money he used but of what he brought to the game” (15).

Abraham Flexner from Louisville, Kentucky, first attracted public attention in 1908 for his book The American College, which condemned higher education for its reliance on lectures vs small classes and hands-on teaching. His prescient analysis attracted the attention of Andrew Carnegie, who was keen to reform medical schools. In 1910, The Carnegie Foundation published The Flexner Report, which for the first time set national standards for physician training. Within 2 years of publication of the report by Flexner, a nonphysician, 50% of the US medical schools had closed. Thus, Flexner drastically changed medical education. In 1930, Flexner, backed by Louis Bamberger, with Princeton’s Institute for Advanced Study, recruited the likes of Albert Einstein and Jay Robert Oppenheimer.

Buffett indicated that Flexner had studied what both the people with the money do, and what the people who are implementing the ideas do with the money. Buffett indicated that Carnegie did not go out and visit all the medical schools himself. He got Flexner to do it. George Eastman wanted to start a great medical school in Rochester and didn’t know how to do it. He called Flexner and said, “Tell me how to do it.” Buffett said he believed in getting things done through other people. Buffett recalled a New York Times editorial about Flexner when Flexner died in 1959: “No other American of his time has contributed more to the welfare of this country and humanity in general.” Buffett has set himself up for a similar epitaph.

DOCTOR VISITS
Americans reduced the number of times they visited physicians during the past 10 years, a time when the cost of health insurance, deductibles, and copays soared (16, 17). Among people aged 18 to 64, the average number of visits to physicians and hospitals decreased from 4.8 visits in 2001 to 3.9 in 2010, according to a Census Bureau report released in October 2012. The report also found that people reporting “poor,” “fair,” or “good” health were more likely to be uninsured than those reporting “excellent” or “very good” health. Insurance status is a very strong predictor of health. Nearly 39% of people living in poverty did not visit a medical provider in 2010. The percentage of the uninsured who received routine checkups decreased from 13.5% in 2001 to 11.7% in 2010. Most Americans consider themselves very healthy. Nearly 66% reported their health as “excellent” or “very good.” An additional 24% said their health was “good.” A slightly greater percentage of men reported excellent health than women (33.9% vs 31.6%). Just over 92% of the US population in 2011 did not spend a night in the hospital. Nearly 57% of the population took no prescription medicines in 2011. Age is strongly related to prescription medication use; 80% of older adults reported regular prescription use compared with 12.5% of children.

PATIENTS READING THEIR DOCTORS’ NOTES
Delbanco and colleagues (18) from Boston, Massachusetts, evaluated the effect on physicians and patients of facilitating patient access to visit notes over secure Internet portals. Of 13,564 patients with visit notes available, 11,797 opened at least one note and nearly half of them completed a postintervention survey. Just over 80% reported that open notes helped them feel more in control of their care; about 70% of those taking medications reported increased medication adherence; about 30% had privacy concerns; about 5% reported that the notes caused confusion, worry, or offense; and about 30% reported sharing notes with others. The volume of electronic messages from patients to physicians did not change. After the intervention, few physicians reported longer visits or more time addressing patients’ questions outside of visits with little effect on practice size. About 20% of the physicians reported changing documentation content, and about 10% reported taking more time writing notes. About 60% of patients believe they should be able to add comments to a physician’s note. One of three patients believe they should be able to approve the notes’ content, but about 90% of physicians did not agree. At the end of the experimental period, 99% of patients wanted open notes to continue, and no physician elected to stop.

TRANSPARENCY AND ACCOUNTABILITY IN MEDICINE
Dr. Marty Makary, a surgeon at The Johns Hopkins Hospital and lead developer of the surgical checklist adopted by the World Health Organization, is the author of Unaccountable: What Hospitals Won’t Tell You and How Transparency Can Revolutionize Healthcare, published in September 2012. He summarized his points in a recent piece in the Wall Street Journal (19). He suggested five ways to make health care safer:
1. **Online dashboards.** He recommends that every hospital have an online informational “dashboard” that includes its rates of infection, readmission, surgical complications, and “never event” errors (mistakes that should never occur, like leaving a surgical sponge inside a patient). The dashboard also should list the hospital’s annual volume for each type of surgery and patient satisfaction scores.

2. **Safety culture scores.** The people who work in hospitals know whether their institutions are safe or not. Makary, with a colleague at The Johns Hopkins Hospital, J. Byron Sexton, administered an anonymous survey of physicians, nurses, technicians, and other employees at 60 US hospitals. They found that one third of them believed that teamwork at their hospital was bad. They opined that care at hospitals where teamwork is poor is unsafe. The hospitals that had good teamwork had lower infection rates and better patient outcomes. Good teamwork meant safer care.

3. **Cameras.** Cameras, of course, are used frequently in health care, but usually no video is made. Reviewing tapes of cardiac catheterization procedures, arthroscopic surgery, and other procedures could be used for peer-based quality improvement. One physician investigator analyzed videotapes of colonoscopy procedures and after he announced that he was going to do so, the average length of the procedures increased by 50% and the quality scores increased by 30%. The physicians performed better when they knew someone was checking their work. The same sort of intervention has been used for hand washing. Some patients have requested copies of their procedure videos and were willing to pay for them. Patients are hungry for transparency.

4. **Open notes.** He suggests that patients be permitted to examine the notes taken by their physicians. Makary switched from taking notes in the presence of patients to dictating the notes in their presence. He found that patients would remember something while he was dictating that they had not mentioned earlier.

5. **No more gagging.** Although there are many signs that health care is moving toward increased transparency, there is also some movement backwards. Increasingly, patients checking in to see physicians are being asked to sign a gag order, promising never to say anything negative about their physician online or elsewhere. Additionally, victims of a medical mistake are being asked by hospital lawyers to never speak publicly about the injury, a condition of any settlement. These types of gag orders would be best banned. As he states, “They are utterly contrary to a patient’s right to know and to the concept of learning from our errors.”

Transparency can also help to restore the public’s trust. Many Americans believe that medicine has become an increasingly secretive, even arrogant industry. With more transparency—and the accountability that it brings—we can address the cost crisis, deliver safer care, and improve how we are seen by the communities we serve.

**ILLICIT DRUG USE AND PRESCRIPTION DRUG ABUSE**

The Mental Health Services Administration interviewed 67,500 people aged 12 and older in 2011 and found that 22.5 million Americans, nearly 9% of the population, said they regularly used illicit drugs (such as marijuana, cocaine, hallucinogens, and inhalants) or abused prescription drugs (such as pain relievers, tranquilizers, stimulants, and sedatives) (20). In 2011, 6.1 million people in the US abused narcotic pain pills, tranquilizers,stimulants, and sedatives, down from 7 million in 2010. Pain pill abuse dropped from 2.1% of the population in 2009 to 1.7% in 2011. Still, the number of people addicted to pain relievers grew from 936,000 in 2002 to 1.4 million in 2011. About one third of the addicts were 18 to 25 years of age. While cocaine abuse has dropped from 2.4 million regular users in 2006 to 1.4 million in 2011, heroin abuse is rising, growing from 161,000 in 2007 to 281,000 in 2011. Marijuana remains the most commonly abused drug at all ages. Among youth, drinking alcohol and smoking cigarettes declined, but marijuana use has increased steadily since 2008. The study found that 12.4% of 8th and 10th graders had used marijuana in the previous month, the highest rate since 2003. Most states now operate prescription drug monitoring programs, which can identify physicians who prescribe excessive doses of the drugs and patients who seek multiple prescriptions from different physicians.

**LANCE ARMSTRONG**

Did he win those seven Tour de France jerseys or not? In Europe he passed 137 drug tests but in the US he was convicted (21, 22). Was he racing against other substance abuse users or were they clean and he was the only one impure? I suspect there were very few racers in the Tour de France who weren’t on some kind of “dope.” Could Lance Armstrong have won any, much less all seven of those races, without some kind of performance boost? I doubt it because all the others were doing the same thing. That does not mean that Lance Armstrong or any of the others were right. I hope the performance enhancers are out of his system and out of the systems of all racers in the Tour de France. He still came in first in seven Tour de France races. Whether first means he won or not is a question that remains. Armstrong beat cancer and founded a fine foundation. He was one of the most talented athletes in the world. Armstrong broke the rules of the “official” system by submitting to the operative system’s rules. The how-it-really-works system of competitive cycling virtually required him to drug and to lie about it if he was to be a success. His competitors went down the same path. Not only should Armstrong bear the weight of responsibility for his actions, but the entire world of competitive cycling should not have looked the other way so often when cyclists have drugged.

**OLDER DRIVERS**

Today, nearly 34 million drivers in the USA are 65 years of age or older (23). By 2030, about 57 million, about one quarter of all licensed US drivers, will be ≥65 years of age. The oldest drivers have the highest rates of fatal crashes, often because they are too frail to survive their injuries. The Figure shows the frequency of fatal crashes per 100 million miles traveled by age group. Texas, 29 other states, and the District of Columbia
have some special license requirements for older drivers, ranging from more vision testing to more frequent renewing of their licenses. Starting at age 79, Texas drivers must renew their license in person rather than by mail or online and get a vision test. Starting at age 85, drivers must renew their licenses every 2 years, instead of every 6. These requirements began in 2007, a result of “Katie's law,” after a 2006 Dallas-area crash in which a 90-year-old driver ran a stoplight and killed a 17-year-old who was driving to school.


**ROAD KILLERS**

The Federal Aid Highway Act of 1956 started the planet's largest public works: the 42,795-mile national system of interstate and defense highways. Ginger Strand, in a book entitled *Killer on the Road*, describes what happened as these highways came about (24). The expressways, the nation's first limited-access divided highways, produced the highway killer, variously known as the "Hitman," the "Freeway Killer," the "Interstate Killer," the "Killer on the Road," the "I-5 Killer," and the "Beltway Sniper." Highways and violence quickly became intertwined. By the 1980s, when the interstate network was completed, highways were considered a dangerous place, not just because of accidents, but also because of hitchhiking, breakdowns, rest areas, truck stops, and aggressive drivers. The book by Strand provides brief biographies of some of these road killers. After graduating from college in 1954 from Southern Methodist University, I hitchhiked to Idaho to work in the forest service. That would be unwise to do today.

The highways were developed for several reasons. Eisenhower, president at the time, had seen Germany's autobahns during the war and wanted Americans to have the same thing. Ike was looking for a stimulus program. He and his economic advisors believed road building would be an effective way to "prime the pump" of the economy and avoid recession. The highway program was thus first and foremost an attempt to counter recession. Defense was only added to the interstate network's name after the highway bill failed to be approved the first time it went to Congress. The highways thus became part of the Cold War drive to heighten the nation's civil defenses. The roads were designed to evacuate cities and move military troops and tanks. One mile in every five had to be straight so that airplanes could land on the interstate in a war emergency. The defense part, however, was mainly a myth. The main reason was economic stimulus. By the time the bill was passed, defense was so far from anyone's mind that no one even thought to ask the military to weigh in on highway standards. Highways fostered mobility and mobility represented prosperity, connection, growth. It meant growth for the economy, and the nation needed to grow its auto industry. Since one in every 7 workers in the USA directly or indirectly built or serviced the automobile, the roads were built in a way to induce Americans to buy cars.

Teenagers across the country saw cars as a route to everything good: adulthood, self-determination, achievement, sex. Almost as soon as they were invented, cars became a key element in the American dream and the open road soon joined it. Selling more cars meant manufacturing more cars; manufacturing more cars meant creating more jobs; creating more jobs meant more people to buy more cars—and on and on it went. Although it was sold to the public as a program for jobs and civil defense, the interstate highway program was driven by the principle of growth, the last of the big New Deal programs.

The large-scale economic effect of highway building was to drive up inflation and intensify economic upswings and downswings—exactly the opposite of what Ike had hoped. The highway bill would do little for the real economic losers.

**PLAY**

My mother was not particularly good at it. She worked all the time. Although I have met and befriended masters of play, I'm not particularly good at it either. Stuart Brown, a 79-year-old physician in California, and Christopher Vaughan have written a book entitled *Play: How it Shapes the Brain, Opens the Imagination, and Invigorates the Soul* (25). They share case studies that show how incorporating play—whatever it is people love to do—makes them better at everything, from work to relationships.

**TATTOOS**

According to a piece by Kim Painter in *USA Today*, 23% of women and 19% of men in the USA have one or more tattoos. According to a Harris Poll, most people like their tattoos but at least 15% regret they have them. Bencini and colleagues (27) in Milan and Bergamo, Italy, treated 352 people from 1995 to 2010 and described factors that make some tattoos harder to remove than others. The physicians used repeated laser treatments spaced several weeks apart. The devices used, called Q-switched lasers, removed tattoos from 47% of patients in 10 sessions and from nearly 75% in 15 sessions. (In the US, a laser session costs $200 to $600.) Tattoos were harder to remove if they were >12 inches in diameter, had colors other than black.
or red, had been in place for >3 years old, were on feet or legs, and were on smokers. Smoking apparently impairs the natural healing procedures that help clear ink after treatment.

**RESILIENCE**

It is of course the ability to bounce or spring back, the ability to recover strength, spirits, good humor, etc., quickly, and buoyancy. Jane McGonigal, the inventor of the game SuperBetter and the author of "Reality is Broken: Why Games Make Us Better and How They Can Change the World," recently had a piece in the *Dallas Morning News* entitled “The Productive Value of Wasting Time” (28). Worldwide we spend 7 billion hours a week playing video games and 300 million minutes a day on Angry Birds.

She suggests that engaging in some activities we assume to be nonproductive—as tiny exercises—may actually be a smart way to spend time, especially at work. These practices, she spins, can make people more resourceful problem solvers, more collaborative, and less likely to give up when the going gets tough. In other words, they make people more resilient. Her personal goal is to waste at least 4 minutes every hour.

There are four aspects to the ability to snap back and go on after a hit—physical, mental, emotional, and social—and each can be developed with activities that appear to fritter away time. *Physical resilience,* she writes, is crucial because it allows our heart, lungs, and brain to react efficiently to stressful situations. A sedentary lifestyle is the number one obstacle to being able to endure and bounce back. Willpower gets stronger the more we exercise it. Tackling pointless but mildly challenging tasks, such as snapping one's fingers exactly 50 times or counting backward from 100 by sevens, she states, is a scientifically backed way to improve focus and determination and thus mental resilience. *Emotional resilience* has to do with being less afraid of failure and more open to using different strategies. We should try to experience, on average, three positive emotions for every one negative emotion over the course of a day. And *social resilience* is about the relationships that help us find resources when we need them. Gratitude and touch help us develop habits that connect us to others. Greater resilience, she emphasizes, will make us more capable.

**ALGORITHMS**

Christopher Steiner, a former reporter for *Forbes* magazine and currently an Internet entrepreneur, writes that the first known algorithm dates back to 2500 BC and was found on clay tablets near Baghdad. It recorded Sumerian instructions for how to equally divide grain harvests between varying numbers of men. In his book, *Automate This: How Algorithms Came to Rule Our World,* the 10 chapters explore different sorts of contemporary algorithms and their uses, from their embrace by record labels to their potential to transform health care (29). Algorithmic trading, whereby traders recede into the background and leave it to the algorithms to identify and act on arbitrage opportunities, has taken over Wall Street in the past 3 decades. But Wall Street is not the driving force behind the culture-wide algorithmic fetish. Steiner has qualms with the proliferation of algorithmic decision-making. Although he believes that we need to accept our algorithmic overlords, before doing so we should vigorously and transparently debate the rules they will impose. The real question isn't whether to live with algorithms, but how to live with them.

**LIVING ALONE**

About 32 million Americans live by themselves, comprising about 28% of the nation's 115 million households (30). The 7.9 million women aged ≥65 years who live alone make up almost half of all women living solo; about 3.3 million men ≥65 years live alone. In 1960, only 13% of US households had only one occupant; by 2011, 28% of US households had a single occupant, including 10% of those ≥65.

**DIMINISHING INCOME**

In January 2009, the median household income in the USA was nearly $55,000 (31). By June 2012, it had fallen to $51,000, adjusted for inflation. That's $4019 in lost real income, nearly a month's income every year. The real median household income in 2000 in the USA was $55,500. Some of the decline is due to smaller family size, lower fertility rates, and more Americans living alone. But some was also due to the subpar economic growth across the 2000s. Real income for middle-income households rose by roughly 30% from 1983 to 2005, according to the Congressional Budget Office.

So what explains the falling real incomes? Slow growth is certainly one explanation, but another culprit has been rising prices, especially for food, gasoline, medical procedures, and college tuition. Rising health care costs have also forced employers to take money that used to go into higher wages to pay higher premiums. During the last nearly 4 years, black Americans have had real income fall by more than 11%. Every age group except the elderly has seen a decline in income. Those aged 65 to 75 saw an average 6.5% gain in income, though most were not working and collected Medicare and Social Security. The last time incomes fell this fast was during the late 1970s.

**ONLINE MANNERS**

Elizabeth Bernstein (32), writing in the *Wall Street Journal,* recently asked, “Why are we so nasty to each other online? Whether on Facebook, Twitter, message boards or websites, we say things to each other that we would never say face-to-face.” Bernstein suggests that anonymity is a powerful force. “Hiding behind a fake screen name makes us feel invincible, as well as invisible.” But there is no anonymity on Facebook. She argues that even when we reveal our real identities we still misbehave online. Some have argued that browsing Facebook lowers our self-control. She goes on to write that “most of us present an enhanced image of ourselves on Facebook. This positive image—and the encouragement we get . . . boost our self-esteem. And when we have an inflated sense of self we tend to exhibit poor self-control.”

**FEARLESS OVERTAKING MALES**

The following observations are from a recent editorial by David Brooks (33). In elementary and high school, male
BIRTHS IN WOMEN IN THEIR TEENS AND TWENTIES

The number of US births has been falling since 2007, when it peaked at 4.3 million, just before the worst economic downturn since the 1930s (34). The 2011 data from the National Center for Health Statistics show that the number of births to girls aged 15 to 19 years dropped 20% to just fewer than 330,000, the lowest since 1946. Teen birth rates fell 8% to 31 per 100,000, the lowest recorded since 1940. The rate has fallen more than 3% a year since 1991. The number of births to women aged 20 to 24 declined 3%, and the birth rate dropped 5% to 85 per 1000, the lowest ever recorded in the USA. For ages 25 to 29, the birth rate of 107 per 1000 women was the lowest since 1976. Although the recession may have led women in their 20s to postpone starting a family, the economy usually does not affect teens, whose births are largely unintended and unplanned. Good news!

BALDNESS

According to a piece in *The Wall Street Journal*, men with shaved heads are perceived to be more masculine, dominant, and, in some cases, to have greater leadership potential than those with longer locks or those with thinning hair, according to a recent study from the University of Pennsylvania Wharton School (35). That finding may explain why the “buzz look” has caught on among business leaders in recent years. Some executives say the style makes them appear younger or at least makes their age less evident and gives them more confidence than a comb-over or monk-like pate.

The study was carried out by Albert Mannes, who tested people’s perception of men with shaved heads. In one experiment he showed photos of 344 men in two versions: one showing the man with hair and the other showing him with his hair digitally removed so his head appeared shaved. The subjects reported finding the men with shaved heads more dominant than their hirsute counterparts. Men with shorn heads were even perceived as an inch taller and about 13% stronger than those with fuller manes. The study found that men with thinning hair were viewed as the least attractive and least powerful of the bunch, a finding that tracks with other studies showing that people perceive men with typical male-pattern baldness, which affects roughly 35 million Americans, as older and less attractive. Dr. Mannes indicated that he was inspired to conduct the research after noticing that people treated him differently when he shaved off his own thinning hair.

The look is catching on. A 2010 study from razor maker Gillette found that 13% of respondents said they shave their heads, citing reasons as varied as fashion, sports, and already thinning hair. Another investigator at the University of Louisville indicates that a bare scalp “is nature’s way of telling the rest of the world that you are a survivor.” He adds that the deliberate shaved head look conveys aggressiveness and competitiveness and shows a “willingness to stand against social norms.”

Other features that signal dominance include narrow eyes and lips and broad faces and square jaws. For women, the equation is trickier. Dominant features may be less helpful at work than youthful, feminine features, which are deemed more attractive.

POPULATION REPRESENTED BY EACH MEMBER OF THE HOUSE OF REPRESENTATIVES

The House of Representatives consists of 435 members, and each represents an average of 711,000 persons (36). In 1839,
the House included 242 members. After the 1910 Census, with the population just over 92 million, the number of House members was increased to 435 from 394, with the average district then including just over 210,000 people. In 1929, Congress permanently fixed the number of representatives at 435, where it remains today, even though our population is now 315 million persons. Each representative today has over 710,000 constituents. By comparison, many other countries with representative governments have larger representative bodies with more favorable ratios: the United Kingdom has 62 million people and 650 members of Parliament, one for every 95,000 residents; Japan's 127 million people elect 480 representatives, one for every 264,000; France's National Assembly has 577 members, each representing 118,000 people. Since 1998, the reelection rate for US House incumbents has been nearly 95%.

William Clifford Roberts, MD
31 October 2012

Emerging targeted therapies in triple-negative breast cancer

Crown J, O’Shaughnessy J, Gullo G


Standard chemotherapy regimens can prove effective for patients with early triple-negative breast cancer (TNBC); however, patients with advanced disease typically respond poorly and rapidly progress, and the outcome is poor. New targeted therapies are therefore an urgent unmet medical need for this patient population. Translational and clinical studies into new TNBC treatments have been facilitated by the increased understanding of the aberrant signal transduction pathways regulating growth and survival and the development of chemoresistance in TNBC. Some of the established targeted agents that have been approved in other indications may prove beneficial to patients with TNBC; however, in the absence of approved targeted agents for the treatment of TNBC, most new agents remain experimental. Increased understanding of molecular profiles of TNBC subtypes is likely to improve therapeutic strategies with targeted agents. Novel strategies have reached clinical evaluation in patients with TNBC, including targeting angiogenesis vascular endothelial growth factor and proliferation signaling (receptor tyrosine kinases and mammalian target of rapamycin). AggressiveTNBCs have been found to associate closely with BRCA1 mutation or dysregulation. The recent development of new investigational agents targeting DNA repair, either directly with poly(adenosine diphosphate-ribose) polymerase inhibitors or indirectly through agents targeting DNA repair, either directly with poly(adenosine diphosphate-ribose) polymerase inhibitors or indirectly through DNA-binding or DNA-damage potentiation, is a major focus of current clinical studies. These and other targeted therapies represent a new approach to TNBC therapy.

Carcinogenesis

Boswellic acid exerts anti-tumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family

Takahashi M, Sung B, Shen Y, Hur K, Link A, Boland CR, Aggarwal BB, Goel A

Carcinogenesis 2012 Sep 15 [Epub ahead of print]. Reprinted with permission from Oxford University Press.

Colorectal cancer (CRC) is a complex disease with genetic and epigenetic alterations in many key oncogenes and tumor suppressor genes. The active principle of a gum resin from Boswellia serrata, 3-acetyl-11-keto-beta-boswellic acid (AKBA), has recently gained attention as a chemopreventive compound due to its ability to target key oncogenic proteins such as 5-lipoxygenase and NF-κB. AKBA has been shown to inhibit the growth of CRC cells; however, the precise molecular mechanisms underlying its anti-cancer activities in CRC remain unclear. We hypothesized that boswellic acids may achieve their chemopreventive effects by modulating specific miRNA pathways. We found that AKBA significantly up-regulated expression of the let-7 and miR-200 families in various CRC cell lines. Both let-7 and miR-200 are putative tumor suppressive microRNAs. AKBA modulated the expression of several downstream targets of the let-7 and miR-200 families, such as CDK6, and vimentin and E-cadherin. These data were further strengthened by miRNA knockdown studies, which revealed that inhibition of let-7 facilitated enhanced cancer cell proliferation, migration and invasion. In addition, AKBA also induced similar modulation of the let-7 and miR-200 downstream genes in CRC tumors orthotopically implanted in nude mice. These results indicate that AKBA-induced anti-tumor effects in CRC occur, at least, partly through the up-regulation of specific miRNA pathways. Our data provide novel evidence that anti-cancer effects of boswellic acids are due in part to their ability to regulate cellular epigenetic machinery, and further highlight the promise for this phytochemical in the preventative and therapeutic applications of CRC.

Foot and Ankle International

Effect of heating on the mechanical properties of insole materials

Brodsky JW, Brajtrending J, Coleman SC, Raut S, Polo FE

Foot Ankle Int 2012;33(9):772–778. Reprinted with permission from DataTrace.

Background: The most common method of customizing shoe insoles to the shape and surface of the foot is to heat and then mold the materials. The effect of heating on the mechanical properties of these materials is unknown.

Methods: The properties of individual and common combinations of insole materials were tested before and after heating. Individual materials tested were soft Plastazote (SP), medium Plastazote (MP), Puff (P), and Nickelplast (N); combinations of materials that were tested were SP + F and MP + F, each with and without Poron (P). Three samples of each were tested five times. Materials were heated and then compressed with an MTS servohydraulic device. Load transmission and percent compression at maximal load were measured on single materials and their combinations. Stress-strain curves were measured.

Results: Compared to unheated material, the heated material transmitted higher forces. After heating, the combinations transmitted maximal load at a lower percentage of compression (i.e., became stiffer). Heating also changed the stress-strain curves of the three-material combinations, causing them to transmit maximal pressure at a lower strain.

Conclusion: Heating insole materials changed their mechanical properties. The materials became stiffer and less effective in the attenuation of applied forces.

Clinical relevance: The common practice of heating insole materials to improve their contact with the foot reduced the pressure-reducing properties of the materials, which may decrease their clinical effectiveness.
The practical diagnostic value of fecal analysis in the evaluation of patients with chronic nonbloody diarrhea is controversial. It is possible that variations in its value depend on how it is done and how the results are interpreted, rather than on its intrinsic value. In the authors’ city, stool analysis has been made easily accessible, with commitment to quality assurance and interpretation. To evaluate its practical value, the results of stool analysis obtained on stool specimens submitted by gastroenterologists were retrospectively reviewed. The results indicate that stool analysis has substantial practical diagnostic value in patients with chronic diarrhea.

Noncovalent assembly of anti-dendritic cell antibodies and antigens for evoking immune responses in vitro and in vivo

Targeting of Ags directly to dendritic cells (DCs) through anti-DC receptor Ab fused to Ag proteins is a promising approach to vaccine development. However, not all Ags can be expressed as a rAb directly fused to a protein Ag. In this study, we show that noncovalent assembly of Ab-Ag complexes, mediated by interaction between dockerin and cohesin domains from cellobiose-degrading bacteria, can greatly expand the range of Ags for this DC-targeting vaccine technology. rAbs with a dockerin domain fused to the rAb H chain C terminus are efficiently secreted by mammalian cells, and many Ags not secreted as rAb fusion proteins are readily expressed as cohesin directly fused to Ag either via secretion from mammalian cells or as soluble cytoplasmic Escherichia coli products. These form very stable and homogeneous complexes with rAb fused to dockerin. In vitro, these complexes can efficiently bind to human DC receptors followed by presentation to Ag-specific CD4+ and CD8+ T cells. Low doses of the HA1 subunit of influenza hemagglutinin conjugated through this means to anti-Langerin rAbs elicited Flu HA1-specific Ab and T cell responses in mice. Thus, the noncovalent assembly of rAb and Ag through dockerin and cohesin interaction provides a useful modular strategy for development and testing of prototype vaccines for elicitation of Ag-specific T and B cell responses, particularly when direct rAb fusions to Ag cannot be expressed.

Outcomes of axillary artery side graft cannulation for extracorporeal membrane oxygenation

The most common complication in the axillary artery group was hyperperfusion syndrome of the ipsilateral upper extremity (n = 20, 24.7%), followed by bleeding from the arterial outflow graft (n = 14, 17.3%). Lower extremity ischemia and fasciotomy were more frequent after femoral arterial cannulation (n = 27, 16%, and n = 18, 10.8%, respectively). The predictors for a poor in-hospital outcome for the entire group of patients were age and postoperative cerebral vascular accident. The cannulation method was not a predictor of in-hospital outcomes.

Insuring the uninsured: potential impact of Health Care Reform Act of 2010 on trauma centers

Background: Viability of trauma centers is threatened by cost of care provided to patients without health insurance. The health care reform of 2010 is likely to benefit trauma centers by mandating universal health insurance by 2014. However, the financial benefit of this mandate will depend on the reimbursement provided. The study hypothesis was that compensation for the care of uninsured trauma patients at Medicare or Medicaid rates will lead to continuing losses for trauma centers.

Methods: Financial data for first hospitalization were obtained from an urban Level I trauma center for 3 years (n = 6,630; 2006–2008) and linked with clinical information. Patients were grouped into five payment categories: commercial (29%), Medicaid (8%), Medicare (20%), workers’ compensation (6%), and uninsured (37%). Prediction models for costs and payments were developed for each category using multiple regression models, adjusting for patient demographics, injury characteristics, complications, and survival. These models were used to predict payments that could be expected if uninsured patients were covered by different insurance types. Results are reported as net margin per patient (payments minus total costs) for each insurance type, with 95% confidence intervals, discounted to 2008 dollar values.
Results: Patients were typical for an urban trauma center (median age of 43 years, 66% men, 82% blunt, 5% mortality, and median length of stay 4 days). Overall, the trauma center lost $5,655 per patient, totaling $37.5 million over 3 years. These losses were encountered for patients without insurance ($14,343), Medicare ($4,838), and Medicaid ($15,740). Patients with commercial insurance were profitable ($5,295) as were those with workers’ compensation ($6,860). Payments for the care of the uninsured at Medicare/Medicaid levels would lead to continued losses at $2,267 to $4,143 per patient.

Conclusion: The health care reforms of 2010 would lead to continued losses for trauma centers if uninsured are covered with Medicare/Medicaid-type programs.

Level of evidence: Economic analysis, level II.

MEDICINE

Natural history of adults with congenitally malformed aortic valves (unicuspid or bicuspid)
Roberts WC, Vowels TJ, Ko JM


Appreciation of the frequency of the congenitally malformed aortic valve has come about during the last 50 years, a period during which aortic valve replacement became a predictably successful operation. Study of patients at necropsy with either a congenitally unicuspid (1 true commissure) or bicuspid (2 true commissures) valve in whom no aortic valve operation has been performed has not been conducted during these 50 years, to our knowledge. We studied 218 patients at necropsy with congenitally malformed aortic valves: 28 (13%) had a unicuspid valve and 190 (87%), a bicuspid valve. Their ages at death ranged from 21 to 89 years (mean, 55), and 80% were men. Of the 218 adults, the aortic valve functioned normally during life in 54 (25%) and abnormally in 164 (75%): aortic stenosis in 142 (65%), pure aortic regurgitation without superimposed infective endocarditis (IE) in 2 (1%), and IE superimposed on a previously normally functioning aortic valve in 20 (9%). IE occurred in a total of 31 (14%) of the 218 patients: involving a previously normally functioning valve in 20 (65%) and a previously stenotic valve in 11 (35%). Of the 218 patients, at least 141 (65%) died as a consequence of aortic valve disease (124 patients) or ascending aortic tears with or without dissection (17 patients). An estimated 1% of the population, maybe higher in men, has a congenitally malformed aortic valve. Data from this study suggest that about 75% of them will develop a major complication. Conversely, and encouragingly, about 25% will go through life without a complication.

SKINMED

Pralatrexate (Folotyn)
Abramovits W, Oquendo M, Granowski P, Gupta A, Cather J


T-cell lymphoma accounts for 10% to 15% of all cases of non-Hodgkin lymphoma in the United States (approximately 5000 to 6000 cases a year). Peripheral T-cell lymphoma (PTCL) comprises a subgroup of rare and aggressive non-Hodgkin lymphomas that develop from T cells in different stages of maturity outside of the thymus. Cutaneous T-cell lymphoma is a subgroup that falls within the T-cell lymphoma population but is classified differently than other PTCLs. Most cases of CTCL are considered indolent and can often be treated with less aggressive therapies. Eight percent to 55% of CTCL cases undergo transformation, and once this transformation occurs, the disease acts similarly to other PTCLs and its classification changes to that of a
PTCL. Transformed CTCL requires aggressive systemic therapy. Pralatrexate is the first Food and Drug Administration–approved drug for relapsed and refractory PTCL and has also gained compendia approval for treatment of CTCL. Pralatrexate is an antifolate chemotherapeutic inhibitor of dihydrofolatereductase. It has a high affinity for the one carbon-reduced folate carrier, which leads to better cellular internalization of the drug and has a greater antitumor effect than methotrexate. Several clinical trials have been conducted to evaluate the use of this drug in PTCL and other malignancies such as non–small cell lung cancer. This review offers focused information for dermatologists about pralatrexate and its use as a novel treatment for relapsed or refractory PTCL.

SPINE

Incidence, mode, and location of acute proximal junctional failures following surgical treatment for adult spinal deformity


Study design: Multi-center, retrospective series.

Objective: Analyze the incidence, mode, and location of acute proximal junctional failures (APJF) following surgical treatment for adult spinal deformity.

Summary of background data: Early proximal junctional failures above adult deformity constructs are a serious clinical problem; however, the incidence and nature of early APJFs remains unclear.

Methods: A total of 1,218 consecutive adult spinal deformity surgeries across 10 deformity centers were retrospectively reviewed to evaluate the incidence and nature of APJF, defined as any of the following within 28 weeks of index: minimum 15 degrees post-operative increase in proximal junctional kyphosis, vertebral fracture of upper instrumented vertebrae (UIV) or UIV+1, failure of UIV fixation, or need for proximal extension of fusion within 6 months of surgery.

Results: There were 68 APJF cases identified out of 1,218 consecutive surgeries (5.6%). Patients had a mean age of 63 years (range 26–82), mean fusion levels of 9.8 (range 4–18), and mean time to APJF of 11.4 weeks (range 1.5 to 28). Fracture was the most common failure mode (47%), followed by soft-tissue failure (44%). Failures most often occurred in the thoracolumbar region (TL-APJF) compared to the upper thoracic region (UT-APJF), with 66% of patients experiencing TL-APJF compared to 34% UT-APJF. Fracture was significantly more common for TL-APJF relative to UT-APJF ($P = 0.00$), while soft-tissue failure was more common for UT-APJF ($P < 0.02$). TL-APJF patients were also older ($P = 0.00$), had fewer fusion levels ($P = 0.00$), and had worse post-operative SVA ($P < 0.01$).

Conclusions: APJFs were identified in 5.6% of patients undergoing surgical treatment for adult spinal deformity, with failures occurring primarily in the TL region of the spine. There is evidence that the mode of failure differs depending on the location of UIV, with TL failures more likely due to fracture and UT failures more likely due to soft-tissue failures.

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