This Week in the Journal

Article Summaries

Perspective

The Stem-Cell Market — Patents and the Pursuit of Scientific Progress
F. Murray

Expanding the Black Box — Depression, Antidepressants, and the Risk of Suicide
R. A. Friedman and A. C. Leon

Focus on Research: Discovery of New Infectious Diseases — Bartonella Species
G. P. Wormser

Original Articles

Eprodisate for the Treatment of Renal Disease in AA Amyloidosis
L. M. Dember and Others

Natural History and Outcome in Systemic AA Amyloidosis
H. J. Lachmann and Others

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma
M. Terzolo and Others Brief Report: Bacteremia, Fever, and Splenomegaly Caused by a Newly Recognized Bartonella Species
M. E. Eremeeva and Others

Special Articles

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000
E. S. Ford and Others

Review Articles

Current Concepts: Local Therapy and Survival in Breast Cancer
R. S. Punglia, M. Morrow, E. P. Winer, and J. R. Harris
CLINICAL PROBLEM-SOLVING

A Hand-Carried Diagnosis — A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise
C. L. Greenstone, S. Saint, and R. H. Moseley

EDITORIALS

Advances in the Treatment of Amyloidosis
S. V. Rajkumar and M. A. Gertz

Adjuvant Mitotane Therapy of Adrenal Cancer — Use and Controversy
D. E. Schteingart

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Why Does Rheumatoid Arthritis Involve the Joints?
P. E. Lipsky

CORRESPONDENCE

Hepatitis E Vaccine

Improving the Management of Chronic Disease

Amiodarone for Atrial Fibrillation

Solicitation of Deceased and Living Organ Donors

Into the Woods

Intraaortic Vegetations and Infective Endocarditis

Acute Wiiitis

BOOK REVIEWS

Sex-Selective Abortion in India: Gender, Society, and New Reproductive Technologies
Ethics and Intersex

The Health of Sexual Minorities: Public Health Perspectives on Lesbian, Gay, Bisexual, and Transgender Populations

Law in Public Health Practice

**CORRECTIONS**

The Rise of In-Store Clinics — Threat or Opportunity?

Current Concepts: The Serotonin Syndrome

Left Ventricular Assist Devices and Drug Therapy in Heart Failure
The Stem-Cell Market — Patents and the Pursuit of Scientific Progress
Fiona Murray, Ph.D.

University of Wisconsin researcher James Thomson and his colleagues wowed the scientific community when they reported in November 1998 that they had isolated and cultured human embryonic stem cells. They also precipitated intense debate. Although moral dilemmas and federal funding of stem-cell research have received the most media attention, behind-the-scenes concern has centered on the market for stem cells — the ownership, control, pricing, and availability of stem-cell lines. For many academic researchers hoping to build on Thomson's discovery, the difficulty of obtaining stem cells was immensely frustrating.

This difficulty arose because not only did Wisconsin have material rights to the cell lines its researchers generated, but Thomson had filed U.S. patent applications on his discoveries, resulting in intellectual property rights. These latter rights, owned by the University of Wisconsin and managed by its technology-transfer office, the Wisconsin Alumni Research Foundation (WARF), encompassed both Thomson's stem cells and the core techniques used to develop them. For this reason, these rights governed research on almost all available human embryonic stem-cell lines.

These patents have now been reexamined by the U.S. Patent and Trademark Office, thanks to a challenge brought by a consumer watchdog group. The preliminary decision of the Patent Office, issued in April 2007, is that the patents should be revoked, on the grounds that Thomson's invention was not a significant advance beyond already published work. Whatever is ultimately decided, this case provides important lessons about universities' use of material and intellectual property rights to shape the future of scientific research.

Traditionally, there have been two separate markets for scientific knowledge. Knowledge generated in academia has been governed by norms facilitating full and rapid publication, disclosure, and sharing: in addition to publishing, academic scientists are generally expected to comply with requests for their materials and methods, and few restrictions are placed on colleagues after materials are shared. In return, scientists receive recognition for scientific priority and rewards for publishing their findings. In contrast, knowledge generated in the private sector has been governed by property rights protecting patents. Knowledge is disclosed in patent applications in exchange for temporary monopolies, whereby scientists prohibit...
others from using their materials while they, through commercialization, capture the value created. If private-sector scientists choose to share their materials or methods with colleagues outside their organization, they can craft a contract allowing them to reap part of any future profits.

As academic research began increasingly to produce knowledge of interest to the private sector, many universities responded — especially after the Bayh–Dole Act of 1980 streamlined the rules for academic patenting — by publishing and patenting ideas simultaneously. As originally conceived, such patents would permit academic scientists to provide the private sector with incentives to “buy” and commercialize academic discoveries without detrimental effects on the academic market. Lately, these systems have started to impinge on each other, with potentially serious consequences for scientific progress. In the 1980s, firms such as Cetus and DuPont attempted to impose stringent contractual terms on academic scientists who used the companies’ basic research tools. Universities, in turn, increasingly sought contracts from scientists at other universities who pursued research using materials their employees had produced.

Human embryonic stem cells, with their potential both for expanding our understanding of biology and for commercial use, represent a classic example of knowledge that should be accessible to both academia and industry. Although it ought to be possible to create a stem-cell market that provides both rapid, unconditional access to academic researchers and more circumscribed access to commercial scientists, along with higher prices and profit sharing, the University of Wisconsin has instead imposed terms and conditions on academic researchers that, I believe, represent an encroachment of private-sector barriers on the free exchange of scientific ideas.

As the developer of human embryonic stem cells, the university has the same rights over its materials that academic institutions have always held. Thomson and his colleagues may keep these materials proprietary or share them on any terms they wish. If their research had been funded by federal grants, they would have been subject to the National Institutes of Health guidelines promoting wide and rapid exchange of materials. Having been funded by Geron, the research was not subject to such strictures. Because they published their findings in an academic journal, Thomson and his coauthors were, however, subject to the journal’s requirements to make their materials available. The policy at Science, which published the 1998 study, precludes publication of articles that come with “unreasonable restrictions”; the journal has little recourse, however, if restrictions are imposed after publication.

In addition to material rights, the Patent Office granted WARF three extremely broad patents covering the stem cells and the methods for creating them. In the decade before these patent rights were (preliminarily) deemed invalid, they permitted WARF to prohibit any U.S. researchers, in the public or private sector, from “making, using, selling, offering to sell, or importing” what it had patented and from using its patented idea as the basis for another invention without a contractual agreement. WARF could, if it chose, control any research involving its human embryonic stem cells as well as the use of any other human embryonic stem cells made through its methods — which, with a few recent exceptions, encompassed all available cell lines.

Armed with these rights, WARF has used two forms of contracts to control the human embryonic stem-cell market: licenses governing the use of patented material or technology, which typically define the scope of use and require payment of an up-front fee plus royalties from sales of any products derived from the licensed technology, and material transfer agreements governing the transfer of tangible research materials, with negotiable arrangements regarding the scope of research use, publications, transfer to third parties, and ownership of any technology developed.

WARF signed a license agreement with Geron, giving it exclusive rights to develop therapeutic and diagnostic products from neural stem cells, cardiomyocytes, and pancreatic islet cells and nonexclusive rights to develop products and commercialize research products that are based on other cell types. Other companies could obtain only nonexclusive rights. WARF’s agreements with academic researchers included critical limitations on the purposes for which stem-cell lines could be used and on the sharing of cells with other researchers, allowing WARF to propagate its contractual conditions throughout future commercial and academic development alike.
Expanding the Black Box — Depression, Antidepressants, and the Risk of Suicide
Richard A. Friedman, M.D., and Andrew C. Leon, Ph.D.

On May 2, 2007, the Food and Drug Administration (FDA) ordered that all antidepressant medications carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults 18 to 24 years of age. Since October 2004, antidepressants have been required to have a black-box warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior in children and adolescents.

The new warning also states that there is no evidence of an increased risk for adults older than 24 years of age and that the risk is actually decreased for adults 65 years of age or older. Strikingly, the label states that “depression and other serious psychiatric disorders are themselves associated with increases in the risk of suicide,” which makes it the first black-box warning to note that a disease itself carries risk — and implies that there is risk in not using the very medication being warned about.

The new warning was developed in the wake of a December 2006 meeting of the FDA’s Psychopharmacologic Drugs Advisory Committee, which focused on the...
controversial link between antidepressants and suicide risk in adults. During an often contentious public session, the advisory committee heard from psychiatric experts and from aggrieved family members, who sometimes expressed outrage at the FDA when they spoke of the death of loved ones who had taken antidepressants. In the end, the committee voted 6 to 2 in favor of extending the black-box warning to include adults 18 to 24 years of age.

The notion that antidepressants might be associated with an increased risk of suicidality (suicidal ideation, behavior, or both) in some patients is hardly new. Clinicians have known for years that during the first few weeks of treatment with antidepressants, some patients become “activated” — energized and agitated — before their depressed mood lifts, and that combination makes them more likely to act on preexisting suicidal impulses. But because suicidal thinking, feeling, and behavior are core symptoms of depression, there is no way to know whether suicidal symptoms that develop during treatment are due to the underlying illness or the medication.

The FDA used the best available data in attempting to disentangle the effects of treatment from those of illness by comparing the rates of suicidal symptoms among patients taking antidepressants with rates among those taking placebo. The advisory committee considered the results of comprehensive meta-analyses of an enormous data set: data on 99,839 participants who had enrolled in 372 randomized clinical trials of antidepressants conducted by 12 pharmaceutical companies during the past two decades.

The primary analyses were restricted to participants in trials for psychiatric disorders. There were 8 suicide deaths: in 5 of 39,729 participants assigned to the investigational drug, 2 of 27,164 assigned to placebo, and 1 of 10,489 assigned to an active comparator. In addition, 501 participants had suicidal feelings or thoughts or nonfatal suicide attempts — 243 while receiving an investigational drug, 194 while receiving placebo, and 64 while receiving an active comparator. No increased risk of suicidal behavior or ideation was perceptible when analyses were pooled across all adult age groups. In age-stratified analyses, however, the risk for patients 18 to 24 years of age was elevated, albeit not significantly (odds ratio, 1.55; 95% confidence interval, 0.91 to 2.70).

Why, then, did the committee recommend expanding the black-box warning to include this age group? First, the threshold for threat to safety is generally lower than that for efficacy, and the data did not provide strong evidence of an absence of risk. Second, and most important, the trend across age groups toward an association between antidepressants and suicidality (see chart) was convincing, particularly when superimposed on earlier analyses of data on adolescents from randomized, controlled trials.1

These new meta-analyses had other key strengths: the data set was vastly larger than any previously assembled to study suicidality or interventions for a psychiatric disorder, and the results of independent analyses by two groups of FDA reviewers using different statistical methods were virtually identical.

Yet the data come from studies designed primarily to assess short-term efficacy, not long-term safety, which is of critical importance. In fact, the suicidal symptoms highlighted in the analyses came from adverse-event reports, not prospectively collected data obtained with the use of depression-rating scales. And adverse-event reports are subject to ascertainment bias. For instance, participants who report common side effects of antidepressant treatment, such as sexual dysfunction, would be more likely to be asked about other adverse effects and perhaps more likely to report suicidal symptoms than would subjects taking placebo. Similarly, a patient in a blinded trial who took an overdose of an antidepressant would be more likely than one who took an overdose of placebo to present at an emergency room, triggering an adverse-event report. Furthermore, younger participants might conceivably be more likely than older participants to report adverse events. And the meta-analyses ignored attrition, which might have varied with age.

But it is confounding by indication that poses the greatest difficulty for interpretation: Is suicidality caused by the disease or the treatment? The data do provide a hint. More than 20% of the data came from 43 studies of treatment for nonpsychiatric indications (e.g., obesity, smoking cessation, and insomnia) and 34 trials for nonbehavioral indications (e.g., fibromyalgia, diabetic neuropathy, and stress urinary incontinence), but these data were not included in the primary analyses. The risk per person-year of treatment was substantially lower in trials for nonpsychiatric indications, suggesting that depression played a key role in suicidality and that antidepressants do not themselves generate new suicidal symptoms.

Many other potentially useful
Analyses were not conducted, primarily because the requisite data were not among those requested by the FDA. For instance, it is generally believed that the risk of suicidality associated with treatment emerges early on, perhaps during the first 2 weeks of therapy, yet information on the timing of events was not available. Furthermore, the most persuasive feature of the data on adolescents that were presented to the advisory committee in 2005 was that only 3 of 15 randomized, controlled trials involving patients with major depression showed efficacy of antidepressants. The risk–benefit ratio in individual trials in adults was not examined in the current meta-analyses; instead, one aggregated pair of approximate response rates was presented: 50% response to active treatment and 40% to placebo. Without efficacy data, not even the most superficial risk–benefit estimate could be calculated.

The new black-box warning is clearly an attempt to balance the small risk posed by antidepressants against their well-documented benefits. But this new label has the potential to confuse both patients and physicians. After all, if depression and other psychiatric illnesses are “associated with increases in the risk of suicide,” as the warning states, and antidepressants are known to be effective treatments for such disorders, why not just state the obvious: that untreated depression and psychiatric illness carry a significant risk? Because such a statement would too closely resemble a treatment recommendation, which is outside the purview of the FDA.

Whether the new warning will do more good than harm is not clear. There are already some signs that the warning will discourage depressed patients and their families from seeking treatment and frighten physicians away from prescribing antidepressants. After the FDA mandated the first black box in October 2004, a survey found that rates of prescriptions for antidepressants for children and adolescents were 18% lower in July 2004 than they had been in July 2003. And for the first time in more than a decade, the Centers for Disease Control and Prevention reported a slight increase in the suicide rate among teenagers in 2004. It is too early to know whether this is a random fluctuation or the start of a real increase, but there are consistent ecologic data linking the decrease in the adolescent suicide rate during the past decade with the steady increase in the use of antidepressants in this population. Moreover, in a study of adolescents who had committed suicide in New York City during a 10-year period, antidepressants were very rarely detected in postmortem studies.

There may be controversy about the risk posed by antidepressants, but there is none about the risk associated with untreated depression: estimates of the lifetime risk of suicide in depressed persons range from 2.2 to 15%, depending on the population under study—not to mention the considerable suffering and functional impairment caused by this illness. In contrast, the FDA meta-analyses reveal an absolute risk of suicide in patients taking investigational antidepressants of 0.01%. Granted, this rate reflects risk during the short duration of a randomized trial, typically 4 to 12 weeks, but suicide is clearly an extremely rare treatment-emergent phenomenon.

How should physicians deal with the new black-box warning? The real killer in this story is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease. Still, clinicians need to tell their depressed patients that some people who take antidepressants have an increase in suicidal symptoms, especially early in treatment, and they need to follow their patients very closely during the first 4 to 6 weeks of treatment.
Careful microbiologic evaluation of patients with various illnesses has led to the discovery of many important pathogens in recent decades, including human immunodeficiency virus (HIV), legionella species, *Borrelia burgdorferi* (the agent of Lyme disease), human herpesvirus 8 (HHV-8), and numerous others. Success in these endeavors, however, was critically dependent on the availability of the appropriate technology for both the detection of the microorganism and its characterization to the level necessary to permit clear differentiation from already recognized pathogens. The delay between the recognition of a particular clinical syndrome and the identification of its causative agent has been highly variable. Whereas HIV, for example, was discovered within 2 to 3 years after the recognition of AIDS, it took more than 120 years to establish that HHV-8 was the cause of Kaposi’s sarcoma.

*Bartonella* are small, curved, pleomorphic, gram-negative rods. A characteristic feature of these bacteria is their adherence to and invasion of erythrocytes, although this phenomenon is dependent on the erythrocytes’ species of origin.

A unique facet of infection with *Bartonella* is the ability of these microorganisms to stimulate neovascular proliferation in tissues, presumably by causing endothelial-cell proliferation and migration. Although highly fastidious, *Bartonella* are often cultivable, and available methods for analyzing the genetic and protein compositions of the isolated microorganism permit very precise molecular characterization. Having used such an approach, Eremeeva et al. presented compelling evidence in this issue of the *Journal* (pages 2381–2387) that a new *Bartonella* species, *Bartonella rochalimae* sp. nov., should be added to the list of recognized human pathogens.

Of the 19 recognized and extant species and subspecies in the expanding *Bartonella* genus before the report by Eremeeva et al., perhaps 9 had been linked to human infections, but only 3 of them had been implicated in such infections frequently. The spectrum of clinical illness varies with the species causing the infection, but even among patients infected with the same species, the clinical features can be surprisingly variable. At times, the clinical illness caused by these microorganisms is so distinctive that *Bartonella* infection would be at or near the top of the differential diagnosis, whereas in other patients the presentation is completely nonspecific.

*B. henselae* is now regarded as the principal cause of cat scratch disease, the most frequently recognized *Bartonella* infection in humans. The cause of cat scratch disease was not conclusively elucidated until more than 40 years after its recognition as a clinical entity in 1950. The hallmark of this infection is the prominent enlargement of lymph nodes that drain lymph from cutaneous sites where *B. henselae* was introduced by the
PERSPECTIVE

endocarditis (i.e., cases in which culture-negative subacute bacterial infection are increasingly appreciated cause of those with AIDS. Both of these bartonella species are also an increasingly appreciated cause of internal organs, occurring especially (but not exclusively) in immunocompromised patients, such as compromised patients, such as those with AIDS. Both of these bartonella species are also an increasingly appreciated cause of culture-negative subacute bacterial infection (i.e., cases in which bite or scratch of a cat (the reservoir for this bartonella species) or possibly by the bite of a cat’s fleas. In the majority of cases, either a papule or pustule or residual evidence of a bite or scratch remains visible, though the skin site must be examined carefully to discern it.

*B. quintana*, transmitted by the human body louse (*Pediculus humanus*), is the cause of a relapsing febrile illness associated with prominent limb pain. The term “trench fever” was first applied to this condition in a publication describing an outbreak among British military personnel during World War I. Because of its association with human body lice, infection with this bartonella species is closely associated with homelessness in urban areas and with poor personal hygiene.

Both *B. quintana* and *B. henselae* are causes of bacillary angiomatosis, which consists of small lesions showing histologic evidence of neovascular proliferation (see photograph on page 2346). These lesions are typically found on the skin but can also involve regional lymph nodes and a variety of internal organs, occurring especially (but not exclusively) in immunocompromised patients, such as those with AIDS. Both of these bartonella species are also an increasingly appreciated cause of culture-negative subacute bacterial infection (i.e., cases in which blood cultures are negative for conventional pathogens). Both can cause febrile illnesses in patients with AIDS, but only *B. henselae* has been linked to bacillary peliosis, an unusual disorder characterized by the development of numerous blood-filled cystic structures as large as several millimeters in diameter; these infected lesions typically occur in the liver, spleen, or lymph nodes of patients with AIDS or other highly immunocompromised patients.

Infection with *B. bacilliformis*, the first member of this genus to be recognized, is strikingly focally distributed geographically, being mainly confined to altitudes of 1 to 3 km on the western slopes of the Andes in Colombia, Peru, and Ecuador, with most cases occurring in Peru. This limited distribution is attributable to the ecological requirements of the vector that transmits the infection, a particular sand fly (*Lutzomyia species*, especially *Lutzomyia verrucarum*). Symptomatic acute infection with *B. bacilliformis*, known as Oroya fever, is characterized by fever, lymphadenopathy, hepatosplenomegaly, and hemolytic anemia, the last of which is caused by adherence to and invasion of erythrocytes by the bacterium. Diagnosis is aided by microscopical examination of a blood smear from an infected patient, in which bacteria attached to or inside erythrocytes can often be readily detected (see smear above). In patients infected with *B. bacilliformis*, skin and mucosal lesions characteristic of verruga peruana (which has morphologic similarities to bacillary angiomatosis) may eventually develop (see photograph above). Oroya fever and verruga peruana were convincingly shown to be different aspects of the same infection by Daniel Carrión, a medical student who died from Oroya fever in 1885 after deliberate inoculation with blood from a verruga peruana skin lesion. Persistently infected humans are the main reservoir of *B. bacilliformis*.

The infected patient described by Eremeeva et al. had a mild illness with fever and anemia; given her travel history, she would have been given a diagnosis of Oroya fever had these investigators been less conscientious about precisely identifying the bacterium recovered from her blood. Since the only closely related microorganism that had previously been recognized was found in a flea, it is conceivable that the newly recognized infection was transmitted by a vector other than a sand fly. A flea vector could mean that this infection will be distributed somewhat differently from Oroya fever. Meticulous bedside-to-bench research like that conducted by Eremeeva et al. is vital to the discovery of new or previously unrecognized infectious diseases.
**ORIGINAL ARTICLE**

**Eprodisate for AA Amyloidosis**

Amyloid A (AA) amyloidosis, a complication of chronic inflammatory conditions, develops when proteolytic fragments of serum amyloid A protein are deposited in tissues as amyloid fibrils. This placebo-controlled trial investigated the effect of eprodisate, a small molecule that inhibits amyloid fibril polymerization and tissue deposition in patients with renal AA amyloidosis. As compared with placebo, the drug slowed a decline in renal function. Eprodisate is a member of a new class of compounds that interfere with interactions between amyloidogenic proteins and glycosaminoglycans.

SEE P. 2349; EDITORIAL, P. 2413

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**ORIGINAL ARTICLE**

**Outcome in Patients with Systemic AA Amyloidosis**

This study evaluated clinical features, organ function, and survival in a group of 374 patients with amyloid A amyloidosis. Median survival after diagnosis was 133 months; renal dysfunction was the predominant disease manifestation. Mortality, amyloid burden, and renal prognosis all significantly correlated with the serum amyloid A concentration during follow-up.

SEE P. 2361; CME, P. 2442

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**ORIGINAL ARTICLE**

**Adjuvant Mitotane for Adrenocortical Carcinoma**

This retrospective analysis assessed the efficacy of adjuvant mitotane treatment in prolonging recurrence-free survival in adrenocortical cancer, which carries a high risk of recurrence. Survival was significantly prolonged in patients receiving mitotane, as compared with those who did not. Adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.

SEE P. 2372; EDITORIAL, P. 2415

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**BRIEF REPORT**

**Bacteremia, Fever, and Splenomegaly Caused by a Newly Recognized Bartonella Species**

A 43-year-old woman returned from a trip to Peru and had fever, rash, and splenomegaly. A new bartonella species has been identified as the causative agent.

SEE P. 2381; PERSPECTIVE, P. 2346

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**SPECIAL ARTICLE**

**Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000**

Mortality due to coronary heart disease has declined substantially in the United States in recent decades. A previously validated model was used to estimate the roles of specific cardiac treatments and changes in risk factors in this decline. Approximately 47% of the decrease in mortality was attributed to therapeutic interventions and 44% to changes in risk factors.

SEE P. 2388; CME, P. 2443

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**CURRENT CONCEPTS**

**Local Therapy and Survival in Breast Cancer**

Some investigators have viewed breast cancer as a local disease that then spreads; others have seen it as a systemic disease from the start. This review argues for another view, since the failure to achieve initial local control allows some tumors to disseminate later, reducing a patient’s chance of long-term survival. Recent evidence supports a larger role for aggressive, local therapy for breast cancer.

SEE P. 2399; CME, P. 2441

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**CLINICAL PROBLEM-SOLVING**

**A Hand-Carried Diagnosis**

A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise. Her colleagues had noticed yellowing of her eyes over the past few days.

SEE P. 2407

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**CLINICAL IMPLICATIONS OF BASIC RESEARCH**

**Mediating Inflammation in Rheumatoid Arthritis**

The integrity of the synovium depends on the adhesion molecule cadherin-11. Mice that are deficient in this molecule are resistant to induced inflammatory arthritis.

SEE P. 2419
Eprodisate for the Treatment of Renal Disease in AA Amyloidosis

Laura M. Dember, M.D., Philip N. Hawkins, F.Med.Sc., Bouke P.C. Hazenberg, M.D., Peter D. Gorevic, M.D., Giampaolo Merlini, M.D., Irena Butrimiene, M.D., Avi Livneh, M.D., Olga Lesnyak, M.D., Xavier Puéchal, M.D., Ph.D., Helen J. Lachmann, M.D., Laura Obici, M.D., Robert Balshaw, Ph.D., Denis Garceau, Ph.D., Wendy Hauck, Ph.D., and Martha Skinner, M.D., for the Eprodisate for AA Amyloidosis Trial Group*

ABSTRACT

BACKGROUND
Amyloid A (AA) amyloidosis is a complication of chronic inflammatory conditions that develops when proteolytic fragments of serum amyloid A protein (SAA) are deposited in tissues as amyloid fibrils. Amyloid deposition in the kidney causes progressive deterioration in renal function. Eprodisate is a member of a new class of compounds designed to interfere with interactions between amyloidogenic proteins and glycosaminoglycans and thereby inhibit polymerization of amyloid fibrils and deposition of the fibrils in tissues.

METHODS
We performed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of eprodisate in patients with AA amyloidosis and kidney involvement. We randomly assigned 183 patients from 27 centers to receive eprodisate or placebo for 24 months. The primary composite end point was an assessment of renal function or death. Disease was classified as worsened if any one of the following occurred: doubling of the serum creatinine level, reduction in creatinine clearance by 50% or more, progression to end-stage renal disease, or death.

RESULTS
At 24 months, disease was worsened in 24 of 89 patients who received eprodisate (27%) and 38 of 94 patients given placebo (40%, P=0.06); the hazard ratio for worsening disease with eprodisate treatment was 0.58 (95% confidence interval, 0.37 to 0.93; P=0.02). The mean rates of decline in creatinine clearance were 10.9 and 15.6 ml per minute per 1.73 m² of body-surface area per year in the eprodisate and the placebo groups, respectively (P=0.02). The drug had no significant effect on progression to end-stage renal disease (hazard ratio, 0.54; P=0.20) or risk of death (hazard ratio, 0.95; P=0.94). The incidence of adverse events was similar in the two groups.

CONCLUSIONS
Eprodisate slows the decline of renal function in AA amyloidosis. (ClinicalTrials.gov number, NCT00035334.)
The amyloidoses constitute a group of diseases in which proteins are deposited extracellularly in the tissues as insoluble fibrils, causing progressive organ dysfunction and death. Amyloid A (AA) amyloidosis, also referred to as secondary amyloidosis, is a rare but serious complication of chronic inflammatory diseases and chronic infections. The amyloidogenic protein in AA amyloidosis is a proteolytic fragment of serum amyloid A protein (SAA), an acute-phase reactant produced by the liver. The kidney is the organ most frequently affected in AA amyloidosis. Ongoing deposition of amyloid in the kidney results in proteinuria and progressive loss of renal function. The gastrointestinal tract, the liver, the autonomic nervous system, and, less frequently, the heart, are other sites of AA amyloid deposition.

Treatments that reduce production of the amyloidogenic protein can improve organ function and survival in immunoglobulin-light-chain–related (AL) amyloidosis and hereditary transthyretin-associated (ATTR) amyloidosis. In AA amyloidosis, production of SAA can sometimes be decreased by treatment of the underlying inflammatory condition. In many patients, however, production of SAA cannot be sufficiently suppressed, and deposition of AA amyloid fibrils and their deposition in the tissues persist. No treatment directly targets AA amyloid formation.

Several lines of investigation suggest that glycosaminoglycans, such as heparan sulfate, are critical in the pathogenesis of amyloidosis. Interactions between amyloidogenic proteins and glycosaminoglycans promote fibril assembly and stabilize amyloid deposits in tissues. Eprodisate (Kiacta, Neurochem) is a negatively charged, sulfonated molecule of low molecular weight that has structural similarities to heparan sulfate. The compound, a member of a new class of agents that interfere with interactions between amyloidogenic proteins and glycosaminoglycans, inhibits the development of amyloid deposits in the tissues in mouse models of AA amyloidosis. To determine whether eprodisate prevents the progression of AA amyloidosis in humans, we conducted a multicenter, randomized, double-blind, placebo-controlled trial in patients with AA amyloidosis–associated nephropathy.

**Methods**

**Participants**

Patients with AA amyloidosis and kidney involvement were enrolled from 27 centers in 13 countries. The diagnosis of AA amyloidosis required histologic demonstration of Congo red staining and birefringence with the use of polarized microscopy and reactivity with anti-AA antibodies by immunohistochemical analysis, immunofluorescence, or immunoelectron microscopy. Kidney involvement was defined as 24-hour urinary excretion of more than 1 g of protein in two 24-hour urine collections obtained at least 1 week apart within 3 months before study entry, or creatinine clearance of less than 60 ml per minute according to two measurements performed at least 1 week apart within 3 months before study entry. The exclusion criteria were kidney disease other than AA amyloidosis, creatinine clearance less than 20 ml per minute, serum creatinine concentration more than 3 mg per deciliter (265 μmol per liter), diabetes mellitus, elevated liver enzymes (alanine transaminase, aspartate transaminase, or alkaline phosphatase more than 5 times the upper limit of normal), or bilirubin more than 1.5 times the upper limit of normal. The study was approved by the institutional review boards at each center. All patients provided written informed consent.

**Study Procedures**

Patients were randomly assigned in equal proportions to receive eprodisate or placebo. The placebo, provided by Neurochem, consisted of capsules that were identical in appearance to active drug. The identity of the study medication was indicated on a card inside an individual sealed envelope. Patients were stratified according to nephrotic status (nephrotic versus non-nephrotic) and treatment center. Classification as nephrotic required a 24-hour urinary excretion of more than 3 g of protein, a serum albumin concentration of less than 3.4 g per deciliter, and either the presence of peripheral edema or the use of diuretics to treat peripheral edema.

The study drug was administered orally twice daily at least 1 hour before or 2 hours after a meal. Because eprodisate is excreted by the kidney, the initial dose was based on creatinine clearance. Patients with creatinine clearance rates of less than
30 ml per minute received a total of 800 mg of eprodisate per day in two divided doses, those with rates of 30 to 80 ml per minute received a total of 1600 mg of eprodisate per day in two divided doses, and those with rates of more than 80 ml per minute received a total of 2400 mg of eprodisate per day in two divided doses. Doses were decreased during the study if creatinine clearance decreased. Treatment of the underlying inflammatory disease was determined by the patient’s physician. For those patients who were being treated with angiotensin-converting–enzyme inhibitors, cytotoxic agents, tumor necrosis factor (TNF) antagonists, or colchicine, stability of the dose was required for 3 months before enrollment.

Patients underwent randomization and the study drug was initiated at a baseline visit within 1 month after the screening evaluation. Follow-up visits occurred at 1, 4, 8, 12, 16, 20, and 24 months after randomization, and patients were contacted by telephone at 2, 6, 10, 14, 18, and 22 months after randomization. At each visit, creatinine clearance and urinary protein excretion were measured by 24-hour urine collection. Compliance with study medication was assessed by pill counts at each visit and expressed as the percentage of the number of pills prescribed that had been taken.

At baseline and at the 12- and 24-month visits, abdominal fat was collected by aspiration for Congo red staining and quantification of amyloid content by an enzyme-linked immunosorbent assay with murine monoclonal antibodies to SAA. Staining of abdominal fat and quantification of amyloid were performed in the laboratory of one of the investigators by persons who were unaware of treatment assignment.

Study medication was continued for 24 months unless the patient had progression to end-stage renal disease, had an adverse event that precluded further use of study medication, withdrew from the study, or required a rescue medication. Rescue medications included cytotoxic agents, colchicine, and anti-TNF agents initiated because of manifestations of AA amyloidosis.

SAA concentration was determined by latex nephelometry with a Dade Behring BNII autoanalyzer in the laboratory of one of the investigators. Erythrocyte sedimentation rates were measured at the study sites. All other laboratory measurements were performed at central laboratories (Covance Central Laboratory Services).

OUTCOME MEASURES
The primary end point was a composite assessment of renal function or death. Disease was classified as worsened if the serum creatinine concentration was twice the baseline value, creatinine clearance decreased by 50% or more from baseline, progression to end-stage renal disease occurred, or the patient died. End-stage renal disease was defined as the need for initiation of maintenance dialysis. Disease was classified as improved if creatinine clearance increased by at least 50% from baseline and none of the indicators of worsened disease were present. Disease was classified as stable if none of the indicators of either worsened or improved disease were present. Each patient’s disease status was determined by an end-point adjudication committee composed of a subgroup of investigators who were unaware of the patient’s treatment status.

Among the major secondary outcomes were slope of creatinine clearance, change in proteinuria, resolution or development of chronic diarrhea, and change in the amyloid content of abdominal fat. In all analyses that included creatinine clearance, the measured value was normalized for body-surface area.

STATISTICAL ANALYSIS
Two analyses of the primary composite end point were performed. The proportions of patients in the two treatment groups who had worsened, improved, or stable disease at the 24-month visit were compared by the Cochran–Mantel–Haenszel row mean-scores test, with the last observation carried forward for those who discontinued participation before 24 months. The times to first event of worsened disease in the two treatment groups were compared by Cox proportional-hazards analysis. Patients with no follow-up data after the baseline visit were classified as having worsened status. The P value for the Cox proportional-hazards analysis was calculated by the Wald chi-square test. For both the Cochran–Mantel–Haenszel test and the Cox proportional-hazards model, the patients were stratified according to baseline nephrotic status. The analyses were performed according to the intention-to-treat principle.
Additional Cox proportional-hazards analyses were performed with adjustment for potentially important baseline variables and time-dependent variables. Event-free survival was estimated with the use of the Kaplan–Meier method, and comparisons between survival curves were made with the use of the log-rank test. The slopes of creatinine clearance for the two treatment groups were compared by the Iman–Conover test. All statistical analyses were two-sided, and P values less than 0.05 were considered to indicate statistical significance.

With a sample size of 180 patients, the study had 85% power at a two-sided alpha level of 0.05 to detect an absolute difference of 20% in the proportion of patients in the treatment groups who had worsened disease. This calculation assumes a rate of worsening disease of 40% in the placebo group.

Interim safety analyses of data were performed by an independent data and safety monitoring board unaware of treatment assignment. The safety analyses were performed after 30 patients had been followed for at least 4 months and every 8 months thereafter until completion of the study. Interim analyses of efficacy were not performed.

The study was designed by a group of the investigators in collaboration with the sponsor, Neurochem. Data were collected by the study teams at each site and transmitted to the sponsor. The complete data set was maintained at Quintiles Canada. Statistical analyses and data interpretation were conducted by the investigators, by Neurochem, and by consultants from Quintiles Canada and Syreon with the use of SAS software, version 8.2. The investigators made the decision to publish the findings, were responsible for writing the article, had unrestricted access to the data, and were not limited by the sponsor with regard to statements made in the article. Drs. Dember, Balshaw, and Hauck vouch for the integrity and completeness of the data.

**RESULTS**

**PATIENTS**

Between July 11, 2001, and February 14, 2003, a total of 261 patients were screened and 183 were randomly assigned to treatment with eprodisate (89 patients) or placebo (94 patients). The final study visit occurred on December 2, 2004. A total of 124 patients (63 in the eprodisate group and 61 in the placebo group) completed 2 years of the study (Fig. 1). Approximately half the patients who discontinued participation early did so because of progression to end-stage renal disease or death.

Table 1 lists the baseline characteristics of the patients. Rheumatoid arthritis (49% of patients) and familial Mediterranean fever (19%) were the most common underlying inflammatory diseases. Underlying chronic infection was more frequent in the eprodisate group than in the placebo group, and several of the patients in the eprodisate group with chronic infection also had a chronic inflammatory disease. The median serum creatinine concentration at baseline was slightly higher in the placebo group than in the eprodisate group (1.3 mg per deciliter vs. 1.1 mg per deciliter [115 μmol per liter vs. 97 μmol per liter], P=0.05). The mean diastolic blood pressure in the supine position was slightly lower in the eprodisate group than in the placebo group (78 mm Hg vs. 82 mm Hg, P=0.01), but no significant differences between groups in either systolic or diastolic blood pressure were found at any of the follow-up visits. The mean compliance with drug administration was 95.3±8.7% in the eprodisate group and 94.6±12.8% in the placebo group. Blinding of treatment assignment was maintained for all patients for the duration of the study.

**PRIMARY COMPOSITE END POINT**

Because improvement of renal disease was so infrequent in both groups (improvement occurred in only one patient in the eprodisate group and two patients in the placebo group), patients with improved or stable disease were grouped together, as prespecified, for the analysis of disease status. At the end of follow-up, disease was worsened in 24 of 89 patients assigned to eprodisate (27%) and 38 of 94 assigned to placebo (40%, P=0.06). When the original three-category classification of patient outcomes (improved, stable, or worsened disease) was maintained, the P value for the difference between the two treatment groups was 0.08.

According to Cox proportional-hazards analysis, treatment with eprodisate was associated with a 42% reduction in the risk of worsening renal disease or death (hazard ratio, 0.58; 95% confidence interval [CI], 0.37 to 0.93%; P=0.02) (Ta-
The risk reduction with eprodisate was maintained after adjustment of the analysis for potentially important baseline variables and for SAA concentration as a time-dependent variable (Table 2). The benefit of eprodisate on the primary composite end point of renal function or death was due to its effect on the progression of renal disease (Table 2). There was no significant difference between the two groups in the risk of death.

**SECONDARY OUTCOMES**

The mean (±SE) slope of creatinine clearance was −10.9±5.1 ml per minute per 1.73 m² of body-surface area per year in the eprodisate group, as compared with −15.6±4.0 ml per minute per 1.73 m² per year in the placebo group (P=0.02). The change in the urinary protein excretion between baseline and study completion varied substantially within both treatment groups, but overall there was no significant difference in either group between the mean (±SD) baseline and final values (−0.03±3.5 g per 24 hours in the eprodisate group and −0.22±3.1 g per 24 hours in the placebo group, P=0.92). Similarly, there was no significant difference between treatment groups in the proportion of patients with chronic diarrhea at study completion (4% in the eprodisate group).
Table 1. Baseline Demographic and Clinical Characteristics of Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eprodisate (N = 89)</th>
<th>Placebo (N = 94)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (% of patients)</td>
<td>55</td>
<td>61</td>
<td>0.45</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50±14</td>
<td>52±13</td>
<td>0.40</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.1±17.6</td>
<td>64.9±13.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130±23</td>
<td>132±19</td>
<td>0.22</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78±12</td>
<td>82±11</td>
<td>0.01</td>
</tr>
<tr>
<td>Underlying disease (% of patients)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>70</td>
<td>64</td>
<td>0.40</td>
</tr>
<tr>
<td>Hereditary fever syndromes</td>
<td>17</td>
<td>22</td>
<td>0.35</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>21</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>3</td>
<td>7</td>
<td>0.22</td>
</tr>
<tr>
<td>Duration of biopsy-proven amyloidosis (mo)</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Median</td>
<td>22.4</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.2–387.0</td>
<td>0.4–230.7</td>
<td></td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>SAA§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mg/liter)</td>
<td>16.0</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range (mg/liter)</td>
<td>6.5–41.2</td>
<td>7.6–51.7</td>
<td></td>
</tr>
<tr>
<td>&lt;10 mg/liter (% of patients)</td>
<td>35</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>10–50 mg/liter (% of patients)</td>
<td>47</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>51–100 mg/liter (% of patients)</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>&gt;100 mg/liter (% of patients)</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/liter)¶</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Median</td>
<td>9.2</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3.8–22.7</td>
<td>5.1–26.5</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)‖</td>
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<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Median</td>
<td>58.5</td>
<td>77.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>37.0–96.0</td>
<td>40.0–104.0</td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl) screwed</td>
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<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.8–1.7</td>
<td>0.9–1.8</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m² of body-surface area)</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Median</td>
<td>65.9</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>39.9–101.1</td>
<td>36.8–79.7</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance &lt;60 ml/min/1.73 m² (% of patients)</td>
<td>46</td>
<td>57</td>
<td>0.11</td>
</tr>
<tr>
<td>Proteinuria (g of protein/24 hr)</td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Median</td>
<td>3.1</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.2–5.4</td>
<td>1.2–6.0</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome (% of patients)††</td>
<td>38</td>
<td>42</td>
<td>0.65</td>
</tr>
</tbody>
</table>
group vs. 1% in the placebo group, \( P=0.34 \)) or in the change in the amyloid content of abdominal fat between baseline and study completion (41±1664 ng per milligram of fat in the eprodisate group vs. −132±824 ng per milligram of fat in the placebo group, \( P=0.45 \)). SAA concentrations fluctuated substantially within both groups throughout the study but did not differ significantly between the groups at any time point.

**THE NEPHROTIC SYNDROME**

Within both treatment groups, disease worsening occurred more frequently among patients with than among those without the nephrotic syndrome, and the effect of eprodisate on the primary composite end point was more apparent among patients with the nephrotic syndrome (Fig. 2B). However, there was no significant interaction between baseline nephrotic status and treatment effect (\( P=0.23 \)).

**ADVERSE EVENTS**

The frequency and types of adverse events were similar in the two treatment groups (Table 3). Five patients in each group died during or within 15 days after completion of administration of the study drug. The causes of death in the eprodisate group were ischemic stroke in two patients, the nephrotic syndrome in one patient, gastrointestinal hemorrhage in one, and pneumonia in one. The deaths in the placebo group were due to ischemic stroke, amyloid cardiomyopathy, bowel perforation, sepsis, and pancytopenia in one patient each. None of the deaths were considered by the investigators to be related to the study drug. Two patients in the eprodisate group became pregnant. In both cases, the study medication was discontinued as soon as the pregnancy was known. Both patients elected to terminate the pregnancy.

**DISCUSSION**

We found that eprodisate reduced the progression of AA amyloidosis–associated renal disease. Eprodisate decreased the risk of the primary end point, a composite of worsening renal function or death, by 42%, and the reduction in risk was largely independent of baseline renal function or
SAA concentration throughout the study. As compared with placebo, eprodisate significantly reduced the risk of a doubling of serum creatinine, the risk of a 50% reduction in creatinine clearance, and the slope of decline in creatinine clearance. These benefits are clinically meaningful and were evident early in the course of treatment. The adverse-event profiles of the drug and the placebo were not significantly different.

The risk reductions associated with eprodisate for the dichotomous renal end points (doubling of serum creatinine or a 50% or greater decrease in creatinine clearance) are substantial, as is the effect of the drug on the slope of creatinine clearance. The decline in creatinine clearance was 4.7 ml per minute per 1.73 m² per year greater in the placebo group than in the eprodisate group, a relative difference of 30%. The effect of the drug on progression to end-stage renal disease was not significant (hazard ratio, 0.54; P=0.20). Many of the patients had substantial renal impairment at baseline. Creatinine clearance was less than 60 ml per minute for more than half the patients and between 20 ml per minute and 30 ml per minute for 13% of the patients. It is possible that the drug would have a greater benefit if initiated at earlier stages of disease.

Although eprodisate decreased the rate of deterioration in renal function, it did not affect proteinuria. In AA amyloidosis, proteinuria probably results from damage caused by the amyloid deposits as well as from glomerular toxicity of the SAA oligomers or protofibrils, which are the precursors to mature fibrils. Rapid resolution of proteinuria has been reported in AA amyloidosis when the underlying inflammatory disease is in remission and SAA concentrations have returned to normal, despite the persistence of glomerular amyloid deposits.19,20 According to its putative mechanism of action, eprodisate should prevent new amyloid formation but have no effect on the concentration of SAA and might not reduce the formation of SAA oligomers or protofibrils. The benefit of the drug for renal deterioration may result from a reduction in the rate of amyloid formation, whereas the persistence of fibril precursors may explain its lack of effect on proteinuria. The benefit of eprodisate was more appar-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates of adjusted models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.58 (0.37–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Underlying disease†</td>
<td>0.56 (0.35–0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline serum creatinine concentration</td>
<td>0.61 (0.38–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline creatinine clearance</td>
<td>0.57 (0.37–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline urinary protein excretion</td>
<td>0.56 (0.35–0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline use of ACE inhibitor or ARB</td>
<td>0.60 (0.37–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline blood pressure‡</td>
<td>0.57 (0.36–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline SAA concentration</td>
<td>0.61 (0.38–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>SAA concentration throughout study</td>
<td>0.59 (0.37–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Components of primary composite outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of serum creatinine concentration</td>
<td>0.41 (0.19–0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥50% Reduction in creatinine clearance</td>
<td>0.48 (0.28–0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0.54 (0.22–1.37)</td>
<td>0.20</td>
</tr>
<tr>
<td>Death</td>
<td>0.95 (0.27–3.29)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* All models were adjusted for the stratification variable of nephrotic status. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, and SAA serum amyloid A protein.
† Underlying disease was categorized as rheumatoid arthritis, familial Mediterranean fever, or other.
‡ Mean arterial blood pressure values were calculated from systolic and diastolic blood pressure measurements.
ent in the subgroup of patients with the nephrotic syndrome. High-grade proteinuria is probably an indicator of activity of the underlying inflammatory disease and identifies patients at greatest risk for progression of amyloid-associated organ dysfunction.

As expected, treatment with eprodisate did not affect SAA levels. Eprodisate had no detectable effect on the amyloid content of abdominal fat, a finding consistent with the observation that the amyloid content of abdominal fat persists or decreases very slowly after 2 or more years in patients with AL or ATTR amyloidosis after interventions that eliminate new amyloid production (Skinner M et al. and Hazenberg B et al.: unpublished data).

Our trial has some limitations. Although the study was randomized, serum creatinine concentrations were slightly higher in the placebo group than in the eprodisate group. A difference in baseline renal function could explain the better outcomes in the eprodisate group, but the risk reduction associated with eprodisate persisted when the analyses were adjusted for baseline creatinine concentration or creatinine clearance. In addition, treatments for the underlying inflammatory diseases were not standardized. However, the treating physicians were unaware of treatment assignment, inflammatory markers did not differ between groups throughout the duration of the study, and the effect of eprodisate on the primary outcome was maintained after time-dependent adjustment for SAA levels. Thus, it is unlikely that differences in the status of the underlying inflammatory disease were responsible for the observed benefit of the drug. The numbers of adverse events in the eprodisate and placebo groups were similar, but additional experience will be needed to further evaluate the safety of the drug.

**Figure 2. Kaplan–Meier Estimates of Event-free Survival.**

Panel A shows survival for all patients. Survival for patients with (Panel B) and for those without (Panel C) the nephrotic syndrome are also shown. An event is any component of the composite end point of worsened disease. The number of patients at risk for the end point drops markedly between 20 and 24 months because many patients completed their final study visit just before 24 months. Only patients who completed their final study visit at 24 months or later are included in the at-risk population at 24 months.
Table 3. Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Eprodisate (N = 89)</th>
<th>Placebo (N = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse event</td>
<td>87 (98)</td>
<td>87 (93)</td>
</tr>
<tr>
<td>Most common nonserious adverse events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>37 (42)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 (38)</td>
<td>26 (28)</td>
</tr>
<tr>
<td>Upper respiratory symptoms</td>
<td>29 (33)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (29)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>24 (27)</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Abdominal pain or dyspepsia</td>
<td>23 (26)</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Cough or bronchitis</td>
<td>23 (26)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Edema</td>
<td>16 (18)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (11)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (10)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (10)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Tachycardia, palpitations, or atrial fibrillation</td>
<td>8 (9)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Toothache</td>
<td>8 (9)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (8)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6 (7)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (7)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Patients with at least one serious adverse event‡</td>
<td>32 (36)</td>
<td>39 (42)</td>
</tr>
<tr>
<td>Most common serious adverse events§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (2)</td>
<td>1 (1)</td>
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<tr>
<td>Gastrointestinal hemorrhage</td>
<td>0</td>
<td>2 (2)</td>
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<tr>
<td>Pneumonia</td>
<td>3 (3)</td>
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<td>Gastroenteritis</td>
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<td>Infection</td>
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<td>Hyperkalemia</td>
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<tr>
<td>Renal impairment</td>
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<td>Nephrotic syndrome</td>
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<tr>
<td>Dyspnea</td>
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<td>2 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (6)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

* P > 0.05 for all comparisons between treatment groups.
† The most common nonserious adverse events are defined as those experienced by at least 5% of the patients in the eprodisate group.
‡ A serious adverse event is defined as any event that was fatal, life-threatening, or disabling; resulted in hospitalization or prolongation of a hospitalization; was associated with a congenital abnormality or cancer; or was regarded by the investigator as serious.
§ The most common serious adverse events are defined as those experienced by at least 2% of all patients or by at least two patients in either group.
The trial has several strengths. The sample size of 183 patients is substantial for this rare disease. The patients were heterogeneous with respect to underlying disease, race or ethnic group, and duration of disease, making it likely that we can generalize the findings to patients with AA amyloidosis due to a variety of inflammatory conditions. Compliance in the study was high, and the end points were rigorous and clinically meaningful.

In conclusion, eprodisate delays the progression of AA amyloidosis–associated renal disease. The drug directly targets formation of AA amyloid rather than the underlying inflammatory condition and is a member of a new class of compounds designed to interfere with amyloid–glycosaminoglycan interactions. This treatment approach has potential applicability to other types of amyloidosis, including AL amyloidosis, familial amyloidosis, and Alzheimer's disease.15,21

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APPENDIX

The composition of the EFAAT Group committees is as follows: Protocol Steering Committee — L.M. Dember, P.N. Hawkins, B.P.C. Hazenberg, M. Skinner; Data and Safety Monitoring Committee — A. Bhargava, A. Faragasso, K. Levy; End-Points Adjudication Committee — L.M. Dember, B.P.C. Hazenberg, P.N. Hawkins, M. Skinner; Investigateurs: Finland — K. Kaarla, Rheumatism Foundation Hospital, Helsinki; France — G. Graudet, Hôpital Ténon, Paris; E. Hachulla, Hôpital Claude Huriez, Lille; X. Puéchal, Centre Hospitalier du Mans, Le Mans; Israel — A. Lifshitz, Sheba Medical Center, Tel-Hashomer; I. Rosner, Bnai Zion Medical Center, Technion Faculty of Medicine, Haifa; Italy — G. Merlini, L. Obici, Amyloidosis Center, Foundation IRCCS Policlinico San Matteo, Pavia; Lithuania — I. Butrimiene, G. Kirdaite, D. Pavilienaita, A. Venalis, Vilnius University Institute of Experimental and Clinical Medicine, Vilnius; the Netherlands — J. Bijzet, B.P.C. Hazenberg, University Medical Center Groningen, University of Groningen, Groningen; Poland — A. Filipowicz-Sosnowska, Institute of Rheumatology, Warsaw; P. Wiland, A. Chlebicki, Medical University, Wroclaw; Russia — O. Lesnyak, N. Kisoyakova, A. Sibiryakova, Regional Hospital No. 1, Yekaterinburg; E.L. Nasonov, M. Stanislav, Russian Academy of Medical Sciences Institute of Rheumatology, Moscow; Spain — J.A. Jover, Hospital Clinico Universidad San Carlos, Madrid; J. Muñoz Gómez, Hospital Clinic, Barcelona; X. Tena Marsá, Hospital Universitari Germans Trias i Pujol, Badalona; J. Valverde Garcia, Hospital Universitari de Bellvitge, Barcelona; Tunisia — H. Ben Maia, F. Ben Moussa, R. Gougha, H. Kaaroud, Hôpital Charles Nicolle, Tunis; Turkey — H. Direskeneli, M. Temel, Marmara University Faculty of Medicine, Istanbul; A. Gul, S. Kamali, University of Istanbul (Capa), Istanbul; G. Hatemi, H. Ozdogan, University of Istanbul, Cerrahpasa Faculty of Medicine, Istanbul; United Kingdom — P.N. Hawkins, H.J. Lachmann, National Amyloidosis Center, Royal Free Hospital, London; J.A. Hunter, Garntavel General Hospital, Glasgow; United States — L.M. Dember, M. Skinner, Boston University School of Medicine, Boston; M.D. Benson, Indiana University School of Medicine, Indianapolis; A. Dispenzieri, Mayo Clinic, Rochester, MN; P.D. Gorevic, Mt. Sinai Medical Center, New York.

REFERENCES

EPRODISATE FOR AA AMYLOIDOSIS


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Natural History and Outcome in Systemic AA Amyloidosis


From the National Amyloidosis Centre and Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine (H.J.L., H.J.B.G., J.A.G., J.R.G., J.D.G., P.N.H.), and the Department of Primary Care and Population Sciences (C.A.S.), Royal Free and University College Medical School, London.


ABSTRACT

BACKGROUND
Deposition of amyloid fibrils derived from circulating acute-phase reactant serum amyloid A protein (SAA) causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders. Little is known about the natural history of AA amyloidosis or its response to treatment.

METHODS
We evaluated clinical features, organ function, and survival among 374 patients with AA amyloidosis who were followed for a median of 86 months. The SAA concentration was measured serially, and the amyloid burden was estimated with the use of whole-body serum amyloid P component scintigraphy. Therapy for inflammatory diseases was administered to suppress the production of SAA.

RESULTS
Median survival after diagnosis was 133 months; renal dysfunction was the predominant disease manifestation. Mortality, amyloid burden, and renal prognosis all significantly correlated with the SAA concentration during follow-up. The risk of death was 17.7 times as high among patients with SAA concentrations in the highest eighth, or octile, (≥155 mg per liter) as among those with concentrations in the lowest octile (<4 mg per liter); and the risk of death was four times as high in the next-to-lowest octile (4 to 9 mg per liter). The median SAA concentration during follow-up was 6 mg per liter in patients in whom renal function improved and 28 mg per liter in those in whom it deteriorated (P<0.001). Amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 mg per liter, and survival among these patients was superior to survival among those in whom amyloid deposits did not regress (P=0.04).

CONCLUSIONS
The effects of renal dysfunction dominate the course of AA amyloidosis, which is associated with a relatively favorable outcome in patients with SAA concentrations that remain in the low-normal range (<4 mg per liter).
R eactive systemic AA amyloidosis can complicate chronic inflammatory disorders that are associated with a sustained acute-phase response. AA amyloid fibrils are derived from the acute-phase reactant serum amyloid A protein (SAA) protein through a process of cleavage, misfolding, and aggregation into a highly ordered abnormal β-sheet conformation. Amyloid fibrils associate with other moieties, including glycosaminoglycans and serum amyloid P component (SAP), forming deposits that disrupt the structure and function of tissues and organs. SAA is an apolipoprotein constituent of high-density lipoprotein that is synthesized by hepatocytes under the transcriptional regulation of proinflammatory cytokines. The median plasma concentration of SAA in healthy persons is 3 mg per liter, but the concentration can increase to more than 2000 mg per liter during the acute-phase response. Sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis, although for reasons that are not known, amyloidosis occurs only in a small proportion of patients with chronic inflammatory disorders.

Few systematic clinical studies of AA amyloidosis have been reported, and recent data on its clinical features, natural history, and long-term outcome are scanty. We report the clinical features and course in 374 patients with AA amyloidosis who were followed at a single national center during a period of 15 years. In addition to conventional clinical follow-up assessment, the amyloid burden was estimated annually with the use of SAP scintigraphy, and the plasma concentration of the AA amyloid precursor protein was monitored by monthly measurement of SAA.

Methods

Patients

We included in this study all 374 patients with systemic AA amyloidosis who were referred to the U.K. National Amyloidosis Centre during a period of 15 years, to August 2005. The diagnosis of AA amyloidosis was confirmed in 320 patients by immunohistochemical testing and in 54 patients by noninvasive means. Inclusion criteria were amyloid deposition on SAP scintigraphy; evidence of an overt chronic inflammatory disease, no mutations in the genes encoding transthyretin, the fibrinogen A α-chain, apolipoprotein A-I, apolipoprotein A-II, and lysozyme (to rule out hereditary forms of amyloidosis); negative serum free light-chain assay; negative monoclonal immunoglobulin screening, including the use of serum and urine immunofixation (to rule out monoclonal light-chain [AL] amyloidosis); and the absence of neuropathy and of cardiac amyloidosis, both of which are uncommon in the AA type of amyloidosis. A biopsy was performed if any of these criteria were not met. The study was approved by the ethics committee of the Royal Free Hospital, and all patients provided written informed consent.

Congo Red Staining and Immunohistochemical Testing

The Congo red method was used to detect amyloid in tissue sections. Amyloid was identified as the AA type on immunohistochemical testing with the use of monoclonal antibodies specific to SAA (Euro-Diagnostica).

Clinical Assessment

Patients underwent an initial clinical assessment and annual review at our center. Blood samples were scheduled to be obtained monthly to determine the SAA concentration, and a mean of 10.6 samples per patient per year were obtained. Quantitative estimation of the distribution and extent of visceral amyloid deposits was performed with the use of whole-body 123I-labeled SAP scintigraphy. Blinded assessments of amyloid deposits were performed at baseline and annually by an investigator with expertise in the interpretation of SAP scans. The whole-body amyloid burden was classified as 0 when there was no abnormal localization of the tracer; as small when uptake in one or more organs was discernible but the intensity of the blood-pool background signal remained normal; as moderate when abnormal uptake in one or more organs was sufficiently intense for the blood-pool background signal to be partially lost when the gray scale was normalized to encompass the target-organ signal; and as large when the blood-pool background was lost with adjustment of the gray scale to encompass the target-organ uptake.

Regression of amyloid was defined as a reduction in tracer uptake in affected organs or an increase in the blood-pool background signal, or both; an accumulation of amyloid was defined as an increase in tracer uptake in affected organs, an abnormal tracer uptake in a previously unaffected organ, or a decrease in the blood-pool background signal; and a stable amyloid burden was defined as unchanged tracer localization. Clinically important organ involvement and changes in or-
gan function were defined according to international consensus criteria.17 Deteriorating kidney function was categorized as either the onset of end-stage renal failure, defined by a requirement for long-term dialysis, or as an increase of 25% or more in the serum creatinine concentration or a decrease of 25% or more in creatinine clearance measured by 24-hour urine collection. In patients in whom the serum creatinine concentration or creatinine clearance did not deteriorate by 25% or more, renal function was deemed to have deteriorated if urinary protein excretion had increased by 50% or more and by more than 1 g per day (24 hours). Renal function was categorized as improved if the serum creatinine concentration or creatinine clearance improved by 25% or more, or if these values did not worsen if 24-hour urinary protein excretion decreased by more than 50% and by more than 0.5 g. Patients whose condition met none of these criteria were classified as having stable kidney function. SAA was assayed with the use of latex-enhanced immunonephelometry (BN II analyzer, Dade Behring) with the use of the World Health Organization’s International Reference Standard.5,18,19

**TREATMENT**

Treatment was undertaken with the objective of suppressing underlying inflammatory disease (Table 1) and reducing the SAA concentration as

### Table 1. Underlying Disorders and Treatment in 374 Patients with AA Amyloidosis.*

<table>
<thead>
<tr>
<th>Underlying Disorder</th>
<th>No. of Patients (%)</th>
<th>Examples of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammatory arthritis</td>
<td>224 (60)</td>
<td>Immunosuppressive agents: chlorambucil (Leukeran, GlaxoSmithKline) or cyclophosphamide (Cytoxan, Bristol-Myers Squibb); methotrexate (Rheumatrex, Wyeth–Ayerst). Biologic agents: anti-TNF therapies and interleukin-1–receptor antagonists</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>123 (33)</td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>64 (17)</td>
<td></td>
</tr>
<tr>
<td>Other chronic inflammatory arthritides</td>
<td>37 (10)</td>
<td></td>
</tr>
<tr>
<td>Chronic sepsis</td>
<td>56 (15)</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>20 (5)</td>
<td>Surgery, physiotherapy, and antibiotics</td>
</tr>
<tr>
<td>Injection-drug abuse</td>
<td>13 (4)</td>
<td>Drug rehabilitation programs and antibiotics</td>
</tr>
<tr>
<td>Complications of paraplegia (infected pressure sores, urinary infection)</td>
<td>8 (2)</td>
<td>Physiotherapy, treatment of pressure ulcers, procedures for urinary drainage, and antibiotics</td>
</tr>
<tr>
<td>Other</td>
<td>7 (2)</td>
<td>Surgery and antibiotics</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>5 (1)</td>
<td>Surgery and antibiotics</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3 (1)</td>
<td>Antituberculous therapy</td>
</tr>
<tr>
<td>Periodic fever syndromes</td>
<td>32 (9)</td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>20 (5)</td>
<td>Colchicine</td>
</tr>
<tr>
<td>TNF-receptor–associated periodic fever syndrome</td>
<td>6 (2)</td>
<td>Anti-TNF therapy</td>
</tr>
<tr>
<td>Muckle–Wells syndrome</td>
<td>4 (1)</td>
<td>Interleukin-1–receptor antagonist</td>
</tr>
<tr>
<td>Hyper-IgD and periodic fever syndrome</td>
<td>2 (&lt;1)</td>
<td>Anti-TNF therapies and interleukin-1–receptor antagonist</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>17 (5)</td>
<td>Anti-TNF therapies, surgical resection, immunosuppressive agents</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>22 (6)</td>
<td></td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>7 (2)</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Neoplasia (lymphoma, mesothelioma)</td>
<td>4 (1)</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4 (1)</td>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Other</td>
<td>7 (&lt;2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (6)</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages may not sum to 100 because of rounding. A patient may have had more than one underlying disease. TNF denotes tumor necrosis factor.
much as possible. Patients also received supportive care, including, when required, renal-replacement therapy.

**STATISTICAL ANALYSIS**

Survival and time from the diagnosis of amyloidosis to end-stage renal failure (dependence on dialysis) were estimated in Kaplan–Meier analyses. Changes in renal function were analyzed in the subgroup of 257 patients who had a creatinine clearance greater than 20 ml per minute (0.3 ml per second) at baseline — that is, those in whom progression to end-stage renal failure was not deemed to be inevitable. Relationships of a variety of factors with survival and with the development of end-stage renal failure were examined with the use of Cox regression analysis. Potential covariates were categorized as factors that were fixed at the baseline assessment (age, sex, race or ethnic group, calendar year when amyloidosis was diagnosed, initial amyloid burden and renal function, evidence of hepatic amyloid, underlying disease, and duration of inflammatory disease before diagnosis) or as factors that could vary between annual follow-up assessments. Race or ethnic group was self-reported. Factors that could vary (changes in amyloid burden, serum albumin concentration, median SAA concentration, creatinine clearance, proteinuria, and the development of end-stage renal failure) were incorporated into the Cox model as time-dependent covariates.

The data set that was extracted consisted of yearly summaries (medians) of SAA values for each patient (e.g., the median SAA value for year 1 was calculated as the median value of all the measurements obtained during the first year of follow-up), and these values were updated in the Cox model at yearly intervals. Changes in the amyloid burden were assessed annually and updated in the model at each annual follow-up assessment, along with renal-function status and serum albumin concentration; end-stage renal failure was incorporated in the model as a binary variable with a value of 0 before the onset of end-stage renal failure and of 1 thereafter. Continuous measurements were categorized into octiles, and unadjusted relative risks were examined to assess whether it was appropriate to simplify the models by including each measurement in the model as a continuous covariate (possibly after log transformation). Variables that were significant in the univariate models (P<0.01) were analyzed in a multivariate regression model with the use of a backward-selection procedure and SAS software, version 9.1.

**RESULTS**

**BASELINE CHARACTERISTICS**

Baseline characteristics of the 374 patients are listed in Table 2. The most frequent underlying disorder was inflammatory arthritis (Table 1). Rare causes of AA amyloidosis included vasculitis, sickle cell anemia, malignant disease, epidermolysis bullosa, and cyclic neutropenia. For 23 patients, the precise nature of the inflammatory disorder could not be established, despite extensive investigation. The median duration of symptomatic inflammatory disease before the diagnosis of amyloidosis was 17 years, and there were no significant differences in latency among the various underlying disorders.

The predominant feature of amyloidosis at diagnosis was renal dysfunction; in 97% of patients, more than 500 mg of protein per day was excreted or the serum creatinine concentration was more than 1.5 mg per deciliter (133 μmol per liter), or both; at diagnosis, 43 patients (11%) had end-stage renal failure. Median protein excretion among the 333 patients not requiring dialysis was 3.9 g per day (interquartile range, 1.9 to 6.3); of these patients, 12% had urinary protein excretion of more than 10 g per day, and 2% had urinary protein excretion of more than 20 g per day; the serum albumin concentration was less than 3.5 g per deciliter in 184 patients (55%). Among those not requiring dialysis, the median serum creatinine concentration at baseline was 1.2 mg per deciliter (interquartile range, 0.8 to 2.4) (106 μmol per liter [interquartile range, 71 to 212]); the serum creatinine concentration was less than 3.0 mg per deciliter (265 μmol per liter) at diagnosis in 75% of patients.

Hepatomegaly was present on examination at baseline in 35 patients (9%), but hepatic amyloid deposits were evident on SAP scintigraphy in 85 patients (23%). Serum alkaline phosphatase concentrations greater than 1.5 times the upper limit of the normal range (which varies according to age, sex, and method of analysis), a value that is widely regarded as suggesting liver involvement in amyloidosis, were present in 21 patients with hepatic amyloidosis but also in 25 patients who had normal liver signal on SAP scintigraphy. The median SAA concentration in these patients was...
Table 2. Characteristics of Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 374)</th>
<th>Patients with Creatinine Clearance &gt;20 ml/min (N = 257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>210 (56)</td>
<td>140 (54)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>307 (82)</td>
<td>214 (83)</td>
</tr>
<tr>
<td>South Asian</td>
<td>27 (7)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>40 (11)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Age at diagnosis — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Range</td>
<td>9–87</td>
<td>9–78</td>
</tr>
<tr>
<td>Duration of inflammatory disease at diagnosis — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Range</td>
<td>0–68</td>
<td>2–68</td>
</tr>
<tr>
<td>Amyloid load on SAP scintigraphy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>96 (26)</td>
<td>71 (28)</td>
</tr>
<tr>
<td>Moderate</td>
<td>213 (57)</td>
<td>144 (56)</td>
</tr>
<tr>
<td>Large</td>
<td>63 (17)</td>
<td>42 (16)</td>
</tr>
<tr>
<td>Hepatic amyloid deposits at baseline — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present at baseline</td>
<td>41 (11)</td>
<td>NA</td>
</tr>
<tr>
<td>Developed during follow-up</td>
<td>110 (33)</td>
<td>59 (23)</td>
</tr>
<tr>
<td>Death during follow-up</td>
<td>163 (44)</td>
<td>101 (39)</td>
</tr>
<tr>
<td>Baseline laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAA — mg/liter</td>
<td>28</td>
<td>26.5</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.7–1610</td>
<td>0.7–1610</td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.7–206</td>
<td>0.7–187</td>
</tr>
<tr>
<td>Serum creatinine — mg/dl</td>
<td>1.78</td>
<td>1.12</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.37–13.9</td>
<td>0.37–3.32</td>
</tr>
<tr>
<td>Creatinine clearance — ml/min</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–186</td>
<td>20–186</td>
</tr>
<tr>
<td>Proteinuria — g of protein/day</td>
<td>3.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–26.0</td>
<td>0–21</td>
</tr>
<tr>
<td>Albumin — g/dl</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.8–4.9</td>
<td>0.8–4.9</td>
</tr>
</tbody>
</table>

* To convert the values for creatinine to millimoles per liter, multiply by 88.4. To convert the values for creatinine clearance to milliliters per second, multiply by 0.01667. SAP denotes serum amyloid P component, and NA not applicable.  
† Race or ethnic group was self-reported.
Figure 1. Changes in Amyloid Burden from Baseline to Most Recent Follow-up in 221 Patients and Changes in Amyloid Burden and Renal Function during Follow-up in 178 Patients with a Baseline Creatinine Clearance of More Than 20 ml per Minute.

Patients for whom at least one follow-up assessment was available were included in the analysis. In Panel A, the median SAA value is indicated (P<0.001, by the Kruskal–Wallis test). In Panel B, the median SAA value during follow-up was 6 mg per liter in the 54 patients whose renal function improved, 28 mg per liter in the 86 patients whose renal function worsened (P<0.001, by the Kruskal–Wallis test). Within each category of change in renal function, median values of SAA differed significantly among patients in whom the amyloid burden had regressed, those in whom it remained stable, and those in whom it progressed. For patients whose renal function improved, median SAA concentrations were compared with the use of the Mann–Whitney test; for those whose renal function remained stable or worsened, significance was calculated with the the Kruskal–Wallis test. The change in the amyloid burden was measured with the use of 123I-labeled SAP scintigraphy. The dots represent the median SAA values for each patient, and the lines represent the median values in each group.

51 mg per liter, a finding that is consistent with increased production of alkaline phosphatase as an acute-phase reactant. No patient had jaundice, elevated serum aminotransferase concentrations, or hepatic synthetic dysfunction.

Cardiac failure attributable to amyloidosis was present in only 1 patient, and findings consistent with cardiac infiltration were present in only 2 of 224 patients who underwent echocardiography. No patient had symptomatic autonomic neuropathy, and although adrenal amyloid deposits were evident on SAP scintigraphy in 41% of the patients, only five required long-term adrenocorticoid replacement therapy.

SAP scintigraphy was diagnostic of amyloidosis at baseline in all but four patients, each of whom...
had nonfunctioning atrophic kidneys and had undergone splenectomy. In 370 patients (99%), the scans showed striking splenic amyloid deposits, and in 331 patients (89%), the scans also showed renal or adrenal deposits, or both.

**CLINICAL COURSE AND OUTCOME**

The cohort was followed for a median of 86 months (range, 2 to 447) after diagnosis, representing 2673 person-years. Forty-seven patients (13%) were lost to follow-up, and data for them were censored as of the date of the last contact. A total of 221 patients underwent serial SAP scintigraphy; in 27 (12%) the amyloid burden increased, in 107 (48%) it was unchanged, and in 87 (39%) there was evidence of regression from baseline to the most recent follow-up assessment (Fig. 1 and 2). SAA values were significantly lower in patients in whom amyloid deposits regressed (median, 7 mg per liter) than in those in whom the amyloid burden increased (median, 54 mg per liter) (P<0.001).

A total of 163 patients (44%) died, and the median survival from diagnosis was 133 months (95% confidence interval [CI], 100 to 153) in the Kaplan–Meier analysis. The median SAA concentration during each year of follow-up was strongly associated with survival (Table 3); the relative risk of death among patients with an SAA concentration of less than 4 mg per liter (the lowest octile) was almost 18 times lower than among patients with an SAA concentration of 155 mg per liter or greater (the highest octile). Even among those in the second-lowest octile, the very modest elevation in the SAA concentration of 4 to 9 mg per liter, which is widely cited as within the normal reference range, was associated with a risk of death that was increased by a factor of 4, as compared with those with SAA concentrations in the lowest octile.

Other factors associated with increased mortality were older age (relative risk of death, 1.53 for each additional decade of age [95% CI, 1.34 to 1.74]; P<0.001) and end-stage renal failure (relative risk, 2.97 [95% CI, 2.10 to 4.21]; P<0.001) (Table 4). In contrast, underlying periodic fever syndromes and evidence of regression of amyloid on serial SAP scintigraphy were both associated with reduced mortality (relative risk of death, 0.36 [95% CI, 0.14 to 0.88; P=0.03] and 0.13 [95% CI, 0.02 to 0.94; P=0.04], respectively) (Table 4).

Among the 257 patients who had a creatinine clearance greater than 20 ml per minute at baseline, 59 (23%) had progression to end-stage renal failure; the estimated median time to end-stage renal failure from diagnosis was 256 months in the Kaplan–Meier analysis. The relative risk of end-stage renal failure was 1.24 (95% CI, 1.08 to 1.43; P=0.002) for each doubling of the SAA concentration. Among 178 patients for whom at least one

**Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.**

<table>
<thead>
<tr>
<th>SAA Octile (mg/liter)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥4 to &lt;9</td>
<td>3.9 (1.5–10.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥9 to &lt;16.7</td>
<td>5.1 (2.7–9.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥16.7 to &lt;28</td>
<td>7.0 (3.7–13.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥28 to &lt;45.6</td>
<td>9.1 (4.8–17.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>≥45.6 to &lt;87</td>
<td>12.1 (6.9–21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥87 to &lt;155</td>
<td>17.0 (8.6–33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥155</td>
<td>17.7 (8.7–36.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.*
### Table 4. Factors Significantly Associated with the Risk of Death or Progression to End-Stage Renal Failure (Cox Regression Models).*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted Relative Risk (95% CI)†</th>
<th>P Value</th>
<th>Adjusted Relative Risk (95% CI)‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated with death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Factors at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per additional decade of age)</td>
<td>1.62 (1.45–1.81)</td>
<td>&lt;0.001</td>
<td>1.53 (1.34–1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race</td>
<td>2.03 (1.18–3.52)</td>
<td>0.01</td>
<td></td>
<td></td>
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<tr>
<td><strong>Underlying disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>0.23 (0.14–0.38)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Periodic fever syndromes</td>
<td>0.21 (0.09–0.49)</td>
<td>&lt;0.001</td>
<td>0.36 (0.14–0.88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>0.31 (0.11–0.85)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined disease</td>
<td>0.27 (0.10–0.73)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amyloid burden on SAP scintigraphy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.55 (1.04–2.33)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>1.99 (1.22–3.25)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of inflammatory disease (per 5-yr interval)</strong></td>
<td>1.09 (1.02–1.17)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factors that could change during follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (≥0.5 g/dl)</td>
<td>0.78 (0.72–0.86)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAA (by a factor ≥2)</td>
<td>1.39 (1.28–1.51)</td>
<td>&lt;0.001</td>
<td>1.27 (1.16–1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (by a factor ≥2)</td>
<td>1.44 (1.26–1.64)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (≥5 ml/min)</td>
<td>0.95 (0.93–0.97)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>2.85 (2.10–3.89)</td>
<td>&lt;0.001</td>
<td>2.97 (2.10–4.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Change in amyloid deposits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressed</td>
<td>1.41 (0.91–2.18)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressed</td>
<td>0.15 (0.08–0.32)</td>
<td>&lt;0.001</td>
<td>0.13 (0.02–0.94)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Assessment during follow-up was available, renal function improved in 54 patients and deteriorated in 86 patients, and improvement was associated with median SAA values of 6 mg per liter and 28 mg per liter, respectively (P<0.001 by the Kruskal–Wallis test) (Fig. 1). Among the 92 patients in whom values for creatinine clearance remained stable or improved, the nephrotic syndrome abated in 33 patients after a median of 29 months, as defined by the disappearance of edema, a decrease in urinary protein excretion to less than 3 g per day, and an increase in the serum albumin concentration to 3.5 g per deciliter or more.

Cox regression analyses (Table 4) indicated that the relative risk of progression to end-stage renal failure was four times as high among patients who had underlying Crohn’s disease or chronic sepsis as among those who did not (P=0.01 and P=0.006, respectively) and two times as high among patients who had hepatic amyloid deposits at baseline as among those who did not (P=0.04). The relative risk of progression to end-stage renal failure was also increased among patients whose renal function was relatively worse at baseline, with an increase by a factor of 5 for each doubling of the baseline serum creatinine concentration (P<0.001).

Five patients had a very rapid and striking relapse of proteinuric renal dysfunction when there was a flare of inflammatory disease activity during follow-up. For example, the amyloid-related nephrotic syndrome resolved gradually over a period of 4 years in a patient whose underlying rheuma-
toid arthritis was in sustained complete remission, yet when an intense acute-phase reaction associated with community-acquired pneumonia developed in this patient, the nephrotic syndrome recurred within 2 weeks. Her renal function normalized again during the ensuing 2 years.

**DISCUSSION**

This study involving patients with AA amyloidosis included specific quantitative measurements of the whole-body amyloid burden on SAP scintigraphy and the circulating AA amyloid fibril precursor SAA. Observations that challenge the still widespread perception of amyloidosis as an inexorably progressive disease include the demonstration that AA amyloid deposits often regress and that survival is prolonged in patients in whom the circulating SAA concentration remains at low values.

Although the spleen, adrenal glands, liver, and gut are frequent sites of AA amyloid deposition, renal involvement dominated the clinical course in the patients in this study. Evidence of amyloid cardiomyopathy and autonomic neuropathy were extremely rare, as compared with previously reported series.\(^{20,21}\) None of the patients had clinically significant liver amyloidosis; furthermore, nearly one third of the patients with an elevated serum alkaline phosphatase concentration, which has been suggested as a marker of hepatic amyloid by an international consensus panel,\(^{17}\) had no evidence

<table>
<thead>
<tr>
<th>Table 4. (Continued.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td><strong>Associated with progression to end-stage renal failure</strong></td>
</tr>
<tr>
<td>Factors at baseline</td>
</tr>
<tr>
<td>Underlying disease</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Chronic sepsis</td>
</tr>
<tr>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Amyloid burden</td>
</tr>
<tr>
<td>Small</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Large</td>
</tr>
<tr>
<td>Hepatic amyloid deposits</td>
</tr>
<tr>
<td>Duration of inflammatory disease (per 5-yr interval)</td>
</tr>
<tr>
<td>Serum creatinine (by a factor ≥3)</td>
</tr>
<tr>
<td>Factors that could change during follow-up</td>
</tr>
<tr>
<td>Serum albumin (≥0.5 g/dl)</td>
</tr>
<tr>
<td>SAA (by a factor ≥3)</td>
</tr>
<tr>
<td>Change in amyloid deposits</td>
</tr>
<tr>
<td>Progressed</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>Regressed</td>
</tr>
</tbody>
</table>

* Race or ethnic group was self-reported.
† In the univariate (unadjusted) analyses, factors that were not significant (P>0.01) were sex, year of diagnosis of AA amyloidosis, evidence of hepatic amyloid deposits at baseline, and proteinuria.
‡ In the multivariate (adjusted) model, patients who had periodic fever syndromes were compared with those who had any of the other underlying diseases, and patients in whom amyloid deposits regressed were compared with those in whom amyloid deposits remained stable or progressed.
of liver deposits on SAP scintigraphy. The features of amyloidosis in terms of the duration of underlying disease, clinical presentation, distribution of amyloid deposits, and outcome were similar in patients with different types of underlying inflammatory disorders, with the exception of a worse renal outcome in patients with chronic sepsis or Crohn’s disease. It is possible that the high frequency of surgical intervention and administration of immunosuppressive drugs contributed to renal failure in patients with Crohn’s disease.

Factors associated with a poor prognosis included older age, a reduced serum albumin concentration, end-stage renal failure at baseline, and the degree by which the SAA concentration was elevated during follow-up. Increased production of SAA was the most powerful risk factor for end-stage renal failure and death, but it is also one that may be ameliorated through antiinflammatory treatment.

Despite the high correlations among SAA production, amyloid burden, and renal function overall within the cohort, the association between the median SAA concentration and the status of the amyloid deposits did differ among individual patients (Fig. 1). Thus, although amyloid deposits regressed in about 60% of patients whose median SAA concentration was less than 10 mg per liter, the deposits were stable in the remainder. Similarly, although the amyloid deposits progressed in all patients whose median SAA concentration was more than 120 mg per liter, deposits among individual patients with moderately elevated SAA concentrations were stable, regressed, or progressed. The efficiency with which SAA is converted into amyloid or the rate at which amyloid deposits are turned over within the tissues, or both, may differ from patient to patient, although neither mechanism has been elucidated.

There were also differences between individual patients in the relationship between amyloid burden and renal function. Renal function improved in 17 patients in whom the amyloid burden was merely stable, and it deteriorated in 15 patients in whom amyloid deposits regressed. The basis for renal recovery in association with a stable amyloid burden and a low SAA concentration is unknown. However, progressive kidney dysfunction in patients in whom the amyloid deposits regressed was undoubtedly influenced by additional renal insults, including drugs, sepsis, hypovolemia, and hypertension, as well as by the extent of irreversible renal damage occurring before diagnosis. Discrepancies between the course of the amyloid deposits and the direction of change in organ function are salient reminders that the molecular mechanisms of tissue damage in amyloidosis actually remain little understood.

In contrast to the improvement in amyloid-associated renal dysfunction after successful antiinflammatory therapy that typically took months to years, the relapse of renal dysfunction after renewed inflammatory disease activity could be remarkably rapid. This finding probably reflects the conversion of abundant SAA into its fibrillar form on a template of residual amyloid deposits. This finding is reminiscent of the long-recognized phenomenon of the “amyloid-enhancing factor” that has been observed in experimentally induced murine AA amyloidosis, in which substantial amyloid deposits can develop in less than 24 hours in mice injected with ex vivo amyloid material and subsequently given an inflammatory stimulus.

Treatment of AA amyloidosis depends on control of the underlying inflammatory disorder. Successful pharmacologic approaches in our patients ranged from nonspecific immunosuppression for those with inflammatory arthritis treated with chlorambucil to highly specific inhibition of interleukin-1 for those with the Muckle–Wells syndrome (an autosomal dominant fever syndrome characterized by urticaria, progressive perceptive deafness, and amyloidosis). Surgical treatments included excision of solitary cytokine-secreting Castleman’s tumors (angiofollicular lymph-node hyperplasia) and amputation of osteomyelitic limbs. Surprisingly, 23 patients (6%) who presented with AA amyloidosis had clinically covert inflammatory disease that could not be characterized. The majority of these patients had been presumed by their referring physicians to have primary AL amyloidosis, yet on immunohistochemical testing, we confirmed AA amyloid in all of them. Antiinflammatory treatment must be empirical in such patients but should be guided, we believe, as in all patients with AA amyloidosis, by frequent measurement of SAA concentrations.

In conclusion, AA amyloidosis usually presents with proteinuric renal dysfunction, for which patients with chronic inflammatory disorders should be evaluated routinely. The period of latency between the onset of inflammation and clinical presentation with AA amyloidosis appears to vary and is often prolonged, but the progression of
amyloid can be rapid. In the present study, decreased production of SAA was associated with a favorable renal outcome, stabilization or regression of amyloid deposits, and prolonged survival.

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REFERENCES


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Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

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ABSTRACT

BACKGROUND
Adrenocortical carcinoma is a rare neoplasm characterized by a high risk of recurrence after radical resection. Whether the use of mitotane is beneficial as an adjuvant treatment has been controversial. Our aim was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival.

METHODS
We performed a retrospective analysis involving 177 patients with adrenocortical cancer who had undergone radical surgery at 8 centers in Italy and 47 centers in Germany between 1985 and 2005. Adjuvant mitotane was administered to 47 Italian patients after radical surgery (mitotane group), whereas 55 Italian patients and 75 German patients (control groups 1 and 2, respectively) did not receive adjuvant treatment after surgery.

RESULTS
Baseline features in the mitotane group and the control group from Italy were similar; the German patients were significantly older (P=0.03) and had more stage I or II adrenocortical carcinomas (P=0.02) than did patients in the mitotane group. Recurrence-free survival was significantly prolonged in the mitotane group, as compared with the two control groups (median recurrence-free survival, 42 months, as compared with 10 months in control group 1 and 25 months in control group 2). Hazard ratios for recurrence were 2.91 (95% confidence interval [CI], 1.77 to 4.78; P<0.001) and 1.97 (95% CI, 1.21 to 3.20; P=0.005), respectively. Multivariate analysis indicated that mitotane treatment had a significant advantage for recurrence-free survival. Adverse events associated with mitotane were mainly of grade 1 or 2, but temporary dose reduction was needed in 13% of patients.

CONCLUSIONS
Adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.
ADRENOCORTICAL CARCINOMA IS A RARE neoplasm characterized by a dismal prognosis, with only 16 to 38% of patients surviving for more than 5 years after diagnosis.\textsuperscript{1-3} Although a majority of patients have resectable disease at presentation,\textsuperscript{4-6} as many as 75 to 85% have a relapse after radical resection.\textsuperscript{7,8} This high recurrence rate has prompted investigators to consider the use of adjuvant therapy,\textsuperscript{1,3,9} and mitotane (a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane [DDT]) has been widely used for this purpose.\textsuperscript{10-21} However, available studies do not provide data as to whether adjuvant mitotane is efficacious, mainly because of the low statistical power of the studies.

We reviewed the outcome of patients with adrenocortical carcinoma who had undergone radical surgery at tertiary referral centers in Italy from 1985 through 2003. During this period, adjuvant mitotane treatment was routinely used in some centers but not in others, providing an opportunity to compare two contemporary groups of patients. To control further for potential biases, we included a second independent control group for comparison with mitotane-treated patients in our analysis, a cohort of German patients who were treated with surgery only. The primary aim of the study was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival; secondary aims were assessments of overall survival and adverse events.

**METHODS**

**ITALIAN PATIENTS**

We performed a retrospective analysis among patients with adrenocortical carcinoma who had undergone radical surgery between January 1985 and December 2003 at eight tertiary referral centers in Italy. All patients who had undergone radical resections were included in the study. Follow-up for this study was closed in December 2004.

Patients had to meet the following inclusion criteria: an age of 18 years or older and the availability of preoperative and postoperative computed tomographic (CT) or magnetic resonance imaging (MRI) scans. Exclusion criteria were macroscopically incomplete resection, incomplete tumor staging, concomitant cancers within the previous 5 years, clinically significant concomitant disease, and adjuvant therapies other than mitotane (chemotherapy or radiotherapy) after surgery. Of 131 patients identified, 102 met all entry criteria. Of those, 29 patients were excluded: 21 had undergone an incomplete resection, 3 had other concomitant tumors, 4 had undergone other adjuvant therapies, and 1 had heart failure.

All data were obtained by reviewing patients’ histories, discharge summaries, medical records, and source documents. Data were retrieved by trained medical personnel using specifically tailored data forms. We collected data on the date of diagnosis, the date of surgery, the pathology report, the tumor stage at diagnosis, the hormonal workup, details concerning mitotane treatment (treatment duration and regimen, side effects, and reasons for discontinuation), the date of recurrence, and either the date and cause of death or the date of the last follow-up visit. The institutional ethics committee at each clinical center approved the study. All patients provided written informed consent.

Complete resection was defined as no evidence of macroscopic residual disease on the basis of surgical reports, histopathological analysis, and postoperative imaging. All histologic diagnoses were confirmed by experienced pathologists. In 89% of the patients, two expert pathologists who were unaware of study-group assignments reevaluated the histologic analysis according to the Weiss criteria (nuclear atypia, atypical mitoses, frequent mitoses, small percentage of clear cells, diffuse architecture, necrosis, and the invasion of venous, sinusoidal, or capsular structures).\textsuperscript{22,23} Follow-up visits, which included imaging of the chest and abdomen, were performed every 6 months until either disease progression occurred or the study period ended.

Tumor staging at diagnosis was based on imaging studies and was corroborated by the findings during surgery. Staging was reported according to the McFarlane–Sullivan criteria: stage I, a tumor diameter of 5 cm or less; stage II, a tumor diameter of more than 5 cm; stage III, tumor infiltration of neighboring structures or positive lymph nodes; and stage IV, infiltration of neighboring structures and positive lymph nodes or distant metastases.\textsuperscript{24,25} Disease recurrence was defined as radiologic evidence of a new lesion during follow-up.

Adjuvant mitotane (Lysodren, Bristol-Myers Squibb) was routinely recommended at four of the Italian centers, whereas patients were followed without treatment at the other four centers. Mito-
tane-related adverse events were graded with the use of the National Cancer Institute’s Common Terminology Criteria for Adverse Events. 26

GERMAN PATIENTS
A second control group was derived from the German Adrenocortical Carcinoma Registry, which contained data for 345 patients at the time of analysis (August 2006). Clinical data for these patients were collected by trained medical personnel using structured evaluation forms containing comprehensive information on diagnostic procedures, surgical outcomes, and follow-up similar to those used to evaluate the Italian study population (further details are available at www.nebennierenkarzinom.de). The German Adrenocortical Carcinoma Registry was approved by the ethics committee at the University of Würzburg, and patients gave written informed consent.

Follow-up data were available for 333 patients. Of those, 181 patients who were at least 18 years of age presented without distant metastases, and 148 of these patients had undergone radical surgery with curative intent. Detailed surgical reports indicated no residual disease in 111 patients. Thirty-six patients were excluded because they had undergone adjuvant therapies, including mitotane (22 patients; median duration of treatment, 7.5 months), radiotherapy (7), cytotoxic drugs (1), or combinations of these treatments (6). The remaining 75 patients met the inclusion and exclusion criteria of the Italian observation group. They had undergone radical resection between 1985 and 2005 in 47 centers throughout Germany. The histologic diagnosis for each patient was made by the local pathologist. In 73% of patients, tumor material was made available to the study pathologist, who confirmed the diagnosis in all cases. Information on the functional status of adrenocortical carcinoma (whether the tumor was hormone-secreting) was available for 50 patients.

OUTCOMES
The primary aim of our study was to compare recurrence-free survival in patients who received adjuvant mitotane therapy after radical resection with that of patients who did not receive adjuvant therapy. Secondary outcome measures were overall survival and adverse events associated with mitotane therapy. Recurrence-free survival was measured from the date of surgery to the date of recurrence; for patients who did not have a relapse, the data were censored at the date of the last follow-up visit. Overall survival was measured from the date of surgery to the date of death, and the data were censored at the date of the last follow-up visit.

STATISTICAL ANALYSIS
All statistical analyses were performed with Statistical software (StatSoft). Rates and proportions were calculated for categorical data and medians and ranges for continuous data. Differences in continuous variables were analyzed by means of the two-tailed Mann–Whitney U test. For categorical variables, differences were analyzed by means of the chi-square test. Survival curves were computed according to the Kaplan–Meier method and were compared by means of the log-rank test. A Cox proportional-hazards regression analysis was used to assess in univariate and multivariate analyses the predictive role of the treatment administered and of clinical and pathological variables on disease recurrence and overall survival. The likelihood ratio was used to assess the significance of covariates included in each model. Heterogeneity in the effect of adjuvant treatment in subgroups of patients was evaluated with the use of standard tests for interaction. Missing data were dealt with by excluding patients from particular analyses if their files did not contain data for the required variables. All reported P values are two-sided. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS
PATIENTS
The characteristics of patients according to group are provided in Table 1. The groups of Italian patients (the mitotane group and control group 1) were evenly distributed with respect to age and stage of disease, whereas the German patients (control group 2) were significantly older than the patients in the mitotane group (P=0.03). Patients with stage IV adrenocortical carcinoma had infiltration of adjacent organs; none had distant metastases. A higher proportion of men was present in control group 1 than in the mitotane group (P=0.05), whereas sex distribution in control group 2 did not differ significantly from that in the mitotane group. The mitotane group and control group 1 were evenly distributed with respect to tumor stage, whereas the proportion of adrenocortical carcinomas of stage I or II was higher
in control group 2 than in the mitotane group (P=0.02). Of the 152 patients who could be evaluated, 50% had secreting tumors, with no major difference between groups. The median follow-up period after surgery was 56.7 months (range, 12 to 164) in the mitotane group, 67.6 months (range, 12 to 161) in control group 1, and 43.0 months (range, 9 to 230) in control group 2.

### OUTCOME RESULTS

Recurrence was documented in 23 patients in the mitotane group (48.9%), 50 in control group 1 (90.9%), and 55 in control group 2 (73.3%). Mito-

tane treatment was associated with longer recurrence-free survival, as compared with either control group (Fig. 1A). The median recurrence-free survival was 42 months in the mitotane group, 10 months in control group 1 (P<0.001), and 25 months in control group 2 (P=0.005), according to the log-rank test.

Death from adrenocortical cancer was reported for 12 patients in the mitotane group (25.5%), 30 in control group 1 (54.5%), and 31 in control group 2 (41.3%). Three patients in the mitotane group and one in control group 1 died from other causes and had no evidence of recurrence. Me-

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### Table 1. Baseline Characteristics of the Patients. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mitotane Group (N=47)</th>
<th>Control Group 1 (N=55)</th>
<th>P Value</th>
<th>Control Group 2 (N=75)</th>
<th>P Value</th>
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</thead>
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<tr>
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<td></td>
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<td>0.03</td>
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<tr>
<td>Median</td>
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<td>44</td>
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<td>21–73</td>
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<td>18–83</td>
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<td>Sex — no. (%)</td>
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<td>0.05</td>
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<td>0.1</td>
</tr>
<tr>
<td>Male</td>
<td>11 (23.4)</td>
<td>23 (41.8)</td>
<td></td>
<td>27 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (76.6)</td>
<td>32 (58.2)</td>
<td></td>
<td>48 (64.0)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage — no. (%)</td>
<td></td>
<td></td>
<td>0.90</td>
<td></td>
<td>0.02†</td>
</tr>
<tr>
<td>I</td>
<td>3 (6.4)</td>
<td>4 (7.3)</td>
<td>9 (12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>27 (57.4)</td>
<td>31 (56.4)</td>
<td>54 (72.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11 (23.4)</td>
<td>15 (27.3)</td>
<td>11 (14.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6 (12.8)</td>
<td>5 (9.1)</td>
<td>1 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size — cm</td>
<td></td>
<td></td>
<td>0.40</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Median</td>
<td>10.5</td>
<td>10.0</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5.0–22.0</td>
<td>4.0–22.0</td>
<td>3.0–28.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional status of tumor — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients evaluated</td>
<td>47</td>
<td>55</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secreting tumor</td>
<td>24 (51.1)</td>
<td>22 (40.0)</td>
<td>0.30</td>
<td>30 (60.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Glucocorticoids with or without androgens</td>
<td>22 (46.8)</td>
<td>15 (27.3)</td>
<td>25 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td>2 (4.3)</td>
<td>5 (9.1)</td>
<td>4 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0</td>
<td>1 (1.8)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsecreting tumor</td>
<td>23 (48.9)</td>
<td>33 (60.0)</td>
<td>20 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiss score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients evaluated</td>
<td>45</td>
<td>46</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6 (3–9)</td>
<td>6 (3–8)</td>
<td>0.20</td>
<td>5 (2–9)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* All P values are for comparisons between each control group and the mitotane group. Percentages may not total 100 because of rounding.
† The P value refers to the overall tumor-stage distribution.
‡ The Weiss score ranges from 0 to 9, with a score higher than 2 indicating the presence of adrenal cancer.
median overall survival was 110 months in the mitotane group, as compared with 52 months in control group 1 (P = 0.01) and 67 months in control group 2 (P = 0.10), according to the log-rank test (Fig. 1B).

Among patients in all the groups, recurrences were managed with surgery (56.2%), mitotane (70.3%), cytotoxic chemotherapy (42.2%), or other therapies (7.5%); these approaches were often used in combination. Six of 128 patients with recurrence did not receive any specific treatment.

To adjust for imbalances in the distribution of potential prognostic factors between comparisons of recurrence-free survival and overall survival, two multivariate Cox models were fitted to the data, in which age, sex, and tumor stage were included.

Figure 1. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.
as covariates together with treatment group (mitotane group vs. control group 1 vs. control group 2). Since data on tumor secretory activity and Weiss score were not available for all patients in control group 2, two further multivariate models that included these two variables were fitted on data for the Italian patients. However, since secretory activity and the Weiss score were not found to be associated with either recurrence-free or overall survival and since the inclusion of these variables did not modify hazard-ratio estimates, only the results of the multivariate analyses of the full data set of 177 patients are presented (Tables 2 and 3). In the univariate analysis, only age was significantly associated with recurrence-free survival and overall survival (P<0.001). After adjustments for age, sex, and tumor stage, both the Italian and the German control groups showed a higher risk of both recurrence (hazard ratio, 3.79; 95% confidence interval [CI], 2.27 to 6.32; and hazard ratio, 2.93; 95% CI, 1.74 to 4.94, respectively) and death (hazard ratio, 2.47; 95% CI, 1.26 to 4.85; and hazard ratio, 1.96; 95% CI, 1.00 to 3.87, respectively) than did the mitotane group. No heterogeneity in the hazard ratios was observed across subgroups of patients identified by the prognostic factors included in the model (all P values for interaction, >0.2).

### Mitotane Dose and Adverse Events

In the mitotane group, 20 patients received 3 to 5 g daily, and 27 patients received 1 to 3 g daily. The median duration of treatment was 29 months (range, 6 to 164) with no significant difference between the two regimens; 21 patients were treated for 4 years or more.

The adverse events associated with mitotane therapy are listed in Table 4. Grade 3 gastrointestinal events were observed in 15% of patients and neurologic grade 3 events in 20% of patients who received the higher-dose regimen; neither of these problems was seen in patients receiving the lower-dose regimen. Temporary discontinuation or dose reduction was necessary in four patients receiving higher doses of mitotane and in two patients receiving lower doses.

### Discussion

Our study suggests a benefit associated with the use of adjuvant mitotane therapy after radical re-

---

**Table 2. Predictive Factors for Recurrence-free Survival, According to Univariate and Multivariate Analyses.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age†</td>
<td>0.98</td>
<td>0.96–0.99</td>
</tr>
<tr>
<td>Sex‡</td>
<td>1.20</td>
<td>0.83–1.72</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.91</td>
<td>0.92–3.95</td>
</tr>
<tr>
<td>III</td>
<td>2.14</td>
<td>0.98–4.71</td>
</tr>
<tr>
<td>IV</td>
<td>2.22</td>
<td>0.85–5.80</td>
</tr>
<tr>
<td>Secreting tumor§</td>
<td>1.29</td>
<td>0.87–1.90</td>
</tr>
<tr>
<td>Weiss score¶</td>
<td>0.96</td>
<td>0.61–1.50</td>
</tr>
<tr>
<td>Study group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotane group</td>
<td>2.91</td>
<td>1.77–4.78</td>
</tr>
<tr>
<td>Control group 1</td>
<td>1.97</td>
<td>1.21–3.20</td>
</tr>
<tr>
<td>Control group 2</td>
<td>2.91</td>
<td>1.77–4.78</td>
</tr>
</tbody>
</table>

* The model for the multivariate analysis included age (as a continuous variable), sex (as a dichotomized variable), and tumor stage (in four strata) as covariates. No significant interactions between treatment group and age, sex, or tumor stage were observed, but the low power of these analyses must be considered, given the small number of events.
† The hazard ratio is for each additional year of age.
‡ Female sex was the reference category.
§ Nonsecreting adrenocortical carcinoma was the reference category.
¶ A Weiss score of 6 (median value) or less was the reference category.
section of adrenocortical carcinoma. As compared with patients treated with mitotane, patients in both the Italian and the German control groups appeared to have a significantly increased risk of recurrence (by factors of 3 and 2, respectively). The apparent benefit of mitotane therapy was even more marked when multivariate analyses were used. Similarly, overall survival appeared to be superior in patients receiving adjuvant mitotane.

Our study had certain limitations, since it was not a randomized trial. Indeed, potential problems such as selection bias, diagnostic bias, stage migration, and bias in follow-up or ascertainment of outcome in observational retrospective series are well recognized. To reduce selection bias in the Italian centers, we included all consecutive eligible patients in the study group of the given center (in the mitotane group and control group 1) on the basis of the treatment policy of that center, as established by specific management algorithms and not dependent on the characteristics of patients. Control group 2 was derived from a large nationwide registry of patients with adrenocortical carcinoma, and the 75 patients in this group were extracted from a subgroup of 333 patients for whom follow-up data were available. Thus, it is reasonable to assume that control group 2 was representative of all patients with resected adrenocortical carcinoma in Germany during the study period. Furthermore, no patients were excluded on the basis of treatment adherence or outcome.

The possibility that patients with different unmeasured characteristics were unevenly distributed between the Italian groups or that surgery may have been more complete in some centers than in others cannot be completely excluded. It should be noted, however, that the only difference in the distribution of known or potential prognostic factors between the two groups of Italian patients was the higher proportion of male patients in control group 1, which is unlikely to have affected the results, since the sex of patients was not an independent predictor of survival. Patients in the German control group, in contrast, were older, and more had early-stage cancers than did patients in the mitotane group. However, these differences would have predicted a better prognosis in the German control group than in the mitotane group. Accordingly, when adjustments were made for the differences in the distribution of these factors with the use of multivariate analyses, larger hazard-ratio estimates were obtained, reinforcing the possibil-

| Table 3. Prognostic Factors for Overall Survival, According to Univariate and Multivariate Analyses. |
|---------------------------------|-------------------|-------------------|
| Variable                        | Univariate Analysis | Multivariate Analysis* |
|                                 | Hazard Ratio | 95% CI | P Value | Hazard Ratio | 95% CI | P Value |
| Age†                            | 0.98 | 0.96–1.00 | 0.05 | 0.98 | 0.96–1.00 | 0.02 |
| Sex‡                           | 0.90 | 0.55–1.47 | 0.68 | 0.78 | 0.46–1.33 | 0.36 |
| Tumor stage                     |                 | 0.26 |      |     |            |      |
| I                               | 1               |     |      |     |            |      |
| II                              | 3.81 | 0.93–15.68 | 3.68 | 0.90–15.23 | 0.29 |
| III                             | 4.47 | 1.03–19.86 | 4.22 | 0.97–18.43 |      |
| IV                              | 5.54 | 0.65–19.85 | 4.40 | 0.79–24.58 |      |
| Secreting tumor§                | 1.32 | 0.78–2.24 | 0.30 |     |            |      |
| Weiss score¶                    | 1.04 | 0.57–1.89 | 0.89 |     |            |      |
| Study group                     |                 |      |      |     |            |      |
| Mitotane group                  | 1               | 0.05 | 1  | 0.03 |            |      |
| Control group 1                 | 2.28 | 1.17–4.46 | 2.47 | 1.26–4.85 |      |
| Control group 2                 | 1.73 | 0.89–3.39 | 1.96 | 1.00–3.87 |      |

* The model for the multivariate analysis included age (as a continuous variable), sex (as a dichotomized variable), and tumor stage (in four strata) as covariates. No significant interactions between treatment group and age, sex, or tumor stage were observed, but the low power of these analyses must be considered, given the small number of events.
† The hazard ratio is for each additional year of age.
‡ Female sex was the reference category.
§ Nonsecreting adrenocortical carcinoma was the reference category.
¶ A Weiss score of 6 or less (median value) was the reference category.
ity that the use of mitotane was associated with a true prognostic improvement. Differences in histologic classification among the three groups were unlikely, since data from most of the patients were reviewed by expert pathologists who all used the same classification criteria. Diagnostic and staging protocols were similar in all centers, and patients in the three groups underwent surgery during the same period. Finally, follow-up was sufficiently complete in the three groups, with only six patients lost to follow-up. Thus, as far as can be stated in a retrospective study, major biases appear to have been minimal.

Our study compared adjuvant mitotane therapy with no adjuvant therapy in two groups of similar patients, whereas historical controls or no controls were used in previous studies. Strengths of our study include the large number of patients, the long duration of follow-up, the use of intention-to-treat analysis, and the inclusion of two independent, concomitant groups of patients who received no adjuvant therapy after their initial surgery. Notwithstanding the retrospective nature of this study, which warrants caution in the interpretation of its results, the study provides important evidence for the efficacy of adjuvant treatment with mitotane after radical resection of adrenocortical carcinoma.

Adrenocortical carcinoma is a heterogeneous disease characterized by a generally dismal prognosis, with few patients having either long recurrence-free intervals or overall survival. This observation points to the importance of identifying prognostic factors. In our study, tumor stage did not appear to have significant prognostic value. However, more advanced stages were associated with increased risk of either disease recurrence or death, and the failure to attain statistical significance for overall survival may be due to the low number of patients with stage I tumors. In addition, the tumor stage may affect prognosis primarily as it affects the feasibility of radical surgery, which was an inclusion criterion of the study. It is known that patients with adrenocortical carcinoma have an extremely poor prognosis when surgical removal of the tumor is not feasible.

Age was the only consistent prognostic factor associated with an improved outcome. However, the bulk of previous evidence suggests that age does not play a major role in prognosis. Similarly, the majority of studies have reported no correlation between sex and survival, and there is only limited evidence that the Weiss score is predictive of long-term outcome. The functional status of the tumor is also usually not related to prognosis, although in advanced disease, hypercortisolism may contribute to an unfavorable outcome.

Adjuvant mitotane treatment was associated with some adverse events, which may be considered acceptable, given the disease. However, because of the retrospective nature of our study, underreporting of adverse events cannot be fully excluded. Adverse events were manageable, though a temporary reduction of the mitotane dose was necessary in some patients. Mitotane was not terminated because of adverse events in any of the patients.

In summary, our study indicates that adjuvant treatment with mitotane can be administered with beneficial effects on outcome in patients with adrenocortical carcinoma. We believe that our retrospective analysis should renew interest in adjuvant therapy.

### Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1234</td>
<td>4200</td>
</tr>
<tr>
<td>Constitutional or gastrointestinal symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia or fatigue</td>
<td>1234</td>
<td>1610700</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>8500</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td></td>
<td>1310300</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>20700</td>
</tr>
<tr>
<td>Hepatic symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated γ-glutamyltransferase</td>
<td></td>
<td>2310700</td>
</tr>
<tr>
<td>Elevated aspartate or alanine aminotransferase</td>
<td></td>
<td>19400</td>
</tr>
<tr>
<td>Neurologic symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
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<td>45200</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td>21400</td>
</tr>
<tr>
<td>Vertigo</td>
<td></td>
<td>45400</td>
</tr>
<tr>
<td>Other symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1234</td>
<td>01000</td>
</tr>
<tr>
<td>Gynecomastia</td>
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<td>31000</td>
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</tbody>
</table>

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Owing to the adrenolytic action of mitotane, all patients received prophylactic glucocorticoid replacement therapy. Therefore, detailed monitoring of mitotane-induced adrenal insufficiency was not performed. Because of the retrospective nature of the study, underreporting of low-grade side effects must be considered a possibility.
 vant therapy as a key issue in the treatment of this disease. In the future, prospective, randomized trials will be needed to confirm that adjuvant mito-
tate treatment is sufficiently effective to be con-
considered as the standard of care after complete re-
section of adrenocortical carcinoma.

Supported by a grant (2005067583-005) from the Ministero dell’Università e della Ricerca Scientifica e Tecnologica and a grant (106-080) from the Deutsche Krebshilfe.
No potential conflict of interest relevant to this article was reported.

We thank Uwe Maeder of the Tumor Center at the University Hospital in Würzburg for help in establishing the database for the German Adrenocortical Carcinoma Registry.

APPENDIX

The following investigators contributed two or more patients to the German control group: H. Willenberg, P. Goretzki (University Hospital, Düsseldorf); M. Rothmund, P. Langer (University Center, Marburg); M. Quinkler, W. Oelkers (University Hospital Charité, Berlin); H. Denecke (Leopoldina Hospital, Schweinfurt); H.-L. FEhn (University Hospital, Lübeck); M. Morcos (University Hospital, Heidelberg); F. Beuschlein (University of Freiburg, Freiburg); M. Brauchhoff (University Hospital, Halle); N. Reisch (University Hospital, Munich); K. Muessig (University Hospital, Tübingen); C. Fottmer (University Hospital, Mainz); K. Hengst (University Hospital, Mün-
ster); and J. Lübbren (Endokrinologikum, Hamburg).

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tical carcinoma: a clinical study and treat-
ment results of 52 patients. Cancer 1995;
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secutive series of 96 patients. Br J Cancer 
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Bacteremia, Fever, and Splenomegaly Caused by a Newly Recognized Bartonella Species


SUMMARY

Bartonella species cause serious human infections globally, including bacillary angiomatosis, Oroya fever, trench fever, and endocarditis. We describe a patient who had fever and splenomegaly after traveling to Peru and also had bacteremia from an organism that resembled Bartonella bacilliformis, the causative agent of Oroya fever, which is endemic to Peru. However, genetic analyses revealed that this fastidious bacterium represented a previously uncultured and unnamed bartonella species, closely related to B. clarridgeiae and more distantly related to B. bacilliformis. We characterized this isolate, including its ability to cause fever and sustained bacteremia in a rhesus macaque. The route of infection and burden of human disease associated with this newly described pathogen are currently unknown.

HUMAN INFECTION WITH BARTONELLA PROBABLY HAS OCCURRED FOR centuries, but only in the past several decades have the prevalence of infection in humans and the diversity of infecting species been recognized. In 1990, a new species called Bartonella henselae was shown to cause bacteremia and bacillary angiomatosis in patients with the acquired immunodeficiency syndrome (AIDS).1,2 Previously, there had been only two known bartonella species that infected humans: B. quintana, identified in Europe during World War I as the agent causing relapsing bacteremia in tens of thousands of troops afflicted with trench fever, and B. bacilliformis, endemic only in the Andes, where it causes a hemolytic bacteremia called Oroya fever and the angioproliferative cutaneous manifestations of verruga peruana. After the discovery of B. henselae, B. quintana was isolated from bacillary angiomatosis lesions from homeless patients with AIDS who had body lice,3,4 B. henselae was identified as the agent of cat scratch disease,5 and both species were identified as a substantial cause of culture-negative endocarditis.6

CASE REPORT

A 43-year-old American woman had a fever after traveling in Peru for 3 weeks. She visited Lima for several days, and then traveled to Nazca, where she resided in a lodge in a desert area at sea level. She then traveled to the Sacred Valley of Urubamba, followed by Cuzco and Machu Picchu, where she hiked and spent one night. Her trip concluded in the Amazon Basin near Iquitos. She received numerous insect bites, predominantly on the legs and feet.

Sixteen days after returning to the United States, the patient had fever, insomnia, myalgia, nausea, headache, and mild cough. During the first 4 days of fever, her temperature was as high as 38.9°C; it decreased during the next 3 days, but the
day before presentation she had a recurrent fever, with a maximum temperature of 38.9°C. Six days before presentation she had a diffuse macular rash. She came to the clinic 8 days after the onset of fever. Physical examination revealed a temperature of 37.3°C, an enlarged spleen palpated 4 to 5 cm below the left costal margin, and healing insect bites on the legs and feet. Microscopical examination of a peripheral-blood specimen did not show bacteria or malaria parasites within erythrocytes. Laboratory values revealed a mild anemia that resolved 6 weeks after treatment (Table 1). A blood specimen from the patient was cultured, and she was given oral levofloxacin for 5 days as empirical treatment for enteric fever. One week later, she was asymptomatic and afebrile, and the spleen was not palpable. The patient did not own pets and had not been exposed to cats during or after her travel to Peru. There was no other recent travel, and her traveling companion remained well.

Methods

A blood specimen from the patient was cultured in a 40-ml culture bottle (BACTEC Standard/10 Aerobic/F, Becton Dickinson) at the time of presentation. On day 15 of incubation, the automated culture system signaled a positive culture. Samples were submitted to one laboratory for Gram’s staining, acridine orange staining, and subculturing and to another for subculturing. A 5-ml aliquot of blood was centrifuged at 5000×g for 45 minutes. The supernatant and pellet were plated onto heart infusion agar containing 5% fresh defibrinated rabbit blood and chocolate agar, and the plates were incubated at 28°C or 35°C in a candle-extinction jar. Fluorescence microscopy of the positive blood-culture broth stained with acridine orange was performed with the use of an epifluorescence microscope (excitation wavelength, 450 to 490 nm; mean emission wavelength, >515 nm). Subsequently, the morphologic characteristics of the isolate were examined by means of transmission electron microscopy after negative staining.

On the basis of the presumptive identification of the isolate (designated BMGH) as a bartonella species, serum samples collected at presentation and follow-up were also assayed, with the use of class-specific conjugates labeled with fluorescein isothiocyanate, to determine reactivity against the isolate from the patient. In the IgM assays, sam-

### Table 1. Laboratory Data at Presentation and at Follow-up.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presentation (9/4/03)</th>
<th>1 Day (9/5/03)</th>
<th>Follow-up 6 Weeks (10/28/03)</th>
<th>18 Months (4/7/05)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>32.1</td>
<td>33.2</td>
<td>35.6</td>
<td>37.5</td>
<td>36.0–46.0</td>
</tr>
<tr>
<td>Erythrocyte count (×10⁶/mm³)</td>
<td>3.8</td>
<td>4.0</td>
<td>4.2</td>
<td>4.3</td>
<td>4.0–5.2</td>
</tr>
<tr>
<td>Platelet count (per mm³²)</td>
<td>351,000</td>
<td>416,000</td>
<td>474,000</td>
<td>363,000</td>
<td>150,000–350,000</td>
</tr>
<tr>
<td>White-cell count (per mm³³)</td>
<td>6,100</td>
<td>5,700</td>
<td>6,700</td>
<td>8,200</td>
<td>4,500–11,000</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>72</td>
<td>64</td>
<td>65</td>
<td>71</td>
<td>40–70</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>10</td>
<td>12</td>
<td>10</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>&lt;1.5</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>31</td>
<td>16</td>
<td>0–35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>28</td>
<td>25</td>
<td>0–35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.0</td>
<td>1.9</td>
<td>0.3–1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>69</td>
<td>51</td>
<td>30–120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reciprocal titers of antibody against BMGH isolate by indirect fluorescence-antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>4,096</td>
<td>512</td>
<td>&lt;64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>512</td>
<td>4,096</td>
<td>&lt;64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.
amples were first depleted of IgG with the use of a protein-G removal device (Mini Rapi-Sep-M, Pan-Bio). A reciprocal titer of 64 or more represents a positive result for B. henselae or B. quintana.9,10

**AMPLIFICATION BY POLYMERASE CHAIN REACTION AND SEQUENCE ANALYSIS**

DNA from the BMGH isolate was extracted, and sequencing was performed as previously described.11-15 Oligonucleotide primers (from the Centers for Disease Control and Prevention Core Facility), gene targets, and GenBank accession numbers for nucleotide sequences generated in this study are listed in Table 1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org). We aligned the sequences using ClustalW software and drew the phylogenetic tree using Molecular Evolutionary Genetics Analysis software, version 3.0.16 The distance matrix was calculated with the use of Kimura-2 parameters, and the tree was obtained with the use of the unweighted pair group method with arithmetic mean, based on a comparison of 1328 sites.

**ONE-DIMENSIONAL AND TWO-DIMENSIONAL GEL ELECTROPHORESIS**

For one-dimensional sodium dodecyl sulfate–polyacrylamide-gel electrophoresis (SDS-PAGE), bacterial proteins were electrophoresed on an 8 to 16% gradient gel and stained with Coomassie blue. For two-dimensional SDS-PAGE, subcellular fractions were prepared17,18 and a protease-inhibitor cocktail was added. Cytosolic proteins were precipitated and dialyzed overnight with the use of phosphate-buffered saline and then concentrated with a centrifuge filter (Amicon Ultra-4; Millipore). Two-dimensional gel electrophoresis was then performed19 (by Kendrick Laboratories): isoelectric focusing was carried out in glass tubes with the use of 2% pH 4–8 ampholines (BDH) for 9600 volt-hours. The tube gels were separated on 10% acrylamide slab gels and stained with silver nitrate.20

**INOCULATION OF A RHESUS MACAQUE WITH THE BMGH ISOLATE**

To evaluate the ability of the isolate to cause disease, we next inoculated a rhesus macaque previously infected with the simian immunodeficiency virus. BMGH (culture passage 2) was grown for 6 days to confluency on 5% fresh defibrinated rabbit blood agar. The plates were scraped into M199 medium with Earle’s salts and mixed, and 100 to 150 ml of the mixture (1.89x10^8 colony-forming units per milliliter) was inoculated intradermally in each of eight separate sites. In addition, 0.8 ml of inoculum was further diluted to a final volume of 4 ml with M199 medium with Earle’s salts and was inoculated intravenously. Blood specimens from the inoculated macaque were cultured in a 2-ml EDTA tube (Becton Dickinson) twice a week and incubated at 35°C as previously described.3 All protocols and procedures were reviewed and approved by the institutional animal care and use committee.

**RESULTS**

A bartonella-like bacterium was isolated from a blood specimen from the patient. Fifteen days after inoculation, a positive signal was detected in the BACTEC bottle inoculated with the blood specimen. No organisms were detected on Gram’s staining, but clusters of organisms were found on acridine-orange staining (Fig. 1A). Agar plates inoculated with broth from the blood culture with a positive signal grew confluent colonies after 10 days of incubation. Small, gram-negative bacilli with multiple, unipolar flagella were visualized on transmission electron microscopy (Fig. 1B). The appearance of the BMGH isolate was indistinguishable from that of B. bacilliformis. Repeat blood cultures were performed 6 weeks after the first set, and the patient was treated with a second course of antibiotics, oral clarithromycin for 10 days. The follow-up cultures were negative.

Using the homologous BMGH antigen, we found a significant increase in the IgG antibody level and a significant decrease in the IgM antibody level in the serum samples at 6 weeks, each differing by a factor greater than four as compared with the serum samples at presentation (Table 1). The titers were consistent with an acute infection caused by this bartonella organism.

Comparison of the gene sequences of the 16S ribosomal DNA (rDNA), the gltA and rpoB fragments, and the 16S–23S intergenic spacer region showed that the BMGH isolate is a new bartonella species, most closely related phylogenetically to B. clarridgeiae. The sequence of an 1171-bp fragment of the BMGH 16S rDNA had 99.2 to 99.7% similarity to that of B. clarridgeiae, with nine variable nucleotide positions (four that were consistently different from those found in the five
B. clarridgeiae isolates tested) (Table 2 of the Supplementary Appendix).

Among the bartonella species, sequences of BMGH gltA and rpoB fragments were again most similar to B. clarridgeiae (95.9% and 91.7% similarity, respectively) (Table 3 of the Supplementary Appendix), a finding that is consistent with the proposed criteria for a new bartonella species. Searching with the use of the Basic Local Alignment Search Tool revealed that the 1439-bp fragment of the 16S–23S intergenic spacer region was most similar to that of the uncultured bartonella F17688 (GenBank accession no. AF415211), amplified from a flea (pulex species) removed from a human in Cuzco, Peru. The 970-bp sequence available for bartonella F17688 had 99.8% similarity with the corresponding sequence of the 16S–23S intergenic spacer region of the BMGH isolate (with only two differences detected). Phylogenetic analysis of this fragment resulted in the placement of the BMGH isolate and the uncultured bartonella F17688 in the same clade as B. clarridgeiae (Fig. 2), but the eight B. clarridgeiae isolates from different geographic regions formed a phylogenetic lineage that differed from that of the BMGH and F17688 isolates (supported by 100% of the bootstrap replications). These genetic data indicate that BMGH is a new bartonella species, which we have named B. rochalimae, that is distinct from B. clarridgeiae.

The one-dimensional protein profiles show distinct differences between BMGH and the two B. clarridgeiae isolates, two B. bacilliformis isolates, B. henselae, and B. quintana (Fig. 1G of the Supplementary Appendix). The two-dimensional protein profiles of both the cytosolic and total-outer-membrane protein subcellular fractions of BMGH (Fig. 1C and 1D in the Supplementary Appendix) also showed a profile distinct from those of B. bacilliformis (Fig. 1A and 1B in the Supplementary Appendix) and B. clarridgeiae (Fig. 1E and 1F in the Supplementary Appendix).

After experimental inoculation of the macaque with BMGH, bacteremia was detected first on day 14 and also on days 17, 22, and 24 (0.75, 1.50, 12.75, and 11.25 colony-forming units per milliliter, respectively). Isolates were confirmed to be BMGH by means of amplification and sequencing of the 16S rDNA. The animal had an increase in temperature (from 37.6°C to 38.7°C on day 3) and a decrease in hematocrit (from 40.1% to 33.9% on day 7, with a gradual increase to 38.3% by day 70).

**DISCUSSION**

The bartonella genus consisted of a single species in 1992, but there are now 19 officially recognized and extant species and subspecies. At present, humans are the sole reservoir host for only two spe-
cies of bartonella: *B. quintana* and *B. bacilliformis*. One additional species, *B. henselae*, has been isolated occasionally from immunocompromised humans, but the domestic cat is the primary mammalian reservoir for this species. Distinct epidemiologic risk factors are significantly associated with the acquisition of these three bartonella species that infect humans: homelessness and exposure to human body lice for *B. quintana*, scratches from kit­
tens infested with fleas for *B. henselae*, and visits to or residence in a geographically restricted region of the Andes where the sand-fly vector is found for *B. bacilliformis*.

Our patient presented with fever, splenomegaly, anemia, and a history of insect bites after a trip to Peru that included travel to a region in which *B. bacilliformis* is endemic. On the basis of clinical, epidemiologic, and microbiologic evi-

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**Figure 2. Phylogenetic Tree of the 16S–23S Intergenic Spacer Region in Bartonella Species.**

The new isolate, BMGH, is most closely related to, but distinct from, *Bartonella clarridgeiae*. The numbers at the nodes are the percentages of 1000 bootstrap replications that support the configuration shown. Only bootstrap percentages greater than 80 are shown. The names of *B. clarridgeiae* isolates and GenBank accession numbers are shown after the species name. The homologous sequence of *Brucella melitensis* was used as the outgroup. Bartonella species isolated and propagated from humans are indicated with an asterisk.
dence, we initially assumed that the small, motile, fastidious bacterium isolated from her blood was *B. bacilliformis*. However, molecular characterization of the organism revealed a new species of bartonella, closely related to, but distinct from, *B. claridgeiae*. The mammalian reservoir for *B. claridgeiae* is the domestic cat, and the prevalence of *B. claridgeiae* bacteremia in cats varies worldwide, from less than 10% in the United States to 36% in Europe.25,26 Despite the substantial prevalence of *B. claridgeiae* in cats, it has never been isolated in a human or amplified from human tissue specimens, including those from patients with cat scratch disease or bacillary angiomatosis.4,27

*B. bacilliformis* has caused multiple outbreaks of Oroya fever in persons living in certain regions of Peru, Ecuador, and Colombia. Many of these persons received a diagnosis of infection with *B. bacilliformis* on the basis of clinical findings and examination of blood smears or blood cultures. Although we did not observe intraerythrocytic organisms on the blood smear from our patient, the fever, anemia, splenomegaly, and isolation of a bartonella species raise the possibility that some cases of Oroya fever could represent infection with this new bartonella species. It will be of interest to determine the prevalence of this new species in humans residing in the Andes and to identify whether it also can cause a form of infection similar to verruga peruana, the chronic form of infection with *B. bacilliformis*.

*B. bacilliformis* and *B. quintana* are transmitted to humans by arthropods. Our patient noted insect bites on her legs and feet during her trip to Peru, but the source insect could not be identified. Using a polymerase-chain-reaction assay, Parola et al.22 identified a sequence for the 16S–23S intergenic spacer region in a pulex flea found on a person in Cuzco, Peru, that was nearly identical to the BMGH sequence — suggesting a possible vector.

In conclusion, we have identified a new bartonella species that caused an illness with features resembling Oroya fever in a patient who had recently traveled to Peru. Whether a zoonotic reservoir exists and the mechanism by which human infection occurs are currently unknown. This case illustrates the importance of culturing specimens from patients to test for bartonella species, performing careful molecular characterization of bartonella isolates, and remaining vigilant for new bartonella species that are pathogenic in humans.

To fulfill the rules of the International Code of Nomenclature of Bacteria (Lapage SP, Sneath PHA, Lesef EF, Skerman VBD, Seeliger HPR, Clark WA. International code of nomenclature of bacteria (1990 revision). Washington, DC: American Society for Microbiology, 1992.), we provide the following description of the novel species identified in this report. Description of *Bartonella rochalimae* sp. nov.*Bartonella rochalimae* (ro.cha.li.ma'e. N.L. gen. masc. n. rochalimae, of Rochalima, named in honor of Henrique da Rocha-Lima, an early Brazilian investigator of the etiology of rickettsial diseases). Small, motile, fastidious gram-negative rod with multiple, unipolar flagella that grows on fresh defibrinated rabbit-blood agar at 35°C in a candle extinction jar. *Bartonella rochalimae* is differentiated genetically from other *Bartonella* species on the basis of unique sequences of 16S rDNA, glnA and rpoB genes, and 16S–23S intergenic spacer region. The bacterium infects and is pathogenic for humans and macaques. The type strain is BMGH (available as American Type Culture Collection no. BAA-1498), isolated from a 43-year-old woman with splenomegaly, fever, anemia, and recent travel to Peru.

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

We thank Nafisa Ghori for her assistance with the electron microscopy and Wilhelm von Morgenland, Linda Hirst, and the Research Services Staff for their technical assistance with the primate inoculation at the California National Primate Research Center, University of California at Davis.


Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000


ABSTRACT

BACKGROUND
Mortality from coronary heart disease in the United States has decreased substantially in recent decades. We conducted a study to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in cardiovascular risk factors.

METHODS
We applied a previously validated statistical model, IMPACT, to data on the use and effectiveness of specific cardiac treatments and on changes in risk factors between 1980 and 2000 among U.S. adults 25 to 84 years old. The difference between the observed and expected number of deaths from coronary heart disease in 2000 was distributed among the treatments and risk factors included in the analyses.

RESULTS
From 1980 through 2000, the age-adjusted death rate for coronary heart disease fell from 542.9 to 266.8 deaths per 100,000 population among men and from 263.3 to 134.4 deaths per 100,000 population among women, resulting in 341,745 fewer deaths from coronary heart disease in 2000. Approximately 47% of this decrease was attributed to treatments, including secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for acute myocardial infarction or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Approximately 44% was attributed to changes in risk factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%), although these reductions were partially offset by increases in the body-mass index and the prevalence of diabetes, which accounted for an increased number of deaths (8% and 10%, respectively).

CONCLUSIONS
Approximately half the decline in U.S. deaths from coronary heart disease from 1980 through 2000 may be attributable to reductions in major risk factors and approximately half to evidence-based medical therapies.
Rates of death from coronary heart disease in the United States underwent profound secular changes during the 20th century.\textsuperscript{1,2} After peaking around 1968, age-adjusted rates were cut in half. Two factors may have contributed to this decline.

First, there have been substantial decreases in the prevalence of some major cardiovascular risk factors, including smoking, elevated total cholesterol, and high blood pressure.\textsuperscript{3-8} However, the prevalence of both obesity and diabetes has increased alarmingly.\textsuperscript{9-11}

Second, there has been a revolution in the treatments for established coronary heart disease, with major breakthroughs in evidence-based therapies, including the use of thrombolysis, coronary-artery bypass grafting (CABG), coronary angioplasty and stents, and angiotensin-converting–enzyme (ACE) inhibitors and statins.

The annual direct and indirect costs for coronary heart disease were $142.5 billion in 2006, and they continue to rise.\textsuperscript{12} Determining the respective contributions of prevention and therapy to the declines in mortality from coronary heart disease is therefore becoming increasingly important, for the purposes of both understanding past trends and planning future strategies. Estimates of the contribution from reductions in risk factors before 1990 have ranged from 50 to 54\% in the United States\textsuperscript{13,14} and from 44 to 76\% in other industrialized countries.\textsuperscript{15-22} However, to our knowledge, no U.S. studies have considered the dramatic changes since 1990 or have attempted to quantify the relative contributions of specific therapies and trends in risk factors. We therefore applied a model that has been used successfully in several other countries to examine trends in U.S. deaths from coronary heart disease between 1980 and 2000.

Methods

Mortality Model and Data Sources
To examine the contributions of various factors to the changes in rates of death from coronary heart disease among U.S. adults 25 to 84 years of age, we used an updated version of the IMPACT mortality model, which was previously validated in Europe, New Zealand, and China.\textsuperscript{19,20} This model has been described in detail elsewhere.\textsuperscript{19,19,23,24} It incorporates major population risk factors for coronary heart disease (smoking, high blood pressure, elevated total cholesterol, obesity, diabetes, and physical inactivity) and all usual medical and surgical treatments for coronary heart disease.

Wherever possible, data sources specific to the U.S. population were used to construct the U.S. model. When more than one data source was available, we chose the source that we considered to be most representative, least biased, and most up-to-date. Detailed information on the IMPACT model and data sources for the U.S. analysis is provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Deaths Prevented or Postponed
Data on the total U.S. population and age distribution in 1980 and 2000 were obtained from the U.S. Census Bureau. Deaths according to age and sex and mortality rates associated with coronary heart disease in 1980 and 2000 were obtained from the National Vital Statistics System of the National Center for Health Statistics. We calculated the number of deaths from coronary heart disease that would have been expected in 2000 if the mortality rates in 1980 had remained unchanged by multiplying the age-specific mortality rates for 1980 by the population for each 10-year age stratum in the year 2000 (thus accounting for the aging of the population). Subtracting the number of deaths observed in 2000 from the number expected then yielded the drop in the number of deaths (prevented or postponed) in 2000 that the model would have to explain.

Treatments and Mortality Reductions
The prevalence of coronary heart disease by diagnosis, the estimated frequency of use of specific treatments, the case fatality rate by diagnosis, and the risk reduction due to treatment, all stratified by age and sex, were obtained from published sources (Tables 2 through 5 in the Supplementary Appendix). The number of deaths prevented or postponed as a result of each intervention in each group of patients in the year 2000 (Table 1) was calculated by multiplying the number of people in each diagnostic group by the proportion of those patients who received a particular treatment, by the case fatality rate over a period of 1 year, and by the relative reduction in the 1-year case fatality rate that was accounted for by the treatment.\textsuperscript{19,20} For example, in the United States in 2000, approximately 102,280 men between the
Table 1. Estimated Deaths Prevented or Postponed by Medical or Surgical Treatments in the United States in 2000.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Eligible Patients</th>
<th>Patients Receiving Treatment</th>
<th>Relative Risk Reduction</th>
<th>Mean Case Fatality Rate</th>
<th>Absolute Risk Reduction</th>
<th>Deaths Prevented or Postponed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>percent</td>
<td>Best Estimate</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>670,715</td>
<td>—</td>
<td>—</td>
<td>0.094</td>
<td>21.570</td>
<td>9,045</td>
</tr>
<tr>
<td>Resuscitation in the community</td>
<td>204,330</td>
<td>43</td>
<td>0.05</td>
<td>0.094</td>
<td>0.050</td>
<td>4,435</td>
</tr>
<tr>
<td>Resuscitation in the hospital</td>
<td>13,415</td>
<td>100</td>
<td>0.33</td>
<td>0.094</td>
<td>0.342</td>
<td>4,095</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>670,715</td>
<td>20</td>
<td>0.24</td>
<td>0.094</td>
<td>0.019</td>
<td>2,410</td>
</tr>
<tr>
<td>Aspirin</td>
<td>670,715</td>
<td>84</td>
<td>0.15</td>
<td>0.094</td>
<td>0.014</td>
<td>7,735</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>670,715</td>
<td>7</td>
<td>0.31</td>
<td>0.094</td>
<td>0.025</td>
<td>340</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>670,715</td>
<td>16</td>
<td>0.04</td>
<td>0.094</td>
<td>0.004</td>
<td>805</td>
</tr>
<tr>
<td>Primary angioplasty</td>
<td>670,715</td>
<td>21</td>
<td>0.07</td>
<td>0.094</td>
<td>0.007</td>
<td>1,070</td>
</tr>
<tr>
<td>Primary CABG</td>
<td>670,715</td>
<td>8</td>
<td>0.39</td>
<td>0.094</td>
<td>0.037</td>
<td>1,925</td>
</tr>
<tr>
<td>Treatments in 1980 subtracted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–1,245</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>665,260</td>
<td></td>
<td>0.065</td>
<td></td>
<td>13.575</td>
<td>6,960</td>
</tr>
<tr>
<td>Aspirin and heparin</td>
<td>60</td>
<td>0.33</td>
<td>0.065</td>
<td>0.021</td>
<td>6,350</td>
<td>3,250</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>17</td>
<td>0.15</td>
<td>0.065</td>
<td>0.010</td>
<td>790</td>
<td>410</td>
</tr>
<tr>
<td>Glycoprotein IIb/Illa antagonists and clopidogrel</td>
<td>21</td>
<td>0.09</td>
<td>0.065</td>
<td>0.006</td>
<td>595</td>
<td>310</td>
</tr>
<tr>
<td>CABG</td>
<td>20</td>
<td>0.43</td>
<td>0.065</td>
<td>0.028</td>
<td>2,760</td>
<td>1,415</td>
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<tr>
<td>Angioplasty</td>
<td>30</td>
<td>0.32</td>
<td>0.065</td>
<td>0.021</td>
<td>3,080</td>
<td>1,575</td>
</tr>
<tr>
<td>Secondary prevention after myocardial infarction</td>
<td>2,866,965</td>
<td></td>
<td>0.057</td>
<td></td>
<td>28.565</td>
<td>12,255</td>
</tr>
<tr>
<td>Aspirin</td>
<td>38</td>
<td>0.15</td>
<td>0.057</td>
<td>0.007</td>
<td>5,135</td>
<td>2,285</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>29</td>
<td>0.23</td>
<td>0.057</td>
<td>0.012</td>
<td>6,750</td>
<td>2,765</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>26</td>
<td>0.20</td>
<td>0.057</td>
<td>0.010</td>
<td>5,155</td>
<td>2,125</td>
</tr>
<tr>
<td>Statin</td>
<td>36</td>
<td>0.22</td>
<td>0.057</td>
<td>0.011</td>
<td>4,700</td>
<td>2,175</td>
</tr>
<tr>
<td>Warfarin</td>
<td>9</td>
<td>0.22</td>
<td>0.057</td>
<td>0.012</td>
<td>2,175</td>
<td>870</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>21</td>
<td>0.26</td>
<td>0.057</td>
<td>0.012</td>
<td>4,650</td>
<td>2,040</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Estimated deaths prevented or postponed for selected medical or surgical treatments in the United States in 2000. Includes only treatments that have been shown to be beneficial in randomized trials.
### Secondary prevention after CABG or PTCA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deaths 1980</th>
<th>Deaths CABG 1990 to 2000</th>
<th>Deaths CABG in 1980 subtracted</th>
<th>Deaths angioplasty, 1990 to 2000</th>
<th>Deaths Aspirin in the community</th>
<th>Deaths Statins in the community</th>
<th>Deaths Heart failure in hospital admission</th>
<th>Deaths Heart failure in the community</th>
<th>Deaths Hypertension</th>
<th>Total treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>40</td>
<td>0.15</td>
<td>0.019</td>
<td>1.310</td>
<td>655</td>
<td>2.800</td>
<td>0.4</td>
<td>0.2</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>33</td>
<td>0.23</td>
<td>0.019</td>
<td>1.460</td>
<td>595</td>
<td>3.010</td>
<td>0.4</td>
<td>0.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>26</td>
<td>0.20</td>
<td>0.019</td>
<td>1.010</td>
<td>410</td>
<td>2.080</td>
<td>0.3</td>
<td>0.1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>38</td>
<td>0.22</td>
<td>0.019</td>
<td>1.550</td>
<td>665</td>
<td>3.365</td>
<td>0.5</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>9</td>
<td>0.22</td>
<td>0.019</td>
<td>0.450</td>
<td>180</td>
<td>915</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>32</td>
<td>0.26</td>
<td>0.019</td>
<td>1.655</td>
<td>665</td>
<td>3.360</td>
<td>0.5</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

### Secondary-prevention treatments in 1980 subtracted

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deaths 1980</th>
<th>Deaths CABG 1990 to 2000</th>
<th>Deaths CABG in 1980 subtracted</th>
<th>Deaths angioplasty, 1990 to 2000</th>
<th>Deaths Aspirin in the community</th>
<th>Deaths Statins in the community</th>
<th>Deaths Heart failure in hospital admission</th>
<th>Deaths Heart failure in the community</th>
<th>Deaths Hypertension</th>
<th>Total treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>40</td>
<td>0.15</td>
<td>0.019</td>
<td>1.310</td>
<td>655</td>
<td>2.800</td>
<td>0.4</td>
<td>0.2</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>33</td>
<td>0.23</td>
<td>0.019</td>
<td>1.460</td>
<td>595</td>
<td>3.010</td>
<td>0.4</td>
<td>0.2</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>26</td>
<td>0.20</td>
<td>0.019</td>
<td>1.010</td>
<td>410</td>
<td>2.080</td>
<td>0.3</td>
<td>0.1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
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<td>0.22</td>
<td>0.019</td>
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<td>665</td>
<td>3.365</td>
<td>0.5</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
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<td>0.019</td>
<td>0.450</td>
<td>180</td>
<td>915</td>
<td>0.1</td>
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<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>32</td>
<td>0.26</td>
<td>0.019</td>
<td>1.655</td>
<td>665</td>
<td>3.360</td>
<td>0.5</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages may not sum to 100 because of rounding. Data sources are described in the Supplementary Appendix. CABG denotes coronary-artery bypass grafting, AMI acute myocardial infarction, ACE angiotensin-converting enzyme, and PTCA percutaneous transluminal coronary angioplasty (with or without stenting).

† The number of deaths prevented or postponed includes 475 that were prevented or postponed owing to treatment with gemfibrozil and niacin for primary prevention of hyperlipidemia.
ages of 55 and 64 years were hospitalized with acute myocardial infarction. Some 84% were given aspirin, with an expected mortality reduction of 15%. The expected age-specific, 1-year case fatality rate was approximately 5.4%. The number of deaths prevented or postponed as a result of the change in risk factors was estimated as the number of deaths from coronary heart disease in 1980 (the base year), the subsequent reduction in that risk factor (Table 2 in the Supplementary Appendix), and the regression coefficient quantifying the change in mortality from coronary heart disease per unit of absolute change in the risk factor (Table 6 in the Supplementary Appendix). For example, in 1980, there were 26,352 deaths from coronary heart disease among 12,629,000 women who were 55 to 64 years of age. The mean systolic blood pressure in this group decreased by 3.09 mm Hg between 1980 and 2000. The largest meta-analysis showed an estimated age- and sex-specific reduction in mortality of 50% for every reduction of 20 mm Hg in systolic pressure, yielding a logarithmic (ln) coefficient of -0.035.

The number of deaths prevented or postponed as a result of this change was then estimated as follows:

\[
\text{number of deaths} = (1 - e^{(-0.035 \times 3.09)}) \times 26,352 \approx 2701.
\]

The population-attributable risk fraction was used to determine the effect of changes in the prevalence of smoking, diabetes, and physical inactivity. The population-attributable risk fraction was calculated conventionally as \([P \times (R-R-I)] + [(1+P) \times (R-R-I)]\), where \(P\) is the prevalence of the risk factor (Table 2 in the Supplementary Appendix) and \(R\) is the relative risk of death from coronary heart disease associated with that risk factor (Table 7 in the Supplementary Appendix). The number of deaths prevented or postponed was then estimated as the number of deaths from coronary heart disease in 1980 (the base year) multiplied by the difference between the population-attributable risk fraction in 1980 and that in 2000 (Table 2).

For example, the prevalence of diabetes among men 65 to 74 years of age increased from 14.5% in 1980 to 20.7% in 2000. Given a relative risk of 1.93, the population-attributable risk fraction increased from 0.119 to 0.161. Additional deaths from coronary heart disease in 2000 that were attributable to an increased prevalence of diabetes were therefore calculated as follows:

\[
\text{deaths from coronary heart disease in 2000} = (123,055 \times (0.161 - 0.119)) = 5168.
\]

Because independent regression coefficients and relative risks for each risk factor were obtained from multivariate analyses, we assumed...
Table 2. Deaths from Coronary Heart Disease That Were Prevented or Postponed as a Result of Changes in Population Risk Factors in the United States, 1980 to 2000.†

<table>
<thead>
<tr>
<th>Risk Factor†</th>
<th>Absolute Level of Risk Factor</th>
<th>Change in Risk Factor</th>
<th>Beta Regression Coefficient for Change in Mortality Rate§</th>
<th>Relative Risk</th>
<th>Deaths Prevented or Postponed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking prevalence (%)</td>
<td>36.3</td>
<td>24.6</td>
<td>−11.7</td>
<td>−32.2</td>
<td>39,925</td>
</tr>
<tr>
<td>Men</td>
<td>2.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>2.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>129.0</td>
<td>123.9</td>
<td>−5.1</td>
<td>−4.0</td>
<td>68,800</td>
</tr>
<tr>
<td>Men</td>
<td>−0.0334</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>−0.0413</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>5.67</td>
<td>5.33</td>
<td>−0.34</td>
<td>−6.1</td>
<td>82,830</td>
</tr>
<tr>
<td>Men</td>
<td>−0.9458</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>−0.9121</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical inactivity (%)</td>
<td>29.6</td>
<td>27.3</td>
<td>−2.3</td>
<td>−7.8</td>
<td>—</td>
</tr>
<tr>
<td>Men</td>
<td>1.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>25.6</td>
<td>28.2</td>
<td>+2.6</td>
<td>10.1</td>
<td>−25,905</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td>0.0297</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td>0.0297</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes prevalence (%)</td>
<td>6.5</td>
<td>9.4</td>
<td>+2.9</td>
<td>44.2</td>
<td>—</td>
</tr>
<tr>
<td>Men</td>
<td>1.93</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Women</td>
<td>2.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>149,635</td>
</tr>
</tbody>
</table>

* Percentages may not sum to 100 because of rounding. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters). To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. Data sources are described in the Supplementary Appendix.
† The total adult population in 1980 was 177,745,055. For systolic pressure, the numbers of deaths exclude patients receiving treatment for hypertension, and for total cholesterol, the numbers exclude patients receiving statins.
‡ Data are from the National Center for Health Statistics, except for data on physical inactivity, which are from the Behavioral Risk Factor Surveillance System.
§ The change in the mortality rate per unit of measurement for the risk factor is shown.
that there was no further synergy between the treatment and risk-factor sections of the model or among the major risk factors.

The number of deaths prevented or postponed as a result of changes in risk factors was systematically quantified for each specific patient group to account for potential differences in effect. Lag times between the change in the risk-factor rate and the change in the event rate were not modeled; it was assumed that these lag times would be relatively unimportant over a period of two decades.20,23,34,35

**COMPARISON OF ESTIMATED AND OBSERVED MORTALITY CHANGES**

The model estimates for the total number of deaths prevented or postponed by each treatment and for each risk-factor change were rounded to the nearest multiple of 5 (e.g., 696 became 695). All these figures were then summed and compared with the observed changes in mortality for men and women in each age group. Any shortfall in the overall model estimate was then presumed to be attributable either to inaccuracies in our calculated estimates or to other, unmeasured risk factors.19,20,24

**SENSITIVITY ANALYSES**

We tested all the above assumptions and variables in a multiple-way sensitivity analysis, using the analysis-of-extremes method.19,20,24,36 For each variable in the model, we assigned a lower value and an upper value, using 95% confidence intervals when available and otherwise using ±20% (for the number of patients, use of treatment, and compliance). For example, for aspirin treatment in men 55 to 64 years of age who were hospitalized with acute myocardial infarction, the best estimate was 696 deaths prevented or postponed. The minimum estimate from the multiple-way sensitivity analysis was 259, and the maximum estimate was 1501 (Table 3).

### RESULTS

From 1980 to 2000, the age-adjusted rate of coronary heart disease fell from 542.9 to 266.8 cases per 100,000 population among men aged 25 to 84 years and from 263.3 to 134.4 among women aged 25 to 84 years. In 1980, a total of 462,984 deaths among people in this age group were recorded as due to coronary heart disease, according to the International Classification of Diseases, 9th Revision (codes 410–414 and 429.2).41 In 2000, a total of 337,658 such deaths were recorded, according to the International Classification of Diseases, 10th Revision (codes I20–I25).42 However, had the age-specific death rates from 1980 remained in 2000, an additional 341,745 deaths from coronary heart disease would have occurred.

The U.S. IMPACT model explained approximately 308,965 (90%) of this decrease in the number of deaths from coronary heart disease. Under the assumptions of the sensitivity analysis,

| Table 3. Example of a Multiple-Way Sensitivity Analysis.† |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Estimate                | No. of Patients (a)†     | Proportion Receiving Treatment (b)‡ | Relative Mortality Reduction (c)‡ | 1-Year Case Fatality Rate (d)‡ |
| Best                    | 102,280                 | 0.84                      | 15                       | 5.4                     |
| Minimum                 | 81,824                  | 0.67                      | 11                       | 4.3                     |
| Maximum                 | 122,736                 | 0.99                      | 19                       | 6.5                     | 1501

* In the United States in 2000, about 102,280 men aged 55 to 64 years were hospitalized with acute myocardial infarction, of whom approximately 84% were given aspirin. Aspirin use reduced the case fatality rate by approximately 15%. The underlying 1-year case fatality rate in these men was approximately 5.4%. The calculated number of deaths prevented or postponed was approximately 696. A multiple-way sensitivity analysis was then performed. Lower and upper bounds for each variable were estimated with use of 95% confidence intervals, when available, or failing that, with use of calculated bounds of ±20% (treatment uptake, however, was capped at 99%). Multiplying all lower-bound estimates together yielded the lower-bound estimate of deaths prevented or postponed, and multiplying all upper-bound estimates together yielded the upper-bound estimate of deaths prevented or postponed.

† Numbers of patients are from the National Hospital Discharge Survey37 and the Medical Expenditure Panel Survey.38
‡ Treatment data are from Rogers et al.,39 data on mortality reduction are from the Antithrombotic Trialists‘ Collaboration,40 and case fatality rates are from Capewell et al.26
the minimum and maximum numbers of deaths from coronary heart disease that were explained were 175,230 (51%) and 545,755 (160%). The agreement between the number of estimated deaths and the number of observed deaths was reasonably good for men across all groups and for women under the age of 75 years (Fig. 1). Changes in medical treatments accounted for approximately 47% and risk-factor changes accounted for approximately 44% of the decrease in deaths (Tables 1 and 2).

**MEDICAL AND SURGICAL TREATMENTS**

Approximately 159,330 of the deaths from coronary heart disease that were prevented or postponed were attributable to medical therapies (minimum estimate, 58,065; maximum estimate, 347,395) (Table 1). The largest reductions in deaths came from the use of secondary-prevention medications or rehabilitation after acute myocardial infarction or after revascularization (a total reduction of approximately 35,800 deaths) and from the use of initial treatments for acute myocardial infarction or unstable angina (approximately 35,145 deaths), followed by treatments for heart failure and hypertension, statin therapy for primary prevention, and treatments for chronic angina. The use of revascularization for chronic angina resulted in a reduction of approximately 15,690 deaths in 2000, as compared with deaths in 1980, or approximately 5% of the total.

**RISK FACTORS**

Approximately 149,635 fewer deaths from coronary heart disease were attributable to changes in risk factors (minimum estimate, 117,165; maximum estimate, 198,360) (Table 2). Decreases in the total cholesterol concentration (by 0.34 mmol per liter), systolic blood pressure (by 5.1 mm Hg), and smoking prevalence (by 11.7%) were estimated to have prevented or postponed approximately 82,830, 68,800, and 39,925 deaths, respectively. The 2.3% decrease in physical inactivity prevented or postponed approximately 17,445 deaths. In contrast, the increase in the body-mass index (the weight in kilograms divided by the square of the height in meters) of 2.6 and the 2.9% increase in the prevalence of diabetes resulted in approximately 25,905 and 33,465 additional deaths overall, respectively (Table 2).

**PROPORTIONAL CONTRIBUTIONS TO THE DECREASE IN DEATHS**

Sensitivity analyses showed that the proportional contributions of specific treatments and risk-factor changes to the overall reduction in deaths from coronary heart disease in 2000 were relatively consistent (Tables 1 and 2). Thus, all initial treatments for acute myocardial infarction together accounted for approximately 21,570 fewer deaths, representing 6.3% of the total decrease of 341,745 deaths. The minimum estimated contribution was 9045 fewer deaths (2.6%), and the maximum was 37,720 (11.0%). The contribution of treatments for acute myocardial infarction therefore remained consistently smaller than that of secondary prevention or therapies for heart failure, irrespective of whether best, minimum, or maximum estimates were compared (Table 1).

**DISCUSSION**

The burden of coronary heart disease in the United States remains enormous, even though associated mortality rates fell by more than 40% between 1980 and 2000. These two decades saw rapid growth in costly medical technology and pharmaceutical treatments for coronary heart disease, as well as substantial public health efforts to reduce the prevalence of risk factors. The observed decrease in deaths in each age group, and the vertical lines the extreme minimum and maximum estimates in the sensitivity analysis.
the prevalence of major cardiovascular risk factors. Establishing the relative contributions of these two approaches is therefore of considerable importance. We found that reductions in major risk factors probably accounted for approximately half the decrease in deaths from coronary heart disease, as in most other industrialized countries studied.\textsuperscript{15-22} Earlier U.S. studies likewise suggested a contribution of approximately 54% of the reduction in deaths between 1968 and 1976\textsuperscript{14} and approximately 50% between 1980 and 1990.\textsuperscript{13}

Irrespective of the assumptions used, we found that the largest contributions from medical therapies consistently came from secondary prevention, followed by treatments for acute coronary syndromes, then heart failure. Revascularization by means of CABG or angioplasty for stable or unstable disease together accounted for approximately 7% of the overall drop in deaths from coronary heart disease, a finding that is consistent with the results of previous studies in the United States\textsuperscript{35} and elsewhere.\textsuperscript{19-22,44}

Although most of the changes in treatments and risk factors between 1980 and 2000 led to reductions in deaths from coronary heart disease, two major exceptions are noteworthy. Our analysis estimated that increases in the body-mass index accounted overall for about 26,000 additional deaths from coronary heart disease in 2000 and increases in the prevalence of diabetes for about 33,500 additional deaths; both figures are consistent with the results of other recent studies.\textsuperscript{45,46} Efforts to address these two risk factors should therefore receive particular attention in future measures to improve the public health.\textsuperscript{10,11}

Modeling studies have a number of potential strengths, including the ability to transparently integrate and simultaneously consider huge amounts of data from many sources and then test explicit assumptions by means of sensitivity analyses. Our analysis of extremes suggested that the proportional contributions to the overall reductions in deaths from specific treatments and risk-factor changes remained reasonably consistent, irrespective of whether best, minimum, or maximum estimates were considered (Tables 1 and 2). This was reassuring, as was the general consistency with the results of most studies performed elsewhere (Fig. 2).\textsuperscript{15-17,19,20}

However, all modeling analyses should be interpreted with appropriate caution. All require the gathering of data from numerous sources, each with recognized limitations. We sometimes had to use data from studies that might have been limited by geographic, ethnic, or selection bias or by the need to extrapolate to older age groups. Risk estimates were not necessarily fully independent of each other. Furthermore, most interactions were averaged across broad groups. We therefore made the explicit assumptions detailed in the Supplementary Appendix. Furthermore, we analyzed only the estimated reduction in deaths from coronary heart disease, not life-years gained or improvement in the quality of life.\textsuperscript{47} Analyses of these changes are warranted, as well as comparisons among racial and ethnic groups and economic analyses.

The estimates of changes in risk factors remain imprecise. Furthermore, we did not explicitly consider the effect of lag times; however, they may be relatively unimportant over a 20-year period.\textsuperscript{20,23,33,35} Although major efforts were made to address overlaps, residual double counting of some individual patients remains possible. We
also assumed that, after adjustments for reduced dosing and imperfect compliance, the efficacy of treatments in randomized, controlled trials could be generalized to usual clinical practice.48-49 Both assumptions may have potentially overestimated the true treatment effect.

In conclusion, our analyses suggest that approximately half the recent decrease in deaths from coronary heart disease in the United States may be attributable to reductions in major risk factors and approximately half to evidence-based medical therapies. Future strategies for preventing and treating coronary heart disease should therefore be comprehensive, maximizing the coverage of effective treatments and actively promoting population-based prevention by reducing risk factors.

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

The findings and conclusions in this article are those of the authors and do not represent the views of the Centers for Disease Control and Prevention.

REFERENCES


Local Therapy and Survival in Breast Cancer

Rinaa S. Punglia, M.D., M.P.H., Monica Morrow, M.D., Eric P. Winer, M.D., and Jay R. Harris, M.D.

The effect of local therapy on the survival of patients with breast cancer has been debated for decades. Three viewpoints have been proposed on the basis of various hypotheses concerning the biology of breast cancer. Is breast cancer a local disease that spreads predictably over time to develop distant metastases? Is it a systemic disease from the outset, with distant metastases present well before diagnosis? Or is the truth somewhere in between, with many cancers being localized at diagnosis and, if untreated or recurrent, acquiring the ability to metastasize and kill? These differing views have vastly different implications for the treatment of patients. Recently, several lines of evidence have emerged that suggest answers to these questions.

Three Theories of Cancer Spread

Throughout the first half of the 20th century, the prevailing theory of the development of distant metastasis in breast cancer was shaped by the thinking of Dr. William Halsted and his disciples. The “Halstedian” theory proposed that breast cancer begins as a strictly local disease and that tumor cells spread over time in a contiguous manner away from the primary site through lymphatics. According to this theory, even distant metastases are the result of direct extensions of local involvement (affecting the breast, the chest wall, axillary and supraclavicular lymph nodes, or any combination of the sites). The Halstedian approach thus dictated that aggressive local therapy for control of disease in the breast, chest wall, and regional lymph nodes would have a substantial effect on survival. His ideas also provided justification for ever more radical breast-cancer surgery.

The “systemic” view arose in reaction to the Halstedian theory, since disease develops at distant sites in many women with breast cancer, even though the primary cancer is well controlled locally with aggressive surgery. On the basis of this information, Dr. Bernard Fisher and others promulgated the view that breast cancer is a systemic disease and that it can be divided into two distinct groups: tumors that have the ability to metastasize to distant sites and those that lack this ability. According to this view, which prevailed in the last half of the 20th century, if distant metastases were destined to develop, such metastases had already occurred at the time of diagnosis of the breast tumor. Because the length of a patient’s overall survival is a function of distant disease, this theory predicted that treatments that improve local control would have little or no effect on overall survival. Instead, the emphasis was on the importance of effective systemic therapy in breast-cancer treatment. Over the past three decades, the development of systemic therapy has indeed been associated with substantial improvements in the overall survival of patients with clinically localized breast cancer. During this time, patients were counseled that the prevention of a local recurrence was of limited importance with regard to survival, since such
a recurrence could be treated when it developed, and that the development of a local recurrence would not lead to the development of metastatic disease.

Although it is clear that the Halstedian view is not correct for all breast cancers, it is not clear that the systemic view is entirely correct either. A third hypothesis synthesized aspects of these two opposing approaches. In this view, breast cancer is “a heterogeneous disease . . . [with] a spectrum of proclivities extending from a disease that remains local throughout its course to one that is systemic when first detectable.”5-6 This theory holds that for many breast cancers, there is a time when tumor cells have not metastasized to distant sites but that it is generally not known whether this time has passed at the point of diagnosis for any patient. According to this view, failure to achieve initial local control will allow some tumors to disseminate later to distant sites, reducing a patient’s chance for long-term survival. The spectrum theory acknowledges that the greater the likelihood that systemic spread (now known to occur primarily through direct hematogenous routes) has occurred at the time of diagnosis in a patient, the lower the likelihood that local therapy will influence the patient’s survival.

**Evidence from Clinical Trials**

Until recently, most evidence from clinical trials seemed to support the systemic view of breast cancer. Randomized trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP), which studied the effect of improving local control by increasing the extent of surgery or adding radiation therapy after total mastectomy (NSABP B-04) or breast-conserving surgery (NSABP B-06), demonstrated similar survival for the different treatment groups despite substantial improvement in local control with additional surgery and radiation therapy. The results from these trials were widely interpreted as providing strong evidence for the systemic theory. However, in these trials, there were insufficient events (in this case, deaths) to detect small, but clinically important, differences in overall mortality.

Evidence has emerged that casts doubt on the validity of the systemic theory for all patients with breast cancer. First, there is evidence that mammographic screening reduces breast-cancer mortality. The summary findings from a meta-analysis of randomized studies of mammographic screening demonstrated that in screened populations, the relative risk of death from breast cancer was significantly reduced (relative risk, 0.85; 95% confidence interval [CI], 0.73 to 0.99), as compared with that in unscreened populations.9 Between 1990 and 2003, the rate of death from breast cancer among women of all ages, adjusted to the 2000 population, fell from 33.1 to 25.2 per 100,000 women, a decrease of 24%.10 It is estimated that about half of this reduction can be attributed to the increased use of screening mammography.11

Thus, in some patients, earlier diagnosis (with screening) can prevent the development of distant metastases. The reduction in mortality with earlier diagnosis strongly suggests that the likelihood of distant dissemination of the cancer can be influenced by the timing of the diagnosis. If the systemic theory were completely correct, early detection would have little effect on breast-cancer mortality. The fact that screening decreases mortality implies that at least some breast cancers develop the propensity to spread distantly over time and suggests that strict classification of breast cancers according to the systemic theory as either having or not having metastatic potential is not possible.

Second, there is mounting evidence from randomized clinical trials supporting a link between local control and overall survival in breast cancer. One such link was discovered from studying the addition of radiation therapy after mastectomy and adjuvant systemic therapy in women with breast cancer at high risk for local recurrence. Randomized trials have shown not only decreased local recurrences with radiation therapy but also an improvement in overall survival for both premenopausal12-15 and postmenopausal14,16 women.

Finally, because a single randomized study may not have the statistical power to detect small, but clinically meaningful, differences in survival, pooled analyses or meta-analyses of randomized trials have been undertaken to investigate the relationship between local control and mortality in breast cancer. A recent study by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) presented the findings from 78 randomized clinical trials evaluating the extent of surgery and the use of radiation therapy.17 This report analyzed data from 42,000 patients with breast cancer who had been treated in trials beginning before 1995 and examined more extensive versus less extensive surgery, radiation therapy versus no radiation therapy, and extensive surgery versus radiation therapy.
The most striking finding from the EBCTCG study was that improved local control at 5 years resulted in a highly statistically significant improvement in both breast-cancer survival and overall survival at 15 years. Furthermore, the absolute reduction in the 5-year rate of local recurrence between treatment groups was proportional to the absolute reduction in 15-year breast-cancer mortality. Treatments that had little or no effect on decreasing the 5-year rate of local recurrence had no benefit in terms of reducing 15-year breast-cancer mortality; however, treatments that led to an improvement in the 5-year rate of local recurrence also resulted in a reduction in breast-cancer mortality at 15 years (Fig. 1). The absolute benefit for breast-cancer mortality was similar for a given reduction in local recurrence, regardless of the method of achieving the reduction (i.e., by more extensive surgery or by the addition of radiation therapy). Among treatments that had more than a 10% reduction in the 5-year risk of local recurrence, breast-cancer mortality was reduced by 1.6% at 5 years, 3.7% at 10 years, and 4.9% at 15 years.17 For the trials in the EBCTCG meta-analysis17 that studied radiation therapy, the addition of radiation therapy significantly improved 15-year absolute overall survival after breast-conservation surgery, by 5.3% (P = 0.005), and after mastectomy in node-positive patients, by 4.4% (P = 0.001).

The findings from the mammographic screening trials and the EBCTCG meta-analysis of local therapy17 should end the debate among the theories of breast-cancer spread. The fact that both earlier diagnosis and improved local control improve overall survival refutes the systemic hypothesis that breast cancers either metastasize early in their development or will never metastasize, so that survival is not affected by the time of diagnosis or control of local disease. It is now clear that treatments that substantially reduce local recurrence have a resulting decrease in breast-cancer mortality and overall mortality, firmly supporting a causal link between local control and overall survival in some patients.

The effect of local therapy on survival must be considered in the context of systemic therapy. Adjuvant systemic therapy itself reduces the likelihood of both local and distant recurrence. The 2005 update from the EBCTCG meta-analysis of systemic therapy4 found that chemotherapy reduced local recurrence by 37% in women under the age of 50 years (hazard ratio, 0.63; 95% CI, 0.52 to 0.76) and that hormonal therapy reduced such recurrence by more than 50% in women of all ages (hazard ratio, 0.47; 95% CI, 0.38 to 0.59). These reductions in local recurrence with systemic therapy are reported in studies with and those without radiation therapy, but the magnitude of the reduction appears to be greater with the combination of systemic therapy and radiation therapy18-20 than with systemic therapy alone.18,21,22

A subgroup analysis in the EBCTCG meta-

![Figure 1. Effect of a Reduction in the 5-Year Risk of Local Recurrence on Breast-Cancer Mortality at 15 Years.](image-url)
analysis of local therapy\textsuperscript{23} showed that the use of radiation therapy after mastectomy in node-positive patients improved 15-year survival only in patients who also received adjuvant systemic therapy and not in patients who were treated with mastectomy alone. In patients at high risk for distant metastases, such as women with positive lymph nodes, radiation therapy in the absence of systemic therapy can improve survival only in the rare patient with residual local disease who has no distant dissemination. In contrast, in node-positive patients treated with mastectomy and adjuvant systemic therapy, radiation therapy will potentially contribute to survival in patients in whom systemic therapy eradicates microscopic metastases but not residual local disease.

Current systemic therapy is primarily effective against micrometastatic involvement. If systemic therapies that can eradicate clinically evident disease are developed, the influence of local therapy on mortality will be reduced and possibly eliminated. Some observers have hypothesized that there is an inverted-U-shaped, or parabolic, relationship between the benefit of local therapy on survival and the increasing effectiveness of systemic therapy (Fig. 2).\textsuperscript{24}

![Figure 2. Hypothetical Benefit of Local Tumor Control on Survival with Increasing Effectiveness of Systemic Therapy.](image)

The benefit of local therapy on survival has an inverted-U-shaped, or parabolic, relationship with increasingly effective systemic therapy, so that the survival benefit derived with better local therapy increases with increasingly effective systemic therapy, but only to a certain threshold of effectiveness, and then declines.\textsuperscript{24}

Understand Recurrent Disease

Is there a biologic explanation for the association between local control and survival? In the EBCTCG meta-analysis of local therapy,\textsuperscript{17} for every four local recurrences that were prevented at 5 years, there was about one less death from breast cancer at 15 years. This finding suggests that in about 25% of local recurrences, the cancer cells in the recurrent tumor have acquired the ability or have the opportunity to spread distantly, leading to an increased risk of death from metastatic disease. An increase in distant metastases after the diagnosis of local recurrence has been documented in both the breast-conservation and post-mastectomy settings.\textsuperscript{25-30} Indeed, breast cancers that are diagnosed after breast-conserving therapy and that are thought to be true recurrences as defined by tumor location, genetic assays, or histopathologic features carry a worse prognosis in terms of survival than do new primary breast cancers in the ipsilateral breast.\textsuperscript{31,32}

Local recurrences after breast-conserving therapy and after mastectomy are distinct clinical entities. Local recurrence after breast-conservation therapy typically presents as a mass, thickening, or retraction at the lumpectomy site within the treated breast or, more commonly, as a new abnormality seen on mammography. This finding emphasizes the need for follow-up monitoring of such patients with both physical examination and breast imaging. In contrast, the most common presentation of local recurrence after mastectomy is an asymptomatic nodule on or under the skin of the chest wall, typically near the mastectomy scar. Whereas local recurrences after breast-conserving therapy typically occur at a fairly constant rate during the decade after initial treatment, most local recurrences after mastectomy occur within 4 years after surgery. Retrospective and prospective studies have helped clinicians to establish the incidence of local recurrences and risk factors for their development. Table 1 lists the major risk factors for local recurrence after breast-conservation therapy and after mastectomy with our assessment of the strength of the association for each risk factor. Regional recurrences in the axillary, supraclavicular, or internal mammary lymph nodes may occur with or without simultaneous local recurrence.

In summary, clinicians caring for patients with
breast cancer can no longer be cavalier about the possibility of a local recurrence, yet data from the Surveillance, Epidemiology, and End Results registry indicate that about 12% of patients treated with breast-conserving surgery for invasive breast cancer do not receive radiation therapy.\textsuperscript{35} Similar concern exists over the abandonment of axillary dissection in patients found to have metastases to the sentinel node. The importance of local control should not be interpreted to mean that mastectomy should be considered the standard management strategy for breast cancer. Pooled analyses of randomized trials comparing mastectomy with breast-conserving therapy have shown equivalent survival.\textsuperscript{36} Instead, these findings emphasize the need for meticulous attention to maintaining local control through careful selection of patients for breast-conserving therapy, excision to negative margins,\textsuperscript{37} and the use of additional radiation dose to the tumor bed (boost).\textsuperscript{38} Although these strategies are important for all patients, they are particularly relevant for subgroups of women at increased risk for local recurrence after breast-conserving treatment, such as those who are under 35 years of age.\textsuperscript{39-44} Studies have indicated that most women with breast cancer are willing to undergo systemic chemotherapy for the possibility of very small (0.1 to 5.0%) improvements in survival.\textsuperscript{45-47} The survival benefits of achieving local control documented in the EBCTCG meta-analysis\textsuperscript{17} are of similar magnitude or greater than those accepted by patients for systemic therapy, yet they have received considerably less attention.

\section*{Future Directions}

The recognition of the influence of local control on survival not only has important implications for treatment decisions today but also should influence our approach to clinical and translational research in the years to come. Since more effective local control can be beneficial only in patients at risk for local recurrence, there is a need to identify more robust predictors of local recurrence. Gene-expression analyses have been used to identify patients at increased risk for distant recurrence.\textsuperscript{48,49} There is also the suggestion that expression profiling may be helpful in identifying patients at greater risk for local recurrence.\textsuperscript{50} We will need to gain a better understanding of the interplay between tumor biology, the anatomic extent of disease, and the risk of local recurrence. At the same time, it will be important to determine whether the risk reduction from improved local therapy varies across molecular subtypes of breast cancer. Breast-cancer care is a multidisciplinary endeavor, and progress in treatment will also require multidisciplinary research efforts that carefully consider the importance of local control.

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\begin{table}[h]
\centering
\caption{Risk Factors for Local Recurrence after Breast-Conserving Therapy and after Mastectomy.\textsuperscript{a}}
\begin{tabular}{|l|c|}
\hline
Risk Factor & Consistency of Association \\
\hline
\textbf{After breast-conserving therapy}\textsuperscript{†} & \\
Positive margin of resection & +++ \\
Young age of patient & ++ \\
Lack of systemic therapy & + \\
Close margin of resection & + \\
Lymphovascular invasion & + \\
Axillary-node involvement & + \\
\hline
\textbf{After mastectomy}\textsuperscript{‡} & \\
Increasing number of positive axillary lymph nodes & +++ \\
Lack of systemic therapy & ++ \\
Positive margin of resection & ++ \\
Close margin of resection & + \\
Tumor size & + \\
Young age of patient & + \\
Lymphovascular invasion & + \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} The strength of the association between each risk factor and local recurrence is classified as consistently reported (+++), often reported (++), or sometimes reported (+).
\textsuperscript{†} Data are from Clarke et al.\textsuperscript{17} and Morrow and Harris.\textsuperscript{33}
\textsuperscript{‡} Data are from Wong and Harris.\textsuperscript{34}


A 73-YEAR-OLD WOMAN PRESENTED WITH NEW-ONSET PERIORBITAL PURPURIC, nonblanching, nonpruritic lesions. The lesions appeared spontaneously and were not associated with any recent trauma. She did not take aspirin, nonsteroidal antiinflammatory drugs, or any other anticoagulant agents. On physical examination, no similar skin lesions were found elsewhere. In addition, laboratory studies revealed mild impairment of renal function and nephritic-range proteinuria. The blood count showed mild thrombocytopenia (platelet count, 80,000 per cubic millimeter), whereas the prothrombin time and partial-thromboplastin time were normal. Approximately 3 years earlier, the patient had received a diagnosis of multiple myeloma and acquired monoclonal immunoglobulin light-chain amyloidosis, for which she had not required any treatment. Therapy with cyclophosphamide and dexamethasone was initiated. The skin lesions waxed and waned repeatedly, with no apparent response to therapy. The patient died from pneumonia 6 months after the lesions first appeared.

Amyloid purpura appears in a minority of patients with amyloidosis. The purpura typically occurs above the nipple line and is often seen in the webbing of the neck, the face, and the eyelids. Factor X deficiency, resulting from the binding of factor X to amyloid fibrils, is thought to be one cause of the bleeding diathesis that may occur in patients with amyloidosis.
A Hand-Carried Diagnosis

Clinton L. Greenstone, M.D., Sanjay Saint, M.D., M.P.H., and Richard H. Moseley, M.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 34-year-old black woman presented to a walk-in clinic with a 3-day history of malaise. Her colleagues had noticed yellowing of her eyes over the past few days.

Scleral icterus, which is usually apparent when total serum bilirubin levels exceed 3 mg per deciliter (51 μmol per liter), is frequently first noticed not by the patient but by others. It may result from an excess of either unconjugated bilirubin (commonly due to hemolysis or ineffective erythropoiesis) or conjugated bilirubin due to hepatocellular or cholestatic disease. In this patient, viral hepatitis is the most probable cause of jaundice and associated malaise. Biliary tract disease, alcoholic liver disease, and autoimmune hepatitis should also be considered.

The patient said she had no fever, chills, sweats, nausea, vomiting, diarrhea, abdominal or chest pain, cough, or dyspnea. There was no history of sickle cell disease or trait or recent travel. She said that she had not eaten raw oysters or seafood. She was employed as a pharmacy technician and said that she did not have any contact with blood products. She had no history of blood transfusions, injection-drug use, or tattoos. She had had one sexual partner for the previous 2 years, and her last sexual contact occurred 6 months earlier without barrier protection; she and her partner had previously used condoms. She had taken Ortho-Novum (Ortho-McNeil), her only medication, for the previous 2 years, but she discontinued this medication 5 months earlier when she broke up with her last partner because of his infidelity. She was a nonsmoker and said that she did not use alcohol or illicit drugs.

The patient has painless jaundice. Although it appears to be an acute process, the duration of her illness may be longer than the 3 days she has noticed scleral icterus. Intrahepatic cholestasis is a recognized complication of oral contraceptives, particularly the combination of ethinyl estradiol and norethindrone. However, the 5-month delay from the discontinuation of contraceptive use to the appearance of jaundice would be inconsistent with this diagnosis. Other hepatobiliary disorders associated with oral-contraceptive use and jaundice, albeit rare and typically related to more than 2 years of use, include hepatic-vein thrombosis, peliosis hepatis, and hepatocellular carcinoma. The incubation period for sexually transmitted hepatitis B virus infection is shorter than the 6 months since the patient’s last unprotected sexual contact. Her work in a pharmacy raises the possibility of hepatic injury from surreptitious use of drugs.

On examination, her temperature was 38.0°C, blood pressure 110/78 mm Hg, and heart rate 100 beats per minute. Skin examination revealed no rash or spider angiommas. She had scleral icterus. There was no lymphadenopathy or thyromegaly. Chest
and cardiac examinations were normal. On abdominal examination, she had active bowel sounds and mild tenderness on deep palpation in the right upper quadrant. On percussion, the liver measured 12 cm in length with a smooth edge. There was no splenomegaly, fluid wave, or shifting dullness. There were no caput medusae. The rectal examination revealed normal tone with light brown, guaiac-negative stool. Neurologic examination was normal, without hyperreflexia or asterixis.

There are no signs of chronic liver disease. Fever and tachycardia are consistent with infectious hepatitis. Jaundice and these signs can also be seen with hyperthyroidism, but the examination provides no additional support for this diagnosis. Cholestatic jaundice, mediated by proinflammatory cytokines, can be observed with extrahepatic bacterial infections; occasionally, jaundice may precede, by several days, other manifestations of sepsis. Although nonspecific, her mild right-upper-quadrant tenderness could be due to gallbladder disease or an intraabdominal abscess. Viral hepatitis remains the most likely diagnosis.

The white-cell count was 9800 per cubic millimeter. The hemoglobin level was 12.8 g per deciliter, with a normal mean corpuscular volume. The hematocrit was 36.5%, and the platelet count was 270,000 per cubic millimeter. Analysis of the peripheral-blood smear showed a normal differential count with no band forms, basophilic stippling, or schistocytes. The serum electrolyte levels were normal. The albumin level was 3.7 g per deciliter, alkaline phosphatase 800 U per liter (normal range, 53 to 128), alanine aminotransferase 100 U per liter (normal range, 10 to 35), aspartate aminotransferase 65 U per liter (normal range, 5 to 40), total serum bilirubin 4.5 mg per deciliter (76.9 μmol per liter) (normal range, 0.3 to 1.2 [5.1 to 20.5]), direct bilirubin 3.8 mg per deciliter (64.9 μmol per liter) (normal range, <0.2 [<3.4]), and γ-glutamyltransferase 1051 IU per liter (normal range, 0 to 30). Tests for hepatitis B surface antibody, hepatitis B surface antigen, hepatitis A IgM antibody, and hepatitis C antibody were ordered.

The patient’s hepatic laboratory values exhibit a cholestatic injury pattern (a ratio of serum alanine aminotransferase to alkaline phosphatase of 2 or less and an associated elevation in the serum γ-glutamyltransferase level). Despite the absence of leukocytosis and a normal differential count, given the low-grade fever and right upper-quadrant tenderness on examination, an extrahepatic process needs to be excluded by means of abdominal imaging (either an abdominal ultrasound or computed tomography). Extrahepatic cholestasis can result from a broad range of disorders besides choledocholithiasis, including intrinsic and extrinsic tumors, parasitic infections, cholangiopathy associated with the acquired immunodeficiency syndrome, and pancreatitis. Her history does not particularly support these diagnoses, although her unprotected sexual contact with her promiscuous partner warrants testing for the human immunodeficiency virus (HIV) antibody. Viral hepatitis, particularly Epstein–Barr virus infection, may occasionally present with features of cholestasis, but screening for hepatitis A, B, and particularly C (in which seroconversion can be delayed for months) is expected to have a low yield in this case.

Intrahepatic cholestatic disorders to consider if the results of abdominal imaging are nondiagnostic include primary biliary cirrhosis, although this condition is more likely in a middle-aged white woman. Another such condition to consider is primary sclerosing cholangitis. However, this condition is more likely in men. An overlap syndrome of autoimmune hepatitis in which the immune attack is directed predominantly to the bile ducts and infiltrative processes such as sarcoidosis, tuberculosis, and lymphoproliferative disorders may also be considered. Drugs such as trimethoprim–sulfamethoxazole are associated with cholestatic liver injury, but the patient’s history does not provide support for this diagnosis.

An abdominal ultrasound study showed a homogeneously enlarged liver measuring 13 cm in length. There were no gallstones, and there was no pericholecystic fluid or thickening of the gallbladder wall. The common bile duct was not dilated. The pancreatic head and spleen appeared normal. A chest radiograph revealed no abnormalities.

The ultrasound findings are consistent with intrahepatic cholestasis, although bile-duct dilatation may not always occur in disorders associated with partial or intermittent extrahepatic obstruction. The hepatomegaly may represent an acute inflammatory, infiltrative (granulomatous or neoplastic), or congestive process. In addition to further
serologic tests (e.g., antimitochondrial antibody), the evaluation of intrahepatic cholestasis with hepatomegaly may include a liver biopsy. In the absence of biliary-duct dilatation and cholelithiasis, hospitalization is not necessary at this time, but the prothrombin time should be determined.

The prothrombin time was normal. Antinuclear antibody and antimitochondrial antibody titers were ordered. The patient was sent home and advised to rest and increase her fluid intake while awaiting the test results. She was asked to return to the clinic for follow-up in 3 days or sooner if new symptoms or signs arose.

The absence of liver failure with a normal neurologic examination and prothrombin time provide support for the decision to pursue outpatient evaluation of presumed intrahepatic cholestasis. In a patient with laboratory evidence of cholestasis, an antimitochondrial-antibody titer greater than 1:40 would be compatible with the diagnosis of primary biliary cirrhosis.

The patient returned to the clinic 3 days later. She now reported a new rash, which she described as having started on her abdomen and then spread to her arms and legs. She also noted nausea without vomiting. On examination, her temperature was 37.9°C, respiratory rate 16 breaths per minute, and heart rate 98 beats per minute. Her skin was warm and moist, with diffuse erythematous, papular lesions ranging from 0.5 to 1.3 cm in diameter on the torso, arms, and palms. The aspartate aminotransferase level was 80 U per liter, alanine aminotransferase 125 U per liter, total serum bilirubin 5.5 mg per deciliter (94.0 μmol per liter), direct bilirubin 4.5 mg per deciliter (76.9 μmol per liter), alkaline phosphatase 950 U per liter, and γ-glutamyltransferase 1275 IU per liter. Tests for hepatitis B surface antigen and surface antibody, hepatitis C antibody, hepatitis A IgM antibody, antinuclear antibody, and antimitochondrial antibody were all negative.

Although papular eruptions can occur in cholestatic disorders such as sarcoidosis and lymphoma, the rash in combination with the time since unprotected sexual contact make secondary syphilis the probable diagnosis. A rapid plasma reagin test and fluorescent treponemal antibody absorption test should be performed. Cholestatic jaundice is one of the protean manifestations of syphilis. The patient’s HIV status should also be determined; persons with HIV and syphilis coinfection are reported to have more organ involvement than HIV-negative patients with syphilis.

The rapid plasma reagin test showed a titer of 1:128; the fluorescent treponemal-antibody titer was reactive. Syphilitic hepatitis was diagnosed, and the patient was treated with two injections of 2.4 million units of penicillin G benzathine that were given 1 week apart. Her symptoms and liver-test abnormalities completely resolved within 2 weeks after the initial injection. An HIV test was negative. The rapid plasma reagin titers at 3, 6, and 9 months were 1:64, 1:16, and 1:4, respectively.

The rash on the palms of the patient’s hands narrowed the broad differential diagnosis of intrahepatic cholestatic disorders and pointed to syphilis. The clinical manifestations of syphilis resemble many other diseases. This case illustrates the clinical pearl that uncommon presentations of common diseases occur more frequently than common presentations of uncommon diseases, although there is little to suggest that syphilis should have been considered sooner.

**COMMENTARY**

Syphilitic hepatitis is a rare complication of primary and secondary syphilis. The majority of the cases reported in the past few decades have involved findings similar to those in our patient, with cholestatic jaundice, hepatomegaly, and elevations in alkaline phosphatase levels that are much greater than the elevations in aminotransferase or bilirubin levels. Since syphilis is known as “the great imitator,” and syphilitic hepatitis is rare, it is not surprising that the diagnosis of cholestatic jaundice due to Treponema pallidum infection was delayed.

The time from inoculation with T. pallidum to the presentation of primary syphilis with a chancre is inversely proportional to the inoculation dose and is typically 10 to 90 days. It is not uncommon for women to present with secondary syphilis, since chancres are painless, may reside unseen in the vagina, and typically resolve spontaneously within 3 to 6 weeks. The usual time from inoculation to the appearance of manifestations of secondary syphilis is 60 to 180 days.
Our patient’s presentation with secondary syphilis 6 months after her last unprotected sexual encounter is on the later side but within this period.

The overall rate of primary and secondary syphilis — the most infectious stages — steadily decreased from a high in the early 1990s to a nadir in 2000, but this rate has since increased again. These patterns, however, are driven by rates among whites (0.5 case per 100,000 persons in 2000, increasing to 1.6 cases per 100,000 in 2004). In contrast, the rate among blacks has fallen since 2000, but remains substantially higher than that among whites (9.0 cases per 100,000 persons in 2004).3 The greatest overall increase in syphilis rates since 2000 has occurred among men who have sex with men (accounting for 70% of the patients with syphilis in 2004), many of whom are HIV-positive. Yet this case reminds us that heterosexual transmission still occurs, and immunocompetent patients are also at risk.

Syphilis in HIV-infected patients with clinically significant immunosuppression is reported to be associated with more protracted constitutional symptoms, greater organ involvement, and more rapid progression to neurologic involvement (e.g., meningitis or optic neuritis) than is syphilis in HIV-negative patients.4,5 The discussant appropriately highlighted the need for HIV testing in our patient. This testing is relevant not only because HIV is a common coinfection, but also because the presence of HIV infection would warrant an evaluation for neurosyphilis by means of a lumbar puncture, whereas such an evaluation would not be necessary in the absence of HIV infection.1,4,5

*T. pallidum* remains sensitive to penicillin, with no resistance reported.6 Long-acting penicillin preparations are still used because of the slow dividing times of *T. pallidum* in vivo; on average, the number of *T. pallidum* organisms doubles once per day.7 Although data are lacking from clinical trials to guide the optimal regimen, according to case reports, the standard treatment of primary and secondary syphilitic hepatitis has typically been 2.4 million units of penicillin G benzathine given intramuscularly weekly for 1 to 3 weeks.8-10 A single, intramuscular injection of penicillin G benzathine at a dose of 2.4 million units provides low but persistent serum levels of penicillin, lasting up to 30 days, and is the standard treatment for primary, secondary, and early latent syphilis.6,11

The response of syphilitic hepatitis to treatment is rapid, with resolution of the biochemical findings and clinical features within 2 to 3 weeks after the start of treatment.10,11 The assessment of the ultimate success of therapy for primary or secondary syphilis should be based on serial monitoring of Venereal Disease Research Laboratory test results or rapid plasma reagin titers. Successfully treated patients will have a decline in titer within 6 months after initiating therapy that is four times greater than that among patients who have not been successfully treated.10 Our patient’s rapid response and falling rapid plasma reagin titers are consistent with successful treatment.

Our patient did not have the Jarisch–Herrheimer reaction, which is characterized by the acute onset of fever, rash, myalgia, headache, and hypotension. Since *T. pallidum* lacks endotoxin, this reaction is now believed to result from the release of large amounts of treponemal lipoproteins that stimulate the production of inflammatory mediators.12,13 Given her high titers, suggesting a large treponemal load, she was at risk for this reaction. In addition to antibiotic therapy, partner notification and contact tracing are essential elements of appropriate follow-up and disease containment.

A critical part of the initial evaluation of patients with jaundice is determining whether hospital admission is warranted. Both the team caring for the patient and our discussant were comfortable with outpatient evaluation, since the patient was considered to be reliable (and proved to be so), and there was no evidence of severe dehydration or liver failure (including no evidence of encephalopathy and a normal prothrombin time). In addition, without ultrasound evidence of bile-duct dilatation and in the absence of toxic effects in the patient’s appearance, the likelihood of acute ascending cholangitis was low. However, as the discussant noted, despite the absence of common-duct dilatation on ultrasonography, there is still a 10% chance of extrahepatic obstruction from choledocholithiasis.14

The key to the diagnosis in our patient was the palmar rash. Despite the known link between secondary syphilis and cholestatic jaundice, both the team and the discussant omitted syphilis from their initial differential diagnosis. This case illustrates the importance of pattern recognition in making diagnoses.

Watchful waiting can be a powerful tool when evaluating outpatients with a stable condition.
Patience in our case averted an unnecessary, costly, and potentially hazardous liver biopsy or endoscopic retrograde cholangiopancreatography. Furthermore, it permitted the disease to unfold and led the patient to literally deliver a hand-carried diagnosis to her physicians.

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References

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All forms of amyloidosis are characterized by the deposition of extracellular fibrils in various tissues. These fibrils are the result of the misfolding of a protein from its normal α-helical configuration into a β-pleated sheet. Amyloid fibrils are rigid, linear, and nonbranching and measure approximately 7.5 to 10 nm in width. The structure of the β-pleated sheet allows the binding of Congo red stain, which emits a characteristic apple-green birefringence under polarized light. The disease is often devastating, and options for treatment are limited.

There are distinct types of amyloidosis, which are classified according to the protein composition of the amyloid deposits. The clinical manifestations, prognosis, and therapy vary greatly depending on the specific type of amyloidosis (Table 1). In immunoglobulin-light-chain–related (AL) amyloidosis (also called primary amyloidosis), an underlying monoclonal plasma-cell disorder produces the constituents of the deposits, which are the variable regions of the immunoglobulin light chains. In AA (secondary) amyloidosis, amyloid fibrils are the cleavage products of SAA. When AA amyloidosis is caused by chronic infections (such as tuberculosis, leprosy, osteomyelitis, or bronchiectasis), antimicrobial therapy can reverse organ dysfunction. In the inflammatory arthritides and spondyloarthropathies, which are now the commonest cause of AA amyloidosis, treatment has centered on the use of chlorambucil and, more recently, inhibitors of tumor necrosis factor α. Both agents reduce the production of the precursor protein by suppressing the inflammatory response and improve survival by causing regression of amyloid deposits. Resorption of AA with such therapy has been verified by radionuclide scans that are specific for amyloid. Colchicine has been successful in the treatment of AA amyloidosis that results from familial Mediterranean fever.

In most forms of familial amyloidosis, the precursor protein is a mutant form of transthyretin. Transthyretin, a tetramer produced by the liver, is...
thyroxin-transporting protein. Liver transplantation supplies the normal transthyretin protein and can cure familial amyloidosis caused by mutant transthyretin. However, there is concern that previously formed amyloid deposits can serve as a nidus for deposition of native transthyretin that the transplanted liver produces and thereby can continue to cause progression of the disease.

A second approach in treating amyloidosis is to stabilize the native structure of the precursor protein and thus prevent its transition to a misfolded protein. Currently, a clinical trial is testing this strategy by using diflunisal in patients with familial transthyretin amyloidosis with neuropathy. Diflunisal binds to the thyroxine-binding sites of the transthyretin tetramer, thereby stabilizing the protein and counteracting its tendency to move to a β-pleated amyloid configuration.

These two approaches target the source of the problem, but they do little to reverse organ dysfunction in a timely manner. A third approach targets amyloid deposits directly, by destabilizing amyloid fibrils so that they can no longer maintain their β-pleated sheet configuration. Studies of compounds that bind serum amyloid P component (SAP), an essential constituent of all forms of amyloid deposits that constitutes 5 to 10% of their weight, suggest the possibility not only of depleting SAP from the fibril but also of causing regression of amyloid deposits.

Dember and colleagues followed a similar approach, which aims to destabilize the glycosaminoglycan backbone of amyloid deposits. Glycosaminoglycans are thought to play an integral role in the pathogenesis of amyloid deposition by binding to amyloid fibrils in tissues. Eprodisate binds to glycosaminoglycan-binding sites on amyloid fibrils and in principle can destabilize them in tissues, thereby causing regression of amyloidosis; in addition, it has the potential to prevent the formation of new amyloid deposits. In the multinational, double-blind, placebo-controlled study reported by Dember et al., eprodisate was administered orally to patients with established AA amyloidosis. The risk of worsening renal function and the rate of decline in creatinine clearance were lower in patients who received eprodisate than in those who received placebo. However, no effect was seen on the progression to end-stage renal disease or death. The primary end point of the study does not conform to the traditional measures of response in AA amyloidosis, which include a reduction in urinary protein of more than 50%.

### Table 1. Treatment of Systemic Amyloidosis.

<table>
<thead>
<tr>
<th>Type of Amyloidosis</th>
<th>Amyloid Protein Component</th>
<th>Current Therapy</th>
<th>Goal of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL or AH (primary)</td>
<td>Immunoglobulin light chain (AL) or (occasionally) heavy chain (AH)</td>
<td>Melphalan plus dexamethasone; alternative is autologous stem-cell transplantation in selected patients with limited organ involvement who are candidates for the procedure</td>
<td>Eradicate clonal plasma cells that are the source of immunoglobulin protein</td>
</tr>
<tr>
<td>AA (secondary to chronic inflammation or familial Mediterranean fever)</td>
<td>Serum amyloid A protein</td>
<td>Treatment of underlying infection or inflammation; colchicine for familial Mediterranean fever</td>
<td>Reduce level of serum amyloid A protein</td>
</tr>
<tr>
<td>Mutant ATTR (familial)</td>
<td>Mutant form of transthyretin</td>
<td>Liver transplantation</td>
<td>Eliminate source of mutant transthyretin</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Wild-type form of transthyretin</td>
<td>No therapy</td>
<td></td>
</tr>
<tr>
<td>Other forms of familial amyloidosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen α-chain</td>
<td>Mutant form of fibrinogen α-chain</td>
<td>Hepatorenal transplantation</td>
<td>Eliminate source of fibrinogen α-chain (liver) and replace affected organ (kidney)</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozyme</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein</td>
<td>Apolipoproteins A-I and A-II</td>
<td>Renal transplantation</td>
<td>Replace affected organ</td>
</tr>
</tbody>
</table>
Adjuvant Mitotane Therapy of Adrenal Cancer —
Use and Controversy

David E. Schteingart, M.D.

Adrenocortical carcinoma is a rare, highly malignant neoplasm with an incidence of 2 cases per 1 million population per year worldwide, representing 0.2% of all cases of cancer. Several treatment strategies in patients with advanced disease have resulted in temporary or partial tumor regression, yet very few patients attain long-term survival. Assessing the effectiveness of most pub-
lished treatment protocols has been difficult, since most series have been limited by the inclusion of relatively few subjects, with tumors at various stages and grades. Several drug regimens have been used, and multiple treatments have been administered in various sequences. In addition, the definition of response has not been uniform, and the duration of response has been unclear.

In patients with apparently localized disease (stages I and II) or regional disease without distant metastases (stage III), radical surgical resection with curative intent offers the best chance for prolonged recurrence-free survival. But metastases develop even in patients who undergo radical resection within 6 to 24 months after the initial surgery.

The dilemma facing physicians when there is no evidence of residual disease is whether to follow patients without initiating treatment or to use adjuvant therapy in the form of local radiation or systemic chemotherapy. Mitotane, an adrenalatic drug with selective activity on adrenocortical cells, has been used as adjuvant therapy with variable results, and there is controversy about its efficacy. Most studies claiming efficacy have been prospective, nonrandomized, single-center trials with various numbers of patients receiving mitotane after surgery and comparison groups receiving surgery alone. Other prospective studies, however, have failed to show a convincing advantage for mitotane treatment. In this issue of the Journal, Terzolo et al. present a retrospective analysis involving a large cohort of patients with adrenocortical carcinoma from 8 centers in Italy and 47 centers in Germany who were followed for up to 10 years. Adjuvant therapy was given to 47 Italian patients after radical surgery, and recurrence-free survival in these patients (the primary outcome) was compared with that of 55 Italian and 75 German patients whose surgery was not followed by mitotane treatment. Patients receiving mitotane had recurrence-free survival that was two to three times as long as that of those not receiving the drug.

Does the study by Terzolo et al. resolve the controversy concerning mitotane as adjuvant therapy in adrenocortical carcinoma and provide information sufficient to recommend adjuvant mitotane therapy to all patients with localized or regional disease? The large number of patients in this study from a carefully collected database involving multiple institutions, along with systematic follow-up, well-matched control groups, and carefully conducted statistical analysis, makes this retrospective study credible. Although bias inherent in a retrospective study may influence the conclusions, these authors have been careful to minimize and acknowledge this problem. Previous reports came from single institutions that had less clear treatment assignments and that used relatively high doses of mitotane with effects that were toxic enough to limit its use. Two of these studies support the use of mitotane as an adjuvant therapy, while others do not. In a series with 82 patients, Kasperlik-Zaluska observed increased survival when treatment with mitotane immediately followed surgery, and Dickstein et al. reported that 3 of 4 patients receiving low-dose mitotane (1.5 to 2.0 g per day) had some benefit. However, another study by Barzon et al. reported no efficacy. In a small, prospective, randomized study by Vasilopoulou-Selin et al., there were no differences in recurrence-free survival among those who received mitotane for 2 to 12 months, received mitotane indefinitely, or received no mitotane. Given the toxic effects that are associated with what had been regarded as therapeutic doses and the lack of evidence for a beneficial effect in the negative studies, the use of mitotane for adjuvant therapy of adrenocortical carcinoma has declined in recent years.

An important question is why such discrepant outcomes exist among published studies. It is possible that unintended selection bias involving subject entry in most studies played a role. It is also possible that the response to the drug is so variable among tumors that a given trial could yield either positive or negative results in apparently similar tumors.

The mechanism of action of mitotane may help explain the various responses. Mitotane effectively destroys normal adrenal glands and hyperplastic adrenal cortices in patients with Cushing’s disease. In contrast, only 23% of patients with advanced adrenal cancer respond to mitotane therapy. Why this difference? Mitotane belongs to the class of drugs that require metabolic transformation for therapeutic action. As a result, active metabolites causing tissue toxicity are produced, either through covalent binding to specific targets within the cells or by oxygen activation with superoxide formation. The concept that mitotane requires metabolic transformation for activity is supported by observations of its variable activity.
in different animal species. The dog adrenal, which is the most responsive to mitotane, is also the most capable of metabolic transformation and covalent binding. In contrast, the human adrenal is less capable of both metabolic transformation and covalent binding and is thus less responsive.

As depicted in Figure 1, the pathway of mitotane metabolism follows the well-known process by which chloramphenicol causes toxicity. Mitotane is hydroxylated at the β-carbon and quickly transformed by dehydrochlorination into an acyl chloride. The acyl chloride either covalently binds to bionucleophiles in the target cells or through loss of water is transformed into an acetic acid derivative for renal excretion. The initial hydroxylation step is carried out in the mitochondria and catalyzed by a P-450 enzyme, giving adrenal selectivity to the action of mitotane.

A limitation of mitotane therapy has been its marked toxicity at daily doses exceeding 6 g. Doses sufficient to achieve “therapeutic” levels of 16 μg per milliliter are usually associated with undesirable toxicity. An important finding in the study by Terzolo et al. is that favorable outcomes were achieved with relatively low doses of mitotane — 1 to 3 g per day was sufficient to produce the desired effect with reduced toxic effects.

Although the variability of published reports on adjuvant mitotane indicates the need for well-designed and well-powered prospective, randomized trials, the rarity of adrenal cancer and the time it would take to collect sufficient data would require a lengthy, multicenter, international study. Meanwhile, we are left with well-designed, multicenter, retrospective studies such as the one conducted by Terzolo et al.

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Martz F, Straw JA. The in-vitro metabolism of 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane (o,p’-DDD) by dog adrenal mitochondria and metabolite covalent binding to mitochondrial macromolecules: a possible mechanism for the adrenocorticoletic effect. Drug Metab Dispos 1977;5:482-6.


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Why Does Rheumatoid Arthritis Involve the Joints?

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A long-standing question in rheumatology is why inflammatory arthritides such as rheumatoid arthritis involve the joints. Many studies have addressed this question; a recent article by Lee et al.\(^1\) provides a new answer that is both obvious and intriguing. Rheumatoid arthritis affects the joints because of the essential role of the synovium in regulating inflammation.

The normal synovial membrane is a thin, glissening tissue that lines the diarthrodial joints. Its name (which contains the root “ovum”) derives from its visual similarity to the thin lining under the shell of a chicken egg. The membrane normally consists of a lining layer that is only a few cells thick and a sublining layer that consists of loose connective tissue. The lining layer contains fibroblast-like synoviocytes and macrophages, and it produces extracellular-matrix molecules and synovial fluid.

In rheumatoid arthritis, there is a dramatic increase in the number of cells in the lining layer, and the sublining layer becomes infiltrated with inflammatory cells, including lymphocytes, macrophages, and mast cells.\(^2\) These cells produce cytokines that, together with locally produced autoantibodies, are thought to drive the chronic inflammatory process. Fibroblast-like synoviocytes contribute to the inflammatory milieu by producing cytokines and other inflammatory mediators, but the relative contributions of the resident synovial cells and the infiltrating inflammatory cells have been controversial. Moreover, the potential role of the synovium in orchestrating the behavior of the inflammatory cells has not been delineated in great detail.

Lee et al. showed that fibroblast-like synoviocytes organize themselves into synovial tissue by means of cell–cell interactions mediated by cadherin-11. In the absence of cadherin-11, the synovium is disorganized and there is muted production of extracellular-matrix molecules (Fig. 1).

Previous studies\(^3\) have shown that fibroblast-like synoviocytes can contribute to synovial inflammation. For example, mice that are partly deficient in a molecule uniquely expressed in the synovium by fibroblast-like synoviocytes are resistant to collagen-induced arthritis.\(^4\) Similarly, Lee et al. observed that mice that are deficient in cadherin-11 are resistant to a form of inflammatory arthritis. The model they used involved the transfer of pathogenic antibodies, indicating that an intact synovial-lining layer with functional fibroblast-like synoviocytes is necessary for the effector phase of inflammatory arthritis after immune reactivity has been generated. Although the detailed molecular events that are attenuated by cadherin-11 deficiency in acute and chronic arthritis have yet to be delineated, it is clear that the synovial lining and functional fibroblast-like synoviocytes have a critical role in the course of inflammatory arthritis. Moreover, cadherin-11, which is a cell-surface molecule and therefore relatively accessible to exogenous agents, represents a potential therapeutic target for controlling inflammatory arthritis.

Rheumatoid inflammation causes damage to both articular cartilage and periarticular bone. This damage was previously thought to result, nonspecifically, from chronic inflammation, and it can be ameliorated by some antiinflammatory therapies.\(^5\) There is, however, a clear indication that damage to bone and cartilage is mediated by distinct physiological pathways. For example, the abundant osteoclasts that are characteristic of rheumatoid inflammation directly damage bone, although they do not appear to affect cartilage.\(^2\) Several studies\(^3\) have suggested that fibroblast-like synoviocytes mediate cartilage damage. The study reported by Lee and colleagues provides support for this hypothesis; cadherin-11 deficiency protected mice from cartilage damage but not from bone erosion, probably because cadherin-11 seems to mediate the migration of fibroblast-like synoviocytes over the articular cartilage and its subsequent damage.

The report by Lee et al. provides a new take on
the synovium. It shows that fibroblast-like synoviocytes mediate both cartilage damage and acute and chronic inflammation. The synovium, therefore, is not an innocent victim of infiltrating inflammatory cells. Rather it is an innkeeper that regulates the entry and behavior of itinerant, potentially troublemaking inflammatory cells as well as its own capacity to damage specific parts of its environment.

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

From the Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD.


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Hepatitis E Vaccine

TO THE EDITOR: The study by Shrestha et al. (March 1 issue), which evaluated a vaccine for hepatitis E virus (HEV), represents a major advance but continues to raise ethical concerns. The trial of the HEV recombinant protein (rHEV) vaccine, conducted by the U.S. military and GlaxoSmithKline, was forced out of a Nepalese community after protests about whether residents would have access to the vaccine after the trial. The study was subsequently relocated to the Nepalese Army. The consent of soldiers may be “unduly influenced . . . by fear of disapproval or retaliation if they refuse,” which is why research involving soldiers should take place only if it “could not be carried out equally well with less vulnerable subjects.” Indeed, the subjects may have been placed at needless risk, because the vaccine may not be developed. GlaxoSmithKline stated that a third party would need to develop the vaccine, given its low profit value. It is crucial that phase 3 trials take place soon and that thereafter any viable vaccine be made accessible, particularly to communities that undertook the risk of testing.

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TO THE EDITOR: Challenges posed by the rHEV vaccine trials conducted in Nepal should not be overlooked. Original plans to test the vaccine in the civilian population were aborted after opposition from the local community leadership. The leadership’s failure to honor ethics approvals for the trial, issued by concerned authorities, raised unique ethical and operational dilemmas. Investigators resolved the dilemmas by testing the vaccine among Nepalese soldiers — a decision that has been debated. In Nepal, hepatitis E is common, and recently even the prime minister and a number of ministers were taken ill by the virus. Prevention and control strategies are urgently needed.

The effectiveness of the rHEV vaccine generates hopes for prevention of disease among high-risk populations. But will the population at risk in Nepal benefit from this vaccine? Experience shows otherwise. International travelers benefit from the parenteral Vi capsular polysaccharide typhoid vaccine, which was tested among natives of Kathmandu. However, Nepalese natives do not benefit from the vaccine, probably owing to the vaccine’s high cost and short-term protective efficacy. Such

THIS WEEK’S LETTERS

2421 Hepatitis E Vaccine
2422 Improving the Management of Chronic Disease
2424 Amiodarone for Atrial Fibrillation
2427 Solicitation of Deceased and Living Organ Donors
2429 Into the Woods
2430 Intraaortic Vegetations and Infective Endocarditis
2431 Acute Wiliitis
examples discourage community support for research. The rationale of medical research cannot be justified if the population in which the research was carried out does not benefit from the results of the research. In this regard, the investigators need to clarify the usefulness of the rHEV vaccine in preventing and controlling disease in the native population of Nepal.

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The authors reply: Our research established that the rHEV vaccine provides highly effective protection and generated a hypothesis that hepatitis E, an underrecognized disease, is so burdensome in places where it is endemic that vaccination could be cost-effective. Nevertheless, since the vaccine is being developed for the developing world, access will define its impact on health.

Basu and Lurie question whether volunteers in our trial were coerced because they were soldiers. We note that the trial began after a decade of capacity building and documenting the high risk of hepatitis E in Nepalese civilians and in the military. Our trial was responsive to a national health need and adhered to international guidelines for informed consent. The trial was approved by ethics review panels in Nepal and the United States and was monitored by independent experts. In particular, we took measures to remove the influence of military commanders over participation by their subordinates. Of more than 40,000 soldiers who were informed about the trial, only 5323 gave informed consent to be screened; of 3023 soldiers with the lowest screening levels of antibody, only 1885 agreed to undergo randomization. The high proportion that declined to participate in the study at each stage of enrollment belies coercion.

GlaxoSmithKline, along with U.S. government agencies, has supported rHEV vaccine research, because the company recognized the value of developing vaccines and medicines against diseases in the developing world — efforts it has undertaken for more than 20 years. Bhattarai asks about access to the vaccine after the trial. We affirm that GlaxoSmithKline embraces the principle of distributive justice and is committed to continue development of the rHEV vaccine so that it can be available in Nepal. Nevertheless, since control of infectious diseases is a global public good, we call for international financing for the introduction of the rHEV vaccine through partnerships similar to those developed for rotavirus and pneumococcal conjugate vaccines.

We emphasize that GlaxoSmithKline is seeking public-sector partners who also are committed to the long and challenging endeavor to add the rHEV vaccine to immunization programs in high-risk countries. Despite competing public health priorities, we remain optimistic that the 95% protective efficacy of the rHEV vaccine can attract support. Adoption of rHEV vaccination programs in Nepal would be a fitting outcome for our trial’s volunteers and our many colleagues who since 1987 have examined options to identify and control hepatitis E.

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Improving the Management of Chronic Disease

To the Editor: The Special Article by Landon and colleagues (March 1 issue) on improving the management of chronic disease at community health centers illustrates the importance of identifying appropriate outcomes when measuring the effectiveness of interventions to improve processes of care. Establishing a more realistic schedule than that used in this study for assessing the effect of

reserved.
the program might have yielded a different picture. Sufficient time needs to be allowed for the measurement of clinical outcomes, particularly regarding outcomes of patients with chronic disease. Process interventions to improve outcomes in chronic disease have been shown to be associated with an increase in health care utilization during the first year. This increase often reflects preexisting needs of the patient that had not been met; it is often not until the second year that a measurable decrease in health care utilization is noted. Physicians and others working to establish evidence-based interventions in the community can identify appropriate outcomes by partnering with families, community stakeholders, and local institutions. Implementation designs that incorporate the collection of locally meaningful outcomes data into realistic, community-sensitive timetables have been reported to result in effective and sustainable programs.3

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TO THE EDITOR: The examination by Landon et al. of the quality of care at community health centers adds to an impressive literature; although this study covered too short a period to capture health outcomes, earlier research has documented such effects. The authors do not report on the broader policy context of this work, however. Health centers face a staggering increase in the number of uninsured patients. Yet not only has the Bush administration eliminated all funding for quality-improvement collaboratives, but its proposals for the fiscal year 2008 budget call for deep reductions in Medicaid (the most important source of funding for health centers) and seek no appropriations for either quality improvement or health-information technology. Moreover, the administration has recently begun to withhold access to data on health center performance that were previously public un-
cific interventions. A better understanding of what is driving these improvements is needed.

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The Authors Reply: Both Sadof and Rosenbaum suggest that we might have observed improvements in intermediate outcomes, given more time. Conceptually, we agree that, to the extent that outcomes of care are directly related to process interventions, more time than the period of our study might be needed to observe meaningful improvements in clinical outcomes such as mortality or the incidence of acute myocardial infarction. There is no reason to expect, however, that the intermediate outcomes we assessed (e.g., control of glycated hemoglobin and control of hypertension) would require such a lag. In addition, as we state, the 1-year postintervention assessment period began 1 year after the completion of the intervention, a timing consistent with that suggested by Sadof.

Smolkin argues that improvements in the processes of care are meaningless if they are not accompanied by improvements in outcomes. With the exception of asthma, the intermediate outcomes we assessed examined the control of important risk factors. Given the required time frame and sample size, we could not assess clinical outcomes such as the incidence of cardiovascular disease or mortality, but we would expect that these outcomes would ultimately be affected by improvements in the processes of care. Moreover, many of the process measures we examined are strongly linked to these meaningful clinical outcomes (e.g., daily aspirin use) but are not directly related to the intermediate outcomes we assessed. Selby and colleagues studied the association between various care-management techniques and the quality of care of patients with diabetes and reported results similar to ours. We agree with their suggestion that quality-improvement efforts should focus on evidence-based processes of care that have been rigorously linked to important clinical outcomes.

Finally, Rosenbaum provides important information on the broad policy context and the challenges facing community health centers. We agree that such centers are an important cornerstone of efforts to provide a safety net for millions of Americans and that every effort should be made to provide adequate funding to meet the needs of the underserved populations they care for.

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Amiodarone for Atrial Fibrillation

To the Editor: In his review article on amiodarone for atrial fibrillation, Zimetbaum (March 1 issue) did not mention that there are two forms of amiodarone-induced thyrotoxicosis (AIT) — an important distinction that has a major influence on subsequent management. In type I AIT, patients usually have preexisting thyroid abnormalities, such as nodular goiter, an autonomous thyroid nodule, or latent Graves’ disease. This syndrome is thought to be due to the Jod–Basedow phenomenon. In type II AIT, the thyroid gland is normal, and thyrotoxicosis results from subacute destructive thyroiditis with the release of preformed thyroid hormone. The uptake of radioactive iodine is
normal or high in type I AIT but low or absent in type II AIT. Moreover, parenchymal blood flow as seen on color-flow Doppler is present in type I AIT but absent in type II AIT. The treatment of type I AIT involves thionamides, potassium perchlorate, or lithium and discontinuation of amiodarone, whereas the treatment of type II AIT involves glucocorticoids.

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TO THE EDITOR: Zimetbaum discusses the difficulties in recognizing the onset of AIT, which is often associated with only mild clinical signs and symptoms. Many patients receiving amiodarone are also treated with warfarin. Thyroid function affects the pharmacodynamics of warfarin: hyperthyroidism potentiates the anticoagulant effect of warfarin, whereas hypothyroidism attenuates the anticoagulant effect. Therefore, an otherwise unexplained rise in the international normalized ratio in such patients can be a valuable clue to the onset of AIT even before the manifestation of other clinical symptoms and should prompt laboratory assessment of thyroid function.

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TO THE EDITOR: Zimetbaum leaves out an important piece of data for deciding whether antiarrhythmic therapy should be recommended for a patient with atrial fibrillation — data on mortality. The results of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), which showed a decrease in recurrence of atrial fibrillation in the antiarrhythmic-therapy groups as compared with placebo, also showed that patients who received the study drug had a mortality ratio of 2.0 (P=0.11.

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for the comparison of amiodarone and placebo). An increase in mortality has been remarkably consistent in numerous studies, none of which have been powered to look at mortality. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial\(^2\) enrolled 4060 patients and at 5 years showed a hazard ratio for mortality of 1.15 (\(P=0.08\)) for treatment with antiarrhythmic drugs. The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial\(^3\) randomly assigned 522 patients with atrial fibrillation to receive either antiarrhythmic therapy or rate control and showed more primary end points, including deaths, in the group undergoing antiarrhythmic therapy. The information on mortality from numerous studies is important to consider as a consistent and troubling signal.

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TO THE EDITOR: Zimetbaum states that neurologic side effects may occur in up to 30% of patients receiving amiodarone therapy and may be more common in the elderly. Treatment-emergent parkinsonism has been reported with amiodarone use\(^1,2\) but is underrecognized and difficult to treat. The drug’s half-life is long and variable, averaging 58 days.\(^3\) Consequently, if parkinsonism is recognized late, several months may elapse before reversal can be expected. Moreover, I have encountered an instance in which use of amiodarone in a patient with preexisting Parkinson’s disease was associated with aggravation of muscular rigidity. This previously ambulatory patient became frozen and virtually immobile within 2 months after the initiation of treatment with amiodarone. Since his family could no longer care for him, he had to be moved to a nursing home. Explicit enumeration of parkinsonism among the treatment-emergent neurologic side effects of amiodarone may promote an earlier recognition of this condition. Use of amiodarone is probably inadvisable in patients with preexisting Parkinson’s disease.

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THE AUTHOR REPLIES: Rehman and Kurnik et al. raise important issues related to amiodarone and its interaction with the thyroid. Mention of these issues was omitted from my article owing to word constraints, but the correspondents’ discussion of these interactions is very welcome.

Cocceani and Skolnik both raise appropriate concerns about the safety and possible increase in mortality associated with the use of amiodarone, particularly among patients with congestive heart failure. It is quite clear from numerous studies they mention that amiodarone does not reduce the rate of death from all causes or from arrhythmia in any population, particularly in patients with congestive heart failure. There may be a trend toward increased mortality in this latter population, but it has not been shown to be significant. Furthermore, implantable cardioverter–defibrillators are increasingly used in this population, which potentially limits the adverse cardiovascular outcomes associated with amiodarone (e.g., bradycardia and torsades de pointes). I believe there are insufficient data and justification to accept Cocceani’s recommendation that amiodarone should be avoided in patients with atrial fibrillation and congestive heart failure.

Armon mentions the potential for exacerbation of parkinsonism associated with amiodarone. This phenomenon is infrequent and has been described in case reports only; however, it is worrisome and clearly warrants a more systematic evaluation.

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Solicitation of Deceased and Living Organ Donors

TO THE EDITOR: The Sounding Board article by Hanto on the ethical challenges posed by solicitation of organ donation (March 8 issue) does not clearly distinguish between directed donation and solicitation. Although effective solicitation requires directed donation to unrelated persons, the converse is not true. Nevertheless, Hanto conflates solicitation and directed donation and concludes that both should be banned.

Hanto’s view that donation of organs to strangers should be nondirected is widely accepted. One justification for this is to prevent ugly discrimination, such as when a member of the Ku Klux Klan would direct organs only to white recipients. But this view of directed donation to specific groups is simplistic. The real concern is that already advantaged people will be unfairly favored. So although we may understand disallowing directed donation to rich people or white people, we might not object if someone were to want to direct a gift to a poor person, a disabled person, or a child. Wilkinson argues that even “Racial conditions placed on donation can be altruistic [and acceptable] if . . . the donor wants the organs to go to groups (say, blacks in the US . . .) that typically do relatively badly in receiving organs.”

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TO THE EDITOR: Hanto claims that the only exception to nondirected organ donation should be directed donation by persons with “preexisting emotional relationships” with the intended recipients. It is not clear why this exception is permitted when directed donation between strangers is not. This policy position appears to be driven primarily by concern about unfair distribution of scarce resources. The ethical concern, however, also applies to directed donation by family members and friends. Presumably, family members and friends have a sense of moral obligation to donate to a particular person in need, which public policy ought to respect. But so may donors who do not have a preexisting personal relationship with a potential recipient. For example, why should we permit directed donation by a family member but prohibit directed donation by a member of a religious community who wants to help a fellow congregant whom the donor does not know personally? Out of concern for fair allocation of organs, it is desirable to encourage nondirected donation, but it is ethically dubious to prohibit directed donation between strangers as long as directed donation by family members and friends is permitted.

(The opinions expressed here should not be construed as being those of the National Institute of Mental Health, the National Institutes of Health, the Department of Health and Human Services, or any other office or agency of the federal government.)

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TO THE EDITOR: An emerging source of living donation by unrelated donors is the overseas black market. There have even been attempts by officials in the Philippines to legitimize this trade and use the availability of organs to lure “medical tourism.” According to an article in a major newspaper in the Philippines, an undersecretary of health stated that “a Filipino kidney is worth more” and proposed increasing the price from the current $3,000 per kidney to $4,000, possibly with the intent of bringing fair compensation to donors. The under-
TO THE EDITOR: Contrary to Hanto's position, we contend that to plead for, strongly urge, or seek to obtain organ donation and the donor's consent by persuasion is unacceptable under any condition. Voluntary and informed consent without coercion protects the principle of respect for donor autonomy. The transplantation community has accepted the use by organ procurement organizations of solicitation over the Internet to increase organ-donor registration. Information about the different effects of brain death, imminent death, and cardiac death on organ donation and on the quality of end-of-life care have not been adequately disclosed to the public to permit potential donors or their families to make informed choices about participation. It has been stated that “the job of organ procurement coordinators who ask for permission to recover organs for transplantation is to get the families to agree to donation by offering the family information on organ donation that will lead to a decision to donate.” Consent for organ donation obtained through incomplete or biased disclosure of information violates the value society places on truthfulness and autonomy and raises questions about the legitimacy of organ procurement from donors who are not provided with adequate information.

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THE AUTHOR REPLIES: I differentiated between directed deceased-donor donation to strangers resulting from solicitation by the recipient and donor-initiated directed donation to “groups on the basis of race, sex, religion, national origin, or similar characteristics” where solicitation is not involved. I am opposed to both forms of directed donation, and some of the ethical arguments against both are similar (e.g., see my discussion of donor autonomy in the article). I disagree with Spital's and Wilkinson's expressed view that a discriminatory condition placed on donation can be an exercise of altruism. Their argument puts the donor and the donor's family in the position of having to determine allocation policy by deciding who they believe is disadvantaged and then directing the organs to them. The current system has worked effectively in considering the needs of all recipients and correcting unexpected aspects of allocation policy that have disadvantaged certain populations (e.g., black people and children).

I'm glad that Snyder et al. agree with me that directed donation to family members and friends is acceptable because of the unique relationships and obligations among such persons. This ethically distinguishing characteristic does not extend to strangers. Beyond that, I have argued that “a clear policy that defines the preexisting emotional relationships that are acceptable must be developed. . . .” I believe that the example of donation within a religious community cited by Snyder et al. would be acceptable to most transplantation centers, although perhaps not all, and it illustrates the need to develop agreed-on guidelines that can be applied uniformly to deceased and living donation.

I agree with Domingo and Salvana that the buying and selling of organs should be condemned.
and have noted that solicitation may increase the chances of the exchange of money, goods, or favors between the donor and recipient. And I agree with Rady and colleagues that informed consent is required for donation and must include full disclosure, understanding, voluntariness, competence, and consent. All organ-procurement coordinators are trained to provide donor families with information about the donation process, as well as its potential benefits, without coercion. The goal is, of course, consent for donation, because of the well-recognized benefits to the donor or donor’s family and to the transplant recipient. Rady et al. argue that the Web sites of organ-procurement organizations may not provide adequate information about donation while advocating for donor registration. Now that honoring donors’ wishes is the law in several states, it is incumbent on the entire transplantation community to work toward creating better mechanisms for ensuring that potential donors are signing their donor cards after becoming fully informed.

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Into the Woods

TO THE EDITOR: The Clinical Problem-Solving article by Safdar et al. (March 1 issue) concerns an immunocompromised woman who received the diagnosis of pulmonary nocardiosis. The authors recommended that if the patient still required immunosuppression after completion of therapy, prophylaxis with trimethoprim–sulfamethoxazole (TMP-SMX) should be given. A role of TMP-SMX prophylaxis has been well established for Pneumocystis carinii pneumonia, but there is no clear evidence that it will prevent patients from acquiring nocardia infections. In two case series, TMP-SMX prophylaxis did not show a benefit in immunocompromised patients with nocardia infection.²,³ In our experience with lung-transplant recipients, all patients with nocardia infection were receiving TMP-SMX prophylaxis. The only data supporting a role for TMP-SMX prophylaxis in nocardia infections comes from a case series of patients with human immunodeficiency virus infection.⁴ It would be extremely difficult to make an assumption that TMP-SMX prophylaxis in doses that are routinely prescribed will prevent the development of nocardia infection. The possibility of either using a higher dose for prophylaxis or increasing the frequency of administration of the drug needs to be elucidated.

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THE AUTHORS REPLY: We agree with Khan and Gubina that breakthrough nocardia infections have been reported in patients receiving TMP-SMX prophylaxis for pneumocystis pneumonia. However, a single-center review of the incidence of nocardia infections in heart-transplant recipients showed an association between the use of TMP-SMX for pneumocystis pneumonia prophylaxis and a reduction in the number of nocardia infections.⁵ Many clinicians continue secondary prophylaxis with
TMP-SMX indefinitely in immunosuppressed patients with nocardia, but we agree that there is little evidence to support this approach.

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Intraaortic Vegetations and Infective Endocarditis

TO THE EDITOR: The mobile aortic thrombus described by Adam et al. (Feb. 22 issue) as suggestive of intraaortic endocarditis does not even warrant a diagnosis of possible endocarditis, according to the Duke criteria. At admission, the patient had definite enterococcal endocarditis, meeting two major criteria: echocardiographic evidence of vegetations and the presence of a typical endocarditis pathogen. The fever initially responded to antibiotics but then relapsed. This is common during treatment of endocarditis, for numerous reasons. The suggestion that the relapse was due to a second pathogen seems unlikely. For unexplained reasons, the supposed aortic vegetation was not examined microscopically during the operation, making it impossible to diagnose it definitively as a mural vegetation. The finding of a mixture of coagulase-negative staphylococci casts further doubt on the conclusion that these bacteria were causing the infection. Mixtures of such bacteria, even from operative sites, usually indicate contamination from skin. The reporting of highly speculative cases serves only to confuse the clinical picture of endocarditis.

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TO THE EDITOR: Adam et al. report a case of intraaortic vegetations as a manifestation of infective endocarditis. Although they reference the 1998 guidelines of the American College of Cardiology and the American Heart Association for the care of patients with valvular heart disease, their chosen treatment does not conform to current recommendations of the American Heart Association and the Infectious Diseases Society of America with regard to diagnosis and management of infective endocarditis. The patient initially received piperacillin and ciprofloxacin. (Minimum inhibitory concentrations of gentamicin and streptomycin for the isolated Enterococcus faecalis are not reported.) The failure of this combination would not be unexpected. The subsequent switch to imipenem monotherapy is not advocated by the guidelines either. Failure with this antibiotic would not be unexpected.

From the standpoint of a microbiologic diagnosis, Adam et al. report that the patient had E. faecalis endocarditis but then also report that the valve and aortic material were infected with two types of coagulase-negative staphylococci (i.e., mixed staphylococci). Either the case represents E. faecalis infective endocarditis plus infection with coagulase-negative staphylococci or, more likely, contamination of the aortic-tissue specimen (and perhaps the valve-tissue specimen) by coagulase-negative staphylococci after excision — raising the question of whether the “floating” aortic lesion was infected at all. Histologic examination of the excised material might resolve the matter.

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Acute Wiiitis

TO THE EDITOR: A healthy 29-year-old medical resident awoke one Sunday morning with intense pain in the right shoulder. He did not recall any recent injuries or trauma and had not participated in any sports or physical exercise recently. He consulted a rheumatology colleague. The Patte’s test was positive, consistent with acute tendonitis isolated to the right infraspinatus.

After further review of his activities during the previous 24 hours, the patient recalled that he had bought a new Nintendo Wii (pronounced “wee”) video-game system and had spent several hours playing the tennis video game. With the Wii system, the player faces a video screen and moves a handheld controller (approximately 14.5 cm by 3.0 cm by 3.0 cm, with a weight of approximately 200 g) containing solid-state accelerometers and gyroscopes that sense three-dimensional spatial movements. In the tennis video game, the player makes the same arm movements as in a real game of tennis. If a player gets too engrossed, he may “play tennis” on the video screen for many hours. Unlike in the real sport, physical strength and endurance are not limiting factors.

The final diagnosis for the isolated right shoul-
der pain was Nintendinitis. However, the variant in this patient can be labeled more specifically as “Wiiitis.” The treatment consisted of ibuprofen for 1 week, as well as complete abstinence from playing Wii video games. The patient recovered fully. Nintendinitis was first described in 1990,1 and there have been many case reports of injuries related to intensive use of recreational technologies, mainly in children and mainly from intensive use of the extensor tendon of the thumb.2-5

With the growing use of this new video-game system, the risk of the Wiiitis variant may be higher than that of Nintendinitis reported in the literature, especially among adults. The available games for the Wii system already include golf, boxing, baseball, and bowling. Future games could involve different and unexpected groups of muscles. Physicians should be aware that there may be multiple, possibly puzzling presentations of Wiiitis.

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SEX-SELECTIVE ABORTION IN INDIA: GENDER, SOCIETY, AND NEW REPRODUCTIVE TECHNOLOGIES

The numbers speak for themselves. In India in 2001, there were 921 girls born for every 1000 boys. In some Indian states, the ratio was lower still — 793 girls for every 1000 boys in Punjab, for example — and census data from 1901 to the present show that in recent years the disparity has been getting worse, not better. In 2001 alone, the imbalance represented more than 5 million missing Indian baby girls.

The reasons for the discrepancy seem as clear as the data themselves, although harder to observe and document than the prenatal determination of fetal sex and subsequent selective abortion of female fetuses. In spite of legislation making the practice of sex-selective abortion illegal, the increased availability of technologies such as ultrasonography and amniocentesis has made it difficult to regulate away.

Sex-Selective Abortion in India examines the problem, detailing the numbers and placing the figures within their cultural and historical context. Indeed, as several authors note, this practice represents a contemporary permutation of a long-standing custom and problem. Female infanticide in India has been documented since the time of British colonial rule. Moreover, contemporary mortality statistics and increasingly disparate ratios throughout the lifespan give strength to the argument that girls and women remain at risk even after birth, almost certainly because access to health care is limited by sex.

The social scientists who wrote this collection of essays identify and analyze the many factors that, for some families, make boys preferable. Such factors include the traditions of sons inheriting a family's wealth and supporting parents in old age and of daughters being seen as a financial drain on the family, which must pay for dowries and other costs associated with the marriage of their daughters — who must be married. The authors remind readers that all such pressures need to be seen through the lens of public policy designed to limit fertility and family size.

There are a lot of data here — statistics are parsed and examined year by year, in some cases at the state level — but only the most interested readers will care to plow through this detail and the chapter-by-chapter repetition of numbers and history. The inclusion of better introductory and concluding chapters to summarize the facts and arguments would have helped readers with a more casual interest. In addition, the tone in the concluding pieces moves from objective to polemic — the authors speak of a “medical mafia” and “techno-docs” — and as a result, the persuasive power of a more dispassionate analysis is lost. The numbers alone are so persuasive that florid rhetoric simply is not needed. Nor is bad science, and some authors misstate facts, seemingly in an effort to make their case more compelling — for example, amniocentesis is not more hazardous than chorionic-villus sampling, and it does not cause congenital hip dislocation or leave needle marks on the baby.

Neeta, 4 Months Pregnant, Undergoes Ultrasonography in New Delhi, India, June 2002.
That ethics argue against sex selection is assumed by the authors of this collection, but a more detailed discussion would have been interesting and valuable, particularly in relation to matters of family balancing. If a family has a girl, is it ever appropriate to select for a boy in a next pregnancy to create “balance”? Technology for sperm sorting may soon make selection before conception possible. Does technique (sperm selection versus abortion) matter? Professional groups in America disagree on the answers to these moral questions. Can a technique be appropriate for one country, culture, or history but not for another? These important and challenging questions are largely unexplored here.

Sex selection is illegal in India, and as a result, identifying patients and practitioners who participate is difficult. Their voices are largely missing from this book, and the loss, though understandable, makes it hard to fully appreciate the motivation and process underlying the selective abortion of girls. Although the book presents a clear argument for a problem, little space is devoted to suggested solutions. It is tempting to believe that the answer lies in controlling technology, but the development of techniques for sperm sorting, early serum screens of maternal blood for fetal DNA, and nonsurgical methods for early pregnancy termination argues that the growth of new technology will continue to outpace efforts to control it.

At least some of the authors acknowledge this, recognizing that the real — and more difficult — task is to change attitudes and society, reshaping values and practice so that, as one author puts it, “Our daughters are not for slaughter.”

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ETHICS AND INTERSEX

This book is a bold attempt to address the vexed question of ethics and intersex. Sharon Sytsma has brought together 20 contributions from a range of professionals. Many of the chapters are written in essay form. Overall, it is difficult to justify rating this book as the main reference to consult on ethical issues related to management of intersex conditions. Nevertheless, several sections illustrate the complexity of the subject.

A certain amount of historical discontent with the way medical professionals have managed intersex conditions pervades the book. It is punctuated by language that reflects this discontent, apparent in the phrase “the concealment model of intersex treatment” and the statement that “intersex is a hothead of deception.” Furthermore, “Sex, Lies, and Pediatricians” is a subheading in one chapter. Indeed, in the same chapter, the current management of intersex conditions is compared with the Tuskegee Syphilis Study (conducted from 1932 to 1972), which examined the natural history of syphilis in blacks but continued even after penicillin became available.

A major debate about the management of intersex conditions has centered on how much information should be disclosed to the family and, in particular, to the affected child as he or she grows up. The medical profession has been perceived as taking an approach to making decisions that is too cavalier. Julie Greenberg, in her chapter “International Legal Developments Protecting the Autonomy Rights of Sexual Minorities,” discusses three possible approaches. The first option is the use of a dominant protocol in which surgery to sculpt the genitalia is performed early in infancy; information is withheld from the parents to avoid traumatic disclosures. In the second option, a middle-ground approach, the physician provides full disclosure to the parents but allows them to decide what is in the best interest of the child. In the third option, a complete moratorium on treatment that is not medically necessary is in place until the child is of sufficient cognitive and developmental maturity to receive full disclosure and make his or her own decision about surgical treatment. This kind of debate finds its way regularly into the popular press — one example is the choice for the title of an article published last year in the New York Times Magazine — “What If It’s (Sort of) a Boy and (Sort of) a Girl?”

Some chapters include useful facts and are essential reading for professionals involved in the intricacies of managing intersex conditions. Terminology and definitions are discussed thoroughly so that the nuances of the terms “gender assignment,” “gender identity,” “gender expression,” and
“gender diversity” can be fully understood. Knowledge and understanding of these terms are mandatory for anyone who has responsibility in the team treatment of a child with an intersex condition.

Greenberg discusses informed consent and international differences in the legal issues surrounding consent. She concludes by proposing that committees of experts drawn from the relevant disciplines should be charged with the responsibility of providing guidance to families of children with intersex conditions, ensuring that any consent proffered by parents is qualified and persistent, accumulating outcome data on various treatments, and providing continuing education to persons with intersex conditions, their families, and their physicians. This is indeed an ambitious goal, and the principles have considerable merit, but they would need to be applied in the local context of legal, ethical, and cultural frameworks, with consideration of the resources available to multidisciplinary teams working in this field of medicine.

A number of chapters cover more specific topics. Examples include discussions of how management decisions in the past might have been different if institutional review boards had been in place, the effects of prenatal sex imprinting and how medical decisions are made with respect to male neonates with micropenises, the different approaches to the management of intersex conditions in Eastern and Western cultures, and adult outcomes of feminizing surgery (data that have fueled the debate about the advisability of early surgery). Also included is a pragmatic discussion of the role of the specialized clinical psychologist in the multidisciplinary team. In another chapter, Sytsma specifically addresses the prenatal treatment of congenital adrenal hyperplasia with dexamethasone and the safety and nonmaleficence issues it raises (Primum non Nocere). Patricia Beattie Jung’s discussion of intersexuality from a Christian perspective provides a point of view that would not have been included in a standard medical text. Jung concludes by proclaiming that “God is not male, female, or intersexed, but rather truly beyond human sexual differentiation.”

Several chapters in this book are a positive contribution to knowledge of the complexity of managing intersex conditions. To that end, it is a useful resource even though the universal audience specified in the preface is probably overly ambitious. It should be clarified, however, that the field has changed since some of the criticisms mentioned in the book were leveled at medical professionals. The term “intersex” has not been used as widely among medical professionals since the publication of a consensus document compiled by a faculty of specialists in the field, myself included (Arch Dis Child 2006;91:554-63). In that document, we proposed replacing “intersex” with “disorders of sex development,” a term we defined and used as a basis for further changes in nomenclature and a simpler classification of the causes of the disorders. The consensus document is a step in the right direction, but it lacks the kind of discussion of ethical issues that this book provides.

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THE HEALTH OF SEXUAL MINORITIES: PUBLIC HEALTH PERSPECTIVES ON LESBIAN, GAY, BISEXUAL, AND TRANSGENDER POPULATIONS


HOMOSEXUALS HAVE NEVER BEEN POPULAR. For millennia, there have been religious objections to same-sex attraction and behavior — people who had sexual contact with members of their own sex were regarded as sinful or depraved. In the late 19th century, medical and psychological views of same-sex desire evolved, but this development, often motivated by a wish to exculpate men and women who were drawn to their own sex, ultimately had the effect of further criminalizing and medicalizing homosexuality.

The official “identification” of homosexuality as a disorder led to shame and fear for many men and women and their families. Between the 1920s and the mid-1980s, unknown numbers of gay men and lesbians in the United States and Britain underwent psychoanalytic, psychological, and medical “treatments” to make them heterosexual. This practice continues today, although now largely under the guise of spiritual healing. Thus it is not too surprising that a book on the public health of sexual minorities does not get around to a discussion of actual health outcomes until the reader is more than halfway through it. This long preamble is necessary, however, because the people
who are the focus of the book are a minority that is largely hidden in history and remains difficult to define or study.

The default assumption in all societies is heterosexuality. Homosexuality, bisexuality, and transgenderism are acknowledged only when society is presented with their evidence, usually in the form of gender nonconformity, or when lesbian, gay, bisexual, or transgender persons make themselves known. This openness has occurred mainly since the 1960s and mostly in wealthy Western countries. Although it has undoubtedly led to enormous leaps forward, we still know relatively little about the public health issues that affect people who are lesbian, gay, bisexual, or transgender. The main stumbling block is defining and measuring the population and its needs. This is where The Health of Sexual Minorities comes in.

Before we can understand the key public health problems and plan an appropriate response, we have to agree on our target. The authors of the first 18 chapters of the book describe what it is like to grow up as a member of a sexual minority in American society, how such human characteristics can be defined and measured, and what role political and judicial systems should play in these matters. The second half of the book deals with the primary public health problems of this population — including infection with the human immunodeficiency virus, mental health issues, substance abuse, and particular cancers — and the community and service responses needed.

The book is particularly good at questioning stale ideologies about growing up gay and challenging assumptions about how people manage their identities at different stages of their lives. It is also insightful in its discernment of the nature and effects of stigma and the consequences (both good and bad) of taking the “I was born that way” approach to lesbian and gay rights. However, the discussion of civil rights is heavy going, and the chapter on how race and sexuality shape Latino health is superficial. I would have preferred a more theory-driven discussion of how antihomosexual prejudice and stigma affect health, why such hostility is ubiquitous in human cultures, and how the book’s unapologetically North American view (only one author comes from outside the United States) might serve the public health needs of sexual minorities in other, particularly low-income, countries. These flaws aside, this is a serious and useful book that should be required reading for public health professionals.

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LAW IN PUBLIC HEALTH PRACTICE

Once upon a time there was a great body of law with vast dormant powers. That law, the police power in public health, has been quietly used by administrators and policymakers alike as a tool for protecting the public health with little fanfare and great humility, starting with the Supreme Court case of Jacobsen v. Massachusetts in 1905. By the late 20th century, a well-established ethos of public health practice did not recognize the inextricable link between the law and the administration of public health that has served so many vulnerable populations in the United States and worldwide. Yet the overarching importance of the law of public health needs no new authority to bolster its force — it is a power that during emergencies or in time of quarantine can overtake a host of civil liberties and traditional patterns of interstate commerce on a state, federal, international, or even municipal level.

The new collection of thoughtful essays in Law in Public Health Practice provides a clear, focused snapshot of the state of the art in public health law for practitioners in the first decade of the 21st century. The very dense text reflects the wisdom of several leaders in health law in New York City, including Wilfredo Lopez, general counsel for health at the New York City Department of Health, and Frank P. Grad of Columbia University, author of the prestigious book Public Health Law Manual, now in its third edition (Washington, DC: American Public Health Association, 2004). The editors of the book also had the courage to embrace new frontiers in public health law, such as the International Health Regulations developed by the World Health Organization (WHO). The stellar team of legal minds and medical practitioners assembled
to summarize the current thinking in public health law pursue their illusive task as one might attempt to catch a wave on the sand — in the past several years, following the events of September 11, 2001, and the aftermath of natural disasters such as Hurricane Katrina, certain areas of public health law have come to the fore, including civilian protection against bioterrorism and emergency preparedness. As noted in the first chapters, the major achievements of public health in the 20th century included the conquest of lethal communicable diseases, the control of smoking and the use of tobacco, and improvements in motor-vehicle safety. In the 21st century, the focus shifts to the use of the law as the superstructure in a variety of settings, with regulation and litigation the weapons in the practitioner’s arsenal.

One consequence of expanded popular awareness of public health law, following recent pandemics and environmental emergencies, is the need to redefine the roles of states, municipalities, and nations under the principles of federalism. In this sense, the editors of the book have erred on the side of caution by allowing the repetition of major themes regarding federalism in several essays.

The outstanding chapter by David P. Fidler and Martin S. Cetron, “International Considerations,” makes a pathbreaking effort to “remedy the neglect of international considerations in the analysis of U.S. public health law,” acknowledging the growing influence of globalization and international law. Departing from recent history, when, as Fidler and Cetron write, “international health diplomacy lost its grounding in U.S. self-interest,” the new International Health Regulations put forward by the WHO embrace the incorporation of human rights principles, acknowledging the need “to balance effective responses to disease risks” with respect for fundamental individual freedoms. The regulations are mindful of restrictions on trade in the General Agreement on Tariffs and Trade that are intended to protect human health and of the U.S. obligation to prevent the exportation of public health threats.

The collective efforts of the editors and authors of this book give renewed vigor to the proposition that around the world, across cultures, and in every generation, public health law is a vibrant requisite of survival — not only for individuals but for all civilization.

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CORRECTION
Left Ventricular Assist Devices and Drug Therapy in Heart Failure

To the Editor: The article by Birks et al. (Nov. 2 issue) is an important contribution to further development of a therapeutic approach to idiopathic dilated cardiomyopathy that remains controversial despite being repeatedly proved. The high recovery rate reported by the authors is encouraging, although it might have been facilitated by patient selection. Thus, Patient 11, with a small left ventricle and normal cardiac index value, underwent implantation of a left ventricular assist device with the diagnosis of idiopathic dilated cardiomyopathy. The survival rate after explantation in the study cohort (81.8% at 4 years) is similar to that among our 35 patients with idiopathic dilated cardiomyopathy who were weaned from left ventricular assist devices since 1995 (78.1% at 6 years). Freedom from recurrence of heart failure is an important contribution to further development of a therapeutic approach to idiopathic dilated cardiomyopathy.

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References

To the Editor: Birks et al. showed the therapeutic benefits of combining clenbuterol with myocardial unloading, but it may be prudent to clarify the wider anabolic and myotoxic effects of clenbuterol. Cardiotoxic effects of clenbuterol are mediated by β1-adrenergic receptors, whereas therapeutic effects of the drug are mediated by β2-adrenergic receptors. Hence, coadministration with a β1-adrenergic receptor antagonist is crucial to the successful use of clenbuterol as an adjunct to unloading of the myocardium. In contrast, in skeletal muscle, both the anabolic and toxic effects of clenbuterol are mediated by β2-adrenergic receptors and cannot be separated by using β2-adrenergic-receptor antagonism. In rats, clenbuterol increases muscle growth at doses lower than those required to induce myofiber death, but the translation of doses to humans is difficult. Notably, clenbuterol induces myofiber death in rat muscle at doses causing submaximal increases in heart rate, suggesting that this myotoxicity is apparent at physiologic doses possibly equivalent to those used by Birks et al. in humans. These findings argue against the arbitrary use of large doses of clenbuterol and highlight the need to reconcile its anabolic and myotoxic effects when considering its therapeutic potential.

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References

To the Editor: The study by Birks et al. raises important questions about the mechanisms of reversibility of ventricular remodeling, which represents a common process of progressive ventricular hypertrophy, enlargement, and cavity distortion over time. The underlying molecular, cellular, and interstitial changes in the myocardium have

been studied extensively in patients with heart failure. Less is known about the mechanisms of reverse remodeling. In the study by Birks et al., significant improvement in clinical status was associated with a decrease in the size of the ventricular cavity, along with functional changes in the myocardium. Have Birks et al. also examined structural changes in the myocardium? Specifically, has the interstitial and replacement fibrosis seen during implantation of the device changed over the course of therapy? If so, this could imply that fibrosis can be reversed.

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References


To the Editor: Birks et al. show that heart failure secondary to nonischemic cardiomyopathy could be reversed with the combined use of a left ventricular assist device and clenbuterol.

A major limitation of this study is the lack of a control group. It is well documented that patients with myocarditis, peripartum cardiomyopathy, and tako-tsubo cardiomyopathy may have spontaneous improvement in left ventricular function, and this cannot be ruled out as an explanation for the improvement described by Birks et al. Although patients with evidence of myocarditis on myocardial biopsy were excluded in their study, the sensitivity of biopsy for the diagnosis of myocarditis is limited. The authors appropriately excluded patients with irreversible myocardial damage such as ischemic cardiomyopathy, and it is not surprising that a patient with anthracycline-induced cardiomyopathy did not benefit.

The important clinical question of whether the approach of Birks et al. results in a likelihood of improvement in left ventricular function that exceeds the likelihood of improvement with conservative therapy can be answered only by performing a randomized, controlled trial.

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References


To the Editor: Myocardial recovery after partial unloading by means of a left ventricular assist device and drug therapy is arguably one of the most fascinating developments in cardiac surgery. Birks et al. report a recovery rate of 46%, which is substantially higher than the rates reported in previous studies (5%, 24%, and 11%). However, from an intention-to-treat perspective, the recovery rate in the study by Birks et al. should be 33.3% (9 of 27 patients). Although lower than the one reported, it still considerably exceeds the rates in previous studies and is no less impressive.

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The authors reply: With regard to the comments of Hetzer et al., the significantly higher rate of recovery observed in our series than that previously reported after implantation of left ventricular assist devices is not due to patient selection. All our patients had severe heart failure while receiving inotropic support, with impending or actual multiorgan failure, including Patient 11, who had an ejection fraction of 15% and acidosis. It is well known that isolated measurements of cardiac output can be misleading in inotrope-dependent patients. With regard to the ejection fraction and apical hypokinesis after explantation, all our patients undergo removal of the inflow cannula with formal repair of the apex, which might explain the differences between our patients and those in whom the inflow cannula is left in place. We share the enthusiasm of Hetzer et al. with regard to long-term recovery.

We agree with Dr. Burniston that it is important to combine the use of clenbuterol with β1-adrenergic-receptor antagonists. With regard to the dosage, we believe it should be carefully adjusted to maintain the heart rate below 100 beats per minute while the patient is monitored for skeletal muscle pain and creatine kinase levels are measured. It is well known that dosages of drugs used in small-animal models cannot be applied to humans.

Dr. Florea points out the importance of studying structural and molecular changes in the myocardium in an attempt to define the mechanisms of recovery. This has been a major focus of investigation in...
our patients.\textsuperscript{1,2,3,4} With regard to fibrosis, we have observed significant diminution in the collagen volume fraction (unpublished data). However, previous studies\textsuperscript{5} have outlined the critical importance of cross-linking of collagen in remodeling, which needs to be studied.

The concern of Drs. Rott and Leibowitz regarding inclusion of patients known to have a high rate of spontaneous recovery does not apply to our series. We excluded patients with myocardiitis, and none of our patients had the apical ballooning syndrome ("tako-tsubo"), which is easily recognizable. As explained in our article and in the literature, patients with advanced peripartum cardiomyopathy have the same poor prognosis that others have. The use of a randomized control group was precluded by the critical condition of our patients, who required urgent mechanical support.

The statement by Dr. Vanderwilt that from an intention-to-treat perspective the rate of recovery is 33\% is incorrect; he included patients with ischemic heart disease and those who died after explantation, including the late death due to carcinoma of the lung. We agree with Dr. Vanderwilt that recovery after implantation of a left ventricular assist device could be one of the important developments in cardiac surgery.

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References


A 40-year-old man with a 4-year history of diabetes mellitus and no history of gallstones was admitted to the health center after acute alcohol intoxication. He had been consuming about 200 ml of whiskey a day for over 15 years. No one in his immediate family had diabetes mellitus. On further questioning, he reported passing bulky, foul-smelling stools, which were difficult to flush, for more than 3 months. He also reported decreased night vision, although his visual acuity was normal. The serum lipase level was 468 U per liter, and the glucose level was 432 mg per deciliter (24 mmol per liter). His liver-function tests were unremarkable. A plain radiograph of the abdomen showed extensive calcification of the pancreas (arrows). The patient was given vitamin and pancreatic-enzyme supplements. His hyperglycemia was easily controlled with low-dose insulin. After stabilization, he was referred for treatment of alcohol addiction.

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Chronic Calcific Pancreatitis

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