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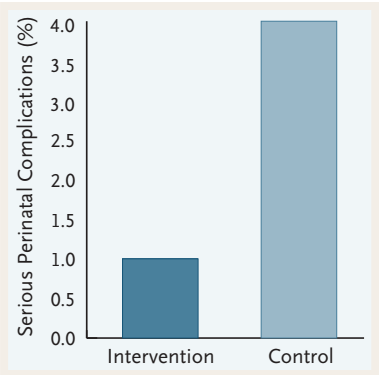
This Week in the Journal

JUNE 16, 2005

ORIGINAL ARTICLE

Randomized Trial of the Treatment of Gestational Diabetes



Consensus is lacking as to whether routine screening and treatment for gestational diabetes mellitus is warranted. This large randomized trial of the treatment of gestational diabetes demonstrated that serious perinatal complications were significantly less common among the offspring of women who received dietary advice, blood glucose monitoring, and insulin therapy as needed to maintain glycemic control than among the offspring of women who received routine care. These findings provide strong support for the implementation of screening for and treatment of gestational diabetes.

SEE P. 2477; EDITORIAL, P. 2544; CME, P. 2566

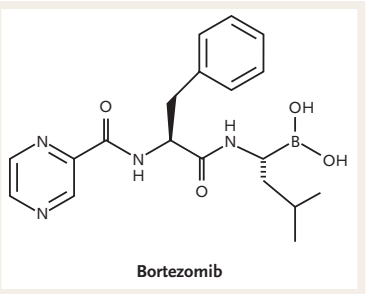
ORIGINAL ARTICLE

Bortezomib vs. Dexamethasone for Multiple Myeloma

Bortezomib, an inhibitor of proteasomes (sites of protein degradation in cells), has activity against advanced multiple myeloma. This study compared bortezomib with high-dose dexamethasone relatively soon after a relapse of multiple myeloma had occurred with other treatments. Bortezomib was superior to dexamethasone in all end points and prolonged overall survival.

Bortezomib is a departure from the conventional treatment of multiple myeloma with alkylating agents and vinca alkaloids. It shows promise for a disease in which progress in chemotherapy has been stalled for decades.

SEE P. 2487; EDITORIAL, P. 2546



Bortezomib

ORIGINAL ARTICLE

Ulcerative Colitis and Antibody to the $\alpha_4\beta_7$ Integrin

In this six-week randomized trial of MLN02 — a humanized antibody to the $\alpha_4\beta_7$ integrin — in patients with ulcerative colitis, MLN02 was associated with higher rates of remission than was placebo (33 percent in the group receiving 0.5 mg per kilogram, 32 percent in the group receiving 2.0 mg per kilogram, and 14 percent in the placebo group; overall P=0.03). These preliminary data suggest that blockade of the $\alpha_4\beta_7$ integrin with a humanized antibody may be an effective therapy for ulcerative colitis.

SEE P. 2499

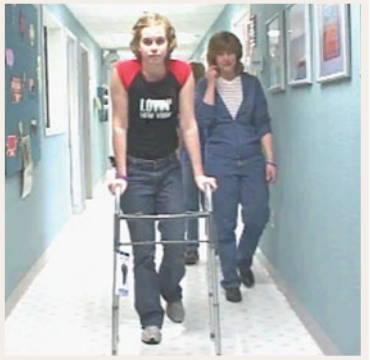
BRIEF REPORT

Survival after Treatment for Rabies

A 15-year-old girl presented with clinical rabies one month after being bitten by a bat. She was treated with ribavirin and amantadine plus agents to induce coma and suppress bursts of activity on electroencephalography. She survived and after five months was alert and communicative, although with generalized choreoathetosis, dysarthria, and an unsteady gait.

Surviving rabies is very rare, and the effectiveness of this treatment regimen will require replication. The goal of this approach is to reduce excitotoxic neural injury.

SEE P. 2508; EDITORIAL, P. 2549; VIDEO AT WWW.NEJM.ORG



SPECIAL ARTICLE

Prevalence and Treatment of Mental Disorders, 1990 to 2003

This study compared results of household surveys conducted in the United States from 1990 to 1992 and from 2001 to 2003 and found no change in the prevalence of mental disorders during that period. The prevalence of treatment increased, but most respondents with mental disorders still did not receive treatment between 2001 and 2003.

SEE P. 2515

CLINICAL PRACTICE

Chronic Stable Angina

A 47-year-old man reports a six-month history of intermittent chest discomfort while playing squash. He describes lower substernal tightness with numbness of the left upper arm only during exertion. He does not smoke. His father died suddenly at the age of 49 years. His blood pressure is 138/84 mm Hg. The level of total cholesterol is 261 mg per deciliter, low-density lipoprotein cholesterol 172 mg per deciliter, and high-density lipoprotein cholesterol 50 mg per deciliter, and the triglyceride level is 113 mg per deciliter. An exercise test is positive, with pain and 1.5 mm of horizontal ST-segment depression at stage 4 of the Bruce protocol. How should the patient's case be managed?

SEE P. 2524; CME, P. 2565

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

A Woman with a Painful Mass in the Abdomen

A 45-year-old woman noted a mass in her lower abdomen that was intermittently painful. An examination disclosed a slightly tender mass, 4 cm in diameter, on the right side of the lower abdomen. Imaging studies showed a solid mass in the right lower abdominal wall. A diagnostic procedure was performed.

SEE P. 2535; CME, P. 2567

PERSPECTIVE

The Celestial Fire of Conscience — Refusing to Deliver Medical Care

R. Alta Charo, J.D.

An interview with Professor Charo can be heard at www.nejm.org.

Apparently heeding George Washington's call to "labor to keep alive in your breast that little spark of celestial fire called conscience," physicians, nurses, and pharmacists are increasingly claiming a right to the autonomy not only to refuse to provide services they find objectionable, but even to refuse to refer patients to another provider and, more recently, to inform them of the existence of legal options for care.

Largely as artifacts of the abortion wars, at least 45 states have "conscience clauses" on their books — laws that balance a physician's conscientious objection to performing an abortion with the profession's obligation to afford all patients nondiscriminatory access to services. In most cases, the provision of a referral satisfies one's professional obligations. But in recent years, with the abortion debate increasingly at the center of wider discussions about euthanasia, assisted suicide, reproductive technology, and embryonic stem-cell research, nurses and pharmacists have begun demanding not only the same right of refusal, but also — because even a referral, in their view, makes one complicit in the objectionable act — a much broader freedom to avoid facilitating a patient's choices.

A bill recently introduced in the Wisconsin legislature, for example, would permit health care professionals to abstain from "participating" in any number of activities, with "participating" defined broadly enough to include counseling patients about their choices. The privilege of abstaining from counseling or referring would extend to such situations as emergency contraception for rape victims, in vitro fertilization for infertile couples, patients' requests that painful and futile treatments be withheld or withdrawn, and therapies developed with the use of fetal tissue or embryonic stem cells. This last provision could mean, for example, that pediatricians — without professional penalty or threat of malpractice claims — could refuse to tell parents about the availability of varicella vaccine for their children, because it was developed with the use of tissue from aborted fetuses.

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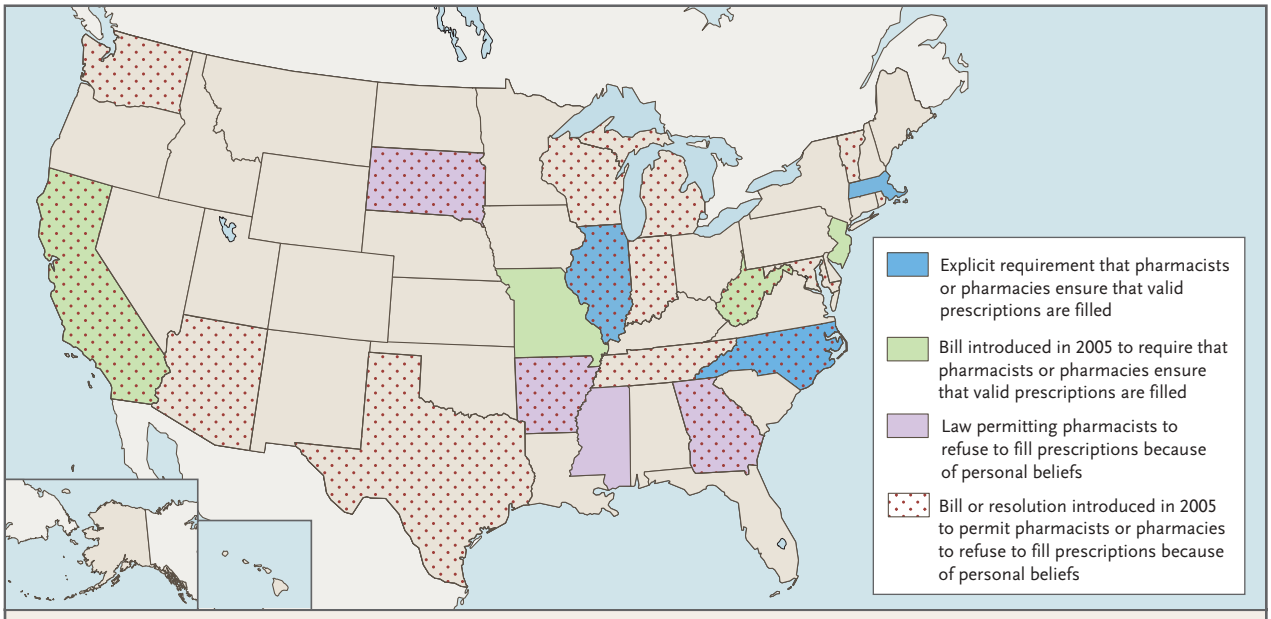
This expanded notion of complicity comports well with other public policy precedents, such as bans on federal funding for embryo research or abortion services, in which taxpayers claim a right to avoid supporting objectionable practices. In the debate on conscience clauses, some professionals are now arguing that the right to practice their religion requires that they not be made complicit in any practice to which they object on religious grounds.

Although it may be that, as Mahatma Gandhi said, "in matters of conscience, the law of majority has no place," acts of conscience are usually accompanied by a willingness to pay some price. Martin Luther King, Jr., argued, "An individual who breaks a law that conscience tells him is unjust, and who willingly accepts the penalty of imprisonment in order to arouse the conscience of the community over its injustice, is in reality expressing the highest respect for law."

What differentiates the latest round of battles about conscience clauses from those fought by Gandhi and King is the claim of entitlement to what newspaper columnist Ellen Goodman has called "conscience without consequence."

And of course, the professionals involved seek to protect only themselves from the consequences of their actions — not their patients. In Wisconsin, a pharmacist refused to fill an emergency-contraception prescription for a rape victim; as a result, she became pregnant and subsequently had to seek an abortion. In another Wisconsin case, a pharmacist who views hormonal contraception as a form of abortion refused not only to fill a prescription for birth-control pills but also to return the prescription or transfer it to another pharmacy. The patient,



State Requirements Governing the Refusal by Pharmacists to Fill Certain Prescriptions.

Illinois has a regulation that requires pharmacies to fill valid contraception prescriptions in a timely manner, but a resolution has been introduced to permit refusals. Massachusetts has a pharmacy-board policy that requires pharmacists to fill valid prescriptions in a timely manner. North Carolina has a pharmacy-board policy that requires pharmacists to ensure that valid prescriptions are filled in a timely manner. Wyoming has a bill that would permit providers to refuse to abide by advance directives that might, in some scenarios, apply to pharmacists who refuse to fill certain prescriptions. Adapted from a map compiled by the National Women's Law Center.

unable to take her pills on time, spent the next month dependent on less effective contraception. Under Wisconsin's proposed law, such behavior by a pharmacist would be entirely legal and acceptable. And this trend is not limited to pharmacists and physicians; in Illinois, an emergency medical technician refused to take a woman to an abortion clinic, claiming that her own Christian beliefs prevented her from transporting the patient for an elective abortion.

At the heart of this growing trend are several intersecting forces. One is the emerging norm of patient autonomy, which has contributed to the erosion of the professional stature of medicine. Insofar as they are reduced to mere purveyors of medical technology, doctors no longer have extraordinary privileges, and so their notions of extraordinary duty — house calls, midnight duties, and charity care — deteriorate as well. In addition, an emphasis on mutual responsibilities has been gradually supplanted by an emphasis on individual rights. With autonomy and rights as the preeminent social values comes a devaluing of relationships and a diminution of the difference between our personal lives and our professional duties.

Finally, there is the awesome scale and scope of the abortion wars. In the absence of legislative options for outright prohibition, abortion opponents search for proxy wars, using debates on research involving human embryos, the donation of organs from anencephalic neonates, and the right of persons in a persistent vegetative state to die as opportunities to rehearse arguments on the value of biologic but nonsentient human existence. Conscience clauses represent but another battle in these so-called culture wars.

Most profoundly, however, the surge in legislative activity surrounding conscience clauses represents the latest struggle with regard to religion in America. Should the public square be a place for the unfettered expression of religious beliefs, even when such expression creates an oppressive atmosphere for minority groups? Or should it be a place for religious expression only if and when that does not in any way impinge on minority beliefs and practices? This debate has been played out with respect to blue laws, school prayer, Christmas crèche scenes, and workplace dress codes.

Until recently, it was accepted that the public square in this country would be dominated by Chris-

tianity. This long-standing religious presence has made atheists, agnostics, and members of minority religions view themselves as oppressed, but recent efforts to purge the public square of religion have left conservative Christians also feeling subjugated and suppressed. In this culture war, both sides claim the mantle of victimhood — which is why health care professionals can claim the right of conscience as necessary to the nondiscriminatory practice of their religion, even as frustrated patients view conscience clauses as legalizing discrimination against them when they practice their own religion.

For health care professionals, the question becomes: What does it mean to be a professional in the United States? Does professionalism include the rather old-fashioned notion of putting others before oneself? Should professionals avoid exploiting their positions to pursue an agenda separate from that of their profession? And perhaps most crucial, to what extent do professionals have a collective duty to ensure that their profession provides nondiscriminatory access to all professional services?

Some health care providers would counter that they distinguish between medical care and nonmedical care that uses medical services. In this way, they justify their willingness to bind the wounds of the criminal before sending him back to the street or to set the bones of a battering husband that were broken when he struck his wife. Birth control, abortion, and in vitro fertilization, they say, are lifestyle choices, not treatments for diseases.

And it is here that licensing systems complicate the equation: such a claim would be easier to make if the states did not give these professionals the exclusive right to offer such services. By granting a monopoly, they turn the profession into a kind of public utility, obligated to provide service to all who seek it. Claiming an unfettered right to personal autonomy while holding monopolistic control over a public good constitutes an abuse of the public trust — all the worse if it is not in fact a personal act of conscience but, rather, an attempt at cultural conquest.

Accepting a collective obligation does not mean that all members of the profession are forced to violate their own consciences. It does, however, necessitate ensuring that a genuine system for counseling and referring patients is in place, so that every patient can act according to his or her own conscience just as readily as the professional can. This goal is not simple to achieve, but it does represent the best effort to accommodate everyone and is the approach taken by virtually all the major medical, nursing, and pharmacy societies. It is also the approach taken by the governor of Illinois, who is imposing an obligation on pharmacies, rather than on individual pharmacists, to ensure access to services for all patients.

Conscience is a tricky business. Some interpret its personal beacon as the guide to universal truth. But the assumption that one's own conscience is the conscience of the world is fraught with dangers. As C.S. Lewis wrote, "Of all tyrannies, a tyranny sincerely exercised for the good of its victims may be the most oppressive. It would be better to live under robber barons than under omnipotent moral busybodies. The robber baron's cruelty may sometimes sleep, his cupidity may at some point be satiated; but those who torment us for our own good will torment us without end for they do so with the approval of their own conscience."

Taking Their Own Lives — The High Rate of Physician Suicide

Eva Schernhammer, M.D., Dr.P.H.

When I was an oncology fellow in Vienna, a colleague who had attended rounds with me on the ward went home afterward and strangled herself. Only later was it learned that she had suffered from depression. In the course of that same year, three more physicians in my immediate circle — two residents and a department head — took their own lives. This stunning series was my first encounter with physician suicide, and it left many of us doctors with an important message: we must care not only for our patients but also for ourselves. In an effort to prevent further such tragedies, a program

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was launched at the hospital to help physicians and nurses grapple with the emotional effects of caring for the chronically ill. But the suicides that had already occurred were never discussed openly, no one undertook a publicly acknowledged serious analysis of the causes, and no other clear safeguards were put into place. The deaths were simply accepted as a fact of medical life.

Although physicians tend to have healthier lifestyles than those of the general public and thus to live longer, it has been known for some time that suicide rates among doctors are higher than those in the general population (see graphs). And when these tragic events make it into the headlines, as did the recent suicide of gifted heart surgeon Jonathan Drummond-Webb, we begin to wonder why these healers apparently cannot heal the hurt in their own lives.

The gap in suicide rates evidently begins as early as medical school, where overall suicide rates are higher than in the age-matched population. This increased rate of suicide is driven largely by higher rates among women: female medical students commit suicide at the same rate as male medical students,[2] whereas in the United States in general, suicide rates are much higher among men. Evidence from a large study of physician suicide indicates that female doctors, in particular, are much more likely than other women to take their own lives. The combined results of 25 studies suggest that the suicide rate among male doctors is 40 percent higher than that among men in general, whereas the rate among female doctors is 130 percent higher than that among women in general.[1]

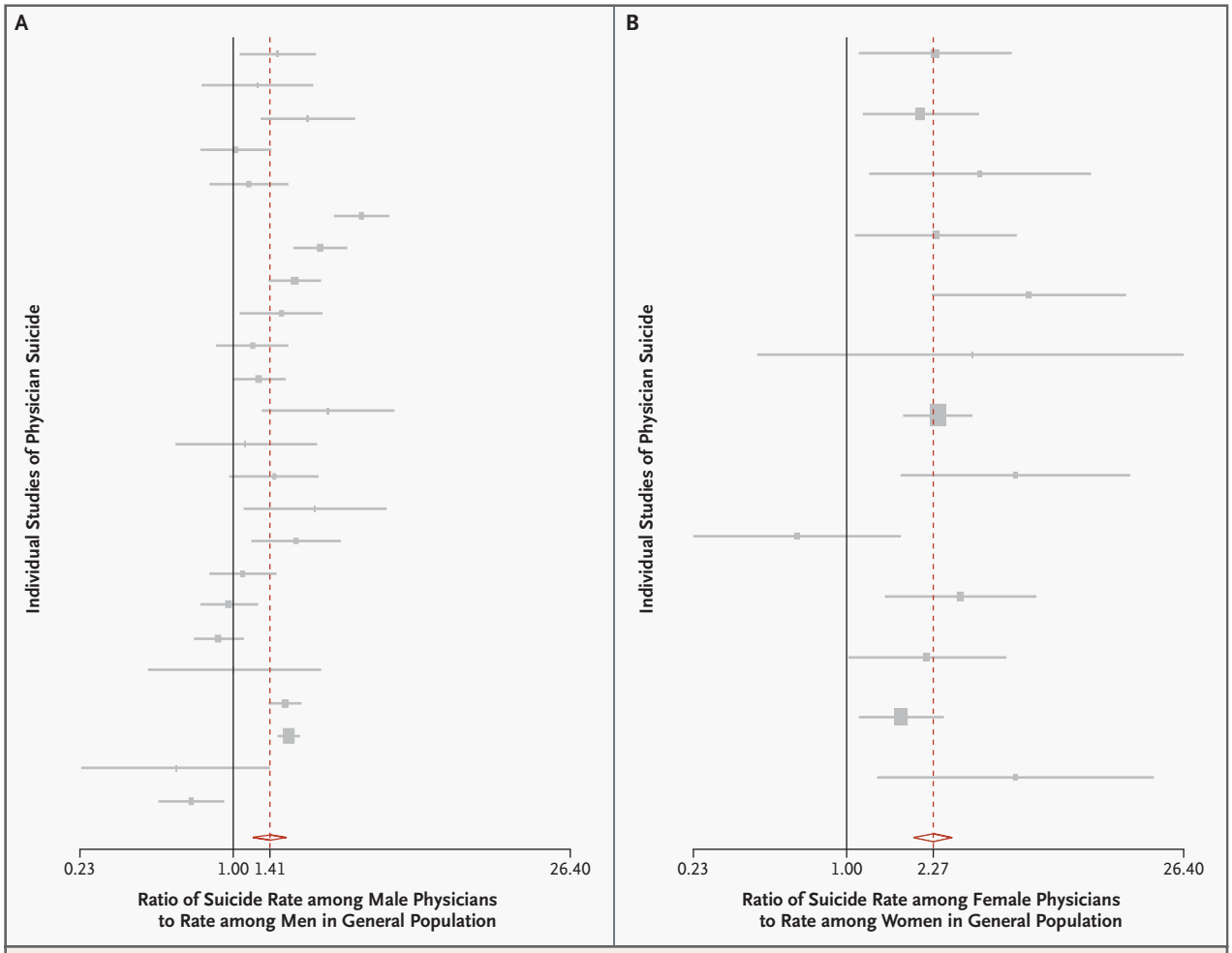
Several factors that may contribute to the suicide of physicians, especially female physicians, deserve closer examination. Physicians may have a higher prevalence of depression than nonphysicians, and depression is clearly an important risk factor for suicide; among female physicians, the risk may be exacerbated by sexual harassment; and when they become suicidal, physicians generally choose effective suicide methods.

A prevalent view is that both biologic and psychosocial factors play a role — and interact — in the decision to commit suicide. There is a higher prevalence of psychiatric disorders among physicians than in the general population. Some 30 to 70 percent of all persons who attempt suicide apparently have an affective disorder (generally depression), a substance-use–related disorder, or schizophrenia.[3] Evidence further suggests that drug abuse and alcoholism, possibly under circumstances of heightened stress or depression, are often associated with the suicides of physicians. Female physicians, in particular, have been shown to have a higher frequency of alcoholism than women in the general population. Drug abuse is also related to specialty, being particularly prevalent among psychiatrists, anesthesiologists, and emergency physicians. Recent reports emphasize that the exposure that anesthesiologists have to drugs as they work represents a risk factor for drug addiction and possibly suicide, indicating that access to drugs may support higher suicide rates among physicians by a variety of pathways. In the general population, according to autopsy studies and other evidence, as many as 25 percent of all persons who commit suicide are drunk at the time of their deaths.

Another way to view the problem is that the professional burden carried by doctors leads to social isolation and an increased probability of undergoing phases of disturbances in their social networks. It has also been noted that physicians tend to neglect their own need for psychiatric, emotional, or medical help and are more critical than most people of both others and themselves. They are more likely to blame themselves for their own illnesses. And they are apparently more susceptible to depression caused by adverse life events, such as the death of a relative, divorce, or the loss of a job.[4]

Being single and not having children have also been linked to an increased risk of suicide, and more female than male physicians are single or childless. Some studies of coping have emphasized that women in general are subject to a double burden — being vulnerable to pressures of both family life and work life. Stress and burnout may be added risk factors for all physicians, and female doctors may feel more stress than their male counterparts because of the difficulty of succeeding in a male-dominated profession.

They may also be the targets of sex-based or sexual harassment, which may, in turn, lead to depression and suicidality. In a study by Frank et al., 48 percent of female physicians reported having experienced sex-based ("gender-based," per study questionnaire) harassment at least once, and 37 percent reported sexual harassment.[5] Moreover, the study established a link between higher rates of harassment and a history of depression or suicide attempts, showing an association between the sever-



Suicide Rates among Male Physicians (Panel A) and Female Physicians (Panel B) in Relation to the Rates in the General Population of the Same Sex.

The size of each box represents the relative size of the study sample, and the horizontal line that intersects the box indicates the 95 percent confidence interval. The dashed red line in each panel indicates the combined estimate. The diamond-shaped box represents the confidence interval. The data are from a meta-analysis by Schernhammer and Colditz.[1]

ity of harassment and the likelihood of depression. Sex-based harassment and sexual harassment are more common in historically male-dominated specialties, such as surgery and emergency medicine. According to unpublished data from a recent U.S. study by Straehley and Longo of the difficulties women face when entering the field of medicine, more than 75 percent of interviewed female surgeons said that they had been harassed. Moreover, according to Frank et al., whose study results concurred with these findings, harassment rates are not declining.[5] It has been argued that the reinforcing of sex stereotypes through the promulgation of the belief that women are innately inferior to men in science may well contribute to the ongoing harassment of female physicians.

Finally, physicians who make suicide attempts are much more likely than nonphysicians to succeed. Among physicians in this country, in fact, there are fewer unsuccessful suicide attempts than completed suicides — a stark contrast to the data for U.S. women in general, for instance, among whom the ratio of unsuccessful attempts to completed suicides is between 10:1 and 15:1.

Not surprisingly, the method chosen predicts the likelihood of success. Women in the general population make more unsuccessful suicide attempts than men, in large part because they prefer

methods that are typically less deadly than those — such as the use of firearms — favored by men. It is possible, therefore, that the higher suicide rate among female physicians simply reflects a combination of the sex difference in the rate of suicide attempts and a higher rate of completion inside the medical profession than outside it.

According to a recent study, doctors most commonly take their own lives by poisoning themselves, often with drugs taken from their offices or laboratories. The fact that greater access to drugs leads to higher suicide rates has long been known — for example, in Australia, an increase in suicides among women coincided with the implementation of a law that made it easier to obtain barbiturates. It seems likely that the higher suicide rate among physicians is related to both their relatively free access to drugs and their medical knowledge, which enhances their ability to use such methods successfully.

There are few interventions in place to help prevent suicide among physicians. Such safeguards might include the provision of discreet and confidential access to psychotherapy and open discussion of the stress encountered in a medical career. The barriers that may prevent physicians from seeking help for mental disorders (such as the threat of losing their medical licenses) must also be addressed. Part of the solution for female doctors must ultimately be to equalize professional conditions in order to reduce stress. In time, perhaps these and other measures will help doctors to do what they do best: save lives, beginning with their own.

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2. Pepitone-Arreola-Rockwell F, Rockwell D, Core N. Fifty-two medical student suicides. Am J Psychiatry 1981;138:198-201.
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5. Frank E, Brogan D, Schiffman M. Prevalence and correlates of harassment among US women physicians. Arch Intern Med 1998;158:352-8.

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Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

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ABSTRACT

BACKGROUND

We conducted a randomized clinical trial to determine whether treatment of women with gestational diabetes mellitus reduced the risk of perinatal complications.

METHODS

We randomly assigned women between 24 and 34 weeks' gestation who had gestational diabetes to receive dietary advice, blood glucose monitoring, and insulin therapy as needed (the intervention group) or routine care. Primary outcomes included serious perinatal complications (defined as death, shoulder dystocia, bone fracture, and nerve palsy), admission to the neonatal nursery, jaundice requiring phototherapy, induction of labor, cesarean birth, and maternal anxiety, depression, and health status.

RESULTS

The rate of serious perinatal complications was significantly lower among the infants of the 490 women in the intervention group than among the infants of the 510 women in the routine-care group (1 percent vs. 4 percent; relative risk adjusted for maternal age, race or ethnic group, and parity, 0.33; 95 percent confidence interval, 0.14 to 0.75; P=0.01). However, more infants of women in the intervention group were admitted to the neonatal nursery (71 percent vs. 61 percent; adjusted relative risk, 1.13; 95 percent confidence interval, 1.03 to 1.23; P=0.01). Women in the intervention group had a higher rate of induction of labor than the women in the routine-care group (39 percent vs. 29 percent; adjusted relative risk, 1.36; 95 percent confidence interval, 1.15 to 1.62; P<0.001), although the rates of cesarean delivery were similar (31 percent and 32 percent, respectively; adjusted relative risk, 0.97; 95 percent confidence interval, 0.81 to 1.16; P=0.73). At three months post partum, data on the women's mood and quality of life, available for 573 women, revealed lower rates of depression and higher scores, consistent with improved health status, in the intervention group.

CONCLUSIONS

Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve the woman's health-related quality of life.

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*Members of the ACHOIS Trial Group are listed in the Appendix.

N Engl J Med 2005;352:2477-86.

Gestational diabetes mellitus occurs in 2 to 9 percent of all pregnancies[1,2] and is associated with substantial rates of maternal and perinatal complications. The risk of perinatal mortality is not increased,[3] but the risk of macrosomia is. Other perinatal risks include shoulder dystocia, birth injuries such as bone fractures and nerve palsies, and hypoglycemia. Long-term adverse health outcomes reported among infants born to mothers with gestational diabetes include sustained impairment of glucose tolerance,[4] subsequent obesity[5] (although not when adjusted for size[6]), and impaired intellectual achievement.[7] For women, gestational diabetes is a strong risk factor for diabetes.[8]

Although the risks associated with gestational diabetes are well recognized, it remains uncertain whether screening and treatment to reduce maternal glucose levels reduce these risks. Given this uncertainty, professional groups disagree on whether to recommend routine screening, selective screening based on risk factors for gestational diabetes, or no screening; some recommend screening,[1,2,9,10] whereas others do not.[11-14] There have been repeated calls for well-designed, randomized trials to determine the efficacy of screening, diagnosis, and management of gestational diabetes.[1,3,15-18] We designed the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial to assess whether the treatment of gestational diabetes would reduce perinatal complications and to assess the effects of treatment on maternal outcome, mood, and quality of life.

METHODS

DESIGN AND STUDY POPULATION

Eligible women had a singleton or twin pregnancy between 16 and 30 weeks' gestation, attended antenatal clinics at the collaborating hospitals, had one or more risk factors for gestational diabetes on selective screening or a positive 50-g oral glucose-challenge test (glucose level one hour after glucose challenge at least 7.8 mmol per liter [140 mg per deciliter]), and had a 75-g oral glucose-tolerance test at 24 to 34 weeks' gestation in which the venous plasma glucose level was less than 7.8 mmol per liter after an overnight fast and was 7.8 to 11.0 mmol per liter (198 mg per deciliter) at two hours.[19] When the study was initiated, women meeting these criteria were classified as having glucose intolerance of pregnancy, on the basis of the World Health Organization (WHO) definition: a glycemic response to a standard oral glucose-tolerance test that was intermediate between the normal and diabetic response, with an onset or recognition of the condition during the present pregnancy.[19] From 1998 onward, the WHO classified any glucose levels above normal as indicative of gestational diabetes.[20] Women with more severe glucose impairment were not eligible for this trial.

Women were advised to follow a normal diet 48 hours before the oral glucose-tolerance test and to fast for 8 hours the night before the test. Blood samples were obtained after the overnight fast and one and two hours after the receipt of the 75-g oral glucose load. Women with previously treated gestational diabetes or active chronic systemic disease (except essential hypertension) were excluded.

The protocol was approved by the ethics committee at each of the 18 collaborating centers (14 in Australia and 4 in the United Kingdom). All women provided written informed consent. None of the funding bodies were involved in the trial design or conduct; collection, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Women were provided with written information about the study, and this information was reviewed with them orally before their oral glucose-tolerance test. They were informed that they would be eligible for randomization only if their results were in the range specified above. If they were assigned to the intervention group, they received a slip indicating a diagnosis of glucose intolerance of pregnancy and the plan for intervention, whereas if they were assigned to routine care, they received a slip indicating that they did not have gestational diabetes. This approach was continued throughout the trial, because there remained uncertainty as to the level of glucose impairment associated with adverse perinatal outcomes[21]; there was wide variation in the glucose levels used to define the need for treatment[22]; some committees,[1,20] but not others,[9] made changes in the nomenclature; and there was still no clear evidence of the benefits and harms of treatment.[17,18] After consent had been obtained, a proportion of the women (not fewer than one in five) who had normal oral glucose-tolerance test results were assigned to the routine-care group to help maintain blinding. Women whose glucose levels exceeded cutoff values for eligibility were informed that they had gestational diabetes.

INTERVENTIONS

Stratification was according to center and singleton or twin gestation. Randomization was performed centrally with the use of numbers generated by computer with variable block sizes of 6, 8, and 10. The full numerical results of the oral glucose-tolerance test were not released to the women or their providers until after birth, before discharge from the hospital.

Women who were randomly assigned to the intervention group received ongoing care by the attending obstetrical team with a physician's support. Interventions included individualized dietary advice from a qualified dietitian, which took into consideration a woman's prepregnancy weight, activity level, dietary intake, and weight gain; instructions on how to self-monitor glucose levels, which the woman was then asked to do four times daily until the levels had been in the recommended range for 2 weeks (fasting glucose levels of at least 3.5 mmol per liter [63 mg per deciliter] and no more than 5.5 mmol per liter [99 mg per deciliter], preprandial levels of no more than 5.5 mmol per liter, and levels two hours postprandially that were no more than 7.0 mmol per liter [126 mg per deciliter]), followed by daily monitoring at rotating times during the day; and insulin therapy, with the dose adjusted on the basis of glucose levels, if there were two capillary-blood glucose results during the 2-week period in which the fasting level was at least 5.5 mmol per liter or the postprandial level was at least 7.0 mmol per liter at 35 weeks' gestation or less, if the postprandial level was at least 8.0 mmol per liter (144 mg per deciliter) at more than 35 weeks' gestation, or if one capillary-blood glucose result during the 2-week period was at least 9.0 mmol per liter (162 mg per deciliter).

The care of the women in the intervention group replicated clinical care in which universal screening and treatment for gestational diabetes are available. Women in the routine-care group and their caregivers were unaware of the diagnosis of glucose intolerance of pregnancy. At the discretion of the attending clinician, if indications arose that were suggestive of diabetes, further assessment for gestational diabetes was permitted, with treatment as considered appropriate. The care of the women in the routine-care group replicated clinical care in which screening for gestational diabetes is not available. The care women and infants received was otherwise according to standard practice at each center. A research assistant extracted data on treatment from the medical records of the woman and her infant to the time of hospital discharge as well as on antenatal, birth, or postnatal complications.

OUTCOME VARIABLES

Primary outcomes among the infants were a composite measure of serious perinatal complications (defined as one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy), admission to the neonatal nursery, and jaundice requiring phototherapy. The presence and severity of shoulder dystocia were assessed by means of a standardized checklist completed by the caregiver present at the birth.

Primary clinical outcomes among the women were the need for induction of labor and cesarean section. Maternal health status was assessed by means of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional role, pain, and vitality; scores on each scale can range from 0 (worst) to 100 (best).[23] Maternal psychological outcomes included measures of anxiety, depression, and health-related quality of life. Anxiety was assessed with the use of the short form of the Spielberger State–Trait Anxiety Inventory,[24] a self-rating scale consisting of 6 items (scores below 15 are considered normal). The presence of depression was reflected by a score of more than 12 on the Edinburgh Postnatal Depression Scale.[25] Questionnaires were mailed six weeks after study entry and at three months post partum to 916 women (92 percent of the total) recruited to the study after funding for this assessment became available.

Secondary outcomes among the infants included components of the composite primary outcome, gestational age at birth, birth weight, and other measures of health. Secondary outcomes among the women included the number of prenatal visits to a health professional, the mode of birth, weight gain during pregnancy, the number of antenatal admissions, and the presence or absence of pregnancy-induced hypertension (defined as a blood pressure of at least 140/90 mm Hg on two occasions four or more hours apart) and other complications.

STATISTICAL ANALYSIS

Statistical analyses were based on the intention to treat and used SAS software, version 8.2 (SAS Institute). Analyses were adjusted for maternal age, race

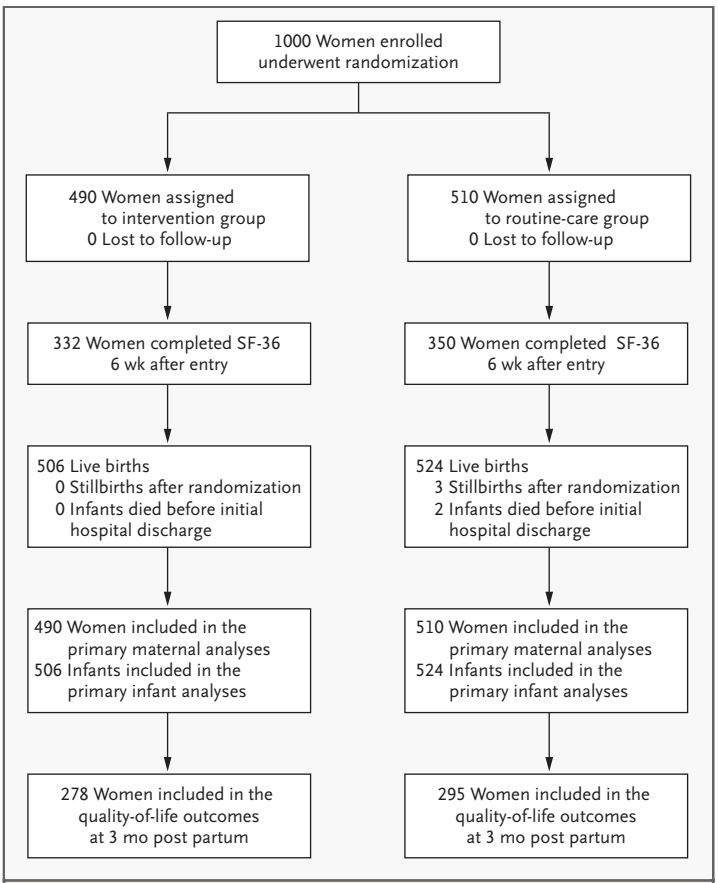

Figure 1. Enrollment and Outcomes.

or ethnic group, and parity. Binary outcomes are presented as relative risks, with 95 percent confidence intervals; the number needed to treat to benefit (i.e., the number of patients who would need to be treated for a benefit in one patient) and the number needed to treat to harm (i.e., the number of patients who would need to be treated for harm to occur in one patient), with their 95 percent confidence intervals,[26] are presented for primary clinical outcomes. Relative risks were calculated with the use of log binomial regression. Continuous variables were analyzed by means of analysis of variance if they were normally distributed and by means of nonparametric tests if their distribution was not normal. The health state utility was calculated from the SF-36 according to the method of Brazier et al.[27] With no evidence of increased variance owing to the small number of twins in the study, no adjustment was made for clustering of babies with the same mothers. A P value of 0.05 was considered to indicate statistical significance; all P values were two-sided. A step-down Sidak adjustment was made for analyses involving multiple primary clinical end points.[28]

We estimated that we would need to enroll 1000 women for the study to have a statistical power of 80 percent (two-sided alpha value of 0.05) to detect a reduction in the risk of a serious perinatal outcome from 5.2 percent to 2.0 percent, using outcomes reported for all South Australian births[29] and data from Women's and Children's Hospital in Adelaide. Data were reviewed once in January 1999 by our independent data-monitoring committee, whose members were unaware of the treatment assignments, after the enrollment of 460 women. The study protocol included a prespecified stopping rule for a difference in a major end point of at least 3 SD between the groups.

RESULTS

Of the 1000 women enrolled in the study, 490 were assigned to the intervention group and 510 to the routine-care group (Fig. 1). Recruitment started in September 1993 and stopped in June 2003, after 1000 women had been enrolled. Clinical outcomes were obtained up to the time of hospital discharge for all women and their 1030 infants.

On the whole, the two groups were similar at entry. As compared with the women in the routine-care group, women in the intervention group were older and were less likely to be white or primiparous (Table 1). Ninety-three percent of the women had been found to be at risk for gestational diabetes on the basis of the oral glucose-challenge test, and the remainder on the basis of risk factors.

PRIMARY OUTCOMES

The rate of serious perinatal outcomes among the infants (defined by one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy) was significantly lower in the intervention group than the routine-care group (1 percent vs. 4 percent; P=0.01, adjusted for maternal age, race or ethnic group, and parity (Table 2). Thus, the number needed to treat to prevent a serious outcome in an infant was 34 (95 percent confidence interval, 20 to 103). A higher percentage of infants born to women in the intervention group than of infants born to women in the routine-care group were admitted to the neonatal nursery (71 percent vs. 61 percent, adjusted P=0.01). The length of stay in the neonatal nursery among the infants who were ad-

mitted did not differ significantly between groups (median of 1 day for both groups; interquartile range, 1 to 2 days in the intervention group and 1 to 3 days in the routine-care group; adjusted P=0.81). There was no significant difference in the percentage of infants who had jaundice requiring phototherapy in the two groups (adjusted P=0.72) (Table 2).

The induction of labor was significantly more common in the intervention group than in the routine-care group (39 percent vs. 29 percent; adjusted P<0.001) (Table 2). The rates of cesarean delivery were similar in the two groups (adjusted P=0.73) (Table 2), as were the reasons for cesarean delivery.

Step-down Sidak adjustments were made to correct for the analyses of multiple primary clinical end points (Table 2). The results remained consistent across these analyses, with the intervention group having a reduced risk of serious perinatal outcomes (corrected P=0.04) and an increased likelihood of admission to the neonatal nursery for the infant (corrected P=0.04) and use of induction of labor for the mother (corrected P=0.003).

Maternal health status was measured in 682 women (68 percent) who completed the questionnaires six weeks after enrollment and 573 women (57 percent) who completed them three months post partum. Women who completed assessments were slightly older than, but otherwise similar to, women who did not.

All measures on the SF-36[23] showed trends in favor of the intervention group, although not all were significant (Table 3). At three months post partum, fewer women in the intervention group than in the routine-care group had a score on the Edinburgh Postnatal Depression Scale[25] suggestive of depression (23 vs. 50 [8 percent vs. 17 percent]). The level of anxiety was similar in the two groups (Table 3).

Table 1. Baseline Characteristics of the Women.*

Characteristic	Intervention Group (N=490)	Routine-Care Group (N=510)
Age — yr	30.9±5.4	30.1±5.5
Primiparous — no. (%)	212 (43)	251 (49)
Body-mass index†		
Median	26.8	26.0
Interquartile range	23.3–31.2	22.9–30.9
Race or ethnic group — no. (%)‡		
White	356 (73)	396 (78)
Asian	92 (19)	72 (14)
Other	42 (9)	42 (8)
Gestational age at entry — wk		
Median	29.1	29.2
Interquartile range	28.2–30.0	28.2–30.0
OGCT — mmol/liter		
Median	8.8	8.8
Interquartile range	8.2–9.7	8.3–9.7
OGTT for positive OGCT — no. (%)	461 (94)	471 (92)
Fasting	4.8±0.7	4.8±0.6
2-hr		
Median	8.6	8.5
Interquartile range	8.1–9.3	8.1-9.1
Previous pregnancy ending in perinatal death — no./total no. (%)	12/278 (4)	7/259 (3)

* Plus–minus values are means ±SD. OGCT denotes oral glucose-challenge test, and OGTT oral glucose-tolerance test.
† Data are from the first trimester. The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported.

SECONDARY OUTCOMES

No perinatal deaths occurred among the infants of mothers in the intervention group, but there were five perinatal deaths (three stillbirths and two neonatal deaths) among infants born to women in the routine-care group (Fig. 1 and Table 2). Two stillbirths were unexplained intrauterine deaths at term of appropriately grown infants, and the other, at 35 weeks' gestation, was associated with preeclampsia and intrauterine growth restriction. One infant had a lethal congenital anomaly, and one infant died after an asphyxial condition during labor without antepartum hemorrhage.

There was no significant difference in the rates of shoulder dystocia between the intervention and routine-care groups (1 percent and 3 percent, respectively) (Table 2). No infant in the intervention group had a bone fracture or nerve palsy, whereas in the routine-care group, one infant had both a fractured humerus that was not related to a difficult birth and a radial-nerve palsy, one infant had Erb's palsy related to shoulder dystocia, and one infant had Erb's palsy alone (Table 2).

Infants born to women in the intervention group had significantly lower mean birth weights than infants born to women in the routine-care group (P<0.001) (Table 4), and they were also born at an earlier gestational age, in keeping with the higher incidence of induction of labor in their mothers (Table 5). Significantly fewer infants in the intervention

Table 2. Primary Clinical Outcomes among the Infants and Their Mothers.*

Outcome	Intervention Group	Routine-Care Group	Unadjusted Relative Risk (95% CI)	Unadjusted P Value	Adjusted Relative Risk (95% CI)†	Adjusted P Value†	Step-Down Sidak P Value
	no. (%)						
Infants							
Total no.	506	524					
Any serious perinatal complication‡	7 (1)	23 (4)	0.32 (0.14–0.73)	0.004	0.33 (0.14–0.75)	0.01	0.04
Death	0	5 (1)		0.06		0.07	
Stillbirth	0	3 (1)§		0.25		0.26	
Neonatal death	0	2 (<1)		0.50		0.50	
Shoulder dystocia¶	7 (1)	16 (3)	0.45 (0.19–1.09)	0.07	0.46 (0.19–1.10)	0.08	
Bone fracture	0	1 (<1)		1.00		0.38	
Nerve palsy	0	3 (1)‖		0.25		0.11	
Admission to neonatal nursery**	357 (71)	321 (61)	1.15 (1.05–1.26)	0.002	1.13 (1.03–1.23)	0.01	0.04
Jaundice requiring phototherapy	44 (9)	48 (9)	0.95 (0.64–1.40)	0.79	0.93 (0.63–1.37)	0.72	0.98
Women							
Total no.	490	510					
Induction of labor††	189 (39)	150 (29)	1.31 (1.10–1.56)	0.002	1.36 (1.15–1.62)	<0.001	0.003
Cesarean delivery	152 (31)	164 (32)	0.96 (0.80–1.16)	0.70	0.97 (0.81–1.16)	0.73	0.98
Elective	72 (15)	61 (12)	1.23 (0.89–1.69)	0.20	1.17 (0.85–1.60)	0.33	
Emergency	80 (16)	103 (20)	0.81 (0.62–1.05)	0.11	0.87 (0.68–1.13)	0.31	

* CI denotes confidence interval.
† Values were adjusted for maternal age, race or ethnic group, and parity.
‡ Serious perinatal complications were defined as one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy. The number needed to treat to benefit was 34 (95 percent confidence interval, 20 to 103).
§ Gestational ages at delivery for the three stillborn infants were 35, 37, and 40 weeks.
¶ Shoulder dystocia was recorded by the primary caregiver present at the birth.
‖ One infant had both a fractured humerus and a radial-nerve palsy. One infant had both shoulder dystocia and Erb's palsy.
** The number needed to treat to harm was 11 (95 percent confidence interval, 7 to 29).
†† Indications for the induction of labor in the intervention and routine-care groups were as follows: gestational diabetes in 23 percent and 4 percent, respectively; preeclampsia in 6 percent and 12 percent, respectively; past due dates in 8 percent of each group; fetal compromise in 5 percent and 2 percent, respectively; and other indications in 5 percent and 3 percent, respectively. The number needed to treat to harm was 11 (95 percent confidence interval, 7 to 31).

group were large for gestational age at birth, and significantly fewer had macrosomia (defined by a birth weight of 4 kg or greater) (Table 4). There was no significant difference between groups in the proportion of infants who were small for gestational age.

Women in the intervention group had fewer antenatal clinic visits after enrollment than did women in the routine-care group, but they had more visits to the physician and were significantly more likely to see a dietitian and a diabetes educator (Table 5). One hundred women in the intervention group (20 percent) received insulin therapy, as compared with 17 in the routine-care group (3 percent). Weight gain from the booking appointment to the last antenatal visit was less in the intervention group than in the routine-care group (Table 5). The rates of antenatal hospital admissions were similar in the two groups. Fewer women in the intervention group than in the routine-care group received a diagnosis of preeclampsia during the antenatal period (Table 5).

DISCUSSION

In this randomized clinical trial, treatment of women with gestational diabetes — including dietary advice, blood glucose monitoring, and insulin therapy — reduced the rate of serious perinatal outcomes (defined as death, shoulder dystocia, bone fracture, and nerve palsy) from 4 percent to 1 percent. These benefits were associated with an increased use of

Table 3. Quality of Life during Pregnancy and Three Months after Giving Birth.*

Variable	Intervention Group	Routine-Care Group	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
6 Wk after enrollment				
No. of women	332	350		
SF-36 score‡				
Physical functioning	56.4±23.1	54.0±22.7	2.5 (–1.0 to 6.0)	0.16
Physical role	40.7±41.4	32.4±38.1	8.6 (2.5 to 14.6)	0.01
Bodily pain	63.1±24.6	59.0±24.1	4.1 (0.4 to 7.8)	0.03
General health	73.4±17.4	72.5±18.9	1.0 (–1.8 to 3.7)	0.48
Vitality	50.0±21.0	46.7±20.3	3.1 (0.1 to 6.1)	0.04
Social functioning	73.5±24.0	70.9±23.2	2.9 (–0.7 to 6.5)	0.11
Emotional role	77.5±35.3	69.1±40.9	9.4 (3.5 to 15.2)	0.002
Mental health	75.1±15.4	73.8±16.6	1.4 (–1.1 to 3.8)	0.27
Overall physical component	38.8±9.4	37.3±9.0	1.5 (–0.1 to 2.9)	0.04
Overall mental component	50.9±9.2	49.6±10.4	1.2 (–0.3 to 2.7)	0.11
Health state utility	0.72±0.11	0.70±0.11	0.03 (0.01 to 0.04)	0.005
Anxiety§	11.2± 3.7	11.5±4.0	–0.4 (–1.0 to 0.2)	0.17
3 Mo post partum				
No. of women	278	295		
SF-36 score‡				
Physical functioning	85.8±19.5	83.6±19.6	3.2 (0.1 to 6.3)	0.05
Role physical	79.9±33.7	75.9±36.3	5.3 (–0.4 to 11.1)	0.07
Bodily pain	77.7±23.0	77.3±21.6	1.1 (–2.6 to 4.7)	0.57
General health	76.8±17.5	74.2±18.2	3.2 (0.2 to 6.1)	0.03
Vitality	60.0±19.3	57.7±19.7	2.2 (–1.1 to 5.4)	0.19
Social functioning	81.4±21.3	70.0±23.3	3.2 (–0.4 to 6.8)	0.09
Role emotional	78.9±35.0	78.5±35.7	1.6 (–4.3 to 7.4)	0.60
Mental health	77.0±15.4	77.4±16.7	0.1 (–2.7 to 2.6)	0.96
Overall physical component	51.2±8.5	50.0±8.5	1.5 (0.1 to 2.9)	0.03
Overall mental component	48.6±10.0	48.4±10.9	0.3 (–1.5 to 2.1)	0.72
Health state utility	0.79±0.10	0.78±0.11	0.01 (–0.01 to 0.03)	0.22
Anxiety score§	10.6±3.9	10.8±3.8	–0.3 (–0.9 to 0.4)	0.41
EPDS score >12 — no. (%)	23 (8)	50 (17)	0.46 (0.29 to 0.73)	0.001

* The quality of life was first measured six weeks after enrollment. Plus–minus values are means ±SD. CI denotes confidence interval, and EPDS the Edinburgh Postnatal Depression Scale.
† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for all outcomes except an EPDS score higher than 12, for which the treatment effect is expressed as the relative risk.
‡ Scores for the SF-36 can range from 0 (worst) to 100 (best).
§ Anxiety was measured by means of the short form of the Spielberger State–Trait Anxiety Inventory; scores below 15 are considered normal.

induction of labor for the mother and an increased rate of admission to the neonatal nursery for the infant, both of which may be related to the knowledge of the diagnosis by the attending physician. The earlier gestational age at birth as a consequence of the induction of labor may have contributed to the reduction in serious perinatal outcomes. Others have reported an increased rate of cesarean delivery associated with the diagnosis and treatment of gestational diabetes.[12] In our study, the rate of cesarean delivery was similar in the two groups.

We chose primary clinical outcomes to assess the effects of treatment for gestational diabetes on both the mothers and the infants. Differences be-

Table 4. Secondary Outcomes among the Infants.*

Outcome	Intervention Group (N=506)	Routine-Care Group (N=524)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
Birth weight — g	3335±551	3482±660	−145 (−219 to −70)	<0.001
Large for gestational age — no. (%)‡	68 (13)	115 (22)	0.62 (0.47 to 0.81)	<0.001
Macrosomia (≥4 kg) — no. (%)	49 (10)	110 (21)	0.47 (0.34 to 0.64)	<0.001
Small for gestational age — no. (%)§	33 (7)	38 (7)	0.88 (0.56 to 1.39)	0.59
5-Min Apgar score <7 — no. (%)	6 (1)	11 (2)	0.57 (0.21 to 1.53)	0.26
Hypoglycemia requiring IV therapy — no. (%)¶	35 (7)	27 (5)	1.42 (0.87 to 2.32)	0.16
Neonatal convulsions — no. (%)	1 (<1)	2 (<1)	0.52 (0.05 to 5.69)	1.00
Respiratory distress syndrome — no. (%)‖	27 (5)	19 (4)	1.52 (0.86 to 2.71)	0.15

* Plus–minus values are means ±SD. CI denotes confidence interval, and IV intravenous.
† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for birth weight and as the relative risk for the other outcomes.
‡ Large for gestational age was defined by a birth weight exceeding the 90th percentile on standard charts.[30]
§ Small for gestational age was defined by a birth weight below the 10th percentile on standard charts.[30]
¶ The hypoglycemia level requiring therapy was determined by the clinician.
‖ The respiratory distress syndrome was defined by the need for supplemental oxygen in the neonatal nursery beyond four hours after birth.

tween groups remained significant after adjustment for known confounders (maternal age, race or ethnic group, and parity) and for analyses involving multiple primary end points.

Infants born to mothers receiving intensive therapy had lower birth weights than those born to women receiving routine care, an observation that may be explained at least in part by the earlier gestational age at birth in this group, related to the increased use of induction of labor. Infants in this group were no more likely to be small for gestational age, but they were significantly less likely to be large for gestational age and to have macrosomia. Infants who are large for gestational age are prone to impaired glucose tolerance or diabetes in later life, and girls[4] have an increased risk of gestational diabetes.[6] Long-term follow-up is needed to assess whether the lower birth weights among the infants in the intervention group will translate into reduced rates of these later complications.

Despite the increased rate of admission to the neonatal nursery in the intervention group, there were no significant differences between the groups of infants in secondary clinical outcomes, such as hypoglycemia requiring intravenous therapy. As compared with the women in the routine-care group, the women in the intervention group made more visits to the medical clinic and were more likely to see a dietitian and diabetes educator. However, they made fewer antenatal clinic visits, a difference that was most likely related to their increased likelihood of induction and their infants' earlier gestational age at birth. The reduction in the risk of preeclampsia in the intervention group may be related to the earlier gestational age at birth.

A potentially controversial aspect of our study design from an ethical standpoint was the fact that women were not informed of their diagnosis of "gestational diabetes" during the course of the study, after the change in the WHO criteria. However, despite changes in the nomenclature for gestational diabetes,[1,19,20] there continued to be no conclusive evidence regarding the effects of treatment of gestational diabetes[17,18] and there were wide variations in clinical practice during the time of this study.[22] Women in the study received standard pregnancy care consistent with care in which screening for gestational diabetes is not routine.

Our trial also revealed an improved health-related quality of life among women in the intervention group, both during the antenatal period and three months after birth, together with a reduction in the incidence of depression after birth. These findings are contrary to reports suggesting a decline in women's perception of their own health after they receive a diagnosis of gestational diabetes.[31,32] However, results for these outcomes should be interpreted with caution, since the analysis included only a subgroup of the women.

There has been a lack of data from large ran-

Table 5. Secondary Clinical Outcomes among the Women.*

Outcome	Intervention Group (N=490)	Routine-Care Group (N=510)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
No. of antenatal clinic visits after enrollment				<0.001
Median	5.0	5.2		
Interquartile range	1–7	3–7		
No. of physician clinic visits after enrollment				<0.001
Median	3	0		
Interquartile range	1–7	0–2		
Visit with a dietitian — no. (%)	453 (92)	51 (10)	9.19 (7.08 to 11.94)	<0.001
Visit with a diabetes educator — no. (%)	460 (94)	56 (11)	8.56 (6.69 to 10.96)	<0.001
Weight gain from first prenatal visit to last visit — kg	8.1±0.3	9.8±0.4	−1.4 (−2.3 to −0.4)	0.01
Antenatal admission — no. (%)	141 (29)	139 (27)	1.10 (0.90 to 1.34)	0.34
Antenatal preeclampsia — no. (%)	58 (12)	93 (18)	0.70 (0.51 to 0.95)	0.02
Gestational age at birth — wk				0.01
Median	39.0	39.3		
Interquartile range	38.1–40.0	38.3–40.4		
Any perineal trauma — no. (%)	255 (52)	254 (50)	1.05 (0.93 to 1.19)	0.42
Postpartum hemorrhage (≥600 ml) — no. (%)	29 (6)	32 (6)	0.96 (0.59 to 1.56)	0.86
Puerperal pyrexia (≥38°C) — no. (%)	17 (3)	29 (6)	0.63 (0.35 to 1.13)	0.12
Length of postnatal stay — days				0.80
Median	4	4		
Interquartile range	3–5	3–5		
Breast-feeding at hospital discharge — no. (%)	413 (84)	412 (81)	1.04 (0.98 to 1.10)	0.17

* Plus–minus values are means ±SD. CI denotes confidence interval. Preeclampsia was defined by a blood pressure of at least 140/90 mm Hg on two occasions more than four hours apart.

† Values were adjusted for maternal age, race or ethnic group, and parity. The adjusted treatment effect is expressed as the mean difference between groups for weight gain from the first visit to the last visit and as the relative risk for all outcomes given as numbers and percentages.

domized clinical trials on the effects of screening and treatment of women with gestational diabetes mellitus. An observational study is currently in progress to assess associations between maternal glucose levels and perinatal outcomes,[20] and an ongoing randomized trial in the United States is addressing the effect of therapy for mild gestational diabetes, as did our study.[33] Our results indicate that treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glycemic control reduces the rate of serious perinatal complications, without increasing the rate of cesarean delivery.

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APPENDIX

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ORIGINAL ARTICLE

Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

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ABSTRACT

BACKGROUND

This study compared bortezomib with high-dose dexamethasone in patients with relapsed multiple myeloma who had received one to three previous therapies.

METHODS

We randomly assigned 669 patients with relapsed myeloma to receive either an intravenous bolus of bortezomib (1.3 mg per square meter of body-surface area) on days 1, 4, 8, and 11 for eight three-week cycles, followed by treatment on days 1, 8, 15, and 22 for three five-week cycles, or high-dose dexamethasone (40 mg orally) on days 1 through 4, 9 through 12, and 17 through 20 for four five-week cycles, followed by treatment on days 1 through 4 for five four-week cycles. Patients who were assigned to receive dexamethasone were permitted to cross over to receive bortezomib in a companion study after disease progression.

RESULTS

Patients treated with bortezomib had higher response rates, a longer time to progression (the primary end point), and a longer survival than patients treated with dexamethasone. The combined complete and partial response rates were 38 percent for bortezomib and 18 percent for dexamethasone ($P<0.001$), and the complete response rates were 6 percent and less than 1 percent, respectively ($P<0.001$). Median times to progression in the bortezomib and dexamethasone groups were 6.22 months (189 days) and 3.49 months (106 days), respectively (hazard ratio, 0.55; $P<0.001$). The one-year survival rate was 80 percent among patients taking bortezomib and 66 percent among patients taking dexamethasone ($P=0.003$), and the hazard ratio for overall survival with bortezomib was 0.57 ($P=0.001$). Grade 3 or 4 adverse events were reported in 75 percent of patients treated with bortezomib and in 60 percent of those treated with dexamethasone.

CONCLUSIONS

Bortezomib is superior to high-dose dexamethasone for the treatment of patients with multiple myeloma who have had a relapse after one to three previous therapies.

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During the past 10 years, advances in the treatment of multiple myeloma have improved survival moderately.[1] In newly diagnosed disease, only high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation provides a survival benefit.[2,3] The optimal therapy for relapsed myeloma is not established, but high-dose dexamethasone is commonly used.[4-6] Response rates with this treatment are similar to those with vincristine, doxorubicin, and dexamethasone (VAD), and the dexamethasone component is estimated to account for 85 percent of the effect of VAD.[7,8]

The proteasome inhibitor bortezomib induces apoptosis, reverses drug resistance of multiple myeloma cells, and affects their microenvironment by blocking cytokine circuits, cell adhesion, and angiogenesis in vivo.[9-12] In a phase 2 study of relapsed and refractory myeloma, 27 percent of heavily pretreated patients had a complete or partial response with bortezomib.[13,14] On the basis of these results, bortezomib received approval for the treatment of relapsed and refractory multiple myeloma. The phase 3 randomized trial reported here compared bortezomib with high-dose dexamethasone in patients with multiple myeloma who had had a relapse after one to three other therapies.

METHODS

PATIENTS

Eligible patients had measurable progressive disease after one to three previous treatments. They had a score on the Karnofsky performance scale of at least 60, a platelet count of at least 50,000 per cubic millimeter, a hemoglobin level of at least 7.5 g per deciliter, an absolute neutrophil count of at least 750 per cubic millimeter, and a creatinine clearance of at least 20 ml per minute. Patients were excluded if they had previously received bortezomib or had disease that was refractory to high-dose dexamethasone (defined by a less-than-partial response or progressive disease within 6 months after receipt of at least 500 mg of dexamethasone during a 10-week period or discontinuation of the drug due to associated grade 3 or higher adverse events), had at least grade 2 peripheral neuropathy, or had any clinically significant coexisting illness unrelated to myeloma. Review boards at all the participating institutions approved the study, and all patients provided written informed consent. The study was conducted according to the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice.

STUDY DESIGN AND TREATMENT

This randomized (1:1), open-label, phase 3 study was conducted at 93 centers in the United States, Canada, Europe, and Israel from June 2002 to October 2003. Randomization was stratified according to the number of previous treatments (1 vs. >1), time to progression after the last treatment (≤6 months vs. >6 months), and β_2-microglobulin values (≤2.5 mg per liter vs. >2.5 mg per liter). Bortezomib (at a dose of 1.3 mg per square meter of body-surface area) was administered by intravenous bolus on days 1, 4, 8, and 11 of cycles 1 through 8 (21-day cycles) and on days 1, 8, 15, and 22 of cycles 9 to 11 (35-day cycles), for a maximum treatment period of 273 days. Oral dexamethasone (40 mg) was administered on days 1 to 4, 9 to 12, and 17 to 20 of cycles 1 through 4 (35-day cycles) and on days 1 to 4 of cycles 5 through 9 (28-day cycles), for a maximum treatment period of 280 days. Patients in the dexamethasone group with confirmed disease progression were permitted to cross over to receive bortezomib in a companion study. Platelet and red-cell transfusions and the administration of neutrophil growth factors and epoetin alfa were allowed. All patients were to receive bisphosphonates intravenously every three to four weeks unless such treatment was clinically contraindicated.

The primary objective was to compare the time to disease progression in the two treatment groups. Secondary end points included overall and one-year survival, the response rate (complete plus partial response), the duration of the response, the time to the first evidence of a confirmed response, the time to a first infection of grade 3 or higher, the incidence of a grade 3 or higher infection, and the time to a first skeletal event (including new fractures, except vertebral compression or rib fractures, bone irradiation, bone surgery, and spinal cord compression).

The Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial was designed as a collaborative effort by Dr. Richardson, the coinvestigators, the Investigators' Management Team (Drs. Anderson, Dalton, Harousseau, and San-Miguel), and the sponsor, Millennium Pharmaceuticals. Data were collected by the sponsor, and the final analysis was performed by the sponsor in collaboration with Dr. Richardson. All authors had full access to the primary data and the final analysis. Drs. Richardson and Anderson vouch for the pub-

lished results. The sponsor placed no limits on the analysis or content of the manuscript, and all authors supported the decision to publish the results.

ASSESSMENTS

Time to progression and response rates were determined by a computer-programmed algorithm (validated by a three-member independent review committee), according to the European Blood and Marrow Transplant Group.[15] Briefly, a complete response was defined by the absence of monoclonal immunoglobulin (M protein) in serum and urine, as confirmed by immunofixation. A partial response was defined by a reduction of M protein in serum of at least 50 percent and a reduction in urine of at least 90 percent. A minimal response was defined by a reduction of M protein in serum of 25 to 49 percent and a reduction in urine of 50 to 89 percent. Progressive disease was defined by any of the following: an increase of M protein in serum or urine of more than 25 percent, an increase in bone marrow plasma cells of more than 25 percent, new or increased bone lesions or plasmacytomas, or new hypercalcemia. Complete, partial, and minimal responses were confirmed by repeated measurements of M protein in serum and urine after six weeks, and progressive disease was confirmed by repeated measurements of M protein in serum and urine after one to three weeks. Near-complete response, a subcategory of partial response, was defined as a complete response with a positive immunofixation test (lower limit of detection, 0.15 to 0.25 mg per milliliter).[13] Efficacy data were based on analysis of blood and urine samples by a central laboratory, unless progression of myeloma occurred as an isolated bone lesion, growth of a plasmacytoma, or an increase in plasma cells in the bone marrow without a change in M protein.

Patients were evaluated every 3 weeks during the first 39 weeks. Follow-up was then performed every six weeks until disease progression, after which follow-up for skeletal events and survival was performed every three months. Patients with a complete response continued to receive treatment for two cycles after the confirmation of the response. Patients who discontinued treatment before disease progression were followed every 3 weeks for 39 weeks or until disease progression.

Safety was assessed throughout the study for all patients who received at least one dose of the assigned study drug until 30 days after the last dose and was graded according to the National Cancer Institute Common Toxicity Criteria (version 2). The onset and intensity of peripheral neuropathy and other neurotoxic effects were assessed with the neurotoxicity subscale of the Gynecologic Oncology Group's Functional Assessment of Cancer Therapy.[16,17] A serious adverse event was defined as any event that resulted in death, was life-threatening, required hospitalization, resulted in persistent or substantial disability, or had important medical consequences.

STATISTICAL ANALYSIS

The time to disease progression in the treatment groups was compared with the use of the stratified log-rank test; the Kaplan–Meier method was used to estimate the distribution of the time to progression in each group. The stratified Cox proportional-hazards model was used to estimate the hazard ratio and 95 percent confidence intervals. Analyses of overall and one-year survival, the time to a first skeletal event, and the time to a grade 3 or higher infection were performed with the use of this method. Response rates were compared with the Cochran–Mantel–Haenszel chi-square test, with adjustment for stratification factors. The incidence of grade 3 or higher infection was compared with the use of Fisher's exact test. Analyses of subgroups prospectively defined according to the number of previous treatments were performed with the use of the same methods. Treatment differences for all end points were tested at a two-sided α level of 0.05. The sample size of 310 patients per treatment group provided 80 percent power to detect a 30 percent difference in the time to disease progression between the two groups.

An interim analysis of the time to progression on the basis of the method of O'Brien and Fleming was planned when at least 50 percent of required disease-progression events (in 231 patients) had occurred.[18] A statistically significant difference was to be declared at the interim analysis if the stratified log-rank P value for the time to progression was 0.005 or less or, failing this, if at the final analysis the P value was 0.048 or less. At the interim analysis, patients taking bortezomib had a significant prolongation of the median time to disease progression ($P<0.001$) and a significantly improved overall survival ($P=0.04$), as compared with patients receiving dexamethasone. As a result of the interim analysis and the recommendation of the data-monitoring committee, all patients in the dexamethasone group were offered bortezomib. Data for the final analyses of the time to disease progression and the response were censored before December 15, 2003. Safety

analyses, including survival, were censored before January 14, 2004. In analyses of the time to progression, duration of the response, and time to the response, data for patients who started alternative chemotherapy (including crossover to bortezomib), who were lost to follow-up, or who died before documentation of progressive disease were censored at the last assessment. In analyses of survival, data for patients were censored before January 14, on the date they were last known to be alive, regardless of disease progression or alternative therapy. Analyses were performed with SAS statistical software (version 8.2, SAS Institute).

RESULTS

PATIENTS AND TREATMENT

A total of 669 patients with relapsed multiple myeloma were randomly assigned to receive bortezomib (333) or high-dose dexamethasone (336). At the time of the final analysis, 85 patients in the bortezomib group and 55 patients in the dexamethasone group were still receiving a study drug. Baseline demographic and other characteristics of the two groups were balanced (Table 1).

The treatment groups were similar in the number and type of prior therapies (Table 1); 38 percent of patients had received only one prior treatment, and in 95 percent of these patients, the initial treatment included an alkylating agent or an anthracycline. Sixty-seven percent of patients had received a hematopoietic stem-cell transplant or other high-dose therapy. On retrospective review, 14 patients in the bortezomib group (4 percent) and 23 in the dexamethasone group (7 percent) were found to have received more than three prior therapies. In accordance with the statistical analysis plan, these patients were included in the intention-to-treat population.

EFFICACY

The median time to disease progression was 6.22 months (189 days) in the bortezomib group and 3.49 months (106 days) in the dexamethasone group (hazard ratio for the bortezomib group, 0.55; P< 0.001) (Fig. 1A).

Table 1. Baseline Characteristics of Patients with Multiple Myeloma, According to Treatment Group.

Characteristic	Bortezomib (N=333)	Dexamethasone (N=336)
Age — yr		
Median	62	61
10th and 90th percentiles	48, 74	47, 73
Male sex — no. (%)	188 (56)	200 (60)
Type of myeloma		
No. of patients	333	336
IgG/IgA/IgD/IgM — %	60/23/2/<1	59/24/1/0
Light chain — %	12	13
Nonsecretory — %	1	1
Unspecified — %	<1	0
Interval since diagnosis		
No. of patients	331	332
Median — yr	3.5	3.1
10th and 90th percentiles — yr	1.3, 7.8	1.4, 7.2
Karnofsky performance scale ≥70% —no./total no. (%)	304/322 (94)	312/325 (96)
Serum β_2-microglobulin		
No. of patients	324	328
Median — mg/liter	3.7	3.6
10th and 90th percentiles — mg/liter	2.0, 8.8	2.1, 10.1
C-reactive protein		
No. of patients	301	299
Median — mg/liter	4.0	4.0
10th and 90th percentiles — mg/liter	4.0, 23.1	4.0, 20.1

A total of 627 patients (315 in the bortezomib group and 312 in the dexamethasone group) were judged to be suitable for evaluation if they had received at least one dose of a study drug and had measurable disease at baseline. The response rate (including both complete response and partial response) was 38 percent in the bortezomib group and 18 percent in the dexamethasone group (P< 0.001) (Table 2). Complete response (including a negative immunofixation test) was achieved in 20 patients who received bortezomib (6 percent), as compared with 2 patients who received dexamethasone (<1 percent, P<0.001), with either a complete response or a near-complete response in 41 patients who received bortezomib (13 percent), as compared with 5 patients who received dexamethasone (2 percent, P<0.001). The median time to a response was 43 days for patients in both groups. The median duration of the response was 8 months in the bortezomib group and 5.6 months in the dexamethasone group.

At one year of follow-up, patients who received bortezomib had a higher rate of overall survival (80 percent) than those who received dexamethasone (66 percent, P=0.003). This is a 41 percent decrease in the risk of death in the bortezomib group during the first year after enrollment (hazard ratio for the bortezomib group, 0.57; P=0.001) (Fig. 1B and 1C). The analysis of overall survival includes data from 147 patients in the dexamethasone group who had disease progression and subsequently crossed over to receive bortezomib in a companion study (44 percent).

The time to a first skeletal event and the rate of grade 3 or higher infections did not differ significantly between the two treatment groups. The median time to a first skeletal event could not be estimated in either group, and the hazard ratios were not significantly different (P=0.32). The proportion of patients with grade 3 or higher infections was 13 percent in the bortezomib group and 16 percent in the dexamethasone group (P=0.19).

SUBGROUP ANALYSIS

The median time to disease progression among patients who had received one previous therapy

Table 1. (Continued.)

Characteristic	Bortezomib (N=333)	Dexamethasone (N=336)
Hemoglobin		
No. of patients	331	335
Median — g/liter	108	109
10th and 90th percentiles — g/liter	86, 132	86, 129
Platelet count		
No. of patients	330	335
Median — cells/mm³	193,000	188,000
10th and 90th percentiles — mm³	88,000; 316,000	94,000; 279,000
Creatinine clearance ≤ 20 ml/min — no./total no. (%)	8/330 (2)	5/323 (2)
No. of previous therapies		
Median — no.	2.0	2.0
1 — no. (%)	132 (40)	119 (35)
2 or 3 — no. (%)	186 (56)	194 (58)
≥4 — no. (%)	14 (4)	23 (7)
Type of previous therapy — no./total no. (%)		
Corticosteroids	325/332 (98)	332/336 (99)
Alkylating agents	302/332 (91)	310/336 (92)
Anthracyclines	256/332 (77)	257/336 (76)
Thalidomide	160/332 (48)	168/336 (50)
Vinca alkaloids	248/332 (75)	242/336 (72)
Stem-cell transplantation or other high-dose therapy	222/332 (67)	229/336 (68)
Experimental or other therapy	11/332 (3)	8/336 (2)

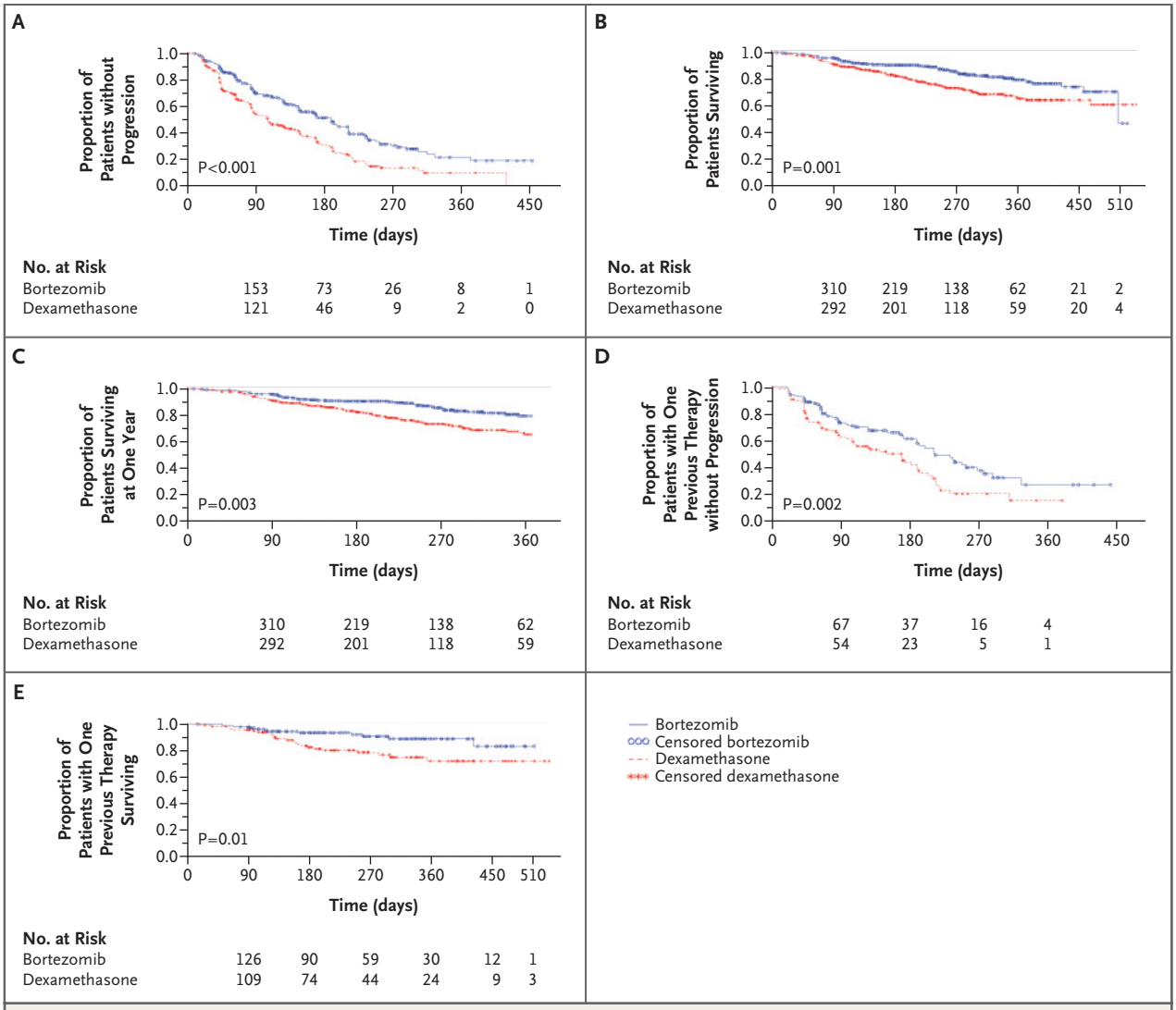

Figure 1. Kaplan–Meier Plots of the Time to Disease Progression and Survival in the Bortezomib and Dexamethasone Groups.

Panel A shows the time to disease progression in the intention-to-treat populations (a total of 669 patients) for bortezomib and dexamethasone. Panel B shows the overall survival in both groups in the intention-to-treat population. The survival curves cross at approximately 500 days because of the death of one patient in the bortezomib group at 504 days. At that time, the curve had accounted for 330 of the 333 patients (with 50 deaths and data for 280 patients censored), with only 1 death and two censored data points after the curves cross. Panel C shows the survival data censored at one year in both groups of the intention-to-treat population, indicating that at 360 days the probability of survival was 80 percent in the bortezomib group and 66 percent in the dexamethasone group. Data were generated as comparisons of survival probabilities on the basis of normal approximations. Panel D shows the time to disease progression for patients in both groups of the intention-to-treat population who had received only one previous line of therapy (a total of 251 patients). Panel E shows the overall survival for the subgroup of 251 patients who had received only one previous line of therapy. P values for all analyses are from stratified log-rank tests. A listing of the total number of patients for whom data were censored in all five analyses is available in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

was 7.0 months in the bortezomib group and 5.6 months in the dexamethasone group (hazard ratio for the bortezomib group, 0.56; P=0.002) (Fig. 1D). With more than one previous treatment, the median times were 4.9 and 2.9 months, respectively (hazard ratio for the botezomib group, 0.55; P<0.001). Patients who received bortezomib as second-line therapy also had a higher response rate

than did those who received dexamethasone (45 percent vs. 26 percent, P=0.004), as did those who had received two or more previous treatments (34 percent vs. 13 percent, P<0.001). The median duration of a response for patients receiving bortezomib or dexamethasone as second-line treatment was 8.1 and 6.2 months, respectively, and for patients who had received more than one previous treatment, 7.8 and 4.1 months, respectively. Overall survival was significantly longer among patients who received bortezomib, both for those who had received one previous treatment (hazard ratio, 0.42; P=0.01) (Fig. 1E) and for those who had received more than one previous treatment (hazard ratio, 0.63; P=0.02).

SENSITIVITY ANALYSIS

To determine whether inadvertent inclusion of patients who had disease that was refractory to high-dose dexamethasone might have biased the results, a post hoc review of all previous therapy was performed, and patients who may have had disease that was refractory to high-dose dexamethasone (i.e., more than 500 mg within a 10-week period) were sought. As specified in the protocol, refractoriness to dexamethasone was defined as a lack of complete or partial response to a regimen containing high-dose dexamethasone or disease progression within six months after the last dose. Of 269 patients who had received high-dose dexamethasone as part of their previous therapy, 60 had disease that was potentially refractory to dexamethasone (32 patients who were randomly assigned to receive bortezomib and 28 who were randomly assigned to receive dexamethasone). Patients were considered to have refractory disease in this analysis if they met the criteria for such disease (53 patients) or if missing data made it impossible to conclude that they had refractory disease (7 patients). After the exclusion of these patients from sensitivity analyses regarding the time to progression, overall survival, and response rate, bortezomib remained significantly superior to dexamethasone for all end points. The median time to progression was 6.22 months (189 days) in the bortezomib group and 3.49 months (106 days) in the dexamethasone group (P<0.001), the hazard ratio for overall survival was 0.55 with bortezomib (P=0.002), and the response rate (including both complete response and partial response) was 39 percent in the bortezomib group and 18 percent in the dexamethasone group (P<0.001).

Table 2. Best Confirmed Response to Treatment.*

Best Confirmed Response	Bortezomib (N=315)	Dexamethasone (N=312)	P Value†
	no. of patients (%)		
Complete or partial response	121 (38)	56 (18)	<0.001
Complete response, immunofixation-negative	20 (6)	2 (1)	<0.001
Partial response	101 (32)	54 (17)	<0.001
Nearly complete response, immunofixation-positive‡	21 (7)	3 (1)	<0.001
Minor response	25 (8)	52 (17)	ND
No change	137 (43)	149 (48)	ND
Progressive disease	22 (7)	41 (13)	ND
Could not be evaluated	10 (3)	14 (4)	ND

* All patients who received at least one dose of a study drug and who had measurable disease at baseline were evaluated for a response. Of the 669 patients enrolled, only 627 could be evaluated, since 6 did not receive a study drug and 36 did not have measurable disease (as defined by a serum M protein level that could be measured quantitatively, a urinary M protein level that could be measured quantitatively, or a measurable soft-tissue plasmacytoma).

† P values were calculated with the Cochran–Mantel–Haenszel chi-square test, with adjustment for stratified randomization. ND denotes not determined.

‡ All criteria for a complete response were met except that immunofixation remained positive.

DRUG EXPOSURE, PATIENT DISPOSITION, AND SAFETY

A total of 663 patients received at least one dose of study drug and are included in the safety population (331 patients in the bortezomib group and 332 patients in the dexamethasone group). The duration of treatment was similar in the two groups; 56 percent of patients completed five three-week cycles of bortezomib, and the same proportion completed three five-week cycles of dexamethasone; 29 percent of patients in the bortezomib group completed eight twice-weekly cycles of bortezomib, and 36 percent of patients in the dexamethasone group completed four cycles of high-dose dexamethasone. Nine percent and 5 percent of patients completed all planned therapy in the bortezomib and dexamethasone groups, respectively.

A total of 121 patients in the bortezomib group (37 percent) had adverse events necessitating early discontinuation of treatment. These events included peripheral neuropathy (8 percent) and thrombocytopenia, various gastrointestinal disorders, fatigue, hypercalcemia, and spinal cord compression (2 percent each). Of the patients who discontinued treatment early because of hypercalcemia (seven patients), all had progressive disease. Of the patients who discontinued treatment because of spinal cord

compression (seven patients), five had progressive disease, one had unconfirmed progressive disease, and one did not have progressive disease. The investigator identified the adverse event as the primary reason for discontinuation in all but one of these cases. In the dexamethasone group, 96 patients discontinued treatment early because of adverse events (29 percent), which included psychotic disorder, hyperglycemia, or thrombocytopenia (2 percent each). Disease progression led to early discontinuation in 98 patients receiving bortezomib (29 percent) and in 174 receiving dexamethasone (52 percent, P<0.001). There were eight deaths considered possibly related to a study drug: four in the bortezomib group (three from cardiac causes and one from respiratory failure) and four in the dexamethasone group (three from sepsis and one sudden death of unknown cause).

Certain adverse events (including gastrointestinal events, thrombocytopenia, and peripheral neuropathy) were more prominent in the bortezomib group (Table 3). Grade 3 adverse events were reported in 61 percent of patients receiving bortezomib and in 44 percent of patients receiving dexamethasone (P<0.01). The most common grade 3 or 4 adverse events (reported in more than 10 percent of patients in either group) were thrombocytopenia, anemia, and neutropenia in patients receiving bortezomib and anemia in patients receiving dexamethasone. The bortezomib group and the dexamethasone group had similar rates of grade 4 events (14 percent and 16 percent, respectively) and serious adverse events (44 percent and 43 percent, respectively), as defined by the National Cancer Institute Common Toxicity Criteria (version 2). Deaths within 30 days of the last dose of the study drug were reported for 14 patients receiving bortezomib (4 percent; 1 percent drug-related) and 25 patients receiving dexamethasone (8 percent; 1 percent drug-related), with disease progression the most commonly reported cause of death (2 percent in each group).

Improvement or resolution of grade 2 or higher peripheral neuropathy was reported in 44 of 87 patients in whom peripheral neuropathy developed during treatment with bortezomib (51 percent), with a median time to resolution of 107 days (approximately 3.5 months) from the onset of the adverse event. Of those 44 patients, 40 had resolution (a return to baseline), and 4 had improvement without complete resolution at the last assessment.

Among the bortezomib-treated patients with thrombocytopenia, the platelet count returned toward the baseline value between treatment cycles (Fig. 2). Thrombocytopenia of grade 3 (platelet count, <50,000 per cubic millimeter) or grade 4 (platelet count, <10,000 per cubic millimeter) was more common in patients receiving bortezomib (grade 3, 26 percent; grade 4, 4 percent) than it was in patients receiving dexamethasone (grade 3, 5 percent; grade 4, 1 percent). However, the percentage of clinically significant bleeding episodes, more commonly associated with grade 3 thrombocytopenia in both treatment groups, was similar and included 13 patients receiving bortezomib (4 percent) and 15 patients receiving dexamethasone (5 percent). Two deaths were associated with bleeding in the dexamethasone group (subdural hematoma in one case and gastrointestinal hemorrhage in the other); there were no bleeding-associated deaths in the bortezomib group.

The incidence of cardiac disorders during treatment with bortezomib and dexamethasone was 15 percent and 13 percent, respectively. No particular cardiac disorder occurred at an incidence of more than 10 percent in either group; seven patients receiving bortezomib (2 percent) and eight receiving dexamethasone (2 percent) had congestive cardiac failure during the study. However, it was noteworthy that the incidence of herpes zoster infection was higher in patients receiving bortezomib (13 percent) than it was in patients receiving dexamethasone (5 percent, P<0.001).

DISCUSSION

In this study of patients with multiple myeloma who had a relapse after having received one to three previous therapies, the overall rate of response (complete response plus partial response) to bortezomib was 38 percent, as defined by the stringent criteria of the European Blood and Marrow Transplant Group, with a complete response rate of 6 percent and a near-complete response rate of 7 percent. This result compares favorably with the less rigorously defined response rates (i.e., a greater than 50 percent reduction in M protein) of 17 to 47 percent reported with thalidomide[19-30] and 25 to 50 percent with VAD.[31-34]

High-dose dexamethasone was considered by the investigators and the regulatory agencies to be the best drug for comparison. There is no generally accepted standard therapy for patients with relapsed myeloma, and the choice of treatment de-

Table 3. Adverse Events during Treatment Reported by 15 Percent or More of Patients Receiving Bortezomib or Dexamethasone, Including Grade 3 and Grade 4 Events.

Event	Bortezomib (N=331)			Dexamethasone (N=332)		
	All Adverse Events	Grade 3 Events	Grade 4 Events*	All Adverse Events	Grade 3 Events	Grade 4 Events†
	number (percent)					
≥1 Event	331 (100)	203 (61)	45 (14)	327 (98)‡	146 (44)‡	52 (16)
Diarrhea	190 (57)	24 (7)	0	69 (21)‡	6 (2)‡	0
Nausea	190 (57)	8 (2)	0	46 (14)‡	0‡	0
Fatigue	140 (42)	17 (5)	1 (<1)	106 (32)‡	12 (4)	0
Constipation	140 (42)	7 (2)	0	49 (15)‡	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (1)	29 (9)‡	1 (<1)‡	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)‡	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)‡	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)‡	18 (5)‡	4 (1)§
Anemia	87 (26)	31 (9)	2 (1)	74 (22)	32 (10)	3 (1)
Headache	85 (26)	3 (1)	0	43 (13)‡	2 (1)	0
Anorexia	75 (23)	9 (3)	0	14 (4)‡	1 (<1)§	0
Cough	70 (21)	2 (1)	0	35 (11)‡	1 (<1)	0
Paresthesia	68 (21)	5 (2)	0	27 (8)‡	0§	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)‡	4 (1)‡	0‡
Rash	61 (18)	4 (1)	0	20 (6)‡	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)‡	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)‡	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Pain in limb	50 (15)	5 (2)	0	24 (7)‡	2 (1)	0
Muscle cramps	41 (12)	0	0	50 (15)	3 (1)	0

* More than one patient in the bortezomib group had additional grade 4 adverse events, including hypercalcemia, hyponatremia, sepsis, disease progression, renal failure, and gastrointestinal hemorrhage.
† More than one patient in the dexamethasone group had additional grade 4 adverse events, including hyperglycemia, sepsis, septic shock, dyspnea, respiratory failure, renal failure, cerebrovascular accident, pulmonary embolism, psychotic disorder, and death.
‡ P<0.01. Proportions were compared with the use of Fisher's exact test.
§ P<0.05. Proportions were compared with the use of Fisher's exact test.

pends on prior therapies, age, performance status, bone marrow reserve, and coexisting illnesses. High-dose dexamethasone is widely used in North America and Europe for relapsed myeloma and has been the drug used for comparison in several large studies of newly diagnosed myeloma.[5-7,35,36]

To reduce the potential biases with an open-label design, all assessments of M protein and calcium levels were confirmed at a central laboratory. The duration of treatment was similar in the two groups, and the interval between disease assessments was short (three weeks in both groups). Moreover, patients with disease that was refractory to high-dose dexamethasone were excluded, because they would have been expected to have either no response to dexamethasone or a response of short duration.

Randomization was stratified for three prognostic factors, and the treatment groups were well balanced with respect to demographic characteristics and the number and types of previous therapies. As initial treatment, 95 percent of patients who entered the trial at first relapse had received anthracycline-based therapy (e.g., VAD), alkylating-agent combinations (e.g., melphalan and prednisone), or both. In addition, 67 percent had received a

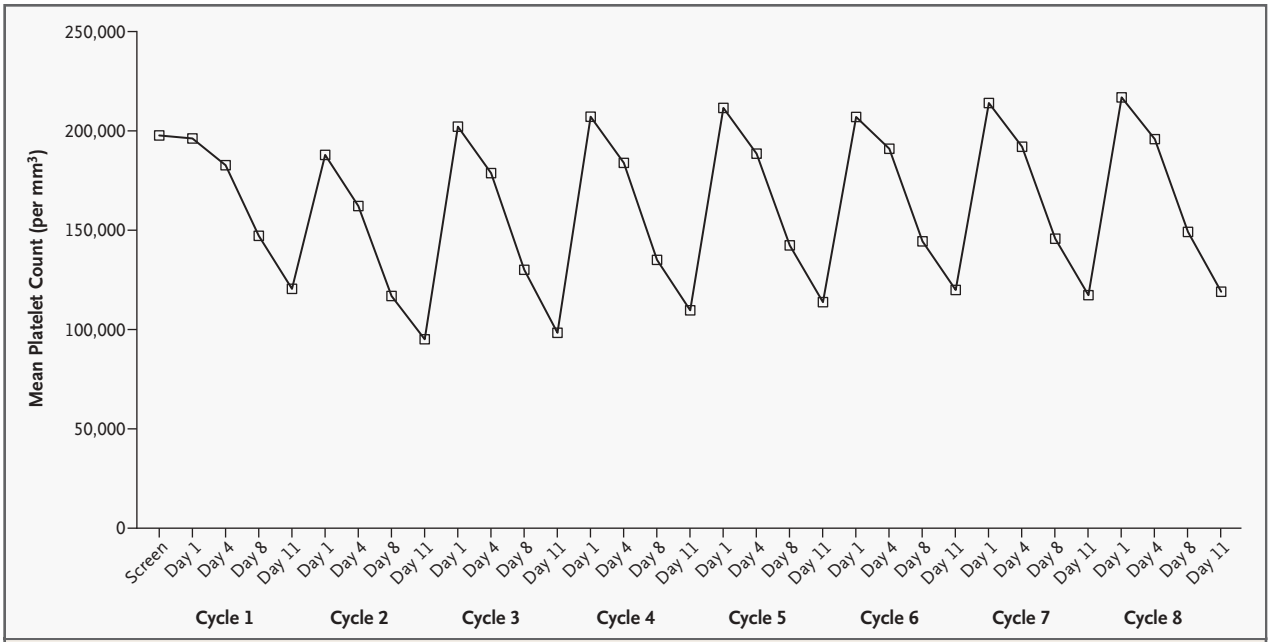

Figure 2. Mean Platelet Count among 331 Patients during Eight Three-Week Cycles of Treatment with Bortezomib.

The platelet counts decreased during the treatment phase of each cycle of treatment with bortezomib and approached the baseline value during the rest period of each cycle.

hematopoietic stem-cell transplant or other high-dose therapy, and 98 percent had received some form of corticosteroids as part of their previous regimens (e.g., melphalan and prednisone or VAD), although patients with disease that was refractory to previous high-dose dexamethasone were excluded.

There was a survival advantage for patients receiving bortezomib, despite the fact that 44 percent of patients in the dexamethasone group had crossed over to receive bortezomib after disease progression. As a result of early closure of the dexamethasone group, the median follow-up of surviving patients in both groups was limited to 8.3 months.

A clinical benefit from bortezomib was demonstrated for patients who had received only one or more than one previous treatment. Time to progression and survival were significantly improved in the bortezomib group as compared with the dexamethasone group, and the overall response rate was significantly higher for bortezomib. As expected from the recently reported experience at the Mayo Clinic,[37] response rates were higher in both groups among patients who had received only one prior treatment.

Inadvertent inclusion of patients with disease that was refractory to high-dose dexamethasone was a potential source of bias in this study. Therefore, we conducted sensitivity analyses of the time to progression, response rate, and survival in which patients who may have had disease that was refractory to previous high-dose dexamethasone were removed on the basis of a post hoc review of all prior therapy. Removal of these patients from the analyses had no significant effect on the results.

The rates of grade 4 adverse events, serious adverse events, and discontinuation of treatment because of adverse events were similar in the two groups; however, the overall rate of grade 3 events was significantly higher in the bortezomib group. The major side effects of bortezomib were consistent in type and frequency with those described previously.[13,38] The incidence of herpes zoster infection was higher in the bortezomib group, but the infection was manageable with appropriate antiviral therapy. As previously observed, thrombocytopenia was cyclical.[13,38,39] Despite the higher incidence of thrombocytopenia in patients receiving bortezomib, the incidence of clinically significant bleeding was similar in the two groups. The rates of discontinuation because of neuropathy were similar to those among heavily pretreated patients

with more advanced disease, with resolution and improvement that were consistent with the findings in other studies.[40]

In conclusion, this study demonstrates that bortezomib is superior to high-dose dexamethasone for the treatment of relapsed multiple myeloma in patients who have received one to three previous therapies other than bortezomib. The benefits of bortezomib included a longer time to progression, a higher complete response rate, and longer overall survival, both in the total population and in the subgroup receiving bortezomib as second-line therapy. The results of this study support investigation of bortezomib in the initial treatment of multiple myeloma.

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APPENDIX

In addition to the authors, the following investigators (listed in alphabetical order) participated in the APEX study: **Austria** — H. Ludwig (Vienna); **Belgium** — M. Andre (Charleroi), D. Bron (Brussels), M. Delforge (Leuven), C. Doyen (Yvoir), W. Feremans (Brussels), J. Van Droogenbroeck (Brugge), P. Zachee (Antwerp); **Canada** — A. Belch (Edmonton), C. Shustik (Montreal); **France** — M. Attal (Toulouse), F. Boue (Clamart), J. Bourhis (Villejuif), B. Coiffier (Pierre Benite), J. P. Fermand (Paris), E. Gyan (Paris), C. Hulin (Vandouvre), J.P. Marie (Paris), J. J. Sotto (Grenoble); **Germany** — H. Durk (Hamm), G. Ehninger (Dresden), H. Einsele (Tübingen), M. Engelhardt (Freiburg), A. Glasmacher (Bonn), M. Gramatzki (Erlangen), S. Hegewisch-Becker (Hamburg), C. Huber (Mainz), G. Kobbe (Düsseldorf), M. Kropff (Münster), M. Nowrousian (Essen), O. Sezer (Berlin); **Ireland** — C. Morris (Belfast); **Italy** — M. Baccarani (Bologna), T. Barbui (Bergamo), F. Mandelli (Rome); **Israel** — J. M. Rowe (Haifa); **the Netherlands** — H. Lokhorst (Utrecht), M.H. Van Oers (Amsterdam), E. Vellenga (Groningen); **Sweden** — B. Bjorkstrand (Stockholm), A. Gruber (Stockholm), S. Lenhoff (Lund); **United Kingdom** — J. Cavet (Manchester), C. Craddock (Birmingham), C. Dearden (Sutton Surrey), G. Jackson (Newcastle), M. Kovacs (London), G.J. Morgan (Marsden), A. Rahemtulla (London); **United States** — Y. Abubakr (Jacksonville, Fla.), E. Agura (Dallas), R. Alexanian (Houston), M. Alsina (Tampa, Fla.), D. Avigan (Boston), N. Bahlis (Cleveland), K. Barton (Maywood, Ill.), W. Bensinger (Seattle), J. Berdeja (Loma Linda, Calif.), J. Catlett (Washington, D.C.), A. Chanan-Khan (Buffalo, N.Y.), R. Comenzo (New York), J. Densmore (Charlottesville, Va.), J. Fay (Dallas), L. Fehrenbacher (Vallejo, Calif.), H. Fernandez (Miami), J. Giguere (Greenville, S.C.), J. Glass (Shreveport, La.), P. Gordon (Oakland, Calif.), J. Hamm (Louisville, Ky.), M. Hussein (Cleveland), J. Ifthikharuddin (Rochester, Minn.), S. Jagannath (New York), M. Jagasia (Nashville), A. Jakobowiak (Ann Arbor, Mich.), A. Klein (Boston), A. Krishnan (Duarte, Calif.), D. Kuter (Boston), M. Lacy (Rochester, Minn.), S. Limentani (Charlotte, N.C.), T. Martin (San Francisco), J. Mason (La Jolla, Calif.), B. Mavromatis (Washington, D.C.), V. Morrison (Minneapolis), R. Orlowski (Chapel Hill, N.C.), A. Pecora (Hackensack, N.J.), J. Phelan (Rochester, Minn.), J. Posada (Temple, Pa.), K. Rai (New York), R. Schilder (Philadelphia), W. Schmidt (Charleston, S.C.), R. Shadduck (Pittsburgh), D. Siegel (Hackensack, N.J.), S. Singhal (Chicago), S. Tarantolo (Omaha, Nebr.), D. Vesole (Milwaukee), R. Vij (St. Louis), and M. Zangari (Little Rock, Ark.). **Independent Review Committee:** M.A. Dimopoulos (University of Athens School of Medicine, Athens), R. Meyer (Hamilton Regional Cancer Center, Hamilton, Ont., Canada), and S. Treon (Dana–Farber Cancer Institute, Boston).

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ORIGINAL ARTICLE

Treatment of Ulcerative Colitis with a Humanized Antibody to the $\alpha_4\beta_7$ Integrin

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ABSTRACT

BACKGROUND

Selective blockade of interactions between leukocytes and vascular endothelium in the gut is a promising strategy for the treatment of inflammatory bowel diseases.

METHODS

We conducted a multicenter, double-blind, placebo-controlled trial of MLN02, a humanized antibody to the $\alpha_4\beta_7$ integrin, in patients with active ulcerative colitis. We randomly assigned 181 patients to receive 0.5 mg of MLN02 per kilogram of body weight, 2.0 mg per kilogram, or an identical-appearing placebo intravenously on day 1 and day 29. Eligible patients also received concomitant mesalamine or no other treatment for colitis. Ulcerative colitis clinical scores and sigmoidoscopic assessments were evaluated six weeks after randomization.

RESULTS

Clinical remission rates at week 6 were 33 percent, 32 percent, and 14 percent for the group receiving 0.5 mg of MLN02 per kilogram, the group receiving 2.0 mg per kilogram, and the placebo group, respectively (P=0.03). The corresponding proportions of patients who improved by at least 3 points on the ulcerative colitis clinical score were 66 percent, 53 percent, and 33 percent (P=0.002). Twenty-eight percent of patients receiving 0.5 mg per kilogram and 12 percent of those receiving 2.0 mg per kilogram had endoscopically evident remission, as compared with 8 percent of those receiving placebo (P=0.007). For the minority of patients in whom an MLN02 antibody titer greater than 1:125 developed, incomplete saturation of the $\alpha_4\beta_7$ receptor on circulating lymphocytes was observed and no benefit of treatment was identifiable.

CONCLUSIONS

In this short-term study, MLN02 was more effective than placebo for the induction of clinical and endoscopic remission in patients with active ulcerative colitis.

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Ulcerative colitis is an inflammatory disease characterized by bloody diarrhea, abdominal cramps, and fatigue.[1] Initial therapy for most patients consists of mesalamine compounds.[2,3] Although these drugs can be effective and have acceptable side effects,[4] many patients do not have a response and thus require treatment with corticosteroids.[5] Corticosteroid therapy, despite its efficacy, is frequently associated with adverse effects.[6] Accordingly, identifying alternative treatments is a priority.

One approach is to inhibit the migration of leukocytes into inflamed intestinal tissue by blocking cellular adhesion molecules.[7] Integrins are heterodimeric proteins that regulate cellular movement. The $\alpha_4\beta_7$ integrin, which is primarily involved in the recruitment of leukocytes to the gut,[8] is present on the cell surface of a small population of circulating T lymphocytes. The major ligand for $\alpha_4\beta_7$, mucosal addressin-cell adhesion molecule 1,[9] is selectively expressed on the endothelium of the intestinal vasculature[10] and is present in increased concentrations in inflamed tissue.[11] Blockade of this interaction might be effective therapy for inflammatory bowel diseases.[12-15]

MLN02 (Millennium Pharmaceuticals), a humanized[16] monoclonal antibody, specifically recognizes the $\alpha_4\beta_7$ heterodimer but does not cross-react with the individual component monomers. Theoretically, this characteristic should convey specificity for the vasculature of the gut. Preliminary studies in tamarins[17] and humans[18] suggested that a dose of MLN02 of 2.0 mg per kilogram of body weight was safe and possibly effective. Therefore, we assessed the efficacy of MLN02 therapy in patients with active ulcerative colitis.

METHODS

PATIENTS

We conducted this randomized, double-blind, placebo-controlled study at 20 university medical centers between December 2000 and February 2003. The investigational review board at each center approved the protocol. All patients gave written informed consent.

Eligible patients were adults with active disease. Active disease was defined as an ulcerative colitis clinical score[18] of 5 to 9 points, with a score of at least 1 on either stool frequency or rectal bleeding, and a modified Baron score[19] of at least 2 on sigmoidoscopic examination, with the disease a minimum of 25 cm from the anal verge. Participants had received either no therapy for ulcerative colitis or mesalamine, provided it had been administered for at least four weeks, with a stable dose for two weeks before screening. Criteria for exclusion were therapy with oral corticosteroids within four weeks before screening or parenteral corticosteroids within six weeks, topical therapy with mesalamine or corticosteroids within one week before screening, immunosuppressive therapy within the preceding three months, severe disease (as evidenced by a hemoglobin concentration below 10 g per deciliter, toxic megacolon, or an ulcerative colitis clinical score above 10), abnormal laboratory results (white-cell count below 3000 per cubic millimeter; platelet count below 100,000 per cubic millimeter; serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase concentration greater than 2.5 times the upper limit of normal; serum creatinine concentration greater than 1.5 times the upper limit of normal; positive stool test for pathogens; or proteinuria), or the inability to comply with the protocol.

BASELINE STUDIES

Patients were screened 14 and 7 days before randomization. They were given a physical examination and blood tests, and a stool sample for pathogens and demographic information were obtained. Eligible patients were scheduled for a screening visit immediately before randomization, which included sigmoidoscopy and the determination of baseline ulcerative colitis clinical scores, modified Baron scores, Riley scores,[20] and scores on the inflammatory bowel disease questionnaire.[21]

The ulcerative colitis clinical score, a modification of the scoring system of the Mayo Clinic,[2] consists of four items — rectal bleeding, stool frequency, functional assessment by the patient, and global assessment by the physician. Items are scored on a scale from 0 (normal) to 3 (severe disease). The composite score ranges from 0 (inactive disease) to 12 (severe disease activity). The modified Baron score, which represents an endoscopic classification, ranges from 0 to 4, with 0 denoting normal mucosa, 1 granular mucosa with an abnormal vascular pattern, 2 friable mucosa, 3 microulceration with spontaneous bleeding, and 4 gross ulceration. Inflammation in rectal-biopsy specimens was graded with the acute-inflammation subscale of the Ri-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	MLN02, 0.5 mg/kg (N=58)	MLN02, 2.0 mg/kg (N=60)	Placebo (N=63)
Age — yr	41.6±14.7	43.8±14.6	38.9±13.4
Male sex — no. (%)	33 (57)	30 (50)	35 (56)
Months since diagnosis	78.0±84.9	74.8±77.8	82.9±83.5
Current smoker — no. (%)	0	4 (7)	4 (6)
Mesalamine			
Use — no. (%)	48 (83)	50 (83)	53 (84)
Dose — molar equivalents/day†	22.4±9.0	21.9±9.7	21.9±9.8
Ulcerative colitis clinical score	7.0±1.4	7.3±1.5	6.7±1.6
Stool frequency	2.3±0.9	2.3±0.8	2.2±0.9
Rectal bleeding	1.5±0.8	1.6±0.8	1.4±0.8
Assessment by the patient	1.3±0.7	1.5±0.7	1.2±0.8
Assessment by the physician	1.9±0.3	1.9±0.3	1.8±0.4
Modified Baron score	3.0	3.0	3.0
Riley histopathological score	5.9±1.3	6.2±1.0	5.7±1.5
Score on inflammatory bowel disease questionnaire	139.6±34.2	131.4±30.1	142.6±31.6
Hemoglobin concentration — g/dl	13.5±1.6	13.2±1.8	13.2±1.7
White-cell count — $\times 10^{-3}$/mm^3	8.7±2.8	8.2±2.6	8.5±2.2

* Plus–minus values are means ±SD. The modified Baron scores are median values.
† Molar equivalents were derived by dividing the average daily dose of the 5-aminosalicylic acid compound by 1/100 of the molecular weight of the compound (i.e., 153.14, 346.21, and 398.4 for mesalamine formulations, osalazine, and sulfasalazine, respectively). For example, a total daily dose of 3.6 g of mesalamine equals 23.5 molar equivalents.[23]

ley score,[20] which ranges from 0 (no inflammation) to 7 (severe acute inflammation). Health-related quality of life was evaluated with the inflammatory bowel disease questionnaire.[21] Scores range from 32 to 224, with higher scores indicating a better quality of life.

RANDOMIZATION

Patients were randomly assigned to receive 0.5 mg of MLN02 per kilogram, 2.0 mg of MLN02 per kilogram, or placebo in an equal ratio (according to a computer-generated schedule) with the use of permutated blocks of three. The randomization was stratified according to the use of mesalamine. Each patient received two intravenous infusions, one at the baseline visit (day 1) and a second on day 29. Neither the investigators nor the patients were aware of the treatment assignment. The placebo was identical in appearance to MLN02.

The use of corticosteroids, immunosuppressive agents, antibiotic drugs, nicotine supplements, or antidiarrheal agents was not permitted. Use of mesalamine was continued at a stable dose.

FOLLOW-UP

Patients were seen one, two, four, and six weeks after randomization. At each visit, the ulcerative colitis clinical score was calculated and blood for serum chemistry was obtained. Sigmoidoscopy was repeated at weeks 4 and 6. The endoscopist was instructed to take biopsy specimens from the most severely affected area 15 cm from the anal verge. The inflammatory bowel disease questionnaire was administered at weeks 4 and 6. Blood samples for pharmacokinetic and pharmacodynamic studies were drawn in a subgroup of 30 patients. Serum MLN02 concentrations were measured with use of a competitive-binding enzyme-linked immunosorbent assay (ELISA). ELISA was also used to measure human antihuman antibodies in serum at weeks

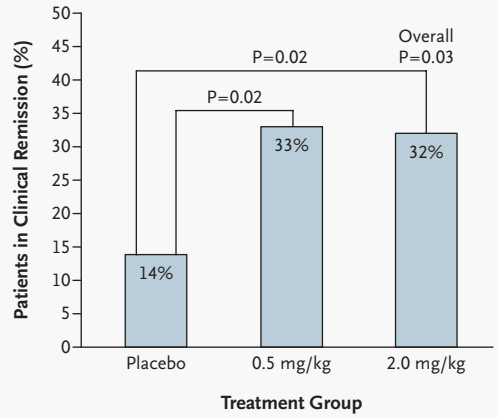

Figure 1. Percentage of Patients in Clinical Remission at Week 6 According to Treatment Group.

P values were derived by means of the Cochran–Mantel–Haenszel test, with adjustment for the use of mesalamine.

4 and 8. An antibody titer of 1:5 or greater was considered positive.

OUTCOME MEASURES

The primary outcome measure was clinical remission at week 6, defined as an ulcerative colitis clinical score of 0 or 1 and a modified Baron score of 0 or 1 with no evidence of rectal bleeding. Secondary outcomes were the changes in the ulcerative colitis clinical scores, the modified Baron scores, the Riley scores, and the scores on the inflammatory bowel disease questionnaire. We also evaluated the proportion of patients with clinical response (an improvement of 3 points or more on the ulcerative colitis clinical score), endoscopically evident remission (a modified Baron score of 0), and endoscopic response (an improvement of the modified Baron score of at least 2 grades) at week 4 and week 6. Adverse events were classified with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA).[22]

STATISTICAL ANALYSIS

Descriptive statistics were used to evaluate differences in demographic characteristics. The effects of cigarette smoking, disease activity, and mesalamine use were evaluated in univariate analyses. For the primary analysis, the Cochran–Mantel–Haenszel chi-square test, with adjustment for mesalamine use, tested the null hypothesis that the rate of clinical remission was not different among the three treatment groups. Patients who withdrew prematurely were classified as not achieving remission. A similar approach was used to compare the rates of clinical response.

The changes from baseline to weeks 4 and 6 in the ulcerative colitis clinical scores, the Riley scores, and the scores on the inflammatory bowel disease questionnaire were assessed by analysis of covariance with adjustment for mesalamine use and the baseline score. For patients who withdrew prematurely, the last observation available before withdrawal was carried forward for the ulcerative colitis clinical score and the score on the inflammatory bowel disease questionnaire. The modified Baron scores were compared with the use of analysis of covariance based on ranks.

The rates of endoscopic remission and response at weeks 4 and 6 were compared by means of the Cochran–Mantel–Haenszel chi-square test. The modified Baron score was compared by means of the Wilcoxon rank-sum test.

For all analyses of endoscopic and histopathological scores, missing values were not imputed. Fisher's exact test was used to compare the incidence of adverse events between the patients who received MLN02 and those who received placebo. Statistical tests were two-sided, with a P value of 0.05 as the criterion for statistical significance. Analyses were performed according to the intention-to-treat principle.

We anticipated that 10 percent of patients receiving placebo would enter clinical remission. We determined that randomization of 180 patients allowed for 80 percent power to detect a difference of 20 percent between the patients given MLN02 and those given placebo, with the use of a two-sided test with an alpha error of 0.05.

The study was designed and implemented by the steering committee in collaboration with Millennium Pharmaceuticals, which analyzed the data. The investigators wrote the manuscript. The academic authors had access to the data and vouch for the validity and completeness of the data and the data analysis. A data safety and monitoring board reviewed the safety data.

RESULTS

Between December 2000 and November 2002, 249 patients were evaluated. Of these, 68 (27 percent) did not undergo randomization. The common reasons for exclusion were low disease activity (19 patients), laboratory abnormalities or serious diseases (14), a positive assay for *Clostridium difficile* toxin

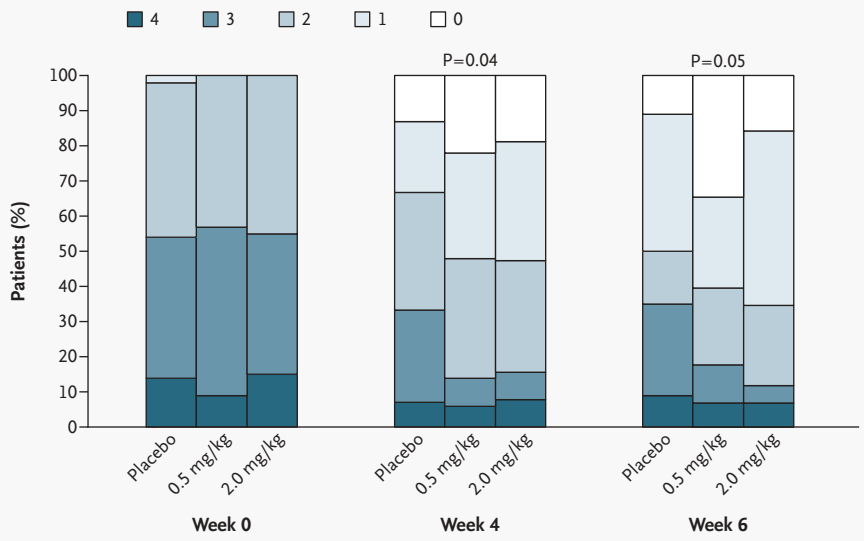

Figure 2. Distribution of Modified Baron Scores over Time According to Treatment Group.

Overall P values were calculated with the use of an analysis of covariance based on ranks, with fixed effects for treatment and use of mesalamine. For the modified Baron score, 0 denotes normal mucosa, 1 granular mucosa with an abnormal vascular pattern, 2 friable mucosa, 3 microulceration of the mucosa with spontaneous bleeding, and 4 denuded mucosa (gross ulceration).

(11), inadequate documentation of disease (9), and a requirement for contraindicated medication (7). Eight eligible patients withdrew consent.

Of 181 patients who underwent randomization, 58 were assigned to receive 0.5 mg of MLN02 per kilogram, 60 to receive 2.0 mg of MLN02 per kilogram, and 63 to receive placebo. The baseline characteristics of the groups were similar (Table 1).

The number of patients who withdrew from the study was 1 of 58 (2 percent) in the group receiving 0.5 mg of MLN02 per kilogram, 5 of 60 (8 percent) in the group receiving 2.0 mg per kilogram, and 3 of 63 (5 percent) in the placebo group. No important differences were observed among the three groups in the reasons for withdrawal.

PRIMARY OUTCOME

After six weeks, the proportion of patients in clinical remission differed significantly among the three groups. In the group receiving 0.5 mg of MLN02 per kilogram, 19 of 58 patients (33 percent) achieved remission, as compared with 19 of 60 (32 percent) in the group receiving 2.0 mg per kilogram and 9 of 63 (14 percent) in the placebo group (overall P=0.03) (Fig. 1). Each comparison between the MLN02 groups and the placebo group was significant (P=0.02 for both the group receiving 0.5 mg per kilogram and the group receiving 2.0 mg per kilogram). Neither the use of mesalamine nor any other prognostic factor that was examined influenced these results.

CLINICAL RESPONSE

One of the secondary outcomes was the change in the ulcerative colitis clinical score. At week 6, the proportions of patients in the group receiving 0.5 mg per kilogram, the group receiving 2.0 mg per kilogram, and the placebo group whose score improved at least 3 points were 66 percent, 53 percent, and 33 percent, respectively (P=0.002).

ENDOSCOPIC REMISSION AND RESPONSE

Figure 2 shows the distribution of the modified Baron scores. Patients assigned to receive MLN02 had a lower median score than those assigned to placebo at week 4 (modified Baron score, 1.0 vs. 2.0; P=0.01) and week 6 (1.0 vs. 1.5, P=0.02). At week 6, 16 of 58 patients (28 percent) who received 0.5 mg of MLN02 per kilogram were in endoscopic remission, as compared with 7 of 60 patients (12 percent) who received 2.0 mg per kilogram and 5 of 63 patients (8 percent) who received placebo (P=0.007

Table 2. Ulcerative Colitis Clinical Scores, Modified Riley Scores, and Scores on the Inflammatory Bowel Disease Questionnaire over Time According to Treatment Group.*

Variable	MLN02, 0.5 mg/kg (N=58)		MLN02, 2.0 mg/kg (N=60)		Placebo (N=63)		P Value†		
	No. of Patients	Mean Score	No. of Patients	Mean Score	No. of Patients	Mean Score	Overall	0.5 mg of MLN02 vs. Placebo	2.0 mg of MLN02 vs. Placebo
Composite ulcerative colitis clinical score									
Baseline	58	7.0±1.4	60	7.3±1.5	63	6.7±1.6			
Week 4	58	3.5±2.8	60	3.9±3.1	63	5.0±2.7	0.001	0.006	0.02
Week 6	58	3.3±2.9	60	3.9±3.2	63	4.8±2.8	0.007	0.008	0.06
Modified Riley score‡									
Baseline	58	5.9±1.3	60	6.2±1.0	61	5.7±1.5			
Week 4	49	3.9±2.5	53	4.5±2.5	53	5.4±1.7	<0.001	0.002	0.08
Week 6	46	3.6±2.7	44	3.7±2.9	43	4.8±2.4	0.03	0.03	0.06
Score on the inflammatory bowel disease questionnaire									
Baseline	58	139.6±34	60	131.4±30	63	142.6±32			
Week 4	58	171.7±39	60	164.6±37	63	159.3±32	0.02	0.05	0.28
Week 6	58	175.5±42	60	167.6±40	63	162.5±34	0.03	0.03	0.37

* Plus–minus values are means ±SD.
† P values were derived by analysis of covariance, with adjustment for mesalamine use and the baseline value.
‡ For all analyses of endoscopic and histopathological scores, missing values were not imputed.

for the comparison between the MLN02 groups and the placebo group). Furthermore, patients who received 0.5 or 2.0 mg per kilogram were more likely to improve two or more endoscopic grades than those who received placebo (48 percent and 35 percent, respectively, vs. 16 percent; P=0.001).

OTHER MEASURES OF DISEASE ACTIVITY

Patients who received MLN02 had greater improvement in ulcerative colitis clinical scores and Riley scores than those who received placebo (Table 2). Their scores on the inflammatory bowel disease questionnaire also improved.

PHARMACOLOGY

The mean (±SD) maximum MLN02 concentration was 12.5±2.5 μg per milliliter in the low-dose (0.5 mg per kilogram) group (11 patients) and 52.0±10.4 μg per milliliter in the high-dose (2.0 mg per kilogram) group (11 patients). The serum half-lives were 9 and 12 days, respectively. In both groups, saturation of $\alpha_4\beta_7$ on more than 90 percent of the CD4+CD45RO+ T cells in the peripheral circulation were observed at both week 4 and week 6.

ADVERSE EVENTS AND ANTIBODIES TO MLN02

There were no substantial differences among the three groups in the prevalence of adverse events (Table 3). Three noteworthy events were observed in patients treated with MLN02. A 50-year-old woman, in whom hives and mild angioedema developed during her second infusion, tested positive for MLN02 antibodies with a titer of 1:3125. Of 103 participants who received two infusions of MLN02, she was the only one in whom a clinically relevant infusion reaction developed. A primary cytomegalovirus infection developed in a second patient, whose condition improved without antiviral therapy. Lobar pneumonia developed in a patient three days after spinal surgery and was successfully treated.

No differences in laboratory results were identified among the treatment groups. Notably, there was no difference in the total blood lymphocyte, T-cell, and B-cell counts between patients treated with MLN02 and those who received placebo.

Human antihuman antibodies developed by week 8 in 44 percent of the patients who received MLN02. Overall, 24 percent of patients were positive for antibody at a titer of greater than 1:125.

Corresponding values for the groups receiving 2.0 mg per kilogram and 0.5 mg per kilogram were 11 percent and 38 percent, respectively. In patients with this concentration of antibody, the rate of clinical remission was 12 percent, which was similar to the rate in the placebo group (14 percent). Furthermore, in patients with this concentration of antibody, $\alpha_4\beta_7$ binding sites on circulating CD4+CD45RO+ T lymphocytes became unsaturated. Conversely, in the 76 percent of patients who either tested negative or had lower titers of antibody, the clinical-remission rate was 42 percent and these binding sites remained saturated.

DISCUSSION

These results indicate that selective blockade of the movement of CD4+CD45RO+ T cells by MLN02 is an effective therapy for moderately severe ulcerative colitis. Patients who received MLN02 were more than twice as likely to enter remission as those who received placebo, a difference that was both statistically significant and clinically meaningful. Furthermore, endoscopic improvement, endoscopic remission, and histopathological improvement occurred more frequently in patients who were assigned to active treatment. Parallel improvement in health-related quality of life was also observed. Eighty-two percent of the patients had not responded to mesalamine and probably would have received corticosteroids. Given that many patients ultimately become dependent on corticosteroids,[24] MLN02 may be an attractive alternative for those in whom mesalamine treatment fails. However, despite a high rate of adverse events with prolonged use, corticosteroid therapy can be both effective and relatively inexpensive. Thus, future trials of MLN02 should include patients in whom therapy with corticosteroids is ineffective.

No important differences in the occurrence of adverse events were identified among the treatment groups. No deaths, cancers, or opportunistic infections were observed. A primary cytomegalovirus infection developed in one patient, but this case was not consistent with such reactivation of viral infection as might be seen in the setting of compromised immunity. The patient recovered without treatment. The only other complication related to infection, lobar pneumonia, occurred postoperatively; thus, it is difficult to ascribe a causal relation to treatment with MLN02.

Despite the use of techniques of molecular engineering to minimize sensitization, human antihuman antibodies can develop after treatment with monoclonal antibodies.[25,26] The clinical outcomes of antibody formation are more relevant than the frequency of their occurrence. Hypersensitivity reactions related to human antihuman antibodies are a clinically significant adverse event associated with the use of therapeutic antibodies.[27,28] Although antibodies to MLN02 developed in 44 percent of the patients treated with MLN02, only one patient had an infusion reaction. However, 24 percent of patients with a human antihuman antibody titer of greater than 1:125 showed a loss of saturation of $\alpha_4\beta_7$ binding sites, and the clinical remission rate in this group was similar to that in the placebo

Table 3. Adverse Events.

Variable	MLN02, 0.5 mg/kg (N=58)	MLN02, 2.0 mg/kg (N=60)	Placebo (N=63)	P Value*
	no. of patients (%)			
Adverse event†				
Ulcerative colitis aggravated	29 (50)	22 (37)	24 (38)	0.50
Nausea	15 (26)	11 (18)	10 (16)	0.32
Headache	12 (21)	11 (18)	13 (21)	0.85
Frequent bowel movements	10 (17)	5 (8)	10 (16)	0.56
Fatigue	8 (14)	5 (8)	7 (11)	0.98
Nasopharyngitis	8 (14)	8 (13)	5 (8)	0.26
Abdominal pain	6 (10)	5 (8)	8 (13)	0.48
Abdominal tenderness	4 (7)	1 (2)	8 (13)	0.07
Arthralgia	4 (7)	7 (12)	5 (8)	0.75
Dizziness	6 (10)	4 (7)	1 (2)	0.10
Rash	6 (10)	4 (7)	4 (6)	0.77
Blood in stool	6 (10)	3 (5)	8 (13)	0.27
Vomiting	6 (10)	2 (3)	5 (8)	0.77
	no. of events			
Serious adverse events				
Exacerbation of colitis	4	9	5	0.51
Infusion reaction with angioedema	1	0	0	1.00
Infection	1	2	0	0.55
Nausea and vomiting	0	1	1	1.00
Degenerative disk disease	0	2	0	0.54
	no. of patients			
Patients with serious adverse events	6	12	6	0.28

* P values were calculated with the use of Fisher's exact test and are for the comparison of the combination of the groups receiving MLN02 with the placebo group.

† All events that occurred in at least 10 percent of patients in any of the three treatment groups are shown.

group. The development of neutralizing antibodies has been reported with other humanized antibodies.[26,29,30] Given these observations, cointerventions such as the administration of intravenous corticosteroid[31] at the time of MLN02 infusion, concomitant use of antimetabolites,[32] or as suggested by our data, use of a higher initial dose of MLN02[33] may be necessary to reduce the risk of sensitization. Whether these interventions are relevant for MLN02 therapy requires evaluation in future studies.

Our study had several limitations. First, only one third of patients who received MLN02 entered remission. Therefore, future studies should evaluate a higher dose of the drug. However, this approach may not yield greater efficacy, since no dose–response relationship was observed in the current trial and saturation of $\alpha_4\beta_7$ on CD4+CD45RO+ peripheral T cells at both doses of MLN02 had occurred when the primary end point was assessed. Second, since we did not study patients treated with corticosteroids or antimetabolites, it is possible that coadministration of these drugs with MLN02 might either enhance or antagonize the effects of MLN02. Finally, we were not able to evaluate whether selective blockade of $\alpha_4\beta_7$ is a preferable strategy to the more broadly inhibitory approach of blocking the α_4 integrin with natalizumab, which has been successful in the treatment of both Crohn's disease[14] and multiple sclerosis.[15]

The lymphocytosis that occurs after treatment with natalizumab, an antibody directed toward the α integrin monomer, was not observed in our study.[14,15] This important finding supports the hypothesis that MLN02 selectively blocks a small population of T cells involved in intestinal immunity. We speculate that this property will ultimately be shown to result in less impairment of systemic immunity than occurs with universal blockade of all α integrin–mediated interactions between leukocytes and endothelium.

In conclusion, we have shown in this short-term study that MLN02 is an effective treatment for patients with active ulcerative colitis. However, the role of MLN02 in clinical practice is not yet known, and additional long-term studies are needed.

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APPENDIX

The following persons and institutions (all in Canada) participated in the study: London Health Sciences Centre, London, Ont.: B. Feagan, J.W.D. McDonald, W. McCaw, P. Walton-Mennill; Montreal General Hospital, Montreal: G. Wild, N. Pellerin, J. Cousineau; Hôtel-Dieu de Québec, Quebec, Que.: R. Dubé, S. Lepire, P. Paré; Mount Sinai Hospital, Toronto: G.R. Greenberg, S. Irwin; Jewish General Hospital, Montreal: A. Cohen, N. Desjardins, J. Rivard; Mount Sinai Hospital, Toronto: A.H. Steinhart, S. Mikolainis; Ottawa Civic Hospital, Ottawa: A. Rostom, P. Waddell; Health Sciences Centre, Winnipeg, Man.: C. Bernstein, P. Rawsthorne, S. Chubey; St. Paul's Hospital, Vancouver, B.C.: S. Whittaker, S. Patterson, B. McDougall, H. Kooner; St. Michael's Hospital, Toronto: J. Baker, B. Winter, E. Dubcenco, G. Stewart; Queen Elizabeth II Health Sciences Centre, Halifax, N.S.: D. MacIntosh, C.N. Williams, J. Stewart; Saint-François d'Assise, Quebec, Que.: C. Dallaire, F. Bernard; University of Alberta Hospital, Edmonton: R.N. Fedorak, M. Harriott, S. Appelman-Eszczuk; Vancouver General Hospital, Vancouver, B.C.: F. Anderson, I. Wong; Royal Victoria Hospital, Montreal: A. Bitton, M. Bernier; Centre Hospitalier Affilié Universitaire de Québec–Hôpital St. Sacrement, Quebec, Que.: P. Paré, S. Rousseau, J. Emond; Sunnybrook and Women's Health Sciences Centre, Toronto: F. Saibil, M. Morgan; Health Sciences Centre, Calgary, Alta.: R. Panaccione, N. Racicot; Hôpital Maisonneuve–Rosemont, Montreal: A. Archambault, S. Bélanger. *Steering Committee:* B. Feagan (chair), R.N. Fedorak, G.R. Greenberg, J.W.D. McDonald, P. Paré, G. Wild. *Robarts Clinical Trials Coordinating Center Personnel:* B. Bergman, M. Brine, T. Clayton, M. Irlam, B. Jasevicius, L. Jensen, W. Johnson, D. LeBer, E. Liddiard, S. MacDonald, J. Rémillard, I. Ruocco, B. Sarazin, B. Sharpe, L. Smith, H. Sun, M. Vandervoort, C. Wong. *Millennium Personnel:* J. Kuesters, M. Webster, J. Madruga, J. Ott, N. Herring, and K. Lloyd were responsible for the clinical study; M. Briskin and P. Ponath developed MLN02 through modeling and humanization design; M. Green assayed the antibodies; C. Horvath performed analyses of pharmacokinetics and pharmacodynamics; and K. Kishimoto and J. Guiterrez-Ramos provided advice. *Data Safety and Monitoring Board:* D. Jewell (chair), J. Mahon, R. Rothstein.

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BRIEF REPORT

Survival after Treatment of Rabies with Induction of Coma

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SUMMARY

We report the survival of a 15-year-old girl in whom clinical rabies developed one month after she was bitten by a bat. Treatment included induction of coma while a native immune response matured; rabies vaccine was not administered. The patient was treated with ketamine, midazolam, ribavirin, and amantadine. Probable drug-related toxic effects included hemolysis, pancreatitis, acidosis, and hepatotoxicity. Lumbar puncture after eight days showed an increased level of rabies antibody, and sedation was tapered. Paresis and sensory denervation then resolved. The patient was removed from isolation after 31 days and discharged to her home after 76 days. At nearly five months after her initial hospitalization, she was alert and communicative, but with choreoathetosis, dysarthria, and an unsteady gait.

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A related video is available at www.nejm.org

RABIES IN HUMANS IS A FATAL ILLNESS CHARACTERIZED BY SEVERE encephalopathy and generalized paresis. When the disease is not treated, death typically occurs within five to seven days after the onset of symptoms. Medical management may prolong survival up to 133 days.[1,2] There is scant evidence to indicate that any treatment alters median survival, although five people have survived after receiving immunoprophylaxis before the onset of symptoms.[3,4] We report the survival of a patient with rabies who was treated with an intense antiexcitotoxic strategy while the native immune response matured but who received no immune prophylaxis.

CASE REPORT

The patient was a 15-year-old girl who rescued and released a bat that struck an interior window. She sustained a 5-mm laceration to her left index finger from the bat. The wound was washed with peroxide. No medical attention was sought, and no rabies postexposure prophylaxis was administered. The patient continued to excel in school and play sports until one month after exposure, when she experienced generalized fatigue and paresthesia of the left hand. Two days later diplopia developed and she felt unsteady. The next day, she had nausea and vomiting without fever. A neurologist noted partial bilateral sixth-nerve palsy and ataxia. The results of magnetic resonance imaging and angiography of her brain were unremarkable. By the fourth day after the onset of symptoms, blurred vision, weakness of the left leg, and a gait abnormality were present. On the fifth day, fever (38.8°C), slurred speech, nystagmus, and tremors of the left arm developed. With the progression of symptoms and an elicited history of a bat bite, the patient was transferred to our facility.

On the first hospital day, the patient was febrile (temperature, 38.2°C) and semiobtunded but answered simple questions and complied with simple commands during diagnostic maneuvers. She had scanning speech, bilateral sixth-nerve palsies, decreased upward gaze, dysarthria, myoclonus, intention tremor of the left arm, and ataxia. Samples of serum, cerebrospinal fluid, nuchal skin, and saliva were submitted to the Centers for Disease Control and Prevention (CDC) for the diagnosis of rabies. Repeated brain magnetic resonance imaging and angiography showed no abnormalities. The patient began salivating, with uncoordinated swallowing, and was intubated for airway protection. On the second hospital day, the presence of rabies virus–specific antibody in her cerebrospinal fluid and serum was confirmed by the CDC. Attempts to isolate rabies virus, detect viral antigen, and amplify viral nucleic acid from two skin biopsies and nine saliva samples were unsuccessful.

The patient's parents were counseled about her diagnosis and prognosis. We offered both hospice care and an aggressive approach on the basis of an untested strategy that combined antiexcitatory and antiviral drugs with supportive intensive care. We provided information about the probable failure of antiviral therapy and the unknown effect of the proposed therapy, as well as the possibility of severe disability if the patient were to survive. The patient's parents requested that we institute aggressive care on the basis of the principles we had discussed.

We administered ketamine at 2 mg per kilogram of body weight per hour with midazolam at 1 to 3.5 mg per kilogram of body weight per hour to suppress background activity on electroencephalography so that only one to two seconds of cerebral activity were interspersed (Fig. 1). Oxygen delivery was optimized without inotropic agents by red-cell transfusion to maintain the hemoglobin level at more than 10 g per deciliter, appropriate volume loading, and mechanical ventilation targeting arterial normoxia and mild hypercapnia.[5] Adequacy of oxygen delivery to organs was monitored by intermittent assessment of venous saturation, and brain and somatic oxygenation by near-infrared spectroscopy.[6] Heparin (10 U per kilogram per hour) was administered prophylactically.[7]

After the induction of coma and on the basis of discussions with scientists at the CDC, we instituted antiviral therapy. Studies in animals have shown little penetration of ribavirin into the central nervous system, and it has had little effect in animal models, but we administered the drug with the rationale that elevated protein levels in the cerebrospinal fluid indicated permeability of the blood–brain barrier (Table 1) and that ribavirin might protect against rabies myocarditis.[3] Ribavirin was administered on the third hospital day, with a loading dose of 33 mg per kilogram followed by a maintenance dose of 16 mg per kilogram every six hours. Interferon alfa was not used because of its neurotoxicity. Neither rabies vaccine nor rabies immune globulin was administered because of the patient's demonstrated immune response and the potential for harm from a potentiated immune response.[8] Amantadine (200 mg per day, administered enterally) was added on the fourth hospital day because of its in vitro activity against rabies virus, as well as its antiexcitotoxic activity, which is distributed more rostrally in the brain than is that of ketamine.[9,10]

High doses of benzodiazepines with supplemental barbiturates were necessary to maintain burst suppression. Limited availability of preservative-free midazolam necessitated the use of midazolam containing 1 percent benzyl alcohol. Biochemical evidence of hemolysis and acidosis was detected by the fifth hospital day. The hemoglobin level declined from 13.7 to 10.9 g per deciliter, whereas the lactate dehydrogenase level rose from 420 to 1020 U per liter over seven days, a finding that was consistent with hemolysis, probably after a cumulative total of 276 mg per kilogram of ribavirin had been administered. An arterial base excess of 2.7 mmol per liter declined to −3.8 mmol per liter over five days, which was consistent with metabolic acidosis, without a change in the blood lactate level, probably reflecting the cumulative total of 362 mg per kilogram of benzyl alcohol. Ribavirin was reduced to 8 mg per kilogram for nine doses, and midazolam was tapered to 1.5 mg per kilogram per hour, with phenobarbital supplementation to maintain burst suppression.

There were minimal systemic effects of brainstem and peripheral neuropathy. The patient had transient evidence of both deficiency and excess of antidiuretic hormone on the fifth through seventh hospital days. Clinical autonomic denervation developed on the fifth hospital day, with reduced cardiac variability (Fig. 1) and higher central venous pressure.[1,11-13] Salivation decreased on the eighth hospital day. The patient's skin became flushed, and ileus developed. Increased levels of liver aminotransferase (52 IU per liter), lipase (1193 U per milli-

liter), and amylase (288 U per milliliter) were noted. Lipase and amylase peaked on the 15th to 18th hospital days (at 2532 U and 539 U per milliliter, respectively), but without enlargement of the pancreas on sonography. A lumbar puncture on the eighth hospital day showed an increased level of rabies-virus antibody in both the serum and cerebrospinal fluid (Fig. 1 and Table 1). Ketamine was tapered over 24 hours, and diazepam was given to replace midazolam.

On the 10th hospital day, the patient responded to suctioning with increases in pulse and blood pressure. A high fever developed on the 12th hospital day, without leukocytosis or culture evidence of infection. The patient's fever did not respond to acetaminophen, ibuprofen, ketorolac, or external cooling. On the 14th day, therapy was intensified with ketamine, high-dose diazepam, and amantadine, without effect on her fever (Fig. 1). Studies in both animals and humans describe marked poikilothermia in rabies.[1,14] A reduction in the room temperature by 5.5°C on the 15th day was followed by a 3.6°C drop in core body temperature. Ketamine and diazepam were lowered and amantadine continued for one week.

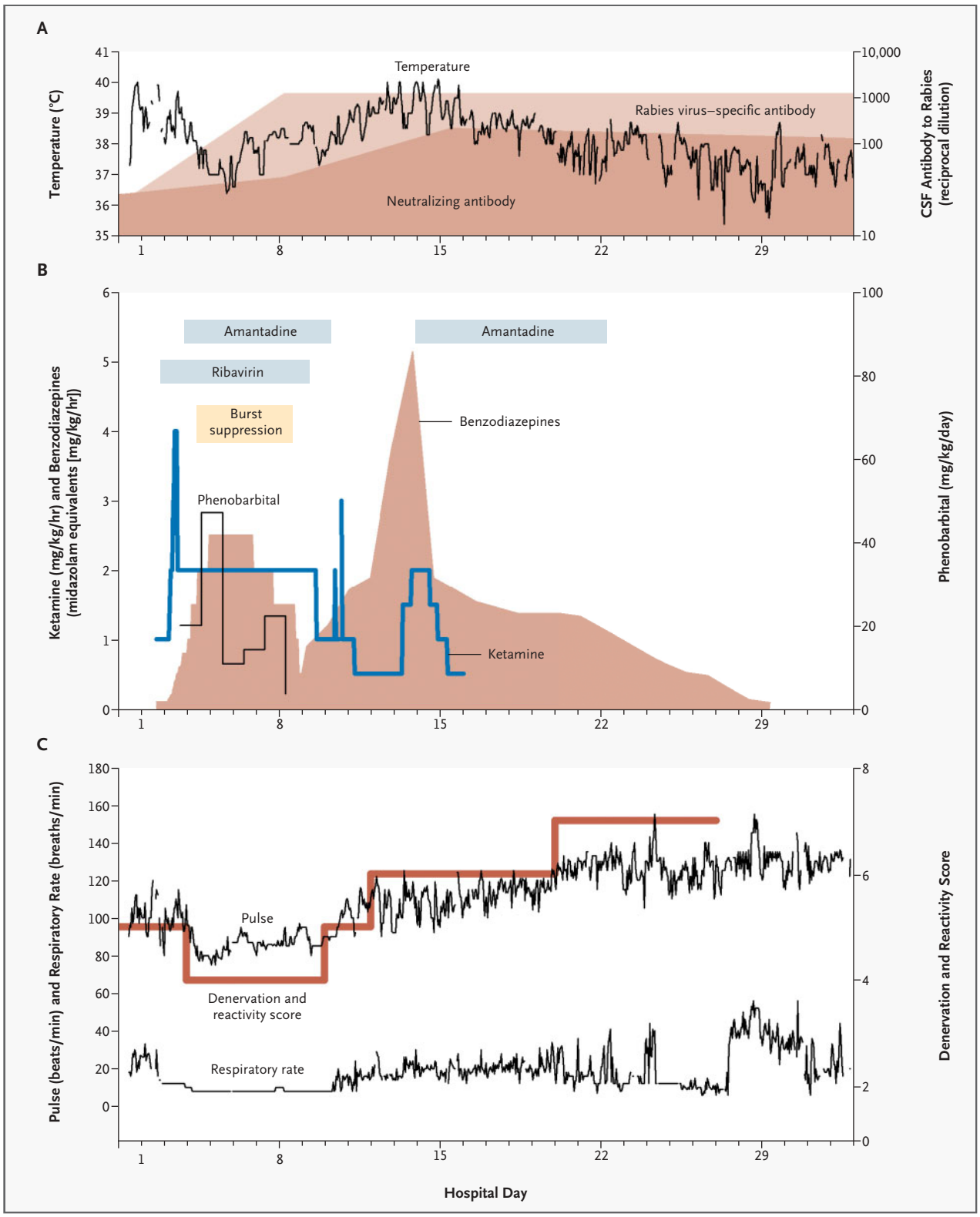
Although the electroencephalographic findings improved after the initial tapering of drugs, the patient had briskly reactive pupils but no other cranial-nerve function on the ninth day. Motor examination showed complete flaccidity, without spontaneous movement or movement in response to pain and the absence of deep-tendon reflexes. Patellar deep-tendon reflexes developed on the 12th day, when the patient also opened her mouth in response to sternal pressure. She blinked when eyedrops were administered and regained eye movements on the 14th day. By the 16th day, she opened her mouth to assist with care and raised her eyebrows in response to speech. On the 19th day, she wiggled her toes and squeezed hands in response to commands, fixed her gaze preferentially on her mother, and had an apneustic breathing pattern associated with dystonic opening of her jaw. Computed tomography of her head was normal.

On the 20th day, patellar and ankle deep-tendon reflexes became hyperreflexic, and deep-tendon reflexes in the biceps and triceps developed. Her attention span was 10 to 30 seconds. On the same day, the patient had respiratory distress associated with diaphoresis, tearing of the eyes, the production of thick secretions, and prolonged episodes of coughing and gagging. This condition responded to applications of lidocaine to her hypopharynx. On the 22nd day, she had episodes of prolonged expiratory phase, responsive to albuterol or suctioning. On the 23rd day, she sat in bed, holding her head erect. On the 26th day, she clearly objected to new staff members, a tremor developed in her jaw, and she showed passive tone when her extremities were moved. She was extubated on the 27th day and later slept for 8 consecutive hours and had 60 seconds of sustained alertness. There was persistent jaw dystonia and limited spontaneous movement. On the 30th day, she cried spontaneously and acknowledged sadness as opposed to fear or pain. Deep-tendon reflexes in her biceps and triceps became hyperreflexic, whereas patellar and ankle reflexes normalized. She reported having no skin hyperesthesia or dysesthesia.

Given her continued neutralizing antibody response to rabies virus in cerebrospinal fluid and blood and our inability to isolate the virus or detect viral nucleic acid in saliva, the patient was considered cleared of transmissible rabies and removed from isolation on the 31st day. After rehabilitation, she was discharged to her home on the 76th day (Fig. 2). In a clinic visit 131 days after her initial hospitalization, she smiled, laughed, and interacted with the examiner; her speech was dysarthric (Video Clip 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). The patient was able to dress herself, ate a normal diet, slept well, and attended high school part-time. She had constant buccolingual choreoathetosis with generalized choreoathetosis and in-

Figure 1 (facing page). Relationship between Vital Signs in a Patient with Rabies and the Treatment Regimen.

Panel A shows the relationship between temperature and titers of total rabies virus–specific antibody and neutralizing antibody in cerebrospinal fluid (CSF), according to hospital day. A pronounced febrile inflammatory syndrome in the second week was associated with the emergence of neutralizing antibodies in the CSF. Panel B shows the effects of the administration of ketamine, benzodiazepines (in midazolam equivalents, with 3 mg midazolam equal to 1 mg diazepam), phenobarbital, amantadine, and ribavirin. Burst suppression was achieved after an initial sleep pattern was established by electroencephalography. In Panel C, a loss of variability in pulse and respiratory rate and salivary secretions (with an arbitrary score of 4) was followed by a return of heart-rate variability (with a score of 5) and then hyperreactivity (including tearing of the eyes, the production of thick secretions, coughing, and gagging, with a score of 6) and later bronchospasm (with a score of 7).



termittent dystonia and ballismus, which produced a lurching gait and fine-motor difficulties (Video Clip 2 in the Supplementary Appendix). She was able to write legibly but slowly and to type with her index fingers. She had normal extremity tone, bilateral upward-going toes, and no clonus. She had decreased dorsiflexion in the left ankle and decreased grip in the left hand. She had intact sense of position and light touch.

DISCUSSION

At the time of the patient's transfer to our facility, a search of the recent literature had confirmed the futility of antiviral therapy and immune modulation in the treatment of clinical rabies. This finding was confirmed by experience at the CDC. We noted that the pathology of the human brain in cases of rabies reflected secondary complications rather than any clear primary process and that a normal immune system cleared the virus.[2,7,15,16] Clinical reports included the hypothesis that death resulted from "neurotransmitter imbalance" and autonomic failure; supportive care was predicted to succeed.[5,7,15,17,18] A search of the literature regarding neurotransmitters in rabies identified ketamine as an *N*-methyl-D-aspartate (NMDA)–receptor antagonist with specific activity against rabies in animal models.[19] We conceived a strategy to try to protect the brain from injury while enabling the immune system to mount a natural response and clear the virus. Hypothermia was ruled out because of its effects on immune function.[20] We elected to induce therapeutic coma using γ-aminobutyric acid (GABA)–receptor agonism with benzodiazepines and barbiturates, along with NMDA-receptor antagonism with ketamine and amantadine, to reduce excitotoxicity, brain metabolism, and autonomic reactivity.[21-23]

This improvised approach was a logical extension of previous efforts to prevent complications through aggressive critical care.[5,7,18] The induction of coma was associated with a remarkably uneventful course in the intensive care unit, suggesting that much of the dysautonomia characteristic of rabies can be avoided with therapeutic sedation anesthesia. An alternative hypothesis is that this patient would not have developed substantial dysautonomia. Autonomic hyperreflexia emerged while the drugs were being tapered, which suggests a parallel to the hypersensitivity to environmental stimuli seen in tetanus, with a general preservation of higher cortical function.[7,24] Induction of coma through GABA agonism with NMDA antagonism may have conferred specific benefit. Although similar strategies have not shown consistent clinical efficacy for protection against excitotoxicity, our high-dose, multimodal regimen was more aggressive and the insult less cytopathic.

The patient survived, but with neurologic impairment. Although her improvement continued five months after her initial hospitalization, we cannot predict the long-term outcome. In addition to this girl, there are five well-documented survivors of rabies. All of the patients had received either occupationally related preexposure rabies vaccination or postexposure prophylaxis.[4] Our patient survived with only naturally acquired immunity, although her exposure to rabies virus consisted of minimal

Table 1. Evolution of Inflammation and Levels of Rabies Virus–Specific Antibody in Cerebrospinal Fluid, According to Hospital Day.*

Hospital Day	White Cells	Red Cells	Glucose	Protein	CSF IFA		CSF RFFIT	Serum IFA		Serum RFFIT
	cells/mm³		mg/dl		IgM	IgG		IgM	IgG	
1	22	130	57	75	32	32	47	32	128	102
8	121	0	54	80	32	2048	89	128	512	229
16	57	3	70	90	32	2048	556	32	2,048	651
45	15	1225	56	107	32	2048	285	8	8,192	1188
52	72	2950	46	113	32	2048	493	4	32,768	1604
66	8	1	48	71	<4	2048	1300	<4	32,768	1183

* CSF denotes cerebrospinal fluid, IFA indirect immunofluorescence antibody titer, and RFFIT rapid fluorescence focus inhibition test. Antibody values are expressed as the reciprocal dilution. The bat exposure occurred on September 12, 2004. Hospital days are numbered from October 18, 2004.

trauma at a distal body site, probably with a limited quantity of inoculum. She was young and athletic. The bat that bit her was not recovered, and we were unable to isolate or detect rabies virus from saliva, cerebrospinal fluid, or nuchal-biopsy specimens. We therefore cannot rule out the possibility that her survival was due to an unusual, more temperate or attenuated variant of the virus or a rare host polymorphism. Therapy may have been more effective than in past cases because of the inferred limited exposure to rabies virus, early recognition of the disease, and aggressive management.

Clearly, our experience with this patient requires replication in other patients and proof-of-concept experiments in animal models. Although our primary therapeutic intent was to provide protection against excitotoxic neuronal injury, the patient may have benefited from the dual action of ketamine and amantadine, drugs with activity against rabies virus. She incurred possible toxic effects associated with ribavirin (hemolysis, pancreatitis, and mitochondrial toxicity) and benzyl alcohol (acidosis). Further review of the literature indicates that rabies virus infection of the heart is infrequent and limited in extent.[12,13]

Ribavirin is variably toxic to mitochondria, and we measured profoundly depleted serum levels of coenzyme Q10 (0.30 μg per milliliter; range, 0.57 to 3.03) during the second month of her convalescence in association with persistently depressed myocardial contractility.[25] Rabies virus is largely restricted to the nervous system, so depletion of coenzyme Q10 was probably associated with her critical illness or administered drugs. For patients whose disease is diagnosed before their immune response to rabies virus can be detected, we suggest considering the use of ribavirin, but at a more limited dose or with concurrent supplementation with coenzyme Q10. Given that manifestations of dysautonomia were easily managed, we recommend a longer-acting benzodiazepine with less preservative for future patients.

Survival of this single patient does not change the overwhelming statistics on rabies, which has

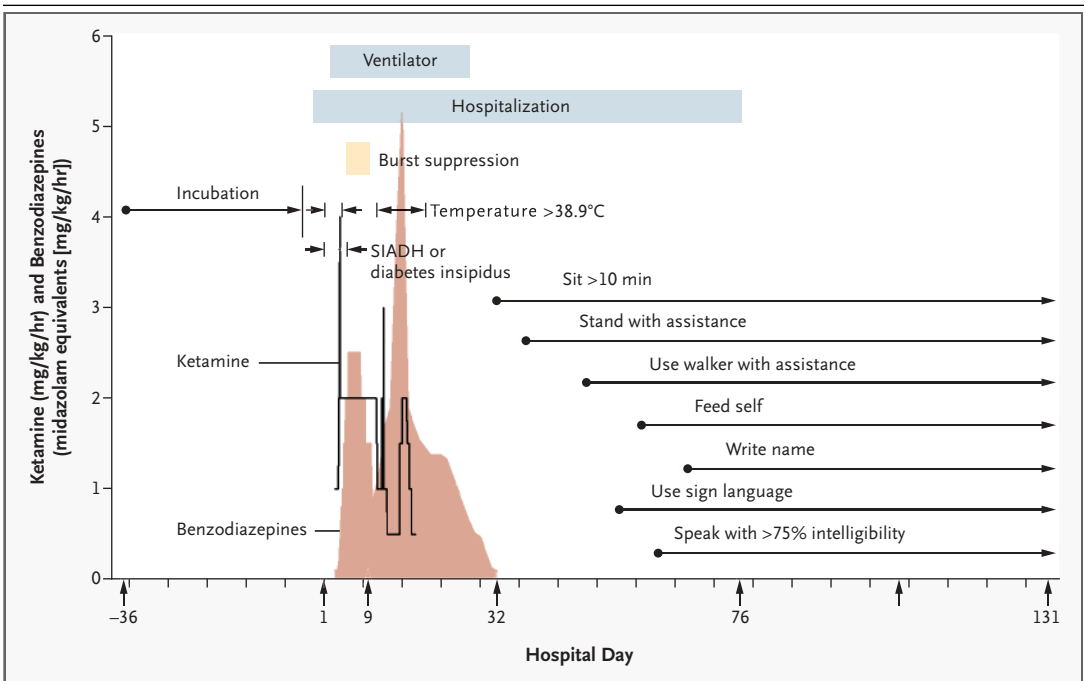


Figure 2. Timeline by Hospital Day from the Time of Inoculation with Rabies Virus until Two Months after Discharge from the Hospital.

The incubation period extends from the day on which the patient was bitten by a bat until her first symptoms appeared. Hospitalization includes both the referral and accepting hospitals. The therapeutic coma induced by ketamine and midazolam and the period of burst suppression are shown for reference. Disorders of temperature (more than 38.9°C) and the syndrome of inappropriate antidiuretic hormone (SIADH) or diabetes insipidus are indicated. The patient was transferred from intensive care on the 32nd hospital day. A selected list of rehabilitation milestones is shown.

the highest case fatality ratio of any infectious disease. Any regimen may be ineffective in cases associated with extremes of age, massive traumatic inoculation, or delayed diagnosis and must be coupled with strategies to reduce the risk of complications from long-term treatment in the intensive care unit.

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SPECIAL ARTICLE

Prevalence and Treatment of Mental Disorders, 1990 to 2003

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ABSTRACT

BACKGROUND

Although the 1990s saw enormous change in the mental health care system in the United States, little is known about changes in the prevalence or rate of treatment of mental disorders.

METHODS

We examined trends in the prevalence and rate of treatment of mental disorders among people 18 to 54 years of age during roughly the past decade. Data from the National Comorbidity Survey (NCS) were obtained in 5388 face-to-face household interviews conducted between 1990 and 1992, and data from the NCS Replication were obtained in 4319 interviews conducted between 2001 and 2003. Anxiety disorders, mood disorders, and substance-abuse disorders that were present during the 12 months before the interview were diagnosed with the use of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Treatment for emotional disorders was categorized according to the sector of mental health services: psychiatry services, other mental health services, general medical services, human services, and complementary–alternative medical services.

RESULTS

The prevalence of mental disorders did not change during the decade (29.4 percent between 1990 and 1992 and 30.5 percent between 2001 and 2003, P=0.52), but the rate of treatment increased. Among patients with a disorder, 20.3 percent received treatment between 1990 and 1992 and 32.9 percent received treatment between 2001 and 2003 (P<0.001). Overall, 12.2 percent of the population 18 to 54 years of age received treatment for emotional disorders between 1990 and 1992 and 20.1 percent between 2001 and 2003 (P<0.001). Only about half those who received treatment had disorders that met diagnostic criteria for a mental disorder. Significant increases in the rate of treatment (49.0 percent between 1990 and 1992 and 49.9 percent between 2001 and 2003) were limited to the sectors of general medical services (2.59 times as high in 2001 to 2003 as in 1990 to 1992), psychiatry services (2.17 times as high), and other mental health services (1.59 times as high) and were independent of the severity of the disorder and of the sociodemographic characteristics of the respondents.

CONCLUSIONS

Despite an increase in the rate of treatment, most patients with a mental disorder did not receive treatment. Continued efforts are needed to obtain data on the effectiveness of treatment in order to increase the use of effective treatments.

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The U.S. Surgeon General's report on mental health[1] and the President's New Freedom Commission on Mental Health[2] have both called for expanding treatment for mental disorders. Planning this expansion requires accurate data on the prevalence and rate of treatment of mental disorders. In the 1980s, the Epidemiologic Catchment Area (ECA) Study found that 29.4 percent of the adults interviewed had had a mental disorder at some time in the 12 months before the interview (referred to as a "12-month mental disorder"), according to the criteria of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III).[3] A fifth of those with a 12-month disorder received treatment. Half of those who received treatment did not meet the criteria for a 12-month disorder according to the ECA Study or the DSM-III. A decade later, the National Comorbidity Survey (NCS) found that 30.5 percent of people 15 to 54 years of age had conditions that met the criteria for a 12-month mental disorder according to the criteria of the DSM-III, revised (DSM-III-R).[4] A fourth of these patients received treatment. Roughly half those who received treatment did not meet the criteria for a 12-month mental disorder according to the NCS or the DSM-III-R.

The results of the ECA study and the NCS are no longer valid owing to changes in the delivery of mental health care. The Substance Abuse and Mental Health Services Administration found that annual visits to mental health specialists (i.e., psychiatrists and psychologists) increased by 50 percent between 1992 and 2000.[5] The National Ambulatory Medical Care Survey found that the number of people receiving treatment for depression tripled between 1987 and 1997.[6] The Robert Wood Johnson Foundation Community Tracking Survey found that the number of people with a serious mental illness who were treated by a specialist increased by 20 percent between 1997 and 2001.[7]

The aim of our study was to present more comprehensive data on national trends with regard to the prevalence and rate of treatment of 12-month mental disorders based on the NCS, conducted from 1990 to 1992,[4] and the NCS Replication (NCS-R), conducted from 2001 to 2003.[8] In our study, unlike the study by the Substance Abuse and Mental Health Services Administration and the National Ambulatory Medical Care Survey, we examined data on the rate of treatment inside and outside the health care system. Unlike the Community Tracking Survey, which contained only rough data based on screening measures of prevalence, our study analyzed detailed diagnostic assessments.

METHODS

SAMPLES

The NCS and NCS-R are nationally representative, face-to-face household surveys of respondents 15 to 54 years of age (NCS) or 18 years of age and older (NCS-R). In the NCS, the response rate was 82.4 percent, and the total number of completed interviews was 8098; in the NCS-R, the response rate was 70.9 percent, and the total number of completed interviews was 9282.[4,8] All respondents had a diagnostic interview that focused on mental disorders. Respondents who had received a diagnosis of a mental disorder and a randomly selected subgroup of those who did not were interviewed to assess risk factors, treatment, and consequences of having a mental disorder. Weights were used to adjust for bias due to differences in responses and within-household differences in the probability of selection. Residual discrepancies between data from the U.S. Census and data on our sample with regard to demographic and geographic distributions were corrected with a final weight. A detailed discussion of samples and weights has been presented elsewhere.[4,8] The data presented in this report are from the part II assessment of respondents in the overlapping age range of the two samples (among respondents 18 to 54 years old, 5388 completed interviews in the NCS, and 4319 in the NCS-R).

RECRUITMENT AND CONSENT

Introductory explanatory materials that were mailed to households included the NCS and NCS-R survey samples before an interviewer visited to answer any remaining questions respondents might have and to obtain informed consent and schedule interviews. As an incentive to respond, respondents included in the NCS received $25 and those included in the NCS-R received $50. A subgroup of those who did not initially agree to be interviewed received higher incentives ($50 in the NCS, and $100 in the NCS-R) to encourage them to complete a screening interview. The human-subjects committees of the University of Michigan and Harvard Medical School approved these procedures.

DIAGNOSTIC ASSESSMENT

Diagnosis was based on the World Health Organization's Composite International Diagnostic Interview (CIDI) in conjunction with the DSM-III-R in the

NCS[9] and CIDI in conjunction with the fourth edition of DSM (DSM-IV) in the NCS-R.[10] Diagnoses included anxiety disorders (e.g., panic disorder, generalized anxiety disorder, phobias, and posttraumatic stress disorder), mood disorders (e.g., major depression, dysthymia, and bipolar disorder), and substance-abuse disorders (e.g., alcohol and drug abuse and dependence). Interviews conducted for clinical reappraisal documented good concordance and conservative estimates of prevalence, as compared with diagnoses made by clinicians who were unaware of the responses given in the diagnostic interview.[11,12] Twelve-month disorders were considered to be present if they had occurred at any time during the 12 months before the interview, even if the disorders had subsequently remitted with treatment.

Because the criteria of the DSM-III-R and of the DSM-IV differ too greatly to justify direct comparisons of prevalence in the data from the NCS and NCS-R, the trend analysis was based on a recalibration of both surveys according to a summary rating of severity that was developed for the NCS-R and then applied (imputed) to the data from the NCS. This rating has been described in detail elsewhere.[13] In brief, a serious disorder was defined as either one that met the 12-month criteria for schizophrenia, any other nonaffective psychosis, bipolar I disorder or bipolar II disorder, or substance dependence with a syndrome of physiological dependence, a suicide attempt or having a suicide plan in conjunction with a diagnosis of a disorder according to the criteria of the NCS-R and DSM-IV, a self-report of "severe" impairment in role functioning in two or more areas owing to a mental disorder, or a self-reported functional impairment associated with a mental disorder consistent with a score of 50 or less according to the Global Assessment of Functioning Scale (scores range from 0 to 100, with higher scores indicating better functioning).[14] A mental disorder that did not meet the criteria for a serious disorder was classified as a moderate or mild disorder on the basis of the subject's responses to disorder-specific questions on the Sheehan Disability Scales for the assessment of clinical severity.[15]

The imputation of scores for severity of disorder to cases included in the NCS was based on estimates calculated with the use of logistic-regression equations in the NCS-R in which symptom measures available in both surveys were used to predict the presence of a serious disorder in one respondent as compared with all other respondents, a serious-to-moderate disorder as compared with mild disorders in all other respondents, and the presence of any disorder as compared with no disorder. The accuracy of prediction was good with all three equations (area under the curve, 0.7 for a serious disorder, 0.8 for a serious-to-moderate disorder, and 0.8 for any disorder). The coefficients in these equations were used to generate predicted probabilities for each respondent included in both surveys for each nested outcome, and these probabilities, in turn, were used to impute discrete scores on the scale for severity (with a range from none to serious).

TREATMENT

All respondents who were interviewed to assess risk factors in both surveys were asked whether they had sought treatment for an emotional disorder within the 12 months before the interview from a list of providers and settings. Responses were classified according to the providers in the sector of mental health services — psychiatrist, other mental health specialist, general medical provider (e.g., a general medical doctor or a nurse practitioner), or complementary–alternative medical provider.

ANALYSIS

Trends were assessed with the use of risk ratios, defined as the proportional increase in the prevalence in the NCS-R as compared with the NCS. Variation in trends among subgroups in the sample, which were defined according to sociodemographic characteristics, was assessed with the use of pooled logistic-regression analysis. Predictors included time, sociodemographic characteristics, and interactions between time and the sociodemographic characteristics. Trends in treatment were also assessed, as a function of the severity of the disorder. Standard errors were obtained with the use of the Taylor series linearization method.[16] Adjustment for imprecision in the imputed scores for severity was made with the use of the multiple-imputation method.[17] Ten independent pseudosamples were drawn from the original NCS-R sample for this purpose, with the use of predicted probabilities of severity that were converted into dichotomous case classifications on the basis of probability distributions. The pseudosamples were used to build uncertainty with regard to classification into the standard error of the estimate; this was done by defining the square of the standard error as the sum of the average design-adjusted coefficient-variance estimates within the 10 pseudosamples and the variance of the coefficients across these pseudo-

samples. Logistic-regression coefficients and standard errors were exponentiated to create odds ratios with 95 percent confidence intervals. The significance of sets of multiple predictors was evaluated with the Wald χ^2 tests with the use of design-adjusted, multiply-imputed coefficient variance–covariance matrixes.

RESULTS

TRENDS IN PREVALENCE

The estimated prevalence of a 12-month mental disorder that met the criteria of the DSM-IV did not differ significantly between the surveys (29.4 percent between 1990 and 1992 and 30.5 percent between 2001 and 2003, P=0.52). There was no significant change in the prevalence of serious disorders (5.3 percent vs. 6.3 percent, P=0.27), moderate disorders (12.3 percent vs. 13.5 percent, P=0.30), or mild disorders (11.8 percent vs. 10.8 percent, P=0.37), and no statistically significant interactions between time and sociodemographic characteristics in the prediction of prevalence (data not shown).

TRENDS IN TREATMENT

The prevalence of treatment for an emotional disorder within the 12 months before the interview was 12.2 percent between 1990 and 1992 and 20.1 percent between 2001 and 2003 (risk ratio, 1.65, P<0.001) (Table 1). The association between greater severity and receipt of treatment was positive, significant (P<0.001), and did not differ over time. It was substantively moderate in the pooled data, however, calculated with the use of a Pearson's contingency coefficient (a polychotomous extension of the phi coefficeint of 0.14). Only a minority of respondents with a serious mental disorder received treatment (24.3 percent between 1990 and 1992 and 40.5 percent between 2001 and 2003). Approximately half those who received treatment (49.0 percent between 1990 and 1992 and 49.9 percent between 2001 and 2003) had none of the disorders considered here (Table 1).

The trends in the rate of treatment according to the sectors of mental health services were similar to the overall trends in two respects (Table 1). First, the severity of a disorder was significantly related to the rate of treatment (P<0.001), and second, this association did not change significantly over time. A significant difference in these trends was found among sectors (P<0.001). In the sector of general medical services, the rate of treatment increased from 3.9 percent to 10.0 percent (risk ratio, 2.59), in that of psychiatry services it increased from 2.4 percent to 5.2 percent (risk ratio, 2.17), and in the sector of other mental health services it increased from 5.3 percent to 8.4 percent (risk ratio, 1.59). In the sector of human services, it increased from 2.6 percent to 3.5 percent (risk ratio, 1.32; P=0.07), the rate in the sector of complementary–alternative medical services decreased from 3.3 percent to 2.7 percent (risk ratio, 0.81; P=0.07).

A shift in the distribution of treatment among the sectors occurred because of differences within the sectors. The distribution of treatment in the sector of general medical services increased from 31.5 percent to 49.6 percent (P<0.001), in that of psychiatry services from 19.6 percent to 25.8 percent (P=0.007), in that of other mental health services from 43.5 percent to 41.9 percent (P=0.59), in that of human services from 21.5 percent to 17.2 percent (P=0.11), and in that of complementary–alternative medical services from 26.8 percent to 13.2 percent (P<0.001). The changes in distribution did not vary significantly according to severity of disorder.

SOCIODEMOGRAPHIC VARIABLES AND TREATMENT

We examined associations between seven sociodemographic variables and the measures of the six sectors in which treatment was provided (Table 2). Of the 42 associations, 10 were found to be significant with the use of a threshold of 0.001 as an approximate control for type 1 error. Predictors of the receipt of treatment within any sector of mental health services included age greater than 24 years, female sex, non-Hispanic white race, and marital status (separated, widowed, divorced, or never married). Race was self-reported. Predictors of treatment specific to the sector of services included age (older age correlated positively with treatment in the sector of general medical services and negatively with that of other mental health services), sex (female sex correlated positively with treatment in the sector of general medical services and negatively with that of complementary–alternative medical services), marital status (respondents who had never married were more likely than those who were currently married to receive treatment in the sector of other mental health services), education (more years of education correlated negatively with treatment in the sector of general medical services), and urban as compared with rural area (rural areas related negatively to sector of services). These associ-

Table 1. Treatment of 12-Month Disorders According to Severity and Sector of Mental Health Services among 5388 Respondents to the National Comorbidity Survey (NCS), 1990–1992, and 4319 Respondents to the National Comorbidity Survey Replication (NCS-R), 2001–2003.*

Variable	Any	PSY	OMH	GM	HS	CAM
			percentage ±SE†			
NCS						
Serious	24.3±3.8	7.3±2.2	11.4±2.5	8.2±3.0	4.5±1.9	8.4±1.9
Moderate	25.4±2.4	5.8±1.2	13.6±1.6	8.6±1.4	5.5±1.1	7.1±1.2
Mild	13.3±2.4	2.5±1.2	4.9±1.3	4.3±1.4	3.0±1.2	3.0±0.8
Any	20.3±1.5	4.8±0.8	9.7±1.0	6.8±1.0	4.3±0.7	5.7±0.7
None	8.8±0.7	1.4±0.3	3.5±0.4	2.6±0.4	1.9±0.3	2.3±0.3
Total	12.2±0.6	2.4±0.3	5.3±0.3	3.9±0.4	2.6±0.3	3.3±0.3
NCS-R						
Serious	40.5±4.7	14.4±3.3	19.4±3.5	22.1±3.5	6.5±1.6	6.2±1.5
Moderate	37.2±3.0	13.0±1.6	15.8±1.8	19.5±2.4	5.5±1.2	4.6±1.0
Mild	23.0±3.8	5.1±1.3	9.0±2.2	11.8±2.9	3.9±1.5	2.9±0.9
Any	32.9±2.0	10.5±1.0	14.1±1.3	17.3±1.3	5.1±0.8	4.3±0.6
None	14.5±0.9	2.9±0.4	5.9±0.6	6.8±0.6	2.7±0.4	1.9±0.3
Total	20.1±0.8	5.2±0.3	8.4±0.5	10.0±0.5	3.5±0.3	2.7±0.3
			risk ratio ±SE‡			
Ratio of NCS-R to NCS						
Serious	1.68±0.35	2.01±0.84	1.72±0.49	2.91±1.33	1.53±0.70	0.74±0.25
Moderate	1.47±0.19§	2.27±0.57§	1.17±0.19	2.29±0.46§	1.01±0.29	0.65±0.17
Mild	1.74±0.35§	2.17±1.14	1.85±0.57	2.82±1.04	1.34±0.64	0.97±0.38
Any	1.62±0.15§	2.21±0.40§	1.46±0.18§	2.58±0.41§	1.19±0.25	0.76±0.14
None	1.65±0.16§	2.05±0.50§	1.71±0.26§	2.57±0.46§	1.42±0.32	0.86±0.16
Total	1.65±0.10§	2.17±0.27§	1.59±0.15§	2.59±0.29§	1.32±0.19	0.81±0.10
	χ^2 P Value	χ^2 P Value	χ^2 P Value	χ^2 P Value	χ^2 P Value	χ^2 P Value
Statistical significance¶						
Severity	194.6 <0.001	112.2 <0.001	118.1 <0.001	105.3 <0.001	23.0 <0.001	82.9 <0.001
Time	56.8 <0.001	34.5 <0.001	22.7 <0.001	72.4 <0.001	3.3 0.07	3.3 0.07
Time-by-severity	0.5 0.93	0.2 0.98	3.0 0.40	0.3 0.96	0.9 0.82	1.2 0.76

* Mental disorders were diagnosed according to the criteria of the DSM-IV. Respondents in both surveys were 18 through 54 years of age. Any denotes any sector of mental health services, PSY the sector of psychiatry services, OMH other mental health services, GM general medical services, HS human services, CAM complementary–alternative medical services, and χ^2 the Wald χ^2 test. Standard errors (SEs) are the design-based multiply-imputed standard errors of the estimated values.

† Percentages are the proportions of respondents in the total sample who received any treatment or treatment within the indicated sector of mental health services.

‡ The risk ratio is not always equal to the ratio of the estimated percentages, because of the use of the multiple-imputation method.

§ P values of less than 0.05 (in a two-sided test) indicate statistical significance.

¶ Each χ^2 test for severity has 3 degrees of freedom. Each χ^2 test for time has 1 degree of freedom. Significance tests for interactions between time and severity evaluate the significance of changes between the two surveys. Each time-by-severity χ^2 test has 3 degrees of freedom.

ations are all moderate in magnitude (Pearson's contingency coefficient, 0.04 to 0.07). Income was the only sociodemographic variable that was not significantly related to treatment in any sector of mental health services. Interactions with time and severity of disorder were shown to be nonsignificant with the use of a threshold of 0.001 (Table 2).

DISCUSSION

Although there are limitations to our study, there were five important results. First, no notable change occurred in the prevalence or severity of mental disorders in the United States between 1990 and 1992 or between 2001 and 2003. There are two

Table 2. Sociodemographic Characteristics That Were Predictors of the Receipt of Treatment for Any 12-Month Mental Disorder in the Total Sample of 9707 Respondents and as a Proportion of Treatment Provided in All Sectors of Services.*

Characteristic	Any	PSY	OMH	GM	HS	CAM
	odds ratio (95 percent confidence interval)					
Age group						
18–24 yr	0.6 (0.5–0.8)†	0.6 (0.4–1.0)	2.6 (1.7–3.9)†	0.4 (0.3–0.6)†	2.1 (1.2–3.8)†	0.9 (0.6–1.5)
25–34 yr	0.9 (0.7–1.1)	0.6 (0.4–0.8)†	1.9 (1.3–2.6)†	0.6 (0.4–0.8)†	1.5 (0.9–2.6)	1.2 (0.8–1.7)
35–44 yr	1.1 (0.9–1.4)	0.7 (0.5–0.9)†	1.7 (1.3–2.3)†	0.8 (0.6–1.1)	1.3 (0.8–2.2)	1.1 (0.8–1.5)
45–54 yr‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	<0.001	0.007	<0.001	<0.001	0.07	0.70
Sex						
Female	1.7 (1.4–1.9)†	0.7 (0.6–0.9)†	1.0 (0.8–1.2)	1.8 (1.4–2.3)†	1.1 (0.8–1.5)	0.7 (0.5–0.8)
Male‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	<0.001	0.01	0.71	0.001	0.69	<0.001
Race or ethnic group§						
Hispanic	0.6 (0.5–0.9)†	0.5 (0.3–0.8)†	1.0 (0.6–1.6)	0.8 (0.5–1.2)	1.5 (0.8–2.7)	0.8 (0.4–1.4)
Non-Hispanic black	0.5 (0.4–0.7)†	0.9 (0.6–1.5)	0.7 (0.5–1.1)	0.5 (0.5–1.4)	1.9 (1.2–3.0)†	0.6 (0.4–1.0)
Other	0.5 (0.4–0.7)†	0.9 (0.5–1.7)	1.0 (0.4–2.5)	0.8 (0.2–2.6)	0.7 (0.3–1.9)	0.7 (0.3–1.5)
Non-Hispanic white‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	<0.001	0.02	0.47	0.68	0.01	0.22
Marital status						
Separated, widowed, or divorced	1.8 (1.5–2.2)†	1.0 (0.7–1.3)	1.8 (1.4–2.5)†	0.6 (0.4–0.8)†	1.3 (0.8–2.1)	1.5 (1.0–2.3)
Never married	1.3 (1.1–1.6)†	1.2 (0.8–1.6)	1.3 (1.0–1.8)†	0.8 (0.5–1.1)	1.0 (0.6–1.6)	0.9 (0.6–1.4)
Married‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	<0.001	0.59	<0.001	0.003	0.39	0.05
Education						
0–11 yr	1.1 (0.8–1.5)	0.9 (0.6–1.3)	0.6 (0.4–0.9)†	2.6 (1.7–4.1)†	0.4 (0.2–0.8)†	1.1 (0.7–1.8)
12 yr	1.0 (0.8–1.3)	0.8 (0.6–1.2)	0.6 (0.4–0.9)†	2.2 (1.5–3.2)†	0.8 (0.5–1.2)	1.0 (0.7–1.5)
13–15 yr	1.2 (0.9–1.4)	0.7 (0.5–0.9)†	0.8 (0.6–1.0)	2.1 (1.4–3.1)†	0.8 (0.5–1.2)	0.8 (0.6–1.2)
≥16 yr‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	0.32	0.04	0.02	<0.001	0.03	0.48

possible explanations for this result: that the prevalence of mental disorders would have been higher in the early 2000s than in the early 1990s were it not for the increase in the rate of treatment, and that this increase did not result in a decrease in the number and type of disorders. Consistent with the first possibility is the fact that an economic recession began shortly before and deepened throughout the field-study period of the NCS-R, even though the attacks on September 11, 2001, occurred in the middle of the field-study period. The prevalence of mental disorders might have increased in the absence of an increase in the rate of treatment. However, there is more evidence that is consistent with the second explanation. Studies show that most treatment for mental disorders falls below the minimal standards of quality.[18] In addition, such treatment is typically brief, which means that treatment would influence the duration of an episode of mental disorder more than it would the prevalence of mental disorders in the 12 months before the interview.

Finally, the increase in the rate of treatment was largely in the sector of general medical services, and treatment was provided to patients without disorders that were classified according to criteria of the NCS-R and DSM-IV. Controlled treatment trials have provided no evidence that pharmacotherapy significantly improves mild disorders, making it unlikely that pharmacotherapy could prevent

Table 2. (Continued.)*

Characteristic	Any	PSY	OMH	GM	HS	CAM
	odds ratio (95 percent confidence interval)					
Income¶						
Low	1.1 (0.8–1.4)	1.2 (0.8–1.9)	1.0 (0.7–1.6)	0.9 (0.5–1.4)	2.1 (1.1–3.8)†	1.4 (0.9–2.2)
Low-average	0.9 (0.7–1.1)	0.9 (0.6–1.4)	1.0 (0.7–1.4)	1.2 (0.8–1.8)	1.9 (1.1–3.2)†	1.6 (1.1–2.5)†
High-average	0.9 (0.7–1.1)	0.8 (0.5–1.2)	0.9 (0.7–1.3)	1.1 (0.8–1.6)	1.6 (1.0–2.7)†	1.5 (1.0–2.1)
High‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	0.25	0.07	0.94	0.21	0.10	0.08
Urban vs. rural area‖						
Large MSA–central city	1.6 (0.9–2.6)	0.8 (0.3–2.1)	3.2 (1.3–7.6)	0.7 (0.3–1.4)	0.3 (0.1–0.7)	2.9 (1.0–8.4)†
Large MSA–suburb	1.5 (0.9–2.4)	0.7 (0.2–2.0)	3.0 (1.3–7.2)	0.7 (0.4–1.4)	0.5 (0.2–1.1)	2.6 (0.9–7.3)
Small MSA–central city	1.5 (0.9–2.4)	0.5 (0.2–1.4)	4.0 (1.7–9.4)	1.0 (0.5–1.9)	0.4 (0.2–0.9)†	1.9 (0.7–5.6)
Small MSA–suburb	1.4 (0.8–2.4)	0.5 (0.2–1.4)	3.2 (1.4–7.4)	1.1 (0.6–2.0)	0.5 (0.2–1.1)	1.6 (0.6–4.4)
Adjacent area	1.2 (0.8–1.9)	0.6 (0.2–1.6)	3.6 (1.5–8.6)	1.1 (0.5–1.7)	0.5 (0.2–1.1)	2.0 (0.8–5.2)
Rural area‡	1.0	1.0	1.0	1.0	1.0	1.0
P value	0.35	0.23	0.06	0.36	0.10	0.006

* Odds ratios have been adjusted for the severity of the disorder and for the time period. Any denotes any sector of mental health services, PSY psychiatry services, OMH other mental health services, GM general medical services, HS human services, and CAM complementary–alternative medical services.
† P values of less than 0.05 (in a two-sided test) indicate statistical significance.
‡ Respondents in this category served as the reference group.
§ Race was self-reported.
¶ Income was defined as a multiple of the federal poverty line (for 1990 in the NCS and for 2001 in the NCS-R) for a family with the same composition as that of the respondent: low denotes a ratio of income to poverty (I:P) of less than 1.5:1, low-average an I:P between 1.5:1 and <3:1, high-average an I:P between 3:1 and <6:1, and high an I:P of ≥6:1.
‖ Urban vs. rural area was coded according to the definitions of the U.S. Census Bureau for 1990 (NCS) and 2000 (NCS-R) to distinguish between large metropolitan statistical areas (MSAs) (at least 2 million residents) and smaller MSAs (<2 million) and between central cities and the suburbs of such cities.

a significant increase over time in the prevalence of such disorders.

Second, a substantial increase in the rate of treatment occurred between 1990 to 1992 and 2001 to 2003 in the proportion of the population treated for emotional disorders, even though the majority of those with such disorders still received no treatment. The increased rate of treatment may have been due to aggressive, direct-to-consumer marketing of new psychotropic medications[19]; the development of new community programs to promote the awareness of mental disorders and provide screening and help in seeking care[20]; the expansion of primary care, managed care, and behavioral "carve-out" programs of mental health services[21]; and new legislation and policies to promote access to these services.[22] Presumably, increased access played an independent role in the increase in the proportion of the population treated for emotional disorders.[23] Insurance coverage expanded throughout the decade, whereas cost sharing by consumers declined.

Third, the increase in the rate of treatment varied among the sectors of mental health services, leading to a shift in the type of treatment, most notably an increase of more than 150 percent in the rate of treatment in the sector of general medical services. Despite the hope that mental disorders might be treated more efficiently owing to this shift, the data show that many patients receiving treatment in this sector of services did not complete the clinical assessment or receive treatment or the appropriate ongoing monitoring in accordance with accepted standards of care.[18] In addition, a high proportion of patients continued to receive treatment provided in the sectors of human services and complementary–alternative medical services for which rigorous evidence of effectiveness is lacking.

Fourth, the increase in the rate of treatment was

unrelated to sociodemographic variables. As a result, the increase did not reduce the sociodemographic differences shown in the baseline NCS.[24] Indeed, in absolute terms, these inequalities increased. For example, in both the NCS and the NCS-R, among non-Hispanic blacks and whites, blacks were only 50 percent as likely to receive psychiatric treatment as whites when both received a diagnosis of a disorder of the same severity, but the fact that the rate of psychiatric treatment increased by more than 100 percent suggests that this difference resulted in an absolute gap in the receipt of treatment between non-Hispanic blacks and whites that increased by more than 100 percent.

Fifth, although a small positive association was found in both surveys between the severity of the disorder and the receipt of treatment, severity did not interact with time in predicting receipt of treatment. Thus, the proportional increase in the rate of treatment was essentially the same for all levels of severity. The positive association between severity and treatment has been interpreted as evidence of rationality in the distribution of treatment resources.[24] However, the fact that in roughly half the respondents who received treatment, the mental disorder did not meet the criteria of the DSM for any disorder assessed in the NCS and NCS-R has led to controversy with regard to the relationship between severity and the need for treatment.[25,26] Some commentators have argued that treatment resources should be focused on serious disorders.[27] Others have argued that the treatment of mild disorders[28] and subthreshold syndromes[29] might be cost-effective and might prevent the onset of serious disorders in the future. No comparative data on cost-effectiveness are available to use in considering these contending views.

Two limitations of the study need to be noted. First, severity was assessed indirectly between 1990 and 1992 with the use of imputation, and second, the adequacy of treatment was not assessed. Both the strong relationship of imputed values to direct measures of severity in the NCS-R and the use of the multiple-imputation method to adjust for the increase in error variance when testing for significance tend to minimize concern with regard to the first limitation. The second limitation is of more concern, because research has shown that many patients with a mental disorder receive inadequate treatment.[18] We were unable to study the adequacy of treatment, however, because the information on processes of care in the NCS was insufficient for such an analysis.

Our data suggest two directions for future research and policy analysis. First, because most people with a mental disorder do not receive treatment, efforts are needed to increase access to and demand for treatment. The persistence of low rates of treatment among traditionally underserved groups calls for special initiatives.[30] The Surgeon General's report on undertreatment among racial and ethnic groups[1] and the National Institute of Mental Health initiative with regard to undertreatment among men[31] may provide useful models that should be evaluated. Programs to expand resources for treatment in targeted locations might also be of value,[32] as might initiatives such as legislation to encourage the use of mental health services by vulnerable elderly patients.[22] Efforts are also needed to evaluate widely used treatments for which there are as yet no data on effectiveness and to increase the use of evidence-based treatments. The expansion of disease-management programs, quality-assurance programs for treatment, and the use of "report cards" are important steps in this direction. Substantial barriers continue to exist, however, including competing clinical demands and distorted treatment incentives.[33,34] Initiatives aimed at overcoming these barriers are under way.[35,36] Future surveys of trends in the prevalence and treatment of mental disorders need to include data on treatment processes, such as those in the NCS-R, to permit changes in the quality of treatment to be tracked.

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APPENDIX

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CLINICAL PRACTICE

Chronic Stable Angina

Jonathan Abrams, M.D.

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

A 47-year-old man reports a six-month history of intermittent chest discomfort while playing squash. He describes lower substernal tightness with numbness of the left upper arm only during exertion. He does not smoke. His father died suddenly at the age of 49 years. His blood pressure is 138/84 mm Hg. The level of total cholesterol is 261 mg per deciliter (6.7 mmol per liter), of low-density lipoprotein cholesterol 172 mg per deciliter (4.4 mmol per liter), and of high-density lipoprotein cholesterol 50 mg per deciliter (1.3 mmol per liter), and the triglyceride level is 113 mg per deciliter (2.9 mmol per liter). The result of an exercise test is positive, with pain and 1.5 mm of horizontal ST-segment depression at stage 4 of the Bruce protocol. How should the patient's case be managed?

THE CLINICAL PROBLEM

The diagnosis of chronic stable angina pectoris includes predictable and reproducible left anterior chest discomfort after physical activity, emotional stress, or both; symptoms are typically worse in cold weather or after meals and are relieved by rest or sublingual nitroglycerin. The presence of one or more obstructions in major coronary arteries is likely; the severity of stenosis is usually greater than 70 percent.

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PATHOPHYSIOLOGY

Angina occurs when there is regional myocardial ischemia caused by inadequate coronary perfusion and is usually but not always induced by increases in myocardial oxygen requirements. Cardinal features of chronic stable angina include complete reversibility of the symptoms and repetitiveness of the anginal attacks over time, typically months to years. New, prolonged, or recent-onset symptoms are characteristic of unstable angina. Coexisting conditions, such as poorly controlled hypertension, anemia, or thyrotoxicosis, can precipitate or accentuate angina.

As coronary atherosclerosis progresses, there is deposition of plaque external to the lumen of the artery; the plaque may extend eccentrically and outward without compromising the lumen (Fig. 1). Thus, stress testing or angiography may not suggest coronary disease, even in the presence of significant atherosclerosis. As atherosclerosis worsens, encroachment of the plaque mass into the lumen can result in hemodynamic obstruction and angina[1] (Fig. 1). Disordered endothelial vasomotor function of the coronary arteries is common in patients with angina and results in diminished vasodilatation or even vasoconstriction in response to various stimuli, including exercise.[5,6] Occasionally, patients with severe aortic-valve disease or hypertrophic cardiomyopathy have angina-like chest pain in the absence of overt coronary disease.

CLASSIFICATION OF ANGINA PECTORIS

Chest pain is characterized as classic, or typical, angina; as atypical angina, which includes symptoms that have some but not all the features of angina; and as nonanginal

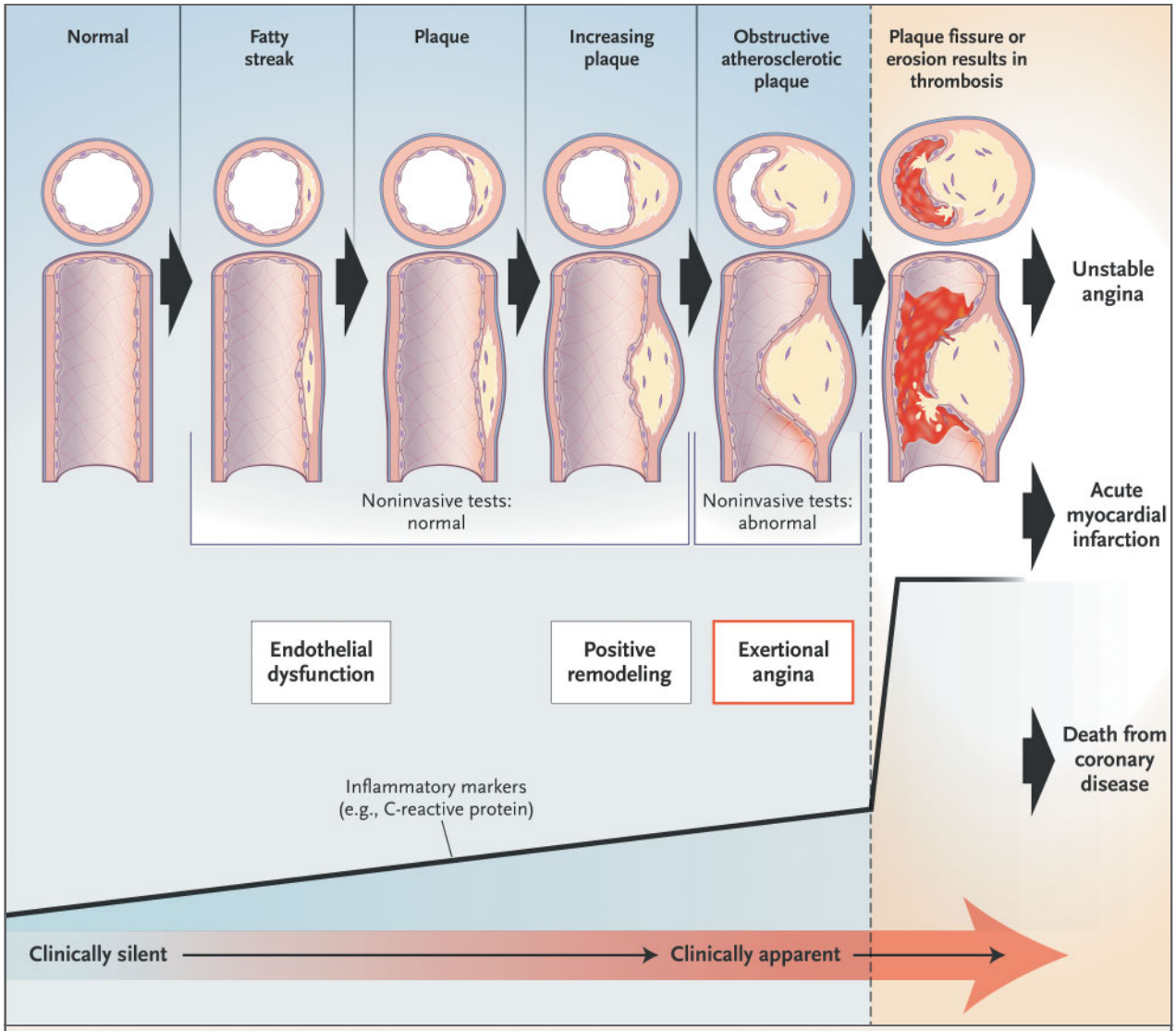

Figure 1. Typical Progression of Coronary Atherosclerosis.

As the plaque burden increases, the atherosclerotic mass tends to stay external to the lumen, which allows the diameter of the lumen to be maintained; this is known as the Glagov effect, or positive remodeling.[1] As plaque encroaches into the lumen, the coronary artery diameter decreases. Myocardial ischemia results from a discordant ratio of coronary blood supply to myocardial oxygen consumption. Luminal narrowing of more than 65 to 75 percent may result in transient ischemia and angina. In acute coronary syndromes, vulnerable plaque is a more important factor than is the degree of stenosis; acute coronary events result from ulceration or erosion of the fibrous cap, with subsequent intraluminal thrombosis.[2,3] Vulnerable plaque within the vessel wall may not be obstructive and thus may remain clinically silent until it causes rupture and associated consequences. (The figure has been modified from Greenland et al.,[4] with permission.)

chest pain, which has none of the features of angina (Table 1).[7] Chest pain that occurs during rest or at night[8] is well described in persons with chronic stable angina, particularly women.[9-11]

Atypical presentations of angina are more common in women than in men. Women with ischemia are more likely than men to report variable pain thresholds, inframammary pain, palpitations, or sharp, stabbing pain.[12,13] Overall, chest pain in women is quite common and usually is not due to coronary artery disease.[9,10,13] Data from the Women's Ischemia Syndrome Evaluation initiative of the National Heart, Lung, and Blood Institute indicate that many women with anginal symptoms have in-

Table 1. Symptoms of Angina.*

Classic (Typical)	Atypical, Noncardiac
Sensations in chest of squeezing, heaviness, pressure, weight, vise-like aching, burning, tightness	Pain that is pleuritic, sharp, pricking, knife-like, pulsating, lancinating, choking
Radiation to shoulder, neck, jaw, inner arm, epigastrium (can occur without chest component); band-like discomfort	Involves chest wall; is positional, tender to palpation; can be inframammary; radiation patterns highly variable
Relatively predictable	Random onset
Lasts 3–15 min	Lasts seconds, minutes, hours, or all day
Abates when stressor is gone or nitroglycerin is taken	Variable response to nitroglycerin

* Data are from Sangareddi et al.[7]

ducible ischemia and a reduced coronary flow reserve yet no significant obstruction on coronary angiography.[9,10,13] Atypical presentations of angina are also more frequent in older patients (who often have exertional dyspnea, weakness, or sweating) than in younger patients and in patients with diabetes (who often have atypical or even silent ischemic episodes) than in those without diabetes; a high level of suspicion for coronary disease is needed in these groups. The severity of angina should be assessed to aid in management decisions (Table 2). However, there is no direct correlation between the class of angina and the severity of coronary artery disease as determined on angiography.[7]

STRATEGIES AND EVIDENCE

DIAGNOSTIC STRATEGIES

Stress Testing

Various diagnostic tests are available for the evaluation of suspected coronary disease.[14] Previous Clinical Practice articles in the *Journal* have focused on noninvasive testing for coronary artery disease.[15,16] Table 3 summarizes common stress-testing methods. Adults with typical or atypical features of chest pain, especially those with major risk factors for coronary artery disease, should undergo stress testing. False positive and false negative exercise tests occur in up to 20 to 30 percent of persons (more commonly in women); coronary angiography is often necessary to resolve equivocal test results. Noninvasive testing may provide useful additional prognostic information, such as total exercise time, the inducibility of left ventricular dysfunction, blood-pressure and heart-rate responses, and, most important, the degree of myocardial ischemia.[14-16] In general, poor aerobic performance and disordered heart-rate or blood-pressure responses increase the likelihood of subsequent clinical events.

Coronary Angiography

Coronary angiography remains the diagnostic gold standard for obstructive coronary artery disease, but it may miss extraluminal plaque related to coronary remodeling[1] (Fig. 1). Indications for angiography include poorly controlled symptoms; abnormal results on stress testing, particularly with a substantial burden of ischemia (e.g., 1 mm or more of ST-segment depression); ischemia at a low workload (below 5 to 6 metabolic equivalents); large, inducible single or multiple wall-motion abnormalities; and substantial nuclear-perfusion defects. Atypical chest pain or inconclusive or discordant test results occasionally warrant the use of angiography. Intermediate-grade coronary obstructions (e.g., 50 to 70 percent stenosis) may require additional evaluation, such as assessment of coronary flow reserve. Suspected vasospastic or microvascular angina requires additional specialized testing.

Cardiac Biomarkers

Elevated levels of high-sensitivity C-reactive protein[17] and other markers, including brain natriuretic peptide,[18] have prognostic value with respect to cardiovascular events in patients with stable angina or asymptomatic coronary artery disease. However, the clinical utility of such testing remains uncertain.

THERAPY

It is useful to classify therapeutic drugs into two categories: antianginal (anti-ischemic) agents and vasculoprotective agents. Although medications for angina are widely used (Table 4), therapy to slow the progression of coronary artery disease, to induce the

stabilization of plaque, or to do both is a newer concept (Table 5),[19-21] and these forms of treatment are underprescribed.

Antianginal Agents

All antianginal drugs — nitrates, beta-adrenergic blockers, and calcium-channel blockers — have been shown to prolong the duration of exercise before the onset of angina and ST-segment depression as well as to decrease the frequency of angina.[22-24] Treadmill performance typically increases by 30 to 60 seconds with antianginal drugs as compared with performance with placebo. However, none of these agents have been shown to prevent myocardial infarction or death from coronary disease in patients being treated specifically for chronic stable angina.

Head-to-head comparative trials have not demonstrated that any single class of drugs has greater antianginal efficacy than the others.[22-24] Thus, it is reasonable to begin therapy with agents from any of the three groups.

Beta-blockers work primarily by decreasing myocardial oxygen consumption through reductions in heart rate, blood pressure, and myocardial contractility. Although beta-blockers have not been shown to reduce the rate of coronary events or mortality specifically in patients with chronic stable angina, they are identified as class I drugs (i.e., there is evidence or general agreement that they are useful and effective), according to the 2002 American College of Cardiology–American Heart Association guidelines for the management of stable angina.[24] This classification is based on older trials showing that these agents prolong survival after myocardial infarction and on recent data showing that they have a similar benefit after primary angioplasty for acute non–ST-elevation myocardial infarction.[25] There have been no large trials assessing the effects of beta-blockers on survival or on rates of coronary events in patients with chronic stable angina. The side effects associated with beta-blockers (Table 4) are often overemphasized; these drugs can be used effectively in many patients with chronic obstructive pulmonary disease or peripheral vascular disease.[26]

Calcium antagonists dilate coronary and systemic arteries, increase coronary blood flow, and decrease myocardial oxygen consumption. Although the safety of long-acting calcium-channel blockers has been questioned, data from ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[27] and the results of a recent meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration[28] indicate that the use of these drugs for hypertension does not increase morbidity or mortality.

Table 2. Classification and Severity of Angina.*

Class I
No angina with ordinary physical activity (e.g., walking, climbing stairs)
Angina with strenuous or prolonged exertion

Class II
Early-onset limitation of ordinary activity (e.g., walking rapidly or walking >2 blocks; climbing stairs rapidly or climbing >1 flight); angina may be worse after meals, in cold temperatures, or with emotional stress

Class III
Marked limitation of ordinary activity

Class IV
Inability to carry out any physical activity without chest discomfort
Angina occurs during rest

* The classification is from Sangareddi et al.[7]

Nitrates dilate systemic and coronary arteries, including some coronary stenoses, and particularly the systemic veins; venous pooling of blood decreases cardiac work and chamber size. Sublingual or oral spray nitroglycerin relieves acute episodes of angina within 5 to 10 minutes; prophylactic use before activity can be helpful in persons with frequent angina. Whereas long-acting nitrates decrease angina and prolong exercise performance, experimental data and data from catheterization laboratories suggest that nitrates increase vascular oxidative stress and may induce paradoxical coronary arterial vasoconstriction.[29] Both appear to contribute to the development of nitrate tolerance.[30,31] Prevention of tolerance requires an intermittent dosing strategy, with a nitrate-free interval of 12 to 14 hours (Table 4). Phosphodiesterase type 5 inhibitors (e.g., sildenafil, vardenafil, and tadalafil) and nitrates should not be used within 24 hours of one another because of the potential for serious hypotension.

Combination Therapy

Underdosing with antianginal agents is common. Even when the dosage is appropriate, physicians should anticipate the need for treatment with two or three agents in many patients.[22,24] Certain drug combinations are recommended, and others should be avoided because of potential hypotension or bradycardia (Table 4). Data from randomized clin-

Table 3. Common Stress-Testing Procedures for the Evaluation of Chest Pain.*

Test	Protocol	Positive Result	Comments	Estimated Sensitivity (%)	Estimated Specificity (%)
Standard treadmill or bicycle exercise	Patient able to perform adequate amount of physical activity Baseline ECG is normal or near normal (e.g., minimal ST-segment depression) Should not be used if patient has left-bundle-branch block or electronic pacemaker	New horizontal or downsloping ST-segment depression ≥1 mm or ≥2 mm in presence of baseline repolarization abnormality	Blood-pressure response, exercise duration, ventricular arrhythmias, Duke treadmill score, and heart rate recovery should also be assessed Functional capacity and Duke treadmill score have significant prognostic value	65–70	70–75
Exercise stress echocardiography	Patient able to perform physical activity Two-dimensional echocardiogram immediately after exercise	One or more new segmental wall-motion abnormalities (hypokinesis, akinesis, or dyskinesis), left ventricular dilation, or both	Useful for abnormal baseline ECG (should not be used if patient has left-bundle-branch block or electronic pacemaker) Technically high-quality echocardiogram is essential	80–85	80–85
Dobutamine stress echocardiography	For patients unable to exercise adequately with or without abnormal ECG Incremental dobutamine infusion	Inducible segmental left ventricular wall-motion abnormalities, worsening of existing wall-motion abnormalities, or left ventricular dilation	Technically high-quality echocardiogram is essential	80–85	85–90
Exercise myocardial perfusion SPECT, with quantitative analysis	For patients able to perform physical activity Should be used when results of baseline ECG preclude assessment of ischemia (e.g., nonspecific ST-T changes) Can be used in patients with left-bundle-branch block or electronic pacemaker	Inducible single or multiple perfusion abnormalities; left ventricular dilation	Also can provide information on left ventricular function and wall motion	85–90	85–90
Pharmacologic myocardial perfusion SPECT, with quantitative analysis	For patients unable to exercise adequately Intravenous adenosine or dipyridamole Can be used in patients with left-bundle-branch block or electronically paced rhythm	Provides information similar to that provided by exercise SPECT		80–90	80–90
Electron-beam computed tomography	Calcium score closely correlates with extent of coronary atherosclerosis	If score is >100, consider follow-up stress test	Cannot predict coronary obstructions or detect vulnerable plaque or degree of stenosis Poor specificity	—	—

* Estimates of sensitivity and specificity are derived from multiple databases and from the chronic stable angina guidelines of the American College of Cardiology and the American Heart Association.[26] The sensitivity, specificity, and predictive accuracy of all noninvasive stress-testing methods are influenced by age, sex, degree of coronary atherosclerosis, and, most important, the likelihood of coronary artery disease in the patient being tested. ECG denotes electrocardiogram, and SPECT single-photon-emission computed tomography.

ical trials support the efficacy of combined therapy with two drugs but provide less support for the use of three agents together.

Vasculoprotective Therapy

There is considerable evidence that lifestyle changes and pharmacologic therapy may reduce the progression of atherosclerosis, stabilize plaque, or both in chronic stable angina.[19,21,24,32] Aggressive interventions are warranted to control all cardiovascular risk factors, including diabetes and hypertension (a target blood pressure of ≤130/80 mm Hg is appropriate for both conditions) in persons with coronary artery disease.

Table 4. Recommended Antianginal Drugs.*

Drug Class and Drug	Dosage Range	Adverse Effects	Cautions
Nitrates†		Headache, dizziness, nausea, palpitations Tolerance is a major limiting factor	Contraindicated with medications for erectile dysfunction
Isosorbide dinitrate, short-acting formulations	20–60 mg twice daily		
Isosorbide dinitrate, sustained-release formulations	60–120 mg once daily		
Isosorbide mononitrate, short-acting formulations	20 mg twice daily, 7 hr apart		
Isosorbide mononitrate, sustained-release formulations	60–120 mg once daily		
Nitroglycerin, patch	0.4–0.6 mg, taken for no more than 12–14 hr		
Beta-adrenergic blockers		Fatigue, shortness of breath, wheezing, weakness, dizziness	Should be used with caution in patients with chronic obstructive pulmonary disease, diabetes, depression, severe peripheral vascular disease, coronary vasospasm, sinus or atrioventricular nodal dysfunction, or erectile dysfunction
Propranolol, long-acting formulations	80–240 mg once daily		
Metoprolol, short-acting formulations	50–150 mg twice daily		
Metoprolol, sustained-release formulations	100–300 mg once daily		
Atenolol	25–100 mg once daily		
Calcium-channel blockers		Headache, dizziness, edema Constipation (with verapamil)	Verapamil and diltiazem should be used with caution in patients with low ejection fraction (<30%) or with sinus or atrioventricular nodal dysfunction
Nifedipine, sustained-release formulations	30–90 mg once daily		
Amlodipine	2.5–10 mg once daily		
Verapamil, short-acting formulations	40–120 mg 2–3 times daily		
Verapamil, sustained-release formulations	180–240 mg once or twice daily		
Diltiazem, sustained-release formulations	120–480 mg once daily		

* Recommended combination therapies include a nitrate with a beta-blocker and a dihydropyridine calcium-channel blocker with a beta-blocker. The combination of a dihydropyridine calcium-channel blocker with a nitrate or the combination of a rate-slowing calcium-channel blocker with a beta-blocker is not recommended.
† A nitrate-free interval of 12 to 14 hours daily is necessary.

Lifestyle Changes

Regular exercise reduces the frequency of anginal symptoms, increases functional capacity, and improves endothelial function.[24,33] Patients with chronic stable angina who are receiving medical therapy should exercise regularly, beginning at low levels for 20 to 30 minutes and increasing as symptoms allow. A recent randomized trial that compared the effects of daily exercise with those of angioplasty and stenting among patients with chronic stable angina and single-vessel coronary artery disease demonstrated better outcomes (in terms of major adverse events and improved exercise capacity) at one year in the exercise group than in the revascularization group.[34]

Although dietary modification has not been studied specifically in patients with chronic stable angina, in a trial involving patients with a history of myocardial infarction who had been randomly assigned to follow either a Mediterranean diet or a prudent Western diet, the rate of cardiovascular events was 47 percent lower in the Mediterranean-diet group than in the Western-diet group, and this difference persisted for four years.[35] Trials involving multifactorial risk modification, including exercise, a low-fat diet, and smoking cessation, have demonstrated improvements in the progression of angina and coronary disease.[36]

Vigorous efforts at smoking cessation and weight control are mandatory in patients with chronic stable angina. For patients with diabetes, a multifactorial approach that includes lifestyle changes and medications for glycemic control and coronary risk factors substantially reduces the risk of cardiovascular events.[37]

Pharmacologic Therapy

The use of aspirin at a dose of 81 to 150 mg per day reduces cardiovascular morbidity and mortality by 20 to 25 percent among patients with coronary artery disease. The results of several large, randomized trials indicate that the use of statins reduces the rate of coronary events and mortality in patients with established coronary artery disease and hyperlipidemia by 25 to 35 percent. Furthermore, a 25 to 30 percent reduction in revascularization rates in the large statin trials suggests a decrease in angina during the trials.[38] A recent trial involving patients

Table 5. The Vasculoprotective Regimen for Stable Angina.*

Agent	Indications	Comment
Aspirin	All patients, except those with aspirin allergy or resistance	Dosage, 81–150 mg daily or 325 mg every other day
Statin	All patients, to achieve target LDL cholesterol level ≤100 mg/dl; goal of 70 mg/dl in very high-risk patients (those with diabetes, multivessel disease, or multiple risk factors for coronary artery disease)	May use C-reactive protein level to guide dosage, with target <2 mg/liter, although this strategy has not been prospectively tested
Beta-blocker	All patients with exertion-related or emotion-related chest pain, previous MI, hypertension, depressed left ventricular function (in absence of contraindication)	
Clopidogrel	All patients after PCI or those with aspirin intolerance or resistance	Duration of therapy, 1 year after PCI, indefinitely if aspirin cannot be used
ACE inhibitor	High-risk patients: those with diabetes, chronic kidney disease, hypertension, previous MI, left ventricular systolic dysfunction, or age ≥55 yr	Uncertain utility in low-risk patients

* LDL denotes low-density lipoprotein, MI myocardial infarction, PCI percutaneous coronary intervention, and ACE angiotensin-converting enzyme. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

with stable coronary artery disease demonstrated that treatment with 80 mg of atorvastatin daily slowed the progression of coronary atherosclerosis, as measured by intravascular ultrasound, over a period of 18 months, as compared with treatment with 40 mg of pravastatin daily.[19] In another trial (the PROVE-IT–TIMI 22 [Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 study), the reduction of low-density lipoprotein (LDL) cholesterol levels to a mean of 62 mg per deciliter (1.6 mmol per liter) decreased the number of clinical events further than did a lesser reduction (to 95 mg per deciliter [2.5 mmol per liter]) in subjects with acute coronary ischemia.[20] A recent trial likewise showed a significantly lower rate of cardiovascular events among patients with stable coronary disease who were treated with 80 mg of atorvastatin daily (achieved mean LDL cholesterol, 77 mg per deciliter [2.0 mmol per liter]) than among those treated with 10 mg daily; persistent elevations in aminotransferase levels complicated therapy in 1.2 percent of patients in the high-dose group, as compared with 0.2 percent of those in the low-dose group.[39] The Adult Treatment Panel III of the National Cholesterol Education Program recently recommended target LDL cholesterol levels of 60 to 70 mg per deciliter (1.6 to 1.8 mmol per liter) in high-risk patients with coronary artery disease.[40]

Statins reduce the levels of C-reactive protein, and two recent studies suggest that lowering these levels is as important as decreasing LDL cholesterol levels for the optimal reduction of coronary events.[41,42] Angiotensin-converting–enzyme (ACE) inhibitors have been reported to reduce morbidity and mortality among patients with coronary disease,[21,43] although the recent PEACE Trial (Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial) did not confirm these findings,[44] possibly owing to the relatively low risk among patients in this trial as compared with those in the HOPE trial (Heart Outcomes Prevention Evaluation study) and the EUROPA study (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease).[21,43] ACE inhibitors should be prescribed for patients with chronic stable angina who have a history of myocardial infarction, hypertension, left ventricular systolic dysfunction, or diabetes, as well as for patients with impaired renal function who do not have a contraindication to the use of these agents.

REVASCULARIZATION

Revascularization includes either percutaneous coronary intervention (i.e., balloon angioplasty and stenting) or coronary-artery bypass surgery. More than 1 million percutaneous coronary interventions were performed in the United States in 2003, far surpassing the number of surgical revascularizations. More than 80 percent of percutaneous interventions in the United States in 2004 were performed with the use of drug-eluting stents coated with sirolimus or paclitaxel.

Revascularization (performed by any technique) has not been shown to decrease the risk of myocardial infarction or death from coronary artery disease in patients with chronic stable angina and preserved left ventricular function. However, revascularization should be considered for persons with lifestyle-limiting angina who have a good medical regimen or for those with high-risk factors, such as symptomatic multivessel disease, proximal left anterior descending or left main artery disease, left ventricular systolic dysfunction, diabetes, a large ischemic bur-

den on nuclear or echocardiographic stress testing, early onset of ischemia on stress testing, or ST-segment depression of 2 mm or more.[24,45] Although coronary-artery bypass surgery achieves more complete and durable control of angina than percutaneous coronary intervention (with the use of noncoated stents), subsequent rates of myocardial infarction and death are similar over a five-year period with the two strategies.[46-48] Trials in which the use of noncoated stents were compared with balloon angioplasty have not shown significant differences in the rate of major adverse events, including acute myocardial infarction and death.[49] The long-term effect of drug-eluting stents on outcomes in chronic stable angina is still under evaluation; current data indicate that there have been significant reductions in the rate of restenosis at 6 to 12 months with coated stents, as compared with noncoated stents, resulting in substantial decreases in recurrent angina and the need for revascularization of target lesions. It is not clear how the long-term outcomes compare with those of coronary-artery bypass grafting.[50] Decisions regarding strategies for revascularization should take into account patients' preferences and local experience.[24,45,46,48]

CARDIOPROTECTIVE THERAPY VERSUS PERCUTANEOUS INTERVENTION

Marked regional variability in the use of revascularization procedures suggests excessive use in some geographic areas. Several trials have indicated that treatment with a combination of vasculoprotective agents, along with lifestyle changes — with the option to proceed to percutaneous revascularization if symptoms worsen — results in rates of myocardial infarction and death that are not significantly different from those associated with revascularization in patients with class I or II stable angina whose disease involves one or two vessels.[51-53]

AREAS OF UNCERTAINTY

Some patients who are not candidates for coronary revascularization continue to have severe or limiting angina; almost all have multivessel coronary artery disease and have previously undergone revascularization and have target vessels that are not suitable for the procedure (because they are distal, diffuse, or of small caliber). The optimal approach to management of these cases remains uncertain. One option is the use of enhanced external counterpulsation; results of a sham-controlled, randomized trial, as well as observational data, suggest that this form of therapy decreases the severity and frequency of angina,[24] although objective reductions in ischemia have been variable.[54,55] Another approach is transmyocardial laser revascularization, in which multiple laser channels are made directly into the myocardium.[24,56,57] Both procedures are approved by the Food and Drug Administration (FDA), although the mechanisms by which they relieve angina remain uncertain. The role of promising new agents, including trimetazidine[58] and ranolazine,[59] that alter myocardial metabolism is currently unclear with regard to the treatment of angina; neither drug has received FDA approval.

GUIDELINES

The 1999 guidelines on stable angina, revised in 2002, of the American College of Cardiology, the American Heart Association, and the American College of Physicians,[24,60] represent the most comprehensive available treatise on chronic stable angina. The American College of Cardiology–American Heart Association guidelines on coronary-artery bypass grafting, updated in 2004, are also useful.[45] Recent National Cholesterol Education Program–Adult Treatment Panel III guidelines support aggressive lipid lowering in patients with chronic stable angina.[40] All recommendations in this review are consistent with those guidelines.

SUMMARY AND CONCLUSIONS

The diagnosis of chronic stable angina is made on the basis of anginal symptoms, a noninvasive stress test that is positive for myocardial ischemia, and documentation of coronary atherosclerosis on angiography. Antianginal drugs should be prescribed in effective doses, usually beginning with a beta-blocker; aspirin is mandatory. Management should routinely include lifestyle modifications, including smoking cessation, weight control, and regular exercise, and aggressive control of other cardiovascular risk factors. Drugs to slow the progression of atherosclerosis, including statins and, in many cases, ACE inhibitors, are also indicated. The target LDL cholesterol level in persons with chronic stable angina is below 100 mg per deciliter (2.6 mmol per liter); in high-risk patients, the level is 60 to 70 mg per deciliter. Angiography is generally indi-

cated if symptoms continue despite treatment with antianginal medications or if high-risk features appear on stress testing. I would recommend this, along with the other interventions described above, in a case such as that described in the vignette. Revascularization should be considered for persons with class II and III symptoms, a high risk as determined by diagnostic tests, or angina that the patient finds unacceptable despite medical management.

Dr. Abrams reports having received consulting honoraria from Pfizer and CV Therapeutics and lecture fees from Pfizer and Merck.

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CORRECTION

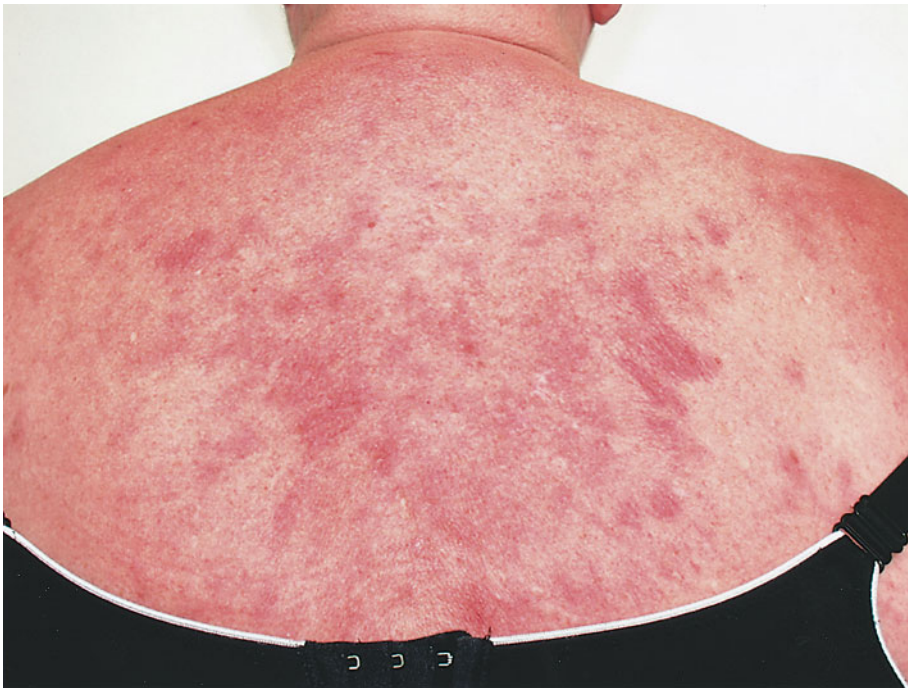
Chronic Stable Angina

Chronic Stable Angina . On page 2527, in the left-hand column, lines 15 through 17 of the third full paragraph should have read ``. . . they have a similar benefit after primary angioplasty for acute ST-elevation myocardial infarction,'' rather than ``for acute non–ST-elevation myocardial infarction,'' as printed.

N Engl J Med 2005;353:2728

IMAGES IN CLINICAL MEDICINE

Bortezomib-Induced Skin Lesions



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A 62-year-old woman had progression of multiple myeloma despite many therapies, including an autologous hematopoietic stem-cell transplantation. Infusions of bortezomib (1.3 mg per square meter of body-surface area) were administered as an intravenous bolus twice weekly for 2 weeks, followed by a 10-day rest period. During the second treatment cycle, a purpuric rash, which was not associated with fever or itching, developed on the patient's trunk, back, hands, and face. A biopsy specimen of the skin lesion revealed a leukocytoclastic vasculitis. The patient was treated with 20 mg of prednisone, and the rash resolved. The rash recurred with subsequent cycles of bortezomib treatment. Bortezomib is a member of a new class of antineoplastic agents that inhibit the proteasome and is being studied as a form of therapy for a wide variety of cancers.

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 18-2005: A 45-Year-Old Woman with a Painful Mass in the Abdomen

Michael G. Muto, M.D., Mary Jane O'Neill, M.D., and Esther Oliva, M.D.

PRESENTATION OF CASE

A 45-year-old woman was admitted to this hospital with a painful abdominal mass.

She had first noticed a mass in her lower abdomen on the right side two and a half years earlier. There was intermittent severe pain at the site that occurred approximately once a month and lasted four to five days; it was worse during some months than others. She described the pain as feeling "like a hot brick." Five weeks before admission, she came to the surgical clinic of this hospital for further evaluation. A slightly tender mass, 4 cm in diameter, was palpated in the right lower abdomen. The remainder of the physical examination revealed no abnormalities.

An abdominal ultrasonographic study performed at this evaluation showed a highly vascular, mixed echoic mass, 3.5 cm by 3.5 cm by 1.0 cm, in the lower right anterior abdominal wall. Abdominal and pelvic computed tomographic (CT) scanning after the oral and intravenous administration of contrast material three weeks before admission confirmed the presence of an irregularly shaped, nonenhancing, heterogeneous lesion within the right lower anterior abdominal wall. The liver was fatty and also contained an enhancing lesion, 1.9 cm in diameter, in the lower right lobe, which showed early washout of contrast material. There were multiple, low-attenuation lesions in the liver that were thought to represent cysts. The other organs appeared to be normal. Magnetic resonance imaging (MRI) performed before and after the administration of gadolinium two weeks before admission to evaluate the liver lesion confirmed the presence of an early enhancing lesion, 1.7 cm by 1.8 cm, in the right lobe of the liver that had a minimally increased signal on a T_2-weighted sequence and was isointense on a T_1-weighted sequence. Multiple bright lesions on T_2-weighted images were present within the liver, and they were thought to be cysts. No lymphadenopathy was seen. MRI of the other abdominal organs showed no abnormalities.

Scoliosis had developed in this patient during her adolescence, and Harrington rods were placed when she was 15 years of age. At 30 years of age, she was treated for a grade 1 cerebellar pilocytic astrocytoma, with two resections and postoperative irradiation with a dose up to 55.8 Gy. As a result of the astrocytoma, she had double vision, which required special corrective lenses, and ataxia, for which she had learned to compensate after rehabilitation therapy. A fibroadenoma of the left breast was excised when she was 28 years of age, as was a fibroadenoma of the right breast when she was

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30 years of age. Three years before admission, bilateral intraductal papillomas of the breasts were excised, with the additional findings of focal atypical ductal hyperplasia and lobular neoplasia in situ. She had had two pregnancies, and both of her daughters were delivered by cesarean section. A hysterectomy because of uterine fibroids had been performed at another hospital three years before admission. At that time, pathological examination confirmed the presence of multiple leiomyomas, benign findings in the endometrium, and chronic cervicitis. The ovaries had not been removed.

She lived with her husband and daughters, who were all well. She did not smoke and drank three to four alcoholic drinks per month. Her only medication was a daily multivitamin.

On admission, the patient's vital signs were normal. The height was 167.5 cm and the weight 49.5 kg. The abdomen had a low, 6-cm scar and was soft, with no organomegaly. An irregular, indurated mass in the right lower quadrant, 4 cm in diameter, with no overlying skin retraction or pitting, was slightly tender to palpation. The remainder of the physical examination showed no abnormalities.

The results of routine laboratory tests performed on admission were within the normal ranges. An electrocardiogram showed a normal sinus rhythm and slight left atrial enlargement. A chest radiograph showed probable pulmonary emphysema with bullous changes in the upper lobes. No infiltrates, masses, effusions, or lymphadenopathy were seen. Harrington rods were noted in the thoracic spine.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Michael G. Muto: May we review the radiologic studies?

Dr. Mary Jane O'Neill: Sagittal and transverse views as visualized on the superficial ultrasonographic imaging of the anterior abdominal wall show that within the fibers of the rectus muscle there is a well-circumscribed, hypoechoic, solid-appearing mass lesion that is displacing the fibers of the right rectus muscle (Fig. 1A). The CT examination shows asymmetry of the rectus; there is a high-density, moderately lobulated mass within the substance of the right abdominal rectus muscle (Fig. 1B). On a CT scan obtained at the same session, there is a relatively ill defined enhancing mass near the surface of the right lobe of the liver (Fig. 1C). The ovaries appeared to be normal.

MRI was performed to evaluate the liver lesion. On the T_1-weighted images, the lesion is dark, without evidence of any hemorrhage. It is ill defined on T_2-weighted images, and it has prominent enhancement after gadolinium administration (Fig. 1D). It is unclear whether this lesion is intraparenchymal or on the surface of the liver, and there are no specific features on imaging of either a benign or a malignant lesion. In a patient of this age and sex, the features that are apparent on MRI would be consistent with focal nodular hyperplasia.

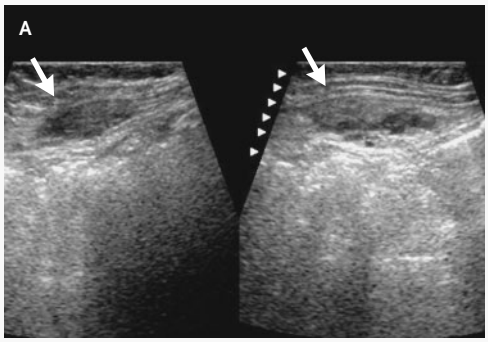
Dr. Muto: This multiparous woman with a history of two cesarean sections and a hysterectomy had a mass of the abdominal wall that had been present for more than two years and was intermittently painful. The radiographic studies showed that the mass was heterogeneous and located in the substance of the right rectus abdominis muscle, 2 cm above the Pfannenstiel incision and 3 cm to the right of midline. Radiographic imaging also showed two normal-appearing retained ovaries in the pelvis and no suggestion of ventral hernia or bowel obstruction. The solitary lesion noted in the liver could not be characterized as benign in appearance. All the other abdominal viscera appeared normal.

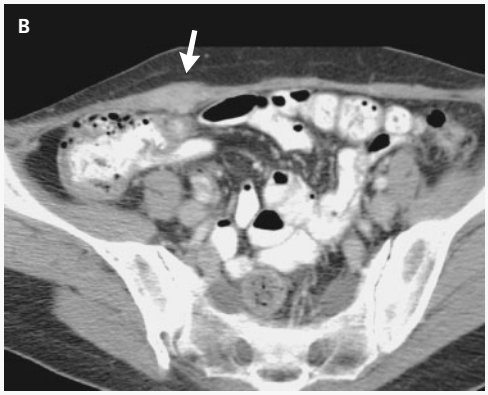
The differential diagnosis of a painful abdominal-wall mass is shown in Table 1.[1]

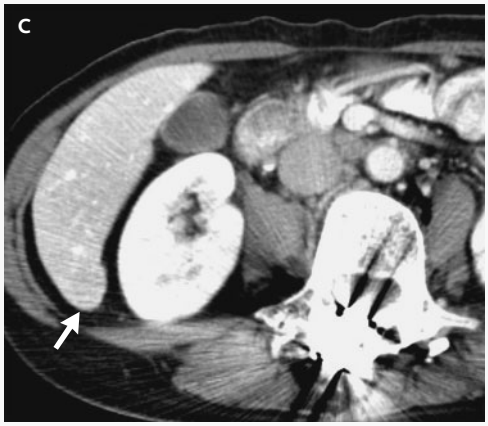
HERNIAS AND ABSCESSES

A wide variety of ventral hernias may occur as a painful abdominal-wall mass. The location of the mass makes an inguinal or femoral hernia improbable in this case. A spigelian hernia occurs at the posterior lateral abdominal-wall fascia through the linea semilunaris, and although it is rare, a mass can appear in this location, particularly if the hernia were to cause incarceration or strangulation. Finally, an incisional hernia must certainly be considered, especially if there have been multiple laparotomies performed through the same incision. In order to understand how an incisional hernia can occur in a region that is cephalad and lateral to the skin incision, it is necessary to review how this incision is performed.

In the Pfannenstiel incision, the skin and fascia are incised transversely. The fascia is then dissected from the underlying rectus abdominis muscles in a







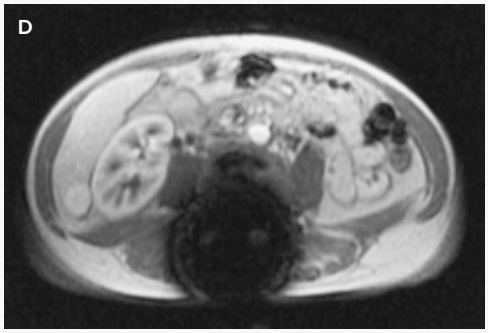


Figure 1. Imaging Studies of the Abdomen.

An ultrasonographic image of the lower right abdominal wall (Panel A) shows a solid, hypoechoic lesion (arrows) in the right rectus muscle. The small arrowheads indicate the placement of the focal zone of the ultrasonographic beam. A CT image (Panel B) through the lower abdomen, which was obtained after the administration of contrast material, reveals an enhancing, solid mass (arrow) in the right rectus muscle. The same study shows a lesion (arrow) near the surface of the right lobe of the liver (Panel C). A T_1-weighted axial MRI scan obtained after the administration of contrast material in the arterial phase shows a small arterially enhancing lesion (Panel D).

cephalad and caudad direction, which creates subfascial spaces above and below the skin incision (Fig. 2). This technique allows the rectus abdominis muscles to be separated along the midline. A vertical laparotomy is then performed. The Pfannenstiel incision is widely used in both obstetrics and gynecology, because it affords generous access to the pelvis and is stronger than a vertical incision and ensures excellent cosmetic results. One drawback to the incision is the creation of the subfascial spaces, which can increase the risk of infection or hematoma formation, as compared with a vertical midline incision. Also, although the subfascial space is readily created during a primary incision, when the incision is reopened, this subfascial space is often heavily scarred and difficult to recreate, resulting in trauma to both the underlying rectus muscle and the fascia. Such trauma may increase the risk of hematoma, infection, or fascial disruption. Therefore, although it is unusual for incisional hernias to develop through a Pfannenstiel incision, they may occur either beneath the skin incision or superolateral to it.

I do not know if any of this patient's three prior laparotomies were complicated by infection or hematoma formation; however, just having three procedures performed through the incision is risk enough for hernia formation to be a consideration. The cyclicity of her pain, the clinical presentation, and the imaging studies, however, are not consistent with this diagnosis.

A diverticular, appendiceal, or tubo-ovarian abscess can secondarily infect the rectus muscle and lead to the development of a chronic abdominal-wall

Table 1. Differential Diagnosis of a Painful Abdominal-Wall Mass.

Ventral hernia
Infection
Trauma
Benign neoplasm
Primary malignant neoplasm
Metastatic neoplasm
Endometriotic implants

abscess. There is no evidence, however, to support an infectious cause in this case. There is also no history of traumatic injury to the muscle, belly rupture, or prior instrumentation.

TUMORS

Any benign or malignant tumor of muscle, integument, nerve, or blood vessels can involve the rectus muscle and occur as a painful mass. Desmoid tumors are benign but locally destructive lesions. These tumors often occur in young women after a pregnancy, and they may grow slowly in the abdominal wall or surgical scar. There is evidence that suggests that these tumors are hormone-sensitive, including the predominance of the lesion in women of reproductive age and regression in menopausal women and among those who are receiving tamoxifen therapy. This tumor would not, however, be expected to present with cyclic pain, and it usually appears as a homogeneously solid mass on CT images, rather than a complex mass.[2]

ENDOMETRIOTIC IMPLANTS

Endometriosis is the ectopic growth of endometrial glands and stroma outside the endometrial cavity. It affects 3 to 10 percent of all women of reproductive age. About 4 of every 1000 women between 15 and 64 years of age are hospitalized with endometriosis each year.[3] The disease is a major cause of infertility and chronic pelvic pain.[4] The most common extrauterine sites involved include the ovary, fallopian tube, and adjacent pelvic tissues. Pelvic spread is thought to occur by retrograde menstruation by way of the fallopian tube, during which viable endometrial cells are implanted in dependent portions of the pelvis. Rarely, the disease occurs outside the pelvis in sites such as the lungs, resulting in cyclic hemoptysis, hemothorax, or pneumothorax, and within retroperitoneal lymph nodes and liver parenchyma. These findings suggest lymphatic or vascular dissemination. Finally, the occurrence of endometriosis in men taking estrogen therapy suggests yet a third pathogenetic mechanism: endometriosis arising as a result of coelomic metaplasia.

Endometriotic implants in scars resulting from episiotomy and cesarean section most often occur at the time of vaginal or cesarean delivery and are the result of direct implantation of viable endometrial cells into the subcutaneous or subfascial spaces that are exposed by the surgical incisions on the abdominal wall or perineal body. The classic manifestations of endometriosis in surgical scars are focal cyclic pain and a slow-growing mass.[5-8] The pain can often be timed to the menses in women who have not undergone oophorectomy. Progressive cycles of bleeding and local inflammatory response lead to the development of a complex vascular or fibrotic mass. The overall incidence of endometriomas occurring in cesarean-section scars has been estimated at 0.03 to 0.15 percent.[9]

Because of the clinical similarity between endometriosis in a surgical scar and an incisional hernia, general surgeons, rather than gynecologists, are often the first to evaluate patients with this disorder. Although the development of endometriosis by way of implanted cells is widely reported in the gynecologic literature, this entity is not well recognized among general surgeons. As a result, the diagnosis is often not considered. In particular, the telltale history of cyclic pain is either not elicited or, as in the case under discussion, not appreciated. As Nirula and Greaney report,[10] among 10 cases of incisional endometriosis in caesarean-section scars, in only 2 cases was the diagnosis suspected preoperatively, and these were diagnosed by a single surgeon who was aware of the disease from prior experience.

The most probable diagnosis in this case is endometriosis of the anterior abdominal wall. Although endometrial cells can implant within a ventral hernia sac, it seems far more likely that implantation occurred beneath the upper flap of the Pfannenstiel incision after the patient's primary or repeated cesarean section or during the hysterectomy.

THE HEPATIC LESION

There is a second finding that must be explained in this case — the suspicious hepatic lesion noted on CT scanning and subsequent MRI. This may be entirely unrelated to the patient's abdominal-wall mass; although it could not be characterized as be-

nign on the basis of radiologic criteria, its features were thought to be consistent with focal nodular hyperplasia. Malignant degeneration of endometriotic implants has been widely reported in the gynecology and gynecologic-oncology literature.[11,12] Clear-cell and endometrioid adenocarcinomas are by far the most common histologic types reported. Endometrioid and clear-cell carcinomas predominate in intraperitoneal and ovarian implants, whereas clear-cell cancers more frequently are associated with extraperitoneal implants.[13]

In conclusion, the most likely diagnosis for this 45-year-old woman's illness was an implant of endometriosis within her surgical scar. Given her ongoing symptoms, complete excision would be the most appropriate procedure for both diagnosis and therapy. If the mass contained evidence of an endometriosis-associated cancer, a liver metastasis should be suspected.

A Physician: Were all three radiologic studies necessary to make this diagnosis?

Dr. Muto: The ultrasonographic study was a reasonable choice for primary imaging of this ill-defined mass. Once a mass was clearly defined, abdominal and pelvic CT scanning was required to rule out an incarcerated hernia. When the CT scanning revealed the unexpected finding of a suspicious-appearing cystic liver lesion, her physicians were obliged to evaluate it further with an MRI scan.

A Physician: Is MRI useful for the diagnosis of endometriosis?

Dr. O'Neill: Pelvic endometriosis has characteristic increased signal intensity on T_1-weighted images; however, when the endometriosis is located within fascial or muscular tissues, it often does not produce the characteristic imaging findings. In this patient, CT scanning would have been the single best imaging test because it can localize the palpable abnormality and allow the clinician to better assess the remainder of the abdomen and pelvis for findings that would affect the differential diagnosis.

Dr. Nancy Lee Harris (Pathology): There was no evidence of endometriosis on the uterus that was removed at hysterectomy. Is the risk of endometriosis in a surgical incision independent of the presence of pelvic endometriosis?

Dr. Muto: Many reported cases had no evidence of pelvic endometriosis.

Dr. Harris: This patient was seen by a general surgeon, whose differential diagnosis included endometriosis in a scar, but the primary diagnosis was a desmoid tumor.

CLINICAL DIAGNOSIS

Desmoid tumor of the abdominal wall.

DR. MICHAEL G. MUTO'S DIAGNOSIS

Endometriosis of the abdominal wall.

PATHOLOGICAL DISCUSSION

Dr. Esther Oliva: A specimen of soft tissue measuring 9.0 cm by 6.0 cm by 1.2 cm was received in the pathology department. Sectioning revealed areas of

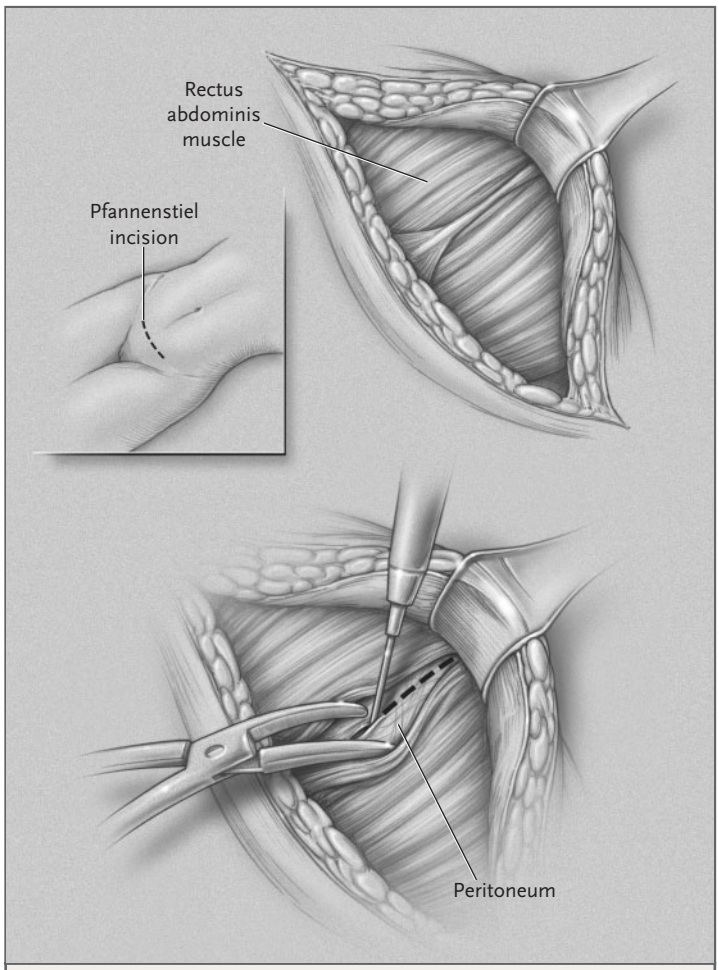


Figure 2. The Pfannenstiel Incision.

The incision begins with a transverse skin and fascial incision (inset). The fascia is dissected from the underlying rectus abdominis muscle in a cephalad and caudad direction, which creates subfascial spaces above and below the skin incision. The rectus abdominis muscles are separated along the midline, and a vertical laparotomy is then performed.

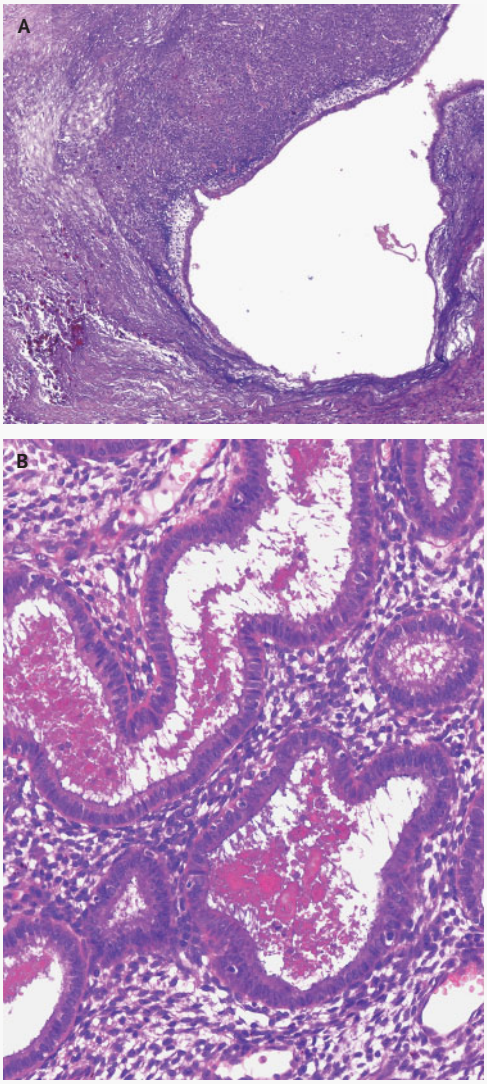


Figure 3. Histologic Sections of the Mass in the Abdominal Wall (Hematoxylin and Eosin).

An endometrial gland, cystically dilated (Panel A), is embedded in an edematous stroma, adjacent to areas of scarring and elastosis. A higher-power view (Panel B) shows endometrial glands lined by cells with tall cytoplasm and basally located nuclei, with no cytologic atypia.

hemorrhage and cyst formation. On microscopical examination, there was a biphasic growth of glands and stroma in a background of fibrous tissue. Some of the glands were cystically dilated (Fig. 3A). The glands were coiled with abundant luminal secretions and were lined by cuboidal and columnar cells with basally located nuclei (Fig. 3B). Cytologic atypia and mitotic activity were absent. The glands were surrounded by a cellular stroma that was composed of small cells with scant cytoplasm and oval-to-elongated nuclei, which were whorled around small blood vessels (Fig. 3B). Edema, focal elastosis, and areas of recent hemorrhage were evident (Fig. 3A).

Endometriosis is defined as the presence of endometrial-type glands and stroma outside the endometrium and myometrium. It most commonly involves the ovaries, the uterine ligaments, the rectovaginal septum, the cul-de-sac and peritoneum of the uterus, the fallopian tubes, the rectosigmoid, the ureter, and the bladder.[14] Endometriosis of the skin and soft tissues makes up 3.5 percent of the cases of extrapelvic endometriosis, and most cases occur in surgical scars.[15] Because endometriosis frequently occurs after gynecologic or obstetrical procedures, most commonly after delivery by cesarean section, it typically involves the lower abdominal wall and, less frequently, the umbilicus. In one series, the incidence of endometriosis in a scar after hysterotomy of a gravid uterus was approximately 1 percent.[16] Although the true incidence of endometriosis in cesarean-section scars is difficult to determine, it has been estimated to be between 0.03 percent and 0.4 percent.[17,18] Endometriosis can also involve the lower genital tract in areas of obstetrical or surgical trauma; the most common are episiotomy scars.[19] Cases of cutaneous or soft-tissue endometriosis have been described after an appendectomy or repair of inguinal hernia.[20] Finally, a small number of cases of spontaneous cutaneous endometriosis have been reported, typically involving the umbilicus and, less commonly, the inguinal and perineal regions.[21-23] Cutaneous or soft-tissue endometriosis is only rarely associated with pelvic endometriosis, a much more common disease.

On gross examination, soft-tissue endometriotic lesions range in size from microscopic to more than 10 cm in largest dimension, and there may be areas of hemorrhage or even cystification, as there were in this case. Frequently there is prominent fibrosis and variable degrees of recent or old hemorrhage associated with the lesions, as was seen in this case; in some cases prominent myxoid change may be seen.[24] Malignant transformation of endometriosis is a well-known phenomenon.[25] The frequency of malignant transformation is estimated to be 1 percent or less in ovarian endometriosis; approximately 75 percent of cancers arising from endome-

triosis originate in the ovary. The incidence of malignant transformation in cutaneous or soft-tissue endometriosis is not known, with only isolated cases reported.[26-29] Areas of cancer typically appear as discrete, firm nodules within the endometriotic tissue; no suspicious foci were seen in this case.

Scar endometriomas are believed to result from spillage of endometrial tissue during surgery with secondary implantation in the abdominal fascia or subcutaneous tissues. However, even though retrograde menstruation occurs in 75 to 90 percent of women and spillage into surgical incisions is probably quite frequent during gynecologic or obstetrical surgery, endometriosis occurs with a much lower frequency, suggesting that additional factors, including environmental and genetic factors (cellular and humoral immune system abnormalities, as well as estrogen abnormalities, among others), may confer susceptibility to the development of endometriosis in a small group of patients.[30-33]

Dr. Isaac Schiff (Obstetrics and Gynecology): Would irrigating the wound extensively before closing a Pfannenstiel incision reduce the risk of endometriosis?

Dr. Muto: There is no literature on the subject, but it is reasonable to think that irrigation might help. In addition, it is important to avoid tearing muscle fascicles or fascia, particularly on the second or third entry through the incision. Using electrocautery to define the planes also helps maintain hemostasis. In this particular case, the clinical time course suggests implantation at the time of hysterectomy. This seems counterintuitive, since endometrium is not usually exposed during a total hysterectomy, and suggests a mode of spread other than direct implantation.

Dr. Harris: Dr. O'Neill, was there any follow-up on the liver lesion?

Dr. O'Neill: Repeated CT scanning of the abdomen and pelvis with contrast material, four months after the operation, showed that the liver lesion was unchanged in size. It may well turn out to be a benign lesion that is unrelated to the endometriosis.

Dr. Harris: Dr. Robert Scully, the former editor of the Case Records and former head of gynecologic pathology, is with us today. Do you have any comments?

Dr. Robert E. Scully (Pathology): It is interesting from a historical viewpoint that when Pfannenstiel was practicing in the 19th century, most gynecologic pathology was done by gynecologists instead of surgical pathologists. Pfannenstiel actually wrote a very nice paper on the epithelial tumors of the ovary in which he illustrated the serous borderline tumors. He was the first one to use the term "borderline" for this group of tumors. It is conceivable that someday someone will report a serous borderline tumor of the ovary that presented in a Pfannenstiel scar, so it will be a Pfannenstiel tumor in a Pfannenstiel incision.

ANATOMICAL DIAGNOSIS

Endometriosis associated with a surgical scar.

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EDITORIALS

Gestational Diabetes Mellitus — Time to Treat

Michael F. Greene, M.D., and Caren G. Solomon, M.D., M.P.H.

Gestational diabetes mellitus, broadly defined as carbohydrate intolerance beginning or first recognized during pregnancy,[1,2] was originally described decades ago and has since been the subject of extensive research. Yet the most recent guidelines of the U.S. Preventive Services Task Force, noting the absence of data to establish a clear link between screening and improved outcomes of affected pregnancies, concluded that "the evidence is insufficient to recommend for or against routine screening for gestational diabetes."[3] The American College of Obstetricians and Gynecologists officially recommends screening for and treatment of gestational diabetes but acknowledges that these recommendations are based on "limited or inconsistent scientific evidence."[1]

Unresolved questions include whether gestational diabetes — diagnosed in 3 to 7 percent of all pregnant women in the United States — poses serious risks to the offspring, and if it does, whether treatment reduces those risks. There are well-recognized associations between gestational diabetes and increased risks of fetal macrosomia, birth trauma, and cesarean delivery,[4] but these associations are confounded to some degree by the presence of maternal obesity. Although greater fetal size at birth is associated with increased risks of shoulder dystocia and birth injury, only a fraction of deliveries complicated by shoulder dystocia result in birth trauma, and in most cases, such trauma (clavicular and humeral fractures and brachial-plexus injuries) does not result in permanent injury. No clear association has been documented between gestational diabetes and perinatal mortality.[4]

Moreover, efforts to demonstrate that interventions to reduce glycemia in pregnancy reduce the risks of such complications as macrosomia and cesarean delivery have yielded inconsistent results. Evidence is largely observational. For example, a recent report described substantially lower rates of macrosomia among the infants of treated women with gestational diabetes than among the infants of untreated women,[5] but other differences between the groups may have influenced the results. A randomized trial involving 300 women (a pilot for an ongoing, larger study), in contrast, showed no significant differences in mean birth weight or rates of macrosomia or birth trauma between the infants of women randomly assigned to tight glycemic control and the infants of women assigned to receive routine care.[6] A possible explanation is that awareness of the glucose levels in the women in the routine care group may have led to behavioral changes that minimized differences between the groups.[7] There are no long-term data to evaluate whether treatment reduces other risks reportedly associated with gestational diabetes, including obesity and type 2 diabetes in the offspring.

There are several plausible reasons why screening for and treating gestational diabetes have not consistently reduced fetal growth rates. One is that fetal size at birth is influenced by multiple factors in addition to maternal glucose levels, including maternal body-mass index, weight gain during pregnancy, and parity. In addition, the dichotomy between "normal" and "diabetic" glucose levels is somewhat arbitrary. For example, women with a single abnormal value during a three-hour oral glucose-tolerance test (a result that is not diagnostic of diabetes) have a significantly higher incidence of infants who are large for gestational age than do women with normal values at all time points.[8] Blood

glucose levels during normal pregnancies appear to be controlled within a very narrow range.[9] Therapeutic goals for normoglycemia may not have been set appropriately, and euglycemia is difficult to achieve in practice.

Regardless of the effects of treatment itself on fetal birth weight, it has been argued that diagnosing gestational diabetes could reduce the incidence of birth trauma by alerting obstetricians to the increased risk. However, Rouse and colleagues estimated that approximately 450 mothers with diabetes would need to undergo cesarean delivery to prevent permanent brachial-plexus injury in one infant[10]; this large number needed to treat is explained by the poor predictive value of methods used to estimate fetal weight and the low risk of permanent fetal injury, even among large fetuses. Furthermore, if a diagnosis of gestational diabetes routinely lowers the threshold for cesarean delivery, as has been suggested,[11] the resulting morbidity and costs may outweigh any benefits.

In this issue of the *Journal*, Crowther et al. report the results of a large, randomized, multicenter trial of treatment for gestational diabetes.[12] Pregnant women underwent a 75-g oral glucose-tolerance test between 24 and 34 weeks' gestation; those with values below 140 mg per deciliter (7.8 mmol per liter) after an overnight fast and between 140 and 198 mg per deciliter (11.0 mmol per liter) at two hours were eligible for randomization. The 490 women assigned to the intervention group were taught to monitor their blood glucose levels, provided with individualized dietary counseling, and given insulin as needed to maintain fasting and premeal glucose levels below 99 mg per deciliter (5.5 mmol per liter) and levels two hours postprandially that did not exceed 126 mg per deciliter (7.0 mmol per liter); this approach is consistent with a management approach in which screening and treatment for gestational diabetes are routine. The 510 women assigned to the control group received routine care that was consistent with the care provided in facilities in which screening for gestational diabetes is not standard. Neither group of women was informed of their glucose levels on diagnostic testing.

The offspring of women in the intervention group, as compared with the offspring of women in the routine-care group, had a significantly reduced risk of a composite primary outcome measure that included perinatal death, shoulder dystocia, bone fracture, and nerve palsy (1 percent vs. 4 percent; adjusted relative risk, 0.33; 95 percent confidence interval, 0.14 to 0.75). There were five deaths (three stillbirths and two neonatal deaths) among the offspring of mothers in the routine-care group, as compared with none in the intervention group. Macrosomia (defined as a birth weight of 4 kg or greater) was significantly more common among the infants of mothers in the routine-care group than among the infants of mothers in the intervention group (21 percent vs. 10 percent, $P<0.001$). The rates of cesarean delivery were similar in the intervention and routine-care groups (31 percent and 32 percent, respectively), although the rates of induction of labor and admission of infants to the neonatal intensive care unit were significantly higher among women in the intervention group. (Physicians' awareness of the diagnosis of gestational diabetes was likely to have prompted these interventions.) Postpartum assessment of mood and the quality of life, performed in a subgroup of the women, indicated improved health status in the intervention group, suggesting that being aware of the diagnosis or the need for frequent monitoring had no negative effect on their quality of life.

This study provides critical evidence that identifying and treating gestational diabetes can substantially reduce the risk of adverse perinatal outcomes without, at least in this trial, increasing the rate of cesarean delivery. However, this report also raises some questions. One is ethical: Was it reasonable to randomly assign pregnant women with elevated blood glucose levels to no treatment? Given the preceding lack of rigorous evidence that attempts to improve glucose control improve pregnancy outcomes and that diagnosis and treatment carry small but real potential risks for the patient (including discomfort, inconvenience, anxiety, and potentially unnecessary interventions), we believe the answer is yes. Past experience — as with postmenopausal hormone therapy — has made it clear that interventions cannot be assumed to be beneficial on the basis of extrapolation from physiological or observational data.

Another unresolved question is the level of blood glucose at which intervention is routinely warranted. The glucose levels used to determine eligibility in the present study were different from those cur-

rently recommended by U.S. organizations to identify gestational diabetes (for example, an accepted criterion for diagnosis in the United States is two or more values on a 100-g oral glucose tolerance test at or above the following: fasting, 95 mg per deciliter; one hour, 180 mg per deciliter; two hours, 155 mg per deciliter; and three hours, 140 mg per deciliter[1,2]). However, target glucose levels during treatment were similar.

Data from two ongoing studies may help guide thresholds for intervention. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[13] is assessing the relationship between glycemia and perinatal outcomes. Another treatment trial[7] is assessing the benefits of tight glycemic control in pregnant women who receive a diagnosis of gestational diabetes on the basis of findings of elevated glucose levels at two points in time after a 100-g oral glucose load but normal fasting glucose levels.

Recent evidence indicates a worrisome rise in the prevalence of gestational diabetes[14] that is largely explained by the increase in maternal obesity. Efforts to reverse this trend are critical. At the same time, the current report by Crowther et al. provides some long-awaited evidence to support the use of screening and treatment for women at risk.

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Bortezomib for Myeloma — Much Ado about Something

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Multiple myeloma is a neoplastic plasma-cell dyscrasia that will cause more than 11,000 deaths in 2005 in the United States alone.[1] The usefulness of the many therapies for multiple myeloma is limited, and virtually all patients eventually die from the disease. When thalidomide was shown to be effective against relapsed myeloma in 1999,[2] more than 30 years had elapsed since a clinical response to any single agent had been reported in at least 25 percent of treated patients.[3-5] By the early 2000s, it had become clear that another two agents — lenolidomide[6] and bortezomib[7] — had activity against malignant plasma cells.

Bortezomib is the first of a new class of drugs, proteasome inhibitors, that have been shown to be cytotoxic to several tumor types.[8] Because of the benefit observed in patients with relapsed or refractory myeloma in phase 1 and 2 trials,[7,9] the drug was fast-tracked by the Food and Drug Administration (FDA), making it available to patients with this kind of advanced myeloma in May 2003. The Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, which is reported by Richardson et al. in this issue of the *Journal*,[10] supports the FDA's decision.

The APEX trial randomly assigned 669 patients

with relapsed or refractory myeloma who had received one to three previous regimens to receive either high-dose dexamethasone or bortezomib. Patients were stratified according to the number of previous regimens they had received, the time since the last therapy, and levels of serum beta$_2$-microglobulin. The primary end point was the time to disease progression. Secondary end points included response rates and overall survival. Patients who were randomly assigned to receive bortezomib had both a significantly longer median time to disease progression than those assigned to receive dexamethasone (6.22 months vs. 3.49 months, P< 0.001) and higher response rates (complete response, 6 percent vs. less than 1 percent; partial response, 32 percent vs. 17 percent; P<0.001 for both comparisons). Follow-up was truncated at the interim analysis because the results favored bortezomib.

In order to interpret the results of this trial in the context of other myeloma therapies, potential limitations of the trial — including the study design and deleterious effects of the therapies — must be considered. The choice of dexamethasone, a potent synthetic corticosteroid, as a control drug for the phase 3 trial was reasonable, since it is commonly used either as a single agent or in combination with other drugs to treat all phases of myeloma. When dexamethasone is given as a single agent, the response rate ranges from 25 to 44 percent.[11,12] However, the first potential limitation of the APEX study was that only 1 percent of patients had not received any corticosteroids, whereas no patients had received bortezomib. The authors initially addressed this issue by restricting enrollment to patients who did not have disease that had shown previous "resistance" to dexamethasone. However, in a post hoc subgroup analysis, 60 participants were found to have disease that was possibly refractory to dexamethasone and were excluded. The observed superiority of bortezomib persisted, but the lower-than-expected response rate in the dexamethasone group (18 percent vs. the expected 25 to 44 percent) is not explained.[11,12]

A second limitation of the trial design was the intended dose intensity of drugs to be delivered. The choice of a dexamethasone schedule of 40 mg on days 1 to 4, 9 to 12, and 17 to 20 every five weeks[11] rather than every four weeks[12] for induction resulted in a slightly lower dose-intensity schedule (by a factor of 0.6 to 0.8) than that used by others.[12-14] A more striking disparity between the two groups, however, was the duration of induction for bortezomib as compared with that for dexamethasone (1.2 times as long) and the difference in dose intensity during maintenance in favor of bortezomib. Whether these design choices affected the end points cannot be known, but the intensity of the dose could certainly have influenced both response and toxicity.

The third potential limitation of the trial is the short follow-up period — 8.3 months for surviving patients. The positive findings in favor of bortezomib at the interim analysis and the subsequent recommendation of the data monitoring committee that patients in the dexamethasone group be offered premature elective crossover to the bortezomib group resulted in exorbitant censoring and truncation of follow-up. Less than 20 percent of patients were followed for one year, yet the one-year overall survival is reported as 80 percent versus 66 percent (P=0.003). This short follow-up and a loss to follow-up of 22 percent of patients make it uncertain that this survival benefit will withstand the test of time. Similarly, data on approximately 50 percent of patients were censored in the analysis of the time to disease progression: for the bortezomib and dexamethasone groups, respectively, data on 23 percent and 14 percent of patients were censored because of the use of alternative therapy or loss to follow-up, and data on 28 percent and 19 percent because of the mandate of the data-monitoring committee. Once again, how these censoring events affected the overall results is not known.

The difference in the overall tolerability of the therapies is not emphasized by the authors but is not inconsequential. Nearly a third of patients discontinued a study drug because of side effects. Bortezomib was associated with more serious adverse events than dexamethasone (grade 3, 61 percent vs. 44 percent; P<0.01) and a higher rate of drug discontinuation due to adverse events. Most striking was the relative incidence of peripheral neuropathy (all grades, 36 percent in the bortezomib group vs. 9 percent in the dexamethasone group; grade 3, 7 percent vs. <1 percent; P<0.01). Patients who were receiving bortezomib had significantly more fatigue, gastrointestinal symptoms, fever, myelosuppression, headache, anorexia, cough, rash, and pain. The cause of the differences is probably multifactorial. First, the dose intensity of bortezomib was higher than that of dexamethasone. Second, since

the trial was not double-blinded, there may have been a reporting bias against the "new intravenous" therapy as compared with the "old oral" therapy. Third, patients in the bortezomib group had a longer time to disease progression and thus received their assigned therapy for a longer period. This may have caused more cumulative toxicity, though similar numbers of patients in the two groups completed approximately five months of treatment (nearly 30 percent) and nine months of treatment (about 10 percent). Fourth, bortezomib may be more toxic than dexamethasone at the present dose schedules.

The final consideration of "tolerability" is one of cost. The charge by the pharmacy at my center (Mayo Clinic, Rochester, Minn.) to a patient with a body-surface area of 2 m^2 for the nine months of therapy as outlined in the APEX trial would be $45,760 for bortezomib and $170 for dexamethasone. Though no price can be placed on the value of an effective drug to a patient or his or her family and doctor, this differential is sobering.

So where does this leave us? The take-home message of the APEX study is that bortezomib is an effective therapy against relapsed myeloma, a fact to which anyone who has used the drug can attest. It is a much-needed additional tool against this devastating disease. Though other drugs have similar overall response rates as monotherapy, aside from high-dose melphalan, no other single agent has resulted in complete response rates of 6 percent in patients with the relapsed or refractory disease. Moreover, bortezomib markedly enhances the sensitivity of myeloma cells to other chemotherapeutic agents both in vitro[15] and in vivo.[8] At this year's meeting of the American Society of Hematology, there were many preliminary reports of high rates of response to bortezomib, given either as a single agent or in combination with other agents — including dexamethasone, melphalan, doxorubicin, and thalidomide — and radiation.

After a generation without a new agent to treat myeloma, the future is bright. In the past five years, two new classes of drugs have been shown to have activity in patients with myeloma. As we move forward, we cannot ignore effective old therapies. We must determine the optimal sequence and combinations of these agents. Well-designed, randomized trials will guide our understanding, but we must be cognizant of the limitations of such studies. What is a meaningful end point? How does quality of life fit into the analysis? Despite the caveats in the APEX study, the time to disease progression was nearly doubled — albeit in absolute terms, it was a difference of three months at a price of 1.2 times as many serious adverse events and a higher dollar investment. The trial emphasizes the dire need to decipher the molecular basis of myeloma, with subsequent development of rational targeted therapies, since only these steps will lead us to substantial improvements in outcome.

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Recovery from Rabies

Alan C. Jackson, M.D.

Worldwide, some 55,000 people die every year from rabies, mostly in Asian and African countries where canine rabies is endemic. Children are frequently the victims of rabies. In the United States, indigenous cases of rabies in humans usually occur through transmission of rabies virus from wildlife vectors, and molecular characterization of the variants indicates that the majority of these cases originate from insect-eating bats.

In this issue of the *Journal*, Willoughby et al.[1] report the case of a young patient in whom rabies developed after a clear history of having been bitten by a bat. Most of the cases of rabies in the United States do not have such a history, and many of the patients do not even have a known exposure to bats, which makes the diagnosis of rabies very challenging for physicians. Most human cases are associated with a rabies-virus variant found in small silver-haired or eastern pipistrelle bats,[2] and transmission probably occurs as a result of unrecognized bat bites. After a bat bite or a situation in which an unrecognized bite may have occurred (e.g., in an unattended infant found in a room with a bat), the bat should be tested for the presence of rabies-virus antigen. If rabies cannot be ruled out and the patient has not received previous immunization, postexposure rabies prophylaxis should be initiated with the administration of five doses of rabies vaccine and of human rabies immune globulin.

In 2003, a group of physicians and researchers with expertise in rabies reached a consensus on the management of human rabies.[3] At that time, there had been only five well-documented survivors of the disease,[3] and all these patients had received rabies vaccine before the onset of symptoms. At least one of the survivors had a good neurologic outcome. The group said that rabies vaccine, human rabies immune globulin, ribavirin, interferon alfa, and ketamine should be considered when an aggressive approach is desirable. They also noted that combination therapy might be promising, since it had proven efficacy in other viral and nonviral diseases.

An immune response is essential for recovery from rabies, although vaccine would not need to be given if — at the time of diagnosis — a patient had rabies virus–specific antibody, as in the case report by Willoughby et al. Rabies vaccination would be reasonable at presentation when the rabies virus–antibody status of the patient is unknown, especially since all previous survivors of rabies had received rabies vaccine. Antibodies have a very limited ability to cross an intact blood–brain barrier, and the therapeutic usefulness of human rabies immune globulin (which is available for rabies prophylaxis) in rabies encephalitis is probably limited unless the delivery to the central nervous system can be improved. Ribavirin and interferon alfa failed to show efficacy in rabies in a previous report.[4] However, these drugs may still be useful, especially in combination with other agents.

Amantadine, as discussed by Willoughby et al. in the case report, has received less attention, and ketamine (also discussed) is a dissociative anesthetic agent that is a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist. There has been recent speculation that the NMDA receptor may be one of the rabies virus receptors.[5] Tsiang and coworkers reported that ketamine inhibited the genome transcription of rabies virus and restricted viral spread in an experimental rat model of rabies virus infection.[6,7] In contrast to what has been shown in experimental Sindbis virus encephalomyelitis in mice,[8,9] neuronal injury that is mediated by excitatory amino acids has not yet been shown in rabies. Although there is strong experimental evidence that excitotoxicity is important in animal models of stroke and other neurologic diseases, clinical trials of neuroprotective agents in humans have had disappointing results.[10]

Our understanding of exactly why humans die of rabies is incomplete. In human rabies, many neurons are infected by rabies virus, but the neuropathological findings are quite mild, with inflammatory changes and few cells showing evidence of neuronal death, as compared with those in herpes simplex encephalitis, for example. For this reason, it is felt that rabies virus infection produces neuronal dysfunction rather than neuronal death, but the fundamental cause of this dysfunction is not yet well understood, despite a number of research studies of a variety of neurotransmitters and endogenous neurotoxins in animal models.[11] When aggressive treatment is undertaken in critical care units, patients usually die from medical complications or multisystem organ failure.[12]

Since we do not know exactly why most patients

die of rabies, it is difficult to speculate why the patient survived in the report by Willoughby et al. What role did the drug therapy play in her survival? One possibility, mentioned by the authors, is that she may have been infected by an attenuated variant of bat rabies virus, perhaps one never yet isolated, and that the specific therapeutic agents she received may have played an insignificant or only a minor role in the outcome. It is not clear whether induction of coma per se played a role in her recovery. The desired pharmacologic effects of drugs may be associated with depression of the level of consciousness that is not the primary goal of therapy. For example, coma may occur as a result of therapy with antiepileptic medications for control of status epilepticus, in which the goal is to suppress clinical and electroencephalographic seizures. Induction of coma is not known to have beneficial therapeutic effects in rabies or in other infections of the central nervous system. In the future, induction of coma will probably not be shown to be an effective therapeutic approach to the management of rabies or viral encephalitis due to other causes. However, it is probable that the patient's pharmacologic therapy, especially ketamine and ribavirin, produced beneficial antiviral and maybe even neuroprotective effects.

Future research efforts will be needed to assess further the efficacy of the drugs used to treat this patient. The approach taken may also have helped to prevent autonomic complications that may occur in rabies and may lead to death. The success of Willoughby and his clinical colleagues in ensuring the survival of this young patient with rabies should be applauded. The case provides hope that therapeutic approaches can be successful in rabies and that such treatments may become even better in the future. Early diagnosis and prompt initiation of therapy before laboratory confirmation of the diagnosis will be important for future efforts in the management of rabies in humans. An improved understanding of the pathogenesis and mechanisms of neuronal injury and the identification of good therapeutic agents on the basis of both in vitro studies and studies in animals are obviously important steps in combating one of the most deadly neurologic diseases affecting humans.

Dr. Jackson reports having received consulting fees from Chiron.

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CORRESPONDENCE

Transmission of Rabies from an Organ Donor

TO THE EDITOR: Srinivasan and colleagues (March 17 issue)[1] report the transmission of rabies virus from an organ donor to four recipients. Three recipients had neurologic deterioration and encephalitis and died about five weeks after transplantation; one died of intraoperative complications. The authors investigated the medical records of the donor and the recipients and performed serologic and histopathological tests on the recipients' blood, fluids, and tissues with a variety of assays. Although the results of these tests suggest that rabies is the etiologic pathogen that was transmitted from the donor to the recipients, these tests do not provide conclusive information about the original source of the virus. The origin of the pathogen could be identified by means of molecular typing techniques, such as a heteroduplex-mobility assay, gene sequencing, or phylogenetic analysis.[2-4] The conclusion of the study would be different if the genotypes of the viruses isolated from the donor and the recipients were distinctly different. The conclusion that these organ recipients died from rabies infection transmitted by the donor would be more convincing if a high degree of homology among the viral genotypes were demonstrated.

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TO THE EDITOR: Srinivasan et al. report the death of four patients who had received transplanted solid organs and a vascular graft from a donor with rabies. The donor presented with fever, altered mental status, difficulty swallowing, and autonomic dysfunction, which are clinical features of rabies,[1] and apparently he had no ictus suggestive of aneurysmal subarachnoid hemorrhage. An important issue is whether the donor had two coexisting, fatal neurologic diseases (rabies and severe subarachnoid hemorrhage) or whether he had rabies and either an unrelated, minor subarachnoid hemorrhage that would not explain his neurologic presentation and subsequent deterioration or a pseudosubarachnoid hemorrhage, which may be associated with diffuse cerebral edema and other conditions.[2,3] There is extensive information available about the neuropathology of rabies,[4] but there is no support for the speculation that rabies virus might infect and cause pathologic changes in the blood vessels, leading to subarachnoid hemorrhage. Hence, it would have been very informative if the authors had provided the computed tomographic images of the donor's brain showing the subarachnoid hemorrhage.

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THIS WEEK'S LETTERS

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TO THE EDITOR: In France, to limit the transmission of infectious diseases in allogeneic tissue or cells, a quarantine period of at least two months is mandatory when tissue or cell storage is compatible with subsequent clinical use.[1] When such a biologic product is collected from a live donor (e.g., in the case of cord blood or amniotic membranes), repeated testing for infectious markers is performed on completion of the quarantine period. When the biologic product is collected from an organ donor (as in the case of arteries, bones, or cardiac valves), testing for infectious markers is performed two months after transplantation in all the recipients of organs collected from the same donor. Furthermore, any clinically significant event occurring among the organ recipients during the quarantine period is recorded by the Etablissement Français des Greffes and transferred to the relevant biobank. Implementation of such a policy would prevent the transmission of rabies virus in an arterial graft, as in the case described by Srinivasan et al. Indeed, the arterial graft would have been cryopreserved, stored, and subsequently discarded, in view of the encephalitis that occurred in one or more of the recipients who had received an organ from that donor.

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THE AUTHORS REPLY: With respect to Dr. Jenwitheesuk's point about the source of the infections, we believe that the epidemiologic evidence does point overwhelmingly to the organ donor as the source. In addition, sequencing data confirm that the rabies virus in all the recipients was identical.

The subarachnoid hemorrhage in the organ donor was severe and was associated with herniation. We agree with Dr. Jackson's assertion that there is no evidence that the subarachnoid hemorrhage in the organ donor was related to the rabies infection. As we mention in the article, subarachnoid hemorrhage has not been described in previous reports of neurologic imaging in patients with rabies.[1-3] The cause of the subarachnoid hemorrhage in this case remains unknown. One possibility is hypertension in the setting of a positive toxicologic screen for cocaine.

We appreciate learning from Drs. Lapierre and Tiberghien about practices in France with respect to the mandatory quarantine of allogeneic tissues and the central reporting of any adverse events that occur among organ recipients. The required quarantine period they describe, which necessitates cryopreservation of arterial conduits, would indeed have prevented the case of rabies in the recipient of the arterial conduit described in our report. However, some transplantation surgeons prefer fresh arterial conduits to cryopreserved ones, and the successful use of fresh arterial conduits has been reported both in primary transplantation procedures and in the management of vascular complications after transplantation. Whether fresh conduits lead to better outcomes and justify a slightly increased risk of disease transmission remains unknown. Certainly, the ability to track and account for these vascular conduits is essential for the rapid identification of patients who might be at risk for infections from transplants. Improving nationwide detection and central reporting of unexpected or serious outcomes in organ recipients, as described by Drs. Lapierre and Tiberghien, might indeed facilitate the discovery of transplant-related transmission of pathogens by allowing connections to common donors to be made. This concept remains a topic of discussion between the Department of Health and Human Services, including the Centers for Disease Control and Prevention, and members of the organ and tissue transplantation community.

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Glycogen Storage Diseases and Cardiomyopathy

TO THE EDITOR: Arad et al. (Jan. 27 issue)[1] report that *LAMP2* mutations (Danon's disease) are an important cause of hypertrophic cardiomyopathy. That one of their patients had an "adolescent response to cardiac disease," however, strangely misses the point that mental retardation commonly accompanies this disease. Both of the patients in the original cases described by Danon et al.[2] had mental retardation, and in a series of 38 patients, described by Sugie et al.,[3] 70 percent of male patients (14 of 20) and 6 percent of female patients (1 of 18) had mental retardation. Lobrinus et al.[4] and Sugie et al.[5] have also reported that patients with Danon's disease did not reach other neurodevelopmental milestones — most with this disease did not walk until they were 18 months old and many had learning difficulties.

We recommend that patients who present with hypertrophic cardiomyopathy be asked about their educational performance. If there is a history of learning difficulties, they should be referred for further evaluation. If a diagnosis of Danon's disease is made, all first-degree relatives should be offered genetic testing and stratification of the risk of sudden death from cardiac causes.

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THE AUTHORS REPLY: Roos and Cox "recommend that patients who present with hypertrophic cardiomyopathy be asked about their educational performance." We concur. However, our article goes further, suggesting that other clinical findings, such as preexcitation on the electrocardiogram or elevated levels of creatine kinase, should also trigger evaluation of *LAMP2* and *PRKAG2* genes. The central theme of our article is that whereas many *LAMP2* mutations cause Danon's disease, with its associated neurologic and muscular abnormalities, some *LAMP2* mutations produce primary cardiac disease that mimics hypertrophic cardiomyopathy without neuromuscular or behavioral abnormalities. Only two of the six patients in our study had even mild behavioral or psychological abnormalities — relatively common problems among adolescents with cardiac disease.[1] If these patients had been cared for according to standard cardiologic practice,[2] which does not include genetic testing,[3] the cause of their cardiomyopathy would not have been identified.

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What Ails the FDA?

TO THE EDITOR: Okie's Perspective article (March 17 issue)[1] on the Food and Drug Administration (FDA) covers important ground but misses a key issue. No drug is absolutely safe; drug safety is always assessed in relation to the disease being treated. We tolerate greater risk from beneficial therapy when the alternatives are bad.

Risk–benefit analysis requires us to define the

target population for the drug. Clinical trials are the best way to define this population. Direct-to-consumer marketing campaigns, on which drug companies spend billions of dollars, circumvent this process and often encourage patients to demand prescription drugs inappropriately. Rofecoxib (Vioxx) was an important beneficiary of such a campaign. As a result, many people were put at risk although their medical needs could have been met with less toxic drugs.

Today, patients for whom rofecoxib provided the best relief are no longer able to obtain it. In short, pharmaceutical-company greed created an unmet medical need. There is a cost-free way to help the FDA protect patients: stop direct-to-consumer advertising and let trained and knowledgeable physicians determine the best treatment for our patients.

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1. Okie S. What ails the FDA? N Engl J Med 2005;352:1063-6.

TO THE EDITOR: What ails the FDA is the political influence that limits the agency's resources and interferes with its regulatory decisions.[1-3] The FDA has always been underfunded and understaffed in relation to the scope of its responsibilities.[1] Surveillance of drug safety has been impaired by a decrease in the personnel and resources devoted to it because of the emphasis on the rapid review of new drugs and unfunded congressional mandates. The other problems noted by Okie — intimidation of staff scientists, weak leadership, and the pro-industry bias of the former chief counsel — are manifestations of the political manipulation of the FDA by the administration.

Two changes are necessary to restore the FDA to health: a budget that is commensurate with its responsibilities and scientific independence. The FDA could be shielded from political manipulation through the appointment of an independent scientific advisory board to advise Congress about the performance and needs of the agency. By making its recommendations public, the advisory board could help Congress to resist pressure from lobbyists and advocacy groups.

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TO THE EDITOR: Okie's article could lead the reader to the conclusion that an independent drug-safety agency would protect patients better. But Okie omits certain events surrounding the withdrawal of rofecoxib from the market that illustrate the potential downside of separating the FDA's drug-approval function from post-marketing safety surveillance. In particular, she does not mention the fact that experts in drug safety and the relevant therapeutic field who gathered at an FDA advisory committee meeting in February to discuss the safety of cyclooxygenase-2 (COX-2) inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs) voted 17 to 15 that rofecoxib ought to be allowed to be marketed. Nor did Okie mention that David Graham, the FDA epidemiologist who has heartily criticized the agency's handling of the rofecoxib review, is rather more certain in his views of the benefit–risk equation for the drug; he has said that "there really doesn't appear to be a need for COX-2 selective NSAIDs." The point is that drug-safety experts tend to downplay therapeutic benefits, and clinical practitioners tend to downplay risks. What is needed at the FDA is an unrestrained voice for experts on both sides of the equation.

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TO THE EDITOR: To redress the institutionalized influence of the pharmaceutical industry on the FDA's drug-approval process, perhaps third-party payers such as insurance companies and health maintenance organizations need to be invited to join the fray. These payers cover not only the costs of expensive new technology, but also any costs incurred because of unanticipated adverse effects. Who is more motivated to expose problems with efficacy and safety that are deliberately obscured by the pharmaceutical industry? Rather than perpetuate the sham of an unbiased partnership between government and industry committed to protecting and enhancing health, why not expose the powerful fi-

nancial motivations that drive health care decisions? If drug companies are treated as agents of science and discovery, payers ought to be viewed as the corrective agents of scientific scrutiny. A more open discourse involving parties with admittedly different agendas may more successfully illuminate the issues critical to decisions that have consequences for public health and public coffers.

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Obesity and Longevity

TO THE EDITOR: Preston's editorial (March 17 issue)[1] on obesity and its influence on longevity, which accompanies the report by Olshansky et al.,[2] focused my thinking on morbidity versus mortality. Preston wrote that "the current life expectancy at birth in the United States would be one third to three quarters of a year higher if all overweight adults were to attain their ideal weight." This goal is unlikely to be achieved, and even if it were, the gain in life expectancy would be minuscule. As a clinician, however, I see daily the terrible morbidity that obese patients have — complications from diabetes, dyslipidemia and hypertension, wear and tear on the knees and hips, legs swollen from venous insufficiency, backache, and a winding down of physical activity. It seems to me that an emphasis on morbid states that could be averted with the elimination of some (not all) excess weight would permit an educable patient to sit up, take notice, and act. The gain in life expectancy is too small to sell to any patient. The avoidance of suffering is worth the effort.

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TO THE EDITOR: In providing examples of population shifts toward healthier lifestyles, Dr. Preston states incorrectly that "primarily because of behavioral changes, the incidence of AIDS has fallen by nearly 50 percent since 1992." The observed decline in the incidence of AIDS from 1992 to 1994 was an artifact of the change in the surveillance case definition for AIDS that was implemented in January 1993.[1] A substantial decline was then observed in the years 1995 through 1998 after the introduction of highly active antiretroviral therapy for human immunodeficiency virus (HIV) infection.[2] Since 1998, the incidence of AIDS has remained relatively stable.[2] To suggest a shift toward "healthier lifestyles" in the context of HIV infection is particularly misleading, given recent reports of increased levels of unsafe sexual behavior among gay and bisexual men in urban centers throughout the United States, Canada, and Western Europe.[3] These reports highlight the critical need for continued efforts to identify and implement more effective strategies of HIV prevention.

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TO THE EDITOR: Preston states, regarding obesity, that "the U.S. population has already shown the ability to shift to healthier lifestyles." There are few recent data to support his statement. During the past 15 years, the percentage of adults who smoke has decreased by only 1 percent.[1] The number of new cases of AIDS has remained unchanged, at 40,000 per year.[2] The modest reduction in the number of fatal vehicular crashes reflects improved safety equipment and better emergency medical care, not fewer drunk drivers.[3] The incidence of obesity has doubled, dietary fat intake has increased, and serum cholesterol levels have not decreased significantly (from 205 to 203 mg per deciliter).[4]

An antiobesity campaign should focus sharply on creating new social policies that encourage weight loss (e.g., adjustments in insurance premiums, compulsory exercise for students from ele-

mentary school through college, and health-friendly food choices in cafeterias).

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1. Freid VM, Prager K, MacKay AP, Xia H. Health, United States, 2003: with chartbook on trends in the health of Americans. Hyattsville, Md.: National Center for Health Statistics, 2003:169, 212, 228. (DHHS publication no. 2003-1232.)
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TO THE EDITOR: I became alarmed when I observed what my peers were eating at my public high school. In 2003, I began a campaign as a teen advocate for healthful eating. Olshansky and colleagues' forecast for my generation is distressing. Businesses should not be allowed to market unhealthful products to children. They undermine our own personal responsibility to make choices by flooding the marketplace with unhealthful choices. We should educate children and adolescents so that they can make informed choices. It definitely takes more time, effort, and money to eat more healthfully. This "obesity tsunami" can be stopped through education and by subsidizing more nutritious food sources and granting schools an adequate budget to provide nutritious meals.

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TO THE EDITOR: Olshansky et al. highlight once more the fundamental impact of weight control on the risk of disease and, thus, longevity. We all know that weight control is vital for the longevity of each person and for our health care system. A central question regarding increased life expectancy is often insufficiently addressed[1]: What are we going to do during the years gained? At present, the most likely answer would be eating and gaining weight.

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DR. PRESTON REPLIES: Dr. Whitehouse is surely correct that the consequences of obesity in terms of morbidity are significant and that reductions in obesity would improve both levels of fitness and longevity. It is important to recognize that the estimated loss of one third to three fourths of a year of life expectancy that results from obesity patterns is a national average across all body types; the loss of life expectancy for obese people themselves is considerably greater.

Dr. Blanchard argues that behavioral trends during the past 15 years are not as benign as those that I cite, but his citations to data and references are seriously flawed. The source that he refers to for smoking patterns does not show a 1 percent decline during the latest available 15-year interval. Rather, the percentage of adults who are current cigarette smokers declined from 30.1 percent in 1985 to 23.3 percent in 2000.[1] The reference that he and I cite with regard to fatal crashes involving drunk drivers attributes the decline in mortality not to improvements in safety equipment and better medical care but rather to two campaigns fostered by Mothers against Drunk Driving. One focused on legislative change to discourage drunk driving, and the other on assigning designated drivers.[2]

Dr. Blanchard also argues that the incidence of AIDS has not declined in the past 15 years. In their letter, Drs. Simon and Frye point out correctly that the incidence of AIDS has declined since 1995. With adjustment for reporting delays resulting from a 1993 expansion of the definition of AIDS, the number of AIDS cases declined from 62,200 in 1995 to 42,156 in 2000 and has remained roughly constant since that time.[3,4] As Drs. Simon and Frye suggest, this decline probably had more to do with changes in treatment regimens than with behavioral change. However, an earlier decline in the incidence of AIDS "almost certainly reflects prevention efforts within gay communities."[5] Improving health behaviors is not easy, but there is solid evidence that it can be done.

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Triple HIV-1 Infection

TO THE EDITOR: Dual infection with different strains of HIV type 1 (HIV-1) is reported with increasing frequency, attributed mostly to coinfection at the time of the primary infection. However, some patients were superinfected with a second virus after the original seroconversion,[1] which generally accelerated disease progression.[2]

We encountered a case of serial HIV-1 superinfection resulting in a triple infection in a Dutch patient who was originally infected with a subtype B virus. A 35-year-old homosexual man was found to be HIV-1–seropositive in March 2001 and was referred for follow-up. Early in July 2003, the patient presented with acute onset of fever, rhinorrhea, cough, and arthralgia; the symptoms lasted for approximately one week. A plasma sample drawn during the episode of illness on July 24, 2003, showed an extremely high HIV-1 load with a markedly reduced CD4+ cell count (Fig. 1). Analysis of serial samples for viral genotype provided evidence of a novel HIV-1 infection by a circulating recombinant form 01_AE of the virus (subtype CRF01_AE) that dominated the viral population on July 24, 2003 (Fig. 2), and suggested that the patient also harbored a second subtype B virus. An investigation of stored plasma samples indicated that a superinfec-

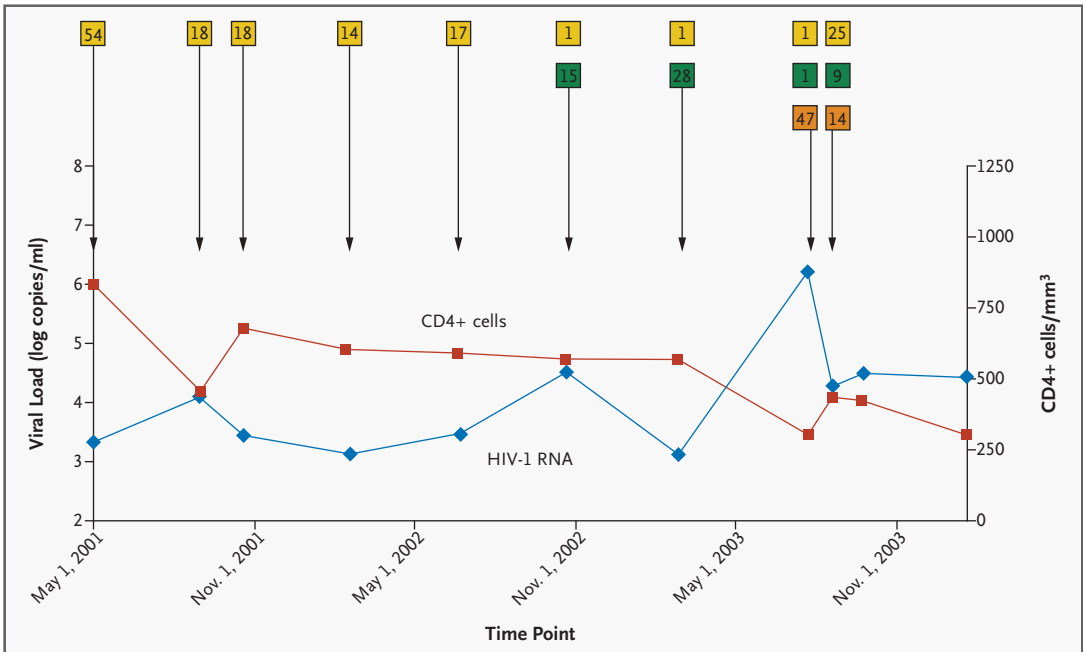

Figure 1. Changes in Plasma HIV-1 RNA Levels, CD4+ Cell Counts, and Viral Sequences in Samples Obtained from a Dutch Patient Serially Infected with Three Strains of HIV-1.
The HIV-1 viral-envelope (*env*) V3 sequences were amplified from plasma with the upstream primer 5'ACAGGGCCATGYAMAAATGT3' and the downstream primer 5'CCCCTCCACAATTAAARCTRTG3', which can amplify both HIV-1 subtypes B and CRF01_AE. A reverse-transcriptase–polymerase-chain-reaction analysis was performed as described elsewhere.[3] Fragments were cloned and sequenced[3]; the number of clones obtained is indicated for each subtype of virus (B1 is shown as yellow, B2 green, and AE orange). Additional amplifications with strain-specific primers confirmed the absence of subtype B2 and CRF01_AE at early time points (data not shown).

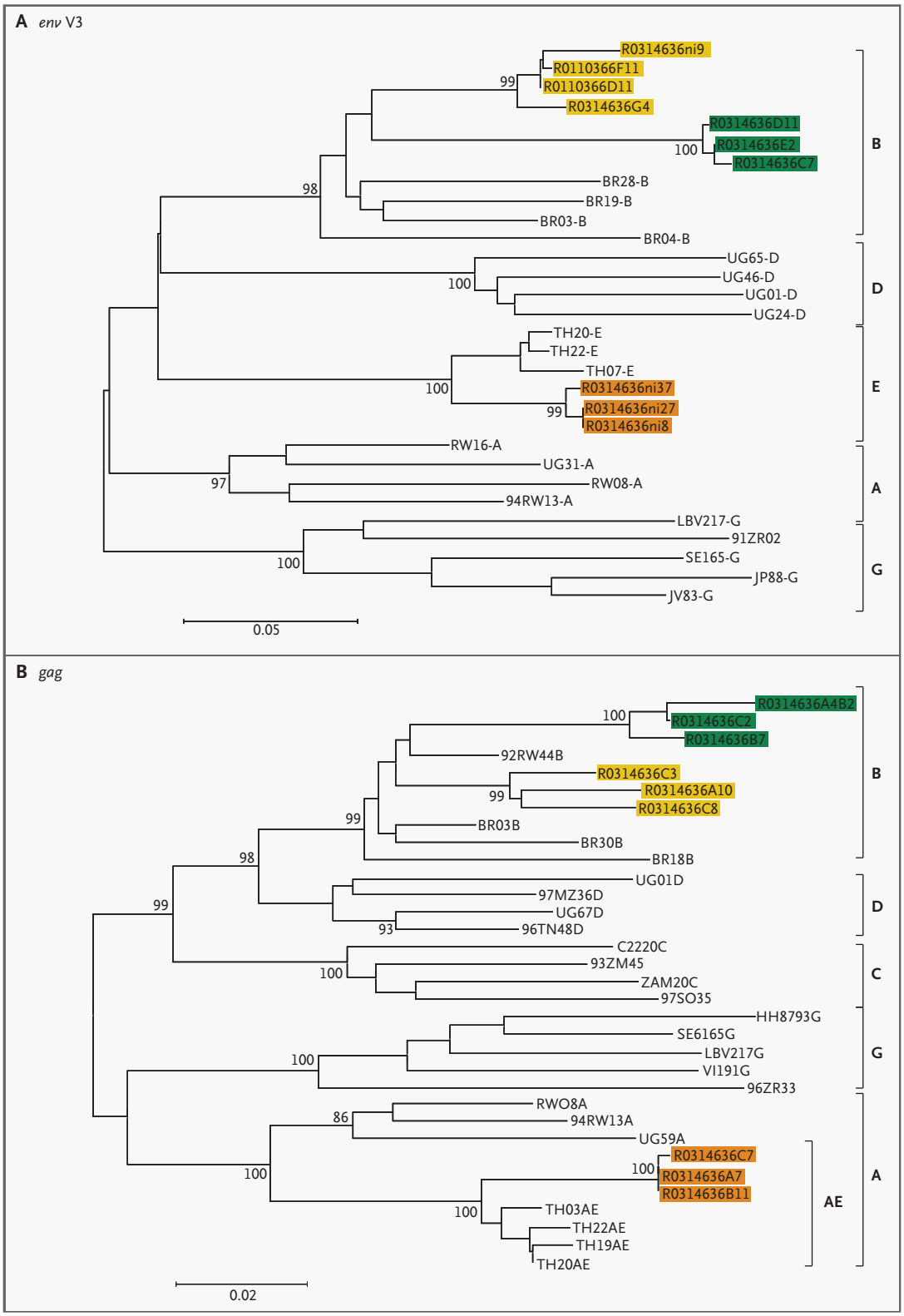

Figure 2 (facing page). Phylogenetic Trees of *env* and *gag* Fragments Obtained from the Same Patient.

In Panel A, the phylogenetic tree shows the different *env* fragments obtained from the patient at the moment of the second superinfection. Reference sequences were downloaded from the HIV sequence database of the Los Alamos National Laboratory (http://hiv-web. lanl.gov). The tree is based on a distance matrix calculated with the use of the Kimura-2-parameter method and constructed with the NJ option available in the Mega software package (www.megasoftware.net). Five hundred bootstrap replicates were analyzed. The colors are the same as in Figure 1. In Panel B, the phylogenetic tree shows the different *gag* fragments obtained from the patient at the moment of the second superinfection. The *gag* fragments were amplified from plasma as described elsewhere,[3] with the primers LOUW-1-gag 5'TTGACTAGCGGAGGCTAGAA3' and SK39 5'TTGGTCCTTGTCTTATGTCCAGAATGC3' and the nested primer set GAG-2I 5'GGGAAAAAATTCGGTTAIGGCC3' and GAGAE-3 5'ACTATTTTATTTAATCCCAGGAT3'.

tion with this second B-type virus (tentatively labeled B2) had occurred between July and October 2002, since the sample obtained on October 22, 2002, was the first to contain B2 RNA sequences (Fig. 1). The patient did not have clinical symptoms nor did his CD4+ cell count decline when he was reinfected with the second subtype B strain, whereas reinfection with a more divergent subtype CRF01_AE strain resulted in acute viral illness, a prominent rise in viral load, and a decline in the CD4+ cell count. Transient superinfection with a subtype B strain has been reported to produce no symptoms.[4]

It is not clear whether any patient with HIV-1 infection can be superinfected or whether characteristics of the host or viral factors modulate susceptibility to superinfection. The main risk factor for serial HIV-1 infections in this patient was probably his reexposure by way of repeated unprotected sexual contact with other men infected with HIV-1. This unusual case illustrates the potential for repeated HIV-1 superinfection in an HIV-1–infected patient who continues to practice unsafe sex, and it underscores the need for continued preventive efforts aimed at ensuring safe sexual practices even among persons already infected with HIV-1.

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BOOK REVIEWS

BIOTERRORISM: PSYCHOLOGICAL AND PUBLIC HEALTH INTERVENTIONS

Edited by Robert J. Ursano, Ann E. Norwood, and Carol S. Fullerton. 363 pp., with CD-ROM. New York, Cambridge University Press, 2004. $110. ISBN 0-521-81472-3.

In the relatively brief time since September 11, 2001, legions of articles have been published, grants submitted, journals launched, and textbooks edited on the subject of terrorism involving biologic agents. Much of the work has focused on the agents themselves or on policies and preparations for bioterrorism within health care systems. In *Bioterrorism*, the editors have attempted to address a fundamental deficiency in the existing database: less than 1 percent of the literature deals specifically with the psychosocial aspects of bioterrorism, even though psychological morbidity is likely to be among the most prevalent health issues in the aftermath of an event. The plausibility of this prediction is convincingly upheld by such recent episodes as the Oklahoma City bombing in 1995, the September 2001 attacks, and the subsequent postal shipments of anthrax. The editors succeed, in many aspects, in elucidating the ideas that "promote mental health and resilience in the face of bioterrorism."

The book's three main sections are designed to flow from the conceptual and philosophical to the operational. The first part deals mostly with historical lessons, which are interspersed with fascinating discussions of psychological aspects of terrorist groups; the second section moves into the clinical realm; and the third involves practical recommendations for incorporating plans to deal with psychological responses in the context of public health interventions.

Bioterrorism presents unique challenges. Attacks are likely to be insidious and, unless conventional weapons are also involved, may not even be suspected until clusters of victims present for medical attention. Illness may be fulminant, disfiguring, and transmissible, thus resonating with the most basic of human fears. Responders will not only have to cope with potentially large numbers of victims in the days and weeks after an attack but will also have to deal in the longer term with a much greater number of unexposed, psychologically damaged people, including their fellow health care providers. A range of illnesses in these victims, from situational anxiety to frank depression to post-traumatic stress disorder, will occur for years after a bioterrorist event and can be predicted to affect a much broader population than those actually infected. The editors of this book are persuasive in their contention that mental health preparedness is a critical aspect of public health, and they have provided a practical framework for planners.

As in any multiauthored textbook, some overlap in content inevitably occurs, and the integration of each chapter into the larger work is not always precise. The book would have benefited from a more succinct and focused introductory section, since the most useful parts of the work are the later chapters that deal with the psychosocial effects of bioterrorism on communities and intervention strategies for recovery. The authors are experts in their fields, and many of them are responsible for what scarce literature exists on the subject. I found myself reading this book in the immediate aftermath of a natural disaster of massive proportions — the tsunami in Asia in December 2004 — and was struck by the relevance of the book to that crisis. Credible bioterrorism scenarios have included casualty estimates on a similar scale to those witnessed in this recent natural disaster. The editors of this book have provided us with the requisite data to mitigate some of the worst effects of terrorism; it is incumbent on clinicians, policymakers, and those who are charged with protecting the public health to integrate this information into our response planning.

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THERAPEUTIC HYPOTHERMIA

Edited by Stephan A. Mayer and Daniel I. Sessler.
629 pp., illustrated. New York, Marcel Dekker, 2005.
$149.95. ISBN 0-8247-5478-6.

THE RECOGNITION THAT MODEST CHANGES in temperature may modulate the outcome after global or focal cerebral ischemia, or both, has led to the use of mild-to-moderate hypothermia to reduce reperfusion injury in diverse clinical settings — for example, after cardiac arrest or head trauma and in neonates after intrapartum hypoxia–ischemia. This book provides a clear overview of this type of intervention and integrates many of the complex issues associated with its implementation in clinical practice.

Although the title is *Therapeutic Hypothermia*, a substantial portion of the book deals with the adverse consequences of hyperthermia in the progression of brain injury — an effect that may be as important as the potential neuroprotective effects of cooling the brain. This influence of changing temperature extends to the period of rewarming after hypothermia and has been associated with rebound cerebral edema, elevation of intracranial pressure, and increased rates of pneumonia.

Although seemingly simple to implement, the lowering and maintenance of core temperature is complex and triggers very active thermoregulatory processes. Several chapters in this book are devoted to the basic practical management of temperature. For example, the optimal site from which to monitor brain temperature varies and appears to be related to the degree of hypothermia. Thus, the nasopharynx and tympanic membrane are the best sites during profound hypothermia, whereas standard core sites provide a reasonable approximation during modest hypothermia. The method of determining arterial blood-gas values is important, because when body temperature is reduced, the blood becomes more viscous and the solubility of the gases in the blood increases, thereby affecting the pH level. Correcting the blood gases for temperature may result in an increase in carbon dioxide with a resultant increase in cerebral blood flow, whereas if the blood gases are not corrected for temperature, this may result in the opposite effect. Changes in cerebral blood flow may exacerbate ongoing brain injury.

Some of the chapters are devoted to potential systemic complications. Notably, the lowering of body temperature interferes with the clearance rates of anesthetics and sedatives, with the potential for prolonged sedation during the recovery phase, which may interfere with the neurologic assessment of the hypothermic patient. The chapter on new methods to induce hypothermia, such as endovascular cooling, points out that these methods are potentially more advantageous than the currently used surface-cooling methods in that the desired core temperature can be achieved more rapidly and with more precision.

Several chapters discuss the clinical application of hypothermia in adults. A criticism of the book is that the two studies that have shown a benefit with the use of modest hypothermia — namely, in patients who remain comatose after out-of-hospital cardiac arrest as a consequence of ventricular fibrillation — are very briefly reviewed, and the significance of the findings may be missed by the casual reader. Conversely, it remains unclear why modest hypothermia has had a limited effect in patients with traumatic brain injury or ischemic stroke, although in both chapters the authors provide an excellent review of the complex issues that may contribute to this observation. Finally, there is the exciting possibility that hypothermia may reduce the extent of myocardial infarct size, although the most effective method of cooling the heart requires further delineation.

Mayer and Sessler are to be commended for producing an excellent textbook that should serve as both a resource for a wide variety of disciplines dedicated to neuroprotection and a spark for future research efforts.

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TRANSFUSION THERAPY: CLINICAL PRINCIPLES AND PRACTICE

Second edition. Edited by Paul D. Mintz. 716 pp. Bethesda, Md., AABB Press, 2005. $185. ISBN 1-56395-185-1.

THIS BOOK IS AN EXCELLENT GUIDE FOR any physician who transfuses blood, because it applies clinically relevant information to the decision to transfuse blood components. The book provides guidance for the clinical practice of blood-component therapy, and unlike standard blood-bank textbooks, it does not detail the scientific

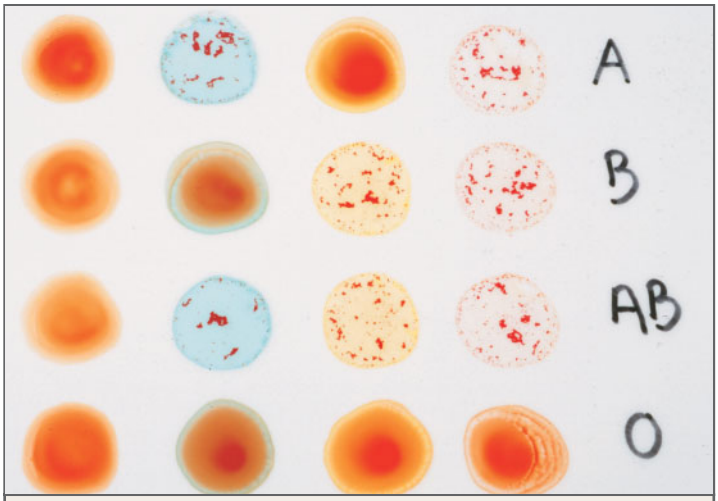
basis of blood groups and blood compatibility or the production and storage of blood components. I especially appreciated the thoughtful approaches to clinical problems by respected and talented colleagues in transfusion medicine. Their discussions gave me better ideas for taking care of patients, for helping me in my struggle to get physicians to use blood wisely, and for new approaches in teaching medical students, residents, and fellows about how interesting and important transfusion medicine can be.

The book provides very good coverage of the use of blood components for hemolytic anemia, stem-cell transplantations, trauma and critical care, organ transplantations, coagulation disorders, neonates, and children. There are additional chapters about red-cell, granulocyte, and platelet transfusions and donor-derived lymphocyte infusions. In addition to standard blood components, other products are addressed, such as immune globulins, fibrin sealants, mononuclear cells, and growth factors.

This second edition is more than 200 pages longer than the first edition, and better because of it. New chapters cover therapeutic apheresis, medical–legal issues, the administration of blood components, and the risks and benefits associated with transfusions. I am convinced that ABO-mismatched blood is erroneously given at least once every year in all medium-to-large hospitals, so I particularly welcome the new chapter on the administration of blood. This chapter provides an authoritative source for improving the bedside use of blood and reducing the risk of giving the wrong blood to the wrong patient — the leading cause of transfusion-related fatalities.

I particularly enjoyed Walter H. Dzik's chapter, in which he critically assesses laboratory testing to guide the use of plasma transfusion before the placement of a central line and before percutaneous and endoscopic organ biopsies, thoracocentesis, lumbar puncture, and angiography. This chapter, which shows why the standard plasma-transfusion dose might correct an international normalized ratio of 3 but not of 1.3, will promote better use of plasma transfusions and avoid unneeded transfusions.

The book has some minor errors and very poor black-and-white halftone reproductions of color photographs. It could have been improved by more illustrations and fewer of the very long tables such as the seven-page appendix on cancer-related anemia and erythropoietin. Despite these caveats, I encourage the use of this book by all physicians who are involved with the use of blood components.



A Test for Blood Type.

Jean Claude Revy/ISM/Phototake.

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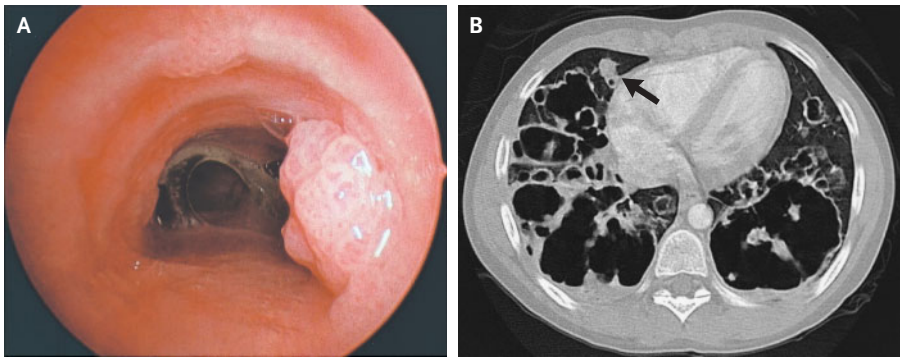
CORRECTIONS

What Ails the FDA? (March 17, 2005;352:1063-6). On page 1064, in the last paragraph in the left-hand column, line 3 should have read, "For new molecular entities (drugs whose active ingredient has never before been approved in the United States) that were given a 'priority review,'" rather than "For drugs given a 'priority review,'" as printed. In the same paragraph, lines 7 and 8 should have read, "For new molecular entities given a 'standard review,'" rather than "For drugs given a 'standard review,'" as printed. In the graph on page 1065, the first entry in the key should have read, "All new molecular entities," rather than "All new drugs," as printed. The title of the graph should have read, "Median Total Time to FDA Approval for New Molecular Entities," rather than "for New Drug Applications," as printed. The second sentence of the legend should have read, "The number at the bottom of each bar is the number of new molecular entities approved," rather than "the number of drugs reviewed," as printed. We regret the errors.

Therapy for Colorectal Cancer (April 28, 2005;352:1820-2). In the letter by Kountouras et al., lines 3 through 7 should have read, "Regional infusion of interleukin-2 or interferon gamma through the hepatic artery, combined with chemotherapy, yields better results than chemotherapy alone in patients with metastatic colorectal disease," rather than "Regional infusion of interleukin-2 or interferon alfa . . .," as printed. We regret the error.

IMAGES IN CLINICAL MEDICINE

Recurrent Respiratory Papillomatosis with Lung Involvement



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A five-year-old girl received the diagnosis of respiratory papillomatosis after an episode of respiratory distress in which the collapse of the right lung required intubation. During bronchoscopy, a single laryngeal papilloma and multiple tracheal papillomas (Panel A) were seen (up to a distance of 1.5 cm above the carina), which partially obstructed the lumen of the airway. In situ hybridization of the pathological specimen with a probe for human papillomavirus serotypes 6 and 11 confirmed that it contained the virus. The patient was treated with interferon and with periodic laser removal of the recurrent laryngotracheal papillomas. Sixteen months later, pulmonary involvement with papillomatosis was evident and was complicated by several pneumonias. Therapy with ribavirin and systemic cidofovir failed. A computed tomographic scan of the chest obtained when the patient was 10 years old showed discrete nodular papillomas (Panel B, arrow) and multiple cavitary lesions in the lung fields. She subsequently died of complications of pneumonia.