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CORRECTIONS

Diabetic Gastroparesis

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It was Mr. G.’s third exacerbation of congestive heart failure in the past 6 months. Eighty-three years old, he had New York Heart Association class IV heart failure, end-stage coronary artery disease, and insulin-dependent diabetes. Although he had never wanted to be put on a ventilator, this time his shortness of breath was so terrifying that he felt he had no choice. After having a good response to diuresis, he was successfully extubated and transferred out of the coronary care unit.

Two days later, a hospitalist suggested to Mr. G. and his wife that given his advanced disease, he should consider going home and receiving hospice care there. Sensing the couple’s fear, she reassured them that death was not imminent and that members of the hospice staff would work to ensure the best possible quality of life. Relieved, Mr. G. acknowledged that he would prefer to avoid rehospitalization.

Introduced in the United States as a grassroots movement more than 30 years ago and added as a Medicare entitlement in 1983, hospice care is now considered part of mainstream medicine, as evidenced by growing patient enrollment and Medicare expenditures (see table). In 2005, more than 1.2 million Americans received hospice care, and between 2000 and 2004, the percentage of Medicare decedents that had been enrolled in hospice programs increased by almost 50%. But despite its increased use, many aspects of hospice care are still misunderstood by both physicians and patients.

For instance, many would not consider Mr. G. to be a candidate for hospice care. He did not have cancer, and his death was probably months, not days, away. The fact is, however, that slightly less than half of hospice patients have terminal cancer; nearly 40% of hospice admissions are for end-stage cardiac disease, end-stage dementia, debility, pulmonary disease, and stroke.¹

Patients and clinicians may also not realize that hospice care at home is free. Medicare is the primary payer for hospice care in approximately 80% of cases, with care most often provided in the patient’s home. Commercial insurers also provide hospice benefits, but the specifics of coverage vary. Under Medicare, most
expenses related to the terminal diagnosis are paid in full, including all medication and equipment and all visits by hospice nurses and home health aides. (Expenses related to other diagnoses remain covered by the patient’s primary insurance provider.) Other hallmark hospice services include intensive emotional and spiritual counseling, 24-hour crisis management, and bereavement support for at least 1 year after the patient’s death.

Hospice care can successfully address the critical end-of-life concerns that have been identified in numerous studies: dying with dignity, dying at home and without unnecessary pain, and reducing the burden placed on family caregivers. Factors contributing to late referral include application of a curative model to end-stage incurable illnesses; Medicare’s per diem hospice reimbursement, which precludes costly, aggressive therapies; and the mistaken view that patients must have a do-not-resuscitate order. However, the most important factors in delayed referrals appear to relate to physician attitudes. In its first position paper on the topic of cancer and dying, the American Society of Clinical Oncology acknowledged that many oncologists and other physicians regard the death of a patient as a professional failure. Many also fear that they will destroy their patients’ hope, which physicians may believe lies only in efforts to increase the quantity rather than quality of life. Furthermore, physicians receive little training in the compassionate discussion of bad news.

To address Mr. G.’s nonmedical needs, a home health aide provided assistance with personal hygiene and dressing for an hour each day, 5 days a week. The hospice social worker offered to have a volunteer shop

<table>
<thead>
<tr>
<th>Variable</th>
<th>2000</th>
<th>2004</th>
<th>% Increase, 2000–2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beneficiaries in hospice care (no.)</td>
<td>534,261</td>
<td>797,117</td>
<td>49</td>
</tr>
<tr>
<td>Payment (billions of $)</td>
<td>2.9</td>
<td>6.7</td>
<td>130</td>
</tr>
<tr>
<td>Time in hospice care (millions of days)</td>
<td>26</td>
<td>52</td>
<td>101</td>
</tr>
<tr>
<td>Decedents who had been in hospice care (%)</td>
<td>22</td>
<td>31</td>
<td>—</td>
</tr>
</tbody>
</table>

*Data are from the Center for Medicare and Medicaid Services and the Medicare Payment Advisory Commission (MedPAC) and include Puerto Rico.*
for groceries and provide companionship. The social worker also talked with the family and identified the need to address Mr. G.’s anxiety and his wife’s fears about the future. Noting that Mr. G. had concerns about whether God was punishing him for past acts, she encouraged visits by the hospice chaplain. Hospice emphasizes an interdisciplinary approach to care. In most cases, at least once every other week, the hospice team — nurses, social workers, a pastoral counselor, the bereavement coordinator, and the medical director — meet to discuss the needs of the patient and family. In the interim, nurses call attending physicians with their recommendations.

One serious challenge in hospice care is that attending physi-
cians typically receive little to no training in the use of medications for pain and symptom management and thus rely on a presumed level of expertise on the part of the hospice nurse. Given the current nursing shortage, however, such an assumption of competency may or may not be well founded. Attending physicians should routinely evaluate recommendations and should have a low threshold for reviewing cases with the hospice medical director.

As a patient’s disease progresses, the hospice plan shifts to accommodate decreasing independence, alterations in symptoms, and changing psychosocial needs. In Mr. G.’s case, the realization that his symptoms could be managed at home lessened his anxiety, which in turn decreased episodes of chest pain. Flash pulmonary edema occurred less frequently; during one such episode, he received intravenous furosemide in his home, since he wanted to avoid further hospitalizations. During 4 months of hospice care, Mr. G.’s condition gradually deteriorated, with increasing weakness, dyspnea, and cardiac cachexia. Near the end, his family and friends gathered, and he died peacefully with his wife and nurse at his side. Despite his family’s grief, they expressed their appreciation that Mr. G. had maintained a reasonably high quality of life and had died in his home as he had wished.

With the growing number of baby boomers seeking more control over all aspects of their health care, the use of hospice care will probably continue to increase. It is especially important, therefore, that physicians become more familiar with what hospice care offers and work to overcome barriers in talking frankly with patients about what lies ahead.

Dr. Gazelle is a member of the Division of General Medicine and Primary Care at Brigham and Women’s Hospital and president of MD Can Help — both in Boston.


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Letting Go of the Rope — Aggressive Treatment, Hospice Care, and Open Access
Alexi A. Wright, M.D., and Ingrid T. Katz, M.D., M.H.S.

More Americans are choosing hospice for end-of-life care, but ironically, hospice patients increasingly are forced to give up effective palliative treatments along with aggressive medical intervention. For Joanne Doolin, a 64-year-old mother of three who spent her last 2 years of life fighting colon cancer that eventually made it impossible to eat, enrollment in hospice care involved a difficult trade-off: with only a few weeks left to live and her daughter’s wedding approaching, Doolin was forced to choose between entering hospice care and continuing to receive total parenteral nutritional support.

Unfortunately, treatment options are often limited by the economic constraints of hospice care. The hospice that was the closest to Doolin’s Boston-area home would accept only patients willing to forgo life-sustaining treatments, including chemotherapy and parenteral nutrition. It cares for only about 20 patients at a time with three nurses, a manager, a part-time chaplain, and a medical director who works there one morning a week. As a small program, it cannot negotiate pricing or spread the cost of expensive medications across many patients. A few large hospices offer what is called open-access care, which allows patients to add hospice care to their current medical treatment, but this option is not available in Massachusetts.

The Medicare hospice benefit reimburses hospices on a per diem basis, paying fixed inpatient and outpatient fees regardless of services provided. Despite adjustments for inflation, the fees have not kept up with the cost of cutting-edge palliative treat-
ments. Many patients who meet the criterion for hospice care — having less than 6 months to live — still opt for palliation from oral chemotherapies, radiation, antiemetics, or blood transfusions. But these treatments can cost more than $10,000 per month — too much for most hospice programs (see Table 1).

Although some observers worry that nationwide open access could bankrupt Medicare, most agree that per diem reimbursement rates remain unacceptably low: in 2006, hospices were paid an average of $563 per patient per day for inpatient care (which represents 2.7% of Medicare’s total hospice payments) (see Table 2). The average outpatient fee was $126 for a typical day of care, an amount that must cover nursing care; contributions from social workers, chaplains, and volunteers; and all drugs and durable medical equipment, as well as 13 months of bereavement support.

Despite differences among hospice programs, patient and family satisfaction is high; in 2005, one third of the 2.4 million Americans who died were receiving hospice care. The largest proportion of patients had cancer, although patients with dementia, heart disease, and fatal lung conditions are increasingly entering hospice care. Diane Meier, director of the Center to Advance Palliative Care at the Mount Sinai School of Medicine in New York, argues that “palliative care and hospice are the only medical disciplines where nurses and physicians focus on the whole person.”

Most patients, however, wait until the last few weeks of life to enroll. In 2005, the median hospice stay was 26 days. One contributing factor is late referrals by oncologists, who routinely

Table 1. Approximate Costs of Drugs Commonly Used by Hospices and Oncologists for Palliative Treatment.*

<table>
<thead>
<tr>
<th>Class and Drug</th>
<th>Dose/24 Hr</th>
<th>Price ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency hospice pack</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-night supply of morphine oral concentrate, lorazepam, haloperidol, prochlorperazine, and Senokot</td>
<td></td>
<td>50.00</td>
</tr>
<tr>
<td><strong>Pain relief and laxatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine oral concentrate</td>
<td>200 mg</td>
<td>186.00</td>
</tr>
<tr>
<td>MS Contin generic</td>
<td>200 mg</td>
<td>294.00</td>
</tr>
<tr>
<td>Oxycodeine ER</td>
<td>160 mg</td>
<td>562.20</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>100 µg</td>
<td>533.60</td>
</tr>
<tr>
<td>Senna</td>
<td>2 tablets</td>
<td>6.60</td>
</tr>
<tr>
<td><strong>Antiemetics, anxiolytics, anticholinergics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>6 mg</td>
<td>115.20</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>20 mg</td>
<td>53.70</td>
</tr>
<tr>
<td>Haloperidol oral concentrate</td>
<td>2 mg</td>
<td>22.56</td>
</tr>
<tr>
<td>Scopolamine patches</td>
<td>1 patch</td>
<td>9.18†</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8 mg</td>
<td>1,113.90</td>
</tr>
<tr>
<td><strong>Oral chemotherapy and supportive care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide</td>
<td>200 mg</td>
<td>1,867.40</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2500 mg</td>
<td>1,883.70</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>150 mg</td>
<td>3,906.60</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4 mg</td>
<td>824.56</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>40,000 units/wk</td>
<td>2,504.00</td>
</tr>
</tbody>
</table>

* Prices represent estimates for a 1-month supply of medicine at average wholesale price (Medi-Span, http://www.medi-span.com, accessed July 27, 2007). Many hospice programs, hospitals, and physicians are able to negotiate lower prices than those listed here; some hospices negotiate a fixed daily rate per patient to cover all necessary medications.

† Each patch lasts 72 hours. The patch is given very close to the end of life.
overestimate patients’ lifespans. Many patients are referred only when no other option remains. In addition, many patients fear that they will not receive enough medical services in hospice care. “It felt like I was trading in the Lamborghini of medical care for an old pick-up truck driving down a rutted road,” said one patient with cancer. Optimal end-of-life support often necessitates careful titration of opioid, antipsychotic, and anxiolytic drugs, which can sometimes require a doctor’s presence. But few patients ever meet a physician after enrolling for hospice care; there are no rules mandating the degree of physician involvement. Medicare does not even collect information on the number, frequency, or duration of visits or on which personnel provide which aspects of care. Each hospice program decides what services to offer, and family members often must fill in the gaps.

Like most patients with terminal illness, Joanne Doolin chose ongoing medical treatment over hospice. She entered a bridge-to-hospice program that provided home nursing care and access to an infusion company for nutrition until she was ready for hospice care. She spent more than a month at home, visited her favorite casino, and attended her daughter’s wedding. But then Doolin’s health suddenly deteriorated, and she needed urgent medical care and pain management. Her family contacted the bridge program’s hospice but could not enroll her in time. During Doolin’s last few hours, care was provided by a haphazard mix of people, including her family, a covering oncologist, a pharmacist, and compassionate local firefighters. One year later, Doolin’s family is still angry over the forced choice between parenteral nutrition and hospice care. They believe she would have suffered less in an open-access hospice program.

The disconnect between pre-hospice and hospice care seems absolute to physicians as well. The Medicare hospice benefit “is so restrictive,” says Thomas Smith, chair of the division of hematology–oncology and palliative care at Virginia Commonwealth University–Massey Cancer Center, in Richmond, “that it requires divorcing yourself from your patient’s care because you can’t be their cancer doctor anymore. As soon as you enroll in hospice, there goes your Aranesp, your Zometa, and your Zofran. . . . I can’t do anything but adjust pain meds and hold hands. These are wonderful things to do, but they won’t keep my office running.”

Many hospice directors counter that oncologists abandon their patients when they can no longer visit the office. A few large hospices and insurance companies are trying to prevent these situations with open-access programs. Last year, Capital Hospice, based in Washington, D.C., paid for palliative chemotherapy, radiation, dialysis, blood transfusions, parenteral nutrition, antibiotics, and other expensive intravenous medications. With an average daily census of 606 patients, the program can spread out the expense. President and chief executive officer Malene Davis likens open access to “two ropes hanging from the ceiling. We’ve asked people to hold on to the aggressive-treatment rope with both hands,” she says, “but when they go on hospice we tell them to let go completely. Open access gives people the choice to let go of active treatment with one hand and grab on to the hospice rope until they feel comfortable letting the other hand go.”

The large insurance company UnitedHealth offers a basic open-access hospice benefit to nearly 26 million members and a smaller hospice program in 11 cities that includes physician home visits and reviews of care.
PERSPECTIVE

LETTING GO OF THE ROPE — AGGRESSIVE TREATMENT, HOSPICE CARE, AND OPEN ACCESS

pany spokesperson says that the cost is negligible as compared with the cost of its other programs. In 2004, Aetna started its Compassionate Care Program, which uses International Classification of Diseases, Ninth Revision, codes and pharmaceutical information to identify members with terminal illnesses; the members are then contacted by nurse case managers, who offer emotional support, care coordination, and information about end-of-life planning and symptom relief. Early results suggest that members appreciate the additional support that tailored case management provides; more members are enrolling in hospice, and the program is reducing rates of unnecessary hospitalizations.

But these programs remain the exception. According to the Center for Medicare and Medicaid Services (CMS), only 2.5% of the country’s 4100 hospices have an average daily census above 400 — commonly considered the minimum requirement for open access (see pie chart). Elsewhere, patients and hospice directors must make tough choices.

The only randomized trial to date examining standard cancer care both with and without hospice support showed no significant difference in survival rates, but it did show significant improvements in quality of life when cancer care and hospice care were combined. Preliminary analysis revealed a 27% cost reduction in the combined-care group, which received less chemotherapy and diagnostic testing and required fewer hospitalizations. Nevertheless, many experts worry that open access may be prohibitively expensive. A 1990 study showed that most patients with cancer would choose to undergo toxic chemotherapy despite marginal potential benefits; a study in 2004 reported increasingly aggressive care at the end of life. Patients with congestive heart failure also face difficult choices, since life-sustaining medications can cost $1,300 per day. “Whoever wrote [Medicare’s hospice] policy has never taken care of sick patients,” argues Diane Meier. “Our patients are fighting for their lives and will do anything to extend the length of time they live, as long as they have some quality of life.”

CMS foresees an annual increase of 9% in hospice spending over the next decade, which will outpace increases for hospitals, physicians, skilled nursing facilities, and home health services. Many expect closer scrutiny of hospice reimbursements by Medicare, particularly for patients with dementia or other illnesses, who often live with the disease for more than 6 months. “Baby boomers are going to want everything — from death coaches to powerful drugs,” says Davis, “but we’ve got to begin grappling with tough choices if we’re going to stay in business for $150 a day.”

Some choices will undoubtedly involve better definitions of palliative treatment. Currently, oncologists focus on how well a tumor responds to chemotherapy, but they will soon have to examine improvement of symptoms and quality of life to justify treatment costs. Meanwhile, patients will simply have to hope for access to a hospice that is large enough to help them.

Dr. Wright is a fellow in hematology–oncology at the Dana-Farber Cancer Institute, and Dr. Katz is a fellow in infectious disease at the Beth Israel Deaconess Medical Center — both in Boston.

Oscar the Cat awakens from his nap, opening a single eye to survey his kingdom. From atop the desk in the doctor’s charting area, the cat peers down the two wings of the nursing home’s advanced dementia unit. All quiet on the western and eastern fronts. Slowly, he rises and extravagantly stretches his 2-year-old frame, first backward and then forward. He sits up and considers his next move.

In the distance, a resident approaches. It is Mrs. P., who has been living on the dementia unit’s third floor for 3 years now. She has long forgotten her family, even though they visit her almost daily. Moderately disheveled after eating her lunch, half of which she now wears on her shirt, Mrs. P. is taking one of her many aimless strolls to nowhere. She glides toward Oscar, pushing her walker and muttering to herself with complete disregard for her surroundings. Perturbed, Oscar watches her carefully and, as she walks by, lets out a gentle hiss, a rattlesnake-like warning that says “leave me alone.” She passes him without a glance and continues down the hallway. Oscar is relieved. It is not yet Mrs. P.’s time, and he wants nothing to do with her.

Oscar jumps down off the desk, relieved to be once more alone and in control of his domain. He takes a few moments to drink from his water bowl and grab a quick bite. Satisfied, he enjoys another stretch and sets out on his rounds. Oscar decides to head down the west wing first, along the way side-stepping Mr. S., who is slumped over on a couch in the hallway. With lips slightly pursed, he snores peacefully — perhaps blissfully unaware of where he is now living. Oscar continues down the hallway until he reaches its end and Room 310. The door is closed, so Oscar sits and waits. He has important business here.

Twenty-five minutes later, the door finally opens, and out walks a nurse’s aide carrying dirty linens. “Hello, Oscar,” she says. “Are you going inside?” Oscar lets her pass, then makes his way into the room, where there are two people. Lying in a corner bed and facing the wall, Mrs. T. is asleep in a fetal position. Her body is thin and wasted from the breast cancer that has been eating away at her organs. She is mildly jaundiced and has not spoken in several days. Sitting next to her is her daughter, who glances up from her novel to warmly greet the visitor. “Hello, Oscar. How are you today?”

Oscar takes no notice of the woman and leaps up onto the bed. He surveys Mrs. T. She is clearly in the terminal phase of illness, and her breathing is labored. Oscar’s examination is interrupted by a nurse, who walks in to ask the daughter whether Mrs. T. is uncomfortable and needs more morphine. The daughter shakes her head, and the nurse retreats. Oscar returns to his work. He sniffs the air, gives Mrs. T. one final look, then jumps off the bed and quickly leaves the room. Not today.

Making his way back up the hallway, Oscar arrives at Room 313. The door is open, and he proceeds inside. Mrs. K. is resting peacefully in her bed, her breathing steady but shallow. She is surrounded by photographs of her grandchildren and one from her wedding day. Despite these keepsakes, she is alone. Oscar jumps onto her bed and again sniffs the air. He pauses to consider the situation, and then turns around twice before curling up beside Mrs. K.

One hour passes. Oscar waits. A nurse walks into the room to check on her patient. She pauses to note Oscar’s presence. Concerned, she hurriedly leaves the room and returns to her desk. She grabs Mrs. K.’s chart off the medical-records rack and begins to make phone calls.

Within a half hour the family starts to arrive. Chairs are brought into the room, where the relatives begin their vigil. The priest is called to deliver last rites. And still, Oscar has
not budged, instead purring and gently nuzzling Mrs. K. A young grandson asks his mother, “What is the cat doing here?” The mother, fighting back tears, tells him, “He is here to help Grandma get to heaven.” Thirty minutes later, Mrs. K. takes her last earthly breath. With this, Oscar sits up, looks around, then departs the room so quietly that the grieving family barely notices.

On his way back to the charting area, Oscar passes a plaque mounted on the wall. On it is engraved a commendation from a local hospice agency: “For his compassionate hospice care, this plaque is awarded to Oscar the Cat.” Oscar takes a quick drink of water and returns to his desk to curl up for a long rest. His day’s work is done. There will be no more deaths today, not in Room 310 or in any other room for that matter. After all, no one dies on the third floor unless Oscar pays a visit and stays awhile.

Note: Since he was adopted by staff members as a kitten, Oscar the Cat has had an uncanny ability to predict when residents are about to die. Thus far, he has presided over the deaths of more than 25 residents on the third floor of Steere House Nursing and Rehabilitation Center in Providence, Rhode Island. His mere presence at the bedside is viewed by physicians and nursing home staff as an almost absolute indicator of impending death, allowing staff members to adequately notify families. Oscar has also provided companionship to those who would otherwise have died alone. For his work, he is highly regarded by the physicians and staff at Steere House and by the families of the residents whom he serves.

Dr. Dosa is a geriatrician at Rhode Island Hospital and an assistant professor of medicine at the Warren Alpert Medical School of Brown University — both in Providence.

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THIS WEEK in the JOURNAL

ORIGINAL ARTICLE
Dexamethasone for Bronchiolitis
Infants with a first episode of wheezing diagnosed as bronchiolitis are often treated with oral dexamethasone. In this trial, children with bronchiolitis and no history of asthma received oral dexamethasone or placebo. There were no clinically significant differences in outcomes between the two groups.
SEE P. 331; EDITORIAL, P. 402; CME, P. 431

ORIGINAL ARTICLE
Salvage Therapy for Metastatic Germ-Cell Tumors
This article summarizes the experience of a single institution in treating patients with metastatic testicular tumors that did not respond to cisplatin-based chemotherapy. High-dose chemotherapy with hematopoietic stem-cell rescue was potentially curative in such cases.
SEE P. 340

ORIGINAL ARTICLE
Partial Thrombosis of the False Lumen in Type B Aortic Dissection
A cohort of 201 patients with type B acute aortic dissection was classified according to whether the false lumen of the aorta was patent, partially thrombosed, or completely thrombosed. Patients with partial thrombosis had a significantly higher mortality rate at 3 years.
SEE P. 349

ORIGINAL ARTICLE
Toxicity of Rofecoxib in Colorectal Cancer
In this clinical trial, rofecoxib (25 mg per day) was studied in the prevention of recurrent colorectal cancer. Although the median duration of study treatment was only 7.4 months, rofecoxib therapy was associated with an increased risk of cardiovascular adverse events (relative risk as compared with placebo, 2.66; P=0.04). The results indicate that even short-term treatment with rofecoxib may result in cardiovascular toxicity.
SEE P. 360

SPECIAL ARTICLE
The Spread of Obesity in a Large Social Network
This article, which describes the person-to-person spread of obesity as a potential contributing factor in the U.S. obesity epidemic, analyzes a densely interconnected social network, using repeated assessments performed from 1971 to 2003 as part of the Framingham Heart Study. Social-network phenomena seem relevant to obesity, which appears to spread through social ties.
SEE P. 370; EDITORIAL, P. 404

CLINICAL PRACTICE
MRSA Skin and Soft-Tissue Infections
A 37-year-old man presents with localized swelling and tenderness of the left leg just below the knee; he suspects a spider bite. Examination shows a 5-by-7-cm area of erythema and warmth. A small area of necrotic skin covers a central, fluctuant 2-by-2-cm area. The temperature is 38.3°C, the pulse rate 115 beats per minute, and the blood pressure 116/78 mm Hg.
SEE P. 380; CME, P. 429

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL
A Boy with Bone Pain, Rash, and Gingival Hypertrophy
A 9-year-old boy with autism was admitted to the hospital because of pain in the hip, rash, and swelling of the gingiva. Three months earlier, pain in his right hip developed, and he eventually refused to walk. Physical examination disclosed no joint swelling, and radiographs of the pelvis and spine were normal. Indomethacin was prescribed; the pain improved, but a petechial rash on the legs and gingival swelling developed.
SEE P. 392; CME, P. 430

HEALTH LAW, ETHICS, AND HUMAN RIGHTS
Cancer and the Constitution
The Abigail Alliance for Better Access to Developmental Drugs sued the FDA, objecting to its policy prohibiting the sale of unapproved drugs and arguing that terminally ill patients with cancer should have access to experimental treatments after phase 1 studies. The author discusses this case and explains why he thinks a ruling in favor of the Abigail Alliance is unlikely.
SEE P. 408

VIDEOS IN CLINICAL MEDICINE
Face Mask and Bag-Valve Ventilation
Providing positive-pressure ventilation with a face mask and a bag-valve device can be a life-saving maneuver. Although seemingly simple, the technique requires an understanding of the airway anatomy, the equipment, and the indications. This video demonstrates the equipment and technique used to provide positive-pressure ventilation with a face mask and a bag-valve device.
SEE P. E4
A Multicenter, Randomized, Controlled Trial of Dexamethasone for Bronchiolitis


A B S T R A C T

BACKGROUND
Bronchiolitis, the most common infection of the lower respiratory tract in infants, is a leading cause of hospitalization in childhood. Corticosteroids are commonly used to treat bronchiolitis, but evidence of their effectiveness is limited.

METHODS
We conducted a double-blind, randomized trial comparing a single dose of oral dexamethasone (1 mg per kilogram of body weight) with placebo in 600 children (age range, 2 to 12 months) with a first episode of wheezing diagnosed in the emergency department as moderate-to-severe bronchiolitis (defined by a Respiratory Distress Assessment Instrument score ≥6). We enrolled patients at 20 emergency departments during the months of November through April over a 3-year period. The primary outcome was hospital admission after 4 hours of emergency department observation. The secondary outcome was the Respiratory Assessment Change Score (RACS). We also evaluated later outcomes: length of hospital stay, later medical visits or admissions, and adverse events.

RESULTS
Baseline characteristics were similar in the two groups. The admission rate was 39.7% for children assigned to dexamethasone, as compared with 41.0% for those assigned to placebo (absolute difference, −1.3%; 95% confidence interval [CI], −9.2 to 6.5). Both groups had respiratory improvement during observation; the mean 4-hour RACS was −5.3 for dexamethasone, as compared with −4.8 for placebo (absolute difference, −0.5; 95% CI, −1.3 to 0.3). Multivariate adjustment did not significantly alter the results, nor were differences detected in later outcomes.

CONCLUSIONS
In infants with acute moderate-to-severe bronchiolitis who were treated in the emergency department, a single dose of 1 mg of oral dexamethasone per kilogram did not significantly alter the rate of hospital admission, the respiratory status after 4 hours of observation, or later outcomes. (ClinicalTrials.gov number, NCT00119002.)
Bronchiolitis is the leading cause of hospitalization for infants in the United States, accounting for 100,000 admissions annually, with hospital charges alone estimated at $700 million. Hospitalization rates for infants with bronchiolitis more than doubled between 1980 and 1996, and the proportion of infant hospitalizations that were due to bronchiolitis more than tripled, from 5% to 16%.

Treatment for bronchiolitis is controversial. Bronchodilators are commonly used, but they have not been shown to have consistent benefits. Although studies suggest that approximately a quarter of infants hospitalized with bronchiolitis receive corticosteroids, the efficacy of these agents has also not been consistently demonstrated. Most positive and negative studies of corticosteroids have been small and heterogeneous in design, but a controlled trial involving 70 infants with moderate-to-severe bronchiolitis was reported by Schuh and colleagues in 2002. They found significant reductions in respiratory scores after 4 hours of observation in infants who received 1 mg of oral dexamethasone per kilogram of body weight, as compared with those who received placebo. Moreover, the admission rate was 19% in the dexamethasone group, as compared with 44% in the placebo group.

A number of experts and reviews have called for further study of corticosteroids for bronchiolitis. The 2003 report published by the Agency for Healthcare Research and Quality (AHRQ) stated that there is “no evidence that any single agent can be recommended for treatment of bronchiolitis,” and it called for a “rigorously designed and adequately sized trial” of agents to include dexamethasone. The goal of our study was to determine the effectiveness of a single dose of oral dexamethasone in infants with moderate-to-severe bronchiolitis.

**Methods**

We conducted the study in 20 emergency departments of the Pediatric Emergency Care Applied Research Network (PECARN) during bronchiolitis season (November through April) from January 2, 2004, through April 30, 2006. Planned start and end dates were the same for all centers. The institutional review boards at all sites approved the study. Written informed consent was obtained from the parent or guardian of each infant included in the study.

We included infants 2 to 12 months of age who were brought to the emergency department with a first episode of bronchiolitis, defined as wheezing (with no prior bronchiolitis, wheezing, or asthma and no bronchodilator use before the current illness), within 7 days after the onset of symptoms. In addition, the episode had to be moderate or severe as defined by a score on the Respiratory Distress Assessment Instrument (RDAI) of 6 or more (on a scale of 0 to 17, with higher scores indicating more severe respiratory symptoms) (Table 1). We excluded infants with a prior adverse reaction to dexamethasone, known heart or lung disease, premature birth (defined as birth before 36 weeks of gestation), immunosuppression or immunodeficiency, treatment with corticosteroids in the previous 14 days, active varicella or recent exposure to varicella, or inability of the parent or guardian to speak English or Spanish. Critically ill infants were also excluded.

Infants were screened for eligibility during times when a research assistant and study clinician (emergency department faculty, fellow, or nurse practitioner) were available. Each center kept a record of all screened infants, including those who arrived when study staff were available and who underwent screening but were not enrolled. Research assistants and all study clinicians received yearly training from site lead investigators in study procedures and respiratory scoring. Site monitors visited each site during and after data collection to audit all study records.

Before enrollment, study clinicians confirmed clinical bronchiolitis and determined the duration of symptoms and the RDAI score. Research assistants or clinicians obtained the medical history from parents or guardians on a standardized data-collection form, which included questions about a history of eczema in the patient, a family history of asthma in the immediate family, and the presence of smokers or pets at home. Infants with eczema or a family history of asthma were considered to have possible atopy and, as recommended in the AHRQ report, were treated as a prespecified subgroup in the analysis. At enrollment and 1 hour and 4 hours after administration of the study medication, a nurse recorded clinical variables (respiratory and heart rates, temperature, and oxygen saturation while the infant was breathing ambient air). A study clini-
cian repeated respiratory scoring 1 hour and 4 hours after the administration of the study medication and assessed each child for discharge or admission after 4 hours.

**Randomization**
We performed computerized randomization by telephone, using the keypad for data entry. Infants were assigned in equal numbers to the dexamethasone and placebo groups with the use of random permuted blocks stratified by center. All emergency department staff, study personnel, and parents and guardians were unaware of the group assignments. Randomization codes were secured until all data entry was complete.

**Study Intervention**
Using the same formulation as in prior studies,20,24 research pharmacies prepared oral dexamethasone solutions (1 mg per milliliter of liquid) from generic dexamethasone phosphate injection solution and identical oral placebo solutions. The preparations were packaged in identical clear plastic vials labeled only with the randomization numbers. A nurse orally administered 1 ml of solution per kilogram, providing 1 mg of dexamethasone per kilogram in the dexamethasone group (maximum, 12 mg). Any episode of vomiting within 20 minutes after administration of the study medication was recorded, but the dose was not repeated.

For ethical, practical, and scientific reasons, all other bronchiolitis treatments were provided according to the clinician’s preference and local standards. Any diagnostic testing, including viral testing, was also left to the clinician’s discretion, and tests were performed with assays available at the participating center. Because testing for other viruses varied, only the results for respiratory syncytial virus were recorded.

After 7 to 10 days, a research assistant, who was unaware of the group assignments, reviewed the chart and conducted a brief standardized telephone interview with the parent or guardian. The interview included questions about whether hospitalization, unscheduled medical visits, or adverse reactions to the study drug (as judged by a physician or the parent or guardian) had occurred within 7 days after the initial emergency department visit.

**Outcome Measures**
The primary outcome was the decision to hospitalize or discharge the infant 4 hours after the administration of the study medication. Infants requiring admission to an intensive care unit before 4 hours of observation had been completed were included in the analysis of admissions. The secondary outcome was the Respiratory Assessment Change Score (RACS) at 4 hours.23 The RACS is calculated as the sum of the change in the RDAI score and a standardized score for the change in the respiratory rate, with a reduction of 1 unit for a decrease of 5 to 15%, 2 units for a decrease of 16 to 25%, and so on.20,23 Thus, negative RACS values signify improvement. Other investigators

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td>During expiration</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>During inspiration</td>
<td>None</td>
</tr>
<tr>
<td>No. of involved lung fields</td>
<td>0</td>
</tr>
<tr>
<td>Retractions</td>
<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>None</td>
</tr>
<tr>
<td>Intercostal</td>
<td>None</td>
</tr>
<tr>
<td>Subcostal</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

* Both wheezing and retractions were scored. The total score on the RDAI is the sum of the scores for each row, with a range of 0 to 17; higher scores indicate more severe disease.
20

Adverse Events

Study clinicians and research assistants monitored the infants for adverse events during observation in the emergency department. Subsequent adverse events were determined at follow-up. A patient-safety committee, made up of people not involved with patient enrollment, tracked all adverse events.

Statistical Analysis

Assuming a 40% admission rate in the placebo group, we calculated the sample size that would be required to provide more than 80% power (with a two-sided alpha level of 0.05) to detect an absolute reduction in hospital admission rates of 12% or more in the dexamethasone group. A biostatistician participated in the study design and performed all analyses. The primary analysis was based on the intention-to-treat principle, with all patients included in their assigned group. A secondary, per-protocol analysis examined the results among infants who actually received the assigned study medication.

Hospital admission rates were compared with the use of Pearson’s chi-square test. The RACS was compared in the two groups by means of a two-sample t-test. Adjusted measures and subgroup effects for admission and RACS were analyzed with the use of logistic regression and linear regression, respectively. Generalized estimating equations and linear mixed models were used to test for an interaction between treatment group and site in the admission and RACS outcomes, respectively. Changes in clinical variables after 4 hours of observation were regressed against baseline values and treatment group as predictors. Length-of-stay measures were compared by means of the two-sample Wilcoxon test. The alpha level was set at 0.05 for all analyses, 95% confidence intervals were calculated, and all comparisons were two-tailed.

Results

A total of 8686 infants were screened for study eligibility (Fig. 1). Among the 7352 infants who did not meet the inclusion criteria, two thirds had either prior wheezing or mild disease; the remainder met other exclusion criteria. For the primary outcome, hospital admission, data were available for all 600 infants in the intention-to-treat analysis. The secondary outcome, the Respiratory Assessment Change Score (RACS), included two variables, respiratory rate and Respiratory Distress Assessment Instrument (RDAI) score, that were compared at baseline and after 4 hours of observation. Follow-up involved a single telephone interview with each infant’s parent or guardian.

have interpreted a change of 2 units or more as clinically important.20

Adverse Events

Study clinicians and research assistants monitored the infants for adverse events during observation in the emergency department. Subsequent adverse events were determined at follow-up. A patient-safety committee, made up of people not involved with patient enrollment, tracked all adverse events.

Statistical Analysis

Assuming a 40% admission rate in the placebo group, we calculated the sample size that would be required to provide more than 80% power (with a two-sided alpha level of 0.05) to detect an absolute reduction in hospital admission rates of 12% or more in the dexamethasone group. A biostatistician participated in the study design and performed all analyses. The primary analysis was based on the intention-to-treat principle, with all patients included in their assigned group. A secondary, per-protocol analysis examined the results among infants who actually received the assigned study medication.

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Results

A total of 8686 infants were screened for study eligibility (Fig. 1). Among the 7352 infants who did not meet the inclusion criteria, two thirds had either prior wheezing (41%) or an RDAI score of less than 6 (25%). Of the 600 infants who underwent randomization, 305 were assigned to the dexamethasone group and 295 to the placebo group; all were included in the intention-to-treat analysis. Two randomly assigned infants were hospitalized before administration of the study drug, leaving 598 treated infants. Five of these infants received the wrong medication because of errors in vial selection, and 1 received an insufficient dose of dexamethasone, leaving 592 patients in the per-protocol analysis. The results of this analysis did not differ qualitatively from those of the intention-to-treat analysis. A detailed subanalysis according to the results of tests for respiratory syncytial virus revealed no significant differences in any of the studied outcomes between infants with positive results and those with negative results (Fig. 2).
Baseline demographic and clinical characteristics were similar in the dexamethasone and placebo groups (Table 2). Similar proportions of infants received inhaled bronchodilator treatment, either with albuterol (77.0% and 80.3%, respectively) or epinephrine (15.5% and 16.7%, respectively). The number of such treatments received was also similar, with a mean of 2.0 treatments with albuterol and 1.2 treatments with epinephrine in each study group.

**Hospital Admission**

We found no significant difference between the study groups with respect to hospitalization. Of the 305 infants in the dexamethasone group, 121 (39.7%) were admitted, as compared with 121 of the 295 infants (41.0%) in the placebo group (absolute difference, −1.3%; 95% confidence interval [CI], −9.2 to 6.5; P = 0.74). Neither was there a significant difference when admission was analyzed in the prespecified subgroup with eczema or a family history of asthma (absolute difference, −1.3%; 95% CI, −11.1 to 8.5). Figure 2 shows the relative risk of admission overall and in this and other subgroups.

**Respiratory Assessment Change Score**

The respiratory status of both study groups improved during treatment and observation in the emergency department, but mean RACS values did not differ significantly between the groups (Table 3). Neither was there a significant difference when RACS values were analyzed in the subgroup with eczema or a family history of asthma (absolute difference, −0.4; 95% CI, −1.3 to 0.6).

**Other Outcomes**

Table 3 also shows differences in the clinical variables between the baseline and 4-hour observations. Changes in the respiratory rate did not differ significantly between the two study groups. Although changes in the RDAI score, oxygen saturation, temperature, and heart rate did differ significantly between the groups, these differences were small.

The mean length of stay for hospitalized patients was 2.55 days in the dexamethasone group and 2.27 days in the placebo group (P = 0.10). Subsequent hospital admissions in the 7 days after the intervention were reported for 12 of 284 children in the dexamethasone group (4.2%) and 10 of 265 children in the placebo group (3.8%).

**Adverse Events**

There were few adverse events. Vomiting within 20 minutes after administration of the study medication occurred in 5.5% of the dexamethasone group and 4.7% of the placebo group. No infant had gastrointestinal bleeding, hypertension, or complicated varicella. Pneumonia was diagnosed in three infants; two were in the placebo group, and an empyema developed in one of these two infants.

**Discussion**

Our multicenter, randomized, double-blind study of 600 infants with acute, moderate-to-severe bronchiolitis in the emergency department showed...
The data do not include two patients who were hospitalized before the administration of study medication. Plus–minus values are means ±SD. RDAI denotes Respiratory Distress Assessment Instrument, and RSV respiratory syncytial virus.

### Table 2. Baseline Characteristics of the Infants According to the Assigned Study Group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexamethasone (N = 304)</th>
<th>Placebo (N = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no./total no. (%)</td>
<td>190/304 (62.5)</td>
<td>178/294 (60.5)</td>
</tr>
<tr>
<td>Age — mo</td>
<td>5.1±2.6</td>
<td>5.1±2.8</td>
</tr>
<tr>
<td>RDAI score</td>
<td>9.0±2.1</td>
<td>9.2±2.4</td>
</tr>
<tr>
<td>Respiratory rate — breaths/min</td>
<td>53±13</td>
<td>53±13</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>157±20</td>
<td>158±21</td>
</tr>
<tr>
<td>Temperature — °C</td>
<td>37.6±0.8</td>
<td>37.7±0.8</td>
</tr>
<tr>
<td>Oxygen saturation — %</td>
<td>96±4</td>
<td>96±4</td>
</tr>
<tr>
<td>No. of days of illness</td>
<td>3.7±2.5</td>
<td>3.6±2.5</td>
</tr>
<tr>
<td>RSV-positive — no. positive/ no. tested (%)</td>
<td>85/127 (66.9)</td>
<td>81/142 (57.0)</td>
</tr>
<tr>
<td>History — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of asthma</td>
<td>165/295 (55.9)</td>
<td>170/284 (59.9)</td>
</tr>
<tr>
<td>History of eczema</td>
<td>76/292 (26.0)</td>
<td>77/281 (27.4)</td>
</tr>
<tr>
<td>Either family history of asthma or history of eczema</td>
<td>187/295 (63.4)</td>
<td>196/284 (69.0)</td>
</tr>
<tr>
<td>Smoker in home — no./total no. (%)</td>
<td>117/300 (39.0)</td>
<td>103/287 (35.9)</td>
</tr>
<tr>
<td>Pet in home — no./total no. (%)</td>
<td>97/299 (32.4)</td>
<td>90/282 (31.9)</td>
</tr>
</tbody>
</table>

* The data do not include two patients who were hospitalized before the administration of study medication. Plus–minus values are means ±SD. RDAI denotes Respiratory Distress Assessment Instrument, and RSV respiratory syncytial virus.

Our findings are consistent with studies that failed to demonstrate the efficacy of corticosteroids in bronchiolitis. A collective review by the Cochrane Collaboration of 13 studies of the use of corticosteroids for bronchiolitis showed no significant differences between corticosteroid and placebo groups in respiratory rates, oxygen saturation, initial admission rates, length of stay, subsequent visits, or readmission rates. The AHRQ report analyzed five placebo-controlled studies of oral corticosteroids, including dexamethasone, and two placebo-controlled studies of parenteral dexamethasone. Only one study showed a significant difference between groups. In 2006, a subcommittee of the American Academy of Pediatrics reviewed the evidence from previous studies and recommended that corticosteroids not be used routinely for bronchiolitis. All of these reviews, however, note the inconclusive nature of the available evidence.

Some studies have suggested a benefit of corticosteroid therapy, and the size, methods, and
findings of these studies have been carefully reviewed.\textsuperscript{5,10} A meta-analysis\textsuperscript{27} of six trials of systemic corticosteroids in infants with bronchiolitis showed a small benefit in the corticosteroid groups, but this effect did not persist when outcomes were analyzed separately or when only studies of first-time wheezing were examined.

The results of our study differ from those of the study by Schuh et al.\textsuperscript{20} The two studies used the same dose of dexamethasone (1 mg per kilogram), with 4 hours of observation in the emergency department and outcomes of hospitalization and RACS, but they differ in certain respects. In the study by Schuh et al., oral dexamethasone (0.6 mg per kilogram) or placebo was continued for 5 days in patients discharged home. This would not, however, affect the study’s main outcomes — hospitalization and RACS after 4 hours. We studied infants in the first year of life, whereas Schuh et al. included children up to 24 months of age. By chance, the dexamethasone group in their study had a significantly higher proportion of infants with family histories of atopy than did the placebo group. Our study groups were balanced in this regard. Their study was substantially smaller and conducted at a single institution, where all infants were treated with a standardized bronchodilator regimen. Given the current wide variation in the use of bronchodilators\textsuperscript{3,4} and uncertainty regarding their effectiveness,\textsuperscript{5,10} we did not try to control bronchodilator use. Our study was not powered to examine possible interactions between bronchodilators and dexamethasone. We did, however, confirm that the types and numbers of bronchodilator treatments were similar in the two groups.

Our study had some limitations. For both ethical and scientific reasons, we sought to exclude children with possible early asthma, who might have benefited from dexamethasone. We therefore studied only young infants with first-time wheezing. Older children or children with recurrent wheezing might have a different response to dexamethasone.

We studied a single oral dose of dexamethasone (1 mg per kilogram). The size of the dose makes it unlikely that more medication would be effective. Oral administration and a 4-hour observation period were chosen to replicate the methods used by Schuh et al.\textsuperscript{20} Although the biologic basis of the effect is not clear, their study and ours were predicated on extensive evidence that oral corticosteroids are effective within 4 hours in patients with asthma\textsuperscript{28–33} and those with croup.\textsuperscript{34–36} It is unlikely that we missed a later benefit of dexamethasone. We collected data on later outcomes, including the length of the hospital stay among infants who were initially admitted, subsequent admissions or unscheduled medical visits, and adverse events in the two study groups. If dexamethasone had been effective after the passage of 4 hours, this result should have been apparent in one or more of these later outcomes.

In summary, in our multicenter study of 600 infants from 2 to 12 months of age who had moderate-to-severe bronchiolitis, we found that treatment with 1 mg of oral dexamethasone per kilogram did not significantly alter the rate of hospital admission or the respiratory status after 4 hours of observation. Neither did such treatment affect the length of the hospital stay among infants who were initially admitted, subsequent ad-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexamethasone Group</th>
<th>Placebo Group</th>
<th>Difference between Groups (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission (%)</td>
<td>39.7</td>
<td>41.0</td>
<td>−1.3 (−9.2 to 6.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>RACS</td>
<td>−5.3±4.7</td>
<td>−4.8±4.6</td>
<td>−0.5 (−1.3 to 0.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>RDAI score</td>
<td>−4.4±3.1</td>
<td>−3.9±3.2</td>
<td>−0.5 (−1.0 to −0.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>−8±15</td>
<td>−7±14</td>
<td>−1.0 (−3.0 to 1.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>0.3±3.3</td>
<td>0.9±3.2</td>
<td>−0.6 (−1.0 to −0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>−13±24</td>
<td>−5±25</td>
<td>−8.0 (−12.0 to −5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>−0.6±0.9</td>
<td>−0.2±1.0</td>
<td>−0.4 (−0.6 to −0.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\* Data for all variables except hospital admission are expressed as the change from baseline to 4 hours. RACS denotes Respiratory Assessment Change Score, and RDAI Respiratory Distress Assessment Instrument.

Table 3. Hospital Admission and Changes in Clinical Variables from Baseline to 4 Hours after Intervention.\textsuperscript{7}
missions or unscheduled medical visits, or adverse events. We recommend evaluation of other treatments and preventive strategies for bronchiolitis.

Supported by a grant (R40MC042980100) from the Maternal and Child Health Research program and by cooperative agreements (U03MC00001, U03MC00003, U03MC00007, and U03MC00008) with the Emergency Medical Services for Children program of the Maternal and Child Health Bureau, Health Resources and Services Administration.

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APPENDIX


REFERENCES


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High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

Lawrence H. Einhorn, M.D., Stephen D. Williams, M.D., Amy Chamness, B.A., Mary J. Brames, R.N., Susan M. Perkins, Ph.D., and Rafat Abonour, M.D.

ABSTRACT

BACKGROUND
Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy.

METHODS
We conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. We gave 173 patients two consecutive courses of high-dose chemotherapy consisting of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter, each for 3 consecutive days, and each followed by an infusion of autologous peripheral-blood hematopoietic stem cells; the other 11 patients received a single course of this treatment. In 110 patients, cytoreduction with one or two courses of vinblastine plus ifosfamide plus cisplatin preceded the high-dose chemotherapy.

RESULTS
Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with nonseminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy.

CONCLUSIONS
Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.
GERM-CELL TUMORS ARE CURABLE EVEN in the presence of metastatic disease.1-3 An international collaboration has established that metastatic germ-cell tumors can be classified into good-, intermediate-, and poor-risk disease, with corresponding cure rates of 90 to 95%, 75%, and 40 to 50%, respectively.4 Hereinafter, we refer to these categories as low-, intermediate-, and high-risk disease, respectively. Patients with tumors that relapse or with tumors that progress despite initial chemotherapy are candidates for salvage therapy. The few patients with anatomically confined disease are amenable to surgical extirpation.5 For most patients, however, the options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine6 or paclitaxel7 for four courses, or high-dose chemotherapy with autologous hematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablatative effects of chemotherapy.8-10 We began treating patients with carboplatin-based high-dose chemotherapy in 1986.11 Earlier studies of such treatment based on high-dose cyclophosphamide were unsuccessful.12

Initially, we used autologous bone marrow cells to rescue the hematopoietic system after high-dose chemotherapy. In February 1996, we shifted to peripheral-blood stem cells, which rapidly engrafted, thereby permitting a second course of high-dose chemotherapy with fewer delays. In this article, we present a retrospective study of 184 consecutive patients treated at Indiana University with high-dose carboplatin plus etoposide (high-dose chemotherapy) and rescue of the hematopoietic system by infusion of peripheral-blood stem cells. Our goal was to examine the efficacy of this treatment for cisplatin-resistant, progressively growing testicular cancer.

METHODS

PATIENTS
We conducted a review of 184 consecutive patients who received high-dose chemotherapy and peripheral-blood stem-cell rescue between February 1996 and December 2004. Patient interviews and medical charts were used to obtain the data analyzed in this study. The institutional review board at Indiana University approved the study. The requirement for informed consent was waived.

Before high-dose chemotherapy was initiated, peripheral-blood stem cells were collected and purified according to a technique that has been described previously.8 We harvested the cells after stimulation of the patient’s marrow with granulocyte colony-stimulating factor and enriched these cells for CD34+ hematopoietic cells. Patients who received high-dose chemotherapy as initial salvage treatment and whose tumor had not progressed within 4 weeks after the last round of this treatment received standard doses of vincristine plus ifosfamide plus cisplatin6 to reduce the bulk of the tumor and prevent progression before we administered high-dose chemotherapy. Patients who had already received ifosfamide-based salvage chemotherapy were offered high-dose chemotherapy without any further treatment. Patients with primary mediastinal nonseminomatous germ-cell tumors or tumors with late relapse (>2 years after previous therapy) were not offered high-dose chemotherapy during the specified period.

All patients received therapy in the outpatient clinic except for patients with complications requiring inpatient care. Antibiotics, including prophylactic acyclovir, fluconazole, ciprofloxacin, and either penicillin or vancomycin, were used routinely.

High-dose chemotherapy consisted of two cycles of 700 mg of carboplatin per square meter of body-surface area plus 750 mg of etoposide per square meter, both given intravenously 5, 4, and 3 days before the infusion of peripheral-blood stem cells. A minimum of 1 million CD34+ cells per kilogram of body weight was required for each cycle of high-dose chemotherapy. There were no planned reductions or escalations in the doses of chemotherapy. The second cycle of high-dose chemotherapy was given after recovery of granulocyte and platelet counts, unless there was a grade 4 nonhematologic toxic effect or no response to the first course. Most patients who had a complete or partial remission after the two cycles of high-dose chemotherapy and who had normal serum levels of human chorionic gonadotropin (hCG) and alpha-fetoprotein received a maintenance oral dose of 50 mg of etoposide per square meter daily for 21 consecutive days every 4 weeks for three cycles.13

Complete remission was defined as no clinically or radiographically detectable disease and normal serum levels of hCG and alpha-fetoprotein. Patients with a resectable residual mass after high-dose chemotherapy were offered surgery. Disease-free survival, defined as no evidence of disease at all follow-up visits after high-dose chemotherapy,
was the primary end point for this analysis. Survival time was measured from the first day of high-dose chemotherapy. Disease-free survival was measured from the initiation of high-dose chemotherapy to tumor progression or death.

**STATISTICAL ANALYSIS**

Analyses were carried out with the use of SAS (version 9.1) and S-PLUS (version 7.0) software.

The Kaplan–Meier method\(^\text{14}\) was used to calculate overall and disease-free survival according to the risk group (low, intermediate, or high), which was defined on the basis of the prognostic scoring algorithm described below. The association of disease-free survival with each prognostic variable was assessed with the use of Fisher’s exact test.

A multivariate proportional-hazards regression analysis was used to construct a prognostic scoring algorithm for disease-free survival. Because the individual prognostic variables correlated with each other significantly, and because our goal was to devise a prognostic scoring algorithm that was easy to implement clinically, we used the branch-and-bound algorithm of Furnival and Wilson\(^\text{15}\) to find the best model among all possible models that contained three prognostic variables. This algorithm fits all possible three-variable models and identifies the model with the highest likelihood score (chi-square statistic). The best four-variable model was also obtained to determine whether the value added by including a fourth variable was meaningful. This model did not perform better than the best three-variable model. We used a bootstrap method in which 1000 samples of 184 patients were randomly selected from the original patient cohort.\(^\text{16}\) For each sample, the branch-and-bound algorithm was applied. Next, the model with the highest frequency of selection among the 1000 samples was identified. The best three- and four-variable models identified by the bootstrap algorithm were both identical to the best three- and four-variable models for the original sample, providing support for the validity of the final model. With the use of the method of Rassi et al.,\(^\text{17}\) the β regression coefficients from the final model applied to the original sample were used to develop prognostic scores (with low scores reflecting a greater probability of disease-free survival) for each variable in the model. These prognostic scores were then summed and split three ways (by comparing the overall patterns of survival according to prognostic score with a Kaplan–Meier plot and forming three groups with similar patterns) to create an overall stratification of patients into low-, intermediate-, and high-risk groups.

**RESULTS**

We analyzed the disease-free and overall survival of patients who received high-dose chemotherapy for at least 1 day. The one patient who was lost to

---

**Table 1. Characteristics of 184 Patients at the Beginning of High-Dose Chemotherapy.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of previous chemotherapy regimens</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>135 (73.4)</td>
</tr>
<tr>
<td>2</td>
<td>45 (24.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>35 (19.0)</td>
</tr>
<tr>
<td>Nonseminomatous germ-cell tumor</td>
<td>149 (81.0)</td>
</tr>
<tr>
<td>Response to initial chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Complete remission (with or without resection of tumor)</td>
<td>75 (40.8)</td>
</tr>
<tr>
<td>Partial remission (normal hCG and alpha-fetoprotein levels)</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>Other (less than complete remission or partial remission with normal hCG and alpha-fetoprotein levels)</td>
<td>100 (54.3)</td>
</tr>
<tr>
<td>Initial IGCCCG stage</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>71 (38.6)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>38 (20.7)</td>
</tr>
<tr>
<td>High risk</td>
<td>75 (40.8)</td>
</tr>
<tr>
<td>Platinum sensitivity</td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>144 (78.3)</td>
</tr>
<tr>
<td>Refractory</td>
<td>40 (21.7)</td>
</tr>
<tr>
<td>Serum hCG level</td>
<td></td>
</tr>
<tr>
<td>≥1000 IU/liter</td>
<td>22 (12.0)</td>
</tr>
<tr>
<td>&lt;1000 IU/liter</td>
<td>162 (88.0)</td>
</tr>
<tr>
<td>Serum alpha-fetoprotein level</td>
<td></td>
</tr>
<tr>
<td>≥1000 μg/liter</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>&lt;1000 μg/liter</td>
<td>176 (95.7)</td>
</tr>
<tr>
<td>Beyer score†</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>136 (73.9)</td>
</tr>
<tr>
<td>1</td>
<td>24 (13.0)</td>
</tr>
<tr>
<td>2</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>3–4</td>
<td>15 (8.2)</td>
</tr>
</tbody>
</table>

* IGCCCG denotes International Germ Cell Cancer Collaborative Group, and hCG human chorionic gonadotropin. Percentages may not sum to 100 because of rounding.
† A score of 1 point was given for platinum-refractory or absolute platinum-refractory disease, and 2 points were given for each primary mediastinal tumor and for a serum hCG level ≥1000 IU/liter.
follow-up was counted in the group of patients in whom treatment failed.

Table 1 lists characteristics of the patients at the start of high-dose chemotherapy. The median age was 31 years (range, 15 to 58). Patients with a low Eastern Cooperative Oncology Group (ECOG) performance status were not excluded, but most patients had an ECOG performance status of 0 or 1. Thirty-five patients had seminoma only, with no elements of nonseminomatous germ-cell tumor, and the remaining 149 patients had nonseminomatous germ-cell tumors. The Beyer score was used to stratify patients in low-, intermediate-, or high-risk categories. With this scoring system, 1 point was assigned for platinum-refractory or absolute platinum-refractory disease and 2 points were assigned for each primary mediastinal tumor and for a serum hCG level greater than or equal to 1000 IU per liter. Platinum-refractory disease was defined as tumor progression within 4 weeks after the most recent cisplatin-based chemotherapy. Absolute platinum-refractory disease was defined as no response to the initial cisplatin-based chemotherapy.

Eleven patients did not receive the scheduled second course of high-dose chemotherapy; five had progressive disease, and four of these five patients died within 10 months after the initiation of high-dose chemotherapy. The fifth patient has no evidence of disease more than 33 months after two salvage surgeries. Five of the 11 patients did not receive a second course of high-dose chemotherapy because of grade 4 toxic effects (nephrotoxicity in 2, hepatotoxicity in 2, and pulmonary toxicity in 1). Of these five patients, two remained continuously disease-free 65 and 43 months after recovering from the toxic effects of the single course of high-dose chemotherapy. One patient who received a single course had apparently false elevations of serum alpha-fetoprotein levels in the absence of liver disease; he has been disease-free for more than 100 months.

During a median follow-up of 48 months (range, 14 to 118), 116 of 184 patients (63%) were continuously disease-free. Of these 116 patients, 104 (90%) were disease-free for more than 2 years. Six additional patients had complete remission of disease, four after receiving paclitaxel plus gemcitabine and two after undergoing subsequent resection of a germ-cell tumor. Figure 1 shows the Kaplan–Meier estimate of survival.

Table 2 lists prognostic variables for the 184 patients in our study. Variables that were significantly associated with progression-free survival were the use of high-dose chemotherapy as second-line as compared with third-line chemotherapy, response of the tumor to cisplatin (platinum sensitivity), response to initial chemotherapy, favorable prognosis, and favorable International Germ Cell Cancer Collaborative Group (IGCCCG) score. Of the 61 patients who had favorable prognostic features, 49 had disease that was in continuous remission for a median of 46 months (range, 25 to 112). A total of 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110).

To develop the prognostic scoring algorithm with the use of multivariate proportional-hazards regression, we included all individual variables (timing of high-dose chemotherapy, hCG level, platinum sensitivity, response to initial chemotherapy, histologic types, and IGCCCG score) in the branch-and-bound algorithm except for an alpha-fetoprotein level greater than or equal to 1000 μg per liter, since only eight patients had an alpha-fetoprotein level of that elevation. The best three-variable model included timing of high-dose chemotherapy, platinum sensitivity or refractoriness, and IGCCCG score (Table 3). The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points
Table 2. Prognostic Variables in 184 Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Disease-free Survival (N=116)</th>
<th>Death or Survival with Disease (N=68)</th>
<th>P Value†</th>
<th>Hazard Ratio (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line</td>
<td>94/135 (69.6)</td>
<td>41/135 (30.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Third-line or subsequent</td>
<td>22/49 (44.9)</td>
<td>27/49 (55.1)</td>
<td>0.003</td>
<td>2.22 (1.37–3.62)</td>
</tr>
<tr>
<td>Markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG &lt;1000 IU/liter</td>
<td>102/162 (63.0)</td>
<td>60/162 (37.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>hCG ≥1000 IU/liter</td>
<td>14/22 (63.6)</td>
<td>8/22 (36.4)</td>
<td>1.00</td>
<td>1.05 (0.50–2.20)</td>
</tr>
<tr>
<td>Alpha-fetoprotein &lt;1000 μg/liter</td>
<td>113/176 (64.2)</td>
<td>63/176 (35.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein ≥1000 μg/liter</td>
<td>3/8 (37.5)</td>
<td>5/8 (62.5)</td>
<td>0.15</td>
<td>2.40 (0.96–5.99)</td>
</tr>
<tr>
<td>Platinum sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>98/144 (68.1)</td>
<td>46/144 (31.9)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>18/40 (45.0)</td>
<td>22/40 (55.0)</td>
<td>0.01</td>
<td>2.16 (1.30–3.60)</td>
</tr>
<tr>
<td>Response to initial chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission or partial remission with normal serum markers</td>
<td>61/84 (72.6)</td>
<td>23/84 (27.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Less than complete remission or less than partial remission with normal serum markers</td>
<td>55/100 (55.0)</td>
<td>45/100 (45.0)</td>
<td>0.01</td>
<td>1.85 (1.12–3.05)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>26/35 (74.3)</td>
<td>9/35 (25.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Nonseminomatous germ-cell tumor</td>
<td>90/149 (60.4)</td>
<td>59/149 (39.6)</td>
<td>0.17</td>
<td>1.56 (0.77–3.14)</td>
</tr>
<tr>
<td>IGCCCG stage (at start of initial chemotherapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>54/71 (76.1)</td>
<td>17/71 (23.9)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>24/38 (63.2)</td>
<td>14/38 (36.8)</td>
<td>1.62</td>
<td>0.80–3.29</td>
</tr>
<tr>
<td>High risk</td>
<td>38/75 (50.7)</td>
<td>37/75 (49.3)</td>
<td>0.006</td>
<td>2.39 (1.35–4.25)</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable‡</td>
<td>49/61 (80.3)</td>
<td>12/61 (19.7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Unfavorable§</td>
<td>67/123 (54.5)</td>
<td>56/123 (45.5)</td>
<td>&lt;0.001</td>
<td>2.76 (1.48–5.16)</td>
</tr>
<tr>
<td>Beyer score¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90/136 (66.2)</td>
<td>46/136 (33.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>19/33 (57.6)</td>
<td>14/33 (42.4)</td>
<td>1.37</td>
<td>0.75–2.49</td>
</tr>
<tr>
<td>3–4</td>
<td>7/15 (46.7)</td>
<td>8/15 (53.3)</td>
<td>0.25</td>
<td>2.02 (0.95–4.29)</td>
</tr>
</tbody>
</table>

* IGCCCG denotes International Germ Cell Cancer Collaborative Group, and hCG human chorionic gonadotropin. Percentages may not sum to 100 because of rounding.
† P values were calculated with the use of Fisher’s exact test and are for the comparison of the patients with disease-free survival with patients who died or survived with disease.
‡ The hazard ratio for disease progression was calculated with the use of the univariate proportional-hazards regression model.
§ Patients with a favorable prognosis had complete remission or partial remission with normal serum markers and received high-dose chemotherapy as initial salvage therapy.
¶ A score of 1 point was given for platinum-refractory or absolute platinum-refractory disease, and 2 points were given for each primary mediastinal tumor and for a serum hCG level ≥1000 IU/liter.
for third-line chemotherapy, 2 for platinum refractoriness, and 2 for advanced IGCCCG stage. High scores indicated a low probability of disease-free survival. Figure 2 illustrates overall survival according to this scoring algorithm, which stratifies patients according to the level of risk (low, 0 points; intermediate, 2 to 3 points; or high, 4 to 7 points). The results of log-rank tests comparing the disease-free survival curves among the three risk groups were all statistically significant (P<0.05).

The toxic effects of high-dose chemotherapy were primarily myelosuppression, mucositis, nausea, vomiting, dehydration, peripheral neuropathy, and otologic abnormalities.8 There were three sudden drug-related deaths; two were due to hepatic failure, and one was due to pulmonary toxic effects. Table 4 lists the toxic effects that were grade 3 or higher. Acute leukemia developed in three patients 11, 21, and 60 months after high-dose chemotherapy. None of these patients had received maintenance therapy with oral etoposide. All three had been treated with high-dose chemotherapy as third-line or later chemotherapy. Two of these patients died during follow-up; the third remained alive with cancer that was in complete remission after antileukemia therapy plus allogeneic bone marrow transplantation. Two of these three patients have been described previously.21 Glioblastoma multiforme developed in one patient 6 years after high-dose chemotherapy. He had received radiation therapy for brain metastases of the germ-cell tumor at the time of the initial diagnosis.

**DISCUSSION**

Cisplatin-containing combination chemotherapy cures 70% of patients with newly diagnosed metastatic germ-cell tumors. Prognostic factors, based on data from more than 5000 such patients, are well established.4 The factors associated with long-term survival after salvage therapy, however, are less well established.

In 1996, Beyer et al.18 reported a multivariate analysis of factors that can predict cure after high-dose chemotherapy. Adverse prognostic variables in the 283 patients in that study included refractoriness to platinum (progression within 4 weeks after treatment with cisplatin), absolute refractoriness to platinum (no response to initial platinum-based chemotherapy), mediastinal nonseminomatous germ-cell tumor, and a serum hCG level greater than or equal to 1000 IU per liter.

---

**Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.**

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>β Regression Coefficient</th>
<th>Prognostic Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third-line or subsequent chemotherapy</td>
<td>2.19 (1.35–3.56)</td>
<td>0.002</td>
<td>0.78</td>
<td>3</td>
</tr>
<tr>
<td>Platinum-refractory disease</td>
<td>1.74 (1.01–3.00)</td>
<td>0.05</td>
<td>0.55</td>
<td>2</td>
</tr>
<tr>
<td>IGCCCG high-risk stage</td>
<td>1.67 (1.00–2.78)</td>
<td>0.05</td>
<td>0.51</td>
<td>2</td>
</tr>
</tbody>
</table>

* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.
† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.
Gastrointestinal toxic effects included colitis, diarrhea, mucositis, nausea, and vomiting. Hepatic toxic effects included a serum albumin level that was less than 2 g per deciliter; a value for alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase that was >5 to 20 times the upper limit of the normal range (ULN); and a bilirubin level that was >3 to 10 times the ULN. Two patients died from acute hepatic failure that developed after the first course of high-dose chemotherapy. Neurologic toxic effects included sensory alterations, parasthesias, and weakness interfering with daily activity. Pulmonary toxic effects included dyspnea interfering with daily activity and symptomatic hiccups interfering with sleep. The acute respiratory distress syndrome developed in one patient.

The improved results in our series, as compared with the 283 patients in the analysis by Beyer et al., reflect the benefit of high-dose chemotherapy given as second-line rather than third-line chemotherapy and the administration of two consecutive rounds of high-dose chemotherapy with hematopoietic stem-cell rescue. We did not use a third agent such as cyclophosphamide, ifosfamide, or thiotepa, as others have, because adding a third agent requires dose reductions of the two most active drugs, carboplatin and etoposide. Only a randomized study could show whether the addition of a third agent is beneficial.

Some variables were associated with very high rates of continuous disease-free survival. Of 35 patients with a pure seminoma (defined as no other cell types and normal serum alpha-fetoprotein levels) that relapsed after first- or second-line chemotherapy, 26 remained disease-free for a median of 43 months (range, 19 to 118). Sixty-one patients had favorable prognostic features; these features included cancer that was in complete or partial remission and normal serum hCG and alpha-fetoprotein levels. The minimum follow-up was 2 years.

The toxic effects of high-dose chemotherapy are listed in Table 4. Toxic Effects of High-Dose Chemotherapy (Grade 3 or Higher) among 184 Patients.

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic (leukemia)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Renal (serum creatinine, 3–6× ULN)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Gastrointestinal toxic effects included colitis, diarrhea, mucositis, nausea, and vomiting. Hepatic toxic effects included a serum albumin level that was less than 2 g per deciliter; a value for alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase that was >5 to 20 times the upper limit of the normal range (ULN); and a bilirubin level that was >3 to 10 times the ULN. Two patients died from acute hepatic failure that developed after the first course of high-dose chemotherapy. Neurologic toxic effects included sensory alterations, parasthesias, and weakness interfering with daily activity. Pulmonary toxic effects included dyspnea interfering with daily activity and symptomatic hiccups interfering with sleep. The acute respiratory distress syndrome developed in one patient.

A prognostic score based on these variables was developed. Primary mediastinal tumors and an hCG level greater than or equal to 1000 IU per liter were each assigned 2 points, whereas all other variables were each assigned 1 point. For patients with a score of 3 or higher, the rate of disease-free survival at 2 years was only 5%, as compared with 51% for patients with a Beyer score of 0. This scoring system, however, was based on data from patients who were treated between 1984 and 1993; most of these patients had received only a single course of high-dose chemotherapy. A total of 91% of these patients received two or more induction regimens before receiving high-dose chemotherapy.

There are some similarities between the prognostic variables in our study (Table 2) and the Beyer scores, but our list of variables reflects some additions and deletions. Beyer and colleagues assigned 2 points for “absolute refractory disease,” defined as progression with initial cisplatin-based chemotherapy. Forty-three of the 283 patients (15%) in that study were assigned to this category. In our series, only 2 of 184 patients had absolute refractory disease. In the study reported by Beyer et al., serum hCG levels greater than or equal to 1000 IU per liter were assigned 2 points. In our series, there was no difference in disease-free survival on the basis of hCG levels (P = 1.00).

Some variables were associated with very high rates of continuous disease-free survival. Of 35 patients with a pure seminoma (defined as no other cell types and normal serum alpha-fetoprotein levels) that relapsed after first- or second-line chemotherapy, 26 remained disease-free for a median of 43 months (range, 19 to 118). Sixty-one patients had favorable prognostic features; these features included cancer that was in complete or partial remission and normal serum hCG and alpha-fetoprotein levels. The minimum follow-up was 2 years.

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Patients with primary mediastinal nonseminomatous germ-cell tumors were not eligible for high-dose carboplatin plus etoposide during this study. From 1988 to 1996, 13 patients with this tumor received high-dose chemotherapy with bone marrow transplantation. None of them survived disease-free for more than 2 years.

In a recent study, 219 patients in the high-risk group were randomly assigned to receive initial treatment with four courses of bleomycin plus etoposide plus cisplatin or two courses of this initial treatment followed by two courses of high-dose chemotherapy with stem-cell rescue. There was no benefit from the high-dose chemotherapy.
Pico et al. randomly assigned 280 patients to receive salvage chemotherapy with either four courses of vinblastine (or etoposide) plus ifosfamide plus cisplatin or three similar cycles followed by a single course of high-dose carboplatin plus etoposide plus cyclophosphamide. The single cycle of high-dose chemotherapy had no effect on the outcome. To our knowledge, these two studies are the only randomized trials of high-dose chemotherapy in patients with germ-cell tumors, and it is disappointing that they did not show an advantage of such treatment.

There should be little or no debate on the use of high-dose chemotherapy for a patient with a germ-cell tumor that is refractory to platinum-based chemotherapy or that is not cured by a cisplatin–ifosfamide regimen as salvage chemotherapy. In our study, 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110), and 22 of 49 patients who received high-dose chemotherapy as third-line or later therapy remained disease-free for a median of 46 months (range, 25 to 112).

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REFERENCES

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Partial Thrombosis of the False Lumen in Patients with Acute Type B Aortic Dissection

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ABSTRACT

BACKGROUND
Patency or thrombosis of the false lumen in type B acute aortic dissection has been found to predict outcomes. The prognostic implications of partial thrombosis of the false lumen have not yet been elucidated.

METHODS
We examined 201 patients with type B acute aortic dissection who were enrolled in the International Registry of Acute Aortic Dissection between 1996 and 2003 and who survived to hospital discharge. Kaplan–Meier mortality curves were stratified according to the status of the false lumen (patent, partial thrombosis, or complete thrombosis) as determined during the index hospitalization. Cox proportional-hazards analysis was performed to identify independent predictors of death.

RESULTS
During the index hospitalization, 114 patients (56.7%) had a patent false lumen, 68 patients (33.8%) had partial thrombosis of the false lumen, and 19 (9.5%) had complete thrombosis of the false lumen. The mean (±SD) 3-year mortality rate for patients with a patent false lumen was 13.7±7.1%, for those with partial thrombosis was 31.6±12.4%, and for those with complete thrombosis was 22.6±22.6% (median follow-up, 2.8 years; P=0.003 by the log-rank test). Independent predictors of postdischarge mortality were partial thrombosis of the false lumen (relative risk, 2.69; 95% confidence interval [CI], 1.45 to 4.98; P=0.002), a history of aortic aneurysm (relative risk, 2.05; 95% CI, 1.07 to 3.93; P=0.03), and a history of atherosclerosis (relative risk, 1.87; 95% CI, 1.01 to 3.47; P=0.05).

CONCLUSIONS
Mortality is high after discharge from the hospital among patients with type B acute aortic dissection. Partial thrombosis of the false lumen, as compared with complete patency, is a significant independent predictor of postdischarge mortality in these patients.
Acutely Aortic Dissection Is a Dangerous Condition with High In-Hospital and Follow-Up Mortality Rates. Dissections confined to the descending aorta (type B) have better in-hospital survival than those involving the ascending aorta (type A). Up to 89% of patients with uncomplicated type B dissections survive to hospital discharge after receiving effective antihypertensive therapy. However, despite a low in-hospital mortality, the short- and long-term prognosis of patients with type B acute aortic dissection after discharge from the hospital is heterogeneous, with reported survival rates ranging from 56 to 92% at 1 year and from 48 to 82% at 5 years.

Given the variable prognosis of type B acute aortic dissection with current management strategies, predictors of poor outcomes have been sought. In addition to aortic diameter, a reported predictor of outcomes in type B acute aortic dissection has been the patency of the false lumen. Studies have suggested that patients with complete thrombosis of the false lumen have improved outcomes, whereas those with a patent false lumen have an increased risk of aortic expansion and death. To our knowledge, partial thrombosis of the false lumen, defined as the concurrent presence of both flow and thrombus, has not been studied. The purpose of this analysis was to evaluate the incidence of partial thrombosis of the false lumen on cross-sectional imaging and to assess its effect on mortality in patients presenting with type B acute aortic dissection.

Methods

The International Registry of Acute Aortic Dissection (IRAD) is a multinational registry of patients with acute aortic dissection evaluated at 22 aortic centers in 11 countries. The registry is supported by grants and receives no commercial funding. Treatment during the index hospitalization is not standardized but is conducted at the discretion of each patient’s treating physician. Full details of the IRAD structure and the methods used have been previously published.

The registry was approved by the institutional review board or ethics committee at each participating center, and a waiver of informed consent for retrospective chart review was granted for the registry. Individual written informed consent was obtained for the follow-up study.

Study Population

We examined data from all patients with type B acute aortic dissection enrolled in IRAD between January 1, 1996, and December 31, 2003. Type B acute aortic dissection was defined as any nontraumatic dissection not involving the ascending aorta and presenting within 14 days of symptom onset. Patients were identified prospectively at presentation or retrospectively from discharge diagnoses and from imaging and surgical databases. Diagnosis was based on confirmatory imaging, intraoperative visualization, or autopsy.

Of the 532 patients enrolled in IRAD with type B acute aortic dissection, 466 were discharged from the hospital alive. Postdischarge mortality data were available for 342 patients. Of these, 141 were excluded from our study, including 64 with a diagnosis of intramural hematoma, 46 for whom imaging data on the false lumen were lacking, and 31 for whom consensus on the status of the false lumen on imaging was lacking. The distinction between an intramural hematoma and a true dissection with complete thrombosis of the false lumen was made by experts at local IRAD centers. Patients were considered to have an intramural hematoma if the hematoma extended outward from the lumen in a crescent shape and maintained a constant circumferential relationship with the aortic wall without a demonstrable intimal flap and with no radiologically apparent intimal tear. Our final study population included 201 patients (38% of those enrolled in the registry).

Data Collection

A standardized form was used to record clinical variables, including information on patient demographics and history, clinical presentation, physical findings, imaging results, medical and surgical treatment, and outcomes, including mortality. The data forms were forwarded to the IRAD coordinating center at the University of Michigan, reviewed for internal consistency and face validity, and then scanned electronically into a Microsoft Access database.

The imaging results were interpreted at each patient’s respective tertiary care center by experienced radiologists and echocardiographers and were entered on the data form. Each patient underwent spiral computed tomography, transesophageal echocardiography, magnetic resonance imaging, or a combination of these procedures.
The status of the false lumen on imaging was classified as patent if flow was present in the absence of thrombus, as partially thrombosed if both flow and thrombus were present, or as completely thrombosed if no flow was present.

Yearly follow-up data were obtained with the use of standardized forms after the patient was discharged. We obtained clinical and imaging data as well as information about mortality, with the date of death when known. When applicable, missing data on mortality were obtained from the Social Security Death Index.

**Statistical Analysis**

Three comparison groups were created on the basis of the status of the false lumen: patent, partial thrombosis, or complete thrombosis. The clinical characteristics of each of the three groups were presented as frequencies and percentages for categorical variables and as means ±SD for continuous variables. Univariate differences among the three groups were compared by the chi-square test for categorical variables and by analysis of variance for continuous variables.

Univariate associations between all clinical variables, including false-lumen status, and post-discharge mortality were calculated by Cox regression analysis. No imputation of missing variables was performed. Stepwise Cox proportional-hazards analysis was performed to identify independent predictors of postdischarge mortality. The initial modeling used variables marginally suggestive of an unadjusted association with mortality (P<0.20). Variables were reviewed for clinical significance before testing. Forward-ascending stepwise selection of variables after adjustment for age, sex, and in-hospital treatment (medical, surgical, or endovascular) was performed sequentially, with a default value for inclusion set at P<0.05. SAS software, version 8.2, was used for all analyses.

**Results**

**Baseline and Imaging Characteristics**

The mean age (±SD) of the 201 patients examined in this analysis was 60.8±13.9 years (Table 1). The majority of patients (69.1%) were male, 28.4% were 70 years of age or older, and 77.0% had a history of hypertension. Other coexisting conditions, such as atherosclerosis (29.8%), prior aortic aneurysm (21.0%), and prior aortic dissection (11.7%), were not uncommon. In comparison with the study population, patients in the IRAD database who were not included in the analysis were older (65.9±12.6 years), more likely to have a history of atherosclerosis (39.7%), and less likely to have had a previous aortic dissection (5.4%).

In more than 90% of patients, the diagnosis of type B acute aortic dissection was confirmed by cross-sectional imaging within 1 day of presentation. The remaining cases were diagnosed within 7 days. On cross-sectional imaging, the false lumen was found to be patent in 114 patients (56.7%), partially thrombosed in 68 (33.8%), and completely thrombosed in 19 (9.5%) (Table 1). The mean number of imaging studies performed per patient was 1.5; the most frequent procedure was computed tomography, which was performed in three quarters of the patients. There were no significant differences in the frequency of performance of different imaging procedures between patients with patent, partially thrombosed, and completely thrombosed false lumens.

**Clinical Features Associated with Status of the False Lumen**

Patients with complete thrombosis of the false lumen were significantly older than those in the other two false-lumen groups, with a mean age of 70.9±12.1 years, versus 57.6±13.5 years in patients with a patent false lumen and 63.3±13.5 years in patients with partial thrombosis of the false lumen (P<0.001). There were no significant differences among the three groups in symptoms or physical findings at presentation (Table 1). With regard to diagnostic testing, patients with complete thrombosis of the false lumen were more likely to have abnormal electrocardiograms and pleural effusions on chest radiography than patients with a patent or partially thrombosed false lumen.

**In-hospital Treatment and Outcomes**

All patients initially received medical therapy to regulate systolic blood pressure and the velocity of left ventricular ejection (change in pressure+ change in time [dP/dt]). One hundred forty-six patients (72.6%) received medical therapy only, 36 (17.9%) underwent surgery, and 19 (9.5%) had endovascular treatment, defined as stent placement, fenestration, or both (Table 1). There were
Table 1. Characteristics of Patients Stratified According to the Status of the False Lumen.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=201)</th>
<th>Status of the False Lumen</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patent (N=114)</td>
<td>Partial Thrombosis (N=68)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>60.8±13.9</td>
<td>57.6±13.5</td>
<td>63.3±13.5</td>
</tr>
<tr>
<td>Age ≥70 yr — no. (%)</td>
<td>57 (28.4)</td>
<td>23 (20.2)</td>
<td>22 (32.4)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>62 (30.8)</td>
<td>30 (26.3)</td>
<td>25 (36.8)</td>
</tr>
<tr>
<td>White race — no./total no. (%)†</td>
<td>159/188 (84.6)</td>
<td>95/109 (87.2)</td>
<td>50/62 (80.6)</td>
</tr>
<tr>
<td>Marfan’s syndrome — no./total no. (%)</td>
<td>11/199 (5.5)</td>
<td>8/113 (7.1)</td>
<td>3/68 (4.4)</td>
</tr>
<tr>
<td>Hypertension — no./total no. (%)</td>
<td>154/200 (77.0)</td>
<td>85/113 (75.2)</td>
<td>52/68 (76.5)</td>
</tr>
<tr>
<td>Atherosclerosis — no./total no. (%)‡</td>
<td>59/198 (29.8)</td>
<td>26/112 (23.2)</td>
<td>25/68 (36.8)</td>
</tr>
<tr>
<td>Previous aortic dissection — no./total no. (%)</td>
<td>23/197 (11.7)</td>
<td>17/111 (15.3)</td>
<td>5/68 (7.4)</td>
</tr>
<tr>
<td>Previous aortic aneurysm — no./total no. (%)§</td>
<td>41/195 (21.0)</td>
<td>21/108 (19.4)</td>
<td>16/68 (23.5)</td>
</tr>
<tr>
<td>Diabetes — no./total no. (%)</td>
<td>13/197 (6.6)</td>
<td>6/111 (5.4)</td>
<td>4/68 (5.9)</td>
</tr>
<tr>
<td>Previous cardiovascular surgery — no./total no. (%)</td>
<td>38/191 (19.9)</td>
<td>24/106 (22.6)</td>
<td>10/68 (14.7)</td>
</tr>
</tbody>
</table>

**Clinical presentation**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Patent (N=114)</th>
<th>Partial Thrombosis (N=68)</th>
<th>Complete Thrombosis (N=19)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain — no./total no. (%)</td>
<td>137/198 (69.2)</td>
<td>79/113 (69.9)</td>
<td>48/68 (70.6)</td>
<td>10/17 (58.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Back pain — no./total no. (%)</td>
<td>136/196 (69.4)</td>
<td>75/111 (67.6)</td>
<td>49/67 (73.1)</td>
<td>12/18 (66.7)</td>
<td>0.71</td>
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<tr>
<td>Abrupt onset of pain — no./total no. (%)</td>
<td>167/193 (86.5)</td>
<td>100/111 (90.1)</td>
<td>53/65 (81.5)</td>
<td>14/17 (82.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Migrating pain — no./total no. (%)</td>
<td>38/188 (20.2)</td>
<td>24/109 (22.0)</td>
<td>12/64 (18.8)</td>
<td>2/15 (13.3)</td>
<td>0.69</td>
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<tr>
<td>Any neurologic deficit — no. (%)</td>
<td>19 (9.5)</td>
<td>11 (9.7)</td>
<td>5 (7.4)</td>
<td>3 (15.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>170.8±36.3</td>
<td>169.9±37.1</td>
<td>174.5±36.4</td>
<td>162.4±30.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic blood pressure — mm Hg</td>
<td>94.8±20.7</td>
<td>94.7±20.9</td>
<td>96.8±20.7</td>
<td>87.8±19.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypotension or shock — no./total no. (%)</td>
<td>4/194 (2.1)</td>
<td>2/111 (1.8)</td>
<td>1/65 (1.5)</td>
<td>1/18 (5.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension — no./total no. (%)</td>
<td>144/196 (73.5)</td>
<td>78/112 (69.6)</td>
<td>52/66 (78.8)</td>
<td>14/18 (77.8)</td>
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<tr>
<td>Any pulse deficit — no./total no. (%)</td>
<td>37/185 (20.0)</td>
<td>21/105 (20.0)</td>
<td>13/63 (20.6)</td>
<td>3/17 (17.6)</td>
<td>0.96</td>
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**Diagnostic imaging**

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<th>Partial Thrombosis (N=68)</th>
<th>Complete Thrombosis (N=19)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph — no./total no. (%)</td>
<td>33/188 (17.6)</td>
<td>19/106 (17.9)</td>
<td>12/66 (18.2)</td>
<td>2/16 (12.5)</td>
<td>0.86</td>
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<tr>
<td>Widened mediastinum</td>
<td>85/184 (46.2)</td>
<td>43/104 (41.3)</td>
<td>33/64 (51.6)</td>
<td>9/16 (56.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Abnormal aortic contour</td>
<td>93/182 (51.1)</td>
<td>49/104 (47.1)</td>
<td>34/63 (54.0)</td>
<td>10/15 (66.7)</td>
<td>0.31</td>
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<tr>
<td>Pleural effusion</td>
<td>25/181 (13.8)</td>
<td>15/103 (14.6)</td>
<td>5/64 (7.8)</td>
<td>5/14 (35.7)</td>
<td>0.02</td>
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<tr>
<td>Electrocardiogram — no./total no. (%)</td>
<td></td>
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<tr>
<td>Abnormal</td>
<td>135/195 (69.2)</td>
<td>68/111 (61.3)</td>
<td>50/67 (74.6)</td>
<td>17/17 (100.0)</td>
<td>0.003</td>
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<tr>
<td>Old Q wave</td>
<td>14/179 (7.8)</td>
<td>6/101 (5.9)</td>
<td>6/63 (9.5)</td>
<td>2/15 (13.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>New Q wave, ST elevations, or ischemia</td>
<td>23/185 (12.4)</td>
<td>11/103 (10.7)</td>
<td>10/65 (15.4)</td>
<td>2/17 (11.8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Nonspecific ST or T wave changes</td>
<td>73/186 (39.2)</td>
<td>33/105 (31.4)</td>
<td>29/64 (45.3)</td>
<td>11/17 (64.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of studies performed per patient</td>
<td>1.5±0.7</td>
<td>1.5±0.6</td>
<td>1.5±0.8</td>
<td>1.4±0.7</td>
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<td>Computed tomography — no. (%)</td>
<td>151 (75.1)</td>
<td>85 (74.6)</td>
<td>49 (72.1)</td>
<td>17 (89.5)</td>
<td>0.29</td>
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<td>Transesophageal echocardiography — no. (%)</td>
<td>78 (38.8)</td>
<td>44 (38.6)</td>
<td>27 (39.7)</td>
<td>7 (36.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Magnetic resonance imaging — no. (%)</td>
<td>37 (18.4)</td>
<td>18 (15.8)</td>
<td>16 (23.5)</td>
<td>3 (15.8)</td>
<td>0.41</td>
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<tr>
<td>Widest diameter of descending aorta — cm</td>
<td>4.5±1.2</td>
<td>4.5±1.2</td>
<td>4.7±1.1</td>
<td>4.1±0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Widest diameter of ascending aorta ≥6 cm — no./total no. (%)</td>
<td>4/115 (3.5)</td>
<td>1/66 (1.5)</td>
<td>2/38 (5.3)</td>
<td>1/11 (9.1)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Treatment**

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<tbody>
<tr>
<td>Surgical — no. (%)</td>
<td>36 (17.9)</td>
<td>24 (21.1)</td>
<td>9 (13.2)</td>
<td>3 (15.8)</td>
<td>0.37†</td>
</tr>
<tr>
<td>Endovascular — no. (%)</td>
<td>19 (9.5)</td>
<td>11 (9.6)</td>
<td>8 (11.8)</td>
<td>0</td>
<td>0.37†</td>
</tr>
<tr>
<td>Medical only — no. (%)</td>
<td>146 (72.6)</td>
<td>79 (69.3)</td>
<td>51 (75.0)</td>
<td>16 (84.2)</td>
<td>0.37†</td>
</tr>
</tbody>
</table>

**In-hospital complications**

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</thead>
<tbody>
<tr>
<td>Neurologic deficit — no./total no. (%)</td>
<td>20/179 (11.2)</td>
<td>15/101 (14.9)</td>
<td>3/63 (4.8)</td>
<td>2/15 (13.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypotension — no./total no. (%)</td>
<td>12/184 (6.5)</td>
<td>5/107 (4.7)</td>
<td>6/61 (9.8)</td>
<td>1/16 (6.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Malperfusion — no./total no. (%)</td>
<td>45/98 (45.9)</td>
<td>30/58 (51.7)</td>
<td>14/33 (42.4)</td>
<td>1/7 (14.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mesenteric ischemia — no./total no. (%)</td>
<td>13/183 (7.1)</td>
<td>9/103 (8.7)</td>
<td>4/59 (6.8)</td>
<td>0/16</td>
<td>0.48</td>
</tr>
<tr>
<td>Acute renal failure — no./total no. (%)</td>
<td>29/184 (15.8)</td>
<td>18/107 (16.8)</td>
<td>10/61 (16.4)</td>
<td>1/16 (6.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Limb ischemia — no./total no. (%)</td>
<td>17/182 (9.3)</td>
<td>13/108 (12.0)</td>
<td>4/59 (6.8)</td>
<td>0/15</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Race was determined by the investigator.
‡ Atherosclerosis includes coronary, peripheral, and cerebrovascular disease.
§ Aortic aneurysm includes thoracic and abdominal aneurysm.
¶ The P value is for the comparison among surgical, endovascular, and medical management.
‖ Endovascular treatment includes fenestration and stent placement.
no significant differences among the three false-lumen groups with regard to choice of therapy or rates of specific in-hospital complications. The median follow-up for the 201 patients examined in this analysis was 2.8 years. Figure 1 shows the Kaplan–Meier mortality curves stratified according to false-lumen status. The mortality rate was highest in patients with partial thrombosis of the false lumen, with 1- and 3-year mortality rates of 15.4±8.8% and 31.6±12.4%, respectively, versus 5.4±4.2% and 13.7±7.1% in patients with a patent false lumen and 0% and 22.6±22.6% in patients with complete thrombosis of the false lumen. Separate log-rank testing revealed a significant increase in mortality in patients with partial thrombosis of the false lumen as compared with patients with a completely patent false lumen (P<0.001). Log-rank testing did not reveal significant differences between patients with complete thrombosis of the false lumen and those with a completely patent false lumen (P=0.17) or with partial thrombosis of the false lumen (P=0.41).

In a further analysis, we included patients with intramural hematoma in the group classified as having complete thrombosis of the false lumen. The number of patients in this group was increased to 41, and the 1- and 3-year mortality rates were increased to 5.6±7.5% and 32.4±19.2%, respectively. However, the difference between the mortality curves according to the log-rank test did not change significantly.

**Predictors of Postdischarge Mortality**

Candidate univariate predictors of postdischarge mortality are shown in Table 2. Patients with type B acute aortic dissection who died during the follow-up period were significantly older and significantly more likely to have a history of aortic aneurysm or atherosclerosis. In addition, they were more likely to have pleural effusions on chest radiography. Independent predictors of mortality are shown in Table 3. After adjustment for age, sex, and in-hospital treatment, the key predictors of mortality were partial thrombosis of the false lumen versus a patent false lumen, a history of aortic aneurysm, and a history of atherosclerosis.

We also assessed the potential effect of surgical or endovascular therapy (both of which tended to be performed independently of false-lumen status) on the relationship between false-lumen status and survival. Thirty-six patients underwent surgery and 19 received endovascular therapy; among the remaining 146 patients, the relative risk of partial thrombosis of the false lumen remained a significant independent predictor of postdischarge mortality (relative risk, 4.01; 95% confidence interval, 1.87 to 8.64; P<0.001).
In this large cohort of patients with type B acute aortic dissection, mortality was high after discharge from the hospital, with nearly one in four patients (24.9%) dying within 3 years. Partial thrombosis of the false lumen was common (present in a third of patients) and was the strongest independent predictor of postdischarge mortality that we identified: the risk of death in these patients was increased by a factor of 2.7 in comparison with patients with a patent false lumen. Previous small observational studies have suggested a lower risk of adverse events and better outcomes in patients with complete thrombosis of the false lumen than in those with a patent false lumen. These studies have linked patency of the false lumen to adverse events resulting from aneurysmal dilatation and rupture during the chronic phase. In our study, partial thrombosis of the false lumen was defined as the concurrent presence of both flow and thrombus in the false lumen; this condition was not considered a distinct physiological state in most previous studies and has not been previously associated with increased mortality.

In our study, complete thrombosis of the false lumen occurred in a small number of patients who were, on average, 13 years older than patients with a completely patent false lumen, a finding similar to that of previous studies. Since only 19 patients (9.5%) were classified as
Table 3. Independent Predictors of Death after Adjustment with the Use of Multivariate Models. a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥70 yr</td>
<td>1.42 (0.74–2.74)</td>
<td>0.29</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.16 (0.62–2.17)</td>
<td>0.64</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>1.33 (0.49–3.58)</td>
<td>0.57</td>
</tr>
<tr>
<td>Endovascular treatment†</td>
<td>1.38 (0.64–3.01)</td>
<td>0.41</td>
</tr>
<tr>
<td>Previous aortic aneurysm‡</td>
<td>2.05 (1.07–3.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atherosclerosis§</td>
<td>1.87 (1.01–3.47)</td>
<td>0.05</td>
</tr>
<tr>
<td>Patent false lumen¶</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Partial thrombosis of the false lumen</td>
<td>2.69 (1.45–4.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Complete thrombosis of the false lumen</td>
<td>1.02 (0.32–3.22)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CI denotes confidence interval.  
† Endovascular treatment includes fenestration and stent placement.  
‡ Aortic aneurysm includes thoracic and abdominal aneurysm.  
§ Atherosclerosis includes coronary, peripheral, and cerebrovascular disease.  
¶ Patent false lumen is the reference group.

having complete thrombosis of the false lumen, comparisons with this group lack statistical power. We did not find a significant difference in mortality between patients with complete thrombosis of the false lumen and patients with a completely patent false lumen. The small number of cases has also impaired the ability to draw conclusions about this group in other studies of type B acute aortic dissection. Only one previous study found that complete thrombosis of the false lumen was a predictor of less aortic enlargement; another study found that dissection-related mortality was lower among patients with complete thrombosis of the false lumen.

Determination of the mechanism by which partial thrombosis of the false lumen portends a poor outcome is beyond the scope of this observational study. However, two possible contributing factors deserve mention. One potential explanation relates the pressure within the false lumen to the presence of partial thrombosis. Whereas a patent false lumen may be perfused by a proximal entry tear and decompressed through distal reentry tears (Fig. 2A), formation of a partial thrombus may occlude these distal tears, impeding outflow and, in the most extreme situation (Fig. 2B), resulting in a blind sac. Studies have shown that pulsatile inflow into a lumen with impaired outflow may lead to a significant increase in the mean arterial and diastolic pressure as compared with that in a lumen with adequate outflow, despite similar systolic pressure.

An increase in pressure within the false lumen will increase wall tension, which may elevate the risk of aneurysm expansion, redissection, and rupture and would thus explain the increased mortality seen in these patients. Complete thrombosis of the false lumen (Fig. 2C) excludes the false lumen from the circulation and is thought to be a prerequisite for complete healing. This is the principle on which endovascular stent therapy is based.

Partial thrombosis may also have a role in the rupture of the false lumen similar to its role in the rupture of abdominal aortic aneurysms. Previous studies have suggested a direct relationship between intraluminal thrombosis and the risk of rupture of an abdominal aortic aneurysm as a result of hypoxia of the arterial wall adjacent to the intraluminal thrombus, which leads to increased local inflammation, neovascularization, and localized wall weakening. This mechanism may be even more pertinent to the false lumen of a dissected aorta, since in this setting the residual outer layers of the aortic wall already have diminished strength. In addition to partial thrombosis of the false lumen, independent predictors of mortality in our study included a history of atherosclerosis and a history of aortic aneurysm. Atherosclerosis has been previously linked to mortality in patients recovering from type B acute aortic dissection. Pathological studies have suggested that the wall of an aeurysmal aortic segment has decreased collagen synthesis, reduced elastin content, and a thinner wall as part of a systemic problem throughout the peripheral vasculature. These biophysical properties of the aorta predispose the entire aorta and its branches to dissection, further aneurysm formation, or rupture in the future and may contribute to the increased mortality in this group.

As with all observational studies, this investigation has limitations that must be kept in mind when the data are interpreted. First, our cohort consists of patients who were treated at aortic specialty centers and for whom imaging data on false-lumen status as well as follow-up vital statistics were available. As a result, these findings do not represent the entire cohort of the IRAD or patients followed at community hospitals. Second, the mortality data available to us did not include

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information on the cause of death. We were therefore unable to evaluate cause-specific mortality or other end points, such as freedom from reoperation, rupture, or redissection, which would be necessary to give more plausibility to our mechanistic hemodynamic theories. However, previous studies have shown that the majority of deaths in such patients are related to catastrophes of the aorta.\textsuperscript{2-4,9}

Third, imaging techniques were not standardized among centers, and imaging data were collected before our study was designed and were
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not subsequently reevaluated. Thus, misclassification of false-lumen status is possible. Follow-up mortality was recorded independently of the designation of false-lumen status on the in-hospital data forms, thereby minimizing any systematic misclassification bias.

Fourth, false-lumen status was determined once during the hospitalization and does not reflect false-lumen status during the follow-up period. In small studies, false-lumen status changed in a minority of patients (18 to 25%) over 10 to 15 months and was not studied in the acute period. Therefore, we believe the likelihood of a change in false-lumen status is low in the early window of interest. However, surgery or endovascular therapy used in a complication-specific approach may alter the status of the false lumen before discharge. We therefore performed a separate analysis confined to patients receiving only medical treatment to demonstrate that the effect of false-lumen status on survival remains significant in this subgroup.

Fifth, although intramural hematoma was strictly defined in the IRAD, the true ability of cross-sectional imaging to distinguish between intramural hematoma and a completely thrombosed false lumen in an acute dissection is largely unknown because of the absence of a gold standard. Moreover, only pathoanatomic studies would be capable of determining whether an intimal tear was present. We therefore reanalyzed the data, including patients with intramural hematoma in the group classified as having complete thrombosis of the false lumen. In this analysis, the differences between mortality curves did not change significantly.

In summary, we analyzed data from the IRAD to evaluate the prognosis in patients with type B acute aortic dissection who survive their initial hospitalization. Mortality is high after discharge from the hospital, with nearly one in four patients dying within 3 years. In patients with partial thrombosis of the false lumen, the risk of death is increased by a factor of 2.7 in comparison with patients with a completely patent false lumen.

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We thank Daniel G. Montgomery, B.S., for his work on an earlier version of Figure 2.

Appendix

The investigators for the International Registry of Acute Aortic Dissection are as follows: Coprincipal investigators: K.A. Eagle, University of Michigan, Ann Arbor; E.M. Isselbacher, Massachusetts General Hospital, Boston; C.A. Nienaber, University of Rostock, Rostock, Germany. Coinvestigators: E. Bossone, National Research Council, Lecce, Italy; A. Evangelista, Hospital General Universitari Vall d’Hebron, Barcelona; R. Fattori, University Hospital S. Orsola, Bologna, Italy; J. Froehlich, University of Michigan, Ann Arbor; D. Gilon, Hadassah University Hospital, Jerusalem, Israel; S. Hutchison, St. Michael’s Hospital, Toronto; J.L. Januzzi, Jr., Massachusetts General Hospital, Boston; A. Llovet, Hospital Universitario 12 de Octubre, Madrid; D. Mukherjee, University of Kentucky, Lexington; T. Myrmel, Tromsø University Hospital, Tromsø, Norway; P. O’Gara and J. Beckman, Brigham and Women’s Hospital, Boston; J.K. Oh, Mayo Clinic, Rochester, MN; L.A. Pape, University of Massachusetts Hospital, Worcester; U. Sechtem and G. Meinhardt, Robert-Bosch Krankenhaus, Stuttgart, Germany; T. Suzuki, University of Tokyo, Tokyo; S. Trimarchi, Policlinico San Donato, San Donato, Italy. Data management and biostatistical support: J.V. Cooper and D.E. Smith, University of Michigan, Ann Arbor.

References

Partial Thrombosis of the False Lumen in Type B Aortic Dissection

Rofecoxib and Cardiovascular Adverse Events in Adjuvant Treatment of Colorectal Cancer

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*A Members of the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) Trial Group are listed in the Appendix.

ABSTRACT

BACKGROUND

Selective cyclooxygenase inhibitors may retard the progression of cancer, but they have enhanced thrombotic potential. We report on cardiovascular adverse events in patients receiving rofecoxib to reduce rates of recurrence of colorectal cancer.

METHODS

All serious adverse events that were cardiovascular thrombotic events were reviewed in 2434 patients with stage II or III colorectal cancer participating in a randomized, placebo-controlled trial of rofecoxib, 25 mg daily, started after potentially curative tumor resection and chemotherapy or radiotherapy as indicated. The trial was terminated prematurely owing to worldwide withdrawal of rofecoxib. To examine possible persistent risks, we examined cardiovascular thrombotic events reported up to 24 months after the trial was closed.

RESULTS

The median duration of active treatment was 7.4 months. The 1167 patients receiving rofecoxib and the 1160 patients receiving placebo were well matched, with a median follow-up period of 33.0 months (interquartile range, 27.6 to 40.1) and 33.4 months (27.7 to 40.4), respectively. Of the 23 confirmed cardiovascular thrombotic events, 16 occurred in the rofecoxib group during or within 14 days after the treatment period, with an estimated relative risk of 2.66 (from the Cox proportional-hazards model; 95% confidence interval [CI], 1.03 to 6.86; P = 0.04). Analysis of the Antiplatelet Trialists’ Collaboration end point (the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; of nonfatal myocardial infarction and chemotherapy or radiotherapy as indicated. The trial was terminated prematurely owing to worldwide withdrawal of rofecoxib. To examine possible persistent risks, we examined cardiovascular thrombotic events reported up to 24 months after the trial was closed.

RESULTS

The median duration of active treatment was 7.4 months. The 1167 patients receiving rofecoxib and the 1160 patients receiving placebo were well matched, with a median follow-up period of 33.0 months (interquartile range, 27.6 to 40.1) and 33.4 months (27.7 to 40.4), respectively. Of the 23 confirmed cardiovascular thrombotic events, 16 occurred in the rofecoxib group during or within 14 days after the treatment period, with an estimated relative risk of 2.66 (from the Cox proportional-hazards model; 95% confidence interval [CI], 1.03 to 6.86; P = 0.04). Analysis of the Antiplatelet Trialists’ Collaboration end point (the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; of nonfatal myocardial infarction and of nonfatal ischemic and hemorrhagic stroke) gave an unadjusted relative risk of 1.60 (95% CI, 0.57 to 4.51; P = 0.37). Fourteen more cardiovascular thrombotic events, six in the rofecoxib group, were reported within the 2 years after trial closure, with an overall unadjusted relative risk of 1.50 (95% CI, 0.76 to 2.94; P = 0.24). Four patients in the rofecoxib group and two in the placebo group died from thrombotic causes during or within 14 days after the treatment period, and during the follow-up period, one patient in the rofecoxib group and five patients in the placebo group died from cardiovascular causes.

CONCLUSIONS

Rofecoxib therapy was associated with an increased frequency of adverse cardiovascular events among patients with a median study treatment of 7.4 months’ duration. (Current Controlled Trials number, ISRCTN98278138.)
Approximately half of all patients undergoing potentially curative surgery for colorectal cancer ultimately have a relapse and die of metastatic disease. This has led to the introduction of cytotoxic adjuvant therapy, the benefits of which are relatively small (5 to 10% improvement in the 5-year survival rate).

A range of laboratory investigations suggest that cyclooxygenase-2 (COX-2) plays an important role in colorectal carcinogenesis during the transition from adenoma to carcinoma and subsequently during invasion and metastasis. Epidemiologic studies have indicated that the incidence of colorectal cancer is reduced by 30 to 70% in subjects taking nonsteroidal antiinflammatory drugs (NSAIDs). It has been hypothesized that the antineoplastic effects of NSAIDs are mediated by the inhibition of COX-2, and the gastrointestinal side effects of NSAIDs by the inhibition of COX-1, suggesting that any anticancer intervention involving selective COX-2 inhibitors, as compared with traditional NSAIDs, would reduce the risks of complications from peptic ulcer.

Rofecoxib (Vioxx, Merck), a potent inhibitor of COX-2, was hypothesized to reduce rates of tumor recurrence in our randomized, placebo-controlled trial — the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) trial — of patients who had undergone potentially curative surgery for colorectal cancer. Recruitment for the VICTOR trial stopped in September 2004, when Merck withdrew the drug worldwide after a significant increase in confirmed cardiovascular thrombotic events was noted in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial. An excess of vascular events was then found in the Adenoma Prevention with Celecoxib (APC) polyph-prevention trial of celecoxib. Evidence from well-designed, randomized trials, and their meta-analysis, provides support for a moderate increase in vascular event rates associated with the use of COX-2 inhibitors, but there is less clarity about the duration of drug exposure that is responsible for the risk and whether it is equivalent in patients with and in those without established cancer, for whom the potential for benefit from reduced cancer progression may be large. In our study, we compared rates of cardiovascular thrombotic events and death during the period of study treatment and for 2 years after trial closure.

**METHODS**

**PATIENTS**

Patients were randomly assigned to receive rofecoxib or placebo at 151 hospitals in the United Kingdom. Inclusion criteria were as follows: histologically proven colorectal carcinoma of stage III (any tumor stage, N1 or 2, and M0) or stage II (T3 or 4, N0, and M0) in patients who had undergone complete resection of the primary tumor without gross or microscopic evidence of residual disease; World Health Organization performance status 0 or 1; and hematologic and biochemical function within the normal range. In addition, all patients had to have completed their potentially curative therapy (surgery alone or surgery plus radiotherapy, chemotherapy, or both) 12 or fewer weeks previously and had to have given written informed consent. Patients with active peptic ulceration or gastrointestinal bleeding in the past year, a history of adverse reactions to NSAIDs, or a known sensitivity to rofecoxib were excluded, as were those receiving long-term NSAID therapy (except for low-dose aspirin, ≤100 mg per day), those younger than 18 years, and women who were pregnant, lactating, or premenopausal but not using contraception. Patients with a history of cancer (other than adequately treated in situ carcinoma of the cervix or basal or squamous-cell carcinoma), inflammatory bowel disease, or severe congestive heart failure were also excluded.

**TRIAL DESIGN**

We planned to randomly assign the use of rofecoxib (one 25-mg tablet daily) or placebo to 7000 patients, with half of each group receiving the study drug for 2 years and the other for 5 years, effectively a four-group design. Local investigators randomly assigned patients through the VICTOR Trial Office, and each patient was assigned to a study drug in a double-blind fashion. The VICTOR Trial Office supplied rofecoxib and placebo to participating hospitals every 6 months.

**PROTOCOL MODIFICATIONS**

Data-collection forms were amended in January 2004 (22 months into the trial) to solicit baseline data on cardiovascular risk factors, both for newly recruited patients and for patients already entered (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).
Information sheets were amended twice to reflect evolving data on the possible adverse cardiovascular effects of rofecoxib. After the worldwide withdrawal of rofecoxib, all investigators and patients were informed, all study treatment was stopped, and follow-up was initiated.

**CARDIOVASCULAR EVENTS**

Blinded systematic review of all reported serious adverse events that were potentially cardiovascular thrombotic events and that were reported during treatment or within 14 days after the treatment period — the primary cardiovascular event end point — was conducted by an independent, expert physician panel selected from academic centers in the United States and Europe by Merck (Table 1 in the Supplementary Appendix). The use of published reporting systems and adjudication by this previously assembled review panel allowed for consistency of adverse-event reporting across the placebo-controlled rofecoxib trials (VICTOR, APPROVe, and Vioxx in Prostate Cancer [VIP]), permitting a patient-level meta-analysis. Thrombotic events were defined as fatal and nonfatal myocardial infarction, unstable angina, sudden death from cardiac causes, fatal and nonfatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism. Also analyzed were serious adverse events meeting the Antiplatelet Trialists’ Collaboration (APTC) criteria: the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; of nonfatal myocardial infarction; and of nonfatal ischemic and hemorrhagic stroke. To avoid the possibility that censoring cardiovascular-event data 14 days after drug discontinuation, which was the approach used in the APPROVe trial, might distort the outcome data by ruling out later toxicity, further analysis was performed on all cardiovascular events that occurred during the treatment period or within 24 months after trial closure. These events were adjudicated by two of the authors. All patients who consented to inclusion in the study were registered centrally, and death certificates were automatically forwarded to the VICTOR Trial Office.

**ETHICS AND INDEMNITY**

Our study was designed by the investigators, and the protocol was peer reviewed and endorsed by the Clinical Trials Committee of the Cancer Research Campaign, the West Midlands Multicenter Research Ethics Committee, and local research ethics committees at participating centers. The trial was supported by an unrestricted grant from Merck, which also provided the rofecoxib and matching placebo and stood to provide indemnity but otherwise had no input into data accrual or data analysis or control over manuscript preparation. The randomization, data collection, monitoring, and follow-up were coordinated by the VICTOR Trial Office (initially located at the University of Birmingham and then relocated to the University of Oxford). Study data were analyzed by three of the authors at the Statistical Centre, University of Warwick, with an agreement to provide Merck with reports of serious adverse events that occurred after randomization and within 14 days after the end of the treatment period, as well as with a copy of the trial database at prespecified analysis points. An independent data and safety monitoring committee was appointed. Pharmacovigilance reports were reviewed by the Medicines and Healthcare Products Regulatory Agency (the U.K. regulatory authority) and by the West Midlands Multicenter Research Ethics Committee. All authors contributed to the writing of the manuscript, and the VICTOR Trial Office vouches for the accuracy and completeness of the data and analysis.

**STATISTICAL ANALYSIS**

Although our trial was not designed to analyze cardiovascular data, it had a statistical power of 90% to detect an increase by a factor of 2 in the overall risk of cardiovascular events, from 0.5 to 1%, in patients taking rofecoxib for up to 2 years. The statistical power was insufficient for comparisons of risk according to duration of study treatment.

Kaplan–Meier curves were used to assess the time from the start of study treatment to the time of reporting of confirmed cardiovascular events (serious adverse events that were cardiovascular thrombotic events or Antiplatelet Trialists’ Collaboration end points). Relative risks for confirmed cardiovascular events in the rofecoxib group, as compared with the placebo group, were calculated with the use of Cox proportional-hazards regression analysis, with study treatment as a factor. Relative risks were also adjusted according to age, use or nonuse of adjuvant chemotherapy, and presence or absence of cardiovascu-
lar risk factors at baseline. All reported P values are two-sided, and P values less than 0.05 were considered to indicate statistical significance.

**RESULTS**

Between April 2002 and September 2004, a total of 2434 patients were recruited at 151 hospitals in the United Kingdom. One patient in the rofecoxib group was found to be ineligible because of an incomplete resection, and one patient in the placebo group was ineligible because random assignment took place more than 12 weeks after surgery. These patients were included in the analyses.

The intention-to-treat population comprised 1217 patients in the rofecoxib group and 1217 patients in the placebo group. Owing to an administrative error at a site pharmacy, one patient in the placebo group and one in the rofecoxib group received the incorrect medication for the first 6 months, and one patient in the rofecoxib group switched to placebo for a period of 3 weeks before switching back. Fifty patients in the rofecoxib group and 57 in the placebo group had not yet started the study treatment when rofecoxib was withdrawn. The intention-to-treat population included in analyses therefore comprised 1167 patients in the rofecoxib group and 1160 patients in the placebo group (Fig. 2 in the Supplementary Appendix). The duration of study treatment was known only approximately for 65 patients receiving rofecoxib and for 62 patients receiving placebo.

Table 1 shows that the assignment of study treatment was balanced on the basis of age, sex, disease site, cancer stage, and receipt or non-receipt of previous adjuvant chemotherapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rofecoxib Group (N = 1167)</th>
<th>Placebo Group (N = 1160)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of cancer — no. (%)</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>II</td>
<td>551 (47.2)</td>
<td>554 (47.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>616 (52.8)</td>
<td>606 (52.2)</td>
<td></td>
</tr>
<tr>
<td>Site of cancer — no. (%)</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Colon</td>
<td>756 (64.8)</td>
<td>767 (66.1)</td>
<td></td>
</tr>
<tr>
<td>Rectum and sigmoid colon</td>
<td>93 (8.0)</td>
<td>77 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>318 (27.2)</td>
<td>316 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy — no. (%)</td>
<td>755 (64.7)</td>
<td>748 (64.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age</td>
<td></td>
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</tr>
<tr>
<td>Median — yr</td>
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<tr>
<td>Interquartile range — yr</td>
<td>58–71</td>
<td>57–71</td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr — no. (%)</td>
<td>574 (49.2)</td>
<td>579 (49.9)</td>
<td></td>
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<td>Male sex — no. (%)</td>
<td>745 (63.8)</td>
<td>742 (64.0)</td>
<td>0.95</td>
</tr>
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<td>White race — no. (%)</td>
<td>1147 (98.3)</td>
<td>1139 (98.2)</td>
<td>0.86</td>
</tr>
<tr>
<td>No history of hypertension — no. (%)†</td>
<td>825 (70.7)</td>
<td>852 (73.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>History of diabetes — no. (%)†</td>
<td>102 (8.7)</td>
<td>65 (5.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>No history of hyperlipidemia — no. (%)‡</td>
<td>601 (51.5)</td>
<td>588 (50.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Current smoker — no. (%)§</td>
<td>141 (12.1)</td>
<td>129 (11.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>History of symptomatic atherosclerotic disease — no. (%)¶</td>
<td>249 (21.3)</td>
<td>222 (19.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Low-dose aspirin use at baseline — no. (%)</td>
<td>101 (8.7)</td>
<td>80 (6.9)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* Race was self-reported.
† The presence or absence of a history was unknown for three patients.
‡ The presence or absence of a history of hyperlipidemia was unknown for 999 patients.
§ The current smoking status was unknown for 20 patients.
¶ A history of symptomatic atherosclerotic disease was a composite measure defined as the presence of at least one risk factor in the “Documented History of Vascular Disease” section and at least two risk factors in the “Cardiac Risk Factors” section of the VICTOR Cardiovascular Risk Assessment Form (Fig. 2 in the Supplementary Appendix).
risk-assessment forms were all received after randomization (half before the trial was unblinded), and it took approximately 18 months after trial closure to construct a validated database for analysis. Slightly more patients in the rofecoxib group than in the placebo group had predefined cardiovascular risk factors (Table 1). The median duration of trial treatment was 7.4 months (interquartile range, 3.1 to 14.0) in the rofecoxib group and 8.2 months (interquartile range, 3.7 to 15.0) in the placebo group, with 33% of all patients having received the study drug for at least 12 months (Table 2). The median duration of follow-up was 33.0 months (interquartile range, 27.6 to 40.1) in the rofecoxib group and 33.4 months (interquartile range, 27.7 to 40.4) in the placebo group.

Before the worldwide withdrawal of rofecoxib, 342 patients receiving rofecoxib and 268 patients receiving placebo discontinued the study drug before its intended completion, but all of these patients were included in the intention-to-treat population of 1167 patients in the rofecoxib group and 1160 patients in the placebo group. The most common medical reasons for early discontinuation of study drug were gastrointestinal pain or heartburn (15 patients in the rofecoxib group and 5 in the placebo group), analgesia required for arthritis (4 and 15, respectively), hypertension (7 and 1), renal impairment (7 and 1), diarrhea (4 and 4), and heart failure (2 in the rofecoxib group). Since only 4% of patients received the study drug for more than 2 years, the randomization variable originally planned to reflect the duration of study treatment (2 years or 5 years) is unimportant.

Thirty-five potential cardiovascular thrombotic events occurring during or within 14 days after the treatment period were adjudicated in a blinded fashion by the independent panel convened by Merck (Table 1 in the Supplementary Appendix), including 11 events that were reported after the unblinding of study treatment in nine patients. Sixteen events in 15 patients receiving rofecoxib were confirmed to be cardiovascular thrombotic events, as compared with seven events in 6 patients receiving placebo. Three of these events occurred while the patients were taking other NSAIDs (sudden death from cardiac causes in a patient in the placebo group who was taking diclofenac, transient ischemic attack in a patient in the rofecoxib group who was taking diclofenac, and peripheral venous thrombosis in a patient in the rofecoxib group who was taking meloxicam).

There were 10 events qualifying as an APTC end point in nine patients receiving rofecoxib, as compared with 6 events in six patients receiving placebo. Rates of confirmed cardiovascular thrombotic events per 100 patient-years are presented in Table 3 and in Kaplan–Meier plots in Figure 1. The median duration of study treatment before a cardiovascular event was reported was 157 days in the rofecoxib group and 195 days in the placebo group (Table 2 in the Supplementary Appendix). The relative risk of a cardiovascular thrombotic event during or within 14 days after the treatment period was 2.66 (95% confidence interval [CI], 1.03 to 6.86) among patients receiving rofecoxib, as compared with those receiving placebo (P=0.04). The relative risk was slightly reduced after adjustment for cardiovascular risk factors (2.41; 95% CI, 0.93 to 6.26; P=0.07). Analysis of the APTC end points showed an unadjusted relative risk of 1.60 (95% CI, 0.57 to 4.51; P=0.37) and an adjusted relative risk of 1.42 (95% CI, 0.50 to 4.03; P=0.52).

Further analysis, in which all cardiovascular events that occurred during the treatment period and all those reported within 24 months after trial closure were combined, was performed. An additional 14 cardiovascular events were noted (Table 3, and Table 2 in the Supplementary Appendix) after adjudication of all adverse events re-

### Table 2. Reported Duration of Study Treatment.*

<table>
<thead>
<tr>
<th>Duration</th>
<th>Rofecoxib Group (N = 1167)</th>
<th>Placebo Group (N = 1160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 days (no.)</td>
<td>112</td>
<td>72</td>
</tr>
<tr>
<td>30 days to &lt;6 mo (no.)</td>
<td>381</td>
<td>368</td>
</tr>
<tr>
<td>6 to &lt;12 mo (no.)</td>
<td>307</td>
<td>323</td>
</tr>
<tr>
<td>12 to &lt;24 mo (no.)</td>
<td>321</td>
<td>348</td>
</tr>
<tr>
<td>≥24 mo (no.)</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Unknown (no.)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median duration (days)</th>
<th>No.</th>
<th>Interquartile range</th>
<th>Total patient-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>226</td>
<td>94–425</td>
<td>889</td>
</tr>
<tr>
<td></td>
<td>249</td>
<td>112–456</td>
<td>946</td>
</tr>
</tbody>
</table>

* The data include those for 65 patients in the rofecoxib group and 62 in the placebo group whose durations of study treatment were known only approximately.
Table 3. Incidence of Confirmed Cardiovascular Adverse Events during and after the Treatment Period.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Event</th>
<th>Rofecoxib Group (N = 1167)</th>
<th>Placebo Group (N = 1160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>Total No. of Patient-Yr</td>
</tr>
<tr>
<td>During or within 14 days after treatment period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular thrombotic event</td>
<td>15 (1.3)</td>
<td>927</td>
</tr>
<tr>
<td>APTC end point</td>
<td>9 (0.8)</td>
<td>928</td>
</tr>
<tr>
<td>All cardiac events</td>
<td>8 (0.7)</td>
<td>928</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sudden death from cardiac causes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac thrombus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All peripheral vascular events</td>
<td>3 (0.3)</td>
<td>922</td>
</tr>
<tr>
<td>Peripheral venous thrombosis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All cerebrovascular events</td>
<td>5 (0.4)</td>
<td>924</td>
</tr>
<tr>
<td>Ischemic cerebrovascular stroke</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>All hemorrhagic events</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatal hemorrhagic cerebrovascular stroke</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ruptured cerebral aneurysm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>During treatment period or within 24 months after trial closure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular thrombotic event</td>
<td>21 (1.8)</td>
<td>3252</td>
</tr>
<tr>
<td>APTC end point</td>
<td>13 (1.1)</td>
<td>3269</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The APTC end point was defined as the combined incidence of death from cardiovascular, hemorrhagic, and unknown causes; of nonfatal myocardial infarction; and of nonfatal ischemic and hemorrhagic stroke.\textsuperscript{35}
ported within 24 months after trial closure. The resulting relative risk of a cardiovascular thrombotic event, unadjusted for cardiovascular risk factors, was 1.50 (95% CI, 0.76 to 2.94; P = 0.24). Analysis of the APTC end points showed an unadjusted relative risk of 1.29 (95% CI, 0.57 to 2.95). Although information on blood pressure and renal function was not collected systematically, three patients in the rofecoxib group presented with congestive cardiac failure during the treatment period. Overall, four patients in the rofecoxib group and two in the placebo group died as a result of thrombotic events occurring during or within 14 days after the treatment period. An additional six deaths from cardiovascular thrombotic events (one patient in the rofecoxib group...
and five in the placebo group), identified by death certification, were reported within 24 months after trial closure. The total numbers of patients who died from cardiovascular causes—five in the rofecoxib group and seven in the placebo group—did not differ significantly.

**DISCUSSION**

The chief limitations of our study are the relatively small number of events available for analysis and the relatively short duration of exposure to the study drug (median, 7.4 months). However, our findings suggest an increased risk of a cardiovascular thrombotic event in patients randomly assigned to receive rofecoxib (as compared with those randomly assigned to receive placebo) as adjuvant treatment for the prevention of a recurrence of colorectal cancer (relative risk of an event during or within 14 days after the treatment period, 2.66; 95% CI, 1.03 to 6.86; \( P = 0.04 \)). These findings are consistent with those obtained in other placebo-controlled studies of treatment with COX-2 inhibitors in patients with colorectal adenoma. Extension of the period of observation of cardiovascular events to 24 months after trial closure did not show a statistically significant adverse effect of rofecoxib (relative risk, 1.50; 95% CI, 0.76 to 2.94; \( P = 0.24 \)). This information was generated by the serious-adverse-event reporting system that was maintained throughout the follow-up period and by central notification of death certification. It is possible that worldwide withdrawal of rofecoxib led to the underreporting of adverse events during the follow-up period.

Bresalier et al.12 reported results of the APPROVe trial, in which 2586 patients with a history of colorectal adenoma were randomly assigned to receive placebo or 25 mg of rofecoxib daily (as in our study). The authors found an increased relative risk of cardiovascular thrombotic events in the rofecoxib group (1.92; 95% CI, 1.19 to 3.11) and claimed that this risk was apparent after 18 months of treatment. Solomon et al.13 reviewed all potentially serious cardiovascular events in 2035 patients with a history of colorectal adenomatous polyps who had been enrolled in the APC study, which compared two doses of the selective COX-2 inhibitor celecoxib (200 mg or 400 mg twice daily) with placebo. The composite end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure was more common in each of the celecoxib groups than in the placebo group (200-mg group: hazard ratio, 2.3; 95% CI, 0.9 to 5.5; 400-mg group: hazard ratio, 3.4; 95% CI, 1.4 to 7.8).

A recent meta-analysis of 138 randomized trials involving 145,373 participants assessed the risk of vascular events from the use of selective COX-2 inhibitors and traditional NSAIDs.14 In all, 121 placebo-controlled trials of selective COX-2 inhibitors (predominantly rofecoxib and celecoxib) were analyzed, and the authors found a proportional increase by nearly a factor of 2 in the risk of myocardial infarction among patients receiving COX-2 inhibitors as compared with placebo (hazard ratio, 1.86; 95% CI, 1.33 to 2.59; \( P = 0.003 \)) but no significant difference in the incidence of stroke. Too few vascular events were available to study the influence of dose, but the investigators noted that two thirds of the vascular events had occurred in the nine long-term trials with treatment periods of 1 year or more. It would appear from our study that patients taking rofecoxib for fewer than 18 months may be at increased risk for a cardiovascular thrombotic event, since 50% of all such reported episodes occurred in patients treated for fewer than 12 months. There has been a thorough statistical critique of the original interpretation of the time-to-event data of the APPROVe investigators, which has challenged their assessment of the data.16

Observational information, typically from the examination of large databases, suggests that treatment with COX-2 inhibitors may enhance cardiovascular risk and that such risk may be greater than, or the same as, that associated with the use of nonselective NSAIDs.17-19 A recent systematic review of observational data reported a dose-related relative risk of cardiovascular events of 1.33 (95% CI, 0.91 to 1.23) with 25 mg of rofecoxib per day or less, as compared with placebo, and a relative risk of 2.19 (95% CI, 1.64 to 2.91) with more than 25 mg of rofecoxib per day.20 The ability of population-based studies to give definitive answers is inevitably limited because of the difficulty in controlling for confounders; however, the summary relative risk in the systematic review20 is similar to that found in the meta-analysis of randomized trials.14 A recent report from the European Medicines Agency21 concluded that epidemiologic evidence and updated trial data continue to point to an increased thrombotic risk with COX-2 inhibitors, possibly
accounting for about three events per 1000 patient-years.

The mechanism linking the use of COX-2 inhibitors to an increased incidence of thrombotic vascular events has not been precisely elucidated. Cyclooxygenase and its prostanoid products have important roles in regulating factors affecting the risk of thrombosis; for instance, thromboxane synthase is regulated by COX-2. It is generally accepted that patients with cancer have a higher risk of thrombosis than does the general population, and a positive correlation has been found between increased expression of thromboxane synthase and shortened survival from bladder cancer. Current data are insufficiently mature to permit commentary on the risks of recurrence of or death from cancer, but prolonged follow-up will provide more informative data.

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APPENDIX

Members of the VICTOR trial were as follows. Independent Data and Safety Monitoring Committee: Finsen Institute, Copenhagen — H.H. Hansen; Centre for Statistics in Medicine, Oxford, United Kingdom — D. Altman; Churchill Hospital, Oxford, United Kingdom — D. Tallbot; Principal investigators: Maiday University Hospital — M. Abulad; North Staffordshire Royal Infirmary — F. Adab; Queen Elizabeth Hospital King’s Lynn — A. Ahmad; St. James University Hospital — S. Ambrose; Wexham Park Hospital — R. Ashford; Singleton Hospital — C. Askili; North Tyneside General Hospital — P. Atherton; Royal Shrewsbury Hospital — S. Awwad; South Tyneside District Hospital — A. Azzabi; Torbay Hospital — N. Bailey; Withybush General Hospital — A. Barnes; St. Mary’s Hospital Newport — C. Bughan; Bexley Conquest Hospital — S. Harriet; Gloucester Royal Hospital — K. Benstead; Nettington City Hospital — E. Bessell; Great Western Hospital — C. Blessing; Bradford Royal Infirmary — C. 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Levine; St. George’s Hospital — F. Loft; Leighton Hospital — J. Logue; Dina Princess of Wales Hospital — P. Mack; Luton & Dunstable Hospital — A. Makris; Whiston Hospital — E. Marshall; Velindre Hospital — T. Maughan; Trafford General Hospital — F. Mazarelo; Peterborought District Hospital — K. McAdam; Eastbourne District General Hospital — F. McKenna; Royal Free Hospital — T. Meyer; Worthing Hospital — T. Miles; Carwell Hill Hospital — J. Monson; West Suffolk Hospital — M. Moody; Ninewells Hospital — A. Munze; North Devon District Hospital — M. Napier; Cumberland Infirmary — J. Nicoll; Northweck Park Hospital — J. Northover; St. Mary’s Hospital Portsmouth — A. O’Callahan; Milton Keynes General Hospital — R. O’Hara; Donet County Hospital — R. Osbourne; Sunderland Royal Hospital — I. Pedley; Charing Cross Hospital — R.H. Phillips; Western General Hospital — H. Phillips; Epsom General Hospital — M. Raja; Penmne Acute Hospitals National Health Service Trust — A. Rate; City Hospital — D. Rea; Southern General Hospital — G. Robertson; Southend Hospital — A. Robinson; Hope Hospital — M. Saunders; York District Hospital — D. Sebag-Monteflore; Cookridge Hospital — M. Seymour; Ipswich Hospital National Health Service Trust — K. Sherwin; Tameside General Hospital — K. Siddiqui; University Hospital Aintree — D. Smith; Pontefract General Infirmary — M. Sne; King George Hospital — S. Snoeks; Alexandra Hospital — S. Sothi; Sthorpe General Hospital — T. Sreenivasan; Noble’s Hospital — S. Stock; Yoshiy Guzann — N. Stuart; Southport & Formby District General Hospital — A. Sun-Myn; University Hospital Hartlepool — M. Tabaqchali; University Hospital of North Tees — M. Tabaqchali; Broomfield Hospital — S. Tahir; Hinchingbrooke Hospital — L.T. Tan; Bedford General Hospital — R. Thomas; Mithton Hospital — M. Tighie; Taunton & Somerset Hospital — M. Tomlinson; Royal Surrey County Hospital — C. Topham; Friarage Hospital — J.C.M. Van der Voet; James Cook University Hospital — N. Wadd; St.ore Mandeville Hospital — N. Warning; Hammersmith Hospital — H. Wasan; Royal Liver Infirmary — A. Watson; Addenbrooke’s Hospital — M. Wells; Ticking Hill Hospital — I. Wilkinson; Withington Hospital — M. Wilson; Royal Albert Edward Infirmary — G. Wilson; George Eliot Hospital — J. Worthing; Hairmyres Hospital — H. Yosef; Queen Elizabeth Hospital London — C.Y. Yui.
REFERENCES


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The Spread of Obesity in a Large Social Network over 32 Years

Nicholas A. Christakis, M.D., Ph.D., M.P.H., and James H. Fowler, Ph.D.

ABSTRACT

BACKGROUND
The prevalence of obesity has increased substantially over the past 30 years. We performed a quantitative analysis of the nature and extent of the person-to-person spread of obesity as a possible factor contributing to the obesity epidemic.

METHODS
We evaluated a densely interconnected social network of 12,067 people assessed repeatedly from 1971 to 2003 as part of the Framingham Heart Study. The body-mass index was available for all subjects. We used longitudinal statistical models to examine whether weight gain in one person was associated with weight gain in his or her friends, siblings, spouse, and neighbors.

RESULTS
Discernible clusters of obese persons (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥30) were present in the network at all time points, and the clusters extended to three degrees of separation. These clusters did not appear to be solely attributable to the selective formation of social ties among obese persons. A person’s chances of becoming obese increased by 57% (95% confidence interval [CI], 6 to 123) if he or she had a friend who became obese in a given interval. Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40% (95% CI, 21 to 60). If one spouse became obese, the likelihood that the other spouse would become obese increased by 37% (95% CI, 7 to 73). These effects were not seen among neighbors in the immediate geographic location. Persons of the same sex had relatively greater influence on each other than those of the opposite sex. The spread of smoking cessation did not account for the spread of obesity in the network.

CONCLUSIONS
Network phenomena appear to be relevant to the biologic and behavioral trait of obesity, and obesity appears to spread through social ties. These findings have implications for clinical and public health interventions.
The prevalence of obesity has increased from 23% to 31% over the recent past in the United States, and 66% of adults are overweight. Proposed explanations for the obesity epidemic include societal changes that promote both inactivity and food consumption. The fact that the increase in obesity during this period cannot be explained by genetics and has occurred among all socioeconomic groups provides support for a broad set of social and environmental explanations. Since diverse phenomena can spread within social networks, we conducted a study to determine whether obesity might also spread from person to person, possibly contributing to the epidemic, and if so, how the spread might occur.

Whereas obesity has been stigmatized in the past, attitudes may be changing. To the extent that obesity is a product of voluntary choices or behaviors, the fact that people are embedded in social networks and are influenced by the evident appearance and behaviors of those around them suggests that weight gain in one person might influence weight gain in others. Having obese social contacts might change a person’s tolerance for being obese or might influence his or her adoption of specific behaviors (e.g., smoking, eating, and exercising). In addition to such strictly social mechanisms, it is plausible that physiological imitation might occur; areas of the brain that correspond to actions such as eating food may be stimulated if these actions are observed in others. Even infectious causes of obesity are conceivable.

We evaluated a network of 12,067 people who underwent repeated measurements over a period of 32 years. We examined several aspects of the spread of obesity, including the existence of clusters of obese persons within the network, the association between one person’s weight gain and weight gain among his or her social contacts, the dependence of this association on the nature of the social ties (e.g., ties between friends of different kinds, siblings, spouses, and neighbors), and the influence of sex, smoking behavior, and geographic distance between the domiciles of persons in the social network.

**Methods**

**Source Data**

The Framingham Heart Study was initiated in 1948, when 5209 people were enrolled in the original cohort. The Framingham Offspring Study began in 1971, when most of the children of members of the original cohort and their spouses were enrolled in the offspring cohort. There has been almost no loss to follow-up other than death in this cohort of 5124 people; only 10 people left the study. In 2002, the third-generation cohort, consisting of 4095 children of the offspring cohort, was initiated. All participants undergo physical examinations (including measurements of height and weight) and complete written questionnaires at regular intervals.

**Network Ascertainment**

For our study, we used the offspring cohort as the source of 5124 key subjects, or “egos,” as they are called in social-network analysis. Any persons to whom the egos are linked — in any of the Framingham Heart Study cohorts — can, however, serve as “alters.” Overall, 12,067 living egos and alters were connected at some point during the study period (1971 to 2003).

To create the network data set, we entered information about the offspring cohort into a computer. This information was derived from archived, handwritten administrative tracking sheets that had been used since 1971 to identify people close...
to the study participants to facilitate follow-up. These sheets contain valuable, previously unused social-network information because they systematically and comprehensively identify relatives and friends named by the ego. The tracking sheets provide complete information about all first-order relatives (parents, spouses, siblings, and children), whether they are alive or dead, and at least one “close friend” at each of seven examinations between 1971 and 2003. The examinations took place during 3-year periods centered in 1973, 1981, 1985, 1989, 1992, 1997, and 1999. Detailed home addresses were also recorded at each time point; we used this information to calculate the geographic distance between people.

Many of the named alters on these sheets also were members of Framingham Heart Study cohorts. This newly computerized database thus identifies the network links among participants at each examination and longitudinally from one examination to the next. As a person’s family changed because of birth, death, marriage, or divorce, and as contacts changed because of residential moves or new friendships, this information was recorded. Furthermore, dates of birth and death were available from separate Framingham Heart Study files.

Overall, there were 38,611 observed social and family ties to the 5124 egos, yielding an average of 7.5 ties per ego (not including neighbors). For example, 83% of the spouses of egos were directly and repeatedly observed at the time of examination, and 87% percent of egos with siblings had at least one sibling in the network. For 10% of the egos, an immediate neighbor also participated in the study; more expansive definitions of neighbors yielded similar results.

A total of 45% of the 5124 egos were connected through friendship to another person in the network. There were 3604 unique, observed friendships, for an average of 0.7 friendship tie per ego. Because friendship identifications are directional, we studied three different kinds of friendships: an “ego-perceived friendship,” in which an ego identifies an alter as a friend; an “alter-perceived friendship,” in which an alter identifies an ego as a friend; and a “mutual friendship,” in which the identification is reciprocal. We hypothesized that a friend’s social influence on an ego would be affected by the type of friendship, with the strongest effects occurring in mutual friendships, followed by ego-perceived friendships, followed by alter-perceived friendships. Our reasoning was that the person making the identification esteems the other person and may wish to emulate him or her.

We included only persons older than 21 years of age at any observation point and subsequently. At the inception of the study, 53% of the egos were women, the mean age of the egos was 38 years (range, 21 to 70), and their mean educational level was 13.6 years (range, no education to ≥17 years of education).

The study data are available from the Framingham Heart Study. The study was approved by the institutional review board at Harvard Medical School; all subjects provided written informed consent.

**STATISTICAL ANALYSIS**

We graphed the network with the use of the Kamada–Kawai algorithm in Pajek software. We generated videos of the network by means of the Social Network Image Animator (known as SoNIA). We examined whether our data conformed to theoretical network models such as the small-world, scale-free, and hierarchical types (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

We defined obesity as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more. Analyses in which the body-mass index was a continuous variable did not yield different results.

We considered three explanations for the clustering of obese people. First, egos might choose to associate with like alters (“homophily”). Second, egos and alters might share attributes or jointly experience unobserved contemporaneous events that cause their weight to vary at the same time (confounding). Third, alters might exert social influence or peer effects on egos (“induction”). Distinguishing the interpersonal induction of obesity from homophily requires dynamic, longitudinal network information about the emergence of ties between people (“nodes”) in a network and also about the attributes of nodes (i.e., repeated measures of the body-mass index).

The basic statistical analysis involved the specification of longitudinal logistic-regression models in which the ego’s obesity status at any given examination or time point (t+1) was a function of various attributes, such as the ego’s age, sex, and
educational level; the ego’s obesity status at the previous time point (t); and most pertinent, the alter’s obesity status at times t and t+1.25 We used generalized estimating equations to account for multiple observations of the same ego across examinations and across ego–alter pairs.26 We assumed an independent working correlation structure for the clusters.26,27

The use of a time-lagged dependent variable (lagged to the previous examination) eliminated serial correlation in the errors (evaluated with a Lagrange multiplier test28) and also substantially controlled for the ego’s genetic endowment and any intrinsic, stable predisposition to obesity. The use of a lagged independent variable for an alter’s weight status controlled for homophily.25 The key variable of interest was an alter’s obesity at time t+1. A significant coefficient for this variable would suggest either that an alter’s weight affected an ego’s weight or that an ego and an alter experienced contemporaneous events affecting both their weights. We estimated these models in varied ego–alter pair types.

To evaluate the possibility that omitted variables or unobserved events might explain the associations, we examined how the type or direction of the social relationship between the ego and the alter affected the association between the ego’s obesity and the alter’s obesity. For example, if unobserved factors drove the association between the ego’s obesity and the alter’s obesity, then the directionality of friendship should not have been relevant.

We evaluated the role of a possible spread in smoking-cessation behavior as a contributor to the spread of obesity by adding variables for the smoking status of egos and alters at times t and t+1 to the foregoing models. We also analyzed the role of geographic distance between egos and alters by adding such a variable.

We calculated 95% confidence intervals by simulating the first difference in the alter’s contem-

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Figure 1. Largest Connected Subcomponent of the Social Network in the Framingham Heart Study in the Year 2000.
Each circle (node) represents one person in the data set. There are 2200 persons in this subcomponent of the social network. Circles with red borders denote women, and circles with blue borders denote men. The size of each circle is proportional to the person’s body-mass index. The interior color of the circles indicates the person’s obesity status: yellow denotes an obese person (body-mass index, ≥30) and green denotes a nonobese person. The colors of the ties between the nodes indicate the relationship between them: purple denotes a friendship or marital tie and orange denotes a familial tie.
Figure 2. Part of the Social Network from the Framingham Heart Study with Information about Body-Mass Index According to Year.

Each circle (node) represents one person in the data set. Circles with red borders denote women, and circles with blue borders denote men. The size of each circle is proportional to the person’s body-mass index. The interior color of the circles indicates the person’s obesity status: yellow denotes an obese person (body-mass index, ≥30) and green denotes a nonobese person. The colors of the ties between the circles indicate the relationship between them: purple denotes a friendship or a marital tie and orange denotes a familial tie. The disappearance of a circle from one year to another indicates the person’s death, and the disappearance of a tie between the circles indicates that the relationship between the two persons no longer exists. The largest connected subcomponent of the whole network and the change in obesity over the 32-year study period are shown in an animation that is available with the full text of this article at www.nejm.org.
Figure 3. Effect of Social and Geographic Distance from Obese Alters on the Probability of an Ego’s Obesity in the Social Network of the Framingham Heart Study.

Panel A shows the mean effect of an ego’s social proximity to an obese alter; this effect is derived by comparing the conditional probability of obesity in the observed network with the probability of obesity in identical networks (with topology preserved) in which the same number of obese persons is randomly distributed. The social distance between the alter and the ego is represented by degrees of separation (1 denotes one degree of separation from the ego, 2 denotes two degrees of separation from the ego, and so forth). The examination took place at seven time points. Panel B shows the mean effect of an ego’s geographic proximity to an obese alter. We ranked all geographic distances (derived from geocoding) between the homes of directly connected egos and alters (i.e., those pairs at one degree of separation) and created six groups of equal size. This figure shows the effects observed for the six mileage groups (based on their average distance): 1 denotes 0 miles (i.e., closest to the alter’s home), 2 denotes 0.26 mile, 3 denotes 1.5 miles, 4 denotes 3.4 miles, 5 denotes 9.3 miles, and 6 denotes 471 miles (i.e., farthest from the alter’s home). There is no trend in geographic distance. Bars for both panels show 95% confidence intervals based on 1000 simulations. To convert miles to kilometers, multiply by 1.6.

Figure 1 depicts the largest connected subcomponent of the social network in the year 2000. This network is sufficiently dense to obscure much of the underlying structure, although regions of the network with clusters of obese or nonobese persons can be seen. Figure 2 illustrates the spread of obesity between adjoining nodes in a part of the network over time. A video (available with the full text of this article at www.nejm.org) depicts the evolution of the largest component of the network and shows the progress of the obesity epidemic over the 32-year study period.

Figure 3A characterizes clusters within the entire network more formally. To quantify these clusters, we compared the whole observed network with simulated networks with the same network topology and the same overall prevalence of obesity as the observed network, but with the incidence of obesity randomly distributed among the nodes (in what we call “random body-mass–index networks”). If clustering is occurring, then the probability that an alter will be obese, given that an ego is known to be obese, should be higher in the observed network than in the random body-mass–index networks. What we call the “reach” of the clusters is the point, in terms of an alter’s degree of separation from any given ego, at which the probability of an alter’s obesity is no longer related to whether the ego is obese. In all of the examinations (from 1971 through 2003), the risk of obesity among alters who were connected to an obese ego (at one degree of separation) was about 45% higher in the observed network than in a random network. The
risk of obesity was also about 20% higher for alters’ alters (at two degrees of separation) and about 10% higher for alters’ alters’ alters (at three degrees of separation). By the fourth degree of separation, there was no excess relationship between an ego’s obesity and the alter’s obesity. Hence, the reach of the obesity clusters was three degrees.

Figure 3B indicates that the effect of geographic distance is different from the effect of social distance. Whereas increasing social distance appeared to decrease the effect of an alter on an ego, increasing geographic distance did not. The obesity of the most geographically distant alters correlated as strongly with an ego’s obesity as did the obesity of the geographically closest alters. These results suggest that social distance plays a stronger role than geographic distance in the spread of behaviors or norms associated with obesity.

We evaluated the extent of interpersonal association in obesity with the use of regression analysis. Our models account for homophily by including a time-lagged measurement of the alter’s obesity. We evaluated the possible role of unobserved contemporaneous events by separately analyzing models of subgroups of the data involving various ego–alter pairings. Figure 4 summarizes the associations.

If an ego stated that an alter was his or her friend, the ego’s chances of becoming obese appeared to increase by 57% (95% confidence interval [CI], 6 to 123) if the alter became obese. However, the type of friendship appeared to be important. Between mutual friends, the ego’s risk of obesity increased by 171% (95% CI, 59 to 326) if an alter became obese. In contrast, there was no statistically meaningful relationship when the friendship was perceived by the alter but not the ego (P = 0.70). Thus, influence in friendship ties appeared to be directional.

The sex of the ego and alter also appeared to be important. When the sample was restricted to same-sex friendships (87% of the total), the probability of obesity in an ego increased by 71% (95% CI, 13 to 145) if the alter became obese. For friends of the opposite sex, however, there was no significant association (P = 0.64). Among friends of the same sex, a man had a 100% (95% CI, 26 to 197) increase in the chance of becoming obese if his male friend became obese, whereas the female-to-female spread of obesity was not significant (38% increased chance; 95% CI, −39 to 161).

Among pairs of adult siblings, one sibling’s chance of becoming obese increased by 40% (95% CI, 21 to 60) if the other sibling became obese. This phenomenon appeared to be more marked among siblings of the same sex (55%; 95% CI, 26 to 88) than among siblings of the opposite sex (27%; 95% CI, 3 to 54), although the difference was not significant (P = 0.16). Among brothers, an ego’s chance of becoming obese increased by 44% (95% CI, 6 to 91) if his alter became obese, and among sisters, an ego’s chance of becoming obese increased by 67% (95% CI, 27 to 114) if her alter became obese. Obesity in a sibling of the opposite sex did not affect the chance that the other sibling would become obese.

Among married couples, when an alter became obese, the spouse was 37% more likely (95% CI, 7 to 73) to become obese. Husbands and wives appeared to affect each other similarly (44% and 37%, respectively). Finally, we observed no effect on the risk that an ego would become obese if an immediate neighbor became obese.
We also investigated two factors that might mediate or modify the effect of an alter’s weight gain: his or her smoking behavior and geographic distance from the ego (see the Supplementary Appendix). We added measures of smoking behavior for the ego and the alter at both the current and previous examinations. The coefficient for the effect of the alter’s obesity was virtually unchanged; smoking behavior does not appear to be instrumental to the spread of obesity. Models that included the geographic distance between the ego and alter corroborated the result shown in Figure 3B: geographic distance did not modify the intensity of the effect of the alter’s obesity on the ego.

**Discussion**

Our study suggests that obesity may spread in social networks in a quantifiable and discernable pattern that depends on the nature of social ties. Moreover, social distance appears to be more important than geographic distance within these networks. Although connected persons might share an exposure to common environmental factors, the experience of simultaneous events, or other common features (e.g., genes) that cause them to gain or lose weight simultaneously, our observations suggest an important role for a process involving the induction and person-to-person spread of obesity.

Our findings that the weight gain of immediate neighbors did not affect the chance of weight gain in egos and that geographic distance did not modify the effect for other types of alters (e.g., friends or siblings) helps rule out common exposure to local environmental factors as an explanation for our observations. Our models also controlled for an ego’s previous weight status; this helps to account for sources of confounding that are stable over time (e.g., childhood experiences or genetic endowment). In addition, the control in our models for an alter’s previous weight status accounts for a possible tendency of obese people to form ties among themselves. Finally, the findings regarding the directional nature of the effects of friendships are especially important with regard to the interpersonal induction of obesity because they suggest that friends do not simultaneously become obese as a result of contemporaneous exposures to unobserved factors. If the friends did become obese at the same time, any such exposures should have an equally strong influence regardless of the directionality of friendship. This observation also points to the specifically social nature of these associations, since the asymmetry in the process may arise from the fact that the person who identifies another person as a friend esteems the other person.

Finally, pairs of friends and siblings of the same sex appeared to have more influence on the weight gain of each other than did pairs of friends and siblings of the opposite sex. This finding also provides support for the social nature of any induction of obesity, since it seems likely that people are influenced more by those they resemble than by those they do not. Conversely, spouses, who share much of their physical environment, may not affect each other’s weight gain as much as mutual friends do; in the case of spouses, the opposite-sex effects and friendship effects may counteract each other.

Obesity in alters might influence obesity in egos by diverse psychosocial means, such as changing the ego’s norms about the acceptability of being overweight, more directly influencing the ego’s behaviors (e.g., affecting food consumption), or both. Other mechanisms are also possible. Unfortunately, our data do not permit a detailed examination. However, some insight into possible mechanisms can be gained from a consideration of the roles of smoking and geographic distance in obesity. The tendency of persons to gain weight when they stop smoking is well known, and the coincidence of a decrease in smoking and an increase in obesity in the overall population has been noted. However, the present study indicates that regardless of whether smoking cessation causes weight gain in individual persons, and regardless of whether smoking-initiation or smoking-cessation behavior itself spreads from person to person, any spread in smoking behavior is not a significant factor in the spread of obesity. This finding indicates that smoking behavior does not mediate the interpersonal effect in the spread of obesity. However, in addition, it suggests that the psychosocial mechanisms of the spread of obesity may rely less on behavioral imitation than on a change in an ego’s general perception of the social norms regarding the acceptability of obesity. This point is further reinforced by the relevance of the directionality of friendship.

Hence, an ego may observe that an alter gains
weight and then may accept weight gain in himself or herself. This weight gain in an ego might, in turn, be determined by various behaviors that an ego chooses to evince, and these behaviors need not be the same behaviors that an alter evinces. The observation that geographic distance does not modify the effect of an alter’s obesity also provides support for the concept that norms may be particularly relevant here. Behavioral effects might rely more on the frequency of contact (which one might reasonably expect to be attenuated with distance), whereas norms might not.

The spread of obesity in social networks appears to be a factor in the obesity epidemic. Yet the relevance of social influence also suggests that it may be possible to harness this same force to slow the spread of obesity. Network phenomena might be exploited to spread positive health behaviors,34-36 in part because people’s perceptions of their own risk of illness may depend on the people around them.37 Smoking- and alcohol-cessation programs and weight-loss interventions that provide peer support — that is, that modify the person’s social network — are more successful than those that do not.34,35,38,39 People are connected, and so their health is connected.40,41 Consequently, medical and public health interventions might be more cost-effective than initially supposed, since health improvements in one person might spread to others.42 The observation that people are embedded in social networks suggests that both bad and good behaviors might spread over a range of social ties. This highlights the necessity of approaching obesity not only as a clinical problem but also as a public health problem.

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REFERENCES


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The clinical problem begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

A 37-year-old man presents for the evaluation of localized swelling and tenderness of the left leg just below the knee. He suspects this lesion developed after a spider bite, although he did not see a spider. Examination of the leg reveals an area of erythema and warmth measuring approximately 5 by 7 cm. At the center of the lesion is a fluctuant area measuring approximately 2 by 2 cm, overlaid by a small area of necrotic skin. The man’s temperature is 38.3°C. The pulse rate is 115 beats per minute. The blood pressure is 116/78 mm Hg. How should this patient be evaluated and treated?

Methicillin-resistant Staphylococcus aureus (MRSA) refers to isolates that are resistant to all currently available β-lactam antibiotics, including penicillins and cephalosporins. MRSA isolates were first recognized shortly after the introduction of methicillin into clinical practice in the early 1960s. Their prevalence slowly increased during the next three decades, although they remained confined almost exclusively to patients who frequented health care facilities; other persons at risk for MRSA colonization or infection included those in contact with a person who had an MRSA infection or with a history of illicit drug use.

In the mid-1990s, MRSA infections began to be detected in the community in persons who did not have contact with the health care system. Molecular typing of isolates from these community-associated cases of MRSA infection has shown that they are largely caused by new MRSA strains.

As compared with health care–associated MRSA isolates, community-associated MRSA isolates are usually susceptible to clindamycin, and they are less often multiply resistant to other non–β-lactam antibiotics. Other distinguishing features of community-associated MRSA isolates include a high prevalence of genes encoding the two-component Panton–Valentine leukocidin; this exotoxin is associated with necrosis of the skin, severe necrotizing pneumonia, and abscess formation, although its role in the pathogenesis of community-associated MRSA infections remains controversial. In addition, small DNA cassettes mediating methicillin resistance have been detected in community-associated MRSA isolates of multiple genetic backgrounds, suggesting easy transfer. These cassettes differ from those in hospital-associated MRSA strains, which are larger and presumably less mobile. The classification of circulating community-associated MRSA strains according to pulsed-field electrophoretic patterns has revealed global, geographic variations. In most areas of the United States, a community-associated MRSA genotype called USA300 has emerged as the major circulating strain and has even emerged as a nosocomial strain in many areas.
Numerous reports have suggested the easy transmission of these new community-associated MRSA isolates in settings where people are in close contact. These settings include households, day-care centers, and military installations. These isolates also may be spread among prison and jail detainees and athletes. Before the 1990s, such evidence of contagion among otherwise healthy members of the community was documented infrequently. Other groups reported to be at increased risk for community-associated MRSA infection include Native Americans and Pacific Islanders and men who have sex with men.

There has been a dramatic increase in the occurrence of *S. aureus* infections in general and community-associated MRSA infections in particular. At Driscoll Children’s Hospital in Corpus Christi, Texas, the number of community-associated MRSA infections increased from 9 in 1999 to 459 in 2003; in 2003, these infections constituted 98% of *S. aureus* infections overall in that institution. In most, but not all, U.S. cities, community-associated MRSA is now the most common pathogen cultured from patients with skin and soft-tissue infections in emergency departments. Epidemic community-associated MRSA disease has also been reported from some rural areas, although epidemic disease has not yet spread to all regions of the United States.

Consistent with the occurrence of epidemic, symptomatic, community-associated MRSA disease in the United States are observations of the increasing prevalence of asymptomatic colonization of MRSA among children and adults in the community. Recent data indicate that 9.2% of healthy children in Nashville have asymptomatic colonization (74% of these infections are community-associated MRSA [Creech CB: personal communication]), as compared with 0.8% in 2001, and 7.3% of adolescents and adults in Atlanta have asymptomatic colonization, including both hospital- and community-acquired MRSA isolates.

Skin and soft-tissue infections represent the majority of the community-associated MRSA disease burden and are the focus of this article. Examples of such infections are shown in Figures 1 and 2. (Other examples are in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Necrotic skin lesions are a common presentation and are often incorrectly attributed to bites by brown recluse spiders (even in areas where these spiders do not live) or insect bites. In addition, necrotizing pneumonia, pleural empyema, necrotizing fasciitis, septic thrombophlebitis with pulmonary embolization, myositis, and severe sepsis with purpura fulminans and the Waterhouse–Friderichsen syndrome have been described in association with community-associated MRSA.
STRATEGIES AND EVIDENCE

Evaluation
Suspicion that community-associated MRSA may be the cause of a skin and soft-tissue infection should be heightened by a history of previous MRSA infection in the patient or a household contact. Table 1 lists other groups likely to be at risk for community-associated MRSA transmission. However, many patients with community-associated MRSA infection have none of these risk factors. Furthermore, no clinical features distinguish with certainty skin and soft-tissue infections caused by MRSA from those caused by methicillin-susceptible S. aureus.38

Information on local antibiotic-resistance patterns (e.g., from local hospitals) can help clinicians to assess the likelihood of community-associated MRSA infection and guide decisions regarding empirical treatment. Some have suggested that management strategies should be tailored to the possibility of community-associated MRSA infection on the basis of an arbitrary threshold of 10% or more methicillin resistance among S. aureus isolates.

Obtaining a specimen for culture and susceptibility testing, which was considered to be unnecessary when the prevalence of MRSA was low, is useful in guiding therapy. Specimens are most commonly obtained at the time of incision and drainage of purulent skin and soft-tissue lesions. In nonpurulent cellulitis that is not amenable to incision and drainage, a possible approach is a biopsy with culture of the material obtained. In practice, this procedure is infrequently performed.39 Moreover, although many patients with MRSA bacteremia also have nasal colonization with the organism,40 it is not known whether screening for such colonization in patients with a skin and soft-tissue infection has useful predictive value. Such screening is not currently recommended.

Treatment
The recommended treatment of community-associated MRSA infection depends on an assessment of the severity of the clinical presentation and the type of skin and soft-tissue infection. Purulent skin and soft-tissue infections without associated systemic signs, such as fever, tachycardia, or hemodynamic instability, are generally managed with incision and drainage, with or without oral antimicrobial therapy; incision and drainage alone may suffice, particularly for abscesses that are small. Lee et al.41 have defined small abscesses as those that are less than 5 cm in length, but this definition may not be appropriate for skin and soft-tissue infections in infants and in certain areas of the body (e.g., the head and neck). In patients with larger abscesses, systemic signs of infection, or both, antimicrobial therapy is generally recommended in addition to incision and drainage (for purulent lesions). The type and route of therapy should be guided by the severity of the clinical syndrome.

Outpatient Therapies
Topical antimicrobial therapy is sometimes used to treat superficial MRSA skin infections such as impetigo, although comparative outcome data are lacking. Bacitracin, alone or in combination with polymyxin and neomycin, mupirocin (Bactroban), and retapamulin (Altabax) are commercially available for this purpose. For bacitracin, in vitro susceptibility factors that predict the clinical outcome have not been defined.42 For mupirocin, isolates with low-level resistance and those with high-level resistance have been identified; the latter do predict clinical failure and may be increasing in prevalence among MRSA isolates.43,44 Retapamulin is newly licensed for children 9 months of age or older. It has good in vitro activity against MRSA infection, but mutants with decreased susceptibility can be selected in vitro.45

For oral systemic treatment, β-lactam antibiotics can no longer be considered to be reliable as empirical therapy for community-acquired skin and soft-tissue infections. The optimal antibiotic

<table>
<thead>
<tr>
<th>Table 1. Persons at Risk for Skin and Soft-Tissue Infections Caused by Community-Associated MRSA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contacts of a patient with proven community-associated MRSA infection</td>
</tr>
<tr>
<td>Children</td>
</tr>
<tr>
<td>Day-care center contacts of hospitalized patients with MRSA infections</td>
</tr>
<tr>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Soldiers</td>
</tr>
<tr>
<td>Incarcerated persons</td>
</tr>
<tr>
<td>Athletes, particularly those involved in contact sports</td>
</tr>
<tr>
<td>Native Americans</td>
</tr>
<tr>
<td>Pacific Islanders</td>
</tr>
<tr>
<td>Persons with a previous community-associated MRSA infection</td>
</tr>
<tr>
<td>Intravenous drug users</td>
</tr>
</tbody>
</table>

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therapy when community-associated MRSA infection is suspected is not clear. Results of susceptibility testing and clinical experience provide support for a primary role of older antibiotics such as clindamycin, trimethoprim–sulfamethoxazole, and tetracyclines, although their effectiveness for skin and soft-tissue infections due to community-associated MRSA has not been rigorously evaluated or compared in clinical trials.

Table 2 lists oral agents that are useful in the outpatient management of community-associated MRSA infections. An observational study showed that clindamycin, a lincosamide antibiotic, was uniformly effective in 39 patients with clindamycin-susceptible community-associated MRSA infection who were mildly to moderately ill. The disadvantages of this medication include its association with diarrhea caused by *Clostridium difficile* and increasing rates of clindamycin resistance in some regions of the world. Clindamycin resistance among community-associated MRSA isolates should be monitored locally, and some experts recommend avoiding empirical therapy with clindamycin when local rates of clindamycin resistance exceed 10 to 15% among MRSA isolates causing skin and soft-tissue infections.

Moreover, the results of testing for clindamycin susceptibility may be misleading; occasional treatment failures have been documented when the results of tests showed that an MRSA isolate was susceptible to clindamycin but resistant to erythromycin. In such cases, use of the D-zone test (Fig. 3) is warranted to detect inducible clindamycin resistance; positive results in 10 to 20% of tested isolates (with one notable outlier) have been reported, but these rates may be increasing.

The Clinical and Laboratory Standards Institute suggests that isolates that are positive on the D-zone test should be reported as being resistant to clindamycin despite a positive result of single-agent susceptibility testing. The institute suggests permissive language to accompany the result of the susceptibility testing: “The isolate is presumed to be resistant based on detection of inducible clindamycin resistance. Clindamycin might still be effective in some patients.” In practice, when the results of the D-zone test become known, the use of clindamycin should be reconsidered on the basis of the clinical response.

Neither trimethoprim–sulfamethoxazole nor tetracyclines are generally recommended as sole empirical therapy for a nonpurulent cellulitis of unknown cause because of concerns regarding the resistance of group A streptococci to these agents. Such resistance is well documented for tetracyclines, although it is less clear for trimethoprim–sulfamethoxazole. However, these agents are reasonable choices in cases in which community-associated MRSA infection is confirmed or strongly suggested by the presence of purulent material. Some clinicians suggest the addition of a β-lactam antibiotic, that is active against streptococci if trimethoprim–sulfamethoxazole or a tetracycline is used for a nonpurulent cellulitis of uncertain cause.

Testing of nearly all community-associated MRSA isolates shows susceptibility to trimethoprim–sulfamethoxazole, but data on the outcomes of treatment are limited. In a study at an outpatient clinic in Boston where almost half of community-associated MRSA isolates were clindamycin-resistant and where trimethoprim–sulfamethoxazole became the most frequently used antimicrobial agent for skin and soft-tissue infections caused by community-associated MRSA, the percentage of patients with clinical resolution of the MRSA infection increased in parallel with trimethoprim–sulfamethoxazole use during the study period (1998 to 2005). In another study, however, treatment failure occurred in 6 of 12 adults who received double-strength trimethoprim–sulfamethoxazole. Few data are available to provide support for the efficacy of doxycycline or minocycline. In one retrospective review of skin and soft-tissue infections caused by community-associated MRSA, the cure rate was 83%.

Linezolid, a newer antimicrobial agent in the oxazolidinone family, is active against almost all community-associated MRSA isolates and group A streptococci. The disadvantages of this agent include its high cost, the lack of routine availability, hematologic side effects, and the potential for resistance among *S. aureus* strains, possibly by multiple mechanisms. Prolonged linezolid administration increases the likelihood of resistance, probably through the accumulation of mutations in multiple copies of the 23S ribosomal RNA *S. aureus* gene.

Rifampin is highly active against susceptible community-associated MRSA isolates, but a high frequency of mutations to rifampin resistance is a contraindication for the use of rifampin alone. Thus, a combination of trimethoprim–sulfamethoxazole or doxycycline with rifampin is sometimes used for the treatment of skin and soft-tissue infections caused by community-asso-
**Table 2. Oral Agents for the Outpatient Treatment of Putative Community-Associated MRSA Infections.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose*</th>
<th>Formulations</th>
<th>Main Side Effects and Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clindamycin (Cleocin)</strong></td>
<td>Adults: 300 mg thrice daily</td>
<td>Table, suspension</td>
<td>Diarrhea caused by <em>Clostridium difficile</em></td>
<td>Many patients dislike the taste of the suspension</td>
</tr>
<tr>
<td></td>
<td>Children: 30 mg/kg of body weight/day, in three or four divided doses</td>
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<tr>
<td><strong>Trimethoprim–sulfamethoxazole (Bactrim, Septra)</strong></td>
<td>Adults: 1 to 2 double-strength tablets twice daily (each tablet containing trimethoprim, 160 mg, and sulfamethoxazole, 800 mg)</td>
<td>Tablet, suspension</td>
<td>Nausea, vomiting, rash, photosensitivity, hematologic suppression (especially thrombocytopenia), the Stevens–Johnson syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: Trimethoprim, 8–12 mg/kg/day, and sulfamethoxazole, 40–60 mg/kg/day, in two divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Adults: 100–200 mg/day, in two or four divided doses</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, deposition in teeth and bones</td>
<td>Contraindicated in children younger than 9 years of age because of potential deposition in teeth and bones</td>
</tr>
<tr>
<td><strong>Doxycycline (Doryx, Adoxa, Doxy-100, Monodox, Vibramycin, Vibra-Tabs)</strong></td>
<td>Children: 2–4 mg/kg/day, in two or four divided doses</td>
<td></td>
<td>Nausea, photosensitivity, deposition in teeth and bones</td>
<td>Contraindicated in children younger than 9 years of age because of potential deposition in teeth and bones</td>
</tr>
<tr>
<td><strong>Minocycline (Dynacin, Minocin)</strong></td>
<td>Adults: 200 mg/day, in two divided doses</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, deposition in teeth and bones, vestibular toxicity</td>
<td>Contraindicated in children younger than 9 years of age because of potential deposition in teeth and bones</td>
</tr>
<tr>
<td></td>
<td>Children: 4 mg/kg/day, in two divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Linezolid (Zyvox)</strong></td>
<td>Adults: 600 mg twice daily</td>
<td>Tablet, suspension</td>
<td>Myelosuppression (usually thrombocytopenia), but can cause anemia or neutropenia, mostly with prolonged use</td>
<td>The cost is relatively high; oral suspension may not be immediately available at many pharmacies</td>
</tr>
<tr>
<td></td>
<td>Children: 30 mg/kg/day, in three divided doses</td>
<td></td>
<td></td>
<td>No suspension is commercially available; capsule powder may be sprinkled on food such as applesauce</td>
</tr>
<tr>
<td><strong>Rifampin (Rifadin, Rimactane)</strong></td>
<td>Adults: 20 mg/kg/day, in two or four divided doses; maximum dose, 600 mg/day</td>
<td>Capsule</td>
<td>Discoloration of body fluids, abnormalities in liver function, drug–drug interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: 20 mg/kg/day, in two or four divided doses; maximum dose, 600 mg/day</td>
<td></td>
<td>Cannot be used alone because resistant mutants are selected at an unacceptably high rate</td>
<td></td>
</tr>
</tbody>
</table>

* Optimal doses have not been established for all drugs listed.
associated MRSA, although data are lacking to provide support for this approach.

Fluoroquinolones should not be used to treat skin and soft-tissue infections caused by community-associated MRSA. Resistance to them develops readily in *S. aureus* and is already widely prevalent.24

**Inpatient Therapies**

Some patients with community-associated MRSA infection will require more aggressive treatment than incision and drainage with or without oral antimicrobial therapy on an outpatient basis. A decision to hospitalize a patient for parenteral therapy (Table 3) depends on several factors, including clinical judgment regarding the severity of the illness. The presence of a large abscess, fever, other signs of systemic infection, or high-risk characteristics such as an age younger than 6 months, diabetes, or immunodeficiency should prompt consideration of hospitalization. The detailed management of invasive disease due to community-associated MRSA is beyond the scope of this review.

Vancomycin is still considered the first-line treatment for hospitalized patients with invasive *S. aureus* infection. However, this drug should be switched if susceptibility testing indicates that a more rapidly bactericidal β-lactam agent such as oxacillin would be appropriate. Microbiologic treatment failure may occur with vancomycin even if there is no increase in the minimal inhibitory concentration (MIC) on susceptibility testing.55,56 *S. aureus* isolates with low-level (so-called intermediate) resistance to vancomycin (MIC, >2 μg per milliliter) as well as those with high-level resistance (MIC, >16 μg per milliliter) have been described, and they may not be identified by means of routine techniques for susceptibility testing.57 Although resistant isolates are believed to be infrequent, global decreased susceptibility (so-called MIC creep) among *S. aureus* isolates has been documented in several locations in the United States,58-60 and this decreased susceptibility may limit the continued effectiveness of vancomycin. Some experts have proposed that the use of a higher dose and maintenance of high serum levels of vancomycin may be beneficial, but the efficacy of these strategies has not been proved.

Parenteral clindamycin may be useful in regions where the likelihood of a resistant organism is low. It should not be used as sole therapy when the patient is moderately to severely ill.

Intravenous trimethoprim–sulfamethoxazole has undergone minimal evaluation for invasive *S. aureus* infection. A study of intravenous drug abusers with serious *S. aureus* infections antedated the epidemic of community-associated MRSA infection, and it indicated that intravenous trimethoprim–sulfamethoxazole was significantly less effective than vancomycin.61 Parenteral linezolid lacks bactericidal activity, which some experts believe is important in treating intravascular infection, a common feature of invasive disease. Moreover, reports of a case of endocarditis caused by a susceptible organism during linezolid therapy and of clinical failure in patients treated with linezolid for endocarditis have raised concerns about its use alone for severe, invasive *S. aureus* infections62,63 (an exception is health care–associated MRSA pneumonia, for which linezolid has proved efficacious64).

Tigecycline, a parenteral glycylcycline–minocycline derivative, was also recently approved by the Food and Drug Administration (FDA) for the

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**Figure 3. The D-Zone Test for Erythromycin-Resistant, Clindamycin-Susceptible Isolates.**

The Clinical and Laboratory Standards Institute advises clinical microbiology laboratories to perform a D-zone test on erythromycin-resistant, clindamycin-susceptible isolates. This test detects inducible clindamycin resistance; blunting of the clindamycin zone of inhibition (arrow) suggests the presence of an *erm* gene in the test isolate that is inducible by erythromycin. The *erm* gene can confer the macrolide–lincosamide–streptogramin B phenotype to an isolate with cross-resistance to macrolide antibiotics such as erythromycin, lincosamide antibiotics such as clindamycin, and streptogramin B antibiotics. E denotes erythromycin, and CC clindamycin concentration.
This approval was granted on the basis of data showing microbiologic eradication in 25 of 32 adults (78%) with complicated skin and soft-tissue infections.

A fixed combination of the streptogramins quinupristin and dalfopristin (Synercid) was licensed by the FDA for the treatment of skin and soft-tissue infections caused by methicillin-sensitive S. aureus. Its use has been limited by the potential for drug–drug interactions and by side effects (including arthralgias, myalgias, and gastrointestinal toxic effects).

Daptomycin, a cyclic lipodepsipeptide, has been approved by the FDA for use in patients with skin and soft-tissue infections. The success rate with the use of daptomycin for these infections is 75% — similar to that of vancomycin. It is also approved for MRSA bacteremia, including that associated with right-sided endocarditis, but it should not be used for pneumonia, for which its efficacy has been limited by its propensity for binding surfactant.

### A R E A S  O F  U N C E R T A I N T Y

The optimal oral antimicrobial regimen for the treatment of skin and soft-tissue infections is not

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose*</th>
<th>Main Side Effects and Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>2–4 g/day, in two to four divided doses</td>
<td>The red-man syndrome (a histamine-release syndrome usually manifested as flushing)</td>
<td>Slowing the rate of administration is usually sufficient management for the red-man syndrome, but accompanying hypotension may require discontinuation of the drug or additional intervention in rare cases. Excretion is slowed in patients with renal failure, and serum levels should be monitored in such patients to avoid drug accumulation; whether such monitoring is routinely necessary in patients with normal renal function is not clear, but it should be performed when multiple nephrotoxic drugs are administered simultaneously.</td>
</tr>
<tr>
<td>Clindamycin (Cleocin)</td>
<td>300 mg thrice daily</td>
<td>Diarrhea caused by C. difficile</td>
<td></td>
</tr>
<tr>
<td>Daptomycin (Cubicin)</td>
<td>4–6 mg/kg/day, in four divided doses</td>
<td>Unknown</td>
<td>Resistance was documented in 6 of 120 patients receiving this therapy†. Excretion is slowed in patients with renal failure, and dosage adjustment is recommended.</td>
</tr>
<tr>
<td>Tigecycline (Tygacil)</td>
<td>100 mg loading dose, then 50 mg every 12 hr</td>
<td>Unknown</td>
<td>Nausea, vomiting, photosensitivity, deposition in teeth and bones. Contraindicated in children younger than 9 years of age because of potential deposition in teeth and bones.</td>
</tr>
<tr>
<td>Linezolid (Zyvox)</td>
<td>600 mg/day, in two divided doses</td>
<td>Myelosuppression (usually thrombocytopenia, but also anemia or neutropenia), mostly with prolonged use</td>
<td>The cost is relatively high.</td>
</tr>
<tr>
<td>Quinupristin and dalfopristin (Synercid)</td>
<td>7.5 mg/kg, every 8–12 hr</td>
<td>Hyperbilirubinemia, arthralgias and myalgias, phlebitis, drug–drug interactions (especially with cytochrome P450 3A4 substrates)</td>
<td>Dosage adjustment may be necessary in patients with hepatic impairment.</td>
</tr>
</tbody>
</table>

* Optimal doses have not been established for all drugs listed.
† Data are from Fowler et al.55
known. A trial addressing this question, sponsored by the National Institutes of Health, is expected to be initiated this year.

The optimal management of recurrent community-associated MRSA disease is also uncertain. Although not well studied, the recurrence rate is believed to be 10% or higher. It is not clear whether recurrences represent autoinoculation or a new MRSA infection. At present, recurrent episodes are generally treated in the same way as the initial episode. In addition, “decolonization” strategies are frequently recommended in such cases, although neither the indications for their use nor their effectiveness in reducing the risk of recurrences is clear. One such strategy is the use of intranasal mupirocin to reduce nasal carriage of MRSA; however, eradication of nasal colonization appears to be transient, and the use of this agent remains controversial. Moreover, the recent identification of a mupirocin-resistance gene in USA300 isolates (which accounted for 97% of isolates in a recent study\(^24\)) and of mupirocin resistance among 11 community-associated MRSA isolates in Boston raises serious concern about exposing populations of staphylococci to this agent.\(^{67}\) Some experts have also proposed adjunctive attempts at skin decolonization. Topical chlorhexidine gluconate or 1 tsp (3.4 g) of bleach diluted in 1 gallon (3.8 liters) of bath water is commonly suggested, although these approaches have not been rigorously evaluated. The optimal strength of the chlorhexidine solution is not known, nor is it clear whether it is more effective if the solution is permitted to remain on the skin before rinsing.

Contagion among the close household contacts of patients, as well as correctional facility, school, and sports-team contacts, is well recognized. Although the risk of transmission has not been well quantified, anecdotal evidence suggests that more than 60% of households of children hospitalized with community-associated MRSA infections have one or more members with a history of a putative MRSA infection in the previous 6 months. If this estimate proves to be correct, it will lend support to the empirical treatment of an entire household (perhaps even including pets) if an effort to eradicate community-associated MRSA colonization in a patient is undertaken. The efficacy of such an approach has not been studied.

The role of fomites needs to be clarified. Hospital-acquired MRSA isolates can survive on a variety of inanimate surfaces, sometimes for weeks. It is unclear whether this is also true for community-associated MRSA isolates; if it is, their presence on such items as clothing, towels, and athletic equipment might contribute to outbreaks. Pets (including dogs and cats), livestock, and birds have been identified as MRSA carriers; their role in MRSA transmission to humans requires further evaluation.\(^{68}\) Local hygiene measures recommended by an expert panel from the Centers for Disease Control and Prevention (CDC) are shown in Table 4.

No vaccine is currently available for \textit{S. aureus}. Many experts believe that it is unlikely that a single-antigen approach will prove to be effective.

### Table 4. Recommended Measures to Limit the Spread of Community-Associated MRSA Isolates.\(^69\)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover draining wounds with clean bandages.</td>
<td></td>
</tr>
<tr>
<td>Wash hands, especially after contact with a contaminated wound.</td>
<td></td>
</tr>
<tr>
<td>Launder clothing after contact with a contaminated area on the skin.</td>
<td></td>
</tr>
<tr>
<td>Bathe regularly with use of soap.</td>
<td></td>
</tr>
<tr>
<td>Avoid sharing items (e.g., towels, bedding, clothing, razors, or athletic equipment) that may become contaminated by contact with wounds or skin flora.</td>
<td></td>
</tr>
<tr>
<td>Clean sports equipment with agents that are effective against staphylococci (e.g., a detergent or disinfectant registered by the Environmental Protection Agency, such as quaternary ammonium compounds or a solution of dilute bleach).</td>
<td></td>
</tr>
</tbody>
</table>

\(^69\) Information is modified from Gorwitz et al.\(^{69}\)

### Guidelines

The CDC has issued guidelines for the prevention and management of community-associated MRSA infections.\(^{69}\) The recommendations in this article are largely concordant with this review.

### Conclusions and Recommendations

With the increasing prevalence of community-associated MRSA infection, the management of skin and soft-tissue infections requires knowledge of local rates of MRSA infection. Many experts suggest an arbitrary threshold of more than 10% methicillin resistance among \textit{S. aureus} isolates...
causing skin and soft-tissue infections acquired in the community and recommend inclusion of antimicrobial therapy against community-associated MRSA when managing a putative *S. aureus* infection.

In a patient such as the man described in the vignette, presenting with an abscess or a purulent and necrotic skin lesion, incision and drainage are the cornerstones of therapy; purulent material should be cultured. In many patients, particularly those with small lesions (<5 cm in length), incision and drainage alone will be adequate therapy. If the skin lesions are large or accompanied by systemic signs of infection or if there is evidence of an increased risk of complicated community-associated MRSA disease, antimicrobial therapy that is active against community-associated MRSA is also recommended. Therapy ultimately should be guided by the results of susceptibility testing of cultures obtained before the initiation of therapy.

Although data directly comparing antimicrobial agents for the treatment of community-associated MRSA infection are lacking, clindamycin, trimethoprim–sulfamethoxazole, or a long-acting tetracycline such as doxycycline is a reasonable initial choice; linezolid is another possibility. Follow-up is essential, since relapse or recurrence may occur.

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Dr. Daum reports serving on paid advisory boards for Clorox, Sanofi Pasteur, GlaxoSmithKline, Pfizer, and the MRSA National Faculty Meeting (sponsored by Astellas and Theravance); receiving lecture fees from Nabi Biopharmaceuticals and Pfizer; and receiving grant support from Clorox, Pfizer, Sage Products, and Sanofi Pasteur. No other potential conflict of interest relevant to this article was reported.

I thank Michael David, M.D., Daniel Glikman, M.D., Stephen Weber, M.D., Loren Miller, M.D., and Sharmeen Younus, Pharm.D., for helpful critical comments and Mark A. Hostetler, M.D., of the Department of Pediatrics, University of Chicago, for the photographs of patients.

**REFERENCES**


36. Skiest DJ, Brown K, Cooper TW, Hoff-


A 60-year-old man presented with progressive swelling of the right side of the scrotum. He reported no history of trauma to this area and no sexually transmitted infections. The alpha-fetoprotein level was elevated at 3100 μg per liter (normal value, <8), and the serum level of the beta subunit of human chorionic gonadotropin was less than 1 IU per liter. Multidetector computed tomography with multiplanar reformation (Panel A) showed a large testicular tumor with lymphangitic spread along the testicular vessels to the associated draining lymph nodes below the renal hilus. Right-sided hydronephrosis is present because of compression of the ureter by the lymphatic metastases. Imaging also showed lung metastases (Panel B, arrows) and ileosacral osseous metastases (Panel C, long arrows) with infiltration of the iliac muscle (Panel C, short arrow) and the sacral spinal channel. Right-sided radical inguinal orchiectomy was performed, and histologic examination confirmed the diagnosis of advanced nonseminomatous germ-cell cancer. The patient subsequently received chemotherapy, which was complicated by fulminant septic shock in the setting of aplasia, which led to the patient’s death from multiorgan failure. These images show classic lymphatic and hematogenous metastatic pathways of advanced testicular cancer.

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Metastatic Germ-Cell Cancer

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Case 23-2007: A 9-Year-Old Boy with Bone Pain, Rash, and Gingival Hypertrophy

Christopher P. Duggan, M.D., M.P.H., Sjirk J. Westra, M.D., and Andrew E. Rosenberg, M.D.

Dr. Laura Chapman (Pediatrics): A 9-year-old boy with autism was admitted to this hospital because of pain in the hip, refusal to walk, and the recent onset of a rash and gingival swelling.

The patient was in his usual state of health until approximately 3 months before admission, when he had an upper respiratory illness with fever; shortly thereafter, he began to have right hip pain, to limp, and to have decreased energy. During the next several weeks, he began to have difficulty climbing stairs, became increasingly irritable, and began moaning in his sleep at night; his appetite decreased, and he lost 3.6 kg. Magnetic resonance imaging (MRI) of the hips at another hospital 7 weeks before admission to this hospital reportedly showed multifocal areas of hyperintensity in the bones and bone marrow edema. A test for antinuclear antibody factor was negative; results of other laboratory tests are shown in Table 1.

One month before admission, he saw an orthopedist at this hospital. On examination, the range of motion of both hips was normal, although he seemed to have pain at the end point of abduction of the right hip. He walked with a wide-based gait. Reflexes were normal. There were no petechiae. Radiographs of the spine and pelvis showed normal alignment of the bones without fracture or dislocation. Consultation with a neurologist and a hematologist were scheduled; however, 4 days later, the symptoms had markedly worsened; he ceased playing and refused to walk or sit up, and his mother noted a rash on his legs. He was admitted to this hospital.

He did not have fever, night sweats, dysphagia, nausea, emesis, dyspnea, cough, or change in urinary or bowel habits. At the age of 5 months, computed tomography (CT) of the head had shown communicating hydrocephalus, which had remained stable and had not required surgical intervention. Autism had been diagnosed at the age of 2 years. At the time of admission, his verbal communication was limited to squealing, single words, and echolalia. He had marked anxiety to strangers and engaged in stereotyped behaviors, including head banging.

At baseline, his motor function was normal, and he was incontinent of stool and urine. There was a cat in the home, which had not been sick. His parents and older sister were well. There was no exposure to insects and no recent travel. There was
a maternal family history of leukemia and breast and bone cancer, a paternal family history of leukemia and uterine and bone cancer, and no family history of neurologic or autoimmune disease. His only medication was clonidine, and he had no known drug allergies.

On physical examination, the patient was alert, and his vital signs were normal. The pupils were reactive to light, and a dilated funduscopic examination was normal. The oropharyngeal and nasal mucosa were normal. The lungs and abdomen were normal. There was a punctate, erythematous rash on the dorsa of the feet that extended to the tops of the thighs and was scattered on the arms and legs; it was not raised or excoriated. There was no tenderness to vertebral palpation. There was full range of passive motion in all joints of the arms and legs, but he grimaced at the end point of abduction of the left hip. There were no deformities, redness, or swelling of the joints. Motor strength was 4/5 throughout, and there was no muscular atrophy. He was able to bear weight, but he was unwilling to bend his knees or hips to sit or to bend over. His gait was wide-based with outstretched arms; he walked slowly and reached for support often, but there was no truncal ataxia. Neurologic examination was normal.

Levels of serum electrolytes, lactate dehydrogenase, creatine kinase, albumin, and total protein and results of renal- and liver-function tests were normal. Levels of C3 and C4 and anticardiolipin IgM and IgG were normal; tests for antinuclear

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range, Age-Adjusted†</th>
<th>Seven Weeks before Admission</th>
<th>First Admission</th>
<th>Third Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>White-cell count (per mm$^3$)</td>
<td>4,500–13,500</td>
<td>5,590</td>
<td>8,400</td>
<td>10,600</td>
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<tr>
<td>Neutrophils (%)</td>
<td>33–59</td>
<td>43</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>33–50</td>
<td>47</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4–11</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0–8</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0–3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35.0–45.0</td>
<td>28.9 (reference range, 33.4–40.1)</td>
<td>32.3</td>
<td>25.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.5–15.5</td>
<td>9.8</td>
<td>11.4</td>
<td>8.4</td>
</tr>
<tr>
<td>Erythrocyte count (per mm$^3$)</td>
<td>4.0×10$^6$–5.20×10$^6$</td>
<td>4.57×10$^6$</td>
<td>3.68×10$^6$</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg/cell)</td>
<td>25.0–33.0</td>
<td>24.9</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume (μm$^3$)</td>
<td>80–100</td>
<td>71</td>
<td>70</td>
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<tr>
<td>Platelet count (per mm$^3$)</td>
<td>150,000–450,000</td>
<td>311,000</td>
<td>327,000</td>
<td>408,000</td>
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<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
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<td>59</td>
<td>59</td>
<td>95</td>
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<tr>
<td>Rheumatoid factor</td>
<td>&lt;12.0</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/liter)</td>
<td>&lt;8.0</td>
<td></td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5–10.5</td>
<td>9.8</td>
<td></td>
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<tr>
<td>Ferritin (ng/ml)</td>
<td>30–300</td>
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<tr>
<td>Iron (μg/dl)</td>
<td>45–160</td>
<td>22</td>
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<tr>
<td>Iron-binding capacity (μg/dl)</td>
<td>228–428</td>
<td>320</td>
<td></td>
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<tr>
<td>Magnesium (mmol/liter)</td>
<td>0.7–1.0</td>
<td>1.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.5–5.5</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* To convert values for calcium to millimoles per liter, multiply by 0.250. To convert values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. To convert values for magnesium to millimoles per liter, multiply by 0.5. To convert values for phosphorus to millimoles per liter, multiply by 0.3229.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. Pediatric ranges are estimates derived from a combination of published normal ranges and internal data from the Massachusetts General Hospital for these age groups.
and anti–double-stranded DNA antibodies were negative. Other laboratory values are shown in Table 1. MRI of the brain on the fourth hospital day showed ventriculomegaly, unchanged from a study performed 6 years earlier. MRI of the cervical, thoracic, and lumbar spine showed no abnormality. On MRJ of the pelvis, T$_2$-weighted images showed multifocal, hyperintense, enhancing lesions throughout the bony pelvis with associated abnormal periosteal enhancement, most striking around the acetabula. A bone scan showed minimal increased uptake in the right sacroiliac joint.

Acetaminophen with codeine was prescribed, and the patient was discharged on the fifth day to follow up with a hematologist. During the next several days, he ceased walking altogether, and his mother believed that his knees were swollen. He was readmitted 4 days later. On the second hospital day, biopsies of iliac crest bone were performed under anesthesia; examination of the specimens disclosed apophyseal cartilage undergoing endochondral ossification, cancellous bone, and hematopoietic marrow with focal edema; flow cytometry showed no abnormal T cells or B cells. Synovial fluid aspirated from the left knee contained 917 white cells, 13% polymorphonuclear leukocytes, 29% lymphocytes, no blasts, and no red cells, and there was no bacterial growth on culture. Indomethacin (at a dose of 3 mg per kilogram of body weight per day) was begun; his gait improved, and he was discharged home with a walker on the fourth day.

During the next 10 days, his mother noted gingival swelling with bleeding, and the rash became confluent. He was readmitted to this hospital. The vital signs were normal. The left maxillary gingiva was hypertrophic, covered the molars, and protruded into the mouth. The right mandibular gingiva was hypertrophic, covered the molars, and protruded into the mouth. The right leg had increased uptake in the right sacroiliac joint.

On the second hospital day, a dermatology consultant noted that the lesions on the right leg had the appearance of perifollicular petechiae, which were slightly palpable. Additional diagnostic tests were performed.

Differential Diagnosis

Dr. Christopher P. Duggan: This 9-year-old child with autism presented with limb pain and a progressive decrease in ambulation, followed by a rash and gingival hypertrophy; there were radiographic changes of periosteal inflammation and elevated acute-phase reactants.

May we review the radiographic studies?

Dr. Sjirk J. Westra: Plain radiographs of the pelvis and the thoracolumbar spine were normal. On T$_1$-weighted MRJ, there was normal architecture of the bone and no gross destructive lesions within the pelvic skeleton. On fat-suppressed, T$_2$-weighted imaging with short-inversion-time inversion recovery (STIR), there were multifocal areas of high T$_2$-weighted signal in the bone marrow of both sacral wings and in the iliac bones around both sacroiliac joints (Fig. 1A) and around the triradiate cartilages (Fig. 1B). These signal changes are indicative of bone marrow edema, located in the metaphyseal equivalents of the pelvic bones. In addition, there was abnormal T$_2$-weighted signal in the periosteum of the left iliac bone (Fig. 1B) and in the left pubic bone adjacent to the hip joint. There were no soft-tissue abnormalities. Fat-suppressed T$_2$-weighted images after the administration of gadolinium showed abnormal enhancement of all lesions and abnormal periosteal enhancement in the posterior aspect of the left acetabulum. A radionuclide bone scan showed only slightly increased uptake over the right sacroiliac joint but was otherwise normal for the patient’s age.

The differential diagnosis of multifocal lesions in the metaphyseal equivalents of the pelvic bones includes multifocal osteomyelitis or a hematologic cancer. We considered Langerhans-cell histiocytosis, although the absence of lytic lesions on the plain radiographs would argue against this diagnosis. The lack of soft-tissue edema and the relatively normal bone scan argue against multifocal osteomyelitis. Because of the predilection of the abnormalities to the metaphyseal equivalents, where bone growth normally takes place, we considered metabolic disorders.

Dr. Zachary M. Grinspan (Pediatrics): The patient...
had a petechial rash on both legs up to his thighs, which localized around the hair follicles, sparing hairless areas of his ankles (Fig. 2A). He also had two purpuric lesions (7 to 8 mm in diameter) on his left lateral malleolus. General anesthesia was administered, and the trachea was intubated for a fluoroscopically guided corticosteroid injection of the sacroiliac joint and biopsy of the iliac bone. A cheek and lip retractor provided visualization of the gingival lesions. The right lower, right upper, and left upper gingiva were swollen, and the gingiva bled easily (Fig. 2B).

Dr. Duggan: The differential diagnosis of acquired limb pain, limp, or both in a child includes both localized and systemic disorders (Table 2). Several features of this case allow us to limit possible diagnoses. Child abuse or other trauma can be observed in patients with developmental delay, but the bilateral radiographic abnormalities argue against isolated trauma as a cause of his pain. Infectious causes including septic arthritis and osteomyelitis are less likely, since the bone lesions are multifocal and there was no recurrent fever. A normal neuromuscular examination reduces the likelihood of myopathies and neuropathies. Leukemia or lymphoma can present with limb pain or limp, and the white-cell count may be normal, but the bone marrow biopsy did not reveal a malignant tumor. Endocrinopathies, including diabetes mellitus and hyperparathyroidism, are not suggested by the clinical presentation or laboratory studies. The imaging studies do not suggest a bone tumor.

Figure 1. MRI of the Pelvis.
Coronal images obtained with the STIR technique (short-inversion-time inversion recovery) demonstrate foci of increased T₂-weighted signal in the bone marrow in the metaphyseal analogues of the pelvis, notably adjacent to both sacroiliac joints (Panel A) and the triradiate cartilages of both acetabula (Panel B). There is high-intensity signal in the periosteum of the left iliac bone (Panel B, arrow).

Figure 2. Clinical Images of the Patient.
Petechiae are present on both legs up to the thigh (Panel A). The petechiae are localized around hair follicles (inset), and hairless areas are spared. A photograph obtained during examination of the oral cavity, with the use of a cheek and lip retractor while the patient was under general anesthesia, shows the gingival lesions (Panel B). The right lower, right upper, and left upper gingiva (arrows) are swollen, and the gingiva bled easily.
Several features of this child’s presentation are consistent with spondyloarthropathy, including his male sex, young age (although presentation is typically in the second decade of life), gradual onset of symptoms, and elevated erythrocyte sedimentation rate. The history does not note morning stiffness or improvement over the course of the day, which are common in spondyloarthropathies. In addition, knee or other joint swelling was not noted on physical examination. The absence of joint swelling, warmth, and redness argues against a diagnosis of rheumatic disease.

CONDITIONS WITH ALTERED INTESTINAL PERMEABILITY
Arthritis is a common complication of diseases with altered intestinal permeability, including celiac disease, infectious enteropathies, and idiopathic inflammatory bowel disease. Could this child have involvement of the sacroiliac joint as a component of undiagnosed colitis or enteritis? A possible link between gastrointestinal diseases and autism has been pursued for many years but never proved. Studies have suggested associations with celiac disease, infectious enteropathies, and idiopathic inflammatory bowel disease. Could this child have involvement of the sacroiliac joint as a component of undiagnosed colitis or enteritis? A possible link between gastrointestinal diseases and autism has been pursued for many years but never proved. Studies have suggested associations with celiac disease, infectious enteropathies, and idiopathic inflammatory bowel disease. Could this child have involvement of the sacroiliac joint as a component of undiagnosed colitis or enteritis?

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS
Chronic recurrent multifocal osteomyelitis is an inflammatory condition that often affects the metaphyses of long bones and has a remitting and relapsing course. It is characterized by the insidious onset of local joint swelling and pain, and increased signal intensity on T₁-weighted images are seen with MRI. Girls are affected more often than boys, and the disorder has an overall favorable prognosis. Chronic recurrent multifocal osteomyelitis could explain several of the findings in this case, but it remains a diagnosis of exclusion since there are no pathognomonic findings. Once the rash and gingival lesions appeared, this diagnosis became less likely.

RHEUMATOLOGIC DISEASES
Juvenile rheumatoid arthritis can present with limb pain and difficulty walking. The negative rheumatoid factor does not rule out rheumatologic conditions since only a minority of children with juvenile rheumatoid arthritis are seropositive at presentation. Spondyloarthropathies are a family of related disorders that include ankylosing spondylitis, Reiter’s syndrome, reactive arthritis, psoriatic arthritis, spondyloarthropathy associated with inflammatory bowel disease, undifferentiated spondyloarthropathy, Whipple’s disease, and Behçet’s disease. These are the second most commonly diagnosed rheumatologic condition, after juvenile rheumatoid arthritis.

Table 2. Differential Diagnosis of Acquired Limp or Limb Pain.

<table>
<thead>
<tr>
<th>Localized Diseases</th>
<th>Systemic Diseases</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Connective-tissue disorders</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Dermatomyositis</td>
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<tr>
<td>Septic arthritis</td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td>Myositis</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Kawasaki’s disease</td>
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<tr>
<td>Chronic recurrent multifocal</td>
<td>Polyanteritis nodosa</td>
</tr>
<tr>
<td>osteomyelitis</td>
<td>Systemic lupus erythematous</td>
</tr>
<tr>
<td>Trauma</td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Chondroma or sarcoma</td>
<td>Spondyloarthropathy</td>
</tr>
<tr>
<td>Bone tumors</td>
<td>Endocrinopathy</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Ewing’s or other sarcoma</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Other disorders</td>
<td>Hematologic diseases</td>
</tr>
<tr>
<td>Legg–Calvé–Perthes disease</td>
<td>Sickle cell disease</td>
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<tr>
<td>Toxic synovitis</td>
<td>Hemoglobinopathy</td>
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<td></td>
<td>Leukemia</td>
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<td></td>
<td>Lymphoma</td>
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<tr>
<td></td>
<td>Neuropathies</td>
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<td></td>
<td>Guillain–Barré syndrome</td>
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<td></td>
<td>Heavy-metal or vitamin A intoxication</td>
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<td></td>
<td>Vitamin deficiency</td>
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<tr>
<td></td>
<td>Rickets</td>
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<tr>
<td></td>
<td>Scurvy</td>
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</tbody>
</table>

1. Vitamin deficiency
2. Neonatal alloimmune neutropenia
3. Vitamin A deficiency
4. Scurvy
5. Scurvy
6. Vitamin D deficiency
7. Scurvy
8. Vitamin A deficiency
9. Scurvy
10. Vitamin D deficiency
11. Scurvy
12. Vitamin A deficiency
13. Vitamin A deficiency
14. Vitamin D deficiency

Lost in the controversy about the purported relationship between autism and MMR vaccination was the finding that urinary levels of methylmalonic acid were higher in the children with autism than in age-matched controls, and a finding consistent with vitamin B₁₂ deficiency. Indeed, a number of studies have shown that children with autism, who characteristically consume a diet highly restricted in color and consistency, are at risk for micronutrient deficiencies, including deficiencies of vitamin A, vitamin D, and
Could this patient’s multiorgan presentation (joints, skin, and oral mucosa) be related to a vitamin deficiency? When a much smaller differential-diagnosis list that might explain his gingival lesions is considered (Table 3), vitamin C deficiency is the one diagnosis that could explain all of his symptoms.

**Scurvy**

Scurvy is one of the earliest recorded diseases in humans, first described in the Ebers papyrus in 1550 B.C. Its successful treatment with oranges and lemons was established by Scottish surgeon James Lind in one of the first recorded controlled clinical trials, published in 1753. Depivation of vitamin C, named ascorbic acid because of its antiscorbutic properties, was subsequently shown to produce symptoms of scurvy after 30 to 40 days.\(^{16,17}\)

Ascorbic acid is a reversible reducing agent that is an essential cofactor for the hydroxylation of proline to hydroxyproline in collagen synthesis and for the hydroxylation of the neurotransmitter dopamine to noradrenaline.\(^{18}\) Many signs and symptoms of vitamin C deficiency relate to its essential role in collagen synthesis, including dermatologic manifestations of petechia, ecchymoses, corkscrew hairs, and hyperkeratosis. Perifollicular hemorrhages, which were seen in this case, are particularly characteristic. Systemic symptoms include lassitude and fatigue (as was noted in this case), and neurologic symptoms can include depression and vasomotor instability. Gingival swelling and hemorrhage and bone disease due to subperiosteal bleeding are common and were manifested in this patient.\(^{19}\)

Why did scurvy develop in this child at this time? Many children with autism have limited dietary intake of energy, macronutrients and micronutrients, which is why a daily complete multivitamin is generally recommended. This child’s symptoms began after an upper respiratory infection; possibly the increased metabolic needs associated with this infection unmasked a subclinical vitamin C deficiency.

**Dr. Nancy Lee Harris** (Pathology): Dr. Whelan and Dr. Seashore, would you comment on your impressions when you saw this child?

**Dr. J. Patrick Whelan** (Pediatric Rheumatology): This patient presented with hip pain that was striking, despite a relatively normal examination. Compression of the pelvis, which puts pressure on the sacroiliac joints, elicited pain, suggesting the sacroiliac joints as a source of the pain. The elevated inflammatory indexes, including C-reactive protein and erythrocyte sedimentation rate, suggested an inflammatory cause. Since pain in the sacroiliac joint may not respond to naproxen, I began indomethacin, another good treatment for this type of pain. In retrospect, the indomethacin may have precipitated the gingival hemorrhage and the petechial rash, both of which developed quite dramatically during the 10 days after starting the drug.

**Dr. Carl Seashore** (Pediatrics): The medical team on the child’s third hospitalization had the benefit of having watched the results of his physical examinations change over time. The development of skin lesions and gingival swelling raised the suspicion of vitamin C deficiency. The medical team reinterviewed the patient’s mother, with the patient present, specifically about the patient’s dietary history. We learned that the patient had increasingly limited his diet since the onset of his bony pain several months earlier, and for the past month or two had consumed only toaster pastries and cola drinks, neither of which contain vitamin C; he refused to eat fruits or vegetables, drank no juice, and did not take a multivitamin. We obtained plain radiographs of the hands and feet, which we thought might show more classic diagnostic features of vitamin C deficiency. The skin lesions were also biopsied.

**Dr. Harris:** Dr. Westra, will you show us the bone images?

**Dr. Westra:** It is ironic that in this hospital, where we may begin with the most advanced techniques, MRI and CT, the diagnosis in this case was made on plain films. On the hand film (Fig. 3A), this patient’s bone age was 1 year behind his chronologic age, and there was widening of and irregularity around the growth plate. Most of the growth of the skeleton takes place around the

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**Table 3. Differential Diagnosis of Gingival Swelling.**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Phenyltoin exposure</td>
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<tr>
<td>Pyogenic granuloma</td>
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<tr>
<td>Aphthous ulcers</td>
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<tr>
<td>Infectious gingivitis</td>
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<tr>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Behçet’s disease</td>
</tr>
<tr>
<td>Dental abscess</td>
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<tr>
<td>Scurvy</td>
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The new england journal of medicine

Figure 3. Plain Radiographs of the Hands and Knees.

A radiograph of the left wrist (Panel A) shows irregularity with widening of the distal ulnar physis (arrow). However, there is normal mineralization of the zone of provisional calcification on the metaphyseal side of the growth plates and surrounding the epiphyses. (The curved band is a tube outside the patient’s hand.) A radiograph of the right knee (Panel B) shows additional findings typical of scurvy: metaphyseal irregularities with spurring (Pelkan’s sign, black arrows); white lines surrounding the epiphyses (Wimberger’s sign), indicative of osteoporosis; a white line of Fränkel in the zone of provisional calcification (white arrowhead) with a lucent line immediately below this (Trummerfeld zone or scurvy line, black arrowheads); and periosteal reactions along the metaphyses (white arrows). The estimated bone age is 2 years behind the patient’s chronologic age.

knee; this patient was delayed 2 years in skeletal maturation in the knee. There is osteoporosis of the epiphysis, which is surrounded by a sclerotic ring (ring sign). Magnified views (Fig. 3B) reveal periosteal elevations due to subperiosteal hemorrhages and irregularities, fragmentation, and spurs at the margins of the metaphysis (Pelkan’s sign), which is typical of scurvy, especially in the healing phase. These irregularities can mimic the metaphyseal corner fractures seen in cases of child abuse. There is a dense zone of provisional calcification at the margins of the growth plate (white line, or Fränkel’s sign), and immediately below that a lucent line (Trummerfeld zone or scurvy line), which is pathognomonic of scurvy. These radiologic findings only become manifest after 3 to 6 months of nutritional deficiency.

Dr. Andrew E. Rosenberg: Can you rule out a component of rickets?

Dr. Westra: There was good mineralization at the ends of the bones; in rickets there would be a lack of mineralization in that area.

Clinical Diagnosis

Scurvy.

Dr. Christopher P. Duggan’s Diagnosis

Scurvy.
Dr. Rosenberg: The specimen of the bone biopsy from the iliac crest performed on an earlier admission (Fig. 4A) contained marrow that was abnormal, with numerous extravasated red cells, edema, and early fibrosis; these correlate with the abnormal findings seen on MRI and CT scanning. The skin biopsy performed on the current admission appears relatively normal at first glance; however, extravasated red cells are present in the dermis around hair follicles (Fig. 4B). This finding indicates recent bleeding and underlies the perifollicular petechiae noted in this patient. The pathologic alterations of the skin and bone are non-specific, but in conjunction with the other clinical findings, they support the diagnosis of scurvy.

The manifestations of scurvy in this patient were caused by deficient production of collagen in connective tissue, particularly that of the supportive sheaths around small blood vessels, and of rapidly growing bone. The skeletal changes in scurvy are most severe in young children such as this patient, because their skeletal tissues are still growing, and the periosteum is not as tightly bound to the surface of the cortex as it is in adults. Deficient collagen in subperiosteal blood vessels leads to rupture and hemorrhage, which mechanically lifts the periosteum from the underlying cortex. Reparative osteoblasts deposit reactive bone, which can be seen on plain radiography, as in this case. Similar findings occur in the metaphysis at the base of the growth plate; reduced collagen production results in decreased bone deposition, in structural weakness, and in both hemorrhage and fractures with minimal stress. With treatment, these pathologic changes of scurvy will completely resolve.

Dr. Seashore: The serum vitamin C level was less than 0.12 mg per deciliter (normal range, 0.20 to 1.90 [7 μmol per liter; normal range, 11 to 108]). The levels of 25-hydroxyvitamin D and parathyroid hormone were also low at 13 ng per milliliter (normal range, 20 to 100) and 9 pg per milliliter (normal range, 10 to 60), but the 1,25-dihydroxyvitamin D level was normal, at 10 pg per milliliter (normal range, 6 to 62). Vitamin C, at a dose of 160 mg daily, and a pediatric multivitamin were begun on the third hospital day, and by the fourth day the patient appeared more comfortable, began sitting up in bed, and was even able to bear weight on his legs. The next day he was discharged home with physical therapy, and at a follow-up visit 1 month later, he showed continuing improvement.

Scurvy.

Dr. Duggan reports receiving consulting fees from and serving on the paid advisory board of Groupe Danone. No other potential conflict of interest relevant to this article was reported.
REFERENCES


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Therapy for Bronchiolitis: When Some Become None
Caroline Breese Hall, M.D.

In past centuries, infant mortality in the first year of life was described as the greatest plague. In infants in the 21st century continue to be plagued by high rates of hospitalization, and bronchiolitis is the number one cause. Despite therapeutic advancements, hospitalizations for bronchiolitis have continued to increase. The annual rate of emergency department visits for bronchiolitis during the season of respiratory syncytial virus, the major cause of this condition, has been estimated as 22.8 per 1000 for children 12 months of age or younger. Yearly costs for bronchiolitis hospitalizations exceed $700 million. Yet even these striking figures underestimate the health care burden imposed by bronchiolitis. They do not reflect the costs associated with the many more frequent office visits of less ill children or with the secondary infections among high-risk family contacts.

A better indicator of the need for control of bronchiolitis is the increasing accumulation of therapeutic studies and the continued conundrums and controversies they engender. The clinical manifestations, course, and pathology of bronchiolitis have been well described, but the pathogenesis has not. Whether the pulmonary disease results from the acute lytic effects of the virus, the infant’s immune response, or both remains unclear. This may partially explain why effective interventions remain elusive.

Current therapeutic options for bronchiolitis are few — primarily antiviral drugs, bronchodilators, and corticosteroids — and all are controversial. Not one is routinely recommended. Yet one or more of these agents, as well as antibiotics, are administered to as many as 50 to 80% of infants with bronchiolitis admitted to hospitals in the United States and other countries. Part of the rationale for their use is their acknowledged benefit of diminishing the respiratory distress from other obstructive airway illnesses, such as asthma. Furthermore, corticosteroids may affect the pathogenesis of bronchiolitis attributed to respiratory syncytial virus. Both clinical and experimental studies indicate that an altered and augmented immune response of the young infant contributes to the phenotypic expression and severity of respiratory syncytial virus disease and may predispose the infant to pulmonary sequelae. The variable compliance with the recommendations against the routine use of corticosteroids may also relate to the conflicting results of the studies. They have been heterogeneous in design and generally involved small numbers of patients, thus reducing the strength of their evidence-based recommendations.

In this issue of the Journal, Corneli and colleagues report on a randomized trial examining whether dexamethasone administered to previously healthy infants presenting with a first episode of wheezing diagnosed as moderate-to-severe bronchiolitis reduces the need for hospitalization. The results, although negative, are important and will probably be accompanied by close scrutiny of the study’s design and the extent of its clinical relevance.

The study, which involved 20 emergency departments, was designed to avoid many of the deficits of previous corticosteroid trials. It was conducted over three respiratory seasons, and personnel at each site received yearly training in study procedures. The infants in the trial received a single oral dose of dexamethasone (1 mg per kilogram of body weight) or placebo, and during the next 4 hours their respiratory status was assessed with use of a standardized scoring instru-
ment. The study is singular in the number of infants enrolled (600) and in the broad spectrum of contributing emergency departments.

Nonetheless, variations in practice among the sites probably existed. The primary outcome — the decision to hospitalize or discharge the infant — was determined by individual physicians, but it was corroborated as a valid measure of the effect of dexamethasone by the secondary outcome — the change in the respiratory status after 4 hours as measured by the Respiratory Assessment Change Score. No significant difference was found between the infants treated with the corticosteroid and those receiving placebo. The trial was designed to closely duplicate the methods of a previous controlled study of 70 infants that demonstrated, in contrast with this trial, significant benefit from the oral administration of dexamethasone as compared with placebo. However, the degree of change in score that is predictive of a relevant change in clinical status has not been determined. The short period of observation also potentially limits the study’s value for predicting the subsequent prognosis.

The strict criteria for inclusion in the study by Corneli et al. enhanced the uniformity of the enrolled population, but these criteria also limited the study’s representation of the overall population of infants presenting with bronchiolitis. What should be considered, therefore, is whether the results of this carefully defined segment of bronchiolitis cases can and should be applied to the treatment of other infants with a first episode of bronchiolitis. If not, will the conclusions be clinically and economically relevant?

Of 8686 patients initially assessed, 93% were considered ineligible, 91% of whom did not meet the inclusion criteria. A notably large proportion, 41%, was excluded because the infants had had a previous episode of wheezing; one fourth were not considered ill enough to meet the criteria for moderate-to-severe bronchiolitis. Still, these infants were judged by their parents or primary physician to be ill enough to require evaluation in an emergency department, and they would make up an even larger proportion of the bronchiolitis cases seen in office practices than the infants who were enrolled in the study.

Infants younger than 2 months and children older than 12 months were also excluded from the study. Knowing the proportion of children with bronchiolitis presenting to the participating emergency departments within these age groups would be of interest. The majority of infants hospitalized with bronchiolitis are less than 6 months of age, and most are 2 to 3 months old. These youngest infants are the most likely to have acute complications, such as apnea, and altered responses to corticosteroid therapy. Children older than 1 year of age, although less likely to be hospitalized because of their larger airways and more competent immune systems, continue to have considerable rates of hospitalization. The characteristics of bronchiolitis among these younger and older children may differ from those of the illness as it occurs in children between 2 and 12 months of age. For this very reason, their exclusion from the study is warranted, but applying the findings of the study to these children is not justified.

An important question is whether corticosteroid administration diminishes the risk of the recurrent wheezing that develops in 20 to 50% of infants diagnosed with bronchiolitis. Although these episodes of recurrent wheezing are most frequent in the first several years after an infant contracts bronchiolitis, they have been linked to the later occurrence of asthma and chronic lung abnormalities. The effect of corticosteroid therapy on the development of later pulmonary dysfunction is unresolved. Among the limited number of studies examining this issue, a few have suggested benefit, but more have not. Follow-up of the children enrolled in the Corneli study could extend its value and answer a major clinical question.

These questions and the potential limitations of the study should not diminish recognition of the soundness of the study’s results and their clinical pertinence. The findings are bolstered by the study’s size and the controlled, randomized design. The conclusions are corroborated by the additional demonstration that the findings were independent of site and extended beyond the 4 hours of initial observation, according to an interview with the parent or guardian and chart review. Corticosteroid therapy did not significantly affect the duration of hospitalization or the need for subsequent medical visits or readmission.

Despite the value of this study, the long history of therapies and recommendations attending bronchiolitis suggest that the study’s results will not appreciably change the nature of the care pro-
vided by the primary physician faced with a young, distressed infant and anxious parents. Withholding therapy is much more difficult than giving it.

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Network Medicine — From Obesity to the “Diseasome”
Albert-László Barabási, Ph.D.

A recent study reported that among people who carried a single copy of the high-risk allele for the FTO gene, which is associated with fat mass and obesity, the risk of obesity increased by 30%. The risk of obesity increased by 67% among people who carried two alleles, and on average they gained 3.0 kg (6.6 lb) or more.1 Given that approximately one sixth of the population of European descent is homozygous for this allele, this link between the FTO gene and obesity appears to be one of the strongest genotype-phenotype associations detected by modern genome-screening techniques.

That obesity has a genetic component is not surprising; researchers have long known that it often runs in families. In this issue of the Journal, Christakis and Fowler suggest that friends have an even more important effect on a person’s risk of obesity than genes do.2 The authors reconstructed a social network showing the ties between friends, neighbors, spouses, and family members among participants of the Framingham Heart Study, making use of the fact that the participants had been asked to name their friends to facilitate follow-up in the study. The authors observed that when two persons perceived each other as friends, if one friend became obese during a given time interval, the other friend’s chances of following suit increased by 171%. Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40%. The results of this study also indicate that obesity is clustered in communities. For example, the risk that the friend of a friend of an obese person would be obese was about 20% higher in the observed network than in a random network; this effect vanished only by the fourth degree of separation.

In the past 7 years, our understanding of networks has undergone a revolution because of the emergence of a new array of theoretical tools and techniques for mapping out real networks. These advances have included some surprises indicating that most real networks in technologi-
cal, social, and biologic systems have common designs that are governed by simple and quantifiable organizing principles. The growing interest in interconnectedness has brought into focus an often ignored issue: networks pervade all aspects of human health. One example of this trend involves social networks and their impact on the spread of obesity or pathogens — from influenza to the severe acute respiratory syndrome or the human immunodeficiency virus. The role of neural networks in various psychiatric and neurodegenerative diseases is another example. In fact, network analysis is poised to play the biggest role at the cellular level, since most cellular components are connected to each other through intricate regulatory, metabolic, and protein–protein interactions. Because of these many functional links, the defects of various genes spread throughout the intracellular network, affecting the activity of genes that otherwise carry no defects.

To understand various disease mechanisms, it is not sufficient to know the precise list of “disease genes”; instead, we should try to map out the detailed wiring diagram of the various cellular components that are influenced by these genes and gene products. Such network-based thinking has already provided insights into the pathogenesis of several diseases. For example, a recent study suggested that 18 of the 23 genes known to be associated with ataxia are part of a highly interconnected subnetwork; in another example, a reverse-engineered subnetwork indicated that the androgen-receptor gene might be used to detect the aggressiveness of primary prostate cancer.

The existence of intricate molecular links between subcellular components and disease genes raises another possibility: that is, diseases may not be as independent of each other as medical practitioners currently consider them to be. For example, could a genetic origin account for the fact that obesity is a risk factor for diabetes? A quick look at the list of genes associated with these two diseases indicates that several genes, including ectoenzyme nucleotide pyrophosphate phosphodiesterase (ENPP1), peroxisome-proliferator–activated receptor γ (PPARγ), and — more recently — FTO, may be implicated in both diseases. In addition to the well-known link between diabetes and obesity, the large number of genes shared by often quite distinct disorders indicates that these diseases may have common genetic origins. Human diseases, therefore, themselves form a network in which two diseases are connected if they share at least one gene. In this disease network, obesity has links to seven diseases, including asthma, lipodystrophy, and glioblastoma (Fig. 1). Thus, the network concept reveals a number of surprising connections between diseases, forcing us to rethink the way in which we classify and separate them.

In the long run, networks may affect all aspects of medical research and practice. Indeed, the fundamental question of where function lies within a cell is slowly shifting from a single-minded focus on genes to the understanding that behind each cellular function there is a discernible network module consisting of genes, transcription factors, RNAs, enzymes, and metabolites. This understanding forces us to view diseases as the breakdown of selected functional modules rather than as single or small groups of genes. Given the many components of such functional modules, there are different paths to disease-inducing systems failure; this explains why often many genes are linked to the same disease phenotype. Similarly, the effects of drugs are not limited to the molecules to which they directly bind; instead, these effects can spread throughout the cellular network in which they act, causing unwanted side effects. Therefore, drug side effects are inherently network phenomena.

Naturally, network-based thinking may account for the environmental and social influences on disease as well. In this context, we must understand the human interactions encompassing social and family links, proximity-based contacts, and transportation networks. For example, recent advances in the study of sexual networks have led to new protocols for drug dispersion. These protocols are expected to be more efficient in combating the acquired immunodeficiency syndrome in underdeveloped countries than current protocols that are based on social need.

The Human Genome Project has revolutionized gene hunting, leading to an explosion in the number of detected associations between genes and disease phenotypes. The beauty of genomewide association studies lies in their ability to quantify their own limitations. For instance, many of the newfound disease-associated genetic mutations account for only a tiny fraction of disease occurrences. There is a tendency to believe that the rest are hidden in more genes.
Although they are often treated separately, most human diseases are not independent of each other. Many diseases are associated with the breakdown of functional modules that are best described as subnetworks of a complex network connecting many cellular components. Therefore, an understanding of the functionally relevant genetic, regulatory, metabolic, and protein–protein interactions in a cellular network will play an important role in understanding the pathophysiology of human diseases (bottom layer). One way to visualize the ensuing potential interrelationships among human diseases is to construct a disease network (middle layer) in which two diseases are connected if they have a common genetic or functional origin. For example, on the basis of our current knowledge of disease genes, obesity is connected to at least seven other diseases such as diabetes, asthma, and insulin resistance, since genes associated with these diseases are known to affect obesity as well. The third network of key importance to human disease is the social network, which encompasses all human-to-human interactions (e.g., familial, friendship, sexual, and proximity-based contacts) that play a role in the spread of pathogens (top layer). These networks also have an important role in the spread of obesity. Efforts to understand the interactions between the cellular, disease, and social networks are part of network medicine, which aims to quantify the complex interlinked factors that may contribute to individual diseases.
As the article by Christakis and Fowler shows, the answer is not always as simple as that. Networks, in this case those that pertain to social influence, may have just as strong an impact on the development of obesity as the otherwise strong genetic effects. The role of links and connections does not stop here. In the past few years, we learned that network effects increasingly affect all aspects of biologic and medical research, from disease mechanisms to drug discovery. It is only a matter of time until these advances will start to affect medical practice as well, marking the emergence of a new field that may be aptly called network medicine.

No potential conflict of interest relevant to this article was reported.

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Cancer and the Constitution — Choice at Life’s End

George J. Annas, J.D., M.P.H.

J.M. Coetzee’s violent, anti-apartheid Age of Iron, a novel the Wall Street Journal termed “a fierce pageant of modern South Africa,” is written as a letter by a retired classics professor, Mrs. Curren, to her daughter, who lives in the United States. Mrs. Curren is dying of cancer, and her daughter advises her to come to the United States for treatment. She replies, “I can’t afford to die in America. . . . No one can, except Americans.”

Dying of cancer has been considered a “hard death” for at least a century, unproven and even quack remedies have been common, and price has been a secondary consideration. Efforts sponsored by the federal government to find cures for cancer date from the establishment of the National Cancer Institute (NCI) in 1937. Cancer research was intensified after President Richard Nixon’s declaration of a “war on cancer” and passage of the National Cancer Act of 1971.

Most recently, calls for more cancer research have followed the announcement by Elizabeth Edwards, wife of presidential candidate John Edwards, that her cancer is no longer considered curable.

Frustration with the methods and slow progress of mainstream medical research has helped fuel a resistance movement that distrusts both conventional medicine and government and that has called for the recognition of a right for terminally ill patients with cancer to have access to investigational cancer drugs. Prominent examples include the popularity of Krebiozen in the 1950s and of laetrile in the 1970s. As an NCI spokesperson put it more than 20 years ago, when thousands of people were calling the NCI hotline pleading for access to interleukin-2, “What the callers are saying is, ‘Our mother, our brother, our sister is dying at this very moment. We have nothing to lose.’” Today, families search the Internet for clinical trials, and even untested chemicals such as dichloroacetate, that seem to offer them some hope. In addition, basing advocacy on their personal experiences with cancer, many families have focused their frustrations on the Food and Drug Administration (FDA), which they see as a government agency denying them access to treatments they need.

In May 2006 these families won an apparent major victory when the Court of Appeals for the District of Columbia, in the case of Abigail Alliance v. Von Eschenbach (hereafter referred to as Abigail Alliance), agreed with their argument that patients with cancer have a constitutional right of access to investigational cancer drugs. In reaction, the FDA began the process of rewriting its own regulations to make it easier for terminally ill patients not enrolled in clinical trials to have access to investigational drugs. In November 2006, the full bench of the Court of Appeals vacated the May 2006 opinion, and the case was reheard in March 2007. The decision of the full bench, expected by the fall, will hinge on the answer to a central question: Do terminally ill adult patients with cancer for whom there are no effective treatments have a constitutional right of access to investigational drugs their physicians think might be beneficial?

The Abigail Alliance for Better Access to Developmental Drugs (hereafter called the Abigail Alliance) sued the FDA to prevent it from enforcing its policy of prohibiting the sale of drugs that had not been proved safe and effective to competent adult patients who are terminally ill and have no alternative treatment options. The Abigail Alliance is named after Abigail Burroughs, whose squamous-cell carcinoma of the head and neck was diagnosed when she was only 19 years old. Two years later, in 2001, she died. Before her death she had tried unsuccessfully to obtain investigational drugs on a compassionate use basis from ImClone and AstraZeneca and was accepted for a clinical trial only shortly before her death.
Her father founded the Abigail Alliance in her memory.6

The district court dismissed the Abigail Alliance lawsuit. The appeals court, in a two-to-one opinion written by Judge Judith Rogers, who was joined by Judge Douglas Ginsburg, reversed the decision. It concluded that competent, terminally ill adult patients have a constitutional “right to access to potentially life-saving post-Phase I investigational new drugs, upon a doctor’s advice, even where that medicine carries risks for the patient,” and remanded the case to the district court to determine whether the FDA’s current policy violated that right.3

**THE RIGHT TO LIFE**

The appeals court found that the relevant constitutional right was determined by the due-process clause of the Fifth Amendment: “no person shall be . . . deprived of life, liberty, or property without due process of law.” In the court’s words, the narrow question presented by *Abigail Alliance* is whether the due-process clause “protects the right of terminally ill patients to make an informed decision that may prolong life, specifically by use of potentially life-saving new drugs that the FDA has yet to approve for commercial marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings.”3

The court answered yes, finding that this right has deep legal roots in the right to self-defense, and that “Barring a terminally ill patient from the use of a potentially life-saving treatment impinges on this right of self-preservation.”3 In a footnote, the court restated this proposition: “The fundamental right to take action, even risky action, free from government interference, in order to save one’s own life undergirds the court’s decision.”3 The court relied primarily on the *Cruzan* case,7 in which the Supreme Court recognized the right of a competent adult to refuse life-sustaining treatment, including a feeding tube:

The logical corollary is that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life. Like the right claimed in *Cruzan*, the right claimed by the *Abigail* Alliance to be free of FDA imposition does not involve treatment by the government or a government subsidy. Rather, much as the guardians of the comatose [sic] patient in *Cruzan* did, the Alliance seeks to have the government step aside by changing its policy so the individual right of self-determination is not violated.3

The appeals court concluded that the Supreme Court’s 1979 unanimous decision on laetrile,8 in which the Court concluded that Congress had made no exceptions in the FDA law for terminally ill cancer patients, was not relevant because laetrile had never been studied in a phase 1 trial and because the Court did not address the question of whether terminally ill cancer patients have a constitutional right to take whatever drugs their physicians prescribe.

**THE DISSENT**

Judge Thomas Griffith, the dissenting judge, argued that the suggested constitutional right simply does not exist. He noted, for example, that the self-defense cases relied on are examples of “abstract concepts of personal autonomy,” and cannot be used to craft new rights. As to the nation’s history and traditions, he concluded that the FDA’s drug-regulatory efforts have been reasonable responses “to new risks as they are presented.”3 Accepting his argument leaves the majority resting squarely on *Cruzan* and the laetrile case. As to *Cruzan*, the dissent argued that “A tradition of protecting individual freedom from life-saving, but forced, medical treatment does not evidence a constitutional tradition of providing affirmative access to a potentially harmful, even fatal, commercial good.”3 As to the laetrile case, the judge noted simply that the Court had agreed with the FDA that, “For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.”3,8

Finally, the dissenting judge argued that if the new constitutional right were accepted, it was too vague to be applied only to terminally ill patients seeking drugs that had been tested in phase 1 trials. Specifically, the judge asked, must the right also apply to patients with “serious medical conditions,” to patients who “cannot afford potentially life-saving treatment,” or to patients whose physicians believe “marijuana for medicinal pur-
poses . . . is potentially life saving?” In other words, there is no principled reason to restrict the constitutional right the majority created to either terminally ill patients or to post–phase 1 drugs.

**DISCUSSION**

The facts as illustrated by stories of patients dying of cancer while trying unsuccessfully to enroll in clinical trials are compelling, and our current system of ad hoc exceptions is deeply flawed. The central constitutional issue, however, rests primarily on determining whether this case is or is not like the right-to-refuse-treatment case of Nancy Cruzan, a woman in a permanent vegetative state whose family wanted tube feeding discontinued because they believed that discontinuation was what she would have wanted. I do not think Abigail Alliance is like Cruzan. Rather, it is substantially identical to cases involving physician-assisted suicide, in which a terminally ill patient claims a constitutional right of access to physician-prescribed drugs to commit suicide.

The Supreme Court has decided, unanimously, that no right to physician-prescribed drugs for suicide exists. There is no historical tradition of support for this right. And although the right seems to be narrowly defined, it is unclear to whom it should apply — why only to terminally ill patients? Don’t patients in chronic pain have even a stronger interest in suicide? Why is the physician necessary, and why are physician-prescribed drugs the only acceptable method of suicide? None of these questions can be answered by examining the Constitution.

Similarly, in Abigail Alliance, the new constitutional right proposed has no tradition in the United States, and it cannot be narrowly applied. For example, why should a constitutional right apply only to people who have a particular medical status? And why should a physician be involved at all? If patients have a right to autonomy, why isn’t the requirement of a government-licensed physician’s recommendation at least as burdensome as the requirement of the FDA’s approval of the investigational drug? And why would the Constitution apply only to investigational drugs for which phase 1 trials have been completed? Why not include access to investigational medical devices, like the artificial heart, or even to Schedule I controlled substances, like marijuana or lysergic acid diethylamide (LSD)? If it is a constitutional right, these should be available too, at least unless the state can demonstrate a “compelling interest” in regulating them.

My prediction is that after rehearing this case en banc, the full Circuit Court will reject the position of the Abigail Alliance for the same reasons that the Supreme Court rejected the “right” of terminally ill patients to have access to physician-prescribed drugs they could use to end their lives. To decide otherwise would entirely undermine the legitimacy of the FDA. Patients in the United States have always had a right to refuse any medical treatment, but we have never had a right to demand mistreatment, inappropriate treatment, or even investigational or experimental interventions. This will not, however, be the end of the matter. After the physician-assisted-suicide cases, the fight appropriately shifted to the states, although so far only one, Oregon, has provided its physicians with immunity for prescribing life-ending drugs to their competent, terminally ill patients. In the Abigail Alliance case, the debate will continue in the forum in which it began — the FDA — and in Congress.

**CONGRESS**

Congressional action also had its birth with the story of one patient with cancer and was also heavily influenced by another individual patient involved in a controversy over removal of a feeding tube. “Terri’s Law” was enacted in Florida in 2003 to try to prevent the removal of a feeding tube from Terri Schiavo; the case was substantially similar to Cruzan. Terri’s case gained national attention 2 years later. In the midst of it, in March 2005, the Wall Street Journal asserted, in an editorial titled “How About a ‘Kianna’s Law’?,” “If Terri Schiavo deserves emergency federal intervention to save her life, people like Kianna Karnes deserve it even more.” At the time, Kianna Karnes was a 44-year-old mother of four who was dying of kidney cancer. Her only hope of survival, according to the editorial, was to gain access to one of two experimental drugs in clinical trials, but neither of the two companies running the trials (Bayer and Pfizer) would make the drugs available to her on a compassionate-use basis. This was because, according to the Wall Street Journal,
the FDA “makes it all but impossible” for the manufacturers “to provide [drugs] to terminal patients on a ‘compassionate use’ basis.”

Almost immediately after the editorial was published, both drug manufacturers contacted Kianna’s physicians to discuss releasing the drugs to her. But within 2 days after publication, she was dead. The Wall Street Journal editorialized, “Isn’t it a national scandal that cancer sufferers should have to be written about in the Wall Street Journal to be offered legal access to emerging therapies once they’ve run out of other options?” It noted that Mrs. Karnes’ father, John Rowe — herself a survivor of leukemia — was working with the Abigail Alliance on a “Kianna’s Law.” That law, formally titled the “Access, Compassion, Care, and Ethics for Seriously Ill Patients Act” or the “ACCESS Act,” was introduced in November 2005 and is an attempt to make it much easier for seriously ill patients to gain access to experimental drugs.

The act begins with a series of congressional findings, including that “Seriously ill patients have a right to access available investigational drugs, biological products, and devices.” The act permits the sponsor to apply for approval to make an investigational drug biologic product, or device available on the basis of data from a completed phase 1 trial, “preliminary evidence that the product may be effective against a serious or life-threatening condition or disease,” and an assurance that the clinical trial will continue. The patient, who must have exhausted all approved treatments, must provide written informed consent and must also sign “a written waiver of the right to sue the manufacturer or sponsor of the drug, biological product, or device, or the physicians who prescribed the product or the institution where it was administered, for an adverse event caused by the product, which shall be binding in every State and Federal court.”

Although Congress is the proper forum to address this issue, this initial attempt has some of the same problems as the Abigail Alliance decision: the patients to whom it applies are ambiguously classified, and clinical research seems to be equated with clinical care. Also troubling is that the patients (and would-be subjects) are asked to assume all of the risks of the uncontrolled experiments, and current rules of research — which protect subjects by prohibiting mandatory waivers of rights — are jettisoned, with the requirement of such waivers becoming the price of obtaining the investigational agent from an otherwise reluctant drug company.

**FDA Proposal**

In direct response to Abigail Alliance, the FDA proposed amending its rules to encourage more drug companies to offer their investigational drugs through compassionate-use programs. These programs first came into prominence during the early days of infection with the human immunodeficiency virus (HIV) and AIDS, when there were no effective treatments and AIDS activists insisted that they have early access to investigational drugs because, in the words of their inaccurate slogan, “A Research Trial Is Treatment Too.”

Because the FDA could not stand the political pressure generated by the activists, the compassionate-use program was developed as a kind of political safety valve to provide enough exceptions to save their basic research rules. In early December 2006, the FDA continued this political-safety-valve approach by issuing new proposed regulations with a title that could have been taken directly from the AIDS Coalition to Unleash Power (ACT-UP): “Expanded Access to Investigational Drugs for Treatment Use.”

The FDA’s expanded-access proposal applies to “seriously ill patients when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition.” Manufacturers are required to file an “expanded access submission,” and the product must be administered or dispensed by a licensed physician who will be considered an “investigator,” with all the reporting requirements that role entails.

Whether or not the proposal is adopted, it will do little to increase access, since the major bottleneck in the compassionate-use program has never been the FDA. The manufacturers have no incentives to make their investigational products available outside clinical trials. This is because direct access to investigational drugs by individuals may make it more difficult to recruit research subjects, and thus to conduct the clinical trials necessary for drug approval, and could also subject the drug manufacturer to liability for serious adverse reactions. Even without a lawsuit, a seri-
ous reaction to a drug outside a trial could adversely affect the trial itself. The drug companies are right to worry that the approaches of the judiciary, Congress, and the FDA will probably make clinical trials more difficult to conduct, because few seriously ill patients who have exhausted conventional treatments would rather be randomly assigned to an investigational drug than have a guarantee that they will receive the investigational drug their physician recommends for them. This could result in significant delays in the approval and overall availability of drugs that demonstrate effectiveness — a result no one favors. Even if patients with cancer are willing buyers, drug manufacturers are not willing sellers.

**GOVERNMENT AND THE MARKET**

Another recurrent theme is the belief that government regulation is evil, a central tenet of the laetrile litigation of the 1970s. The court hearing Abigail Alliance was correct to note that laetrile never underwent a phase 1 trial, but every indication was that the drug, also known as vitamin B17, was harmless, albeit also ineffective against cancer. Laetrile became a legal cause celebre in 1972, when California physician John A. Richardson was prosecuted for promoting laetrile. Richardson was a member of the John Birch Society, which quickly formed the Committee for Freedom of Choice in Cancer Therapy, with more than 100 committees nationwide. It took another 7 years before the FDA prevailed in its case against laetrile before the Supreme Court. The basic arguments against FDA regulation remain the same today: the FDA follows a “paternalistic public policy that prevents individuals from exercising their own judgment about risks and benefits. If the FDA must err, it should be on the side of patients’ freedom to choose.”

**PUBLIC POLICY**

The FDA will prevail again today, not only because there is no constitutional right of access to unapproved drugs but also because even if there were, the state has the same compelling interest in approving drugs as it has in licensing physicians. From a public policy view, the Abigail Alliance court, the Congress, and the FDA all seem to be suffering from the “therapeutic illusion” in which research, designed to test a hypothesis for which quickly formed the Committee for Freedom of Choice in Cancer Therapy, with more than 100 committees nationwide. It took another 7 years before the FDA prevailed in its case against laetrile before the Supreme Court. The basic arguments against FDA regulation remain the same today: the FDA follows a “paternalistic public policy that prevents individuals from exercising their own judgment about risks and benefits. If the FDA must err, it should be on the side of patients’ freedom to choose.”

The cover story for all the proposed changes is patients’ choice. But without scientific evidence of the risks and benefits of a drug, choice cannot be informed, and for seriously ill patients, fear of death will probably overcome fear of unknown risks. This is understandable. As psychiatrist Jay Katz, the leading scholar on informed consent, has noted, when medical science seems impotent to fight nature, “all kinds of senseless interventions are tried in an unconscious effort to cure the incurable magically through a ‘wonder drug,’ a novel surgical procedure, or a penetrating psychological interpretation.” Another Wall Street Journal article, entitled “Saying No to Penelope,” illustrates the impossibility of limiting access to unproven cancer drugs to competent adults. The article tells the story of 4-year-old Penelope, who is dying from neuroblastoma that has proved resistant to all conventional treatments. Her parents seek “anything [that] has a prayer of saving her.” In her father’s words, “The chance of anything bringing her back from the abyss now is very low. But the only thing I know for sure is if we don’t treat her, she will die.” With Penelope hospitalized and in pain, her parents continue “searching Penelope’s big brown eyes for clues as to how long she wants to continue to battle for life.”

It is suggested that the requirement of a physician’s recommendation can safeguard against “magical thinking” and help make informed consent real. But as Katz has noted, although physicians (and, he could have added, drug companies) often justify such last-ditch interventions as simply being responsive to patient needs, the interventions “may turn out to be a projection of their own needs onto patients.”

**PHYSICIANS AND PATIENTS**

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ment,” that cancer may become a chronic illness that is treated with a complex array of drugs, given either together or in a progression.28,29 The right to choose in medicine is a central right of patients, but the choices can and should be limited to reasonable medical alternatives, which themselves are based on evidence.

This is, I believe, good public policy. But it is also much easier said than done.30 Death is feared and even dreaded in our culture, and few Americans are able to die at home, at peace, with our loved ones in attendance, without seeking the “latest new treatment.” There always seems to be something new to try, and there is almost always anecdotal evidence that it could help. This is one reason that even extremely high prices do not affect demand for cancer drugs, even ones that add little or no survival time.31,32

When does caring for the patient demand primary attention to palliation rather than to long-shot, high-risk, investigational interventions? Coetzee’s Mrs. Curren, who rejected new medical treatment for her cancer and insisted on dying at home, told her physician, whom she saw as “withdrawing” from her after giving her a terminal prognosis — “His allegiance to the living, not the dying” — “I have no illusions about my condition, doctor. It is not [experimental] care I need, just help with the pain.”91

No potential conflict of interest relevant to this article was reported.

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17. ACCESS Act (Access, Compassion, Care, and Ethics for Seriously Ill Patients), S. 156, 109th Cong (2005).
previous myocardial infarction, bypass grafting, and other factors.

As suggested by Kiat, we are performing post hoc analyses to better delineate a high-risk subgroup on the basis of the ischemic burden as assessed on MPI at baseline and during a follow-up period of 6 to 14 months.

Nagajothi et al. acknowledge that our intention-to-treat analysis was appropriate but encourage further analysis according to actual treatment received. A detailed analysis of the “crossover” population is under way.

Finally, Mak emphasizes the incremental benefit of the use of dual antiplatelet therapy on the composite end point of death, myocardial infarction, or stroke at 1 year in the CREDO trial. Enrollment in our trial antedated these results. However, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, involving patients with stable coronary artery disease, did not show a compelling benefit of combined treatment with aspirin and clopidogrel in reducing death, myocardial infarction, or stroke in long-term follow-up.

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To the Editor: In his review of diabetic gastroparesis, Camilleri (Feb. 22 issue) states that in our clinical trial of exenatide, nausea and vomiting led to the “cessation of treatment in about one third of patients.” This information is incorrect. Of 282 patients randomly assigned to receive exenatide, 54 withdrew from the study (27 withdrew because of an adverse event, 10 because of protocol violations, 7 because of the patient’s decision, 4 because of loss of glucose control, and 1 because of the physician’s decision, and 5 were lost to follow-up). As stated in our article, 18 of these patients withdrew from the study because of nausea or other gastrointestinal symptoms. This rate is in line with the dropout rates in other recent clinical trials, which range from 1.8 to 5.1%. Mild-to-moderate nausea is the most common adverse event in patients receiving exenatide. However, the development of tolerance to these adverse gastrointestinal effects of exenatide has been suggested in our trial as well as in other long-term phase 3 trials of the drug that have been reported.

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To the Editor: In Table 2 of his article, Camilleri lists the motilin-receptor agonists erythromycin,
clarithromycin, and azithromycin as recommended agents for the treatment of diabetic gastroparesis. I agree with the recommendation regarding erythromycin. However, clarithromycin, azithromycin, and other more acid-stable macrolides and azalides are likely to be poor alternatives. Erythromycin A in an acidic medium such as gastric juice is degraded into its anhydrous hemiketal and spiroketal forms. Both forms are inactive microbiologically, but they have motilin-like activity that is several times greater than that of erythromycin A. It is mostly because of this characteristic that erythromycin has a low oral bioavailability of the microbiologically active drug and considerable gastrointestinal adverse effects. Clarithromycin and azithromycin have modified chemical structures that are more acid-stable and do not form the highly active motilin mimics; consequently, neither drug is likely to be as useful as erythromycin for the treatment of motilin-responsive disorders. Both clarithromycin and azithromycin are also more expensive than erythromycin.

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TO THE EDITOR: Camilleri compares gastrointestinal prokinetic agents with regard to their efficacy and side effects. For metoclopramide, neurologic side effects are reported from one 4-week trial. Tardive dyskinesia and other extrapyramidal effects are not mentioned in the text and are cited only briefly in Table 2 of the article. Since clinical trials of metoclopramide have been short-term trials, this review understates the risk of tardive dyskinesia among patients treated with metoclopramide on a long-term basis.

Metoclopramide is a dopamine-receptor antagonist that causes parkinsonism, acute dystonia, akathisia, and tardive dyskinesia. The risk of tardive dyskinesia after long-term treatment with antipsychotic drugs that are dopamine-receptor antagonists is 5% per year of drug exposure. Although prospective data for metoclopramide are unavailable, the prevalence and severity of tardive dyskinesia are increased after long-term treatment. Diabetes is associated with an increased frequency and severity of tardive dyskinesia. The risk of tardive dyskinesia is underrecognized by physicians who use metoclopramide for long-term treatment; this is especially important in view of the increased use of metoclopramide since the withdrawal of cisapride in 2000.

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THE AUTHOR REPLIES: Heine and Brodows correctly point out that the withdrawal rate attributed to nausea in their clinical trial was overstated in my article. However, in trials involving longer-term treatment that may better reflect clinical experience, as well as in the study by Nauck et al. cited by Heine and Brodows, there is a high prevalence of nausea (average prevalence, approximately 33%). The all-cause withdrawal rate in these randomized, controlled, or open-label treatment trials involving exenatide ranged from 21 to 45%. Approximately 4% of these withdrawals were attributed to a loss of glucose control and 7% were attributed to adverse events. It is unclear whether the withdrawal of consent by approximately 11% of patients and withdrawals because of protocol violations by approximately 10% of patients were due to nausea, which was by far the most frequent adverse event (57% in the article by Heine et al. cited by Heine and Brodows). Nausea and vomiting in patients with diabetes may be wrongly attributed to gastroparesis rather than to iatrogenic disease, which may be reversible.

I agree with Maderazo’s statement regarding the different potencies of macrolides in the stimulation of gastric emptying. I included clarithromycin and azithromycin in Table 2 because this
table reflects national society guidelines, as noted in one of the table footnotes.

The potential for tardive dyskinesia during treatment with metoclopramide is important. However, as indicated in the article by Shaffer et al. (to which Tarsy refers in his letter), well-described risk factors are common in reports of metoclopramide-associated tardive dyskinesia. Moreover, Ganzini et al. calculated that the relative risk of tardive dyskinesia was not significantly elevated with use of metoclopramide (relative risk, 1.67; 95% confidence interval, 0.93 to 2.97), although the risk appeared to be higher among patients with diabetes.

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Since publication of his article, Dr. Camilleri reports having received research support from Novartis.


Case 15-2007: A Woman with Asthma and Cardiorespiratory Arrest

TO THE EDITOR: In the Case Record presented by Wechsler et al. (May 17 issue), many possible causes of death in a patient with asthma are considered. However, the discussants do not sufficiently emphasize that lung mechanics and hemodynamic effects associated with airflow obstruction are the most important physiological disturbances in patients with severe acute asthma. Hemodynamic collapse related to dynamic hyperinflation is a common cause of obstructive shock, pulseless electric activity, and cardiac arrest in intubated patients with asthma.

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TO THE EDITOR: Dr. Shepard is quoted as saying, “The pneumothorax results from the Macklin effect.” I suspect that what she really said was, “The pneumomediastinum results from the Macklin effect.”

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THE DISCUSSANTS REPLY: There are many causes of death in young patients with asthma. In addition to hypoxemia from prolonged bronchospasm, we agree with Lisboa et al. that a progressive increase in intrathoracic pressure associated with dynamic hyperinflation can lead to both diminished venous return and mechanical compression of the heart and associated vasculature, with resultant hemodynamic collapse. It is important to recognize these potential causes of complications in patients with asthma who have respiratory failure, since several ventilatory strategies (including the use of low tidal volumes and low respiratory rates) may minimize these risks.
Since there is extrapulmonary air in the thorax, resulting from rupture of a peripheral alveolus, we agree with Miller that “pneumomediastinum” is a more precise term than “pneumothorax” to describe the location of air due to the Macklin effect in this case.

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Folate Deficiency and Plasma Homocysteine during Increased Oxidative Stress

TO THE EDITOR: Several reports have indicated that elevated plasma levels of the amino acid homocysteine are associated with, or are a primary risk factor for, coronary and vascular disease and Alzheimer’s disease. However, a number of additional studies do not show such a correlation. This discrepancy may arise because there are multiple metabolic fates for homocysteine, depending on the nature and extent of cellular oxidative stress.

Most homocysteine is converted to methionine through folate-dependent and vitamin B₁₂-dependent reactions. Compromise of this conversion as a consequence of folate deficiency can lead to increased export of homocysteine from cells, which fosters an ultimate increase in total plasma homocysteine, the fraction measured in the conventional laboratory assay for homocysteine. However, a growing body of literature underscores that under conditions of oxidative stress, compensatory amplification of the redox-sensitive transsulfuration pathway will consume homocysteine to generate the endogenous antioxidant glutathione. Such conditions may obviate any increase in plasma homocysteine despite folate deficiency.

We set out to determine whether oxidative stress could prevent the anticipated increase in plasma homocysteine levels under folate-deficient conditions. Plasma homocysteine levels were determined in mice that were homozygously lacking apolipoprotein E (APOE−/−) and transgenic mice expressing the human APOE ε4 allele. Notably, the presence of one or more APOE ε4 alleles is correlated with coronary artery disease, stroke, atherosclerosis, and Alzheimer’s disease. Both models show increased oxidative stress and are used in studies of age-related coronary and neurodegenerative disorders. Plasma homocysteine levels were also determined in normal mice and mice expressing the human APOE ε3 allele.

A comparison of values indicated that plasma homocysteine levels were identical in all mice under normal dietary conditions (Fig. 1). As expected, after 1 month of dietary folate deprivation, which has previously been shown to result in a folate-deficient state, normal and APOE ε3
mice had a significant increase in plasma homocysteine levels (P<0.05, by analysis of variance with Tukey's post hoc multiple-comparison test). In contrast, plasma homocysteine levels in the oxidatively stressed APOE−/− and APOE ε4 mice remained unchanged from values obtained in the presence of dietary folate.

These results provide evidence that plasma homocysteine may be an accurate predictor of folate deficiency under otherwise normal conditions but may not reflect folate deficiency in the presence of underlying risk factors known to promote increased oxidative stress. In the future, an accompanying test or series of tests to assess the degree of cellular oxidative stress may be warranted in order to interpret plasma homocysteine values correctly.

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Radiofrequency Ablation of a Tumor Causing Oncogenic Osteomalacia

To the Editor: Oncogenic osteomalacia is a rare syndrome that is usually driven by small, mesenchymal tumors that express phosphatoninins, proteins that decrease the abundance of sodium–phosphate cotransporters in the proximal renal tubule. This decrease causes renal phosphate wasting and leads to the clinical features of oncogenic osteomalacia, which include hyperphosphaturia, hypophosphatemia, reduced or abnormal serum 1,25-dihydroxyvitamin D levels, and osteomalacia.1,2

The standard treatment of oncogenic osteomalacia is surgical excision of the mesenchymal tumor, which rapidly and permanently abrogates all symptoms. However, tumor removal can be complicated, because the lesion is usually small and difficult to distinguish from the surrounding tissue. Complete excision is necessary, because the syndrome typically persists if any tumor tissue remains. To ensure complete excision, surgery may require wide resection margins, causing iatrogenic tissue damage that is disproportional to the tumor, which is small and benign in most cases.

We present the case of a 40-year-old woman with an acquired hypophosphatemic, vitamin D–resistant osteomalacia due to a tumor in the right femoral head that was detected on coregistration of positron-emission tomography and computed tomography (known as PET–CT).3 Laboratory analyses revealed hypophosphatemia (serum phosphate level, 0.45 mmol per liter; normal range, 0.83 to 1.67) and a reduced renal tubular maximum for the reabsorption of phosphate normalized to the glomerular filtration rate (0.2 mmol per liter; normal range, 0.8 to 1.4). In our patient, complete tumor removal by means of an open surgical procedure would have required total hip arthroplasty. Because of her age, we attempted to preserve the healthy hip joint, which was not affected by the tumor. Multiple tissue samples were obtained with the use of needle biopsy guided by CT. Histologic analysis revealed a benign mesenchymal tumor, confirming the diagnosis. We performed CT-guided radiofrequency ablation to destroy the lesion, thereby avoiding arthroplasty. Complete tumor ablation was achieved 6 days later, after a second round of radiofrequency ablation, and was confirmed on the following day by magnetic resonance imaging (MRI) (Fig. 1). A few weeks later, levels of biochemical markers returned to normal, and all symptoms resolved. Clinical follow-up at 1 year was unremarkable.
Radiofrequency ablation is a well-established procedure for selectively removing small volumes of tissue and is an effective palliative treatment for skeletal metastases. Radiofrequency ablation of benign primary bone tumors is generally restricted to osteoid osteoma and is the standard of care in many centers.\(^4\,5\)

This case demonstrates that CT-guided radiofrequency ablation may be used to treat a tumor causing oncogenic osteomalacia. We believe that radiofrequency ablation may broaden the scope of treatment options for oncogenic osteomalacia and may offer an effective, less invasive alternative to classic surgery.

**Figure 1.** MRI and CT Scans of the Tumor before, during, and after Radiofrequency Ablation.

The tumor was 1.7 by 1.5 cm, as measured on a T\(_1\)-weighted MRI scan (Panel A, arrow), a fat-saturated, T\(_1\)-weighted MRI scan (Panel B, arrow), and a fat-saturated, T\(_1\)-weighted MRI scan with gadolinium (Panel C, arrow). Probe placement is shown on a CT scan obtained during the first radiofrequency ablation (Panel D). Follow-up MRI studies revealed remaining tumor tissue, as shown on a T\(_1\)-weighted scan (Panel E, arrow) and a fat-saturated, T\(_1\)-weighted scan with gadolinium (Panel F, arrow). The intrallesional positioning of the electrode was confirmed on a CT scan obtained during the second round of radiofrequency ablation (Panel G). Complete ablation of the tumor was achieved with the second round of radiofrequency ablation, as shown on a T\(_1\)-weighted MRI scan (Panel H, arrow) and a fat-saturated, T\(_1\)-weighted MRI scan with gadolinium (Panel I, arrow).
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CULTURING LIFE: HOW CELLS BECAME TECHNOLOGIES


A flasks or dish containing nutrient medium and living cells is such a usual sight in a biologic or medical laboratory that we hardly notice it. Hannah Landecker’s fascinating, beautifully written account of the history of cell culture restores the sense of wonder felt by the first scientists who grew living cells apart from organisms and by the people who read about their achievements in scientific journals, popular magazines, and newspapers. But this book does much more than that; it sheds a unique light on the history of biology in the 20th century, the rise of biotechnology, and our understanding of what life is.

Landecker is interested in the discovery of the plasticity of life and the far-reaching consequences of this discovery. Culturing Life follows the transformation of living cells into techno-scientific objects between 1907 and 1970. She starts by describing the work of Ross Harrison, the American embryologist who was the first to successfully cultivate isolated cells outside the body. She then investigates the next steps in the transformation of cells in the laboratory — the establishment of the first cell lines, the development of methods of freezing and thawing living cells, the massive diffusion of cell lines in biology laboratories, and studies on the somatic hybridization of cells. She discusses in parallel the technological applications of cells — such as their use in the production of other living entities (viruses, for example) and of devices such as viral vaccines. Finally, Landecker’s chapter on the HeLa cell line follows the rich cultural and symbolic meanings of a cell line made to stand for technological progress, contamination and insufficient quality control, ownership of body parts, patients’ rights, race, and gender.

Landecker focuses on the various material techniques that made cell culture possible. An anthropologist of science, she is attuned to the multiple meanings of “culture” and “milieu,” but she does not use these terms as mere symbols or metaphors. She is interested instead in straightforward descriptions of technical devices, from the development of the mixtures of nutrients that made it possible for cells to survive in a test tube to the use of glycerol in the freezing and thawing of living cells. Landecker focuses on practical, material issues — what scientists do, what materials they use, and what the consequences of their activities are. The scientific activity at the center of the book is the transformation of cells into entities that are detachable from the body, can be kept in a frozen state, are able to multiply indefinitely in an identical or a quasi-identical form, and are circulated, exchanged, and appropriated by biologists.

This is a book about biology, not medicine. Landecker concludes with an invitation to reflect on the ways in which the cultivation of cells apart from organisms has changed our understanding of living matter. Debates about stem cells or cloning tend to focus on a philosophical question: How do new biotechnologies change
the ways we understand the meaning of being human? It may be useful, Landecker proposes, to start by thinking about how these technologies have changed what it means to be biologic. The discovery that the biologic is a fundamentally plastic entity indeed explains much of the real power of biotechnology in present-day culture. In her closing chapter, however, Landecker tells a different story — about the use of cells cultured from amniotic fluid in prenatal diagnosis. In a cytology laboratory, the capacity to grow cells apart from organisms may have far-reaching practical consequences. By reflecting on the catastrophic, artificial, and radically new variety of life that arises in the laboratory, Landecker opens new ways to articulate the ideas of the French philosopher of science Georges Canguilhem about the distinction between the normal and the pathologic. Cultured cells bring into question our understanding of the biologic, but their infinite plasticity, as Landecker eloquently shows, often unfolds in the normative space of medicine.

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BIOETHICS IN LAW


Throughout its nearly 40-year history, modern bioethics has been intimately connected with law. The establishment of U.S. regulations governing human subjects research and the judicial recognition of patients’ rights to consent to or refuse treatment are foundational events in the rise of bioethics. Bioethics grows out of philosophy, theology, and medicine as well, but its debt to law is substantial.

As bioethics reaches middle age, a number of scholars are trying to dissect this complex relationship. Bethany Spielman has written a range of articles on the topic and now this book, which focuses on an important piece of the puzzle — the role of bioethics in the courtroom. Increasingly, bioethicists serve as expert witnesses, submit amicus briefs, and see their work cited in judicial opinions. Judges also consider whether to allow into evidence advice from health care ethics committees and decisions made by institutional review boards.

All of this raises vexing questions. Who has the authority to call themselves a bioethicist? What expertise do bioethicists actually offer? When is a bioethicist’s opinion sufficiently reliable and helpful that a court should consider it? And what weight should a court of law give to bioethics? There is a danger of confusing bioethics and law — both speak of rights and duties, but they are governed by different core documents, norms, and processes.

Bioethics in Law helpfully collects judicial opinions considering bioethics material, testimony, and briefs to explore the ways in which bioethics is entering U.S. courtrooms. Spielman explores how bioethics can help and hurt the judicial process. She argues that when bioethics information and opinion support established legal rights and norms, judges use bioethics, but when it runs counter to law, judges tend to reject it. Spielman generally approves of this, writing, “Legal and bioethical reasoning will, one hopes, remain distinct, continuing to operate alongside each other and to influence each other.” She catalogues a variety of ways in which judges consider bioethics, sometimes to help establish the facts of the case, and sometimes to help clarify the relevant policy and rules. She quotes telling exchanges among bioethics witnesses, lawyers, and judges — some bioethics testimony is clear and relevant, whereas other testimony is painful to read.

Spielman aims this book first at lawyers and bioethicists but writes accessibly for a broader audience. The book will advance the conversation on the relationship between law and bioethics. There are nonetheless some gaps in the book’s coverage. It never addresses the question of who can claim to be a bioethicist (a big controversy in a field that lacks formal credentialing); nor does the book address the role of the bioethicist as a consultant at the lawyer’s table (where influential bioethicists have sat) or as a defendant when bioethicists have been sued (a development that is dismaying to bioethicists but inevitable). The book also would have benefited from more expansive discussion, especially to synthesize the trends Spielman sees and to elaborate normative recommendations. She thanks bioethicists who have shared with her their expert testimony and legal briefs. Given the important material she has collected, it would have been helpful to include a
table documenting how often each type of bioethics evidence or testimony has been offered, whether the court allowed it, and how it was used.

Bioethics in Law offers a treasure trove of information that cannot readily be found elsewhere, shedding light on the complex interaction between bioethics and law. Spielman’s pathbreaking research and thoughtful organization of the issues provide an important resource for those concerned about the confusion over the roles of bioethics and law. After all, as Spielman suggests, we should not want judges to defer to bioethicists to determine our legal rights, but neither should we want judges determining our rights as patients, research subjects, or health professionals by ignoring the insights that bioethics can offer.

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SURVIVAL OF THE SICKEST: A MEDICAL MAVERICK DISCOVERS WHY WE NEED DISEASE

THIS BOOK, INTENDED FOR GENERAL READERS, reviews recent research on a major question at the intersection of evolutionary biology and medicine: Why does evolution, which, as Moalem and Prince write in their introduction, “is supposed to weed out harmful traits and promote helpful ones,” allow serious genetic diseases to persist? The answers, as the authors make clear, are complicated and incomplete, requiring responses from many research communities.

Moalem, a researcher in neurogenetics and evolutionary medicine, and Prince, a former adviser and speechwriter in the Clinton White House, have not written a comprehensive review but instead focus on specific examples of genetic traits that can prove helpful or harmful depending on the environmental context or general evolutionary process, such as the coevolution of parasites and their hosts. The result is a grab bag that contains discussions of Barbara McClintock’s “jumping genes,” bubonic plague, pinworms, telomeres, work on heritability in the former Soviet Union, frozen wood frogs, and Jean-Baptiste Lamarck, to name just a few.

Diabetic Gastroparesis (February 22, 2007;356:820-9). The last sentence of the second paragraph under Impaired Gastric Emptying in Patients with Diabetes (page 821) should have read “In a clinical trial of exenatide, nausea occurred in 57% of patients, and vomiting occurred in 17% of patients; nausea or other gastrointestinal symptoms were identified as the reason for withdrawal from the study in 6% of patients,” rather than “vomiting occurred in 19% of patients, leading to the cessation of treatment in about one third of patients.” Also, the second sentence under Areas of Uncertainty (page 825) should have read “Agents such as the 5-HT4-receptor agonist tegaserod (which is approved for the treatment of patients with the irritable bowel syndrome in whom constipation is predominant and patients with chronic constipation) and acetylcholinesterase inhibitors (e.g., pyridostigmine) have been used off-label in patients with gastroparesis, but data from clinical trials providing support for their use are lacking,” rather than “acetylcholine inhibitors.” The text has been corrected on the Journal’s Web site at www.nejm.org.
Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease (January 25, 2007;356:335–47). The second sentence of the third paragraph under Efficacy (page 341) should have read “In other analyses, posaconazole was superior to fluconazole in reducing the incidence of proven or probable aspergillosis (odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006) during the treatment period and was superior to fluconazole in reducing the incidence of breakthrough proven or probable invasive fungal infections (odds ratio, 0.30; 95% CI, 0.12 to 0.71; P=0.004) and invasive aspergillosis during the exposure period (odds ratio, 0.17; 95% CI, 0.05 to 0.57; P=0.000)” rather than “invasive aspergillosis during the treatment period.” The text has been corrected on the Journal’s Web site at www.nejm.org.

NOTES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal’s Web site (www.nejm.org/meetings). The listings can be viewed in their entirety or searched by location, month, or key word.

NOTICEs

NORTH CAROLINA OCCUPATIONAL SAFETY AND HEALTH EDUCATION & RESEARCH CENTER

The following courses will be offered in Chapel Hill, NC, unless otherwise indicated: “Supervising Lead Abatement Programs” (Aug. 14); “Comprehensive Industrial Hygiene (CIH) Review Course” (Sept. 17–21); “Asbestos Operations and Maintenance” (Oct. 2 and 3); “Building Inspection and Management Planning for Asbestos” (Oct. 8–12;刷新者 course, Sept. 11, Dec. 4); “Occupational Health Nursing: Introduction to Principles and Practice” (Oct. 30–Nov. 1); “Supervising Asbestos Abatement Projects” (Nov. 5–9;刷新者 course, Sept. 10, Dec. 3); “Certified Safety and Professional (CSP) Review Course” (Nov. 12–16); “Designing Asbestos Abatement Projects” (Dec. 5); and “29th Annual Occupational Safety and Health Update: Compliance and Beyond” (Dec. 6 and 7). Contact Occupational Safety and Health Education & Research Center, University of North Carolina, 3300 Hwy. 54 W., Chapel Hill, NC 27516-6248; or call (888) 235-3230 (national) or (919) 962-2101 (NC); or fax (919) 966-7579; or see http:// www.sph.unc.edu/osherc; or e-mail oshercww@sph.unc.edu.

MAYO CLINIC

The following courses will be offered in Rochester, MN, unless otherwise indicated: “MAYO Clinic Gastroenterology & Hepatology Board Review” (Chicago, Sept. 6–9); “MAYO Clinic ERCP A to Z” (Sept. 13 and 14); “MAYO Clinic Hepatology State of the Art” (Sept. 13 and 14); “Internal Medicine Review for Nurse Practitioners and Physician Assistants” (Sept. 27 and 28); “MAYO Clinic Professionalism at Academic Medical Centers: Challenges and Opportunities” (Oct. 4 and 5); “MAYO Clinic Human Factors in Health Care: Practical Applications to Improve Patient Safety” (St. Paul, MN, Oct. 17–19); “Neuroradiology: Practice to Innovation” (Scottsdale, AZ, Nov. 5–9); and “MAYO Clinic OB GYN Clinical Reviews” (Nov. 8 and 9). Contact Mayo School of CME, 200 First St. SW, Rochester, MN 55905; or call (800) 323-2688 (national) or (507) 280-2509 (MN); or fax (507) 284-0532; or see http://www.mayo.edu/cme; or e-mail cme@mayo.edu.

CALL FOR APPLICATIONS

The National Rosacea Society is accepting applications for its research grants program. Deadline for submission is Sept. 15. Contact the National Rosacea Society, 800 S. Northwest Hwy., Suite 200, Barrington, IL 60010; or call (888) 662-5874; or e-mail rosaces@aad.org; or see http://www/rosacea.org/grants/.

9TH SEMINAR OF THE EUROPEAN SOCIETY OF CONTRACEPTION

The seminar, entitled “From Abortion to Contraception,” will be held in Bucharest, Romania, Sept. 21 and 22. Contact Mrs. Nancy Hablis, European Society of Contraception, Opalfenweg 3, 1740 Ternat, Belgium; or call (32) 2 582 08 52; or fax (32) 2 582 55 15; or e-mail congress@contraception-esc.com; or see http://www.escentralloffice@contraception-esc.com.

VIENNA MEDICAL ACADEMY

The following meetings will be held: “XX International Workshop on Helicobacter and Related Bacteria in Chronic Digestive Inflammation (EHGIG)” (Istanbul, Turkey, Sept. 20–22) and “2nd Joint Meeting of the European Federation of Autonomic Societies and the American Autonomic Society” (Vienna, Oct. 10–13). Contact Vienna Medical Academy, Alser Strasse 4, 1090 Vienna, Austria; or call (43) 1 405 13 83 0; or fax (43) 1 407 82 74; or e-mail ehsg2007@medacad.org or efas2007@efasweb.com, respectively; or see http://www.helicobacter.org or http://www.efasweb.com, 2007, respectively.

UNIVERSITY OF TORONTO

The following meetings will be held in Toronto, unless otherwise indicated: “4th Annual G-I-N Conference 2007: Collaboration in Clinical Practice Guidelines” (Aug. 22–25; sponsored by the Guidelines International Network); “International Ocular Blood Flow Symposium” (Oct. 13); “Update in Surgical Oncology 2007” (Oct. 26); “International Interprofessional Wound Care Course” (Oct. 19–22, April 11–14); “CME Update in Pathology 2007” (Nov. 2 and 3); and “Cardiovascular Pathology: Current Concepts” (July 25–27, 2008). Contact the Office of Continuing Education & Professional Development, Faculty of Medicine, University of Toronto, 500 University Ave., Suite 650, Toronto, ON M5G 1V7, Canada; or call (416) 978-2719 or (888) 512-8173; or fax (416) 946-7028; or e-mail ce.med@utoronto.ca; or see http://www.cme.toronto.ca.

MAYO CLINIC SCOTTSDALE

The following courses will be offered: “MAYO Clinic Practical 21st Century Clinical Neurology Review” (Kohala Coast, HI, Aug. 1–4); “20th Annual Advanced Techniques in Endoscopic & Robotic Gynecologic Surgery” (Maui, HI, Sept. 26–29); “2007 Parkinson’s Disease & Other Movement Disorders for the Practitioner” (Kauai, HI, Nov. 8–10); “Update in Hospital Medicine 2007” (Tucson, AZ, Nov. 14–17); and “MAYO Clinic Interactive Surgery Symposium” (Wailea-Maui, HI, Feb. 10–15). Contact CME Department, Mayo Clinic Scottsdale, 13400 E. Shea Blvd., Scottsdale, AZ 85259; or call (480) 301-4580; or e-mail mcs.cme@mayo.edu; or see http://www.mayo.edu/cme.

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Providing positive-pressure ventilation with a face mask and a bag-valve device can be a lifesaving maneuver. Although seemingly simple, the technique requires an understanding of the airway anatomy, the equipment, and the indications.

**Face-mask ventilation** is used in patients who have respiratory failure but are still breathing spontaneously and in patients with complete apnea. Face-mask ventilation can be indicated in any situation in which spontaneous breathing is failing or has ceased, including cardiopulmonary arrest.

**Contraindications**

Face-mask ventilation is rarely contraindicated. However, caution is advised in patients with severe facial trauma and eye injuries. In addition, foreign material (e.g., gastric contents) in the airway may lead to aspiration pneumonitis. In these circumstances, alternative approaches, including endotracheal intubation, may be necessary.

**Equipment**

There are many types of face masks, varying in design, size, and construction materials. Transparent masks are preferred because they allow for inspection of lip color, condensation, secretions, and vomitus. To maintain a good seal, the mask's size and shape must conform to the facial anatomy. Thus, several mask shapes and sizes should be readily available.

Various bag-valve designs are available. All have a self-inflating bag and a non-rebreathing, unidirectional valve. The valve is designed to function during both spontaneous and manually controlled ventilation. Because bag-valve devices can operate without an oxygen source, it is important to ascertain that supplemental oxygen is flowing through the bag-valve device when supplemental oxygen is indicated and available.

Test the bag-valve device’s capability for delivering positive-pressure ventilation before use. This can be achieved by sealing the bag-valve device connector with your thumb and squeezing the bag with reasonable force. If it is difficult to compress the bag or if air is forced between the connector and your thumb, positive pressure can be delivered.

Whenever possible during face-mask ventilation, suction should be readily available. You may need to use airway-management adjuncts, such as disposable oral or nasal airways.

Before beginning face-mask ventilation, examine the patient’s oral cavity. If possible, remove any dental prostheses or other foreign bodies that might be swallowed or aspirated.
One-hand Technique

The most common method used to hold the mask requires placing your thumb and index finger on the body of the mask while your other fingers pull the jaw forward and extend the head. Place your middle and ring fingers on the ridge of the mandible and the fifth finger behind the angle of the mandible.\(^1\,\!^3\)

The tongue is the most common cause of airway obstruction.\(^4\) It is important to minimize the pressure applied to the submandibular soft tissues because pressure may further obstruct the airway by pushing the tongue against the palate.\(^3\) Maintaining an adequate seal while extending the patient’s head, thrusting the jaw forward, and squeezing the bag with the other hand may require considerable manual strength and coordination. Extreme caution is advised in patients with cervical spine injuries, in which flexion or extension of the neck is contraindicated. In this situation, the jaw-thrust maneuver alone, without head extension, is recommended.\(^4\)

Two-hand Technique

You might find it difficult or impossible to maintain an adequate seal with only one hand. This is particularly true in the case of obese or edentulous patients or those with abundant facial hair. In these situations, hold the mask with two hands, with each hand positioned as described in the one-hand technique. A second person should compress the bag-valve device.\(^1\)

Regardless of the technique you use to ventilate the patient with a face mask, you can assess adequate ventilation by inspecting and auscultating the chest and abdomen. The rising and falling of the chest and breath sounds synchronous with the delivered tidal volume suggest adequate ventilation. Epigastric sounds and abdominal distension indicate gastric insufflation and poor ventilation.

Using Oropharyngeal and Nasopharyngeal Airways

Occasionally, it may be difficult or impossible to provide ventilation unless a disposable oral or nasal airway is inserted. These devices are most helpful when the cough and gag reflexes are absent. Insertion in patients with intact reflexes may precipitate coughing, vomiting, and laryngospasm. When the use of a disposable oral or nasal airway is necessary, you must select the appropriate-sized device to avoid worsening the airway obstruction.\(^1\) Estimate the correct size of an oral airway by holding it next to the patient’s mouth. The tip should reach the angle of the mandible.

Insert the oropharyngeal airway by depressing the tongue with a tongue blade and advancing the airway toward the base of the tongue. Alternatively, you can insert the airway upside down and then rotate it 180 degrees as it is being advanced posteriorly.

Nasopharyngeal airways are better tolerated than oral airways when airway reflexes are present. They are useful when the patient’s mouth cannot be opened. The simplest method of estimating their appropriate length is by correlating it with the external anatomy of the face and neck. Nasopharyngeal airways should be lubricated and advanced perpendicular to the face. Use them only with extreme caution in patients with facial injuries, basilar skull fractures, and coagulopathy, weighing the risk of further injury and bleeding against the need for oxygenation.\(^1\)

When the patient is breathing spontaneously, you must synchronize the delivered tidal volume with the patient’s inspiration. Regardless of the presence of spontaneous respiratory effort, when excessive pressure is delivered to the airway, gastric insufflation may occur. This may lead to a vicious cycle of increased intra-abdominal pressure, which requires higher peak inspiratory pressures, predisposing patients to vomiting or regurgitation.
COMPLICATIONS
Complications, including corneal abrasions and blindness in the presence of eye injury, can occur. Soft-tissue injuries, including injuries to the nose and lips, may result when excessive pressure is applied.

SUMMARY
Discontinuation of face-mask ventilation depends on clinical circumstances. Patients may require a more permanent or effective method of airway management, such as endotracheal intubation or tracheostomy. On other occasions, all that is needed for patients to recover completely is effective face-mask ventilation with oxygen.

No potential conflict of interest relevant to this article was reported.

REFERENCES

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A 37-year-old man presented to the emergency department with chest pain of 2 days’ duration. The pain was heavy in character, intermittent, and made worse by deep inspiration and lying flat. The man had no shortness of breath and had been actively working as a gardener until the onset of the pain. He was an active smoker, and his father had had a myocardial infarction at the age of 52 years. He did not have hypertension. Auscultation of the precordium was notable for an aortic regurgitant murmur. Electrocardiography showed left ventricular hypertrophy. Chest radiography revealed a widened mediastinum (Panel A). 3-D reconstruction computed tomographic angiography of the chest showed a 9.5-cm ascending aortic aneurysm (Panel B). The patient underwent an ascending aortic root replacement, during which the aneurysm was visible through the median sternotomy (Panel C), and a Dacron graft was successfully placed (Panel D). The patient had a full and uneventful recovery.

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