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Cystatin C is a cysteine protease inhibitor that is freely filtered by the glomerulus and is therefore a measure of renal function. In this study of elderly persons, the serum cystatin C level was a better predictor of the risk of death and cardiovascular disease than was the serum creatinine level. Cystatin C is a useful alternative measure of renal function, as well as an effective prognostic tool.

SEE P. 2049; EDITORIAL, P. 2122; CME, P. 2149
**Original Article**

** Colonoscopic Screening for Average-Risk Women**

A prior study of colon-cancer screening in men demonstrated that 30 percent of advanced colonic neoplasias found on colonoscopy would have been missed by flexible sigmoidoscopy. In this parallel study of women, the yield of flexible sigmoidoscopy was even lower: 65 percent of advanced lesions found on colonoscopy would have been missed by flexible sigmoidoscopy. These data suggest that in women, flexible sigmoidoscopy is a much less effective screening test for colon cancer than colonoscopy.

SEE P. 2061

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**Original Article**

** Transplantation of Cord Blood in Infantile Krabbe’s Disease**

Asymptomatic newborns in whom infantile Krabbe’s disease was diagnosed at or before birth and who underwent transplantation of umbilical-cord blood had progressive myelination and substantial gains in several developmental skills, although they continued to have substantial delays in gross motor function and language. These data suggest that transplantation of umbilical-cord blood favorably alters the natural history of infantile Krabbe’s disease if performed before the onset of symptoms.

SEE P. 2069; EDITORIAL, P. 2124

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**Original Article**

** Asthma and Invasive Pneumococcal Disease**

This case–control study in Tennessee assessed 635 persons 2 to 49 years of age with invasive pneumococcal disease and 6350 matched controls. Among those with asthma, the risk of invasive pneumococcal disease was about twice that among the controls; among those with high-risk asthma, the risk was more than three times as great. Asthma appears to be an independent risk factor for invasive pneumococcal disease. These data suggest that asthma should be an additional indication for pneumococcal vaccination.

SEE P. 2082

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**Special Article**

**Traditional Birth Attendants and Perinatal and Maternal Mortality**

This cluster-randomized trial in rural Pakistan compared perinatal and maternal outcomes in control districts with the outcomes in districts in which traditional birth attendants were trained and were issued disposable delivery kits and in which obstetrical teams provided outreach clinics for antenatal care. Perinatal mortality was reduced significantly in the intervention districts. An intervention involving training traditional birth attendants and integrating them into an improved health care system was achievable and effective in reducing perinatal mortality in rural Pakistan.

SEE P. 2091

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**Clinical Practice**

**Overweight Children and Adolescents**

A seven-year-old girl is 130 cm tall (the 90th percentile for girls of the same age) and weighs 34.6 kg (above the 95th percentile), with a body-mass index of 20.5 (above the 95th percentile). Physical examination reveals no abnormalities aside from her excess weight. She eats fast food and drinks soft drinks regularly, has limited exercise, and watches television or uses the computer for hours each day. What should you advise?

SEE P. 2100; CME, P. 2150

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**Legal Issues in Medicine**

**Torture, Medical Ethics, and the Law**

George Annas reviews international and U.S. laws and U.S. Supreme Court decisions relevant to torture in wartime. He also discusses the controversy over physicians’ roles in the torture of prisoners in the prisons at Abu Ghraib and Guantanamo Bay and argues that physicians have a special responsibility to prevent and report torture.

SEE P. 2127

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**Case Records of the Massachusetts General Hospital**

**A Man with Shortness of Breath, Edema, and Proteinuria**

An 80-year-old man was admitted to the hospital because of shortness of breath. He had pleural effusions, edema of the legs, and a history of atrial fibrillation, several episodes of congestive heart failure, and increasing proteinuria. Laboratory studies revealed nephrotic-range proteinuria and an IgG paraprotein. A diagnostic procedure was performed.

SEE P. 2111; CME, P. 2151
Sergeant David Emme, a supply officer with a U.S. Army Stryker Brigade, was stationed at a submachine gun on a truck rolling through northern Iraq last November, in a convoy transporting Iraqi volunteers to Mosul for military training. As they entered the town of Talafar, Emme noticed that the streets were unusually quiet: no children were outdoors running toward the vehicles demanding sweets. Emme got on the radio and warned others in the convoy: “Something might happen. They might have some plan for us.” Moments later, as they slowed at a traffic circle, an improvised explosive device (IED) went off right next to Emme’s truck, knocking him out.

Emme’s version of what happened next is patched together, from his own memories and what others told him later. “I remember waking up and wondering who the hell I was, where the hell I was, and why can’t I see or hear? My soldier was screaming for me to get out of the truck and I told him no, because it hurt too much. So he literally threw me out of the truck and guided me to a Stryker,” a lightweight armored vehicle.

The blast wave and fragments from the explosion had blown out Emme’s left eardrum, fractured his skull, injured his left eye, and caused a severe contusion in the left frontotemporal area of his brain. His fellow soldiers rushed him to the nearby military base, where he partially regained his vision and tried to walk before again losing consciousness. He was medically evacuated, first to a combat support hospital in Balad and then to one in Baghdad. There, neurosurgeons performed a craniectomy, removing a large piece of skull from the left temporal region to give Emme’s brain room to swell (see diagram). They implanted the bone under the subcutaneous tissue of his abdomen, hoping that it could be replaced later — if Emme survived. He remained unconscious and remembers nothing about his stops in these hospitals.

“The next time I come to, I’m at Walter Reed — like, 10 days later,” he recalled.

Emme spent about six days in the intensive care unit, sometimes mistaking nurses for CIA agents or believing he was back in Baghdad. Then he was transferred to a room in ward 58, the neuroscience unit at Walter Reed Army Medical Center in Washington, D.C. At some point, he became alert enough to realize that he was having difficulty speaking.

“I called for the nurse. . . . I kept on just trying to say something, but I couldn’t really say anything,” Emme recalled. The nurse asked him questions and waited patiently for him to answer. Finally, she left to check on other patients. About a half hour later, she returned, and Emme managed to articulate his message: “My head hurts.”

In the five months since then, Emme, 32, has made a remarkable recovery from his severe brain injury. He is a clean-cut young man with expressive brown eyes, a scarred left cheek, and a depression on the left side of his head where the missing piece of skull has yet to be replaced. (That will be done after surgeons finish reconstructing his tympanic membrane.) His vision has returned almost to normal. With time and intensive therapy, his speech and cognitive function have dramatically improved.

“Basically, I had to learn what things were again,” Emme explained. Then he corrected himself:
Laura W. Battiata, Emme’s speech and language therapist, said that when Emme was first evaluated, 10 days after his injury, his speech was limited and nonsensical, and he could not understand or follow commands. During the ensuing week, this profound receptive and expressive aphasia rapidly resolved as the brain swelling abated. Once his language deficits had improved, Emme’s therapists were able to test his cognitive skills and found that the traumatic brain injury (TBI) had led to defects in reasoning, memory, and problem solving. Emme embarked on daily cognitive-therapy sessions and attended group sessions three times a week.

“Typically, we’ll work on deductive-reasoning tasks, basic problem-solving tasks,” Battiata explained. A patient might be asked to do math exercises, solve puzzles, plan a trip or a meal, or complete a homework assignment. “We know that counseling and giving patients some strategies to use is beneficial,” Battiata added. “Whether it improves their rate of progress, I think, is not well known.”

Emme got better much more rapidly than many of Battiata’s patients with TBIs, some of whom have severely impaired function and show little progress. She said his residual cognitive defects are mild. Emme’s headaches have abated, and he has begun taking college courses online. Although crowds make him uncomfortable, he has started to socialize, venturing out of his room on the hospital campus: recently, he attended the opening game of the Washington Nationals baseball team with friends. He speaks fluently and eagerly now, occasionally resorting to circumlocution when a word eludes him. During a tour of the Pentagon in December, Emme was excited to meet Paul Wolfowitz, then the deputy secretary of defense. Afterward, he recalled with amusement, “I was telling people about it and I was like, ‘Yeah, I went on that... well, I went on... I went to the, uh... place that had the big bang when they flew planes into it.’”

Among surviving soldiers wounded in combat in Iraq and Afghanistan, TBI appears to account for a larger proportion of casualties than it has in other recent U.S. wars. According to the Joint Theater Trauma Registry, compiled by the U.S. Army Institute of Surgical Research, 22 percent of the wounded soldiers from these conflicts who have passed through the military’s Landstuhl Regional Medical Center in Germany had injuries to the head, face, or neck. This percentage can serve as a rough estimate of the fraction who have TBI, according to Deborah L. Warden, a neurologist and psychiatry...
A blast creates a sudden increase in air pressure by heating and accelerating air molecules and, immediately thereafter, a sudden decrease in pressure that produces intense wind. These rapid pressure shifts can injure the brain directly, producing concussion or contusion. Air emboli can also form in blood vessels and travel to the brain, causing cerebral infarcts. In addition, blast waves and wind can propel fragments, bodies, or even vehicles with considerable force, causing head injuries by any of these mechanisms. Approximately 8 to 25 percent of persons with blast-related injuries die.¹

U.S. soldiers in Iraq and Afghanistan who have serious brain injuries receive immediate care on the battlefield and are then transported to military combat support hospitals, where they undergo brain imaging and are treated by neurosurgeons. Treatment may include the removal of foreign bodies, control of bleeding, or craniectomy to relieve pressure from swelling. Depending on their condition, these soldiers are eventually transferred to one of the DVBIC’s eight participating U.S. hospitals for assessment and treatment.

At Walter Reed, the severity of a TBI is assessed according to the duration of loss of consciousness and post-traumatic amnesia, according to Louis M. French, a neuropsychologist who is the DVBIC’s clinical director. A mild TBI (which is usually not associated with visible abnormalities on brain imaging) is one that causes loss of consciousness lasting less than 1 hour or amnesia lasting less than 24 hours. A moderate TBI produces loss of consciousness lasting between 1 and 24 hours or post-traumatic amnesia for one to seven days. Injuries causing loss of consciousness for more than 24 hours or post-traumatic amnesia for more than a week are considered severe. In magnetic resonance images from patients with moderate or severe TBIs, punctate hemorrhages may be visible in the corpus callosum or other regions, and there may be other evidence of bleeding or swelling.

Pathological studies in brain-injured animals (and limited postmortem studies in humans) suggest that TBIs typically cause damage to nerve axons in many areas of the brain. Although it is unclear what initiates axonal damage, it begins within minutes after the injury occurs, develops over a period of hours to a few days, and leads to the degeneration of some axons’ distal projections and to diffuse loss of synaptic terminals. This loss of neural connections may lead to many of the symptoms associated with brain injuries, and the gradual replacement of lost synapses by the sprouting of nearby, undamaged axons probably underlies the recovery process.² Excitotoxicity and oxidative stress have been suggested as possible mechanisms of cell injury. In addition, in moderate and severe TBIs, hemorrhages, contusion, and pressure caused by swelling may also contribute to tissue damage.

Soldiers with TBI often have symptoms and findings affecting several areas of brain function. Headaches, sleep disturbances, and sensitivity to light and noise are common symptoms. Cognitive changes, diagnosed on mental-status examination or through neuropsychological testing, may include disturbances in attention, memory, or language, as well as delayed reaction time during problem solving. Often, the most troubling symptoms are behavioral ones: mood changes, depression, anxiety,
impulsiveness, emotional outbursts, or inappropriate laughter. Some symptoms of TBI overlap with those of post-traumatic stress disorder, and many of French’s patients have both conditions.

“We are working with a population that tends to be young and healthy going into this, so they’re really in a good position to recover,” French said. “But complicating things, these people have been hurt in complicated and terrible ways. Certainly, if people get even a mild TBI under circumstances of extreme stress,” especially if it is accompanied by other injuries, “that might well affect the outcome.”

Last May, Staff Sergeant Jason Pepper experienced the full force of an IED that exploded in a tree next to his armored personnel carrier in Karbala, Iraq. “It kind of detonated in my face,” Pepper explained. “The signature of the heat and the shrapnel took out my right eye. The heat and the compression took out my left eye. From the blast itself, I had a small skull fracture on the left side, a subdural hematoma, plus a bruised brain. A right forearm that was completely shattered at the elbow and wrist . . . and then, in my left hand is a mixture of plates, pins, screws, rods, and lacing wire — basically an Erector Set in the making.”

Surgeons at a combat support hospital in Baghdad enucleated Pepper’s eyes: “There was nothing left for them to save,” he said. After undergoing several operations in Iraq, Pepper arrived at Walter Reed a week after he was injured and has been receiving treatment and rehabilitation there for much of the past year. He lost his left index finger, so surgeons have been rebuilding his hand by transplanting the middle finger and releasing tendons to give him a pincer grasp. Between operations, he attended occupational-therapy sessions intended to improve his dexterity, aid his recovery from a moderate TBI, and develop his visualization skills.

Pepper, 28, who was a combat engineer, has close-cropped brown hair and an athletic build, and he finds his way around with the aid of a white cane. His musical name and his wry sense of humor charmed cartoonist Garry Trudeau, who wrote Sergeant Pepper into a “Doonesbury” strip after visiting Walter Reed. Pepper’s hobbies used to include video games and softball; “Now,” he said, “I sit there listening to XM radio.” His wife, Heather, complains that he doesn’t want to go out anymore. He has midday migraines and hates being left alone.

French noted that for soldiers like Pepper who have multiple injuries, recovering from a TBI can complicate the process of rehabilitation because of the brain injury’s effects on mood and cognitive function. “If you’re trying to do blind rehab and you’re relying on auditory memory, your attention had better be intact; your auditory memory had better be intact,” he said.

Pepper will be transferred soon to the Edward Hines Jr. VA Hospital near Chicago, where he has chosen to undergo an intensive blind-rehabilitation program that is likely to last two months or longer. Participants live in private rooms in a dormitory and receive training for at least seven hours a day on orientation and mobility, manual skills, sensory skills, daily living skills, and computer access.

For Pepper, Emme, and other soldiers with TBIs, overcoming some of the lingering effects of brain injury may take longer than recovering from other wounds. Doctors help them to manage headaches and sleep disorders; therapists work with them to overcome difficulties with memory or concentration. Warden said stimulants such as methylphenidate or dextroamphetamine are commonly used to treat problems with attention or information processing, and selective serotonin-reuptake inhibitor antidepressants are sometimes prescribed for irritability or angry outbursts. Valproate is frequently prescribed because it can be effective both for migraines and for behavioral symptoms.

Most adults with a mild TBI recover completely within a year, but moderate and severe TBIs are more likely to cause lingering effects. An estimated 5.3 million Americans are living with disabilities that resulted from TBIs, according to the Centers for Disease Control and Prevention. Warden said many patients with such injuries who are treated at Walter Reed are able to return to active duty; others retire from the military and receive medical disability payments. The Department of Veterans Affairs is now planning for the large influx of veterans with TBIs from the current conflicts who will need continuing care during the coming years. “These
are people who are going back into our communities all across the country, who are potentially going to be struggling,” said Warden. “Keep in mind, these patients, because of the nature of their brain injuries, can be the ones at highest risk of falling through the cracks.”

French said that Pepper and Emme have had better-than-average recoveries so far, in part because they are highly motivated and are working hard at their rehabilitation programs.

“Not all of them recover,” noted Colonel Jean Dailey, a nursing supervisor on the neuroscience unit. “It can wear on you.” Dailey added that nurses on her unit have higher turnover rates than those on the hospital’s orthopedic ward, which chiefly treats soldiers with limb injuries. Unlike the young amputees, she said, “these guys’ personalities are not the same” as before they were injured. In fact, she says, “they may never be the same.”


Perinatal Mortality in Developing Countries

Jelka Zupan, M.D.

Each year, 10.7 million children under the age of five years die — 4 million during the first four weeks of life. Another 3.3 million are stillborn. And these are only the official reports. In the less developed countries, which account for 98 percent of reported neonatal deaths and 97 percent of reported stillbirths, these births and deaths are not always registered.

Since 2000, when the United Nations Millennium Declaration was signed, efforts to reduce mortality among children younger than five years of age have been accelerating. It will be difficult to reach the stated goal — cutting the rate by two thirds by 2015 — without reducing the number of neonatal deaths. Many useful interventions can be implemented in resource-poor settings, but weak health care delivery systems remain an important barrier. Research is ongoing on alternative approaches, including the training and deployment of traditional birth attendants, as reported by Jokhio et al. in this issue of the Journal (pages 2091–2099). But the problems involved are so many, and the resources so limited, that the task remains daunting.

The highest neonatal mortality rates and rates of stillbirth occur in sub-Saharan Africa, followed by Asia and Latin America (see graph). In countries where the mortality is highest, almost 10 percent of babies do not survive more than one month.

Neonatal deaths generally result from complications of preterm birth, asphyxia or trauma during birth, infections, severe malformations, or other specifically perinatal causes. The proportion attributable to each cause varies: in areas where neonatal mortality is lower, preterm birth and malformations play a larger role; where mortality is higher, the contributions of asphyxia, tetanus, and infections are greater. Maternal health and nutrition are important for neonatal health, and maternal infections contribute to adverse outcomes.

But the real causes of adverse outcomes are untreated or poorly treated maternal complications, inadequate neonatal care, and harmful home care practices, such as the discarding of colostrum, the application of unclean substances to the umbilical cord stump, and the failure to keep babies warm. The risk of death for a pregnant woman with severe pre eclampsia, for example, is 0.5 percent, and the risk of perinatal death for her child is 13 percent. If the condition remains untreated and eclampsia develops, the risk of death increases to 5 percent for the mother and 28 percent for the baby.

In addition, infections, which cause many infant deaths, have diverse origins; many are community-acquired bacterial infections in previously healthy infants. It is estimated that in about 25 percent of the stillbirths in less developed countries, death occurs shortly before birth and most likely results from complications of delivery.¹

Targeting new interventions for neonatal survival should be easy in one sense: we know when pregnant women and newborns will need care, since we estimate in advance the date of birth and most complications arise during late pregnancy and

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¹ Targeting new interventions for neonatal survival should be easy in one sense: we know when pregnant women and newborns will need care, since we estimate in advance the date of birth and most complications arise during late pregnancy and...
Cystatin C and the Risk of Death and Cardiovascular Events among Elderly Persons


ABSTRACT

BACKGROUND

Cystatin C is a serum measure of renal function that appears to be independent of age, sex, and lean muscle mass. We compared creatinine and cystatin C levels as predictors of mortality from cardiovascular causes and from all causes in the Cardiovascular Health Study, a cohort study of elderly persons living in the community.

METHODS

Creatinine and cystatin C were measured in serum samples collected from 4637 participants at the study visit in 1992 or 1993; follow-up continued until June 30, 2001. For each measure, the study population was divided into quintiles, with the fifth quintile subdivided into thirds (designated 5a, 5b, and 5c).

RESULTS

Higher cystatin C levels were directly associated, in a dose–response manner, with a higher risk of death from all causes. As compared with the first quintile, the hazard ratios (and 95 percent confidence intervals) for death were as follows: second quintile, 1.08 (0.86 to 1.35); third quintile, 1.23 (1.00 to 1.53); fourth quintile, 1.34 (1.09 to 1.66); quintile 5a, 1.77 (1.34 to 2.26); 5b, 2.18 (1.72 to 2.78); and 5c, 2.58 (2.03 to 3.27). In contrast, the association of creatinine categories with mortality from all causes appeared to be J-shaped. As compared with the two lowest quintiles combined (cystatin C level, ≤0.99 mg per liter), the highest quintile of cystatin C (≥1.29 mg per liter) was associated with a significantly elevated risk of death from cardiovascular causes (hazard ratio, 2.27 [1.73 to 2.97]), myocardial infarction (hazard ratio, 1.48 [1.08 to 2.02]), and stroke (hazard ratio, 1.47 [1.09 to 1.96]) after multivariate adjustment. The fifth quintile of creatinine, as compared with the first quintile, was not independently associated with any of these three outcomes.

CONCLUSIONS

Cystatin C, a serum measure of renal function, is a stronger predictor of the risk of death and cardiovascular events in elderly persons than is creatinine.
The presence of renal dysfunction in elderly persons has been associated with an increased risk of death among healthy persons in outpatient care1,2 and among those with several clinical factors, including heart failure,3 acute hospitalization,4 inpatient surgery,5,6 and acute myocardial infarction.7,8 However, the primary clinical tool for measuring renal function, the serum creatinine level, is insensitive for the detection of moderate reductions in renal function and is affected by factors unrelated to renal function, such as age, sex, race, and lean muscle mass. Creatinine-based equations to estimate the glomerular filtration rate (GFR) have been derived to compensate for these nonrenal influences on the relationship between creatinine and GFR, but their precision when applied to elderly patients is unclear.9-11

Cystatin C is a cysteine protease inhibitor produced by nearly all human cells and excreted into the bloodstream. At a molecular weight of 13 kD, the protein is freely filtered by the renal glomerulus and then metabolized by the proximal tubule.12,13 Given its reported superiority over creatinine as a proxy for GFR, we hypothesized that cystatin C would be a stronger and more linear predictor of the risk of illness and death among elderly persons than either the serum creatinine level or the estimated GFR.14 To that end, we compared the associations of cystatin C, creatinine, and the estimated GFR with the risk of cardiovascular events and death in a population-based cohort study of elderly adults.

METHODS

STUDY DESIGN

The Cardiovascular Heath Study (CHS) is a community-based, longitudinal study of adults who were 65 years of age or older at the study’s inception. Its main purpose is to evaluate risk factors for the development and progression of cardiovascular disease in elderly persons.15 The study recruited participants from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and the city of Pittsburgh. To be eligible, persons had to be at least 65 years of age, not institutionalized (i.e., living in the community), expected to remain in the current community for three years or longer, and not under active treatment for cancer, and be able to provide written informed consent without the need for a proxy respondent. The initial 5201 participants were enrolled from January 1989 to June 1990; an additional 687 black participants (with race self-reported) were recruited and enrolled by June 1993. The study design, quality-control procedures, laboratory methods, and procedures for blood-pressure measurement have been published previously.15,16

This analysis includes all 4637 participants who attended the annual study visit in 1992 or 1993 and for whom serum was available for measurement of creatinine and cystatin C. Creatinine measurements were performed in proximity to the 1992–1993 visit, whereas cystatin C was measured in 2003 using frozen serum. Follow-up for events continued until June 30, 2001 (median follow-up, 7.4 years; maximum, 8.1).

RENA L-FUNCTION ASSAYS

All assays were performed in serum specimens that had been obtained from participants after a fast and were stored at −70°C. Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).17 Among 61 healthy persons with three cystatin C measurements during a six-month period, the intrapatient coefficient of variation was 7.7 percent, reflecting the long-term stability of the cystatin C level. The range of detection of the assay is 0.195 to 7.330 mg per liter, with the reference range for young, healthy persons reported as 0.53 to 0.95 mg per liter. The assay remained stable, with no change in the values measured, over five cycles of freezing and thawing.

Serum creatinine was measured by a colorimetric method (Ektachem 700, Eastman Kodak). The mean coefficient of variation for monthly controls was 1.94 percent (range, 1.16 to 3.90). We estimated the GFR with the use of the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation.9,18

MULTIVARIATE ADJUSTMENT

Information on characteristics that might confound the association of renal function with the risk of cardiovascular events and death was obtained from the records of the 1992–1993 visit. These included the demographic factors age, sex, and race (self-reported); the cardiovascular risk factors body-mass index (BMI, the weight in kilograms divided by the square of the height in meters),
Thoracic disease, or cerebrovascular disease.

Cardiovascular causes was defined as death caused by coronary heart disease, heart failure, peripheral vascular disease, or cancer; and self-reported health status (fair or poor vs. good, very good, or excellent).

Outcomes

Follow-up visits were conducted by telephone every six months and in person annually. All events were adjudicated by a CHS outcome-assessment committee. Participants with a history of myocardial infarction or stroke were excluded from the analyses of the incidence of events. Myocardial infarction was ascertained from hospital records and was indicated by a clinical history of cardiac symptoms, elevated cardiac enzyme levels, and serial electrocardiographic changes.19 Cases of possible stroke were adjudicated by a committee of neurologists, neuroradiologists, and internists on the basis of interviews with patients, medical records, and brain imaging studies.20 Deaths were identified by a review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care–utilization database for hospitalizations and from household contacts; 100 percent complete follow-up for ascertainment of mortality status was achieved. Death from cardiovascular causes was defined as death caused by coronary heart disease, heart failure, peripheral vascular disease, or cerebrovascular disease.21

Statistical analysis

To evaluate the association of each renal measurement with the outcomes, we initially created quintiles of the study population according to cystatin C and creatinine levels and estimated GFR. Because creatinine levels differ substantially between men and women, we used sex-specific quintiles for creatinine so as to equalize the distribution of men and women.1 A previous study from the CHS found substantial increases in the risk of death only for persons with creatinine levels greater than 1.5 mg per deciliter (133 µmol per liter) — which corresponds to the highest 6 percent of the cohort1; therefore, we subdivided the fifth quintile of each measure into thirds. These subdivisions of the fifth quintile for each measurement were designated 5a (the lowest third), 5b (the middle third), and 5c (the highest third). For cystatin C and creatinine, the fifth quintile was made up of the participants with the highest values. For estimated GFR, because lower values are associated with worse renal function, the fifth quintile comprised the participants with the lowest values.

We began our analysis by examining the distribution of the adjustment variables, listed above, according to the quintile of cystatin C. The annual risk for each outcome was determined for each of the seven levels of the measures of renal function. To evaluate the joint effects of cystatin C and creatinine on mortality, we also cross-tabulated quintiles of both measures and determined the annual risk within each of the 25 resulting categories.

We used Cox proportional-hazards models to evaluate the association of each measure of renal function, categorized in the seven subgroups, with each outcome. Covariates were identified with use of a model that included cystatin C as a continuous predictor of each outcome; each candidate variable was entered separately, and variables that changed the parameter estimate (beta coefficient) of cystatin C by 5 percent or more were retained in the final model. For each outcome, the same covariates were entered into the models for the categories of cystatin C, creatinine, and estimated GFR. For the outcome of death, we determined the population attributable risk for cystatin C and compared it with those for the other significant predictors in the final model. Predictors that were on a continuous scale were dichotomized by using the fifth quintile as a cutoff point. S-Plus software (version 6.1, Insightsoft) and SPSS statistical software (version 12.0.0) were used for the analyses.

This study was designed by Drs. Shlipak, Katz, Fried, Siscovick, and Stehman-Breen. Drs. Shlipak, Katz, and Siscovick vouch for the data and the analysis. The manuscript was written solely by the listed authors. The CHS was approved by the institutional review boards of the University of Washington.
and the affiliated clinical centers; these analyses were approved by the Committee on Human Research of the University of California, San Francisco. All participants gave written informed consent for enrollment and follow-up in CHS and for the future use of biologic specimens.

RESULTS

CHARACTERISTICS ASSOCIATED WITH CYSTATIN C

Participants with the highest cystatin C levels were older and more likely to be male, but less likely to be black, than participants with lower cystatin C levels (Table 1). Nearly all of the coexisting conditions we assessed were more prevalent among those with elevated levels of cystatin C, who also had a greater waist-to-hip ratio, higher leukocyte count, and higher C-reactive protein levels and lower levels of HDL cholesterol and hemoglobin (Table 1). In contrast, the prevalence of current smoking did not vary significantly among the quintiles of cystatin C; in addition, among current smokers the mean number of cigarettes smoked per day was similar among the cystatin C quintiles, ranging from 12 to 15 (P for trend=0.09).

Table 1. Baseline Characteristics of Elderly Participants in the Cardiovascular Health Study, According to Quintiles of Cystatin C.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quintile 1 (≤0.89 mg per liter)</th>
<th>Quintile 2 (0.90–0.99 mg per liter)</th>
<th>Quintile 3 (1.00–1.10 mg per liter)</th>
<th>Quintile 4 (1.11–1.28 mg per liter)</th>
<th>Quintile 5 (≥1.29 mg per liter)</th>
<th>P Value for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>942</td>
<td>892</td>
<td>943</td>
<td>947</td>
<td>913</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age — yr</td>
<td>73±4</td>
<td>74±4</td>
<td>74±5</td>
<td>76±5</td>
<td>78±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>282 (30)</td>
<td>334 (37)</td>
<td>411 (44)</td>
<td>451 (48)</td>
<td>455 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black race — no. (%)</td>
<td>276 (29)</td>
<td>174 (20)</td>
<td>129 (14)</td>
<td>116 (12)</td>
<td>107 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>505 (54)</td>
<td>477 (53)</td>
<td>498 (53)</td>
<td>557 (59)</td>
<td>596 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes — no. (%)</td>
<td>162 (17)</td>
<td>113 (13)</td>
<td>119 (13)</td>
<td>147 (16)</td>
<td>175 (19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>78 (8)</td>
<td>92 (10)</td>
<td>83 (9)</td>
<td>101 (11)</td>
<td>96 (11)</td>
<td>0.12</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>70±14</td>
<td>72±14</td>
<td>73±14</td>
<td>75±16</td>
<td>74±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.91±0.08</td>
<td>0.94±0.08</td>
<td>0.95±0.07</td>
<td>0.96±0.07</td>
<td>0.96±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol — mg/dl</td>
<td>59±15</td>
<td>55±15</td>
<td>54±13</td>
<td>50±13</td>
<td>48±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol — mg/dl</td>
<td>128±33</td>
<td>128±32</td>
<td>127±33</td>
<td>128±35</td>
<td>125±35</td>
<td>0.07</td>
</tr>
<tr>
<td>Albumin — mg/dl</td>
<td>4.0±0.3</td>
<td>3.9±0.3</td>
<td>3.9±0.3</td>
<td>3.9±0.2</td>
<td>3.9±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocyte count — per mm³</td>
<td>5900±1700</td>
<td>6200±1600</td>
<td>6200±1800</td>
<td>6500±1900</td>
<td>7200±6200</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin — mg/dl</td>
<td>13.7±1.5</td>
<td>13.7±1.3</td>
<td>13.9±1.3</td>
<td>13.8±1.4</td>
<td>13.3±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein — log</td>
<td>0.8±1.1</td>
<td>0.9±1.1</td>
<td>0.9±1.1</td>
<td>1.1±1.1</td>
<td>1.4±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen — mg/dl</td>
<td>318±64</td>
<td>320±63</td>
<td>324±63</td>
<td>335±68</td>
<td>353±80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-reported health fair or poor — no. (%)</td>
<td>171 (18)</td>
<td>159 (18)</td>
<td>163 (17)</td>
<td>198 (21)</td>
<td>275 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy — no. (%)</td>
<td>41 (4)</td>
<td>32 (4)</td>
<td>40 (4)</td>
<td>53 (6)</td>
<td>70 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of MI — no. (%)</td>
<td>59 (6)</td>
<td>63 (7)</td>
<td>77 (8)</td>
<td>105 (11)</td>
<td>164 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke or TIA — no. (%)</td>
<td>32 (3)</td>
<td>28 (3)</td>
<td>39 (4)</td>
<td>43 (5)</td>
<td>107 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF — no. (%)</td>
<td>23 (2)</td>
<td>33 (4)</td>
<td>26 (3)</td>
<td>58 (6)</td>
<td>127 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cancer — no. (%)</td>
<td>116 (12)</td>
<td>106 (12)</td>
<td>111 (12)</td>
<td>140 (15)</td>
<td>155 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD at baseline visit — no. (%)</td>
<td>113 (12)</td>
<td>128 (14)</td>
<td>106 (11)</td>
<td>109 (12)</td>
<td>106 (12)</td>
<td>0.32</td>
</tr>
<tr>
<td>Estimated GFR — ml/min/1.73 m²</td>
<td>88±18</td>
<td>79±14</td>
<td>72±12</td>
<td>66±12</td>
<td>52±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine — mg/dl</td>
<td>0.81±0.16</td>
<td>0.90±0.17</td>
<td>0.97±0.17</td>
<td>1.06±0.20</td>
<td>1.38±0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin C — mg/liter</td>
<td>0.81±0.07</td>
<td>0.95±0.03</td>
<td>1.05±0.03</td>
<td>1.18±0.05</td>
<td>1.61±0.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, MI myocardial infarction, TIA transient ischemic attack, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, and GFR glomerular filtration rate. To convert values for HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert values for fibrinogen to micromoles per liter, multiply by 0.0294; to convert values for creatinine to micromoles per liter, multiply by 88.4. C-reactive protein was measured in milligrams per liter.
CORRELATION AMONG MEASURES OF RENAL FUNCTION

Overall, the cystatin C level had a strong, direct correlation with the creatinine level ($r=0.79$, $P<0.001$) and an inverse correlation with the estimated GFR ($r=-0.63$, $P<0.001$). However, correlations stratified according to the quintile of creatinine were somewhat weak, except in the fifth quintile (correlation coefficients: first quintile, 0.18; second quintile, 0.23; third quintile, 0.29; fourth quintile, 0.23; and fifth quintile, 0.80 [$P<0.001$ for all quintiles]). Correlations of estimated GFR values and cystatin C levels also varied markedly, with stratification according to the quintile of estimated GFR (first through fifth quintiles, $-0.31$ [$P<0.001$], $-0.09$ [$P=0.006$], $-0.06$ [$P=0.08$], $-0.13$ [$P<0.001$], and $-0.75$ [$P<0.001$]).

RISK OF DEATH FROM ALL CAUSES

The incidence of death from all causes was determined for each of the seven categories of cystatin C, creatinine, and estimated GFR, revealing substantive differences (Fig. 1). The cystatin C categories were nearly linearly associated with the risk of death. In contrast, creatinine and estimated GFR appeared to have J-shaped associations with the risk of death. We found no interactions of cystatin C levels with age, sex, race, or BMI; in contrast, creatinine levels had significant interactions with each of these covariates ($P<0.001$).

To explore the joint effects of cystatin C and creatinine in predicting mortality, we determined the incidence of death within each of the 25 subgroups defined by quintiles of cystatin C and creatinine (Fig. 2). Within each quintile of creatinine, increasing levels of cystatin C were associated with increased mortality.

After multivariate analysis, the first and second quintiles of cystatin C had a similar mortality rate, the third and fourth quintiles were associated with significantly, albeit moderately, increased risk, and all three subgroups of the fifth quintile were associated with roughly a doubling of mortality (Table 2). Among the predictors of mortality that were retained in the final model, the highest quintile of cystatin C was associated with the greatest population attributable risk (12.7 percent), followed by fair or poor self-reported health status (10.6 percent) and the presence of diabetes (7.4 percent).

For creatinine, the J-shaped association with mortality persisted in the multivariate analyses, and only the highest creatinine subgroup (5c, accounting for 7 percent of the cohort) had a significantly increased risk of death as compared with the risk in the lowest quintile. Only the two subgroups with
### Table 2. Risk of Adverse Outcomes According to Measures of Renal Function among Elderly Participants in the Cardiovascular Health Study.

<table>
<thead>
<tr>
<th>Measure and Outcome</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5a</th>
<th>Quintile 5b</th>
<th>Quintile 5c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystatin C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of values — mg/liter</td>
<td>≤0.89</td>
<td>0.90–0.99</td>
<td>1.00–1.10</td>
<td>1.11–1.28</td>
<td>1.29–1.39</td>
<td>1.40–1.59</td>
<td>≥1.60</td>
</tr>
<tr>
<td>Death from all causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>942</td>
<td>892</td>
<td>943</td>
<td>947</td>
<td>308</td>
<td>302</td>
<td>303</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>158</td>
<td>164</td>
<td>219</td>
<td>279</td>
<td>131</td>
<td>161</td>
<td>204</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.19 (0.95–1.49)</td>
<td>1.50 (1.21–1.86)</td>
<td>1.94 (1.58–2.38)</td>
<td>3.10 (2.44–3.95)</td>
<td>4.18 (3.32–5.26)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.00</td>
<td>1.08 (0.86–1.35)</td>
<td>1.23 (1.00–1.53)</td>
<td>1.34 (1.09–1.66)</td>
<td>1.77 (1.34–2.26)</td>
<td>2.18 (1.72–2.78)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>942</td>
<td>892</td>
<td>943</td>
<td>947</td>
<td>308</td>
<td>302</td>
<td>303</td>
</tr>
<tr>
<td>No. of deaths</td>
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<td>58</td>
<td>99</td>
<td>122</td>
<td>56</td>
<td>68</td>
<td>82</td>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.47 (0.98–2.20)</td>
<td>2.37 (1.63–3.43)</td>
<td>3.01 (2.10–4.31)</td>
<td>4.70 (3.12–7.07)</td>
<td>6.25 (4.21–9.28)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.00</td>
<td>1.33 (0.88–2.00)</td>
<td>1.93 (1.33–2.80)</td>
<td>1.99 (1.38–2.87)</td>
<td>2.48 (1.63–3.77)</td>
<td>2.73 (1.81–4.13)</td>
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<tr>
<td>Myocardial infarction§</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
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<td>828</td>
<td>862</td>
<td>841</td>
<td>256</td>
<td>250</td>
<td>242</td>
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<tr>
<td>No. of events</td>
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<td>57</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.03 (0.71–1.48)</td>
<td>1.45 (1.04–2.02)</td>
<td>1.54 (1.10–2.16)</td>
<td>2.08 (1.35–3.20)</td>
<td>1.94 (1.22–3.07)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.00</td>
<td>0.97 (0.67–1.41)</td>
<td>1.26 (0.89–1.78)</td>
<td>1.14 (0.80–1.63)</td>
<td>1.44 (0.91–2.28)</td>
<td>1.30 (0.80–2.11)</td>
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<tr>
<td>Stroke</td>
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<td>864</td>
<td>901</td>
<td>903</td>
<td>280</td>
<td>268</td>
<td>258</td>
</tr>
<tr>
<td>No. of strokes</td>
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<td>76</td>
<td>81</td>
<td>81</td>
<td>33</td>
<td>42</td>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.25 (0.89–1.75)</td>
<td>1.22 (0.87–1.71)</td>
<td>1.37 (0.98–1.91)</td>
<td>1.97 (1.29–3.00)</td>
<td>2.82 (1.90–4.19)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.00</td>
<td>1.22 (0.87–1.72)</td>
<td>1.17 (0.83–1.65)</td>
<td>1.15 (0.82–1.62)</td>
<td>1.43 (0.92–2.21)</td>
<td>1.97 (1.31–2.98)</td>
</tr>
</tbody>
</table>
## Creatinine

### Range of values in men — mg/dl

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<th>Range</th>
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<td>≤0.85</td>
<td>0.86–1.05</td>
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<tr>
<td>0.86–1.15</td>
<td>1.16–1.25</td>
</tr>
<tr>
<td>1.26–1.35</td>
<td>1.36–1.55</td>
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<tr>
<td>≥1.56</td>
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</table>

### Range of values in women — mg/dl

<table>
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<th>Creatinine</th>
<th>Range</th>
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<td>≤0.65</td>
<td>0.66–0.75</td>
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<tr>
<td>0.66–0.85</td>
<td>0.86–0.95</td>
</tr>
<tr>
<td>0.96–1.05</td>
<td>1.06–1.15</td>
</tr>
<tr>
<td>≥1.16</td>
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</tr>
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</table>

### Death from all causes

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>No. of deaths</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted†</td>
</tr>
<tr>
<td>571</td>
<td>159</td>
<td>1.00</td>
</tr>
<tr>
<td>1287</td>
<td>298</td>
<td>0.78 (0.64–0.96)</td>
</tr>
<tr>
<td>966</td>
<td>225</td>
<td>0.83 (0.67–1.02)</td>
</tr>
<tr>
<td>716</td>
<td>175</td>
<td>0.83 (0.67–1.02)</td>
</tr>
<tr>
<td>433</td>
<td>125</td>
<td>1.18 (0.93–1.50)</td>
</tr>
<tr>
<td>321</td>
<td>125</td>
<td>1.51 (1.19–1.93)</td>
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</table>

### Death from cardiovascular causes

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>No. of deaths</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted†</td>
</tr>
<tr>
<td>571</td>
<td>159</td>
<td>1.00</td>
</tr>
<tr>
<td>1287</td>
<td>298</td>
<td>0.70 (0.57–0.85)</td>
</tr>
<tr>
<td>966</td>
<td>225</td>
<td>0.84 (0.68–1.04)</td>
</tr>
<tr>
<td>716</td>
<td>175</td>
<td>0.83 (0.66–1.03)</td>
</tr>
<tr>
<td>433</td>
<td>125</td>
<td>1.00 (0.79–1.27)</td>
</tr>
<tr>
<td>321</td>
<td>125</td>
<td>0.95 (0.74–1.22)</td>
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</table>

### Myocardial infarction

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>No. of events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted‡</td>
</tr>
<tr>
<td>526</td>
<td>48</td>
<td>1.00</td>
</tr>
<tr>
<td>1154</td>
<td>97</td>
<td>0.96 (0.69–1.34)</td>
</tr>
<tr>
<td>885</td>
<td>67</td>
<td>1.04 (0.73–1.47)</td>
</tr>
<tr>
<td>659</td>
<td>70</td>
<td>1.06 (0.73–1.53)</td>
</tr>
<tr>
<td>389</td>
<td>32</td>
<td>1.46 (0.99–2.14)</td>
</tr>
<tr>
<td>268</td>
<td>28</td>
<td>1.89 (1.28–2.81)</td>
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</tbody>
</table>

### Stroke

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>No. of strokes</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted**</td>
</tr>
<tr>
<td>551</td>
<td>45</td>
<td>1.00</td>
</tr>
<tr>
<td>1225</td>
<td>103</td>
<td>0.95 (0.67–1.35)</td>
</tr>
<tr>
<td>924</td>
<td>78</td>
<td>0.95 (0.65–1.37)</td>
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<tr>
<td>686</td>
<td>59</td>
<td>1.01 (0.68–1.48)</td>
</tr>
<tr>
<td>405</td>
<td>44</td>
<td>1.29 (0.85–1.97)</td>
</tr>
<tr>
<td>293</td>
<td>38</td>
<td>1.65 (1.07–2.54)</td>
</tr>
<tr>
<td>300</td>
<td>38</td>
<td>1.71 (1.11–2.64)</td>
</tr>
</tbody>
</table>
### Estimated GFR

<table>
<thead>
<tr>
<th>Range of values — ml/min/1.73 m²</th>
<th>≥82.84</th>
<th>73.87–82.83</th>
<th>66.63–73.86</th>
<th>55.70–66.62</th>
<th>53.46–55.69</th>
<th>45.65–53.45</th>
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#### Death from all causes

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<th>No. at risk</th>
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<th>927</th>
<th>935</th>
<th>930</th>
<th>301</th>
<th>315</th>
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<td>206</td>
<td>277</td>
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<td>143</td>
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<tr>
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<th>Adjusted†</th>
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<tr>
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<td>927</td>
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<tr>
<td>No. of deaths</td>
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#### Death from cardiovascular causes

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<th>847</th>
<th>857</th>
<th>838</th>
<th>267</th>
<th>262</th>
<th>247</th>
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</thead>
<tbody>
<tr>
<td>No. of events</td>
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<td>64</td>
<td>65</td>
<td>92</td>
<td>18</td>
<td>29</td>
<td>28</td>
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<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
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<th>Adjusted‡</th>
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<tbody>
<tr>
<td>No. at risk</td>
<td>884</td>
<td>896</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>73</td>
<td>73</td>
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#### Myocardial infarction§

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<thead>
<tr>
<th>No. at risk</th>
<th>843</th>
<th>847</th>
<th>857</th>
<th>838</th>
<th>267</th>
<th>262</th>
<th>247</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>74</td>
<td>64</td>
<td>65</td>
<td>92</td>
<td>18</td>
<td>29</td>
<td>28</td>
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</table>

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>Unadjusted</th>
<th>Adjusted¶</th>
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<tbody>
<tr>
<td>No. at risk</td>
<td>884</td>
<td>896</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>

#### Stroke

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>884</th>
<th>896</th>
<th>888</th>
<th>875</th>
<th>284</th>
<th>288</th>
<th>269</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of strokes</td>
<td>73</td>
<td>73</td>
<td>74</td>
<td>82</td>
<td>29</td>
<td>38</td>
<td>36</td>
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<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>Unadjusted</th>
<th>Adjusted**</th>
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</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>884</td>
<td>896</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>

---

* For cystatin C, creatinine, and the estimated glomerular filtration rate (GFR), the fifth quintile was subdivided into three roughly equal groups, labeled S5a, S5b, and S5c. For estimated GFR, the fifth quintile comprised the participants with the lowest values. To convert values for creatinine to micromoles per liter, multiply by 88.4. CI denotes confidence interval.

† The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

‡ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

§ A total of 476 participants who had myocardial infarction before the 1992–1993 visit were excluded from the analyses of newly diagnosed myocardial infarction (remaining sample size, 4161).

¶ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, hemoglobin level, high-density lipoprotein cholesterol level, and presence or absence of a history of stroke or transient ischemic attack.

** A total of 254 participants who had stroke before the 1992–1993 visit were excluded from the analyses of newly diagnosed stroke (remaining sample size, 4383).

---

For cystatin C, creatinine, and the estimated glomerular filtration rate (GFR), the fifth quintile was subdivided into three roughly equal groups, labeled S5a, S5b, and S5c. For estimated GFR, the fifth quintile comprised the participants with the lowest values. To convert values for creatinine to micromoles per liter, multiply by 88.4. CI denotes confidence interval.

† The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

‡ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, hemoglobin level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

§ A total of 476 participants who had myocardial infarction before the 1992–1993 visit were excluded from the analyses of newly diagnosed myocardial infarction (remaining sample size, 4161).

¶ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, fibrinogen levels, and presence or absence of a history of myocardial infarction.
the lowest estimated GFR levels (5b and 5c) had a significantly increased risk of death in adjusted analyses.

**Risk of Cardiovascular Events**

The association of cystatin C with mortality from cardiovascular causes was even stronger than its association with mortality from all causes (Table 2). As compared with the first quintile in the adjusted analysis, the second quintile had a similar risk, quintiles 3 and 4 had approximately a doubled risk, and the subgroups of the fifth quintile had nearly a tripled risk. None of the creatinine subgroups were at significantly increased risk in the adjusted analysis, and only the subgroup with the lowest estimated GFR values was at increased risk.

The associations of cystatin C with newly diagnosed myocardial infarction and stroke were less strong than was the case for the mortality outcomes. In unadjusted analysis, a significant increase in the risk of myocardial infarction was observed for all subgroups of cystatin C above the second quintile. However, in adjusted analysis, only the subgroup with the highest values (5c) was at significantly increased risk for myocardial infarction. Creatinine and estimated GFR subgroups had no significant association with myocardial infarction in either unadjusted or adjusted analyses. In an unadjusted analysis of newly diagnosed stroke, the fifth cystatin C quintile had twice the risk of the lowest quintile. After multivariate adjustment, the highest two subgroups of the fifth quintile remained at significantly increased risk. In unadjusted analysis, the one or two subgroups of creatinine and estimated GFR that indicated the worst renal function were associated with the risk of stroke; however, no significant associations remained after multivariate adjustment.

**Low, Intermediate, and High Cystatin C Levels**

On the basis of the findings presented in Table 2, we combined subgroups into categories designated low-risk (quintiles 1 and 2), intermediate-risk (quintiles 3 and 4), and high-risk (quintile 5), corresponding to cystatin C levels of less than 1.00 mg per liter, 1.00 to 1.28 mg per liter, and 1.29 mg per liter or more (Table 3). The intermediate-risk group had an annual risk of death of 3.9 percent, which was similar to the average risk of 4.3 percent for the entire cohort. As compared with the low-risk group, the intermediate-risk group had a moderately elevated risk of death from all causes and death from cardiovascular causes; the high-risk group had a substantially greater risk of both outcomes than did either the intermediate-risk or the low-risk group (Table 3). For newly diagnosed myocardial infarction and stroke, being in the intermediate-risk group was not independently associated with greater risk. The high-risk group had a doubling of the risk of myocardial infarction and stroke in the unadjusted analysis and an increase in risk of roughly 50 percent for each outcome after multivariate adjustment.

**Discussion**

In this study, we found cystatin C to be a strong and independent predictor of overall mortality and mortality from cardiovascular causes in a population-based cohort of ambulatory elderly persons. Using cutoff points at the 40th and 80th percentiles of cystatin C, we defined groups at low, intermediate, and high risk with respect to death from all causes and from cardiovascular causes (cystatin C levels: <1.00, 1.00 to 1.28, and ≥1.29 mg per liter, respectively). High cystatin C levels were also independently associated with the risk for newly diagnosed myocardial infarction and stroke. In contrast, only the participants in the highest 7 percent of the cohort with respect to creatinine levels had a significantly increased risk of death from all causes in the adjusted analysis, and we found no independent association of this creatinine category with the risk of death from cardiovascular causes, myocardial infarction, or stroke. The estimated GFR value, derived with use of the MDRD equation, was only a slightly better predictor of mortality than was the creatinine level. Thus, the cystatin C level appears to provide a stronger estimate of the risk of cardiovascular events and death among elderly persons than either the creatinine level or the estimated GFR.

In part, these results are consistent with previous studies demonstrating that renal dysfunction predicts adverse cardiovascular outcomes and death in a variety of clinical settings. However, the insensitivity of creatinine levels and estimated GFR values for detecting renal dysfunction has limited their value as prognostic factors. We previously reported that elevated creatinine levels had a linear association with the rates of cardiovascular events and with mortality.
Not only did cystatin C levels define a subgroup (the top 20 percent) of elderly persons in the CHS cohort who had a substantially elevated risk of death, but they also defined a large subgroup (the lowest 40 percent) at below-average risk of death. This observation is intriguing and provocative, since earlier studies in which creatinine or estimated GFR was used had found only a high-risk group associated with high creatinine levels or low estimated GFR values; renal function had appeared to affect the
risk of death only when it dropped below a certain threshold, such as a GFR of 60 ml per minute per 1.73 m² of body-surface area. The linear association of cystatin C with the risk of death among participants with predominantly “normal” renal function may indicate that differences in renal function well within the normal range have clinical significance. Future research should evaluate distinctions between persons with low, intermediate, and high cystatin C levels to evaluate other potential consequences of declining renal function. In addition, though we observed no interactions with race or sex in our study, this absence of association should be confirmed in other cohorts, since our study may have had inadequate statistical power to detect such interactions.

An additional task for future studies will be to determine whether cystatin C could have value in clinical medicine as an improved measure of renal function in elderly patients. Our findings indicate that cystatin C is a better marker of the risk of death than creatinine or the estimated GFR. However, to establish that cystatin C has clinical value, studies would have to demonstrate that knowledge of cystatin C levels could improve clinical decision making — as in the evaluation of the risk—benefit trade-offs in prescribing medication, administration of intravenous contrast material, or surgical procedures — over that based on creatinine levels. Although its clinical role has not yet been delineated, measurement of cystatin C is approved by the Food and Drug Administration as a diagnostic test for kidney dysfunction.

Cystatin C may have important limitations as a marker of kidney function in certain disease states. In particular, cystatin C levels appear to be elevated in patients with hypothyroidism and depressed in those with hyperthyroidism; yet the effect of thyroid function on cystatin C levels could reflect actual changes in GFR, which appears to vary directly with basal metabolic rate. Knight and colleagues from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study reported that the association of cystatin C with kidney function was influenced by multiple factors; however, their findings may have been biased by their use of creatinine clearance as the gold standard for kidney function, so it is unclear whether these influences are independent of kidney function. In contrast to the findings from PREVEND, we found no significant association between cystatin C levels and the prevalence of current smoking or the number of cigarettes smoked per day. Future research should clarify the effects of tobacco use and clinical disease status on the capacity of cystatin C levels to predict the GFR.

Our study does have certain limitations. Most important, we cannot be certain whether the strong association of cystatin C with the outcomes we studied is due solely to its correlation with kidney function. Cystatin C may have unforeseen toxic effects that also contribute to the strength of its association with mortality and cardiovascular risk. We also cannot exclude the possibility of confounding due to potential associations of cystatin C with diseases that are independent of its correlation with kidney function. Since the adjusted hazard ratios are substantially different from the unadjusted estimates, we may have overlooked additional, residual confounding. In addition, CHS enrolled only elderly persons, so we do not know whether cystatin C would be a stronger predictor of mortality than creatinine for younger persons, in whom lean muscle makes up a greater proportion of body mass. We also did not calibrate serum creatinine to the methods of the Cleveland Clinic for estimating GFR, as has been recommended. However, since we grouped participants according to quintiles of creatinine and estimated GFR, any arithmetic conversion of the creatinine levels would have no impact on our findings, because their distribution would be unchanged.

In summary, we found that cystatin C, an alternative measure of kidney function, was a stronger predictor of the risk of cardiovascular events and death than either creatinine or the estimated GFR. If this result is confirmed in other studies, cystatin C could be a useful prognostic tool in the evaluation of elderly patients.

Supported by a grant (R01 HL073208-01, to Drs. Shlipak, Fried, and Katz) from the National Heart, Lung, and Blood Institute. Dr. Shlipak is also supported by the American Federation for Aging Research and National Institute on Aging Paul Beeson Scholars Program and by the Robert Wood Johnson Foundation Generalist Faculty Scholars Program. Drs. Sarnak and Seliger are supported by K23 awards from the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Fried is supported by an Advanced Research Career Development award from the Office of Research and Development, Medical Service, Department of Veterans Affairs. The Cardiovascular Health Study is supported by contracts (N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103) with the National Heart, Lung, and Blood Institute.

A full list of participating CHS investigators and institutions can be found at http://www.chs-nhli.org.
REFERENCES


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Colonoscopic Screening of Average-Risk Women for Colorectal Neoplasia

Philip Schoenfeld, M.D., Brooks Cash, M.D., Andrew Flood, Ph.D., Richard Dobhan, M.D., John Eastone, M.D., Walter Coyle, M.D., James W. Kikendall, M.D., Hyungjin Myra Kim, Sc.D., David G. Weiss, Ph.D., Theresa Emory, M.D., Arthur Schatzkin, M.D., and David Lieberman, M.D., for the CONCeRN Study Investigators*

ABSTRACT

BACKGROUND
Veterans Affairs (VA) Cooperative Study 380 showed that some advanced colorectal neoplasias (i.e., adenomas at least 1 cm in diameter, villous adenomas, adenomas with high-grade dysplasia, or cancer) in men would be missed with the use of flexible sigmoidoscopy but detected by colonoscopy. In a tandem study, we examined the yield of screening colonoscopy in women.

METHODS
To determine the prevalence and location of advanced neoplasia, we offered colonoscopy to consecutive asymptomatic women referred for colon-cancer screening. The diagnostic yield of flexible sigmoidoscopy was calculated by estimating the proportion of patients with advanced neoplasia whose lesions would have been identified if they had undergone flexible sigmoidoscopy alone. Lesions were considered detectable by flexible sigmoidoscopy if they were in the distal colon or if they were in the proximal colon in patients who had concurrent small adenomas in the distal colon, a finding that would have led to colonoscopy. The results were compared with the results from VA Cooperative Study 380 for age-matched men and women with negative fecal occult-blood tests and no family history of colon cancer.

RESULTS
Colonoscopy was complete in 1463 women, 230 of whom (15.7 percent) had a family history of colon cancer. Colonoscopy revealed advanced neoplasia in 72 women (4.9 percent). If flexible sigmoidoscopy alone had been performed, advanced neoplasia would have been detected in 1.7 percent of these women (25 of 1463) and missed in 3.2 percent (47 of 1463). Only 35.2 percent of women with advanced neoplasia would have had their lesions identified if they had undergone flexible sigmoidoscopy alone, as compared with 66.3 percent of matched men from VA Cooperative Study 380 (P<0.001).

CONCLUSIONS
Colonoscopy may be the preferred method of screening for colorectal cancer in women.
Colorectal cancer is the second most common cause of death from cancer in the United States, and removal of adenomas appears to reduce the risk of death. Evidence-based guidelines state that either flexible sigmoidoscopy or colonoscopy may be appropriate for screening asymptomatic patients, although the use of screening colonoscopy increased in the United States after the publication of the results of colonoscopic-screening studies. Data from Veterans Affairs (VA) Cooperative Study 380 indicated that the diagnostic yield of flexible sigmoidoscopy for advanced colorectal neoplasia (i.e., adenomas that are at least 1 cm in diameter, villous adenomas, adenomas with high-grade dysplasia, or colon cancer) is 70 percent. However, since 97 percent of the patients in the VA Cooperative Study 380 were men, the diagnostic yield of screening colonoscopy has not been defined for women.

Sex-related biologic differences may result in different phenotypic expressions of colorectal cancer between men and women. The age-adjusted prevalence of adenomas and colorectal cancer is higher among men than among women. Given the lower prevalence of colorectal cancer and adenomas among women, the limited availability of colonoscopic resources, and the economic constraints imposed by a policy of universal colonoscopic screening, recent research suggests that flexible sigmoidoscopy rather than colonoscopy should be used in low-risk persons — specifically, women below 60 years of age who do not have adenomas in the distal colon. Although editorialists have voiced some support for the use of this approach, they have also stated that additional data in women are needed to facilitate further revision of the guidelines for colorectal-cancer screening and to educate women about the preferred method.

In this tandem study to VA Cooperative Study 380, our primary objective was to assess the predictive value of the finding of distal-colon neoplasia (i.e., small adenomas or advanced colorectal neoplasia in the distal colon that would be found during flexible sigmoidoscopy) with respect to advanced neoplasia in the proximal colon of women. Our secondary objectives were to quantify the prevalence and location of advanced colonic neoplasias and small adenomas in asymptomatic women; to compare the prevalence of advanced colonic neoplasia in age-matched men and women with negative fecal occult-blood tests and no family history of colon cancer; and to compare the diagnostic yield of flexible sigmoidoscopy in men and women. With this information, we sought to determine whether flexible sigmoidoscopy would be a reasonable alternative to colonoscopy in asymptomatic women.

Methods

Study Patients

The protocol was approved by the institutional review board at each participating institution. From July 1, 1999, through December 31, 2002, we enrolled consecutive, average-risk, asymptomatic women who were 50 to 79 years of age and who had been referred for colorectal-cancer screening at four military medical centers: the National Naval Medical Center in Bethesda, Maryland; Walter Reed Army Medical Center in Washington, D.C.; the Naval Medical Center in San Diego, California; and the Naval Medical Center in Portsmouth, Virginia. Asymptomatic women who were 40 to 79 years of age and who had a history of colon cancer in a first-degree relative were also offered enrollment. Similar to VA Cooperative Study 380, oversampling of women with a family history of colon cancer was performed.

To ensure that the study patients were asymptomatic and at average risk, we excluded women who had had a positive fecal occult-blood test within 6 months before referral; those who had had iron-deficiency anemia within 6 months before referral; women who had had rectal bleeding or hematochezia within the preceding 12 months; those with an unintentional weight loss of more than 10 lb (4.5 kg) within the preceding 6 months; women with a history of adenomas, colorectal cancer, inflammatory bowel disease, or hereditary polyposis syndromes; and women who had had normal findings on colonoscopy or barium enema within the preceding 10 years or normal findings on flexible sigmoidoscopy with the preceding 5 years. If patients had not had a complete blood-cell count, a ferritin measurement, or a fecal occult-blood test within the six months before referral, then these tests were performed before study entry. All women were interviewed before study entry to ensure that they met eligibility criteria and to obtain written informed consent.

Study Protocol

The women completed detailed questionnaires regarding risk factors before undergoing colonoscopy. These questionnaires quantified demographic and...
lifestyle factors that may be associated with advanced colorectal neoplasia or small adenomas.10-16 Bowel preparation included 4 liters of polyethylene glycol and bisacodyl. Over 99 percent of colonoscopic examinations were performed by gastroenterologists or colorectal surgeons. During colonoscopy, the location of all polyps was defined on the basis of the depth of insertion of the colonoscope and anatomical landmarks, including the hepatic flexure, the splenic flexure, and the junction of the sigmoid and descending colon. These landmarks were identified on the basis of the acute angulation at each junction. Since the diameter of a polyp is frequently misjudged with the use of an open-biopsy forceps,17,18 a guidewire (Olympus Colonoscopy Measuring Guidewire)18 was used to estimate the diameter of a polyp before polypectomy was performed. Since general pathologists may mischaracterize the histologic features of polyps,19 histologic specimens from every polyp were reviewed by an expert gastrointestinal pathologist who was unaware of the colonoscopic findings and the initial pathological diagnosis. The interpretation of the expert gastrointestinal pathologist was considered final. The colonoscopic findings were classified on the basis of the most advanced lesion found: cancer, adenoma with high-grade dysplasia, villous adenoma, adenoma of at least 1 cm, adenoma of less than 1 cm, hyperplastic polyp, or normal or other tissue. The most advanced pathological lesion in the entire colon, proximal colon, and distal colon was recorded. To quantify the diagnostic yield of flexible sigmoidoscopy, we used findings in the distal colon as a surrogate for findings on flexible sigmoidoscopy. Since over 50 percent of flexible sigmoidoscopic examinations reach only the junction of the sigmoid and descending colon,20,21 the primary definition of the distal colon was the rectum and sigmoid colon. Optimally, a flexible sigmoidoscopic examination would reach the splenic flexure, although this is achieved in a minority of patients.20,21 Therefore, an alternative definition of the distal colon as the rectum, sigmoid colon, and descending colon was used for supplemental analysis of the primary end point.

**Statistical Analysis**

All statistical analyses were performed with the use of SAS software (version 9.2) and Stata software (version 8.0). For the primary end point, we used Fisher’s exact test to compare the prevalence of advanced neoplasia in the proximal colon among patients without distal-colon neoplasia with that among patients with distal-colon neoplasia. If flexible sigmoidoscopy were a perfect screening tool, 0 percent of women without distal-colon neoplasia would have advanced neoplasia in the proximal colon. Assuming a 10 percent prevalence of distal-colon neoplasia and using a two-sided alpha value of 0.05, we estimated that 1450 women would need to be enrolled for the study to have a statistical power of 80 percent to detect an absolute difference of 3 percent in the prevalence of proximal-colon advanced neoplasia between women with distal-colon neoplasia and women without distal-colon neoplasia.

Our secondary objectives included calculation of the diagnostic yield of flexible sigmoidoscopy: the likelihood that a patient with advanced colorectal neoplasia would have this lesion identified if she underwent flexible sigmoidoscopy alone. Flexible sigmoidoscopy can detect this lesion if there is advanced neoplasia in the distal colon or if there is advanced neoplasia in the proximal colon along with small adenomas in the distal colon, since the finding of small adenomas would trigger the performance of colonoscopy, which would then detect the advanced neoplasia in the proximal colon.

To compare the prevalence of advanced neoplasia and the diagnostic yield of flexible sigmoidoscopy among men and women, we matched men from VA Cooperative Study 380 with women from the present study for age, a negative fecal occult-blood test, and the absence of a family history of colon cancer. Matching for these risk factors was performed because a positive fecal occult-blood test and a family history of colon cancer trigger a colonoscopy.3 Chi-square analysis was used to compare the diagnostic yield of flexible sigmoidoscopy and the percentage of women and men with advanced neoplasia in different age groups. When appropriate, we used relative risks to express the difference in the prevalence of advanced neoplasia between any two groups.

**Results**

**Demographic Characteristics**

A total of 1593 women were eligible for the study, and 1483 (93.1 percent) participated. Colonoscopy was complete to the cecum in 98.7 percent of the women (1463 of 1483), and no clinically significant complications (i.e., perforation, need for hospital-
zation, or clinically important bleeding) occurred. The mean (±SD) age was 58.9 ± 8.1 years, and 15.7 percent of the women had a family history of colorectal cancer (Table 1). Of the 1463 women, 299 (20.4 percent) had a total of 446 neoplastic lesions (Tables 2 and 3). Advanced colorectal neoplasia (i.e., adenomas that were at least 1 cm in diameter, villous adenoma, adenoma with high-grade dysplasia, or invasive colorectal cancer) was present in 72 women (4.9 percent) (Tables 2 and 3), and 227 women (15.5 percent) had small or nonadvanced adenomas. Among the 230 women with a family history of colon cancer, 16 (7.0 percent) had advanced neoplasia and 60 (26.1 percent) had only small adenomas.

The proportion of women with advanced neoplasia varied significantly with age (P=0.01). Advanced neoplasia was found in 3.3 percent of women who were 50 to 59 years of age (26 of 786), 5.5 percent of women who were 60 to 69 years of age (23 of 420), and 11.7 percent of women who were 70 to 79 years of age (19 of 162). The group of women who were 70 to 79 years old was significantly more likely to have advanced neoplasia than the group of women who were 50 to 59 years old (relative risk, 3.56; 95 percent confidence interval, 1.70 to 7.58; P=0.002).

### Diagnostic Yield of Flexible Sigmoidoscopy for Advanced Colorectal Neoplasia

If only flexible sigmoidoscopy had been performed in all women, advanced colorectal neoplasia would

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**Table 1. Characteristics of the 1463 Women.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Women (N=1463)</th>
<th>Women with Neoplasia (N=299)</th>
<th>Women with Advanced Neoplasia (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 yr (%)</td>
<td>6.5</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>50–59 yr (%)</td>
<td>53.7</td>
<td>43.8</td>
<td>36.1</td>
</tr>
<tr>
<td>60–69 yr (%)</td>
<td>28.7</td>
<td>31.1</td>
<td>31.9</td>
</tr>
<tr>
<td>70–79 yr (%)</td>
<td>11.1</td>
<td>20.1</td>
<td>26.4</td>
</tr>
<tr>
<td>Mean (yr)</td>
<td>58.9</td>
<td>61.2</td>
<td>62.9</td>
</tr>
<tr>
<td>Race or ethnic group (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>77.0</td>
<td>73.9</td>
<td>69.4</td>
</tr>
<tr>
<td>Black</td>
<td>11.6</td>
<td>13.7</td>
<td>18.1</td>
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<td>Asian</td>
<td>8.4</td>
<td>10.0</td>
<td>8.3</td>
</tr>
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<td>Hispanic</td>
<td>2.0</td>
<td>1.7</td>
<td>4.2</td>
</tr>
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<td>Other</td>
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<td>0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Height (in.)</td>
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<td>64.2</td>
<td>64.1</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>156.2</td>
<td>158.1</td>
<td>162.6</td>
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<tr>
<td>Body-mass index</td>
<td>26.2</td>
<td>26.6</td>
<td>27.3</td>
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<tr>
<td>≥1 First-degree relatives with colorectal cancer (%)</td>
<td>15.7</td>
<td>20.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Any regular use of NSAIDs (%)</td>
<td>34.2</td>
<td>30.1</td>
<td>25.0</td>
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<tr>
<td>Any use of hormone-replacement therapy (%)</td>
<td>63.1</td>
<td>58.2</td>
<td>55.6</td>
</tr>
<tr>
<td>Current or former smoker (%)</td>
<td>39.0</td>
<td>43.8</td>
<td>51.4</td>
</tr>
<tr>
<td>Alcohol consumption (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>59.0</td>
<td>60.9</td>
<td>62.5</td>
</tr>
<tr>
<td>1–6 drinks/wk</td>
<td>29.0</td>
<td>25.4</td>
<td>22.2</td>
</tr>
<tr>
<td>7–13 drinks/wk</td>
<td>8.2</td>
<td>10.0</td>
<td>11.1</td>
</tr>
<tr>
<td>≥14 drinks/wk</td>
<td>3.8</td>
<td>3.7</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Because of rounding, percentages may not total 100. Race or ethnic group was self-reported. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert height to meters, divide by 39.37. To convert weight to kilograms, divide by 2.2. NSAIDs denotes nonsteroidal antiinflammatory drugs.

† Women who were 40 to 49 years old had a history of colon cancer in a first-degree relative.

‡ For alcohol consumption a drink was defined as one glass of wine, 1 oz (30 ml) of liquor, or one glass of beer.
have been identified in 1.7 percent (25 of 1463 women) and missed in 3.2 percent (47 of 1463) (Table 2). Since 72 women had advanced neoplasia in the colon, the diagnostic yield of flexible sigmoidoscopy was 34.7 percent (25 of 72 cases detected). Thus, 34.7 percent of women with advanced neoplasia would have had their lesions identified if they had undergone flexible sigmoidoscopy alone. After stratification according to age, there was no significant difference in the diagnostic yield of flexible sigmoidoscopy between women who were 50 to 59 years old and either those who were 60 to 69 years old or those who were 70 to 79 years old. After stratification according to the presence or absence of a family history of colon cancer, there was no significant difference in the diagnostic yield of flexible sigmoidoscopy between women without a family history of colon cancer and women with a family history of colon cancer (35.7 percent [20 of 56 cases detected] and 31.2 percent [5 of 16], respectively; P=0.74).

### Distal-Colon Neoplasia and Advanced Neoplasia in the Proximal Colon
When the distal colon was defined as the rectum and sigmoid colon, 93.5 percent of women did not have distal-colon neoplasia (1367 of 1462), whereas 6.5 percent (95 of 1462) had advanced colorectal neoplasia or small adenomas in the distal colon. For these analyses, we excluded one woman for whom information about the location of adenoma was not available. The prevalence of advanced colorectal neoplasia in the proximal colon among women with no distal-colon neoplasia was 3.4 percent (47 cases among 1367 women), as compared with 3.2 percent among women with distal-colon neoplasia (3 cases among 95 women, P=1.00). If flexible sigmoidoscopy had been performed to the junction of the sigmoid and descending colon in all these women and the finding of distal colorectal neoplasia had triggered a colonoscopy, then 94.0 percent of cases of advanced colorectal neoplasia in the proximal colon would have been missed (47 of 50).

Among women without a family history of colon cancer, the prevalence of advanced colorectal neoplasia in the proximal colon was similar for women without distal-colon neoplasia and women with distal-colon neoplasia (3.1 percent [36 cases among 1156 women] and 3.9 percent [3 cases among 77 women], respectively; P=0.70). Among women with a family history of colon cancer, the prevalence of advanced colorectal neoplasia in the proximal colon was higher among women without distal-colon neoplasia than among women with distal-colon neoplasia, although this difference was not significant (5.2 percent [11 cases among 211 women] and 0 percent [0 cases among 18 women], respectively; P=0.32).

When the distal colon was defined as the rectum, sigmoid colon, and descending colon, 90.6 percent of women did not have distal-colon neoplasia (1324 of 1462), whereas 9.4 percent had advanced colo-

---

**Table 2. Colonoscopic Findings in the 1463 Women, According to the Most Advanced Lesion.**

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adenomas*</td>
<td>1164 (79.6)</td>
</tr>
<tr>
<td>Adenomas</td>
<td>299 (20.4)</td>
</tr>
<tr>
<td>Nonadvanced or small adenoma only</td>
<td>227 (15.5)</td>
</tr>
<tr>
<td>Advanced colorectal neoplasia†</td>
<td>72 (4.9)</td>
</tr>
<tr>
<td>Distal adenoma‡</td>
<td>25 (1.7)</td>
</tr>
<tr>
<td>No distal adenoma</td>
<td>47 (3.2)</td>
</tr>
</tbody>
</table>

* Of the 1164 women with no adenomas, 253 had hyperplastic polyps.
† Given these data, the lesion would have been missed in 65.3 percent of women with advanced colorectal neoplasia (47 of 72) if only flexible sigmoidoscopy had been performed. Overall, if only flexible sigmoidoscopy had been performed in all the women, then advanced colorectal neoplasia would have been identified in 1.7 percent (25 of 1463) and missed in 3.2 percent (47 of 1463).
‡ Among the 25 women who had advanced colorectal neoplasia and distal adenoma, 22 (88.0 percent) had advanced colorectal neoplasia in the distal colon and only 3 (12.0 percent) had a small adenoma in the distal colon with advanced colorectal neoplasia in the proximal colon.

**Table 3. Characteristics of the 299 Adenomas Found among the 1463 Women.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonadvanced or small adenoma only</td>
<td>227 (15.5)</td>
</tr>
<tr>
<td>1 lesion</td>
<td>140 (9.6)</td>
</tr>
<tr>
<td>2 lesions</td>
<td>55 (3.8)</td>
</tr>
<tr>
<td>3 lesions</td>
<td>16 (1.1)</td>
</tr>
<tr>
<td>4 lesions</td>
<td>9 (0.6)</td>
</tr>
<tr>
<td>&gt;4 lesions</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td>Advanced colorectal neoplasia</td>
<td>72 (4.9)</td>
</tr>
<tr>
<td>Tubular adenoma ≥10 mm</td>
<td>46 (3.1)</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>26 (1.8)</td>
</tr>
<tr>
<td>Adenoma with high-grade dysplasia</td>
<td>9 (0.6)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>
rectal neoplasia or small adenomas in the distal colon (138 of 1462). With the use of this expanded definition of the distal colon, the prevalence of advanced colorectal neoplasia in the proximal colon was 2.7 percent among women without distal-colon neoplasia (36 cases among 1324 women) and 2.2 percent among women with distal-colon neoplasia (3 cases among 138 women, \( P=1.00 \)). If flexible sigmoidoscopy had been performed to the splenic flexure in all these women and the finding of distal colorectal neoplasia had triggered a colonoscopy, then 92.3 percent of cases of advanced colorectal neoplasia in the proximal colon would have been missed (36 of 39).

**PREVALENCE OF ADVANCED NEOPLASIA IN MEN AND WOMEN**

In VA Cooperative Study 380, the prevalence of advanced neoplasia among men with a negative fecal occult-blood test varied significantly according to age (\( P<0.001 \)): it was 4.6 percent among men 50 to 59 years old (40 cases among 863 men), 10.8 percent among men 60 to 69 years old (132 cases among 1217 men), and 11.4 percent among those who were at least 70 years old (55 cases among 481 men). As compared with the group of men who were 50 to 59 years old, the group of men who were 60 to 69 years old were significantly more likely to have advanced neoplasia (relative risk, 2.34; 95 percent confidence interval, 1.66 to 3.30), as were the men who were at least 70 years old (relative risk, 2.47; 95 percent confidence interval, 1.67 to 3.65). After matching men and women with a negative fecal occult-blood test and the absence of a family history of colon cancer, we found that men were more likely to have advanced neoplasia than women (8.6 percent [190 of 2206] vs. 4.5 percent [54 of 1198]; relative risk, 1.91; 95 percent confidence interval, 1.42 to 2.56; \( P=0.002 \)) (Fig. 1).

**DIAGNOSTIC YIELD OF FLEXIBLE SIGMOIDOSCOPY IN MEN AND WOMEN**

Among men and women who were matched for a negative fecal occult-blood test and the absence of a family history of colorectal cancer, the diagnostic yield of flexible sigmoidoscopy was significantly higher in men (\( P<0.001 \)). A total of 66.3 percent of men (126 of 190) would have had advanced neoplasia detected if flexible sigmoidoscopy alone had been performed, as compared with only 35.2 percent of women (19 of 54). Figure 2 provides a comparison of the diagnostic yield of flexible sigmoidoscopy for men and women, stratified according to age.

**DISCUSSION**

We evaluated the diagnostic yield of screening colonoscopy in asymptomatic women who were referred for colorectal-cancer screening. After matching the women in the current study with men from VA Cooperative Study 380 for a normal fecal occult-blood test and the absence of a family history of colon cancer, we found that almost twice as many cases of advanced colorectal neoplasia were detected in the men, and the prevalence of advanced neoplasia among women who were 50 to 59 years old was less than 3 percent (Fig. 1). Given these findings, it might be argued that screening flexible sigmoidoscopy is more appropriate than colonoscopy for women who are 50 to 59 years old. However, our data also indicate that the diagnostic yield of flexible sigmoidoscopy for advanced neoplasia is much lower among women than among men (35.2 percent vs. 66.3 percent, \( P<0.001 \)). Thus, advanced neoplasia would have been missed in 65 percent of women with advanced neoplasia if they had undergone flexible sigmoidoscopy alone. Also, women...
without distal-colon neoplasia and women with distal-colon neoplasia had similar prevalences of advanced neoplasia in the proximal colon (3.4 percent and 3.2 percent, respectively; \( P=1.00 \)). On the basis of these data, we believe that colonoscopy is the preferred method of screening for colorectal cancer in women and that flexible sigmoidoscopy is an inadequate method of predicting advanced neoplasia in the proximal colon in women.

A comparison of the findings in this study and those in VA Cooperative Study 380 provides data on the variation in the prevalence and phenotypic expression of advanced neoplasia according to age and sex. The prevalence of advanced neoplasia was greater among men than among women in the age group of 60 to 69 years \( (P=0.004) \), and there was a trend toward a higher prevalence among men in the group of men and women who were 50 to 59 years old \( (P=0.15) \) but not in the group of men and women who were at least 70 years old \( (P=0.70) \). This finding suggests that biologic or behavioral factors inherent in women delay the formation of advanced neoplasia. The lower diagnostic yield of flexible sigmoidoscopy among women suggests that there is a right-sided shift for advanced neoplasia in women as compared with men.

Our data indicate that the diagnostic yield of flexible sigmoidoscopy is significantly lower among women 50 to 59 years old than among men in this age group \( (P<0.001) \) and that 70 percent of cases of advanced colorectal neoplasia among women in this age group would be missed if they were to undergo flexible sigmoidoscopy alone. Although advanced colonic neoplasia is less common in average-risk women than in average-risk men who are 50 to 59 years of age \( (2.9 \text{ percent vs. } 4.7 \text{ percent}) \), more cases would be missed in such women than in their male counterparts \( (2.0 \text{ percent vs. } 1.3 \text{ percent}) \), if flexible sigmoidoscopy alone were performed. Therefore, flexible sigmoidoscopy appears to be a much more effective screening tool in men than in women. Since previous cost-effectiveness analyses \(^{22-24} \) have been hampered by the lack of precise data on the prevalence of adenomas and advanced neoplasia in men and women, our data may be used to define the cost-effectiveness of screening colonoscopy among women and men.

Our study has methodologic limitations. We used colonoscopic findings in the distal colon as a surrogate for the findings with flexible sigmoidoscopy. Therefore, our data on flexible sigmoidoscopic findings are estimates. Since patients were sedated before undergoing vigorous colonic lavage and then colonoscopy, which was performed by expert endoscopists, our estimated yield of flexible sigmoidoscopy for distal-colon neoplasia might be higher than that associated with flexible sigmoidoscopy performed in the absence of sedation and by less experienced endoscopists after less vigorous colonic lavage.

In conclusion, we acknowledge that the implementation of national and international colonoscopic-screening programs may be constrained by limitations in the availability of endoscopic resources and in insurance coverage.\(^8,9\) Although the use of colonoscopic screening is becoming widespread in the United States, it is not widely used in any other country. In other countries, the use of one-time flexible sigmoidoscopy is being pursued as a means to reduce the risk of colorectal cancer.\(^{25} \) Given the lack of consensus about the preferred tool for colorectal-cancer screening, we should use the best available information to guide our patients’ choices. Our study indicates that the majority of cases of advanced neoplasia in women would be missed if they underwent flexible sigmoidoscopy alone. In our opinion, colonoscopy is the preferred method of colorectal-cancer screening in average-risk, asymptomatic women.

**Figure 2. Yield of Flexible Sigmoidoscopy (FS) for Advanced Colorectal Neoplasia Anywhere in the Colon in Men and Women, According to Age.**

The yield of FS was defined as the proportion of patients with advanced colorectal neoplasia who were found to have advanced lesions in the distal colon or advanced lesions in the proximal colon along with small adenomas in the distal colon, which would have triggered the performance of colonoscopy. The women were from the current study, and the men were from VA Cooperative Study 380.
COLONOSCOPIC SCREENING OF WOMEN FOR COLORECTAL NEOPLASIA

Supported by an intramural contract with the National Cancer Institute and research grants from the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy. Dr. Schoenfeld is supported by a National Institute of Health Career Development Award (K23-DK-60040) and by an American Society for Gastrointestinal Endoscopy Career Development Award. The Veterans Affairs Cooperative Study Group 380 was supported by a grant from the Veterans Affairs Cooperative Studies Program.


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In addition to the authors, the following investigators participated in the CONCeRN Study: J. Butler, P. Perdue, and P.J. Chandler, Bethesda, Md.; C. Furlong, Portsmouth, Va.; and J. Shad and R. Schindler, San Diego, Calif.

APPENDIX

REFERENCES


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Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe’s Disease

Maria L. Escolar, M.D., Michele D. Poe, Ph.D., James M. Provenzale, M.D.,
Karen C. Richards, M.D., June Allison, R.N., Susan Wood, P.N.P.,
David A. Wenger, Ph.D., Daniel Pietryga, M.D., Donna Wall, M.D.,
Martin Champagne, M.D., Richard Morse, M.D., William Krivit, M.D., Ph.D.,
and Joanne Kurtzberg, M.D.

BACKGROUND
Infantile Krabbe’s disease produces progressive neurologic deterioration and death in
eye childhood. We hypothesized that transplantation of umbilical-cord blood from
unrelated donors before the development of symptoms would favorably alter the natu-
ral history of the disease among newborns in whom the disease was diagnosed because
of a family history. We compared the outcomes among these newborns with the out-
comes among infants who underwent transplantation after the development of sympt-
oms and with the outcomes in an untreated cohort of affected children.

METHODS
Eleven asymptomatic newborns (age range, 12 to 44 days) and 14 symptomatic infants
(age range, 142 to 352 days) with infantile Krabbe’s disease underwent transplantation
of umbilical-cord blood from unrelated donors after myeloablative chemotherapy. En-
graftment, survival, and neurodevelopmental function were evaluated longitudinally
for four months to six years.

RESULTS
The rates of donor-cell engraftment and survival were 100 percent and 100 percent, re-
spectively, among the asymptomatic newborns (median follow-up, 3.0 years) and 100
percent and 43 percent, respectively, among the symptomatic infants (median fol-
low-up, 3.4 years). Surviving patients showed durable engraftment of donor-derived
hematopoietic cells with restoration of normal blood galactocerebrosidase levels. In-
fants who underwent transplantation before the development of symptoms showed
progressive central myelination and continued gains in developmental skills, and most
had age-appropriate cognitive function and receptive language skills, but a few had mild-
to-moderate delays in expressive language and mild-to-severe delays in gross motor
function. Children who underwent transplantation after the onset of symptoms had
minimal neurologic improvement.

CONCLUSIONS
Transplantation of umbilical-cord blood from unrelated donors in newborns with in-
fantile Krabbe’s disease favorably altered the natural history of the disease. Transplan-
tation in babies after symptoms had developed did not result in substantive neurologic
improvement.
Krabbe’s disease, or globoid-cell leukodystrophy, is an autosomal recessive disorder due to deficiency of the lysosomal enzyme galactocerebrosidase and characterized by failure of the process of myelination in the central and peripheral nervous systems, rapidly progressive neurologic deterioration, and death. More than 60 mutations have been identified that result in low enzymatic activity leading to a decreased ability to degrade galactolipids found in myelin. The accumulation of galactolipids results in inflammation, dysmyelination, and demyelination of the developing brain. In the infantile form, symptoms appear before six months of age and include irritability, dysphagia, progressive spasticity, mental deterioration, blindness, deafness, seizures, and death, usually before two years of age.1

Allogeneic hematopoietic stem-cell transplantation has been previously reported to be beneficial in patients with early stages of juvenile Krabbe’s disease.2 Donor stem cells repopulate various tissues, delivering enzymes both inside and outside the vascular compartment; children so treated have had improved neurologic outcomes and improved overall survival.2,4 Bone marrow has traditionally been used as the source of donor stem cells for transplantation. However, many children lack a matched donor, and recruitment of an unrelated adult donor takes too long for the treatment of a rapidly progressive disorder. Banked umbilical-cord blood from unrelated donors is readily available and can be used after myeloablative therapy.5-7

We assessed the safety and efficacy of transplantation of umbilical-cord blood from unrelated donors with partial HLA mismatches for the treatment of two groups of infants with Krabbe’s disease. Krabbe’s disease was diagnosed prenatally or at birth because of a family history of the disease in 11 patients, and they underwent transplantation as newborns; 14 children without a family history of the disease underwent transplantation in infancy after the onset of clinical symptoms.

 METHODS

 PATIENTS
Between August 1998 and August 2004, 11 asymptomatic newborns and 14 symptomatic infants with Krabbe’s disease underwent transplantation of umbilical-cord blood from unrelated donors. The disease was diagnosed in six newborns prenatally and in five shortly after birth. The disease was diagnosed in the 14 symptomatic patients when they were between four and nine months of age. Treatment plans were approved by the institutional review boards of Duke University Medical Center, Durham, North Carolina (22 patients), Cardinal Glennon Children’s Hospital, St. Louis (1 patient), DeVos Children’s Hospital, Grand Rapids, Michigan (1 patient), and Hôpital Sainte-Justine, Montreal (1 patient), and written informed consent was obtained from the parents of all infants. Four patients were enrolled in the Cord Blood Transplantation Study. Assays of leukocyte galactocerebrosidase activity confirmed the diagnosis in all patients.

 SELECTION OF HLA-MATCHED UNITS
Searches for cord-blood units from unrelated donors were conducted through the National Marrow Donor Program, the Cord Blood Transplantation Study banks, and the New York Blood Center. Intermediate-resolution typing for HLA class I alleles (A and B) and high-resolution typing for HLA class II DRB1 alleles were used for matching. The unit of cord blood had to deliver at least 3×10^7 nucleated cells per kilogram of body weight (the count before cryopreservation was used).8 Units matching for four to six of six HLA antigens were tested for galactocerebrosidase9 in 21 of the 25 patients; after 2 to 4 units were tested per patient, units with higher activity were selected when available. The cryopreserved units were thawed, washed, and tested for blood-borne pathogens, hemoglobinopathies, hematopoietic progenitor-cell content, and sterility, as previously described.8,10

 TRANSPLANTATION PROCEDURE
Patients were prepared for transplantation with busulfan and cyclophosphamide. They received cyclosporine and steroids as prophylaxis against graft-versus-host disease and supportive care, as described previously.8,11 Twenty-three patients received horse antithymocyte globulin; one received rabbit antithymocyte globulin. Myeloid engraftment was defined as occurring on the first of three consecutive days on which the absolute neutrophil count was above 500 per cubic millimeter with donor cells. Platelet engraftment was defined by a platelet count of at least 50,000 per cubic millimeter for at least seven consecutive days.

 NEURODEVELOPMENTAL ASSESSMENT
Standardized and validated neurobehavioral tools were used to assess all infants before transplan-
tation and all surviving infants after transplantation. The results were compared with norms for typically developing children. Nineteen patients were assessed both at the Clinical Center for the Study of Development and Learning, University of North Carolina at Chapel Hill, and at Duke University; one patient was evaluated at DeVos Children’s Hospital Neurobehavioral Center; and one at Hôpital Sainte-Justine. Age equivalents were used to permit comparisons across tests and to identify the development of new skills. Cognition, adaptive behavior, receptive language, expressive language, gross motor skills, and fine motor skills were assessed.

**Magnetic Resonance Imaging**

A neuroradiologist who was blinded to the clinical status of the patients reviewed all magnetic resonance imaging (MRI) scans of the brain for abnormalities at baseline and progression of myelination three months to six years after transplantation. Myelination was indicated by the development of a hyperintense signal on T₁-weighted axial images and a hypointense signal on T₂-weighted axial images in age-appropriate regions. These included the posterior limb of the internal capsule, the genu and the splenium of the corpus callosum, the corona radiata, the centrum semiovale, and the subcortical white matter.

**Neurophysiological Studies**

Electroencephalography, nerve-conduction studies, and tests of flash visual evoked potentials (visual evoked potentials on delivery of flash stimuli to the eyes) and brain-stem auditory evoked responses were performed before transplantation and at scheduled intervals and interpreted according to the guidelines established by the American Electroencephalographic Society. Electroencephalograms (EEGs) were considered abnormal if there was focal or generalized slowing or if spikes or sharp waves were present. The flash visual evoked potential was considered normal if the P100 wave was present, and abnormal if it was missing. The brain-stem auditory evoked responses were considered abnormal either if the interpeak latency of waves I to V was prolonged or if any of the obligate wave forms (I, II, III, or V) was missing. Results of nerve-conduction studies were considered abnormal if they showed prolongation of the distal latency, low amplitude, no evoked response, or prolonged latency of the F wave. Study results were interpreted by expert physicians blinded to the clinical status of the patients.

**Statistical Analysis**

The probability of event-free survival (defined as survival with durable engraftment of donor cells) was calculated by Kaplan–Meier analysis. We compared survival among the 11 asymptomatic newborns who underwent transplantation with that among the 14 infants who underwent transplantation after the onset of symptoms and in an untreated control group. Survival data for the untreated group (190 patients) were provided by the Hunter’s Hope leukodystrophy registry. The cutoff date for data analysis was January 28, 2005.

**Results**

**Characteristics of the Patients and Donors**

After myeloablative chemotherapy, 11 newborns (4 boys and 7 girls) ranging in age from 12 to 44 days, with a median weight of 4.0 kg, and 13 of 14 symptomatic infants (8 boys and 6 girls) ranging in age from 142 to 352 days, with a median weight of 7.2 kg, underwent transplantation with banked umbilical-cord blood from unrelated donors with partial HLA mismatches (Table 1). One symptomatic infant had no mismatches. The median age at the initiation of myeloablative chemotherapy in the newborns was 18.5 days and that at transplantation was 28 days. The newborns received a higher median number of nucleated cells in units selected for transplantation than the older infants (22.07 × 10⁷ vs. 17.24 × 10⁷ cells per kilogram, respectively). After thawing, the median numbers of CD34 cells infused were 3.72 × 10⁵ and 2.92 × 10⁵ cells per kilogram, respectively (Table 2).

**Engraftment and Graft-versus-Host Disease**

Neutrophil and platelet engraftment in asymptomatic and symptomatic infants occurred a median of 17 to 18 and 57 to 70 days, respectively, after transplantation (Table 2). As of the last follow-up evaluation (median follow-up, 1024 days after transplantation), 16 of 17 surviving patients continued to have complete donor chimerism, whereas the 1 newborn patient who did not receive antithymocyte globulin continued to have stable mixed donor–recipient chimerism. All surviving patients continued to have normal peripheral-blood galactocerebrosidase activity. The
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The cerebrospinal fluid protein level was elevated in 7 of the 9 newborns and in all 12 symptomatic infants who were evaluated at the time of transplantation; it decreased gradually after transplantation but did not normalize in any patient (Tables 1 and 2). Grade I acute graft-versus-host disease (GVHD) developed in seven newborns, and grade II GVHD in one newborn. Moderate-to-severe acute GVHD

---

**Table 1. Characteristics of the Babies and the Unrelated Donors.**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Transplantation</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>HLA Matches</th>
<th>Blood Type</th>
<th>Pretransplantation Cerebrospinal Fluid Protein (mg/dl)</th>
<th>Unrelated-Donor Galactocerebrosidase (nmol/hr/mg of protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic newborns</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>4.1</td>
<td>4/6</td>
<td>A30/25, B44/53</td>
<td>O−</td>
<td>A+</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>F</td>
<td>4.2</td>
<td>4/6</td>
<td>A23/24, B50/07</td>
<td>O+</td>
<td>O−</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>F</td>
<td>4.8</td>
<td>4/6</td>
<td>A2/33, B39/61</td>
<td>B+</td>
<td>B+</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>F</td>
<td>3.8</td>
<td>5/6</td>
<td>B56/57</td>
<td>O+</td>
<td>O−</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>M</td>
<td>3.9</td>
<td>4/6</td>
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<td>B+</td>
<td>B+</td>
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<td>6</td>
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<td>F</td>
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<td>5/6</td>
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<td>O−</td>
<td>A−</td>
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<td>A11/39/18</td>
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<td>12</td>
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<td>3.8</td>
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<td>DRB19/8</td>
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**Notes:**

- Units with matches for four to six HLA antigens were tested for galactocerebrosidase (normal range, 1 to 6 nmol per hour per milligram).
- Normal cerebrospinal fluid protein levels range from 70 to 120 mg per deciliter for newborns, and from 5 to 40 mg per deciliter for infants. NA indicates that no data were available, and bl denotes blank.

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Median Age at Transplantation: 4.0 days
Mean ±SD: 3.9±0.5

Median Weight: 7.2 kg
Mean ±SD: 7.3±1.2
transplantation of cord blood in infantile krabbe’s disease

Myeloid engraftment was defined by an absolute neutrophil count of at least 500 per cubic millimeter on three consecutive days. Platelet engraftment was defined by a platelet count of at least 50,000 per cubic millimeter without transfusion for at least seven consecutive days. Post-transplantation levels of cerebrospinal fluid protein decreased but remained abnormal. Galactocerebrosidase levels after transplantation were measured at scheduled intervals. Galactocerebrosidase levels were higher than the levels of the graft initially but at the last evaluation were similar to graft levels (range, 0.8 to 5.9 nmol per hour per milligram). The follow-up ranged from 4 to 66 months. AHA denotes autoimmune hemolytic anemia, NA no data available, and NE not evaluated. A dash indicates that the patient died before reaching the end point.

Table 2. Graft Characteristics and Outcomes after Transplantation of Umbilical-Cord Blood.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>No. of Cells Infused</th>
<th>No. of CD34 Cells Infused</th>
<th>Grade of Acute GVHD</th>
<th>Site of Chronic GVHD</th>
<th>Time to Neutrophil Engraftment (days)</th>
<th>Time to Platelet Engraftment (days)</th>
<th>Time to Red-Cell Transplantation (days)</th>
<th>Post-Transplantation Cerebrospinal Fluid Protein (mg/dl)</th>
<th>Post-Transplantation Galactocerebrosidase (nmol/hr/mg of protein)</th>
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<td>60.0±22.0</td>
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* Myeloid engraftment was defined by an absolute neutrophil count of at least 500 per cubic millimeter on three consecutive days. Platelet engraftment was defined by a platelet count of at least 50,000 per cubic millimeter without transfusion for at least seven consecutive days. Post-transplantation levels of cerebrospinal fluid protein decreased but remained abnormal. Galactocerebrosidase levels after transplantation were measured at scheduled intervals. Galactocerebrosidase levels were higher than the levels of the graft initially but at the last evaluation were similar to graft levels (range, 0.8 to 5.9 nmol per hour per milligram). The follow-up ranged from 4 to 66 months. AHA denotes autoimmune hemolytic anemia, NA no data available, and NE not evaluated. A dash indicates that the patient died before reaching the end point.
(grade II, III, or IV) developed in 5 of the 14 older patients. Limited, chronic GVHD of the skin developed in two newborns, and three had brief episodes of autoimmune hemolytic anemia that had resolved four months to two years after transplantation (Table 2).

**Survival**

As of January 28, 2005, all 11 newborns and 6 of 14 symptomatic infants had survived for a median of 36 and 41 months, respectively, after transplantation (Fig. 1). Survival among the newborns was better than among the untreated controls (P=0.001) or the symptomatic infants (P=0.01). Survival among the symptomatic infants was not statistically different from survival among the controls (P=0.28). Six of the newborns have outlived their affected siblings, and five have not yet reached the age at which the sibling died (Fig. 2). Complications after transplantation in the newborns included a catheter-related silent brain infarct diagnosed by MRI (in one patient) and asymptomatic or symptomatic hypertrophic cardiomyopathy (in two patients and one patient, respectively) that resolved as documented on serial echocardiograms after the discontinuation of steroids. In the symptomatic group, four infants died of progressive disease, one of GVHD, one of aspiration pneumonia, one of adenoviral infection, and one from complications after a liver biopsy for GVHD.

**Neurologic Outcomes**

**Brain MRI Scanning**

The 11 children who underwent transplantation as newborns before the onset of symptoms each had two to seven follow-up scans during the period from six months to six years after transplantation. In all 11 children, brain MRI scans after transplantation showed normal progression of myelination, with age-appropriate changes in signal intensity in various white-matter sites. Pretransplantation MRI scans of three newborns showed abnormal hyperintense signals on T2-weighted images in the posterior limb of the internal capsule; scans of another four newborns showed regions of abnormal hyperintense signal within the white matter adjacent to the lateral ventricles, consistent with dysmyelination. In these four babies, the regions of abnormal signal intensity decreased over time on serial scans (Fig. 3).

A total of 44 MRI scans from the symptomatic group (1 to 7 per patient) were available for review. On initial, pretransplantation MRI scans, obtained at four to seven months of age, the surviving symptomatic patients showed abnormal hyperintense signals on T2-weighted images that were typically in the centrum semiovale, the corona radiata, and the white matter and dentate nuclei of the cerebellum. Thirteen of 14 patients had subsequent MRI scans three months to five years after transplantation, which showed disease progression in 12 patients, usually characterized by the development of brain atrophy, worsening hyperintense signal abnormalities on T2-weighted images in the corona radiata, the centrum semiovale, and the posterior...
limb of the internal capsule, and new signal abnormalities in the brain stem. The other patient’s scan stabilized over time.

**Visual Evoked Potentials**

Studies of visual evoked potentials were available for eight newborns before and after transplantation. The results of three studies were initially abnormal but were normal by four months after transplantation. The remaining newborns had consistently normal visual acuity and function. Three patients were not studied because of the physician’s preference.

Twelve of the symptomatic infants underwent testing of visual evoked potentials before and after transplantation. Eight of the 12 had abnormal results both times. Results of the studies of four patients were initially normal but became abnormal on follow-up. One patient underwent testing only before transplantation.

**Brain-Stem Auditory Evoked Responses**

Brain-stem auditory evoked responses were studied in 8 of 11 newborns before and after transplantation. The results were normal in four patients before transplantation and remained normal in two of the four patients after transplantation (follow-up range, 3 to 22 months). The responses were abnormal in the other four patients before transplantation and remained abnormal after transplantation (follow-up range, 3 to 16 months). All patients had normal hearing as measured by serial behavioral audiometry (visual-reinforcement audiometry and autoacoustic emissions) performed after transplantation.

Brain-stem auditory evoked responses were studied in 11 infants in the symptomatic group before transplantation, and all 11 had abnormal responses; 6 were retested one to five years after transplantation and still had abnormal responses.

**Nerve-Conduction Studies**

The results of nerve-conduction studies were abnormal in 9 of 11 newborns studied before transplantation. In seven of nine patients (studied four months to six years after transplantation), nerve conduction improved as compared with the pretransplantation results. Two other children showed initial improvement in the first 12 to 18 months after transplantation, but later studies showed that the results had worsened over time. In the symptomatic group, pretransplantation studies performed in 13 patients had abnormal results, and results were abnormal in 7 patients studied one to three years after transplantation.

**Electroencephalography**

EEGs were available for all patients. Eight of the newborns had normal results both before and four months to six years after transplantation. One patient had a normal EEG before transplantation at the age of 1 month, but EEG examination at 6.5 months of age showed excessive delta activity during a nap. Subsequent EEGs were normal. Another patient showed temporal sharp waves before transplantation, at 10 days of age, with no subsequent tests performed to date. One patient’s pretransplantation EEG was abnormal at one month of age, showing sharp waves and asymmetric delta activity, and was not repeated. No patients had clinical seizures.

In the symptomatic group, all patients had ab-
normal EEGs before and up to three years after transplantation. All surviving patients had clinical seizure activity at the most recent follow-up examination.

Neurodevelopmental Function

Ten of the 11 patients in the newborn group were evaluated after transplantation. In the symptomatic group, 8 of the 14 patients were evaluated in all domains. None of the symptomatic patients improved appreciably in any area (Fig. 4A).

Cognitive Function

The 10 newborns whom we evaluated continued to gain cognitive skills at a normal rate (Fig. 4A). However, two patients scored below normal in some of the subtests because of difficulties with fine motor control.

Adaptive Behavior

Adaptive behavior is a standardized measure of independent and self-help skills and is based on parents’ perceptions of their infant’s abilities. Eight newborns were within the average range and two were below average when most recently tested at 6 months to 5.5 years after transplantation (Fig. 4B).

Language

All but one newborn had normal receptive language (the ability to understand communication through gestures, facial expressions, and words) (Fig. 4C). Expressive language (the ability to express needs with the use of gestures, vocalization, facial expressions, and words) was below average in two patients (Fig. 4D). Articulation difficulties secondary to motor involvement ranged from mild to severe and accounted for the delay in expressive language.

Gross Motor Function

Before transplantation, four of the asymptomatic newborns had subtle motor abnormalities such as a weak sucking reflex, a poor rooting reflex, hypotonia, and hypertonia. The other seven babies appeared normal.

Post-transplantation evaluations of gross motor skills occurred in 10 newborns at 4 to 66 months of age (Fig. 4E). Of the 10 children, 4 had mild-to-severe delays in the development of gross motor skills. Two of the four had subtle motor abnormalities at birth, and two appeared normal. One continued to have severe delays at 33 months.

The remaining six patients gained gross motor skills during the first year of life. During the second and third years of life, progressive spasticity in the lower extremities and truncal weakness developed in two of the six children, who had initially pulled up to stand, which prevented them from walking.
Figure 4. Neurodevelopmental Outcomes of Children with Krabbe’s Disease after Cord-Blood Transplantation.

A unique line represents each patient’s development. Black lines represent symptomatic patients who underwent transplantation as infants, and colored lines asymptomatic patients who underwent transplantation as newborns. The green diagonal line represents typical development of unaffected children. The shaded area indicates the variability in typical development of unaffected children. Eight of the 11 newborns were assessed in all developmental domains before transplantation, and 6 of the 8 were followed up in all domains after transplantation (the other 2 were too young to be scheduled). They were followed up in a predefined schedule every three months during the first year, every six months during the second year, and once a year thereafter. The remaining three patients had less comprehensive evaluations because their hospitals did not have a dedicated multidisciplinary team. One patient had a single gross motor evaluation at 15.5 months, and the other two had at least one evaluation for cognition, adaptive behavior, language, and fine motor skills. Overall follow-up after transplantation in both groups ranged from one to nine assessments; the oldest patient in the asymptomatic-newborn group was 66 months of age and the oldest patient in the symptomatic group was 44 months of age at the last visit. Cognitive Development (Panel A) refers to the child’s ability to solve problems verbally and nonverbally. Six patients have scores for cognitive development at less than one month of age. Four of these subjects have additional cognitive measures at older ages. Adaptive Behavior (Panel B) refers to self-care skills (e.g., eating and drinking independently) and self-calming behavior. Receptive Language (Panel C) refers to the ability to understand communication through gestures, facial expressions, and words. Expressive Language (Panel D) refers to the ability to express needs with the use of gestures, vocalization, facial expressions, and words. Gross Motor Skills (Panel E) refers to proximal large-muscle groups used in locomotion and balance. Fine Motor Skills (Panel F) refers to the ability to use the distal muscle groups in the hands and fingers to manipulate objects.
or standing independently. These children, at 63 and 58 months of age, were able to sit independently, stand with assistive devices, and ride adaptive tricycles. Another patient with gross motor abnormalities had bilateral hip dysplasia at 48 months of age, which complicated her gross motor development, but she was able to walk independently with a walker. Two patients, now five and seven years of age, developed normally until two and three years of age, respectively. Both can walk, run, and jump independently, but neither has acquired more sophisticated gross motor skills (e.g., skipping, balancing, and hopping on one leg). The remaining five children evaluated at 4, 6, 7, 13, and 16 months, respectively, continue to gain gross motor skills appropriately. The patient who was not evaluated after transplantation is able to walk. All the surviving patients in the symptomatic group are severely affected with a developmental level equivalent to that of a one-month-old.

**Fine Motor Function**

Of the 10 newborns tested between 4 and 66 months of age, 8 had average fine motor skills and 2 had severe delays in the development of these skills (Fig. 4F). Of the two newborns with delayed development of fine motor function, one had a tendency to pronate the arms and the other to clasp the thumbs. One older patient has not been tested. All surviving patients in the symptomatic group are severely impaired and cannot manipulate objects with their fingers.

**Growth**

All patients were smaller than average for height, and some for weight (Fig. 5A through 5D). In contrast, head circumference measurements were within 2 SD of normal in patients in both the asymptomatic-newborn group and the symptomatic-infant group (Fig. 5E and 5F).

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**DISCUSSION**

We evaluated the feasibility, safety, and efficacy of cord-blood transplantation from unrelated donors in 11 asymptomatic newborns and 14 symptomatic infants with infantile Krabbe’s disease. In the newborn group, a family history of the disease permitted early diagnosis and treatment before the onset of clinical symptoms. Radiation therapy was avoided because of the known adverse late effects. All newborn patients who had engraftment survived and, as of January 28, 2005, had durable donor chimerism and normal peripheral-blood enzyme activity. The one patient who did not receive antithymocyte globulin continued to have stable mixed donor–recipient chimerism. In contrast to untreated patients, who had overwhelming spasticity, blindness, and early death by one to two years of age, the newborns who underwent transplantation before the onset of symptoms maintained normal vision and hearing and normal cognitive development except for areas influenced by gross motor development. Some have continued to gain gross motor skills. Infants who underwent transplantation after the development of symptoms had a higher rate of death and minimal neurologic benefits from transplantation.

Cord-blood units from unrelated donors with matching at four to six of six HLA loci were selected, rather than bone marrow from unrelated adult donors, in order to permit patients to undergo transplantation in the shortest possible time. We also hypothesized that cord blood may contain a younger population of stem cells capable of tissue repair and regeneration. Because of the known polymorphisms affecting blood galactocerebrosidase activity, 22 multiple donors were screened for each patient to select a donor with high levels of enzyme expression. Patients maintained enzyme levels within the range of the level measured in the cord-blood unit before its selection for transplantation. Because of their small size, all patients underwent transplantation with very high doses of nucleated cells per kilogram of body weight. This resulted in faster engraftment than in older patients who underwent transplantation with cord blood. 23

In previous reports, bone marrow transplantation in mildly symptomatic patients with a later onset of Krabbe’s disease has arrested disease progression, facilitated myelination, and reversed neurologic deficits. 2 In the present study, cord-blood transplantation in symptomatic patients from 4 to 11 months of age resulted in some stabilization of neurologic disease, but the surviving patients remain severely impaired. In these babies, irreversible damage to motor tracts probably preceded the intervention with transplantation. In contrast, we showed that the patients who underwent transplantation as newborns had substantial neurologic benefits and developmental gains, including increased myelination on serial brain MRI scans and,
Figure 5. Growth According to Sex from Birth to the Age of 36, 60, or 72 Months in Asymptomatic Newborns.
Growth for height, weight, and head circumference was plotted for male and female patients who underwent transplantation during the newborn period. The black curves represent standard growth curves (3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th percentiles). The colored lines represent individual patients. Height was at or below the fifth percentile, weight was below the fifth percentile, but head circumference remained in the normal range in all but one patient.
in some patients, improvement in nerve-conduction studies. Vision, hearing, and cognitive abilities were preserved.

Despite the substantial neurodevelopmental gains in the newborns, some degree of deficit in gross motor function became apparent in all the children. Variable motor function, from nearly normal to an inability to walk without assistance, may be attributed to different rates of central myelination. For example, there were patients in whom gross motor function was not progressing, whereas fine motor function continued to develop appropriately, suggesting that motor areas that have myelination early in childhood were affected more than those that are myelinated later.

Some babies may also have had irreversible damage prenatally or in the first few weeks after birth. In others, disease progression may have been slower, permitting rescue of the motor tracts by transplantation. Although definite progression of myelination was seen on MRI, the results of nerve-conduction studies improved substantially in only a subgroup of patients, suggesting that the effects of cord-blood transplantation on myelination may differ in the central and peripheral nervous systems. This hypothesis is supported by previous studies in the “twitcher” mouse (an animal model of globoid-cell leukodystrophy) that show a similar discrepancy in the correction of central and peripheral disease after bone marrow transplantation.24,25

The results in the 11 newborns in whom Krabbe’s disease was diagnosed prenatally or at birth show indisputable benefits with minimal morbidity, despite an aggressive approach. For reasons yet to be explained, cognitive function is preserved despite motor impairment. It is possible that the transplant will delay but not prevent eventual neurologic decline or that the early decline in motor function will stabilize over time. The long-term neurodevelopmental course of these patients can be determined only with further follow-up. The advent of more sensitive neuroimaging technology may clarify the stages of damage in newborns with Krabbe’s disease, thus permitting correlations of early studies with outcomes.

The results of this study show that transplantation of umbilical-cord blood from unrelated donors in newborns with Krabbe’s disease is associated with substantially better neurologic outcomes and survival than is no therapy23 or transplantation after symptoms develop. The marked differences in outcome when transplantation is performed in asymptomatic newborns and when it is performed in older symptomatic infants have implications for decisions regarding the implementation of newborn-screening programs for lysosomal storage diseases.

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We are indebted to the patients and their families for participating in these studies, to the Hunter’s Hope Foundation for providing information about the natural history of untreated patients, and to the staff at the Division of Pediatric Blood and Marrow Transplantation at Duke University and at the Clinical Center for the Study of Development and Learning and the Neurodevelopmental Research Center at the University of North Carolina at Chapel Hill.

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TRANSPANTATION OF CORD BLOOD IN INFANTILE KRABBE’S DISEASE


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CLINICAL TRIAL REGISTRATION
The Journal encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). The National Library of Medicine’s www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee’s requirements.
Asthma as a Risk Factor for Invasive Pneumococcal Disease


BACKGROUND
The risk of invasive pneumococcal disease among persons with asthma is unknown.

METHODS
We conducted a nested case–control study to examine the association between asthma and invasive pneumococcal disease. The study population included persons 2 to 49 years of age who were enrolled in Tennessee’s Medicaid program (TennCare) for more than one year during the study period (1995 through 2002) and who resided in counties participating in a prospective laboratory-based program of surveillance for invasive pneumococcal disease. For each subject with invasive pneumococcal disease, 10 age-matched controls without invasive pneumococcal disease were randomly selected from the same population. TennCare files were queried to identify the presence of coexisting conditions that confer a high risk of pneumococcal disease. For the purpose of our study, asthma was defined by documentation of one or more inpatient or emergency-department diagnoses of asthma, two outpatient diagnoses, or the use of asthma-related medications. High-risk asthma was defined as asthma requiring admission to a hospital or a visit to an emergency department, the use of rescue therapy or long-term use of oral corticosteroids, or the dispensing of three or more prescriptions for β-agonists within the year before enrollment in the study.

RESULTS
A total of 635 persons with invasive pneumococcal disease and 6350 controls were identified, of whom 114 (18.0 percent) and 516 (8.1 percent), respectively, had asthma. Persons with asthma had an increased risk of invasive pneumococcal disease (adjusted odds ratio, 2.4; 95 percent confidence interval, 1.9 to 3.1) as compared with controls. Among those without coexisting conditions, the annual incidence of invasive pneumococcal disease was 4.2 episodes per 10,000 persons with high-risk asthma and 2.3 episodes per 10,000 persons with low-risk asthma, as compared with 1.2 episodes per 10,000 persons without asthma.

CONCLUSIONS
Asthma is an independent risk factor for invasive pneumococcal disease. The risk among persons with asthma was at least double that among controls.
S. pneumoniae is the cause of substantial morbidity and mortality in the United States, particularly among people who are at high risk for pneumococcal infection. Among those at risk, pneumococcal vaccination has been shown to prevent invasive disease from this ubiquitous pathogen. The identification and confirmation of other groups at risk as potential candidates for vaccination are key steps in the prevention of invasive pneumococcal disease.

Unlike the known increase in the risk of invasive pneumococcal disease among persons with other chronic obstructive pulmonary diseases (COPDs) (e.g., emphysema and chronic bronchitis), the risk among persons with asthma is unknown. Guidelines for pneumococcal vaccination specifically exclude persons with asthma, and guidelines for the management of asthma do not include pneumococcal vaccination as a strategy to prevent infectious complications. An estimated 7 percent of the U.S. population has asthma. As the prevalence of this disease steadily increases, clarification of the role of asthma in the epidemiology of invasive pneumococcal disease becomes more important. We examined the association between asthma and invasive pneumococcal disease by conducting a nested case–control study with the use of data from two large, population-based databases. After performing the analysis of this association, we conducted a cohort analysis to ascertain the incidence of invasive pneumococcal disease among persons with and those without asthma who were enrolled in Tennessee’s Medicaid program (TennCare).

METHODS

ASCERTAINMENT OF EPISODES OF INVASIVE PNEUMOCOCCAL DISEASE

Surveillance for episodes of invasive pneumococcal disease has been conducted in five urban counties in Tennessee as a part of the Active Bacterial Core surveillance (ABCs) network of the Centers for Disease Control and Prevention (CDC) since January 1, 1995. In August 1999, six more counties were added to the Tennessee ABCs network, increasing the surveillance population to more than 2.8 million persons. Invasive pneumococcal disease was defined as the isolation of S. pneumoniae from a normally sterile site (e.g., blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid). Each episode was identified through prospective active surveillance, as described previously. Through the ABCs network, serotyping of pneumococcal isolates from persons with invasive pneumococcal disease identified after 1997 was performed. Serotypes included in the 7-valent pneumococcal conjugate vaccine (PCV) were designated as PCV serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV) were designated as PPV serotypes (PCV serotypes plus 1, 2, 3, 5, 7F, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F). Serotypes not included in either vaccine were considered nonvaccine serotypes. The study was approved by the institutional review boards of Vanderbilt University and the Tennessee Department of Health.

STUDY POPULATION

In 1994 in Tennessee, TennCare replaced the federal Medicaid program. TennCare is a state-based capitated managed health care program covering state residents who were eligible for Medicaid benefits and those who were uninsured or uninsurable. Administrative data from the TennCare system are contained in several computerized files: an enrollment file serves as the central registry of those enrolled, a pharmacy file consists of all outpatient and nursing-home prescription records, an inpatient file contains hospitalization records, and an outpatient file consists of encounter records for visits to emergency departments, hospital outpatient visits, and physician visits. Diagnoses in these files are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification, (ICD-9-CM).

We conducted a nested case–control study using the study population of TennCare recipients 2 to 49 years of age who had been enrolled in TennCare for at least one year and who lived in a county included in the ABCs program. The population was a dynamic cohort, because people entered it when they met age and eligibility requirements for enrollment and they left it when they reached 50 years of age, when their enrollment ended, when they died, or when invasive pneumococcal disease developed.

ABCs data on cases of invasive pneumococcal disease from January 1, 1995, through December 31, 2002, were linked to TennCare enrollment data with the use of patient-specific identifiers (Fig. 1). Subjects with invasive pneumococcal disease were those between the ages of 2 and 49 years in whom invasive pneumococcal disease had been detected by the ABCs and who had been enrolled in TennCare.
for at least one year before the index date, defined as the date of isolation of *S. pneumoniae*. The previous year of TennCare eligibility was required to classify cases according to the presence or absence of asthma and other coexisting conditions before an episode of invasive pneumococcal disease. To reduce confounding from tobacco-related lung disease, the upper age limit of 49 years was chosen. Children less than two years of age were not included, because asthma is difficult to diagnose with certainty in very young children. Among subjects with multiple episodes of invasive pneumococcal disease, only the first episode to occur after the subject had been enrolled in TennCare for at least one year was included.

For each subject with an episode of invasive pneumococcal disease, 10 controls were randomly selected from the study population of eligible persons enrolled in TennCare. Controls were matched to case subjects according to age (±1 month) and the index date of the case subject. Eligible controls met the criteria for age and enrollment according to the case subject’s index date and lived in an ABCs county on the index date. For case subjects with an index date between January 1995 and August 1999, eligible controls resided in 1 of the original 5 surveillance counties, whereas eligible control subjects for case subjects with an index date after August 1999 resided in 1 of the 11 surveillance counties. In addition, eligible controls had no history of pneumococcal disease on the basis of ICD-9-CM coded diagnoses in TennCare claims during the year before the index date. For each case subject, all eligible controls were assigned a random number; these numbers were then put into order, and the first 10 were selected as the controls. Controls were assigned the same index date as their respective case subject. Selected controls became ineligible as controls for other case subjects.

**Ascertaining of Asthma**

The presence or absence of asthma was determined by screening inpatient and outpatient claims of each case subject for a diagnosis of asthma accord-
having low-risk asthma. All other subjects with asthma were classified as having high-risk asthma if any of the following criteria were met in the year before the index date: one or more hospitalizations or visits to an emergency department resulting in a diagnostic code for asthma, two or more outpatient physician visits resulting in a diagnostic code for asthma, two or more prescriptions for any short-acting β-agonist medication (albuterol, isoproterenol, metaproterenol, pirbuterol, bitolterol, terbutaline, or levalbuterol), or one or more prescriptions for a medication for chronic asthma (inhaled corticosteroid, long-acting β-agonist, other inhaled antiinflammatory agents such as nedocromil or cromolyn, or a leukotriene-modifying drug, such as montelukast, zafirlukast, or zileuton) during the eligibility period. Subjects with asthma who had a history of one or more hospitalizations or visits to an emergency department for asthma or who were given a prescription for a course of corticosteroids as rescue therapy or a long-term course of oral corticosteroids (120 days or more) or prescriptions for three or more β-agonist medications during the year before the index date were classified as having high-risk asthma. All other subjects with asthma were classified as having low-risk asthma.

**Identification of Coexisting Conditions**

To identify coexisting conditions associated with an increased risk of invasive pneumococcal disease, TennCare claims from the year before the index date for case subjects and controls were reviewed for condition-specific diagnoses according to ICD-9-CM codes and for prescribed medications (described in detail in the Supplementary Appendix, available with the full text of this article at www.nejm.org). High-risk coexisting conditions were defined by the documentation of one or more discharges from a hospital or emergency department with a condition-specific coded diagnosis, two or more outpatient visits with a condition-specific coded diagnosis, or a recorded prescription for condition-specific medications. The high-risk conditions that were examined were infection with the human immunodeficiency virus (HIV), sickle cell disease, diabetes mellitus, cardiac disease, renal disease, hepatic disease including cirrhosis, obstructive pulmonary disease in the absence of asthma, cancer or immunosuppression due to illness or use of medication (including oral corticosteroids), alcohol abuse, and tobacco use. Long-term use of corticosteroids was defined as receipt of prescriptions for oral corticosteroids to be taken for 120 days or more during the year before the index date.

**Statistical Analysis**

The primary objective of the study was to examine the association between asthma and invasive pneumococcal disease. For the nested case–control study, we used conditional logistic-regression analysis to assess the relationship between asthma and the risk of invasive pneumococcal disease, with adjustment for potential confounding factors, including sex, race as determined by TennCare, prolonged use of oral corticosteroids, and the presence of coexisting conditions that confer a high risk of pneumococcal disease.

After the case–control analysis had been completed, a cohort analysis was conducted to determine annual incidence rates of invasive pneumococcal disease among eligible persons enrolled in TennCare who had asthma and eligible enrolled persons who did not have asthma. The numerators for the unadjusted rates were all cases of invasive pneumococcal disease that had been included in the case–control study. The person-years in the denominator were estimated as the number of persons in the study population on July 1 of each study year. The annual incidence rates of invasive pneumococcal disease among persons with asthma and those without asthma were then determined according to the number of cases of invasive pneumococcal disease among persons with asthma and those without asthma per year, divided by the total number of eligible persons enrolled in TennCare on July 1 of each year who had asthma and who did not have asthma (defined according to the study definition of asthma during the previous year). A similar calculation was performed to ascertain the annual incidence of invasive pneumococcal disease among persons with high-risk coexisting conditions and those without high-risk coexisting conditions. The analyses were conducted with the use of Stata software (version 7.0) and SAS software (version 8.2).

**Results**

Of a total of 4581 episodes of invasive pneumococcal disease that had been included in the surveillance counties between 1995 and 2002, 1695 episodes (37.0 percent) occurred in persons 2 to 49 years of age. Of these, 635 episodes (37.5 percent) occurred in persons who...
had been enrolled in TennCare for at least one year before the index date and who were designated as case subjects. For each case subject, 10 age-matched control subjects (for a total of 6350) were selected. The mean age of the case subjects and age-matched controls was 28.5 years (Table 1). Subjects with invasive pneumococcal disease were significantly more likely than controls to be male and black. Asthma was identified in 114 case subjects (18.0 percent) and 516 controls (8.1 percent) (Table 1). Among subjects with invasive pneumococcal disease, there was also a greater prevalence of coexisting conditions that are associated with an increased risk of pneumococcal disease.

Among controls with asthma, during the year before the index date, 8.5 percent had been hospitalized and 18.4 percent had had at least one visit to an emergency department for asthma. Use of corticosteroids as rescue therapy during the year before the index date occurred among 41.5 percent of the control subjects, and 1.4 percent had received oral corticosteroid therapy for more than 120 days during that year. Case subjects with asthma were more likely than controls with asthma to have high-risk asthma (83.3 percent vs. 74.2 percent), to have been hospitalized for asthma within the previous year (24.6 percent vs. 8.5 percent), and to have received long-term oral corticosteroid therapy (7.9 percent vs. 1.4 percent).

After adjustment for sex, race, and high-risk coexisting conditions, asthma was significantly associated with an increase by more than a factor of two in the risk of invasive pneumococcal disease (adjusted odds ratio, 2.4; 95 percent confidence interval, 1.9 to 3.1) (Table 2). These findings were consistent in analyses stratified according to the severity of asthma, the presence or absence of high-risk coexisting conditions, and age (2 to 4 years, 5 to 17 years, and 18 to 49 years).

From 1995 through 2002, the average annual incidence of invasive pneumococcal disease among persons enrolled in TennCare who were 2 to 49 years of age was 6.1 episodes (range, 4.2 to 8.5) per 10,000 persons with asthma, as compared with 2.0 episodes (range, 1.5 to 2.2) per 10,000 persons without asthma. The annual incidence of invasive pneumococcal disease among persons with high-risk asthma was 6.9 episodes (range, 2.8 to 10.0) per 10,000 and among those with low-risk asthma was 3.9 episodes (range, 1.7 to 7.3) per 10,000 (Fig. 2). When only persons who did not have other high-risk coexisting conditions were included in the analysis, the annual incidence of the disease remained higher among those with asthma (4.2 episodes per 10,000 persons with high-risk asthma and 2.3 episodes per 10,000 persons with low-risk asthma) than among those without asthma (1.2 episodes per 10,000). Thus, the excess incidence of invasive pneumococcal disease among persons with asthma among those without coexisting conditions was one to three episodes per 10,000 persons per year.

Serotype analysis was performed on 313 (75.4 percent) of the 415 pneumococcal isolates from subjects with asthma and invasive pneumococcal disease that occurred after 1997, the year serotyping was first available through the ABCs program. Of these isolates, 178 (56.9 percent) were among the seven serotypes included in the pneumococcal conjugate vaccine and an additional 91 (29.1 percent) were serotypes found only in the 23-valent polysaccharide vaccine.
Through the linkage of two large, population-based databases in Tennessee, we identified an increase by more than a factor of two in the risk of invasive pneumococcal disease among persons with asthma, even after adjustment for other risk factors for the disease. This increased risk was present among those with and those without other coexisting conditions and among young children, adolescents, and adults. The validity of the use of the two databases to define the risk of invasive pneumococcal disease appears high, as was confirmed by the finding of well-known associations between invasive pneumococcal disease and traditional risk factors, such as infection with HIV and sickle cell disease. These data provide new insights into the role of asthma as a risk factor for invasive pneumococcal disease and firmly place asthma on the list of conditions that confer an increased risk of this disease.

In studies analyzing the causes of pneumococcal disease or the efficacy of pneumococcal vaccines and describing COPD as a risk factor for invasive pneumococcal disease, asthma usually has not been distinguished from other forms of obstructive lung disease. Descriptions of asthma as an independent risk factor for pneumococcal disease are rare. The most recent recommendations from the CDC for vaccination against *S. pneumoniae* include chronic pulmonary disease (namely, COPD and emphysema) as a risk factor for pneumococcal disease; however, these guidelines state that “asthma has not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids,” and persons with asthma are explicitly excluded among those considered for vaccination. Similarly, pneumococcal vaccination is not included in the most recently published guidelines for the management of asthma. Few studies have delineated asthma as a potential risk factor separate from other forms of obstructive lung disease. In a case–control analysis of the risk cigarette smoking confers on the development of invasive pneumococcal disease, asthma (as distinguished from other forms of obstructive lung disease) was associated with an increase by a factor of 2.5 in the risk of the development of invasive pneumococcal disease before, but not after, adjustment for other risk factors. Whereas in that study,
patient questionnaires were used to ascertain the presence of asthma, we used previously validated criteria that incorporated diagnostic coding and the prescription of asthma-related medications—an approach that probably provided a more accurate assessment of the presence of medically treated asthma in the study population.

The increased risk of invasive pneumococcal disease among persons with asthma has biologic plausibility, because in asthma unique pathologic alterations in the airway can lead to impaired clearance of pathogenic bacteria. The respiratory epithelium and submucosal tissue of persons with asthma exhibit abnormal deposition of collagen and hyperplasia of goblet cells. The hyperplasia leads to increased production of mucin and alterations in secreted mucus, resulting in abnormalities in viscosity and in mucociliary clearance of the airway, increased production of sputum, and airway obstruction. The impaired clearance of airway debris can serve as a focus for localized infection that can develop into invasive bacterial infection. Furthermore, chronic inflammation of the airway among persons with asthma and those with COPD may well contribute to impaired immunity and to a predisposition to bacterial and viral infections.

The incidence of invasive pneumococcal disease among persons with asthma in our study mirrored rates reported among other persons at high risk who may be considered for pneumococcal vaccination, such as persons 65 years of age or older (8.3 episodes of pneumococcal bacteremia per 10,000). In addition, a majority (85.9 percent) of the pneumococcal serotypes associated with invasive pneumococcal disease among persons with asthma were included in the currently licensed pneumococcal vaccines, and the association between asthma and invasive pneumococcal disease was similar to that found among persons with other conditions that are targets for vaccination, such as COPD and diabetes.

Consideration of vaccination is most salient for persons in the study population without other high-risk conditions for which pneumococcal vaccination is already recommended. In this population, asthma resulted in an annual excess of 1 to 3 cases of invasive pneumococcal disease per 10,000 persons. Given the young age of these subjects, they would remain at increased risk for years before becoming eligible for vaccination at 65 years of age or as a result of the development of other high-risk conditions. Thus, the cumulative excess risk over a period of 10 years may be 10 to 30 excess cases of invasive pneumococcal disease per 10,000 persons. These data suggest that pneumococcal vaccination of persons with asthma may be a worthwhile strategy to reduce the incidence of invasive pneumococcal disease in this risk group. However, further studies and more formal cost–benefit analyses are needed to change current recommendations for vaccination.

There were some limitations to our investigation. Case subjects with asthma had higher frequencies of hospitalization and the need to visit an emergency department, of high-risk asthma, and of long-term use of oral corticosteroids than did control subjects without asthma. However, the association between invasive pneumococcal disease and asthma remained after adjustment for long-term use of oral corticosteroids. In addition, ICD-9-CM coded diagnoses of tobacco use recorded in inpatient discharge files and outpatient claims are probably absent from the records for many smokers; thus, the use of diagnostic coding to determine tobacco use probably resulted in underestimation of the true prevalence of tobacco use in the study population. The TennCare database lacks other techniques to elucidate smoking status.
However, the association between asthma and invasive pneumococcal disease is unlikely to be confounded by unmeasured primary tobacco use among young children (two to five years of age), a population with minimal to no tobacco use or tobacco-related lung disease and an asthma-associated risk of invasive pneumococcal disease similar to that noted among older persons. Passive exposure to tobacco, which has also been found to increase the risk of invasive pneumococcal disease, was not quantified in our study population. Thus, the effect of exposure to cigarette smoke on the risk of invasive pneumococcal disease cannot be ruled out by our study. Finally, the study population comprised primarily persons of low socioeconomic status enrolled in a Medicaid program and may not be generalizable to other populations. However, the incidence of invasive pneumococcal disease among persons without asthma in our study mirrored rates reported for the general population (0.3 to 1.6 episodes per 10,000 persons 2 to 49 years of age), which suggests that our findings may be applicable to a broader population. 29

This investigation provided strong evidence of an association between asthma and invasive pneumococcal disease, independent of long-term use of corticosteroids and other obstructive pulmonary disease, that increases among persons with high-risk asthma. This increased risk remained even among those with no other high-risk coexisting conditions. Defining this association argues for the addition of asthma to the list of conditions that increase the risk of invasive pneumococcal disease. As the incidence of asthma continues to climb in the United States, 5-6 the burden of invasive pneumococcal disease due to asthma is likely to increase, and discussions with regard to the feasibility and cost-effectiveness of pneumococcal vaccination among persons with asthma will need to be carefully explored.

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An Intervention Involving Traditional Birth Attendants and Perinatal and Maternal Mortality in Pakistan


BACKGROUND
There are approximately 4 million neonatal deaths and half a million maternal deaths worldwide each year. There is limited evidence from clinical trials to guide the development of effective maternity services in developing countries.

METHODS
We performed a cluster-randomized, controlled trial involving seven subdistricts (talukas) of a rural district in Pakistan. In three talukas randomly assigned to the intervention group, traditional birth attendants were trained and issued disposable delivery kits; Lady Health Workers linked traditional birth attendants with established services and documented processes and outcomes; and obstetrical teams provided outreach clinics for antenatal care. Women in the four control talukas received usual care. The primary outcome measures were perinatal and maternal mortality.

RESULTS
Of the estimated number of eligible women in the seven talukas, 10,114 (84.3 percent) were recruited in the three intervention talukas, and 9443 (78.7 percent) in the four control talukas. In the intervention group, 9184 women (90.8 percent) received antenatal care by trained traditional birth attendants, 1634 women (16.2 percent) were seen antenatally at least once by the obstetrical teams, and 8172 safe-delivery kits were used. As compared with the control talukas, the intervention talukas had a cluster-adjusted odds ratio for perinatal death of 0.70 (95 percent confidence interval, 0.59 to 0.82) and for maternal mortality of 0.74 (95 percent confidence interval, 0.45 to 1.23).

CONCLUSIONS
Training traditional birth attendants and integrating them into an improved health care system were achievable and effective in reducing perinatal mortality. This model could result in large improvements in perinatal and maternal health in developing countries.
The new england journal of medicine

There are an estimated 4 million neonatal deaths and 500,000 maternal deaths worldwide each year. The vast majority of these deaths occur in developing countries, where 43 percent of births are attended by traditional birth attendants, the proportion generally being higher in rural areas. Training traditional birth attendants was a central component of the Safe Motherhood Initiative launched by the World Health Organization, the United Nations Children’s Fund (also known as UNICEF), the United Nations Population Fund, the World Bank, and other organizations, but the lack of evidence from randomized, controlled trials to inform decision making has prohibited widespread implementation of such training. We present the results of a large cluster-randomized, controlled trial of training traditional birth attendants and integrating them into an improved maternal health care system in rural Pakistan.

Organized data on routine health outcomes do not exist in rural Pakistan. The World Health Organization’s estimate of maternal mortality in Pakistan (350 per 100,000 live births in 1995) was modeled from projections of deaths of adult females. In Pakistan, more than 89 percent of deliveries, and 80 percent of maternal deaths, occur at home, and 80 percent of deliveries are attended by only a traditional birth attendant. Only 1 in 20 women with complications of pregnancy or childbirth reaches a facility with emergency obstetrical care. Infant mortality is estimated at 82 per 1000 live births.

STUDY DESIGN
The study was a randomized, controlled trial. Since the intervention included the training of traditional birth attendants, an individualized, randomized design would have led to contamination between intervention and control care; therefore, cluster randomization was required. Financial and logistic considerations dictated the subdistrict (taluka) as the most appropriate unit for randomization.

SETTING
Sindh is one of Pakistan’s four provinces. In Sindh’s 21 districts, an infrastructure of primary and district-level care serves well-defined geographic areas. Larkana, the study district, is largely rural. The Ministry of Health’s Lady Health Workers Programme is an important element in the government of Pakistan’s plan to raise the health status of women and children in rural villages and poor urban areas. A cadre of Lady Health Workers based at primary health centers have a mission of delivering primary health care, including maternal-health and child-health services. Although the women are educated (10 years of schooling), they have no medical or nursing degree, but they do receive 3 to 6 months of training in primary health care and family planning. Recruiting and retaining female medical staff is difficult in rural areas, so the quality of primary maternity services is, in general, poor.

STUDY GROUPS
With a simple cluster-randomization sampling scheme, and with a computer-generated procedure, Larkana’s seven talukas were allocated to intervention or control groups. All pregnant women were eligible for inclusion. Most of the private medical centers and a public tertiary-level hospital providing specialist obstetrical care are located in Larkana City, where residents have better access to services. The city and its immediate environs were therefore excluded.

INTERVENTION CLUSTERS
The intervention was designed to facilitate care based on the available infrastructure and at low-cost and sustainable. In the intervention clusters, a team of obstetricians and female paramedics trained all traditional birth attendants in the taluka who performed at least one delivery per month (Fig. 1). The training lasted three days and involved the use of picture cards containing advice on antepartum, intrapartum, and postpartum care; how to conduct a clean delivery; use of the disposable delivery kit; when to refer women for emergency obstetrical care; and care of the newborn. Infant mortality is estimated at 82 per 1000 live births.

METHODS

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INTERVENTION CLUSTERS
The intervention was designed to facilitate care based on the available infrastructure and at low-cost and sustainable. In the intervention clusters, a team of obstetricians and female paramedics trained all traditional birth attendants in the taluka who performed at least one delivery per month (Fig. 1). The training lasted three days and involved the use of picture cards containing advice on antepartum, intrapartum, and postpartum care; how to conduct a clean delivery; use of the disposable delivery kit; when to refer women for emergency obstetrical care; and care of the newborn. Infant mortality is estimated at 82 per 1000 live births.

METHODS

STUDY DESIGN
The study was a randomized, controlled trial. Since the intervention included the training of traditional birth attendants, an individualized, randomized design would have led to contamination between intervention and control care; therefore, cluster randomization was required. Financial and logistic considerations dictated the subdistrict (taluka) as the most appropriate unit for randomization.

SETTING
Sindh is one of Pakistan’s four provinces. In Sindh’s 21 districts, an infrastructure of primary and district-level care serves well-defined geographic areas. Larkana, the study district, is largely rural. The Ministry of Health’s Lady Health Workers Programme is an important element in the government of Pakistan’s plan to raise the health status of women and children in rural villages and poor urban areas. A cadre of Lady Health Workers based at primary health centers have a mission of delivering primary health care, including maternal-health and child-health services. Although the women are educated (10 years of schooling), they have no medical or nursing degree, but they do receive 3 to 6 months of training in primary health care and family planning. Recruiting and retaining female medical staff is difficult in rural areas, so the quality of primary maternity services is, in general, poor.

STUDY GROUPS
With a simple cluster-randomization sampling scheme, and with a computer-generated procedure, Larkana’s seven talukas were allocated to intervention or control groups. All pregnant women were eligible for inclusion. Most of the private medical centers and a public tertiary-level hospital providing specialist obstetrical care are located in Larkana City, where residents have better access to services. The city and its immediate environs were therefore excluded.

INTERVENTION CLUSTERS
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of obstetricians from the public-sector tertiary care center in Larkana City. These teams offered outreach clinics in two centers (one taluka hospital and one large, rural health center) in each of the three intervention talukas. The teams rotated their visits among the centers, holding eight outreach sessions in each center during the six-month intervention period.

Traditional birth attendants were instructed to register all pregnant women in their catchment areas and to inform the Lady Health Workers about the pregnant women under their care. Subsequently, the traditional birth attendants were issued delivery kits from the primary care centers. The kits included sterilized disposable gloves, soap, gauze, cotton balls, antiseptic solution, an umbilical-cord

Figure 1. Flow Chart Showing the Enrollment and Status of Women in the Trial.
A total of 19,557 women were recruited in the six months from May to October 1998. From March to April 1998, 565 traditional birth attendants, 811 Lady Health Workers in the intervention group, and 819 Lady Health Workers in the control group were trained as appropriate to study group. A spontaneous abortion is defined as loss of a fetus before six months of gestation. For two women in the intervention group, the outcomes of the births were not known.
clamp, and a surgical blade. We anticipated that these kits would improve the standing of the traditional birth attendants among their clients, and the method of distribution was designed to increase the links between traditional birth attendants and the primary care facilities.

**Control Clusters**
In the control clusters, Lady Health Workers enrolled and followed up all pregnant women in their catchment area in the course of their normal monthly home visits to women and children. The traditional birth attendants in the control clusters did not receive any training and were not supplied with delivery kits. No outreach clinics were organized in these talukas, and women in these areas received “usual” care.

**Follow-up**
Follow-up in both groups involved the collection of information by Lady Health Workers, who asked the women, their families, and traditional birth attendants for details of the progress and outcome of each pregnancy that was registered. In cases of maternal death, the cause was ascertained by Lady Health Workers on the basis of oral reports from relatives, neighbors, or traditional birth attendants.

**Outcome Measures**
The primary outcomes were perinatal mortality (stillbirths and live-born babies who died within 28 days after birth) and maternal mortality (deaths during pregnancy and up to 6 weeks post partum, excluding those known to have been due to injury or accident) from any cause, including deaths after spontaneous abortion (loss of a fetus before 6 months of gestation). Only singleton pregnancies were included in the analysis of perinatal outcome.

The secondary outcomes were major complications of pregnancy (hemorrhage, obstructed labor, puerperal sepsis, eclampsia, and abortion), referral by the traditional birth attendant for emergency obstetrical care, type and place of delivery, and delivery attendant. Lady Health Workers who recorded outcomes could not be blinded to the intervention status of the women but were not made aware of the main study objective or the outcome measures for the planned comparison.

**Statistical Analysis**
The sample size of this trial was limited by the available funding. Local information suggested that there were approximately 70,000 deliveries per year in Larkana district. After excluding urban areas, we estimated that 24,000 pregnant women could be recruited in six months. Randomization below the level of the taluka was not practical. With seven clusters (average size, 4000 pregnant women each) and an intraclass correlation coefficient of 0.001, the study would have 80 percent power (two-sided P<0.05) to detect a 23 percent difference in perinatal mortality (estimated at 95 per 1000 live births and stillbirths in the control group) between the study groups. Assuming maternal mortality in the control group of 400 per 100,000 pregnancies, such a sample size would permit us to detect a relative reduction in maternal mortality only as large as 90 percent. However, given the importance of the outcome, and the hypothesis that the outcome would be influenced by the intervention, we included maternal mortality as a primary outcome measure.

The data were entered into a database of epidemiologic information and analyzed with the use of SPSS software, version 10.0. Evaluation was by intention-to-treat analysis. Multilevel modeling to adjust for cluster randomization was performed with the use of MLwiN software, version 1.1. For perinatal and maternal mortality, we used a quasi-likelihood binary-regression model with random intercept to estimate the degree of overdispersion in the cluster-specific death rates. Odds ratios and 95 percent confidence limits were computed for the model coefficients with the use of MLwiN guidelines.

No formal ethics committee exists in this region, but the protocol was discussed and approved after a meeting of Sindh province’s secretary of health, director of health services (Larkana Division), and director of the Lady Health Worker Programme (at which Dr. Jokhio was present). These key people acted as guardians of the women’s interests.

A total of 19,557 women were recruited in the six months from May to October 1998. An exact figure for the eligible women could not be obtained, since there are no reliable birth registers. On the basis of the crude estimate of 24,000 deliveries in a six-month period, the 10,114 women in the intervention group and the 9443 women in the control group represented 84.3 percent and 78.7 percent, respectively, of the eligible total (Fig. 1). Follow-up...
to 42 days post partum was achieved for 10,093 women (99.8 percent) in the intervention group and 9432 women (99.9 percent) in the control group. Pregnancy ended in spontaneous abortion in 255 women (2.5 percent) in the intervention group and 313 women (3.3 percent) in the control group (Table 1). One hundred twenty-six women (1.2 percent) in the intervention group and 130 women (1.4 percent) in the control group had multiple births.

The baseline maternal characteristics were similar for the study groups and across clusters with respect to all measured variables except years of education, which were slightly greater among women in the control group (Table 2). The size of the clusters ranged from 1966 to 3987 women. Of the women in the intervention group, 9184 (90.8 percent) received care by trained traditional birth attendants, and 1634 (16.2 percent) had at least one antepartum visit with the consulting obstetrical teams. Traditional birth attendants used 8172 safe-delivery kits for the intervention group.

The crude perinatal rate of death among the intervention group was 84.8 per 1000 (823 deaths per 9710 live births and stillbirths) as compared with 120 per 1000 (1077 deaths per 8989 live births and stillbirths) in the control group (Table 3). We used random-effects multilevel modeling to determine that the odds ratio for perinatal death in the

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**Table 1. Factors Related to Delivery According to Study Group.**

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Intervention (N=10,114)</th>
<th>Control (N=9443)</th>
<th>Cluster-Adjusted Odds Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home</td>
<td>8373 (82.8)</td>
<td>7614 (80.6)</td>
<td>1.07 (0.79–1.45)</td>
<td>0.65</td>
</tr>
<tr>
<td>At public health facility</td>
<td>623 (6.2)</td>
<td>493 (5.2)</td>
<td>1.23 (0.96–1.57)</td>
<td>0.10</td>
</tr>
<tr>
<td>At private health facility</td>
<td>783 (7.7)</td>
<td>957 (10.1)</td>
<td>0.82 (0.54–1.27)</td>
<td>0.38</td>
</tr>
<tr>
<td>En route</td>
<td>22 (0.2)</td>
<td>18 (0.2)</td>
<td>1.28 (0.56–2.96)</td>
<td>0.56</td>
</tr>
<tr>
<td>Other places</td>
<td>36 (0.4)</td>
<td>35 (0.4)</td>
<td>0.97 (0.58–1.64)</td>
<td>0.91</td>
</tr>
<tr>
<td>Spontaneous abortion‡</td>
<td>255 (2.5)</td>
<td>313 (3.3)</td>
<td>0.73 (0.55–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>9235 (91.3)</td>
<td>8562 (90.7)</td>
<td>1.05 (0.84–1.32)</td>
<td>0.67</td>
</tr>
<tr>
<td>Forceps</td>
<td>399 (3.9)</td>
<td>342 (3.6)</td>
<td>1.10 (0.93–1.29)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>203 (2.0)</td>
<td>213 (2.3)</td>
<td>0.90 (0.67–1.19)</td>
<td>0.46</td>
</tr>
<tr>
<td>Attendant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>949 (9.4)</td>
<td>1023 (10.8)</td>
<td>0.93 (0.59–1.47)</td>
<td>0.75</td>
</tr>
<tr>
<td>Nurse or midwife</td>
<td>568 (5.6)</td>
<td>497 (5.3)</td>
<td>1.14 (0.85–1.54)</td>
<td>0.38</td>
</tr>
<tr>
<td>Traditional birth attendant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trained§</td>
<td>7460 (73.8)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Untrained¶</td>
<td>583 (5.8)</td>
<td>7191 (76.2)</td>
<td>0.02 (0.01–0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Training status unknown</td>
<td>164 (1.6)</td>
<td>269 (2.8)</td>
<td>0.55 (0.33–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Relative</td>
<td>103 (1.0)</td>
<td>126 (1.3)</td>
<td>0.81 (0.46–1.42)</td>
<td>0.62</td>
</tr>
<tr>
<td>Other</td>
<td>10 (0.1)</td>
<td>11 (0.1)</td>
<td>0.85 (0.36–2.00)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* In the intervention group, 21 women were lost to follow-up, and for 2 women, the outcomes of the births were not known. In the control group, 11 women were lost to follow-up. Numbers may not sum to totals and percentages may not sum to 100 because of incomplete information about delivery. CI denotes confidence interval, and a dash not applicable.
† Multilevel modeling was performed to adjust for cluster randomization.
‡ A spontaneous abortion was defined as a loss of a fetus before six months of gestation.
§ A trained traditional birth attendant was a traditional birth attendant for the intervention group who was trained according to the study protocol.
¶ An untrained traditional birth attendant was a traditional birth attendant not trained according to the study protocol.
|| In some cases, the woman was known to have been assisted during delivery by a traditional birth attendant, but it was not possible to ascertain if the traditional birth attendant was trained according to the study protocol.
intervention group, as compared with the control group, was 0.70 (95 percent confidence interval, 0.59 to 0.82); the results were similar for stillbirths and neonatal deaths (Table 4) and across intervention clusters (Table 3). There were 27 maternal deaths in the intervention group and 34 in the control group, corresponding to respective maternal mortality rates of 268 and 360 per 100,000 pregnancies. The cluster-adjusted odds ratio for maternal deaths in the intervention group, as compared with the control group, was 0.74 (95 percent confidence interval, 0.45 to 1.23).

The intervention group had significantly lower rates of puerperal sepsis and hemorrhage as a complication of pregnancy (Table 4). The frequency of a diagnosis of obstructed labor was significantly greater in the intervention group. The frequencies of eclampsia and of spontaneous abortion with associated morbidity did not differ significantly between groups, but the overall numbers of complications recorded were small. Women in the intervention group were more likely than those in the control group to be referred to emergency obstetrical care for treatment (Table 4).

The cause of maternal death, as ascertained by oral report to the Lady Health Workers, is summarized in Table 4.

**DISCUSSION**

There was a significant reduction in perinatal mortality of about 30 percent in the intervention group of this large, cluster-randomized, controlled trial. The estimated percent reduction in maternal mortality was similar but was not statistically significant despite the large size of the trial. The large decrease in puerperal sepsis is consistent with the recorded high use of safe-delivery kits by traditional birth attendants. It is likely that much of the reduction in perinatal mortality was mediated through reduced sepsis, but it was not possible to obtain definitive information.

The training of traditional birth attendants included teaching them to recognize serious complications of pregnancy and delivery, and obstructed labor was more frequently recorded for women in the intervention group. Referral to public health services was also encouraged, and correspondingly, a higher proportion of women in the intervention group than in the control group were referred to an emergency obstetrical care facility. To obtain such care, even in publicly funded hospitals, women and their families must arrange for their own transportation and pay for all drugs and equipment. Intervention did not involve changes in the availability of or access to existing emergency care. This may explain why, despite the increased referrals for emergency care, there was no significant increase in the percentage of women who delivered at a public or private health facility. We do not have information on the acceptance or the outcomes of these referrals.

Limited data have been available on the value of training traditional birth attendants and integrating them into a maternal health care system in developing countries. A clear strength of the present study is its cluster-randomized design. It was not feasible for individual patients to undergo randomization, owing to the risk of contamination if trained traditional birth attendants were expected

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**Table 2. Baseline Maternal Characteristics According to Study Group and Cluster.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cluster 1 (N=3417)</td>
<td>Cluster 2 (N=3987)</td>
</tr>
<tr>
<td></td>
<td>Cluster 3 (N=2710)</td>
<td>Cluster 4 (N=2796)</td>
</tr>
<tr>
<td></td>
<td>Cluster 5 (N=2065)</td>
<td>Cluster 6 (N=1966)</td>
</tr>
<tr>
<td></td>
<td>Cluster 7 (N=2616)</td>
<td>Total (N=9443)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>27.0±5.8</td>
<td>26.6±5.8</td>
</tr>
<tr>
<td></td>
<td>26.5±6.1</td>
<td>26.7±5.9</td>
</tr>
<tr>
<td></td>
<td>26.3±6.3</td>
<td>26.5±6.1</td>
</tr>
<tr>
<td></td>
<td>26.9±6.3</td>
<td>26.8±6.0</td>
</tr>
<tr>
<td></td>
<td>26.6±6.2</td>
<td></td>
</tr>
<tr>
<td>Parity (no.)</td>
<td>3.5±2.8</td>
<td>3.2±2.7</td>
</tr>
<tr>
<td></td>
<td>3.4±2.8</td>
<td>3.5±2.8</td>
</tr>
<tr>
<td></td>
<td>3.6±2.9</td>
<td>3.6±2.9</td>
</tr>
<tr>
<td></td>
<td>3.8±2.9</td>
<td>3.6±2.9</td>
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<tr>
<td></td>
<td>3.7±2.9</td>
<td></td>
</tr>
<tr>
<td>Month of pregnancy when re-</td>
<td>5.0±2.1</td>
<td>4.8±2.1</td>
</tr>
<tr>
<td>cruited (yr)</td>
<td>5.3±2.5</td>
<td>5.0±2.2</td>
</tr>
<tr>
<td></td>
<td>4.9±2.2</td>
<td>4.9±2.3</td>
</tr>
<tr>
<td></td>
<td>5.0±2.3</td>
<td>4.5±1.9</td>
</tr>
<tr>
<td></td>
<td>4.8±2.2</td>
<td></td>
</tr>
<tr>
<td>Woman’s education (yr)</td>
<td>1.2±3.0</td>
<td>1.0±2.7</td>
</tr>
<tr>
<td></td>
<td>1.1±2.8</td>
<td>1.1±2.8</td>
</tr>
<tr>
<td></td>
<td>1.4±3.2</td>
<td>1.3±3.1</td>
</tr>
<tr>
<td></td>
<td>1.1±2.9</td>
<td>1.6±3.4</td>
</tr>
<tr>
<td></td>
<td>1.4±3.2</td>
<td></td>
</tr>
<tr>
<td>Husband’s education (yr)</td>
<td>4.8±5.5</td>
<td>4.1±5.1</td>
</tr>
<tr>
<td></td>
<td>4.2±5.5</td>
<td>4.3±5.3</td>
</tr>
<tr>
<td></td>
<td>4.2±5.2</td>
<td>4.3±5.5</td>
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<tr>
<td></td>
<td>4.0±5.2</td>
<td>5.3±5.7</td>
</tr>
<tr>
<td></td>
<td>4.5±5.4</td>
<td></td>
</tr>
<tr>
<td>Distance from nearest primary</td>
<td>1.7±2.1</td>
<td>3.7±3.9</td>
</tr>
<tr>
<td>health care facility (km)</td>
<td>2.3±2.0</td>
<td>2.7±3.0</td>
</tr>
<tr>
<td></td>
<td>3.1±3.5</td>
<td>2.5±3.2</td>
</tr>
<tr>
<td></td>
<td>2.7±2.9</td>
<td>1.6±1.8</td>
</tr>
<tr>
<td></td>
<td>2.5±3.0</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
traditional birth attendants and perinatal and maternal mortality

The small number of clusters of very large size is a limitation of the trial design. The administrative and training costs of delivering alternative forms of care to a larger number of smaller geographic clusters were prohibitive, and the risk of contamination would have been increased.

No major organizational or demographic differences were anticipated among the talukas, and the baseline characteristics of women in different talukas were similar. The effect of intervention on perinatal mortality seemed consistent across intervention clusters, and adjusting for cluster had no material effect on the estimated risk reductions.

We have no data to ascertain the accuracy of the reports of death or of the reported causes of maternal death. Although the traditional birth attendants and Lady Health Workers could not be blinded to the intervention, observer bias is unlikely to have affected the reporting of the primary outcomes of perinatal and maternal mortality. Lady Health Workers, who collected data on the primary outcomes in both groups, were not aware of the purpose or comparative nature of the study.

The method of providing safe-delivery kits to traditional birth attendants improved their contact with primary care centers and with the Lady Health Workers linked to the attendants. The standing and confidence of traditional birth attendants may also have been improved by their authority to refer women to outreach clinics for antenatal care, although we did not directly assess this.

In the 1990s, it became widely accepted that training traditional birth attendants was likely to cause only a small reduction in maternal mortality. A recent review suggested that training may improve the knowledge, attitudes, and behaviors of traditional birth attendants, but effects on neonatal mortality could not be adequately assessed owing to incomplete reporting and the inadequate quality of available studies. Only 4 of the 63 studies compared outcomes in the study group before and after traditional birth attendant training with those in a control group, and the key features of the study were often not reported.

A recently reported cluster-randomized trial in Nepal showed a 30 percent reduction in neonatal mortality per 1000 live births (similar to our find-

Table 3. Distribution of Outcome Measures According to Study Group and Cluster.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal deaths — no. (per 1000 live births and stillbirths)</td>
<td>232 (71)</td>
<td>361 (94)</td>
</tr>
<tr>
<td>Stillbirths — no. (per 1000 live births and stillbirths)</td>
<td>130 (40)</td>
<td>227 (59)</td>
</tr>
<tr>
<td>Neonatal deaths — no. (per 1000 live births)</td>
<td>102 (33)</td>
<td>134 (37)</td>
</tr>
<tr>
<td>Maternal deaths — no. (per 100,000 pregnancies)</td>
<td>6 (176)</td>
<td>15 (377)</td>
</tr>
</tbody>
</table>

* Perinatal outcomes are for singleton births only.
† Perinatal deaths were defined as stillbirths or live-born infants who died within 28 days after birth. (It was not possible to separate early and late neonatal deaths.)
‡ Stillbirths were defined as fetuses born after six months that never showed signs of life.
§ Neonatal deaths were defined as live-born babies who died within 28 days after birth.
¶ Maternal deaths were defined as death of the mother during pregnancy, delivery, and up to six weeks post partum, excluding deaths known to have been due to injury or accident. In addition to these maternal deaths, one woman in the intervention group died of viral hepatitis, and one in the control group was murdered.

singleton births only.
ings) and a 78 percent reduction in maternal mortality in clusters exposed to different community-based interventions. The interventions did not involve traditional birth attendants but, rather, involved the convening of women’s groups to identify local perinatal problems and formulate strategies to address them; resulting changes included more clean-delivery practices and better links with improved primary care services. The results from that study and the current trial confirm the possibility of large improvements in perinatal and maternal health from interventions at the community level.

Experts from several centers have pointed out the lack of evidence that interventions are effective in reducing maternal and perinatal mortality in developing countries. Ethical and practical constraints have limited the study of potential interventions — for example, the large sample size needed to detect differences in maternal mortality. Despite the large number of women in our study, it was not adequately powered to detect a meaningful change in maternal mortality. It would be unwise to use the large risk reduction in maternal mortality in that study to form the basis for estimates of sample size for future trials. Some people have proposed the use of perinatal mortality as a proxy for maternal mortality, but this suggestion is controversial; in the present study, the change in maternal mortality appeared to mirror closely that in perinatal mortality.

We tried to capitalize on an infrastructure that is already in place but fails to meet women’s needs.

### Table 4. Odds Ratios for Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Intervention Group (N=10,093)</th>
<th>Control Group (N=9432)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal death†</td>
<td>823 (8.47)</td>
<td>1077 (11.9)</td>
<td>0.68 (0.62–0.75)</td>
<td>&lt;0.001</td>
<td>0.70 (0.59–0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stillbirth†</td>
<td>483 (4.97)</td>
<td>638 (7.10)</td>
<td>0.69 (0.61–0.78)</td>
<td>&lt;0.001</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal death†</td>
<td>340 (3.50)</td>
<td>439 (4.88)</td>
<td>0.71 (0.62–0.82)</td>
<td>&lt;0.001</td>
<td>0.71 (0.62–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal death‡</td>
<td>27 (0.27)</td>
<td>34 (0.36)</td>
<td>0.74 (0.45–1.23)</td>
<td>0.24</td>
<td>0.74 (0.45–1.23)</td>
<td>0.24</td>
</tr>
<tr>
<td>Complications of pregnancy§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>174 (1.72)</td>
<td>259 (2.75)</td>
<td>0.62 (0.51–0.75)</td>
<td>&lt;0.001</td>
<td>0.61 (0.47–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructed labor</td>
<td>571 (5.66)</td>
<td>449 (4.76)</td>
<td>1.20 (1.06–1.36)</td>
<td>0.005</td>
<td>1.26 (1.03–1.54)</td>
<td>0.025</td>
</tr>
<tr>
<td>Puerperal sepsis</td>
<td>78 (0.77)</td>
<td>400 (4.24)</td>
<td>0.18 (0.14–0.22)</td>
<td>&lt;0.001</td>
<td>0.17 (0.13–0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>23 (0.23)</td>
<td>29 (0.31)</td>
<td>0.74 (0.43–1.28)</td>
<td>0.28</td>
<td>0.69 (0.36–1.31)</td>
<td>0.25</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>47 (0.47)</td>
<td>54 (0.57)</td>
<td>0.81 (0.55–1.2)</td>
<td>0.3</td>
<td>0.71 (0.38–1.34)</td>
<td>0.29</td>
</tr>
<tr>
<td>Referral to emergency obstetrical care¶</td>
<td>1008 (9.99)</td>
<td>654 (6.93)</td>
<td>1.49 (1.34–1.65)</td>
<td>&lt;0.001</td>
<td>1.50 (1.19–1.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Multilevel modeling was performed to adjust for cluster randomization.
† Percentages for perinatal deaths, stillbirths, and neonatal deaths were calculated from a total of 9710 singleton births in the intervention group, and 8989 in the control group.
‡ Of the 27 maternal deaths in the intervention group, 7 (25.9 percent) were attributed to hemorrhage, 5 (18.5 percent) to obstructed labor, 8 (29.6 percent) to eclampsia, 3 (11.1 percent) to spontaneous abortion, and 4 (14.8 percent) to other causes. Of the 34 maternal deaths in the control group, 15 (44.1 percent) were attributed to hemorrhage, 9 (26.5 percent) to obstructed labor, 3 (8.8 percent) to eclampsia, 6 (17.6 percent) to spontaneous abortion, and 1 (2.9 percent) to other causes.
§ A Lady Health Worker recorded a complication of pregnancy if she ascertained that any of the complications listed had occurred to the woman at any stage of pregnancy or postpartum. The training of Lady Health Workers and traditional birth attendants included oral descriptions and pictorial representations of the complications listed. Hemorrhage was defined as excessive bleeding from the genital tract after 28 weeks of gestation owing to complications of pregnancy, delivery, or the puerperium. Labor was defined as obstructed when it lasted longer than 18 hours. Puerperal sepsis was defined as fever or foul-smelling lochia or both. Eclampsia was defined as maternal seizures before, during, or after delivery. Lady Health Workers recorded spontaneous abortions (loss of the fetus before six months of gestation) that were complicated by excessive bleeding, for example, as complications of pregnancy.
¶ Referral to an emergency obstetrical care facility included referral of the woman to any such facility for any complication during pregnancy, delivery, or the postpartum period.
Our results show that substantial improvement in outcomes is achievable and sustainable within this infrastructure. These data should inform policy decisions directed toward reducing neonatal and maternal mortality in developing countries.\textsuperscript{17,18}

Supported by a grant from Family Health Project of the Sindh government’s health department (for capital costs) and by the University of Birmingham (for data entry).

\section*{REFERENCES}


\section*{CLINICAL PROBLEM-SOLVING SERIES}

The Journal welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see http://authors.nejm.org.
A seven-year-old girl is 130 cm tall (51 in., the 90th percentile for girls of the same age) and weighs 34.6 kg (76 lb, above the 95th percentile), with a body-mass index (defined as the weight in kilograms divided by the square of the height in meters) of 20.5 (above the 95th percentile). Physical examination reveals no abnormalities aside from her excess weight. Her family eats at a quick-service restaurant once a week, and she drinks approximately 16 oz (450 ml) of soft drinks and 8 oz (225 ml) of whole milk per day. Her physical activity is limited to 30 minutes of physical education twice per week and 20-minute recesses three days per week in school. She has approximately 4.5 hours of screen time per day, which is divided among the television sets in her bedroom and in the family room and the family computer. What should you advise?
**ASSESSMENT**

Measurement of the body-mass index represents the first step in assessment and treatment. The term “overweight” is applied when the body-mass index of a child exceeds the 95th percentile for children of the same age and sex, and the term “at risk for overweight” is applied to children or adolescents whose body-mass index is between the 85th and 95th percentiles (Fig. 1). A body-mass index at or above the 95th percentile is highly specific for increased body fat. The crossing of major growth percentile lines upward is an early indication of risk. However, body-mass index must also be considered in the context of the age of the child and the growth patterns of the family. In children who are born small but are genetically programmed to be larger, these adjustments appear to occur in the first five years of life. Less than 5 percent of children cross two major percentile lines upward on the growth charts of the Centers for Disease Control and Prevention after four years of age. Thereafter, children who cross major percentile lines upward may be at increased risk for overweight. Although visceral fat increases the likelihood of morbidity in adults and youth, no widely accepted clinical measure of central adiposity yet exists for youth.

The family history of obesity and obesity-related diseases and the dietary and activity patterns should routinely be assessed (Table 1). The signs and symptoms that are most frequently associated with a congenital or endocrine abnormality underlying overweight are hypogonadism, short stature, dysmorphic features, a somatic abnormality, and mental retardation (Table 2). Clinical experience in tertiary care centers suggests that identifiable endocrine abnormalities or syndromes account for less than 1 percent of cases of overweight. The history and physical examination should also address potential complications of overweight (Table 2).

**LABORATORY TESTING**

A fasting profile of lipoprotein, insulin, and glucose levels has been recommended by some experts for all overweight children. Elevated levels of liv-
Table 1. Assessment of Childhood Overweight.

| Calculate body-mass index: divide the weight in kilograms by the square of the height in meters |
| Family history |
| - Identify obesity in first-degree relatives |
| - Evaluate history of cardiovascular disease, type 2 diabetes, or cancer in first-degree or second-degree relatives |
| Diet |
| - Identify caretakers who feed the child |
| - Identify foods high in calories and low in nutritional value that can be reduced, eliminated, or replaced |
| - Assess eating patterns (e.g., timing, content, and location of meals and snacks) |
| Activity |
| - Identify barriers to walking or riding a bike to school |
| - Evaluate time spent in play |
| - Evaluate school recess and physical education (frequency, duration, and intensity) |
| - Assess after-school and weekend activities |
| - Assess screen time (television, videotapes and DVDs, and video games) |
| History and review of systems (see Table 2) |

er enzymes, which usually indicate hepatic steatosis, occur in approximately 10 percent of overweight children and adolescents in the general population. As with all screening tests, clinicians should decide whether testing is likely to alter the course of treatment they prescribe. The American Diabetes Association recommends a fasting plasma glucose test for children 10 years of age or older who have a body-mass index at or above the 85th percentile and two of the following risk factors: a family history of type 2 diabetes in first-degree or second-degree relatives, nonwhite race, and conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemias, or polycystic ovary syndrome). It is uncertain how many children and adolescents meet these criteria, and the cost-effectiveness of this approach is unknown.

**COMMUNICATION**

Providers report that they are often reluctant to discuss overweight with families because of the associated stigma, the concern that parents will feel blamed, or fears that a discussion of weight will lead to an eating disorder. However, when providers address obesity in obese adults, those adults are more likely to initiate weight-control efforts than when weight is not discussed. In the absence of a complication that needs urgent attention, a neutral approach to weight control in a child may help to avoid a sense of blame or pressure and to assess the family’s readiness to change. For example, the level of parental concern can be elicited by such questions as “Are you concerned about your child’s weight?” and “Has your child’s weight caused her any problems?” Because “obesity” is often a pejorative term and is popularly used to indicate a massive degree of overweight, the term “overweight” is preferable when discussing weight with parents.

**TREATMENT**

Treatment to achieve weight maintenance is recommended for children two to six years of age who have a body-mass index at or above the 95th percentile for their age and sex and who do not have weight-related complications. Weight loss is indicated for two-to-six-year-old children who have a weight-related complication and for older children whose body-mass index is at or above the 95th percentile whether or not they have a weight-related complication. Overweight-related conditions requiring more urgent weight loss include pseudotumor cerebri, sleep apnea, orthopedic abnormalities, type 2 diabetes, and hypertension. Additional factors that increase the need for treatment include major psychological or social complications and an increased risk of a future obesity-associated illness as suggested by a family history of obesity, type 2 diabetes, or cardiovascular disease in a first-degree or second-degree relative.

Family engagement is critical to therapy. If the child, one or both parents, or the guardians are not motivated, any treatment is likely to fail and frustrate everyone involved. Under such circumstances, clinicians should share the basis for their concern about the child’s weight and reinforce positive behaviors that are already in place. Motivation should not be viewed as an all-or-nothing phenomenon but, rather, as a dynamic process that providers can influence over time. Parental concerns other than the child’s overweight also may help to address behaviors that contribute to it. For example, concern about schoolwork, family time, or exposure to televised sex and violence may be a more powerful motivator to control television time than is overweight.

**SPECIFIC INTERVENTIONS**

A systematic review of randomized, controlled trials of lifestyle interventions for the treatment of pediatric overweight concluded that most studies were too small and that the number of studies was insufficient to compare the efficacies of various treatment approaches or components. In the absence of such data, studies of treatments in research
settings and of adult obesity provide useful direction. In children, behavior modification has generally produced losses of 5 to 20 percent of excess weight, of 1 to 3 units of the body-mass index, or both, over 3 to 6 months; changes reported over 6 to 12 months range from a 25 percent loss to a 10 percent increase in excess weight, a loss of 0 to 4 units of the body-mass index, or both. Long-term follow-up, as reported by a single research group, has shown increases of about 3 percent to decreases of about 20 percent in excess weight after 2 to 10 years.

Table 2. Symptoms and Signs of Syndromes Associated with or Complications of Overweight in Children and Adolescents.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Syndrome or Complication</th>
<th>Additional Findings</th>
<th>Additional Studies or Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>Pseudotumor cerebri</td>
<td>Papilledema</td>
<td>Pediatric neurologist</td>
</tr>
<tr>
<td>Snoring</td>
<td>Obstructive sleep apnea</td>
<td>Hypertrophy of tonsils, adenoids, or both</td>
<td>Sleep study</td>
</tr>
<tr>
<td>Daytime somnolence</td>
<td>Pickwickian syndrome or sleep apnea</td>
<td></td>
<td>Blood gases, sleep study</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Gallbladder disease</td>
<td>Elevated serum aminotransferases</td>
<td>Abdominal ultrasonography</td>
</tr>
<tr>
<td>Hip pain or limp</td>
<td>Slipped capital femoral epiphysis</td>
<td></td>
<td>Radiologic examination of hips</td>
</tr>
<tr>
<td>Urinary frequency, nocturia,</td>
<td>Polyhydramnia, polyuria</td>
<td></td>
<td>Urinalysis, fasting blood glucose, glucose tolerance test</td>
</tr>
<tr>
<td>Polydipsia, polyuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular menses or amenorrhea</td>
<td>Polycystic ovary disease</td>
<td>Hirsutism, muscular body build, male-pattern distribution of body fat,</td>
<td>Pediatric endocrinologist or adolescent specialist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short stature, hypogonadism, small hands and feet, infantile hypotonia</td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Binge eating or purging</td>
<td>Eating disorder</td>
<td>Use of laxatives, cathartics, or diuretics</td>
<td>Specialist in eating disorders</td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short stature or growth arrest</td>
<td>Hypothyroidism, Cushing’s syndrome</td>
<td></td>
<td>Thyroid-function tests</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Prader–Willi syndrome, other genetic syndromes</td>
<td></td>
<td>Pediatric endocrinologist</td>
</tr>
<tr>
<td>Depressed affect, insomnia,</td>
<td>Depression</td>
<td></td>
<td>Pediatric psychologist or psychiatrist</td>
</tr>
<tr>
<td>Anhedonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Elevated blood pressure</td>
<td>Cuff size may be too small; consider Cushing’s syndrome</td>
<td>Specialist in pediatric hypertension</td>
</tr>
<tr>
<td>Postaxial polydactyly</td>
<td>Bardet–Biedl syndrome</td>
<td>Retinitis pigmentosa, hypogonadism, mental retardation</td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Small hands and feet</td>
<td>Prader–Willi syndrome</td>
<td></td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilledema</td>
<td>Pseudotumor cerebri</td>
<td></td>
<td>Pediatric neurologist</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>Bardet–Biedl syndrome</td>
<td></td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Erosion of tooth enamel or</td>
<td>Self-induced vomiting</td>
<td></td>
<td>Specialist in eating disorders</td>
</tr>
<tr>
<td>dorsal finger lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Severe obesity, possible glucose intolerance</td>
<td></td>
<td>Fasting insulin, urinalysis</td>
</tr>
<tr>
<td>Violaceous striae</td>
<td>Cushing’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Polycystic ovary disease</td>
<td></td>
<td>Pediatric endocrinologist</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Nonalcoholic fatty liver disease</td>
<td>Elevated serum aminotransferases</td>
<td>Pediatric gastroenterologist</td>
</tr>
<tr>
<td>Genitalia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undescended testicles</td>
<td>Prader–Willi syndrome</td>
<td></td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>Cushing’s syndrome</td>
<td></td>
<td>Pediatric endocrinologist</td>
</tr>
<tr>
<td></td>
<td>Prader–Willi syndrome in girls</td>
<td></td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td></td>
<td>Bardet–Biedl syndrome</td>
<td></td>
<td>Pediatric genetician</td>
</tr>
<tr>
<td>Bowed legs</td>
<td>Blount disease, bowed femurs</td>
<td>Bowed tibias</td>
<td>Radiologic examination; orthopedic surgeon</td>
</tr>
</tbody>
</table>

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Four main interrelated behavioral strategies are used to help families make changes: controlling the environment, monitoring behavior, setting goals, and rewarding successful changes in behavior. The targets for these strategies must be age-specific. For example, it is the parent’s responsibility to monitor the behaviors of young children, whereas adolescents may monitor their own behaviors. Key principles and examples of these weight-control strategies are summarized in Table 3.

**Diet and Activity**

Short-term weight loss in pediatric patients has been achieved in randomized, controlled trials involving various strategies for the control of diet and activity level. These strategies include calorie and fat reduction, adherence to a low-carbohydrate diet, the integration of physical activity into daily routines, participation in structured, vigorous physical activity, and the reduction of sedentary behaviors. If changes in diet and activity level produce a net energy deficit, weight loss will result. A substantial slowing of weight gain may be achieved by relatively small but consistent changes in energy intake, expenditure, or both (200 to 500 kcal per day).

Because consensus is lacking on the most effective ways to achieve long-term weight control, the clinician, child, and family should work together to choose goals that can be achieved in terms of diet and activity. The monitoring of increases or decreases in weight allows the clinician to assess whether the changes in diet and activity level are too limited, sufficient, or too aggressive and to adjust these changes accordingly. Other providers, such as dietitians or nurse practitioners, also can help assess, change, and monitor behaviors. Group treatment of parents and children may provide more cost-effective and efficient delivery of care.

Weight-control interventions in medical settings are unlikely to succeed over the long term without alterations in the environments in which children and adolescents live. For example, efforts to change food choices may not succeed without the availability of healthful choices in school lunches or vending machines or without access to supermarkets where fruits and vegetables can be purchased at reasonable prices. Efforts to increase physical activity may not succeed if neighborhoods are unsafe for outdoor play or if physical education is absent in schools.

**Weight Goals**

A challenge in the treatment of overweight children involves the maintenance of normal growth and development with concurrent reductions in weight and body fat. For most overweight children, the first goal of weight control is weight maintenance. If weight loss is desired, an appropriate starting goal is about 1 lb (450 g) of weight loss per month. The long-term weight goal should be a body-mass index that is below the 85th percentile for age and sex, because the severity of adult obesity appears to be related to the severity and persistence of childhood overweight. Satisfactory weight control can also be assessed according to improvements in coexisting illnesses such as hyperlipidemia, hyperinsulinemia, acanthosis nigricans, and hypertension.

**Complications of Treatment**

Systematic studies of the complications of various approaches to treatment are needed. In one 10-year follow-up of overweight children who were treated in behavioral modification programs to reduce calorie intake and increase physical activity, participants reported substantial rates of major psychiatric disorders, primarily depression, eating disorders, and substance abuse. These rates may reflect a high level of risk among patients seeking treatment rather than effects of the intervention. Population-based surveys of adolescents indicate that an elevated body-mass index is associated with a higher risk of disordered eating behaviors.

Addressing eating and activity behaviors may also exacerbate existing family conflicts, which in turn may require psychological therapy to accompany or precede treatment for weight control. Excessive weight loss reflects extreme calorie restriction. Growth retardation and nutritional insufficiency have been reported in children on highly restrictive diets that provide less than two thirds of the estimated energy needs, but such adverse events are extremely unlikely with respect to the approaches outlined here. Gallstones occur in 10 to 25 percent of adults who lose weight rapidly, but the frequency of this complication in pediatric patients is uncertain.

**Prevention**

The approaches described above also apply to the prevention of overweight in children of normal weight or in children at risk for overweight. School-based randomized trials have demonstrated that...
a reduction in television or total screen time and an increase in the frequency and intensity of activity during physical education classes are effective preventive measures. In the two studies that reported changes in the body-mass index, in children in the treatment group, the body-mass index increased at an annualized rate of about 0.8 to 1.3 units less than in the children in the control group.

Observational studies suggest that breast-feeding may be another preventive strategy. Both breast-feeding and later physical activity have been associated with reduced weight gain or the prevention of weight-related coexisting illnesses; both are generally safe and have other benefits that warrant their implementation. Other strategies that appear promising but have not been tested in randomized trials include the reduced consumption of sugar-sweetened beverages, reduced portion sizes at mealtimes, and increased consumption of fruits and vegetables.

### Areas of Uncertainty

Data from randomized trials to support any particular strategy over others to achieve weight control in children and adolescents or to prevent the development of overweight or to prevent the development of overweight and other chronic diseases, weight maintenance is likely to require ongoing drug therapy. As the authors of the sibutramine trial concluded, “Until more extensive safety and efficacy data are available, medications for weight loss should be used only on an experimental basis in adolescents and children.”

Hypocaloric diets containing less than 20 g of carbohydrate result in rapid weight loss and appear to block hunger. Their use in pediatric patients has been described but requires physician oversight and monitoring. There have been limited published reports of experience with bariatric surgery in the pediatric age group. Available recommendations suggest the limitation of its use to adolescents with a body-mass index of 40 or more who also have obesity-associated coexisting illnesses; the recommendations also specify criteria for referral and treatment.

### Guidelines

An expert committee that included representatives from the American Academy of Pediatrics, the American Dietetic Association, and the National Association of Pediatric Nurse Practitioners has issued consensus recommendations for the assessment and treatment of childhood and adolescent overweight. Consensus recommendations for the use of bariatric surgery in adolescents have also been published and endorsed by the American Pediatric Surgical Association. The recommendations of these organizations agree with those outlined here.

### Summary and Recommendations

Several strategies are useful in the management of overweight patients who are seen in primary care settings, such as the seven-year-old girl described in the vignette. The routine assessment of body-mass index will allow providers to identify modest excesses of weight when the behaviors that contribute to them are tractable. Communication strategies that avoid blame and encourage concern and an interest in change on the part of overweight patients and their families are critical to management.
<table>
<thead>
<tr>
<th>Strategy</th>
<th>General Principles</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control the environment</td>
<td>Identify existing home, school, and family routines or environmental factors associated with increased calorie consumption, inactivity, and sedentary behaviors. Help the child and family identify alternative routines or environmental factors to reduce calorie consumption, increase physical activity, and decrease sedentary behaviors. Help the child and family limit options to those most acceptable and easiest to implement; include these as part of monitoring, goal setting, and rewards for behavioral change.</td>
<td>Eliminate sugar-sweetened beverages from the home. Reduce the frequency of fast food, meals eaten away from home, or both. Limit serving sizes by serving food directly onto plates instead of self-service at table and use smaller plates to make servings appear larger. Remove high-fat and high-calorie snacks from the home and replace them with fresh fruits and vegetables. Remove television sets from children’s bedrooms, budget weekly screen time, and set family rules to limit what can be watched or played as well as when and where. Enroll child in an after-school program of physical activity. Start a new family routine involving daily or weekly physical activity.</td>
</tr>
<tr>
<td>Monitor behavior</td>
<td>Records should be kept to assess changes over time. Measures must reliably define baseline behaviors and assess changes over time. Monitoring should be frequent initially; may become less frequent as new behaviors are established. Monitoring should cover both short-term and long-term behavioral goals, including weight changes. If doubt arises about continued progress or if relapse occurs, reinstitute frequent monitoring.</td>
<td>Individual behavior. No. of sugar-sweetened beverages consumed daily. No. of meals eaten outside the home, no. of fast-food meals/wk, or both. No. of servings of fruits and vegetables eaten daily. No. of hours of television watched weekly. No. of days/wk physical-activity goals are met. Weekly weight measurement. Changes in the environment. No. of sugar-sweetened beverages in the home. Frequency of fast-food meals, meals eaten away from home, or both. No. of days/wk food is served on plates, small plates are used, or both. No. of days per week fruits and vegetables are present in the home. Presence or absence of television in child’s bedroom, established limits for screen time, and rules for family screen time.</td>
</tr>
<tr>
<td>Set goals</td>
<td>Help family set short-term goals for behavioral change and long-term goals for weight change. To enhance motivation, goals should be challenging but achievable. Goals should be agreed to by the patient, not set by the provider; allow the child and family to choose from a range of possible goals. Limit new goals to one or two at a time. Parent or guardian may set goals for his or her own behavior to help the child lose weight. Behavioral goals must be specific, explicit, unambiguous, and subject to self-monitoring (i.e., “If you can’t count it, you can’t change it!”).</td>
<td>Individual goals for the child. I will drink no more sugar-sweetened beverages. I will eat no more than 1 fast food meal/wk. I will eat fresh fruit and vegetables for my after-school snack. I will watch television, videos, or DVDs and play computer and video games for less than 7 hr/wk, and only after dinner and all my school work and chores are completed. Individual goals for the parent. I will praise my child every day that he or she achieves a goal. I will review behavior-monitoring records with my child for 30 min every evening. I will walk my child to school at least 3 days/wk. Family environmental goals. Our home will be free of sugar-sweetened beverages in 14 days. We will go out for dinner no more than 1 night/wk. All meals will be served in the kitchen, directly onto plates instead of self-served at the table. Fruits and vegetables will be available in our home every day. We will remove all televisions from children’s bedrooms. We will eat meals without watching television.</td>
</tr>
</tbody>
</table>
Table 3. (Continued.)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>General Principles</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reward successful</td>
<td>Both positive and negative responses (rewards and disapproval) should be tied to</td>
<td>Praise and attention</td>
</tr>
<tr>
<td>behavioral change</td>
<td>specific behaviors</td>
<td>Praise tied to a specific behavior is better than nonspecific praise: “I am proud of you</td>
</tr>
<tr>
<td></td>
<td>Rewards should be given as soon as possible after completion of the behavioral goal</td>
<td>for eating the carrots instead of chips for your snack” is better than “You are such a</td>
</tr>
<tr>
<td></td>
<td>Rewards should be frequent while the child is learning a new behavior, less frequent</td>
<td>good child”</td>
</tr>
<tr>
<td></td>
<td>as the behavior becomes established</td>
<td>Suggested rewards</td>
</tr>
<tr>
<td></td>
<td>Mixed messages should be avoided; rewards and disapproval should be used</td>
<td>Activities that the child and parents or guardians like to perform together (e.g., skating)</td>
</tr>
<tr>
<td></td>
<td>consistently; rewards should not be given if the goal was not achieved</td>
<td>Activities that are related to goals, such as an active, outdoor excursion, a trip to</td>
</tr>
<tr>
<td></td>
<td>Magnitude of the reward, its value, or both should be consistent with the</td>
<td>buy a favorite fruit or vegetable at a local farm, or athletic shoes or other sports-related</td>
</tr>
<tr>
<td></td>
<td>magnitude of the accomplishment; large or excessively valuable rewards can be</td>
<td>equipment for accomplishing a physical-activity goal</td>
</tr>
<tr>
<td></td>
<td>counterproductive</td>
<td>Extra privileges, such as special time with a parent</td>
</tr>
<tr>
<td></td>
<td>Frequent and specific use of praise and attention should be encouraged, because</td>
<td>Rewards to avoid</td>
</tr>
<tr>
<td></td>
<td>these can be powerful rewards for children</td>
<td>Food (especially sweets or other high-calorie foods that are being limited in the diet)</td>
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<td>Parents should use rewards that they are willing and able to give if the goal is</td>
<td>Money or items with a specified value (these often lead to expectations and negotiations for</td>
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<td>achieved and to withhold if the goal is not achieved</td>
<td>greater rewards over time)</td>
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<td>“Reciprocal contracting,” in which parents or guardians reward children for</td>
<td>Expensive material items</td>
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<td>achieving their goals and children reward parents or guardians for achieving</td>
<td>Items unrelated to the goals</td>
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<td>theirs, should be considered</td>
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<tr>
<td>Problem solving</td>
<td>Iterative cycles should be established to identify barriers to success, identify</td>
<td>Common barriers that require problem solving</td>
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<td>potential solutions to overcome the barriers, make plans to implement those</td>
<td>Resistance to change or sabotage by other family members</td>
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<td></td>
<td>potential solutions, and monitor their success</td>
<td>Expression of love by family members through cooking or food</td>
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<td></td>
<td>With assistance, children and families can identify the most challenging barriers</td>
<td>Eating out in restaurants or at others’ homes</td>
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<td></td>
<td>and invent their own strategies to overcome them</td>
<td>Parties and holidays involving food traditions (e.g., birthday parties, Halloween)</td>
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<td>Group sessions can provide an opportunity for families to share strategies,</td>
<td>School meals</td>
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<td>successes, and lessons learned with other families facing similar challenges</td>
<td>After-school hunger</td>
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<td>Parenting skills</td>
<td>Authoritative rather than authoritarian parenting</td>
<td>Use of eating to cope with stress and anxiety</td>
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<td>Support the child’s autonomy and self-sufficiency</td>
<td>Neighborhood safety concerns</td>
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<td>Modeling of desired behaviors</td>
<td>Transportation difficulties</td>
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<td></td>
<td>Clear communication of expectations and consequences</td>
<td>Perceived limited community resources and opportunities for physical activity</td>
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<td>Consistent and contingent feedback</td>
<td>Provider and child or family have different ideas about what is most important to change</td>
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<td>Use of praise, attention, and other rewards for effective reinforcement of desired</td>
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<td>behaviors; minimal attention to undesired behaviors</td>
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<td>Appropriate setting of limits</td>
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<td></td>
<td>Setting family rules and maintaining a household that is consistent with</td>
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<td></td>
<td>healthful behaviors</td>
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<td>Parents choose what is available to eat but children choose whether to eat and</td>
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<td></td>
<td>how much</td>
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<td>Saying no and setting limits are in the best interest of their child’s health and</td>
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<td>well-being</td>
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<td>Parents or guardians set their own goals and monitor their own behaviors</td>
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<td></td>
<td>Parents or guardians model both successful behavioral change and ways of coping</td>
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<td>with unsuccessful attempts to change behavior</td>
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<td>All parents or guardians and other caregivers communicate a consistent message to</td>
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<td>the child</td>
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<td>Rewards are provided only when earned</td>
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<td>Parents meet daily with the child to review the day’s behaviors, show interest in</td>
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<td>his or her progress, and provide a regular opportunity to praise success</td>
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Most causes and complications of overweight can be identified by medical history and physical examination. A fasting lipid profile is a reasonable test for all overweight children. The medical history (with attention to risk factors for diabetes or other complications), the physical examination (to rule out such conditions as acanthosis nigricans), and the likelihood that test results will affect the management of the case should guide further testing. Treatment should focus on habits of diet or activity that contribute to weight gain or impair weight loss and that can be modified; recommendations should be based on a sensitivity to competing family priorities, particularly in the absence of apparent complications of overweight. Relevant behaviors should be quantified to facilitate monitoring and change, and positive changes should be reinforced. In the case vignette, immediate targets for change suggested by the history include a reduction in the intake of soft drinks and in screen time and an increase in active play. Our initial goal for this patient would be to maintain her current weight for one year and to achieve a body-mass index that is below the 85th percentile for her age, assuming that she undergoes continued linear growth at the 90th percentile. We would recommend weekly to monthly face-to-face or telephone monitoring of behavior and weight goals by the primary care provider. In some settings, nurses, dietitians, or other health professionals may help accomplish frequent follow-up assessments.

We are indebted to Barbara Polhamus for her assistance.
38. Butte NF, Ellis KJ. Comment on “Obesity and the environment: where do we go from here?” Science 2003;301:598.
39. Butte NF, Ellis KJ. Comment on “Obesity and the environment: where do we go from here?” Science 2003;301:598.

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Asphyxia Due to an Inhaled Foreign Body

A three-year-old boy was playing with a small plastic ball while riding in the backseat of a motor vehicle driven by his father. The father heard a gasp, saw that the child was unconscious, and pulled to the side of the road. He suspected the child had aspirated the toy ball and tried to dislodge it by patting the child on the back. Emergency personnel intubated the child at the scene. No foreign body was visualized during the intubation. The child was dead on arrival at the emergency center. During the postmortem examination, a radiograph of the head and neck showed a spherical foreign body located in the oropharynx (arrowheads) and an endotracheal tube passing beneath the foreign body and positioned in the trachea (arrows). The oropharynx contained a toy soccer ball 2.5 cm in diameter (inset).

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A 67-year-old man was admitted to the hospital with a 12-year history of swelling of his left leg. He had emigrated to the United Kingdom from Jamaica at the age of 31 years. When the patient was 41 years old, a golf-ball–sized nodule was excised from the dorsum of his left foot, and he was told he had a fungal infection. At that time, he did not receive any further treatment. At the age of 55 years, the patient noticed that a nodule had developed on his left shin. He did not seek medical attention until the lesion had spread and become so extensive that he was unable to walk (Panels A and B). A skin biopsy revealed a suppurative and granulomatous infiltrate with clusters of brown fungal organisms (muriform cells), a finding diagnostic of chromoblastomycosis (inset). A rhinocladiella species was cultured from skin scrapings. The patient was treated for 24 months with itraconazole and terbinafine, which resulted in improved mobility and substantial drying of the lesions, but warty changes, hyperpigmentation, and lymphedema persisted.

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Case 15-2005: An 80-Year-Old Man with Shortness of Breath, Edema, and Proteinuria

Laura M. Dember, M.D., Jo-Anne O. Shepard, M.D., Francesca Nesta, M.D., and James R. Stone, M.D., Ph.D.

An 80-year-old man was admitted to the hospital because of shortness of breath, pleural effusions, and edema of the legs.

Atrial fibrillation had developed seven years earlier, with bradycardia and syncope, and a pacemaker had been placed. Angina developed two and a half years before admission and was treated with three-vessel coronary-artery bypass grafting. The patient had several episodes of congestive heart failure thereafter. Eleven months before admission, urinalysis revealed 3+ proteinuria, an increase from 1+ one year earlier. Nine months before admission, a subtotal colectomy was performed because of ischemic colitis with bleeding. Bilateral pleural effusions, pulmonary edema, and cardiomegaly were noted on chest radiography. Five months before admission, an increase in exertional fatigue and shortness of breath developed. A chest radiograph showed small pleural effusions, diffuse irregular opacities, cardiomegaly, and pulmonary venous hypertension. The patient received treatment with furosemide, and there was improvement in his symptoms and radiographic findings.

Four months before admission, an abdominal ultrasonographic examination showed cholelithiasis; the liver appeared normal. A stress test showed reduced exercise capacity with no evidence of ischemia. A cardiac ultrasonographic examination showed incomplete closure of the mitral valve that was consistent with papillary muscle displacement, and moderate mitral regurgitation. The left atrium was dilated, with evidence of elevated left atrial pressure. The aortic leaflets were tricuspid and thickened; there was mild aortic insufficiency without stenosis. The left ventricle cavity size was normal, with symmetric left ventricular hypertrophy, segmental left ventricular wall dysfunction, and an estimated ejection fraction of 44 percent. There was mild-to-moderate tricuspid insufficiency and trace pulmonary insufficiency. The right ventricular systolic pressure was estimated to be 43 mm Hg, and the wall showed mild hypokinesis. A right-sided pleural effusion was present.

Three months before admission, a 24-hour collection of urine revealed a moderate amount of lambda Bence Jones protein in a 50-fold concentrated urine specimen, with a large amount of albumin, moderate amounts of \( \alpha \)-globulin, \( \beta \)-globulin, and probably intact immunoglobulin present. Lambda Bence Jones protein was present in the se-
Two months before admission, transthoracic echocardiography showed moderate biventricular failure and mitral regurgitation. One and a half months before admission, an endoscopic retrograde cholangiopancreatographic examination revealed multiple stones in the cystic duct and gallbladder. Abdominal and pelvic computed tomographic scanning showed no discrete hepatic lesions, but there was diffuse, heterogeneously decreased attenuation in the liver; bilateral pleural effusions were larger than in previous studies. A 24-hour urine collection contained 4311 mg of protein. A fine-needle aspiration biopsy of an abdominal fat pad was performed; a Congo red stain for amyloid was negative. One month before admission, the patient was hospitalized elsewhere with shortness of breath and was found to have a pleural effusion, congestive heart failure, and possible pneumonia. His respiratory symptoms improved.

Two weeks before admission, the patient again had shortness of breath; a chest radiograph showed enlargement of the right-sided pleural effusion to the level of the right hilum, with a small left-sided pleural effusion, pulmonary venous hypertension, and diffuse irregular interstitial opacities. Urinalysis showed 3+ protein, 0 to 2 red cells, and 0 to 2 white cells per high-power field and was otherwise normal. Eight days later, an ultrasonographically guided right chest thoracentesis removed 1200 ml of transudative effusion. There was no sign of malignant tumor cells on cytologic examination. Another radiographic scan of the chest showed a persistent, moderately large right-sided pleural effusion, small left-sided pleural effusion, pulmonary venous hypertension, and diffuse irregular interstitial opacities. Urinalysis showed 3+ protein, 0 to 2 red cells, and 0 to 2 white cells per high-power field and was otherwise normal. Eight days later, an ultrasonographically guided right chest thoracentesis removed 1200 ml of transudative effusion. There was no sign of malignant tumor cells.

A chest tube was placed and thoracentesis performed. Analysis revealed a transudative fluid with no malignant tumor cells. A diagnostic procedure was performed.

**Differential Diagnosis**

**Dr. Laura M. Dember:** May we review the radiographs?

**Dr. Jo-Anne O. Shepard:** A chest radiograph that was obtained nine months before admission showed moderately large bilateral pleural effusions, bilateral perihilar pulmonary edema, and cardiomegaly — signs that are most consistent with congestive heart failure. Five months before admission, there was a decrease in the pleural effusions and interstitial edema, but persistent cardiomegaly. The chest radiograph obtained two weeks before admission showed persistent mild interstitial edema; however, there had been a marked increase in the size of the right-sided pleural effusion, filling the lower half of the right hemithorax (Fig. 1).

**Dr. Francesca Nesta:** The transthoracic echocardiogram obtained two months before admission reveals diffuse hypokinesis of the left ventricle with predominant involvement of the base and the middle segments of the posterior wall. The dimensions of the left ventricular chamber are normal. There is
increased thickness of both the interventricular septum and the posterior wall of the left ventricle, indicating symmetric hypertrophy (Fig. 2A and Video Clip 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The left atrium is enlarged, consistent with an increase in left atrial pressure.

The mitral valve is thickened and restricted in opening, but there is no stenosis. There is moderate mitral regurgitation, possibly resulting from both thickening of the mitral valve and hypokinesis of the inferior–posterior wall, which causes papillary muscle displacement, tethering of the mitral valve, and incomplete closure (Fig. 2B). A mild increase in right ventricular systolic pressure but no restrictive filling pattern is observed. Pulsed-wave Doppler evaluation of the mitral inflow (Fig. 2C) shows a restrictive filling pattern, with elevated left ventricular diastolic pressure.

**Dr. Dember:** A progressive systemic illness affecting the kidney, colon, heart, and liver developed during the year before admission in this elderly man with a history of atrial fibrillation and coronary artery disease. Congestive heart failure and recurrent large pleural effusions dominated the clinical picture. In addition, nephrotic-range proteinuria and a monoclonal gammapathy were present. There are several approaches to a differential diagnosis for this case. As a nephrologist, I will focus initially on the kidneys and then consider other affected organs. The renal disease is characterized by nephrotic-range proteinuria (urinary protein excretion, greater than 3000 mg per 24 hours) and what appears, from the serum creatinine concentration,
to be a reasonably well preserved glomerular filtration rate. A substantial portion of the urinary protein is albumin, which is important, given the finding of a monoclonal λ light chain in the urine. The triad of hypoalbuminemia, peripheral edema, and nephrotic-range proteinuria fulfill the criteria for the nephrotic syndrome. The proteinuria had probably been in the nephrotic or near-nephrotic range for the year before the current hospitalization, and may have been present in subnephrotic quantities for at least one year before that. The absence of a substantial number of red cells or any red-cell casts in the urine sediment suggests a pure nephrotic syndrome rather than a combined nephritic–nephrotic process.

CAUSES OF THE NEPHROTIC SYNDROME
There are several causes of the nephrotic syndrome in adults (Table 2). Many possible causes are limited to diseases of the kidney and are thus unlikely in this case. Also unlikely are systemic illnesses that are associated with glomerulonephritis or interstitial renal disease but not the nephrotic syndrome, such as vasculitis or sarcoidosis, respectively. Systemic lupus erythematosus (SLE) can produce ischemic colitis, as was present in this patient, as a result of either mesenteric thrombosis, secondary to the antiphospholipid-antibody syndrome, or mesenteric vasculitis. Constrictive pericarditis can occur in SLE, but there was no history of pericarditis in this case, and this condition would not explain the ventricular wall thickening. Other cardiac processes associated with SLE, such as Libman–Sachs endocarditis or myocarditis could produce congestive heart failure but not a restrictive cardiomyopathy, as was seen here. Finally, there were no hematologic or joint manifestations, and this patient’s age at onset would be unusual for SLE. Similarly, it is difficult to attribute the multisystem manifestations in this case to either cancers or infections that
are associated with the development of the nephrotic syndrome.

The constellation of findings is consistent with systemic amyloidosis (Table 3). Systemic amyloidosis is a group of diseases that have in common the extracellular deposition of insoluble fibrillar proteins with a characteristic β-pleated sheet configuration that allows them to bind to Congo red dye. The accumulation of amyloid fibrils in tissues results in progressive organ dysfunction.

**Systemic Amyloidosis**

The kidney is the most frequent site of amyloid fibril deposition in both immunoglobulin light chain (AL) amyloidosis and serum amyloid A (AA) amyloidosis, and this condition is typically manifested as the nephrotic syndrome, as we see in this patient. The proteinuria can be massive, and the accompanying edema can be resistant to diuretics, as in this case. The accumulation of amyloid fibrils in tissues results in progressive organ dysfunction.

**Organ Dysfunction in Systemic Amyloidosis**

The kidney is the most frequent site of amyloid fibril deposition in both immunoglobulin light chain (AL) amyloidosis and serum amyloid A (AA) amyloidosis, and this condition is typically manifested as the nephrotic syndrome, as we see in this patient. The proteinuria can be massive, and the accompanying edema can be resistant to diuretics, as in this case. The glomerular filtration rate may be normal, but progressive renal impairment typically follows unless new amyloid production can be reduced or eliminated. Renal insufficiency without marked proteinuria occurs less often, when amyloid deposition is restricted to the renal vasculature or tubulointerstitium but spares the glomeruli.

Amyloid deposition in the myocardium restricts the ventricles from dilating fully, so they cannot fill normally. The left ventricular wall is concentrically thickened, with normal or reduced cavity size. The ventricular ejection fraction may be normal or only somewhat decreased, despite substantial amyloid infiltration, but impaired ventricular filling limits cardiac output. 3 Atrial and ventricular arrhythmias and abnormalities in the conduction system are relatively frequent manifestations of cardiac amyloidosis, although I suspect that the atrial fibrillation in this patient was unrelated, since survival for seven years with untreated cardiac amyloidosis is unusual. Although this patient had a history of coronary artery disease, the development of progressive heart failure after coronary artery revascularization is difficult to attribute to previous ischemic injury, and there was no evidence of ischemia on stress testing. Moreover, the echocardiographic findings of left ventricular wall thickening in the absence of a history of hypertension, normal left ventricular cavity size, and elevated left atrial pressure suggest a restrictive rather than an ischemic process. The left ventricular ejection fraction of 44 percent probably indicates severe amyloid disease, but atrial fibrillation or single-chamber ventricular pacing may have contributed as well. Although it was not described in this patient, low voltage on the electrocardiogram is often present in amyloidosis and reflects the infiltrative basis for thickening of the ventricular wall.

Pleural effusions may result from amyloid heart disease, but they can also result from pleural amyloid deposition. In this patient, the refractory nature of the effusions — with a poor response to diuretics and rapid reaccumulation after thoracentesis — is suggestive of pleural involvement. The transudative nature of the effusions is also consistent with pleural amyloid disease, although exudative effusions are present in approximately one third of cases. The interstitial opacities revealed on chest radiography may reflect parenchymal lung involvement, but it is difficult to draw this conclusion when congestive heart failure is part of the picture.

At the time of this patient’s current hospitalization, he had hypotension with a systolic blood pressure of 80 mm Hg. The hypotension was probably due, at least in part, to the cardiac dysfunction, but autonomic dysfunction resulting from amyloidosis may have contributed as well. Other manifestations of autonomic neuropathy, such as orthostatic hypotension, early satiety, and either chronic diarrhea or constipation, were not present.

The patient underwent a partial colectomy for bleeding that was attributed to ischemic colitis. Gastrointestinal bleeding can result from amyloid
deposits in the bowel mucosa, and ischemic colitis can occur as a result of vascular amyloid deposition. It is possible that ischemic colitis developed in this patient as a result of the combination of underlying atherosclerotic disease and reduced perfusion because of the cardiac dysfunction, vascular amyloidosis, or both.

The marked elevation in the serum level of alkaline phosphatase with only a mild aminotransferase elevation is characteristic of hepatic amyloidosis, in which infiltration of the sinusoids, rather than direct hepatocyte injury, occurs. Hepatic congestion due to right-sided heart failure is another frequent cause of abnormal levels of liver enzymes in patients with cardiac amyloidosis, but it would be unlikely to produce the cholestatic pattern of liver enzyme abnormalities seen in this patient. The abnormalities of the liver enzymes are probably not related to the cholelithiasis, since neither stones in the common bile duct nor dilatation of the common bile duct was apparent, and the bilirubin level was normal.

**Types of Systemic Amyloidosis**

The amyloidoses are classified according to the amyloidogenic protein that forms the fibrillary deposits. In AL amyloidosis, the protein is an immunoglobulin light chain or light-chain fragment that is produced by a clone of plasma cells. The plasma-cell burden is usually low, with a specimen from the bone marrow biopsy typically containing 5 to 10 percent plasma cells. However, approximately 10 percent of patients with AL amyloidosis have frank multiple myeloma. AA amyloidosis occurs in association with long-standing inflammation. Serum amyloid A protein, an acute-phase reactant synthesized in the liver, is the amyloidogenic protein. In the familial amyloidoses, an amino acid substitution in a plasma protein renders it amyloidogenic. Transthyretin is the most common amyloidogenic protein in familial disease, but six other proteins (apolipoprotein A-I, apolipoprotein A-II, fibrinogen Aα-chain, lysozyme, gelsolin, and cystatin C) have been identified as underlying rare forms. In senile systemic amyloidosis, wild-type transthyretin forms amyloid deposits predominantly in the heart.

In this case, there was no chronic inflammatory condition to suggest AA amyloidosis. In addition, symptomatic cardiac involvement is unusual in AA amyloidosis. Although the patient had a family history of cardiac disease, the combination of organs involved makes most of the familial amyloidoses unlikely. The age at which the patient presented is typical for senile systemic amyloidosis, but the multiorgan nature of his disease is not consistent with that diagnosis. AL is the most likely type of amyloidosis in this case. The distribution of organ involvement is typical, and the monoclonal immunoglobulin protein in the serum and urine indicates the presence of a plasma-cell dyscrasia. An informative finding is the tongue enlargement noted at admission. MacroGLOSSIA occurs in approximately 20 percent of patients with AL amyloidosis but is not present in other types of amyloidosis. In fact, macroGLOSSIA has a very limited differential diagnosis, and its presence should trigger an evaluation for AL amyloidosis.

Does the negative result of the Congo red staining for amyloid in the subcutaneous abdominal fat rule out the diagnosis of systemic amyloidosis? Needle aspiration of abdominal fat is a simple and relatively noninvasive method of obtaining tissue for staining with Congo red, and the result is positive in approximately 80 percent of patients with AL amyloidosis but is not present in other types of amyloidosis. Thus, the negative result on staining of the abdominal-fat aspirate in this case does not necessarily eliminate amyloidosis as the diagnosis.

**Nonamyloid immunoglobulin deposition diseases**

Diseases other than AL amyloidosis that are characterized by immunoglobulin deposition may cause nephrotic-range proteinuria, but they are unlikely to be the cause of this patient’s illness. In light-
In AL amyloidosis, monoclonal immunoglobulin light chains or heavy chains form nonfibrillary deposits in the glomerular or tubular basement membranes, or both. Deposition of monoclonal immunoglobulin in the lung, heart, and liver can result in organ dysfunction. However, the pace of disease progression is usually slower than in AL amyloidosis, and macroglossia does not occur. In the fibrillary and immunotactoid glomerulopathies, nonamyloid fibrils derived from immunoglobulin molecules are deposited in the mesangium and glomerular capillary walls. Nephrotic-range proteinuria is common and is often accompanied by microscopic hematuria, hypertension, and a reduction in the glomerular filtration rate. However, extrarenal manifestations appear to be rare.

AL amyloidosis is the most likely diagnosis in this case. The diagnosis of amyloidosis requires demonstration of binding of Congo red dye to tissue deposits and birefringence when viewed with polarized-light microscopy. In this patient, there were multiple potential sources of tissue for making a diagnosis. The tissue obtained during the colectomy could be reexamined and stained for amyloid. A bone marrow biopsy could be performed to assess plasma-cell numbers and clonality and could yield the diagnosis of amyloidosis if Congo red-staining material were present in the vessels or in the interstitium. Alternatively, either a kidney biopsy or an endomyocardial biopsy could be performed.

Dr. David C. Judge (General Internal Medicine): My colleagues and I suspected that the patient had amyloidosis, for the reasons outlined by Dr. Dember, but had been unable to confirm the diagnosis. The acute clinical problem was the effusions that were reaccumulating rapidly and that we were trying to drain to keep him comfortable.

Dr. James L. Januzzi (Cardiology): The salient cardiovascular feature in this case was thickening of the myocardium. When an echocardiogram shows thickening of the ventricular myocardium in a patient without hypertension, an infiltrative process, such as amyloidosis, should be considered. We pursued this diagnosis, but the results of the fat-pad biopsy were negative, and the patient was reluctant to undergo a more invasive diagnostic procedure. When his condition began to decline rapidly, we needed to know whether there was any condition other than amyloidosis present that might be amenable to treatment; thus, the decision was made to perform an endomyocardial biopsy. We performed a right heart catheterization, which confirmed the presence of low filling pressures, and performed an endomyocardial biopsy of the right ventricle.

Clinical Diagnosis

Amyloidosis, AL type.

Dr. Laura M. Dember’s Diagnosis

AL amyloidosis involving the kidney, heart, liver, pleura, and possibly lungs, colon, and the autonomic nervous system.

Pathological Discussion

Dr. James R. Stone: Histologic examination of the endomyocardial-biopsy specimen revealed deposits of amorphous extracellular material in a vascular and endocardial distribution. After staining with Congo red, the deposits were pink–orange when viewed with standard light microscopy; when viewed under plane-polarized light, they had classic apple-green birefringence, which is diagnostic of amyloid (Fig. 3A, 3B, and 3C).

The presence of amyloid in tissue is not always readily apparent, and pathologists frequently do not recognize it on examination of sections routinely stained with hematoxylin and eosin. Examination of slides from the resected colon revealed the presence of amyloid in the walls of blood vessels in the submucosa and serosa (Fig. 1 of the Supplementary Appendix).

Although potentially any protein could adopt the extended β-sheet structure and contribute to amyloid formation, specific proteins are prone to this phenomenon. In particular, λ light chains are two to three times more likely to form amyloid than are κ light chains. On histologic examination, amyloid deposits in AL amyloidosis may be present in either a vascular or an interstitial distribution.

Since new treatment strategies are based on the elimination of the specific amyloidogenic protein, it is becoming increasingly important to establish the type of amyloid present in the deposits. For AL amyloidosis, this has traditionally been accomplished indirectly, by demonstration...
of a monoclonal gammopathy. However, monoclonal gammopathies are not uncommon in the elderly, and most do not result in amyloid deposition; there have been reports of the misdiagnosis of AL amyloidosis in elderly patients with monoclonal gammopathy who in fact have a hereditary amyloidosis.\(^{19-21}\) There are ongoing efforts to use immunologic methods to determine the specific protein present in a given amyloid deposit,\(^ {17,22,23}\) but these methods have both high false positive and high false negative rates.\(^ {20-23}\) In this case, immunohistochemical staining for immunoglobulin light chains yielded only nonspecific staining.

Genetic analysis can be used to assess for the hereditary amyloidoses. However, there are more than 20 proteins that can form amyloid, and for many of them, multiple amyloid-inducing mutations have been discovered.\(^ {24}\) Biochemical techniques, primarily liquid chromatography and mass spectrometry, have been applied to identify amyloidogenic proteins.\(^ {21}\) Although still experimental, these new techniques may become the gold standard for the subclassification of amyloid deposits.

This patient had systemic amyloidosis, with a predominantly vascular distribution, which in the setting of a monoclonal gammopathy, is best classified as AL amyloidosis.

**Dr. Judge:** The patient was discharged on the 10th hospital day. Treatment with melphalan and prednisone was initiated on an outpatient basis, but his symptoms did not improve; he died at home of cardiac arrest approximately two months later.

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**ANATOMICAL DIAGNOSIS**

Systemic amyloidosis involving the heart and colon, in the setting of a monoclonal gammopathy; probably AL amyloidosis.

Dr. Dember reports having received consulting fees and grant support from Neurochem.

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**REFERENCES**


6. Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA. Primary (AL)


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SLIDE SETS FOR THE CASE RECORDS AVAILABLE IN DIGITAL FORMAT

Any reader of the Journal who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is eligible to receive digital images, with identifying legends, of pertinent radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs. The images on the CD for each case are in both PowerPoint and 300 dpi jpg format. For some cases, additional images that have not been selected for publication will be included on the CD. These images, which illustrate the current cases in the Journal, are mailed from the Department of Pathology to correspond to the week of publication and may be retained by the subscriber. Each year approximately 250 images from 40 cases are sent to each subscriber. The cost of the subscription is $450 per year. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or Pathphotoslides@partners.org.

Images from individual cases may be obtained at a cost of $35 per case.
The war in Iraq has resulted in an unprecedented number of traumatic brain injuries to U.S. soldiers. As described by Okie in this issue of the Journal, these soldiers have been saved from what in the past might have been a lethal injury by a combination of new protective battlefield equipment and extraordinary resourcefulness on the part of medical first responders and military surgeons. These medical personnel have saved many lives.

Their success breeds another problem, however: how to provide the best long-term care for the survivors of these injuries. Once the bleeding has been stopped and the brain swelling has subsided, the long road to recovery begins. The military and the Veterans Health Administration (VHA) have done their best to use existing knowledge to provide wounded soldiers with the care they need to overcome their injuries. But we owe more to the wounded men and women who have sacrificed on our behalf; as a nation, we should be using all available means to aid them.

Biomedical science has made amazing advances in the development of biohybrid devices and neural prostheses such as artificial retinas. But there is much more to do, and more research is necessary if these nascent developments are to be transformed into therapies that can truly assist seriously injured military personnel. The effort will cost money and require research talent. Congress needs to allocate more resources for research specifically targeted at these problems. Given the traditional role of the VHA in caring for injured veterans, it makes sense to allocate substantial new resources to this agency’s seriously underfunded research program specifically for this purpose.

The advances that have been made have come about because researchers have been able to use the best tools of modern biologic science, including nanotechnology and robotics, to achieve their goals. Sadly, one tool that holds great promise — embryonic stem-cell research — cannot be used in federally funded research. It is ironic that the same government that asked military personnel to make sacrifices and that has developed highly sophisticated methods of combat rescue has limited the research tools that may lead to better ways to repair their injuries.

A report issued by the National Research Council and the Institute of Medicine of the National Academies in late April (available at http://www.nap.edu/books/0309096537/html/) recognizes that stem-cell research is proceeding in many places but that there is no uniform regulatory framework for the endeavor. The report proposes uniform guidelines for this work, but we should go beyond the existing patchwork of research support in the United States; this research needs to be funded and encouraged at the federal level. We need national standards, but most important, the work must go forward. Embryonic stem cells are an appropriate resource for work on the regeneration of organs and nerves. We should give our researchers the fiscal and research resources they need to potentially help wounded veterans return to full function. These men and women have given their best efforts for their country; we owe them nothing less.

Dr. Drazen serves on the Veterans Affairs National Research Advisory Council.


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Chronic Kidney Disease in the Elderly — How to Assess Risk
Lesley A. Stevens, M.D., and Andrew S. Levey, M.D.

Chronic kidney disease is an important problem in the elderly and is associated with a high risk of kidney failure, cardiovascular disease, and death.1,2 The disorder is indicated either by a glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m² of body-surface area or by the presence of kidney damage, assessed most commonly by the finding of albuminuria for three or more consecutive months.3 The severity of chronic kidney disease can be classified according to the level of the GFR, regardless of the cause, as follows: stage 1, kidney damage with a normal or increased GFR; stage 2, kidney damage with a mild decrease in GFR; stage 3, a moderate decrease in GFR; stage 4, a severe decrease in GFR; and stage 5, kidney failure (i.e., a GFR of less than 15 ml per minute per 1.73 m²). The severity of chronic kidney disease is an independent risk factor for cardiovascular disease, even at low levels of albuminuria (30 to 300 mg of albumin per day, the equivalent of microalbuminuria) or a moderate reduction in the estimated GFR (to 30 to 59 ml per minute per 1.73 m², or the equivalent of stage 3 disease).4 Among persons 60 to 69 years of age, approximately 18 percent have albuminuria and 7 percent have an estimated GFR of less than 60 ml per minute per 1.73 m². In persons 70 years of age or older, those percentages increase to 30 and 26, respectively.3

GFR cannot be measured directly and is usually estimated from the serum creatinine concentration or with creatinine-based estimating equations,5 each of which has several limitations. Cystatin C has been proposed as a serum measure that may be superior to creatinine as an index of GFR. In a study reported in this issue of the Journal, Shlipak and colleagues examined the association of measures of kidney function with mortality and cardiovascular disease during 10 years of follow-up among 4637 elderly patients in the Cardiovascular Health Study, a population-based prospective cohort study.6 Neither urinary albumin excretion nor GFR was measured, but levels of serum cystatin C and creatinine were determined. Serum cystatin C was a better predictor of mortality and cardiovascular disease than was either serum creatinine alone or the GFR estimated from serum creatinine. Higher levels of cystatin C were associated with a graded increase in the risk of all outcomes that were examined. A significant increase in the risk of death was observed with values of cystatin C that were as low as 1.0 to 1.1 mg per liter (i.e., the middle quintile), corresponding in this study to a mean (±SD) serum creatinine level of 0.97±0.17 mg per deciliter and an estimated GFR of 72±12 ml per minute per 1.73 m². In contrast, risks were significantly increased only for the highest levels of serum creatinine (i.e., ≥21.26 mg per deciliter for men and ≥20.96 mg per deciliter for women) and for the lowest levels of estimated GFR (i.e., ≤<36 ml per minute per 1.73 m²). One explanation for these findings is that cystatin C is a better marker of filtration than is creatinine. Another explanation is that factors other than GFR that affect serum levels of creatinine and cystatin C differentially confound the relationships between these measures and outcome. We suspect that both explanations are correct.

It is well recognized that serum creatinine alone is unsatisfactory for estimating the level of GFR.7 Physiological processes other than GFR also determine the serum creatinine level (Table 1) — in particular, the generation of creatinine from muscle metabolism. Since muscle mass declines with age, serum creatinine levels may not rise appreciably in elderly persons, even with a reduction in GFR to less than 60 ml per minute per 1.73 m². Equations for estimating the GFR improve on the accuracy of the levels of serum creatinine alone by incorporating demographic and clinical variables as surrogates for physiological determinants of serum creatinine.

In the equation used in the Modification of Diet in Renal Disease (MDRD) Study, the factors of age, sex, and race are surrogates for muscle mass.8 Many chronic illnesses, including cardiovascular disease, affect muscle mass, through malnutrition, inflammation, and deconditioning. Thus, people with chronic illness are more likely to have lower levels of serum creatinine than are healthy people, even for the same level of GFR and the same age, sex, and race. In such persons, estimating equations based on serum creatinine may overestimate GFR. In a cohort study, this relationship between chronic illness and serum creatinine would confound the relationship between creatinine-based estimates of GFR and mortality. This probably accounts for the ob-

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servation in the study by Shlipak et al. of a “J-shaped curve" describing an increased risk of outcomes among participants with the highest levels of estimated GFR and lowest levels of serum creatinine. It would also account for the observation that within defined ranges of cystatin C, a higher serum creatinine level was associated with a lower death rate.

Cystatin C is a nonglycosylated 13,000-dalton basic protein that is filtered by the glomeruli and reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine (Table 1).9 It has not been thoroughly evaluated as a filtration marker. The absence of urinary excretion makes it difficult to study variation in the urinary clearance and generation of cystatin. The generation of cystatin C appears to be less variable across populations and over time than does creatinine. Serum levels of cystatin C may also be affected by extrarenal elimination. Most but not all studies show that serum cystatin C is a better index of GFR than is serum creatinine alone.10 However, as compared with creatinine-based GFR estimates, there may not be an advantage to using cystatin C.10

The relationship between cystatin C and outcomes may also be confounded by factors that affect the serum level of cystatin and that are independent of GFR, including older age, male sex, smoking, higher weight, and higher levels of C-reactive protein.11 Unlike chronic illness, which weakens the relationship between serum creatinine and outcome, these variables strengthen the apparent relationship between serum cystatin C and outcome.

Another important issue to consider in using serum markers to assess GFR is the standardization of assays across clinical laboratories. Serum creatinine assays vary according to positive interference by serum proteins, which is relatively greater at lower levels of serum creatinine. It is well recognized that failure to calibrate the creatinine assay to the laboratory that developed the estimating equation can introduce a systematic error in estimated GFR, particularly at a high GFR.12 Shlipak and colleagues used the equation in the MDRD Study but did not calibrate their assay to the MDRD Study laboratory. Calibration probably would have raised the GFR estimates reported in their study,13 although it would not

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Table 1. Comparison of Creatinine and Cystatin C as Filtration Markers.9

<table>
<thead>
<tr>
<th>Variable</th>
<th>Creatinine</th>
<th>Cystatin C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular properties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>113 daltons</td>
<td>13,000 daltons</td>
</tr>
<tr>
<td>Structure</td>
<td>Amino acid derivative</td>
<td>Nonglycosylated basic protein</td>
</tr>
<tr>
<td><strong>Physiological determinants of serum level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handling by the kidney</td>
<td>Filtered, secreted, and excreted in the urine</td>
<td>Filtered, reabsorbed, and catabolized; not well studied</td>
</tr>
<tr>
<td>Generation</td>
<td>Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and whites</td>
<td>Thought to be constant by all nucleated cells; variation in cystatin levels, independent of GFR, may be due to generation</td>
</tr>
<tr>
<td>Extrarenal elimination</td>
<td>Yes; increases at reduced GFR</td>
<td>Preliminary evidence of increases at reduced GFR</td>
</tr>
<tr>
<td><strong>Use in estimating equations for GFR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic and clinical variables as surrogates for physiological determinants</td>
<td>Age, sex, and race related to muscle mass</td>
<td>Unknown</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Accurate for GFR &lt;60 ml/min/1.73 m²</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>Colorimetric or enzymatic</td>
<td>PENIA</td>
</tr>
<tr>
<td>Assay precision</td>
<td>Very good except at low range</td>
<td>Precise throughout range</td>
</tr>
<tr>
<td>Clinical laboratory practice</td>
<td>Multiple assays; widely used non-standard calibration</td>
<td>Single dominant method; not on most auto-analyzers; not standardized</td>
</tr>
<tr>
<td>Reference standard</td>
<td>IDMS at NIST</td>
<td>None at present</td>
</tr>
</tbody>
</table>

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GFR denotes glomerular filtration rate, PENIA particle-enhanced nephelometric immunoassay, IDMS isotope-dilution gas chromatography–mass spectroscopy, and NIST National Institute of Standards and Technology.
The cystatin C assay is more precise than are assays for serum creatinine, especially in the low range. However, cystatin C has not been standardized across clinical laboratories.

The study by Shlipak et al. suggests that the increased risk of cardiovascular disease among elderly patients with chronic kidney disease may be stronger and occur at higher levels of GFR than previously suspected. It also reinforces the need for an improved understanding of the relationship between cardiovascular disease and chronic kidney disease. Future research that focuses on developing more accurate estimating equations for GFR — on the basis of serum levels of creatinine, cystatin C, or both — would be important. Cohort studies that measure both urinary albumin excretion and estimated GFR and assess their combined association with the risk of various outcomes are needed. Predictive models for cardiovascular disease in patients with chronic kidney disease should be developed, analogous to the Framingham risk score in the general population, to guide clinical decision making and public policy.

What can be done right now to assess the risk among elderly patients? Clinicians should measure albuminuria and estimate GFR from serum creatinine to detect chronic kidney disease. Patients who are found to have chronic kidney disease should undergo appropriate evaluation and treatment according to the cause and stage of their disease. Moreover, patients with chronic kidney disease should be considered to be in the highest risk group for cardiovascular disease and should receive intensive risk-reduction therapy.

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Krabbe’s disease, or globoid-cell leukodystrophy, is an inborn error of lipid metabolism first described in 1916 in two children with spasticity who died in infancy and were found to have “diffuse sclerosis” of the brain. Prominent features of the brain in affected children were decreased white-matter mass with relatively normal gray matter, generalized demyelination, and clusters of globoid cells in the white matter. Subsequent histopathological analyses have demonstrated that the changes in the white matter are due to the death of the myelin-forming oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system, whereas the characteristic globoid cells are reactive.

We are indebted to Josef Coresh, M.D., and to Tom Greene, Ph.D., for contributing greatly to the ideas described here.

From Tufts–New England Medical Center, Boston.


Early Use of Drastic Therapy
Kenneth I. Weinberg, M.D.

Krabbe’s disease, or globoid-cell leukodystrophy, is an inborn error of lipid metabolism first described in 1916 in two children with spasticity who died in infancy and were found to have “diffuse sclerosis” of the brain. Prominent features of the brain in affected children were decreased white-matter mass with relatively normal gray matter, generalized demyelination, and clusters of globoid cells in the white matter. Subsequent histopathological analyses have demonstrated that the changes in the white matter are due to the death of the myelin-forming oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system, whereas the characteristic globoid cells are reactive.
mononuclear phagocytes. The globoid cells found in the brains of children with Krabbe’s disease contain abnormally high levels of galactocerebroside (also known as galactosylceramide). The primary genetic defect is loss-of-function mutations in the gene encoding the lysosomal enzyme galactocerebrosidase (galactosylceramide β-galactosidase), which catalyzes the cleavage of galactocerebroside to galactose and ceramide.

For some lysosomal storage diseases, replacement of the deficient enzyme (e.g., enzyme replacement with recombinant glucocerebrosidase in patients with Gaucher’s disease) may correct the biochemical abnormality and improve clinical status. However, the success of enzyme replacement for metabolic diseases depends on the stability and tissue distribution of the enzyme in vivo and the ability of the enzyme either to enter cells or to metabolize extracellular substrate. At present, enzyme replacement therapy for Krabbe’s disease is not available.

Another potential approach to the treatment of storage diseases is hematopoietic stem-cell transplantation. The scientific premise for such studies is that any genetic disease of lymphohematopoiesis (including primary lymphocyte defects, such as severe combined immunodeficiency and the Wiskott–Aldrich syndrome, and hemoglobinopathies, such as β-thalassemia) can be cured by the replacement of host hematopoietic stem cells that contain deleterious mutations with hematopoietic stem cells from a healthy donor. Treatment generally involves the administration of busulfan to ablate the defective hematopoietic stem cells, thereby creating a selective advantage for the donor-derived hematopoietic stem cells, and the administration of cyclophosphamide and antithymocyte globulin to eliminate the lymphocytes that might mediate immunologic rejection of the allogeneic stem cells. For metabolic diseases, the ultimate goal is to permit the continued production of normal mononuclear phagocytes. Diseases of tissue macrophages that can be treated in this way include lysosomal storage diseases such as Gaucher’s disease and infantile osteopetrosis, a disease of osteoclasts.

For diseases of the central nervous system, hematopoietic stem-cell transplantation can result in the continuous production of normal microglia, which have been shown to be derived from hematopoietic stem cells. Microglia of donor origin may be capable of producing normal amounts of a missing enzyme, thus detoxifying the brain by metabolizing the deleterious substrate. However, a difficulty with the application of hematopoietic stem-cell transplantation to metabolic diseases is the low rate of turnover of macrophages. Normal macrophages may not replace the patient’s abnormal cells for three to six months after transplantation, during which time irreversible damage may occur.

In this issue of the Journal, Escolar et al. describe outcomes of hematopoietic stem-cell transplantation in infants with Krabbe’s disease. Previous studies in murine models and in patients with late-onset Krabbe’s disease had suggested some improvement in the course of the disease after hematopoietic stem-cell transplantation. The study by Escolar et al. involved transplantation with cord-blood cells from unrelated donors. Because these cells are banked as cryopreserved units, transplantation can be performed much more expeditiously than transplantation involving the collection of allogeneic peripheral or bone marrow stem cells from unrelated adult donors.

The babies in the study received busulfan, cyclophosphamide, and antithymocyte globulin. Eleven patients were asymptomatic newborns in whom Krabbe’s disease had been diagnosed either in utero or immediately after birth because of a positive family history. Fourteen patients were older infants in whom the diagnosis had been made after manifestations of Krabbe’s disease had developed. At 4 to 66 months of follow-up, there was 100 percent survival and donor hematopoietic stem-cell engraftment in the asymptomatic group but only 43 percent survival in the symptomatic group. Similarly, survival after hematopoietic stem-cell transplantation for other genetic diseases (such as severe combined immunodeficiency, the Wiskott–Aldrich syndrome, or thalassemia) is decreased by older age, end-organ dysfunction, or decreased performance scores.

In addition to their improved survival, the infants who were asymptomatic at the time of transplantation had ongoing cognitive development after transplantation, whereas the symptomatic patients continued to have rapid disease progression despite donor stem-cell engraftment. Motor abnormalities continue to appear in the initially asymptomatic group but have not been as severe as in untreated patients. The difference in outcome between the two groups indicates that there is a critical time window for the correction of Krabbe’s disease.

The window of opportunity for therapy is consistent with a novel explanation of the pathophysiology of Krabbe’s disease, which has been called the “psychosine hypothesis.” This hypothesis...
holds that the massive dropout of oligodendrocytes and the relative paucity of gangliocerebroside storage material in Krabbe’s disease could be explained by the toxic effects of galactosylsphingosine, or psychosine, a less abundant substrate for galactosylceramidase. Unlike other sphingolipids, psychosine is capable of inducing apoptosis, resulting in irreversible damage to oligodendrocytes in patients who undergo transplantation at an older age. The psychosine hypothesis also may explain the observed motor defects after early transplantation. The long nerve tracts needed for motor function may be more sensitive to a small degree of destruction of myelin than is the central nervous system white matter needed for continued cognitive development. Alternatively, there may be fewer donor-derived cells in motor tracts that are capable of metabolizing psychosine; for example, donor-derived endoneurial macrophages in the peripheral nervous system may be less common than the microglia in the central nervous system.

A possible strategy to overcome the problem of delayed production of donor-derived microglia might be to combine hematopoietic stem-cell transplantation with biochemical therapies, which would permit preservation of myelin-forming cells while donor microglia are still being formed. In this regard, L-cycloserine, which inhibits the production of psychosine, was reported to slow the progression of disease in a “twritcher” mouse model of late-onset Krabbe’s disease. Data are needed to determine whether such strategies might further improve outcomes of transplantation in infants with early-onset Krabbe’s disease.

The article by Escolar et al. also raises broader questions about how we may best confront serious pediatric diseases. Hematopoietic stem-cell transplantation is still considered by most practitioners to be a high-risk therapy of last resort. The tendency has been to test risky therapies first in adults or older children who can make informed decisions about participating and in patients who are already ill from their disease, for whom the risks of therapy seem less extreme. For example, hematopoietic stem-cell transplantation for Krabbe’s disease was previously performed in symptomatic older children with late-onset disease. If the study of Escolar et al. had been restricted to the symptomatic infants, the investigators would have concluded that hematopoietic stem-cell transplantation was ineffective.

The study by Escolar et al. makes it clear that in some circumstances, the subjects who derive the greatest benefit may be those who would otherwise be considered less than ideal research candidates, such as asymptomatic newborns. As we design more studies to assess risky but potentially curative treatments such as hematopoietic stem-cell transplantation, gene therapy, and embryonic stem-cell therapies for fatal, otherwise untreatable genetic diseases, a major challenge to investigators and regulatory and review agencies will be to maximize safety but also recognize the importance of including the very young, even those who are presymptomatic.
Torture is a particularly horrible crime, and any participation of physicians in torture has always been difficult to comprehend. As General Telford Taylor explained to the American judges at the trial of the Nazi doctors in Nuremberg, Germany (called the “Doctors’ Trial”), “To kill, to maim, and to torture is criminal under all modern systems of law . . . yet these (physician) defendants, all of whom were fully able to comprehend the nature of their acts . . . are responsible for wholesale murder and unspeakably cruel tortures.”

Taylor told the judges that it was the obligation of the United States “to all peoples of the world to show why and how these things happened,” with the goal of trying to prevent a repetition in the future. The Nazi doctors defended themselves primarily by arguing that they were engaged in necessary wartime medical research and were following the orders of their superiors. These defenses were rejected because they are at odds with the Nuremberg Principles, articulated a year earlier, at the conclusion of the multinational war crimes trial in 1946, that there are crimes against humanity (such as torture), that individuals can be held to be criminally responsible for committing them, and that obeying orders is no defense.

Almost 60 years later, the question of torture during wartime, and the role of physicians in torture, is again a source of consternation and controversy. Steven Miles, for example, relying primarily on government documents, has noted that at the prisons at Abu Ghraib, Iraq, and Guantanamo Bay, Cuba, “at the operational level, medical personnel evaluated detainees for interrogation, and monitored coercive interrogation, allowed interrogator to use medical records to develop interrogations approaches, falsified medical records and death certificates, and failed to provide basic health care.”

The Red Cross, on the basis of an inspection of Guantanamo in June 2004, alleged that the physical and mental coercion of prisoners there is “tantamount to torture” and specifically labeled the active role of physicians in interrogations as “a flagrant violation of medical ethics.”

Bloche and Marks have reported, on the basis of their interviews with some of the physicians involved in interrogations at Guantanamo Bay and in Iraq, that the physicians believed “that physicians serving in these roles do not act as physicians and are therefore not bound by patient-oriented ethics.” Psychiatrist Robert Jay Lifton has suggested that the reports of U.S. physicians’ involvement in torture from Iraq, Afghanistan, and Guantanamo echo those of the Nazi doctors who were “the most extreme example of doctors becoming socialized to atrocity.”

Nonetheless, the muting of the criticism of such torture prompted Elie Wiesel to ask why the “shameful torture to which Muslim prisoners were subjected by American soldiers [has not] been condemned by legal professionals and military doctors alike.”

The United States has grown accustomed to setting the standard for the world in condemning torture as always criminal and always an inexcusable violation of human rights. It was therefore disturbing to watch the new U.S. attorney general, Alberto Gonzales, try to defend the administration’s policies on torture in the wake of the attacks on September 11, 2001, at a Senate panel hearing on his nomination this past January. The first question Gonzales was asked by Chairman Arlen Specter (R-Pa.) was, “Do you approve of torture?” Gonzales replied, “Absolutely not, Senator.”

Two weeks later, the new secretary of state, Condoleezza Rice, pointedly refused to characterize forced nudity and simulated drowning as techniques of torture, insisting instead that “the determination of whether interrogation techniques are consistent with international obligations and American law [is] made by the Justice Department.” Until September 11, the United States had always and unequivocally condemned torture and those who engage in it, but since U.S. law on torture appears to be obscure to our highest officials charged with enforcing it, it is well worth reviewing.
TORTURE

In 1994, the United States ratified the international Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment and followed that by enacting specific laws against torture. Even before this, Congress had passed the Torture Victim Protection Act of 1991. As the Supreme Court stated in 2004, this act provides “authority that ‘establishes an unambiguous and modern basis for’ federal claims of torture and extrajudicial killing.”10 The act provides that any person (including a noncitizen) can bring a civil action in U.S. courts against any other person who “under actual or apparent authority, or color of law, of any foreign nation” subjects a person to torture or extrajudicial killing. “Torture” is defined there, as in the Convention against Torture, as

any act, directed against an individual in the offender’s custody or physical control, by which severe pain or suffering . . . whether physical or mental, is intentionally inflicted on that individual for such purposes as obtaining from that individual or a third person information or a confession, punishing that individual for an act that individual or third person has committed or is suspected of having committed, intimidating or coercing that individual or a third person or for any reason based on discrimination of any kind.11

Government-sanctioned torture is prohibited in the United States by the 5th Amendment to the Constitution (which has a prohibition against self-incrimination that was adopted specifically to prohibit the use of torture to extract confessions), the 8th Amendment (which prohibits “cruel and unusual punishment”), and the 14th Amendment. Torture is also a crime under state criminal statutes prohibiting assault and battery. An additional federal statute, which also follows the Convention against Torture, makes it a crime for any person “outside the United States” to commit or to attempt to commit torture, which is defined for this purpose as “an act committed by a person acting under the color of law specifically intended to inflict severe physical or mental pain or suffering . . . upon another person within his custody or physical control.”12

This antitorture statute has recently been the subject of conflicting interpretations from the Department of Justice. After September 11, Justice Department lawyers argued (wrongly) that the president, as commander in chief, has the authority to order the torture of prisoners and that, contrary to the Nuremberg Principles, obeying such an order is a valid defense against a charge of a war crime or a crime against humanity.13 The August 1, 2002, memorandum from the Justice Department to Alberto Gonzales, then legal counsel to the president, also concluded that to constitute torture under the statute, the pain inflicted “must be equivalent in intensity to the pain accompanying serious physical injury, such as organ failure, impairment of bodily function, or even death.”13 This memorandum, in which Justice Department lawyers acted more like private attorneys advising their clients (in this case, government officials) on how they might avoid prosecution under the antitorture statute (rather than advising them to follow the law), has been widely and rightly criticized. The Department of Justice withdrew the memorandum shortly after it became public in June 2004.14

One week before the hearing on the nomination of Alberto Gonzales to the post of attorney general, on December 30, 2004, the Justice Department issued a replacement memorandum that set forth its new interpretation of the antitorture law, which is much more consistent with the language of the law and U.S. policy. This memorandum begins by expressing the overriding theme of U.S. law on torture: “Torture is abhorrent both to American law and values and to international norms. This universal repudiation of torture is reflected in our criminal law . . . international agreements . . . customary international law, centuries of Anglo-American law, and the longstanding policy of the United States, repeatedly and recently affirmed by the President.”14 This is all to the good. Unfortunately, the memorandum also raises important issues of hypocrisy and secrecy, stating, in footnote eight, that prior opinions — still secret — approving various interrogation techniques “for [use with] detainees” are not affected by the replacement memorandum. One such opinion, prepared for the Central Intelligence Agency, is reported to authorize the use of 20 interrogation techniques, including “waterboarding,” in which a person is made to believe he or she will drown.15

President Bush said on June 30, 2003, that “torture anywhere is an affront to human dignity everywhere,” and on July 5, 2004, that “America stands against and will not tolerate torture. . . . Torture is wrong no matter where it occurs, and the United States will continue to lead the fight to eliminate it.
the rights of torture victims

Almost 25 years ago, William Curran devoted his “Law–Medicine Notes” feature in the Journal to the subject of torture. He reported on what was then a unique case, Filartiga v. Pena-Irala, in which the Second Circuit Court of Appeals in New York ruled that U.S. courts, under the Federal Alien Tort Statute (also referred to as the Alien Tort Claims Act), had jurisdiction to hear civil cases brought against torturers by noncitizens who were victims of that torture.

The case involved a physician who brought suit in the United States against the inspector general of police of Asunción, Paraguay, for the torture and murder of his 17-year-old son. In his opinion upholding jurisdiction, Judge Irving R. Kaufman summarized universally accepted principles of international human rights law: “The torturer has become — like the pirate and the slave holder before him — hostis humani generis, an enemy of all mankind.” Judge Kaufman and his court could make law only for the Second Circuit, but in 2004, the Supreme Court answered the question of the reach of the Alien Tort Statute for the entire country. The case involved Humberto Alvarez-Machain, a Mexican physician.

Officials of the Drug Enforcement Administration (DEA) believed that when one of their agents, Enrique Camarena-Salazar, was captured in 1985 in Mexico, tortured over a two-day period, and then murdered, Alvarez-Machain had been present and had used his medical skills to extend the interrogation and the torture. Demonstrating how strongly the U.S. government objected to physicians participating in torture, the DEA in 1990 took the extraordinary step of hiring Mexican nationals to kidnap Alvarez-Machain and bring him to the United States for trial. The kidnapping succeeded, but at trial Alvarez-Machain was found not guilty. After returning to Mexico, Alvarez-Machain brought an action against the United States under the Alien Tort Statute, alleging false arrest and arbitrary detention. Alvarez-Machain won at trial, and the Ninth Circuit Court of Appeals affirmed the decision.

In an opinion written by Justice David Souter, the Supreme Court reversed the award. Nonetheless, this opinion determined the meaning and reach of the Alien Tort Statute, enacted by Congress in 1789, which states in its entirety: “The district courts shall have original jurisdiction of any civil action by an alien for a tort only, committed in violation of the law of nations or a treaty of the United States.” The question before the Court was whether, as the Ninth Circuit had ruled, this statute gave U.S. district courts the legal authority to hear a case like that brought by Alvarez-Machain in which the plaintiff alleges a “violation of the law of nations.”

The Court was unable to find any evidence that Congress in 1789 had specific violations of international law in mind but supposed that the most likely ones were Blackstone’s “three primary offenses: violation of safe conducts, infringement of the rights of ambassadors, and piracy.” The Court then cited Filartiga as the beginning of “the modern line of cases.” The Court concluded that federal courts can determine just what the current “law of nations” is but instructed courts to be conservative in determining what international law requires: “We think courts should require any claim based on the present-day law of nations to rest on a norm of international character accepted by the civilized world and defined with a specificity comparable to the feature of the 18th-century paradigms we have recognized [e.g., piracy].”

In support of his position that his arbitrary detention was a violation of international law, Alvarez-Machain cited the Universal Declaration of Human Rights and the International Covenant on Civil and Political Rights. The Court found that the Universal Declaration did not have the force of law and that “the United States ratified the Covenant on the express understanding that it was not self-executing and so did not itself create obligations enforceable in the federal courts.” Treaties and custom are the primary sources of international law. After treaties had been rejected as support for Alvarez-Machain, he was left to argue that arbitrary arrest and detention, like piracy, had attained the status of “binding customary international law.” Given its reluctance to recognize new causes of action, it is not surprising that the Court rejected Alvarez-Machain’s argument on the grounds that it “would support a cause of action in federal court for any arrest, anywhere in the world, unauthorized by the law of the jurisdiction in which it took place.” The case thus stands for the proposition that a brief illegal detention is insufficient grounds for a claim in U.S. courts as a violation of international law.

The decision is more important for its statement that when acts are universally condemned by international law, such as state-sanctioned piracy,
torture, and murder, they can be the basis for a lawsuit under the Alien Tort Statute. The decision reaf-
firms the long-standing view of the Supreme Court that “the domestic law of the United States recognizes the law of nations.” In a case alleging torture, the Court would find torture a violation of international law both because it is universally con-
demned in international law and because the Congress has ratified the Convention against Torture and adopted a law authorizing individual lawsuits to be brought by victims of torture. Thus, under the Alien Tort Statute, the victims of torture at the pris-
on at Guantanamo Bay and Abu Ghraib, for example, may bring a claim against their alleged tortur-
ers in U.S. courts — and it should be expected that many will.

THE GENEVA CONVENTIONS

The road to torture at Abu Ghraib begins arguably with the president’s decision in February 2002 that the Geneva Conventions would not apply to “en-
emy combatants” jailed at Guantanamo Bay. This decision was made over the strong objections of then Secretary of State Colin Powell and without any meaningful input from the career lawyers in the armed services, all of whom objected to jettisoning the Geneva Conventions, an international treaty from which the United States had never before de-
viated. The reasons given for taking prisoners to Guantanamo was that the global war on terror was a “new kind of war” that made the Geneva Conven-
tions inapplicable and that Guantanamo could and should be used as an interrogation center for sus-
pected terrorists that was outside the jurisdiction and, thus, the oversight of U.S. courts.

It seems to have been assumed that if neither the Constitution nor international law applied in Guantanamo Bay, the administration could write its own rules of conduct for the prison, and it did. Secretary of Defense Donald Rumsfeld, for exam-
ple, specifically approved types of torture that could be used in interrogations there, and he specifically involved physicians in it by requiring that prisoners have “medical clearance” before these techniques were applied to them. In the words of Rumsfeld’s directive, the new techniques can be used only af-
after, among other things, “the detainee is medically and operationally evaluated as suitable (consider-
ing all techniques to be used in combination).” These torture techniques made their way to Abu

Ghraib when the commander of the prison at Guan-
tamano Bay, General Geoffrey Miller, was trans-
ferred to Iraq in 2004.

According to the administration, the Geneva Conventions were to apply in Iraq. Had they been followed, the torture and abuse of prisoners at Abu 

Ghraib would not have occurred. The conventions not only prohibit torture and abusive and humiliat-
ing treatment of prisoners but also specifically pro-
tect physicians who follow medical ethics by re-
porting and refusing to participate in torture and abuse of prisoners. The Independent Panel to Re-
view Department of Defense Detention Operations highlighted professional ethics as the core consid-
eration in the prevention of torture and abuse, stating that “all personnel who may be engaged in de-
tention operations, from point of capture to final disposition, should participate in a professional ethics program that would equip them with a sharp moral compass for guidance in situations often riv-
en with conflicting moral obligations.” With re-
gard specifically to physicians, “the Panel notes that the Fay investigation (by the Army) cited some med-
ical personnel for failure to report detainee abuse. As noted in that investigation, training should in-
clude the obligation to report any detainee abuse.”

On June 28, 2004, the day before the Supreme 

Court decided the Alien Tort Statute case, the Court decided that under the statute, prisoners at Guan-
tamano could challenge their imprisonment in U.S. courts as well as bring civil claims for injury and abuse. The Court thus rejected the position of the Bush administration, as stated in oral argument before the Ninth Circuit, that even were the United States engaged in “murder and torture” at Guan-
tamano, U.S. courts could not interfere. In another case that was decided on the same day, the Supreme Court ruled that a U.S. citizen who was captured on the battlefield in Afghanistan and initially held at Guantanamo before being transferred to the Unit-
ed States had the right to a fair hearing under the Constitution to contest his status as an “enemy combatant.” In this opinion, the Court cited pro-
visions of Geneva Convention III (concerning pris-
ioners of war) as authoritative on the “law of war.”

More recently, a district court has ruled explicitly that the Geneva Conventions must be followed at 

Guantanamo. In all these cases, the judicial branch of government has been much more articulate than the executive branch in condemning torture and upholding both U.S. and international law.
INTERNATIONAL AND MEDICAL ETHICS

As Telford Taylor argued at the Nuremberg Trials, the prevention of crimes against humanity, including torture, must be our primary goal. Torture remains widely practiced around the world, even though universally condemned. Amnesty International estimates that 150 countries currently practice torture. Torture is wrong under all circumstances, because it is cruel and degrading to humans and an extreme violation of human rights under international law. Jean-Paul Sartre’s description of torture, written almost 50 years ago during the French–Algerian War, should resonate in the United States after the attacks on September 11: “Torture is senseless violence, born in fear.” Now that the president has proclaimed that torture is always wrong, we must return to the question of how to prevent it effectively during wartime when a high-level or low-level official believes that torture, although illegal, appears nonetheless to be likely to aid the war effort.

Preventing torture is everyone’s business—but three professions seem to be especially well suited to prevent torture: medicine, law, and the military. Each profession has particular obligations. Physicians have the obligations of the universally recognized and respected role of healers. Lawyers have the obligations to respect and uphold the law, including international humanitarian law. And military officers have the obligation to follow the international laws of war, including the Geneva Conventions.

Americans need the blessings of both lawyers and physicians to justify torture. Professor of law Alan Dershowitz, for example, believes that we must accept that torture will be used in extreme situations and try to regularize its practice by requiring prior judicial approval of its use and limiting it to the infliction of “nonlethal pain” — such as “shoving a sterilized needle under the fingernail of a suspect.” Both Dershowitz and the Fox television network’s hit program 24 glamorize torture by portraying ticking-time-bomb scenarios in which a captured terrorist knows where a bomb will soon explode that will kill many innocent civilians. Of course, medicalizing torture does not make it right or effective — even in such a situation. International terrorists have already gone beyond such scenarios by combining the bomb and the terrorist into a single entity, the suicide bomber.

The challenges of the war on terror present an opportunity for medical and legal professional organizations to work together transnationally to uphold medical ethics and international humanitarian law, respectively, rather than to search for ways to avoid legal or ethical dictates. In addition, the war on terror provides physicians and lawyers who are also military officers with an opportunity to clarify their roles in the military services and their obligations under international law and the U.S. Uniform Code of Military Justice.

Almost 30 years ago, Sagan and Jonsen observed in the Journal that because the medical skills used for healing can be maliciously perverted “with devastating effects on the spirit and the body,” it is “incumbent upon the medical profession and upon all of its practitioners to protest in effective ways against torture as an instrument of political control.” Such protest can help in the war against terrorism. Neither the use of torture nor violations of human rights, as another professor of law, the Jesuit Robert Drinan, has observed, will “induce other nations to follow the less traveled road that leads to democracy and equality,” but the “mobilization of shame” and the “moral power” of example can do so. Torture begins by dehumanizing the victim but ends by dehumanizing the torturer. As Telford Taylor put it at Nuremberg, “A nation that deliberately infects itself with poison will inevitably sicken and die.”

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18. The Paquete Habana, 175 U.S. 677 (1900).

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Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

TO THE EDITOR: The trial conducted by Mayer et al. (Feb. 24 issue), showing that recombinant activated factor VII (rFVIIa) is beneficial for treating acute intracerebral hemorrhage, for which treatment options are extremely limited, is very exciting. The trial showed a reduction in hematoma growth (the primary end point); however, it is the associated reduction in mortality that most likely will influence practitioners to use this therapy. Although patients in a deep coma (defined as a score of less than 6 on the Glasgow Coma Scale [GCS]), whose mortality rate is extremely high, were excluded from the trial, the ranges of the baseline GCS scores shown in Table 1 of the article indicate that some of the patients in the placebo group met this exclusion criterion. We wonder how many patients in the placebo group had GCS scores of less than 6 before administration of the study drug, because excluding as few as two deaths in this group would result in a P value for mortality that would no longer be less than 0.05. Since rFVIIa was associated with an increased risk of arterial thromboembolic adverse events (P=0.01), some of which were fatal, balancing the benefits and risks associated with this therapy is extremely important. Moreover, thromboembolic events should continue to be analyzed as prospectively defined outcomes in all future trials.

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Dr. Friedrich reports having received lecture fees from Nova No- varis.


TO THE EDITOR: Mayer and colleagues provided placebo or rFVIIa to more than 84 percent of the patients in each test group who had lesions in the putamen, globus pallidus, or thalamus. The likely primary or contributing cause of bleeding in many of these patients was elevated blood pressure; however, the reduction in blood pressure at three hours was minimal. It is important to know what trends in blood pressure were observed in the respective subgroups between imaging studies.

It is unclear what fraction of the 7 percent incidence of thromboembolic serious adverse events among the patients treated with rFVIIa occurred among those enrolled after the midpoint of the trial, when a change was made to “exclude patients with any history of thrombotic vaso-occlusive disease.” This change raises the possibility that the incidence of adverse thrombosis might be higher in a broader patient population.

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THIS WEEK’S LETTERS

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The authors reply: As Dr. Friedrich notes, patients with GCS scores of 5 or less, indicative of deep coma, were excluded according to our study protocol. However, a single patient in the placebo group was assigned a baseline GCS score of 3. This patient actually had an intermediate level of consciousness but was intubated and sedated for transportation at the time of the screening evaluation. Hence, the local investigator enrolled the patient in the trial, and the patient was included in the intention-to-treat analysis. We do not believe that the inclusion of this patient invalidates the main findings of our study.

As Dr. Sheth notes, the mean systolic blood pressure was elevated at baseline in our patients; elevated blood pressure has been shown to be an important factor contributing to the occurrence of intracerebral hemorrhage. Blood pressure fell progressively between the imaging studies from 178/97 mm Hg at baseline, to 154/85 mm Hg at 24 hours and 150/80 mm Hg at 72 hours, with minimal differences among the treatment groups. Thus, it seems unlikely that differences in blood-pressure control account for the observed treatment effect of rFVIIa. We are currently conducting a more detailed analysis of the effect of blood pressure and other physiological variables on hematoma growth.

We amended the trial protocol to exclude patients with any history of symptomatic thromboembolic or vaso-occlusive disease after enrolling 197 of the 399 subjects. Exactly 13 thromboembolic serious adverse events occurred before this amendment, and 13 occurred after it. In a preliminary analysis of all 485 patients with intracerebral hemorrhage enrolled in our three phase 2 trials conducted to date,1,2 including the current trial, a history of thromboembolic disease was not found to predict acute thromboembolic complications related to rFVIIa administration. In fact, in our planned phase 3 confirmatory trial, we intend once again to include patients with a history of thromboembolic events.

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Treatment of Myelodysplastic Syndromes

To the editor: List et al. (Feb. 10 issue)1 report encouraging results with regard to the efficacy of lenalidomide, a thalidomide analogue, in the treatment of patients with myelodysplastic syndromes and symptomatic anemia whose condition failed to respond to erythropoietin. List et al. tested three dosing regimens, but little is said about their advantages or disadvantages. It appears that the lowest dosing regimen (10 mg per day for 21 days in a 28-day cycle) produced the best response with the least toxicity, but it is unclear what the median duration of response and the number of cytogenetic responses were with this regimen, because no comparison with the more dose-intense regimens is reported. A related question is whether patients with the highest rate of response (those with deletions on chromosome 5q) were evenly distributed among the different treatment groups.

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To the editor: In their Perspective article (Feb. 10 issue),1 Drs. Cazzola and Malcovati state that treatment of myelodysplastic syndromes with antithymocyte globulin or cyclosporine is “effective in small subgroups of patients who do not require transfusions and who have low marrow cellularity.” However, three studies of the use of antithymocyte globulin in the treatment of myelodysplastic syndromes2-4 have been performed in transfusion-dependent patients. About one third of these patients had hematologic improvement and became
transfusion-independent; marrow hypocellularity was not predictive of a response. We believe that until larger studies delineate the place of lenalidomide in the treatment of myelodysplastic syndromes (especially given the drug’s hematologic toxicity), a trial of immune-modulating therapy is warranted in patients with low-risk myelodysplastic syndromes.

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DR. LIST REPLIES: Dr. Chng asks about the optimal dose and schedule of lenalidomide. Three dosing schedules were evaluated in the study, but patients were enrolled sequentially and without stratification according to disease type or karyotype. As shown in our article, there was no significant difference in the response rate among the cohorts; however, the time to a response was longer with the 21-day schedule. Among 12 subjects with a 5q31.1 deletion, 4 received 25 mg per day, 3 received 10 mg per day, and 5 received 10 mg per day for 21 days. Erythroid response was achieved in four patients, three patients, and three patients receiving the respective regimens. Although differences in the adverse-event profiles were noted, the number of patients in each cohort was insufficient to permit us to identify an optimal dose and schedule with statistical confidence. Two multicenter phase 2 trials recently completed enrollment of more than 360 transfusion-dependent participants. These trials are evaluating treatment with either 10 mg per day or the schedule of 10 mg per day for 21 of every 28 days and therefore should provide important insight with regard to tolerance, response rate, and durability with the use of these two schedules of lenalidomide therapy.

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DRS. CAZZOLA AND MALCOVATI REPLY: The use of antithymocyte globulin, for myelodysplastic syndromes is supported only by uncontrolled observations. Saunthararajah and colleagues1 identified three pretreatment variables associated with a response to antithymocyte globulin: younger age, shorter duration of the need for transfusions, and positivity for HLA-DR15. In a study conducted by the National Institutes of Health,2 it was concluded that “hypocellularity was an almost independent factor predicting response.” Our summarizing statement was based on these observations.

Antithymocyte globulin is toxic. In the study by Stadler et al.,3 23 of 35 patients had adverse effects; 4 had serious toxic effects, and 1 of these patients died of cerebral mucormycosis. Thus, we cannot agree with Drs. Stadler and Ganser that “a trial of immune-modulating therapy is warranted in patients with low-risk myelodysplastic syndromes.”

What is warranted is controlled clinical trials that compare the quality of life and survival among patients given immunosuppressive therapy or lenalidomide and those treated exclusively with supportive care.

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EGFR Mutation and Response of Lung Cancer to Gefitinib

TO THE EDITOR: Kobayashi et al. (Feb. 24 issue) report that a second mutation in the gene encoding the epidermal growth factor receptor (EGFR), one resulting in a threonine-to-methionine substitution at amino acid position 790 (T790M), was associated with acquired resistance to gefitinib in their patient and that this mutant gene had been absent from the primary non–small-cell lung cancer. In a reanalysis of the data from the 397 subjects we have previously described, we identified two women who had never smoked who had non–small-cell lung cancer and harbored two EGFR mutations — T790M and a leucine-to-arginine substitution at amino acid position 858 (L858R) — in resected tumor specimens before treatment with chemotherapy or radiotherapy. Both patients later had recurrent disease and eventually died — outcomes suggesting that tumors with both the L858R and T790M mutations are very aggressive. One patient was treated with gefitinib and had progression.

These findings indicate the existence of cases with inherent double mutations and provide evidence that the T790M mutant genotype is an important factor conferring resistance to gefitinib in non–small-cell lung cancers containing EGFR sensitivity mutations. In addition, detecting T790M may be useful for predicting pretreatment resistance to EGFR tyrosine kinase inhibitors. Our observation, together with data from recent reports, may help clarify the role of EGFR mutations in the development of EGFR-related non–small-cell lung cancer and help establish effective strategies against specific subtypes of non–small-cell lung cancer.

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THE AUTHORS REPLY: Dr. Toyooka and colleagues describe two patients whose lung tumors harbored a T790M mutation before treatment with chemotherapy or radiotherapy was begun and suggest that this mutation might be a marker of tumor aggressiveness as well as resistance to gefitinib therapy. In the cases we and others have described, the T790M mutation was not found in specimens from untreated patients. Nevertheless, the possibilities do exist that this second mutation might be present in some tumors at a low frequency at the time of diagnosis and that tumor cells harboring the mutation might be enriched over time during treatment with gefitinib or erlotinib. By analogy, imatinib-resistant BCR-ABL mutations have, on occasion, been detected in specimens from patients with untreated chronic myeloid leukemia. We agree that such interesting findings should motivate further research to improve our understanding of the role of EGFR in non–small-cell lung cancers, to encourage the development of alternative EGFR inhibitors able to overcome such resistance mutations, and to incorporate the knowledge gained into clinical treatment.

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2. Roche-Lestienne C, Soenen-Cornu V, Grardel-Duflos N, et al. Several types of mutations of the Abl gene can be found in chronic myeloid leukemia patients resistant to STI571, and they can preexist to the onset of treatment. Blood 2002;100:1014-8.
TO THE EDITOR: Sanders et al. and Paltiel et al., in their reports on the cost-effectiveness of screening for HIV infection (Feb. 10 issue), have added another level of evidence in support of broader HIV testing. It appears that the benefits of routine counseling and testing will be enhanced if screening somehow leads to a decreased incidence of new infections. However, the frequently used procedure of one-time counseling regarding HIV and the awareness of being HIV-infected do not necessarily reduce risky behavior. Furthermore, although the recent report of 90 percent acceptance of HIV testing in urgent care settings is encouraging, the reproducibility of the results needs to be ascertained in continuity (long-term care) clinics, where patients are not acutely ill and are probably less likely to accede to HIV testing. Given the benefits of broader HIV screening, these and other outstanding problems call for studies that will assist in the process of designing feasible testing procedures that can be used in different clinical and nonclinical settings to increase the early diagnosis of HIV infection and to help prevent new cases. Perhaps the programs should be called “HIV diagnosis and prevention” instead of “HIV counseling and testing.”

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TO THE EDITOR: Routine HIV testing is an important population health strategy that is cost-effective and should be strongly promoted, as Bozzette points out in his editorial on the studies by Sanders et al. and Paltiel et al. Such broad-based approaches, however, require critical examination with respect to potential unintended consequences. For example, routine HIV testing may ultimately give rise to wider social acceptance of persons living with HIV or AIDS. Without appropriate safeguards or support systems, however, the stigma associated with HIV and AIDS may suppress the use of health care services and thus exacerbate health disparities in high-risk, marginalized populations. Such unintended consequences would limit the benefits of routine HIV testing.

Recommendations regarding routine HIV testing must be placed within the current context of recent policy shifts away from the primary prevention of HIV infection and in the context of waning federal support for social programs. The effects of these factors must be considered because they limit access to care and do little to reduce the incidence of infection among those at greatest risk. We encourage the adoption of comprehensive HIV–AIDS initiatives that include routine screening yet do not compromise nonclinical primary-prevention efforts and that are also concerned with reducing stigmatization.

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TO THE EDITOR: Although the methods used in the deterministic cost-effectiveness analysis by Sanders et al. do not appear contentious, at least two aspects of the incremental cost-effectiveness ratio (ICER) can threaten the validity of the results.

First, the end result of a fraction (ICER = change in cost ÷ change in effectiveness) becomes unstable in the presence of small denominators (range, 0.002 to 0.015 year). Consequently, a minimal error in estimating life expectancy or quality-adjusted life-years would have a substantial effect on the
ICER and could even change the conclusions of the study. An analysis based on net health benefit is an alternative method of assessing cost-effectiveness that has several advantages over use of the ICER.\textsuperscript{1} Second, measurement of uncertainty in cost-effectiveness analysis permits statistical inference and helps policymakers decide whether further research is still needed.\textsuperscript{2,3}

I agree that one-time screening for HIV is the optimal alternative, but only if the parameter estimates obtained by the investigators are extremely close to the true unknown values. Measurement of uncertainty permits the value of information to be estimated and should be routinely performed in cost-effectiveness analyses.

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**DR. SANDERS AND COLLEAGUES REPLY:** Dr. Taiwo accurately points out the importance of HIV counseling in reducing an HIV-infected patient’s risk-related behavior. Although such programs improve the cost-effectiveness of screening by decreasing future HIV transmission, our analysis emphasizes that HIV screening can be economically favorable even when the costs and benefits associated with transmission are ignored. Ms. Thrasher and colleagues raise important points about stigma, discrimination, and subsequent health-seeking behavior. These complex issues were not included in our economic analysis, but we agree that they are important for policymakers. In addition, Thrasher et al. are correct in noting that we did not examine the question of whether HIV screening is cost-effective as compared with increased use of primary-prevention methods, since that was not the purpose of our analysis.

We thank Dr. da Silveira for his thoughtful comments about the methods and limitations of cost-effectiveness analysis. We agree that the cost-effectiveness ratio can be sensitive to small changes in the denominator when the incremental benefit is small. In our analysis, although the differences in quality-adjusted life-years were small for the entire screened population, the increase in quality-adjusted life-years for an individual HIV-infected patient was quite large (approximately 1.5 years) and robust. In addition, we believe that the suggested net-health-benefit method is an alternative method of expressing the results of a cost-effectiveness analysis, not an alternative method of assessing the cost-effectiveness of an intervention.

Although the net health benefit has many appealing features, it has two main limitations. First, reporting a net health benefit requires the analyst to choose a societal willingness-to-pay value for a quality-adjusted life-year — a necessity that remains controversial. Second, interpreting a net-health-benefit value is not intuitive for many readers. We also agree that estimation of the value of information can be quite useful, particularly with respect to screening.\textsuperscript{1} However, calculation of the value of information can be challenging, particularly when models are complex, and it can also be inaccurate when many variables in the model are collinear, as in our case. These methodologic issues need to be addressed for the value of information to be used routinely. Meanwhile, deterministic models such as ours remain valuable sources of evidence for policymakers and provide estimates of the incremental cost-effectiveness of interventions that can be used in guiding policy decisions.\textsuperscript{2}

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**DR. PALTIEL AND COLLEAGUES REPLY:** Dr. Taiwo calls for proof that expanded HIV-testing procedures can feasibly be implemented in a variety of real-world settings. Our research group and others have already mounted successful demonstration projects in both inpatient and outpatient settings showing that expanded HIV counseling and testing programs are...
feasible, affordable, and able to identify substantial numbers of new cases of infection.\textsuperscript{1-5} These studies set the stage for broader implementation of HIV testing and have already demonstrated that acceptability of the test increases with time.

Dr. Taiwo also notes that the attractiveness of HIV testing improves if it decreases the incidence of new infections. This is certainly true, but it is not a necessary condition. Our analysis establishes that routine HIV testing is cost-effective according to U.S. standards, even when viewed strictly from the perspective of the individual infected person. Demonstrating that expanded HIV testing reduces rates of HIV transmission would strengthen an already strong case.

Ms. Thrasher and colleagues express the concern that stigmas and cutbacks in funding for prevention and treatment programs may exacerbate health disparities in populations where routine HIV-testing services are expanded. Although we share this concern, there is little evidence that we are aware of either to support or to refute it. Routine HIV testing may very well serve to destigmatize both HIV testing and HIV disease. Whether or not the concern expressed by Thrasher et al. is borne out in practice, it is our view that the appropriate response to waning federal support for HIV prevention and treatment is not to persist in the pursuit of an outdated approach to HIV testing — an approach that ignores the availability of highly accurate, inexpensive screening tests and affordable, life-sustaining therapies. Rather, the appropriate response is to continue to press on all fronts for a coordinated, evidence-based, national policy on HIV and AIDS that links funding for expanded testing with funding for patient care that conforms to national guidelines and that embraces interventions — both preventive and therapeutic — that deliver good value.

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Unhealthy Alcohol Use

TO THE EDITOR: In his review of unhealthy alcohol use (Feb. 10 issue),\textsuperscript{1} Dr. Saitz does not address the important role that biomarkers can play in identifying and treating alcohol-use disorders. At least some patients with alcohol-use disorders are unable or unwilling to provide accurate information on their drinking habits to clinicians. There are, of course, several excellent self-report measures available. The concurrent use of biomarkers can augment their accuracy.\textsuperscript{2,3}

Although we firmly believe that treatment for alcohol-use disorders is often ultimately effective, a return to some level of drinking, especially in the first three months of recovery, is quite common. Often the markers of alcohol consumption, especially carbohydrate-deficient transferrin, will be elevated before the patient voluntarily acknowledges a return to drinking.\textsuperscript{4} The results of biomarker tests can alert the clinician to a recent relapse and thereby allow the treatment regimen to be modified. Finally, feedback given to patients on the basis of the biomarker levels may reinforce recovery efforts or demonstrate the need for the patients to reduce consumption substantially or totally cease drinking.\textsuperscript{5}

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DR. SAITZ REPLIES: As stated in my review, biomarkers — particularly when elevated initially — can be useful in brief intervention. I also agree that evidence supports their use as one of several ways to identify early relapse during treatment for alcoholism. However, in accordance with practice guidelines, I do not recommend biomarkers for screening (which is addressed in Table 2 of my article) because few studies have validated them for identifying the spectrum of unhealthy alcohol use in patients in general health care settings. Many studies of biomarkers have included subjects from specialty treatment centers, and the few that have been conducted exclusively in medical settings have found the tests to be inadequate. In terms of sensitivity and specificity, biomarkers are either not better or are worse than validated questionnaires. Further, the incremental value of biomarkers (the cost per case identified in those with negative questionnaires) is unknown and probably small, since questionnaires detect most cases. For patients who deny drinking, a positive but insufficiently specific test is of uncertain value.

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The Unturned Stone

TO THE EDITOR: AIDS is a well-known predisposing condition for generalized histoplasmosis, which had been ruled out in the patient described in the Clinical Problem-Solving article by Goulet et al. (Feb. 3 issue). Idiopathic CD4+ lymphocytopenia is another immunodeficiency state that should be ruled out in such a case. I would like to know what the absolute lymphocyte count and CD4+ count were in this patient. In idiopathic CD4+ lymphocytopenia, several other opportunistic infections, such as cryptococcal meningitis, toxoplasmosis, Pneumocystis carinii pneumonia, and disseminated warts, have been described. In general, patients with idiopathic CD4+ lymphocytopenia have stable CD4+ cell counts. Even spontaneous resolution of CD4+ lymphocytopenia has been described. In contrast to the situation with HIV-infected patients, no particular therapy directed against a low lymphocyte count is approved. Patients with idiopathic CD4+ lymphocytopenia may need prophylaxis against other opportunistic infections.

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THE AUTHORS REPLY: Dr. Bharadwaj’s comments highlight the importance of searching for an underlying immunodeficiency when an opportunistic infection is found. Idiopathic CD4+ lymphocytopenia is defined by the presence of fewer than 300 CD4+ cells per cubic millimeter or CD4+ cell counts representing less than 20 percent of the total T-cell count in the absence of HIV infection. The cause of this condition remains unknown, although some investigators suggest primary failure of regeneration of stem-cell precursors. The role of long-term prophylaxis against opportunistic infections in patients with this condition remains unclear.

Our patient had been treated with corticosteroids, which are known to cause relative lymphocytopenia. He had lymphocytopenia, with absolute
lymphocyte counts ranging from 400 to 1300 cells per cubic millimeter. In addition to testing for HIV infection, serum immunoglobulin levels were checked to rule out another potential source of immunodeficiency; they were normal. Since our patient had reversible predisposing factors for opportunistic infection (therapy with corticosteroids and infliximab), further testing (including assessment of CD4+ cell counts) and long-term prophylaxis were not recommended. The patient remains in good health without prophylaxis more than 24 months after his hospitalization.

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Zidovudine and Red-Cell Distribution Width

TO THE EDITOR: Zidovudine was the first drug approved for the treatment of HIV infection and is still a mainstay of antiretroviral therapy. Patients taking zidovudine have an increase in the mean corpuscular volume, a variable that is often used to evaluate patients’ adherence to treatment.1-3 However, changes in the mean corpuscular volume are seen only several months after the initiation of zidovudine therapy. Red-cell distribution width (calculated as [standard deviation of red-cell volume ÷ mean cell volume] × 100) is a measure of anisocytosis and is determined by an automated, laboratory-based technique. We speculated that changes in the red-cell distribution width might be useful as an early marker of adherence to zidovudine treatment.

We compared hematologic variables among 47 HIV-infected patients who had initiated treatment for the first time with zidovudine, lamivudine, and lopinavir–ritonavir and whose rate of adherence was higher than 90 percent. Patients with anemia or macrocytosis were excluded. Erythrocyte-related values were determined after one, two, and four months of treatment and every four months thereafter. Most of the patients were men with fewer than 200 CD4 cells per cubic millimeter. The median baseline hemoglobin level was 13.7 g per deciliter (interquartile range, 12.1 to 14.6), the median mean corpuscular volume 87 µm³ (interquartile range, 85.2 to 91.5; normal range, 80 to 100), and the median red-cell distribution width 13.8 percent (interquartile range, 13.1 to 15.2; normal range, 11 to 15). After one month and two months of treatment, 100 percent and 63 percent of the patients, respectively, had a mean corpuscular volume within the normal range (80 to 100 µm³). Meanwhile, the red-cell distribution width was above the upper limit of normal in 100 percent of the patients at these time points. The red-cell distribution width increased significantly, to 17.7 percent (interquartile range, 16.3 to 19.6) and 19.8 percent (interquartile range, 18.7 to 21.6) at one month and two

Figure 1. Median Red-Cell Distribution Width and Median Mean Corpuscular Volume during Treatment with a Zidovudine-Containing Regimen. I bars represent the interquartile range.
months, respectively (P<0.001 for the comparison of both values with baseline). After four months, the mean corpuscular volume was higher than 100 µm³ in all but one patient, and the red-cell distribution width returned to values similar to those at baseline (Fig. 1).

Poor adherence to treatment is an important factor in treatment failure. Traditional methods of monitoring adherence, such as interviewing patients, counting pills, reviewing pharmacy refill logs, and monitoring serum drug levels, are often inaccurate and expensive. During the first two months of zidovudine therapy, the mean corpuscular volume is not useful as a measure of adherence because in most patients the values remain within the normal range. However, during this early period, two populations of erythrocytes coexist: one of normal size and another that has increased in size as a result of the zidovudine therapy. This variability can be measured by determining the red-cell distribution width, and in all the patients in our study, the red-cell distribution width was above the upper limit of normal at these two time points. After four months, there is a new, macrocytic population of erythrocytes, and most patients have a mean corpuscular volume above 100 µm³ and red-cell distribution width that has returned to normal. The red-cell distribution width may be a simple and cheap-to-measure marker of early adherence to zidovudine therapy. In addition, zidovudine therapy should be included in the differential diagnosis of an elevated red-cell distribution width.

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**THE PRICE OF SMOKING**


Is it really worth $40 per pack to smoke cigarettes? According to Duke University health economists, $40 is the real cost that a 24-year-old smoker should consider each time he or she purchases a pack of cigarettes. This amounts to $220,000 for men and $106,000 for women who smoke over their lifetimes. Of the nearly $40-per-pack cost, the smoker bears $33. The remaining costs are borne by the smoker’s family ($5) and by society ($1).

Sloan and colleagues present the most comprehensive analysis yet of the cost of smoking. They combine national data from several sources in an innovative way to develop detailed estimates of the economic impact of smoking. The book breaks new ground in using a lifetime-cost framework that carefully tease out the “internal” and “external” costs of smoking — that is, the part of the cost the smoker bears versus the part imposed on others. They consider the contributions that smokers make to revenues (including health insurance premiums, Medicare, Medicaid, and Social Security) and evaluate whether nonsmokers subsidize smokers in insurance markets. They use their models to evaluate whether current cigarette taxes and payments under the Master Settlement Agreement reached with the tobacco industry in 1998 are set at reasonable levels.

The book is easy to follow, even for a noneconomist. The authors begin by reviewing the existing research on smoking costs and describe the data they use and their analytic approach. They next detail the effect of smoking on mortality, health care expenditures, Social Security, private pensions, and insurance programs. Finally, the authors consider the effect of smoking on the health of family members, especially spouses.

That smoking costs a substantial amount in terms of health care services, lives lost, and other costs will not surprise those who follow the ongoing saga of tobacco as public health enemy number one. It is somewhat more controversial that smoking actually saves Medicare money by killing off sick smokers at earlier ages, even after the smoker’s payroll tax contributions to the program are included. Smoking is also found to save the Social Security program $1,519 per female smoker and $6,549 per male smoker for the same reason. The authors conclude that increases in the cigarette excise tax could be justified because current tax revenues do not cover all the costs imposed on the smoker’s family members and society as a whole. However, they question whether the $206 billion Master Settlement Agreement can be justified and suggest that the answer depends in part on how the funds are used.

This book, with its clear exposition and easy-to-follow organization, should serve as an excellent.
primer for readers who want to bring themselves up to speed on the state of knowledge about smoking-related costs. It will be useful for academics, policymakers, advocates, and those simply wishing to stay informed on this important health and policy issue. In the current era of shrinking state and federal budgets and tight competition for public health dollars, the framework that is laid out in this book will also be useful in evaluating other health-related programs to save dollars. Smokers are no doubt tired of hearing that smoking is bad for their health, but perhaps they will respond to arguments that smoking costs them and their family members dearly in other ways, too.

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UNFILTERED: CONFLICTS OVER TOBACCO POLICY AND PUBLIC HEALTH
Edited by Eric A. Feldman and Ronald Bayer. 394 pp.

On February 27, the Framework Convention on Tobacco Control came into force, 90 days after ratification by the 40th signatory to this first health treaty negotiated under the auspices of the World Health Organization. The treaty codifies policy approaches to tobacco control, mostly as translated from lessons learned in developed countries such as the United States, Canada, and the United Kingdom, where the prevalence of smoking among men declined by more than 50 percent between the mid-1960s and 2001. In this collection of eight national analyses and a perspective on the European Union, a timely story is told from different cultural and political points of view, including those of liberal democracies, where respect for the rights of individual persons must be balanced against collective efforts to support the public good through political action.

Each chapter in this thoroughly referenced book delves into history, sometimes as far back as 500 years, to gain insights into which policies might be responsible for progress in the countries discussed. Furthermore, the book tries to explain why so many idiosyncrasies exist in the complex world of tobacco control. In most cases, the power of information as presented in reports from the Royal College of Physicians and the U.S. Office of the Surgeon General helped drive political action, research, and public opinion to change the view of smoking as a normal activity. Nevertheless, variability in the acceptance of this information created systems of official denial (as evidenced by a lack of enforcement of various laws regarding advertising and smoking in public places) in France, Germany, and Japan. Historically, authoritarian approaches to tobacco control in some cases created a deeply rooted resistance to the paternalistic nature of public health efforts on tobacco control. Germany may have subconsciously justified its resistance to such efforts in the European Union because of sensitivity to its authoritarian history.

A chapter on the history of tobacco control in the European Union presents a lucid explanation of how multinational health policies (such as a ban on cigarette advertising) were trumped by concern for tobacco agriculture in some countries in the European Union. Information from previously secret tobacco-industry documents helps us to dissect the complexities of tobacco-control policies in a political structure that was established not for health advocacy but for support of trade and economic cooperation. Tobacco, to many of the European Union member states, is simply an agricultural commodity and not a health issue. Now, however, the Framework Convention on Tobacco Control provides a broader perspective on international cooperation with respect to tobacco control, including a more focused concern about the health care costs of tobacco use, the adverse effects of cross-border smuggling, and the need to harmonize tobacco taxes for reasons of both health and revenue. One only hopes that the fatuous economic arguments described in this book about the “benefits” of premature mortality attributable to smoking — that it reduces expenditures on social services — will die the quick death they deserve.

A chapter by the esteemed historian and ethicist Allan M. Brandt is provided as cultural background to the mix of national analyses. He adds a fascinating review of how cigarette smoking devolved from a social necessity in the 1950s (as described by the doyen of civility, Emily Post) to pariah behavior necessitated by nicotine addiction in the 1990s. Brandt asserts that a “tipping point” has been
reached in the change in attitudes toward tobacco use, so that progress is now made not as a result of some magic-bullet policy but, rather, as the result of a cultural shift and a change in the perception of risk versus pleasure.

What we are left with in this capable if sometimes dense review of history and policy is a guarded understanding of how evidence, culture, and politics have converged to change the acceptability of tobacco use. A social gradient has emerged in tobacco-control policy: the developed world continues to implement policies that reduce the adverse outcomes of tobacco use while the poor nations of the world continue to accept the financial and cultural “benefits” of the evil weed. As the Framework Convention on Tobacco Control comes into force, further historical precedents may be set as this truly multinational process is implemented and the public health lessons of the countries described in this book are learned elsewhere around the world. However, it is ironic that the country in which many of these lessons have been learned probably will not ratify the treaty. The United States may now find itself a bystander to the global public health history being made with the Framework Convention on Tobacco Control.

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SLEEP DEPRIVATION:
CLINICAL ISSUES, PHARMACOLOGY,
AND SLEEP LOSS EFFECTS

(Lung Biology in Health and Disease, Vol. 193.)
Edited by Clete A. Kushida. 589 pp., illustrated.

Chronic sleep deprivation, which probably affects at least one third of American adults, causes daytime sleepiness and disrupts daily life. Episodes of acute sleep deprivation may be even more common and occur across a spectrum of ages and occupations. In this scholarly and extensively referenced book, which brings together commentary and discussion from a large group of expert investigators, readers will find detailed accounts of many obvious and not-so-obvious problems concerning sleep deprivation. For example, how is sleep deprivation manifested in infants, adolescents, and adults? What clinical tests of psychomotor vigilance and unintentional tendency to sleep are available to determine whether a pilot, a truck driver, or a physician can do his or her job safely under conditions of acute or chronic sleep deprivation? Does the failure of a physician to warn a sleep-deprived patient of potential third-party injury or death constitute negligence? How does sleep deprivation affect “cognitive readiness” in the military? The reader may be surprised to learn that people who get a greater-than-normal amount of sleep appear to have a higher risk of death than those who get less sleep and that insomniacs, in principle among the least rested of all, do not appear to have increased mortality.

Highlights of the book include a remarkable medicolegal perspective on sleep deprivation, a discussion of its social effects, a detailed and apparently unbiased chapter on stimulant therapy, lucid discussions of environmental and behavioral therapies aimed at ameliorating the effects of sleep deprivation, and a scientifically compelling chapter on the recuperative value of naps. There are also authoritative chapters on subjective and objective testing for the tendency to fall asleep and psychomotor vigilance; the effects of inadequate sleep on the performance of children, adolescents, and physicians; and the effects of sleep deprivation on driving, round-the-clock operations, and commercial and public transportation.

The book is not successful in all ways. Given the dense and difficult biologic and sociological information to be reviewed, the uninitiated reader would have been better served by an early overview and a biologic and clinical definition of sleep deprivation, along with a perspective on its importance. The epidemiologic and sociological effects of sleep deprivation are not discussed until page 195, long after the appearance of the numerous perspectives and strategies used in testing for such effects. There are also chapters that contain excellent discussions of sleep disorders in special populations, but they tend to dilute the effect of the discussion of sleep deprivation as a whole.

This book highlights the frustrating paucity of empirical data from well-designed investigations into the many important questions regarding the biology of sleep deprivation. Despite Sun Tzu’s 2300-year-old admonition in The Art of War to avoid fatigue in the military arena, it is not yet precisely clear to what extent human cognitive and social
performance is affected by acute or chronic sleep deprivation or by the disorders that lead to the condition. The lesson, it appears, is that we must now develop a newfound respect for the adverse possibilities of sleep deprivation in all its biologic forms and move on with scientific investigation into those aspects that are most compelling to the individual and society.

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**PSYCHOPHARMACOLOGY: DRUGS, THE BRAIN, AND BEHAVIOR**


In the preface to this book, the authors point out that for thousands of years humans have used psychoactive substances to modify their perceptions and mood. Indeed, some observers believe that such behavior may be a defining characteristic of the human condition. In contrast to the millennial history of drug taking, the era of scientific psychopharmacology is very short; perhaps its proper beginning can be dated to the middle of the 20th century. Since then, the rate of accrual of new knowledge in the field has increased enormously.

The authors aim to produce an introductory textbook on psychopharmacology and to convey some of the excitement that they find in this discipline. They attempt to create an integrated work, linking the basic principles of pharmacology, neurophysiology, and related neuroscience; the key features of the neurotransmitter systems; and the theories and mechanisms of related illnesses, including substance abuse and major psychiatric disorders. The authors have succeeded in reaching all these goals. They cover the important topics with great clarity, and the reader will find all the subjects accessible. “Hooks” at the beginning of each chapter — such as an image of the title page of *Über Coca*, Sigmund Freud’s tribute to the virtues of cocaine — catch the interest of the reader; the authors, while not compromising the thoroughness of their scientific explanations, have greatly enhanced the book’s readability with this technique. A particular delight is that the book is sumptuously illustrated — many of the illustrations are eye-catching and attention-grabbing.

As with any first edition, there are one or two minor flaws in the writing and minor errors in the references. Available to qualified adopters of this textbook are special supplements — a resource CD for instructors, which contains all the figures, illustrations, photographs, and tables from the book, as well as a test bank consisting of 50 questions per chapter. I highly recommend this book to anyone who wishes to learn about psychopharmacology.

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**CORRECTIONS**

Elevated Plasma Factor VIII and D-Dimer Levels as Predictors of Poor Outcomes of Thrombosis in Children (September 9, 2004; 351:1081-8). On page 1084, in Table 1, the range for factor VIII among patients who had no initial elevation in levels of factor VIII and d-dimer should have been 56 to 142 IU per deciliter, rather than 56 to 242, as printed.

Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure (January 20, 2005;352:225-37). On page 226, in the right-hand column, line 8 of the first full paragraph should have read “aldosterone-receptor blocker,” rather than “aldosterone,” as printed.

U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection (March 3, 2005;352:865-74). On page 870, in Figure 1, the number of patients receiving placebo who completed the trial should have been 221, not 206, as printed. We regret the error.