THIS WEEK IN THE JOURNAL

Article Summaries

PERSPECTIVE

HIV in India — The Challenges Ahead
R. Steinbrook

Tuberculosis and HIV in India
R. Steinbrook

Revising Medicare’s Physician Fee Schedule — Much Activity, Little Change
P. B. Ginsburg and R. A. Berenson

Focus on Research: Enterovirus Déjà Vu
J. F. Modlin

ORIGINAL ARTICLES

Emergency Duties and Deaths from Heart Disease among Firefighters in the United States
S. N. Kales, E. S. Soteriades, C. A. Christophi, and D. C. Christiani

NALP1 in Vitiligo-Associated Multiple Autoimmune Disease
Y. Jin and Others

Neurodevelopment and Cognition in Children after Enterovirus 71 Infection
L.-Y. Chang and Others

Redarkening of Port-Wine Stains 10 Years after Pulsed-Dye-Laser Treatment
M. Huikeshoven and Others

CLINICAL PRACTICE

Intermittent Claudication
C. White

IMAGES IN CLINICAL MEDICINE

Evolution of a Thoracic Aortic Aneurysm
S. Kawasaki and T. Kawasaki

Dupuytren’s Contracture
E. Calif and S. Stahl

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Case 9-2007 — A 27-Year-Old Woman with Pain and Swelling of the Legs
J.-M. Vallat, D. P. Cros, and E. T. Hedley-Whyte
EDITORIALS

Firefighting and Death from Cardiovascular Causes
L. Rosenstock and J. Olsen

Modern Genetics, Ancient Defenses, and Potential Therapies
P. K. Gregersen

CORRESPONDENCE

Catheter-Related Bloodstream Infections

Adjuvant Therapy for Early Breast Cancer

Peginterferon and Ribavirin for Hepatitis C

Clinical Diagnostic Reasoning

Acromegaly

Statins and the Effect of BCG on Bladder Cancer

Medical Mystery — Paradoxical Embolism

Neurocysticercosis Uncovered by Single-Dose Albendazole

BOOK REVIEWS

Assessing Race, Ethnicity, and Gender in Health

Skin: A Natural History

Between the Dying and the Dead: Dr. Jack Kevorkian’s Life and the Battle to Legalize Euthanasia

Treatment and Management of Cancer in the Elderly

Principles and Practice of Geriatric Psychiatry

CORRECTIONS

Diagnosis of Ventilator-Associated Pneumonia

Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children
HIV in India — The Challenges Ahead

Robert Steinbrook, M.D.

On April 1, 2007, India will launch a new phase of its National AIDS Control Program (NACP). Its goals include reducing the number of new human immunodeficiency virus (HIV) infections — currently, an estimated 98.5 to 99.5% of India’s 1.1 billion people remain uninfected — improving treatment, and providing therapy to more people. The 5-year program, known as NACP-III, has a budget of about $2.6 billion, two thirds of which is earmarked for prevention and one sixth for treatment (with the remainder primarily for management), and represents a substantial increase in the attention to and spending on HIV/AIDS. More than 80% of the funds will come from outside India — from the World Bank and other international organizations, governments, and philanthropies. Most of the funding has already been committed.

When I visited India earlier this year, it was evident that the HIV epidemic was only one of the country’s many pressing health problems. India must decide whether to commit more of the resources that are fueling its rapid economic growth — and the growth of its private health care industry — to improvements in public health and basic health care. In 2003, public expenditure on health represented only 1.2% of India’s gross domestic product. There are 60 physicians per 100,000 population (as compared with 230 in Britain and 256 in the United States). With regard to HIV, challenges include increasing the number of patients receiving treatment, making additional antiretroviral medications available, improving the monitoring of therapy, training physicians and other health care workers, caring for patients with tuberculosis coinfection (see pages 1198–1199), and reducing stigma and discrimination.

Although prevention will account for a smaller percentage of the total NACP resources than at present, it will remain the focus of India’s AIDS control strategy. The components of the strategy are similar to those in other South Asian countries and include intensive prevention efforts directed at the high-risk groups of commercial sex workers, injection-drug users, and men who have sex with men, as well as “bridge populations” such as truckers and migrant workers. Avahan (Sanskrit for “a call to action”), the India AIDS initiative of the Bill and Melinda Gates Foundation, addresses gaps in India’s national response and aims “to prove that prevention can be done at scale,” according to Ashok Alexander, the program’s director. The components of India’s strategy also include ex-
panded HIV counseling and testing and treatment for sexually transmitted diseases, broad communication of information on prevention, promotion of condom use, an increase in the proportion of blood donation that is voluntary (since payment for donation attracts high-risk donors), improved access to safe blood, and expansion of programs for preventing mother-to-child transmission.

Each year, about 28 million children are born in India. Skilled health care personnel attend less than half of all births; infant mortality is about 55 per 1000 live births. In 2004, only an estimated 4% of all pregnant women received HIV counseling and testing, and only about 2% of HIV-positive pregnant women received antiretroviral prophylaxis, usually consisting of a single peripartum dose of nevirapine. Moreover, HIV-positive pregnant women may benefit from antepartum combination antiretroviral treatment for their own health. Under NACP-III, more pregnant women should receive monitoring of their CD4 cell counts, antiretroviral treatment, regimens designed to prevent HIV transmission (including combinations of antiretroviral drugs), and other services.

In scaling up treatment, India’s domestic pharmaceutical industry has a critical role. A paradox is that Indian companies have become major suppliers of low-cost generic antiretroviral medications to low- and middle-income countries in Africa and elsewhere at a time when there are still major unmet needs for HIV treatment in India. Cipla, a company based in Mumbai, manufactures the largest range of HIV drugs and has the largest market share. Cipla exports 18 times as much antiretroviral medication as it sells domestically, according to Amar Lulla, its

Tuberculosis and HIV in India

Tuberculosis is the most common HIV-related opportunistic infection in India, and caring for patients with both diseases is a major public health challenge. India has about 1.8 million new cases of tuberculosis annually, accounting for a fifth of new cases in the world — a greater number than in any other country (see pie chart). Patients with latent *Mycobacterium tuberculosis* infection are at higher risk for progression if they are coinfected with HIV. Patients with HIV infection have a similar bacteriologic response to tuberculosis treatment as those who are not infected but have higher risks of recurrence and death. The influence of tuberculosis coinfection on the progression of HIV disease is controversial.2

In 2004, about 330,000 people in India died from tuberculosis.1 Two of every five persons — more than 400 million — have latent tuberculosis infection.3 Tuberculosis can be expected to develop in more than half of those who are also infected with HIV. At present, however, only about 5% of new tuberculosis cases in India occur in people with HIV coinfection. The situation differs from that in sub-Saharan Africa, where the incidence of tuberculosis in many countries is higher than in India and as many as 80% of patients with tuberculosis are coinfected with HIV. In Africa, HIV has reversed gains in tuberculosis control that were achieved a quarter-century ago.1,2 Such a reversal is unlikely to occur in India.4

India began its Revised National Tuberculosis Control Program in 1993.5 Its mainstay is the strategy of directly observed treatment, short course (DOTS). Typically, during the initial 2 to 3 months of treatment, medication is administered three times a week under direct observation. During the subsequent 4 to 5 months, at least one of the three weekly administrations is directly supervised.3

After pilot testing, rapid expansion of DOTS began in the late 1990s, and in March 2006, India achieved nationwide coverage (see line graph). Each month, more than 100,000 Indian patients — about two fifths of them persons with a new positive sputum smear — begin treatment. The success rate of treatment — the percentage of new smear-positive patients who are cured (i.e., whose sputum smear is negative) plus the percentage who complete treatment without bacte-
HIV in India — The Challenges Ahead

The National AIDS Control Program provides care, diagnosis, and treatment on a huge scale — offering an example that the National Tuberculosis Control Program may be able to learn from as it expands. Of course, HIV treatment is often more complex and expensive than tuberculosis treatment and must continue indefinitely. When patients with HIV infection are treated at the same facility as those with tuberculosis, effective infection-control measures are essential, given the high risk of nosocomial transmission of tuberculosis. When caring for coinfected patients, physicians must consider many clinical issues, such as those related to the prevention of disease; the timing of treatment; the choice of medications; drug interactions, side effects, and resistance; and potential reinfection with other mycobacterial strains. Antiretroviral therapy is essential for reducing the number of deaths from tuberculosis that are related to HIV infection.

In India, tuberculosis care and HIV care are increasingly being coordinated, but the full benefits have yet to be realized. An example of successful coordination is the referral of people with suspected tuberculosis from voluntary counseling and testing centers for HIV to tuberculosis-control facilities. Between January and September 2006, a total of 15,000 people with suspected tuberculosis who were HIV-positive and 16,420 who were HIV-negative were referred to such facilities by centers in the six Indian states with the highest HIV prevalence (Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland, and Tamil Nadu); tuberculosis was diagnosed in 22.3% and 23.9% of patients in these groups, respectively. DOTS was begun in many of these patients. The control of both tuberculosis and HIV is likely to be most successful if programs collaborate whenever possible and are closely integrated with the rest of medical care.


Copyright © 2007 Massachusetts Medical Society.
Retail drug prices are higher in India than in Africa, in part because of taxes. Eventually, enhanced patent protection for pharmaceuticals in India, which took effect in January 2005, may lead to higher prices. So far, however, no relevant patents have been issued.

Initially, “government activities were not [proceeding] at the speed at which the virus was spreading,” according to Suniti Solomon, director of Y.R.G. CARE, a nongovernmental treatment, research, and education facility in Chennai. In April 2004, India launched its public-sector antiretroviral treatment program at eight centers. As of January 31, 2007, about 56,500 patients were receiving treatment at 103 centers (see graph); about 62% were men, 32% women, and 6% children. Perhaps 10,000 to 20,000 additional patients were receiving treatment in the private and nongovernmental sectors. The goal is to have 250 public centers open within 5 years, providing free antiretroviral treatment to 300,000 adults and 40,000 children. However, there is no way to know whether this response will be sufficient.

Patients with HIV infection in India can receive care in the private sector that is indistinguishable from that provided in leading treatment centers around the world. All the relevant medications and laboratory tests are available. In fact, HIV medications, like other drugs, are sold over the counter. Some doctors and pharmacists, however, provide treatments that make no sense — Solomon says she knows of instances in which a patient was told to take ineffective regimens, such as one zidovudine tablet twice a day for 21 days. The provision of ineffective regimens and the development of drug resistance are major concerns.

The national program provides laboratory tests, such as CD4 cell counts, and medications at no charge to the patient. At present, five first-line antiretroviral medications are provided: the nucleoside analogues lamivudine, stavudine, and zidovudine and the nonnucleoside reverse-transcriptase inhibitors efavirenz and nevirapine. More expensive first-line medications (i.e., tenofovir and emtricitabine) are not provided, nor are second-line medications and more expensive laboratory tests, such as measurement of plasma HIV RNA levels. The immediate priorities are to start patients on first-line regimens, to achieve high rates of compliance through supervised therapy and intensive counseling, to build infrastructure, and to ensure that people are not “dying for lack of access to drugs that are available and affordable,” according to Sujatha Rao, the director general of India’s National AIDS Control Organization.

It seems inevitable that the national program will have to cover additional first-line treatments, second-line treatments, and measurement of plasma HIV RNA levels and that its protocols will eventually reflect the updated recommendations of the World Health Organization. Yet the costs of such tests and second-line medications — which, at about $2,000 a year, are about 10 times those of some first-line regimens — remain formidable. According to Rao, a policy of covering additional drugs is “a big responsibility. Once the government says it will provide you with these drugs, it is a commitment forever.”

The largest AIDS care center in India is the Government Hospital...
of Thoracic Medicine, Tambaram Sanatorium, Chennai. Established in 1928 as a 12-bed private tuberculosis sanatorium, it now has extensive outpatient and laboratory facilities as well as 32 inpatient wards, with a total of 776 beds; 8 of the wards are devoted to patients with HIV. Between April 2004 and February 2007, more than 5000 patients began antiretroviral therapy at the hospital. “Every other government and private hospital would just throw the patient out as soon as they found they were HIV-positive,” says Soumya Swaminathan, deputy director of the Tuberculosis Research Center in Chennai. “At Tambaram, anyone could walk in at any time. They would be taken care of.”

In India, as in much of the world, stigma and discrimination present major barriers to controlling AIDS. In 2005, the HIV–AIDS unit of the Mumbai-based Lawyers Collective, which provides free legal aid, drafted comprehensive antidiscrimination legislation. India’s parliament has yet to consider the bill. There are other antidiscrimination efforts, such as a campaign to persuade the courts to overturn, or the parliament to rewrite, Section 377 of the Indian Penal Code, which makes homosexuality illegal and punishable by imprisonment.

Within the next several months, a more accurate estimate of the number of HIV-infected people in India should be released. Although the estimate is eagerly awaited, its effect, if any, on India’s resolve is a matter of conjecture. Regardless of the number, the new phase of the AIDS control program is just beginning, and the challenges remain immense.

Dr. Steinbrook (rsteinbrook@attglobal.net) is a national correspondent for the Journal.


Copyright © 2007 Massachusetts Medical Society.

Revising Medicare’s Physician Fee Schedule — Much Activity, Little Change

Paul B. Ginsburg, Ph.D., and Robert A. Berenson, M.D.

What garners attention when it comes to Medicare’s payment rates for physicians is the annual drama over possible 11th-hour congressional intervention to prevent cuts under the sustainable growth rate formula. But behind the scenes, Medicare policymakers have been focusing on another aspect of the periodic adjustments: the updating of the relative values in the physician fee schedule and the accuracy of the data on which it relies. Since 1992, Medicare has paid physicians through a fee schedule according to a resource-based relative-value scale (RBRVS). This approach was intended to address distortions produced by basing payments on prevailing charges, which had resulted in relatively low payment rates for evaluation and management services, as compared with procedures and technical services, as well as in large geographic variations not explainable by cost variation. The distortions were thought to discourage physicians from practicing in primary care specialties and in rural areas and to encourage a procedurally oriented style of care.

To develop its fee schedule, Medicare sets payments for services on the basis of relative costs, as determined by estimates of physician work (time and intensity), practice expenses, and malpractice insurance expenses, with geographic adjustments to reflect cost variation. A conversion factor is used to translate this structure into dollar amounts for each service. Private insurers and Medicaid programs often base their payment rates on Medicare’s relative values (using different conversion factors), so changes in Medicare’s relative values can profoundly affect physicians’ revenues.

Keeping the relative values current requires an effective process that reflects changes in medical practice and trends in physician productivity. But during the 15 years since this system was implemented, relative values have defied gravity — going up or staying the same but rarely coming down. For example, in 2006, the Centers for Medicare and Medicaid Services (CMS) raised physician-work values for 227 services
More than 90 human enterovirus serotypes have now been identified in three distinct waves of discovery. The three poliovirus serotypes were first isolated from nonhuman primates in the course of painstaking experiments performed during the first half of the 20th century. The use of small laboratory animals and the advent of cell culture in mid-century led to the description of 61 more enteroviruses that we know as coxsackieviruses, echoviruses, and the “newer” enteroviruses. The application of polymerase chain reaction and genomic sequencing has recently permitted characterization of approximately 30 previously unidentified enterovirus serotypes and undoubtedly will uncover more.

Enterovirus 71 was first isolated in a cell culture from a child with encephalitis in California in 1969, at the end of the second wave. Since that time, this virus has attracted global attention as the cause of large epidemics of acute disease in Eastern Europe in 1975 and 1978 and in Southeast Asia between 1997 and 2000; it has also caused smaller outbreaks in diverse locations in North America, Europe, and Australia. Enterovirus 71 is closely related to coxsackievirus A16, and both belong to a discrete subgroup of type A enteroviruses that are prominently associated with hand, foot, and mouth disease, a self-limited febrile illness distinguished by tender papulovesicular lesions involving the hands, feet, oropharyngeal mucosa, perineum, and buttocks. In most reported outbreaks of enterovirus 71, hand, foot, and mouth disease has been the dominant clinical feature, although a variety of much less common manifestations are reported, including herpangina (another distinctive enterovirus enanthema), interstitial pneumonia, myocarditis, intrauterine infection, and hepatic necrosis in neonates.

However, it is the neurotropic nature of enterovirus 71 that grabs our attention. This serotype, like many enteroviruses, causes viral (or aseptic) meningitis, which typically runs a benign course in both children and adults. In contrast to other enteroviruses, enterovirus 71 possesses a unique ability to invade the ventral brain stem, cerebellum, and spinal cord, producing a spectrum of serious neuromotor syndromes, including acute flaccid paralysis of one or more extremities, cranial-nerve (“bulbar”) paresis, tremors, myoclonus, and ataxia. Enterovirus 71 infection also causes a devastating syndrome of acute pulmonary edema that is hypothesized to result from the destruction of medullary vasomotor and respiratory centers, leading to central sympathetic activation with severe systemic vasoconstriction, overload of the pulmonary vascular bed, and a high fatality rate. In this issue of the Journal, Chang and colleagues (pages 1226–1234) document a high rate of debilitating neuromotor sequelae among survivors of enterovirus 71 brain-stem encephalitis that was acquired during a massive Taiwanese epidemic in 1998.

These serious neurologic outcomes affect infants and young children as rare expressions of enterovirus 71 infection and therefore come to public attention only during large outbreaks in which, in recent years, hand, foot, and mouth disease has been the hallmark of infection. The epidemic in Taiwan affected at least 130,000 persons and resulted in at least 405 hospitalizations for central nervous system disease and 78 deaths, mostly from acute neurogenic pulmonary edema. Smaller outbreaks of hand, foot, and mouth disease were reported in Malaysia in 1997 and Singapore in 2000; in these outbreaks, serious neurologic complications and deaths also occurred in young children. These remarkable epidemics have emerged from a background of endemic person-to-person transmission with sporadic illness and smaller outbreaks of the disease accompanied by meningitis, acute flaccid paralysis, or...
other neurologic syndromes in many locations, including the United States, northern Europe, Japan, Australia, and additional Southeast Asian countries. There is no known reason for the variation in communicability and virulence of enterovirus 71 infections, although differences in the susceptibility of various populations may account for some of it. The 1998 epidemic in Taiwan was preceded by two smaller enterovirus 71 outbreaks there in 1980 and 1986, each associated with hand, foot, and mouth disease and acute flaccid paralysis. We also know that enterovirus 71 antibodies were prevalent in older children and adults before the 1998 epidemic, indicating that the virus had circulated widely in Taiwan during the preceding years, attracting little or no notice. Therefore, this explosive outbreak did not represent a true “virgin-soil” epidemic attributable to the susceptibility of the entire population. But enterovirus 71 infections were infrequent during the 3 or 4 years before the epidemic, and therefore a cohort of susceptible young children accumulated; it was these children who had the highest rates of illness during the epidemic.

Factors intrinsic to the virus itself may also affect its behavior in different settings. The single-strand RNA enteroviruses mutate readily over time as they pass from person to person, and genomic sequencing has been used for more than a decade to track and characterize the spread of many enteroviruses, particularly polioviruses. Studies comparing the RNA genomes of enterovirus 71 isolates from the outbreaks in Malaysia and Singapore show that they vary from the strain that caused the 1998 Taiwanese epidemic by approximately 20% of the bases sequenced, confirming that they are epidemiologically unrelated to it. Therefore, despite the temporal and geographic connectedness of the recent enterovirus 71 epidemics in Southeast Asia, they have not been caused by continuous transmission of a single strain of virus. In addition, both clinical observations and experimental studies in primates have revealed only minor differences in neurovirulence among the different outbreak strains.

With continued observation and study, is is apparent that the epidemiologic behavior, clinical disease, and pathologic features of enterovirus 71 are strikingly similar to those of poliomyelitis. Enterovirus 71 and the three polioviruses cause both endemic and epidemic disease in which acute, severe, and sometimes fatal neuromotor disease occurs as a rare manifestation of common infections, especially in infants and young children. Each of these viruses targets gray matter in the spinal cord and brain stem, causing acute neuronal destruction and inflammation, although the damage induced by enterovirus 71 characteristically extends more widely into the pons and cerebellum, correlating with the greater range and severity of central nervous system disease observed with enterovirus 71 infections. In contrast to most other enteroviruses, enterovirus 71 and the polioviruses are difficult to recover from cerebrospinal fluid in the presence of central nervous system infection.

The recent experience with enterovirus 71 epidemic disease also invokes a sense of déjà vu for those familiar with the history of poliomyelitis. One hundred years ago, few people had heard of poliomyelitis; the world had witnessed only a few enigmatic outbreaks of paralytic polio over a period of several decades, in geographically separate regions with developing economies and emerging urban societies. But over time, these outbreaks increased in frequency and size and ultimately evolved into the major epidemics that swept through cities in northern Europe and North America in the first half of the 20th century.

Will history repeat itself? Do the recent epidemics in Southeast Asia portend annual summertime outbreaks in North America and other regions that have thus far been spared large-scale outbreaks of neurotropic enterovirus 71 infection? Without a crystal ball, it would be presumptuous to make predictions. However, if history is any guide, it would also be foolish not to be better prepared than we are now. It would be prudent to add enterovirus 71 to the list of emerging infections that threaten us, develop a plan to respond to an outbreak, and take the first steps toward developing a vaccine.

Dr. Modlin is chair of the Department of Pediatrics at Dartmouth Medical School, Lebanon, NH.


Copyright © 2007 Massachusetts Medical Society.
Emergency Duties and Deaths from Heart Disease among U.S. Firefighters

National data on deaths among on-duty firefighters between 1994 and 2004 were assessed in relation to estimates of the proportions of time spent by firefighters in various duties. The rate of death from coronary heart disease during active fire suppression was approximately 10 to 100 times as high as the expected rate. This study suggests that firefighting is associated with an unusually high risk of death from cardiac causes.

See P. 1207; Editorial, P. 1261; CME, P. 1287


Implication of NALP1 in Autoimmune Disease

A region on chromosome 17 has been associated with a range of epidemiologically associated autoimmune and autoinflammatory diseases, including vitiligo. Using two sets of genetic markers and two groups of patients, the authors have implicated variants of NALP1 in susceptibility to autoimmune disease.

See P. 1216; Editorial, P. 1263

Neurodevelopment and Cognition in Children after Enterovirus 71 Infection

Enterovirus 71 is a common cause of hand, foot, and mouth disease and encephalitis in Asia and elsewhere. Among 142 children who had enterovirus 71 infection with central nervous system involvement, assessment at 2.9 years after infection revealed poor neurodevelopment and cognitive outcomes for children who had severe central nervous system involvement with cardiopulmonary failure. In most children who had central nervous system involvement alone, neurodevelopment was normal.

See P. 1226; Perspective, P. 1204

Redarkening of Laser-Treated Port-Wine Stains

Pulsed-dye–laser therapy is effective for port-wine stains, but the benefits may not be durable. This follow-up study of patients who had received an average of five laser treatments demonstrated redarkening of port-wine stains 10 years after treatment. Patients should be informed about the possibility of redarkening before beginning treatment.

See P. 1235

Intermittent Claudication

A 58-year-old, previously healthy mail carrier reports cramping pain in his right calf when he walks. The discomfort has progressively worsened over the past 6 months and is interfering with his ability to perform his job; he can now walk no farther than half a block without rest. He has a normal right femoral pulse and a diminished right popliteal pulse; right ankle and foot pulses are absent. How should this patient be evaluated and treated? Should he undergo revascularization?

See P. 1241; CME, P. 1285

A 27-Year-Old Woman with Pain and Swelling of the Legs

A 27-year-old woman had the sudden onset of pain in the feet, more in the left foot than in the right, associated with edema of the lower legs and a rash over the feet and toes. Pain and paresthesia persisted and worsened; a neurologic examination revealed normal motor strength and reflexes but decreased sensation to pinprick in the toes. A diagnostic procedure was performed.

See P. 1252; CME, P. 1286
Emergency Duties and Deaths from Heart Disease among Firefighters in the United States

Stefanos N. Kales, M.D., M.P.H., Elpidoforos S. Soteriades, M.D., Sc.D., Costas A. Christophi, Ph.D., and David C. Christiani, M.D., M.P.H.

ABSTRACT

BACKGROUND
Heart disease causes 45% of the deaths that occur among U.S. firefighters while they are on duty. We examined duty-specific risks of death from coronary heart disease among on-duty U.S. firefighters from 1994 to 2004.

METHODS
We reviewed summaries provided by the Federal Emergency Management Agency of the deaths of all on-duty firefighters between 1994 and 2004, except for deaths associated with the September 11, 2001, terrorist attacks. Estimates of the proportions of time spent by firefighters each year performing various duties were obtained from a municipal fire department, from 17 large metropolitan fire departments, and from a national database. Odds ratios and 95% confidence intervals for death from coronary heart disease during specific duties were calculated from the ratios of the observed odds to the expected odds, with nonemergency duties as the reference category.

RESULTS
Deaths from coronary heart disease were associated with suppressing a fire (32.1% of all such deaths), responding to an alarm (13.4%), returning from an alarm (17.4%), engaging in physical training (12.5%), responding to nonfire emergencies (9.4%), and performing nonemergency duties (15.4%). As compared with the odds of death from coronary heart disease during nonemergency duties, the odds were 12.1 to 136 times as high during fire suppression, 2.8 to 14.1 times as high during alarm response, 2.2 to 10.5 times as high during alarm return, and 2.9 to 6.6 times as high during physical training. These odds were based on three estimates of the time that firefighters spend on their duties.

CONCLUSIONS
Certain emergency firefighting duties were associated with a risk of death from coronary heart disease that was markedly higher than the risk associated with nonemergency duties. Fire suppression was associated with the highest risk, which was approximately 10 to 100 times as high as that for nonemergency duties.
FIREFIGHTING IS KNOWN TO BE A DANGEROUS OCCUPATION. WHAT IS LESS APPRECIATED IS THAT THE MOST FREQUENT CAUSE OF DEATH AMONG FIREFIGHTERS IS HEART DISEASE RATHER THAN BURNS OR SMOKE INHALATION. CARDIOVASCULAR EVENTS, LARGELY DUE TO CORONARY HEART DISEASE, ACCOUNT FOR 45% OF DEATHS AMONG FIREFIGHTERS ON DUTY.\(^1\)\(^2\) IN CONTRAST, SUCH EVENTS ACCOUNT FOR 22% OF DEATHS AMONG POLICE OFFICERS ON DUTY, 11% OF DEATHS AMONG ON-DUTY EMERGENCY MEDICAL SERVICES WORKERS, AND 15% OF ALL DEATHS THAT OCCUR ON THE JOB.\(^2\)\(^3\) THE HIGH RATE OF DEATH FROM CARDIOVASCULAR CAUSES AMONG FIREFIGHTERS RAISES QUESTIONS ABOUT CONTRIBUTING FACTORS. POSSIBLE FACTORS, SUCH AS PHYSICAL EXERTION, EMERGENCY RESPONSES, AND DANGEROUS DUTIES, ARE NOT UNIQUE TO FIREFIGHTING; THEY ARE ALSO CHARACTERISTIC OF THE WORK PERFORMED BY POLICE OFFICERS, MILITARY PERSONNEL, AND PERSONS IN VARIOUS OTHER OCCUPATIONS.\(^4\)\(^5\)

VARIOUS BIOLOGICALLY PLAUSIBLE EXPLANATIONS FOR THE HIGH MORTALITY FROM CARDIOVASCULAR EVENTS AMONG FIREFIGHTERS HAVE BEEN PROPOSED. THESE EXPLANATIONS INCLUDE SMOKE AND CHEMICAL EXPOSURE, IRREGULAR PHYSICAL EXERTION, THE HANDLING OF HEAVY EQUIPMENT AND MATERIALS, HEAT STRESS, SHIFTFORK, A HIGH PREVALENCE OF CARDIOVASCULAR RISK FACTORS, AND PSYCHOLOGICAL STRESSORS.\(^6\)\(^-\)\(^13\) GIVEN THESE OCCUPATIONAL RISKS, 37 U.S. STATES AND 2 CANADIAN PROVINCES PROVIDE BENEFITS TO FIREFIGHTERS IN WHOM CERTAIN CARDIOVASCULAR DISEASES HAVE DEVELOPED.\(^14\) NEVERTHELESS, THE EVIDENCE LINKING FIREFIGHTING TO CARDIOVASCULAR DISEASE CONTINUES TO BE DEBATED.\(^15\)\(^-\)\(^17\) THEREFORE, WHETHER DEATHS FROM CORONARY HEART DISEASE AMONG FIREFIGHTERS ARE TRULY PRECIPITATED BY THEIR WORK AND, IF SO, BY WHICH DUTIES, REMAIN IMPORTANT QUESTIONS.


### DEATHS AMONG FIREFIGHTERS

The U.S. Fire Administration, a branch of the Federal Emergency Management Agency, collects narrative summaries for all reported deaths associated with firefighting in the United States. From these publicly available summaries, we examined data on all deaths that occurred between January 1, 1994, and December 31, 2004.\(^2\)\(^,\)^\(^19\) The data included all firefighters who died while on duty, who became ill while on duty and later died, and who died within 24 hours after an emergency response or training. We excluded deaths that occurred during the first 48 hours after the September 11, 2001, terrorist attacks.

To extract study data, two reviewers independently examined the summary of each reported death that occurred while the firefighter was on duty. A third reviewer resolved any classifications that were not concordant between the first two reviewers. On the basis of the narrative reports, each death was classified as due to cardiovascular causes or to noncardiovascular causes. We then excluded those cases in which death occurred more than 24 hours after the on-duty incident or in which death resulted from a cardiovascular problem other than coronary heart disease (e.g., certain arrhythmias, stroke, aneurysm, or genetic cardiomyopathy).

All records of deaths that were classified by this process as being due to coronary heart disease were selected for further study. Data extracted from these records included the firefighter’s age, sex, and job status (professional or volunteer); the date, cause, and mechanism of death; and the city and state of the fire department.

### DUTIES AT THE TIME OF DEATH

On the basis of the summary report of each death, the deaths were classified according to the specific duty performed during the onset of symptoms or immediately preceding sudden death. These categories were fire suppression; alarm response; alarm return; physical training; emergency medical services, rescues, and other nonfire emergencies; and nonemergency duties. A death was classified as being associated with fire suppression if it occurred while the person was fighting a fire or at the scene of a fire after its suppression. Alarm response involved responses to

### METHODS

#### DEATHS AMONG FIREFIGHTERS

The U.S. Fire Administration, a branch of the Federal Emergency Management Agency, collects narrative summaries for all reported deaths associated with firefighting in the United States. From these publicly available summaries, we examined data on all deaths that occurred between January 1, 1994, and December 31, 2004.\(^2\)\(^,\)^\(^19\) The data included all firefighters who died while on duty, who became ill while on duty and later died, and who died within 24 hours after an emergency response or training. We excluded deaths that occurred during the first 48 hours after the September 11, 2001, terrorist attacks.

To extract study data, two reviewers independently examined the summary of each reported death that occurred while the firefighter was on duty. A third reviewer resolved any classifications that were not concordant between the first two reviewers. On the basis of the narrative reports, each death was classified as due to cardiovascular causes or to noncardiovascular causes. We then excluded those cases in which death occurred more than 24 hours after the on-duty incident or in which death resulted from a cardiovascular problem other than coronary heart disease (e.g., certain arrhythmias, stroke, aneurysm, or genetic cardiomyopathy).

All records of deaths that were classified by this process as being due to coronary heart disease were selected for further study. Data extracted from these records included the firefighter’s age, sex, and job status (professional or volunteer); the date, cause, and mechanism of death; and the city and state of the fire department.

### DUTIES AT THE TIME OF DEATH

On the basis of the summary report of each death, the deaths were classified according to the specific duty performed during the onset of symptoms or immediately preceding sudden death. These categories were fire suppression; alarm response; alarm return; physical training; emergency medical services, rescues, and other nonfire emergencies; and nonemergency duties. A death was classified as being associated with fire suppression if it occurred while the person was fighting a fire or at the scene of a fire after its suppression. Alarm response involved responses to

#### METHODS

#### DEATHS AMONG FIREFIGHTERS

The U.S. Fire Administration, a branch of the Federal Emergency Management Agency, collects narrative summaries for all reported deaths associated with firefighting in the United States. From these publicly available summaries, we examined data on all deaths that occurred between January 1, 1994, and December 31, 2004.\(^2\)\(^,\)^\(^19\) The data included all firefighters who died while on duty, who became ill while on duty and later died, and who died within 24 hours after an emergency response or training. We excluded deaths that occurred during the first 48 hours after the September 11, 2001, terrorist attacks.

To extract study data, two reviewers independently examined the summary of each reported death that occurred while the firefighter was on duty. A third reviewer resolved any classifications that were not concordant between the first two reviewers. On the basis of the narrative reports, each death was classified as due to cardiovascular causes or to noncardiovascular causes. We then excluded those cases in which death occurred more than 24 hours after the on-duty incident or in which death resulted from a cardiovascular problem other than coronary heart disease (e.g., certain arrhythmias, stroke, aneurysm, or genetic cardiomyopathy).

All records of deaths that were classified by this process as being due to coronary heart disease were selected for further study. Data extracted from these records included the firefighter’s age, sex, and job status (professional or volunteer); the date, cause, and mechanism of death; and the city and state of the fire department.
emergency incidents, including false alarms. Alarm 
return included all events that occurred during 
the return from incidents and those that occurred 
within several hours after an emergency call. 
Physical training included all job-related physical-
fitness activities, physical-abilities testing, and 
simulated or live fire, rescue, emergency, and 
search drills. We grouped together emergency 
medical services, rescues, and other nonfire emer-
gencies in a separate category. Finally, we classi-
fied all of the following activities as nonemergen-
cy duties: administrative and fire-station tasks, 
fire prevention, inspection, maintenance, meet-
ings, parades, and classroom activities.

**TIME SPENT ON SPECIFIC DUTIES**

We used data from several sources to estimate 
the average annual proportion of time that fire-
fighters spend in each category. First, we direct-
ly derived point estimates from a municipal fire 
department (Cambridge Fire Department, Cam-
bidge, MA), using fiscal year 2002 data, as in our 
previous study. For Cambridge firefighters, the 
following information was available: the number 
of firefighters, the total number of alarms and 
emergency responses, the distribution of emer-
gency calls and dispatches by hour of the day, a 
breakdown of the types of incidents involved in 
fire and nonfire emergency responses, the average 
time spent per incident and the average response 
time, and the estimated number of hours spent 
each week in training and fire-prevention activities. 
We refer to these data as the municipal estimate.

Second, to conduct a sensitivity analysis, we 
obtained two additional sets of estimates, one 
representing a level of emergency activity that was 
higher than that of the Cambridge Fire Depart-
ment and the other representing a lower level of 
emergency activity. These estimates were derived 
with the use of data for the population served, 
the numbers of uniformed officers, and the num-
ber of emergency incidents and the types of inci-
dents classified as fire and nonfire emergencies. 
To characterize the largest and busiest fire de-
partments, an estimate was developed from 2005 
survey data provided by the International Associa-
tion of Fire Fighters (Moore-Merrell L; personal 
communication) for 17 large urban and suburban 
fire departments (the large metropolitan esti-
mate). To represent firefighters in smaller com-
unities with lower levels of emergency activity, 
an estimate was developed from nationwide Na-
tional Fire Protection Association surveys conduct-
ed from 1994 to 2003 (the national estimate).

**STATISTICAL ANALYSIS**

We made the initial assumption that if specific 
firefighting duties do not have a significant effect 
on the risk of death from coronary heart disease, 
then the number of such deaths that occur dur-
ing any given firefighting duty should be directly 
proportional to the amount of time spent per-
forming that duty. For example, if 10% of a fire-
fighter’s time is spent in responding to alarms, 
10% of deaths from coronary heart disease should 
occur during alarm response. We then sought to 
determine whether this expected pattern is or is 
not supported by the actual data.

Using the chi-square goodness-of-fit test, we 
assessed whether the distribution of actual deaths 
associated with each duty was the same as that 
of expected deaths, based on the estimates of the 
average time dedicated to each firefighting duty. 
We used the three different time estimates (from 
the municipal, large metropolitan, and national 
data) to calculate the ratios of actual to expected 
deaths for each firefighting duty. The 95% confi-
dence intervals (CIs) for these ratios were calcu-
lated on the basis of the multinomial distribu-
tion. Odds ratios for death from coronary heart 
disease during specific duties were calculated 
from the ratios of the observed to expected odds, 
with nonemergency duties used as the reference 
category. The 95% CIs for the estimated odds 
ratios were calculated with the use of the bino-
mial distribution.

Using data from the 2000 firefighters census, 
which stratifies firefighters according to their age 
(in decades) and job status (professionals or vol-
unteers), we calculated the rates of death from 
coronary heart disease for specific duties accord-
ing to age and job status. Our calculations were 
based on death counts in each category per 1 mil-
ion person-years of risk, derived from the average 
number of firefighters at risk in each subgroup 
over the 11-year period of observation.

Analyses were performed with the use of SAS 
software for Windows (version 8.02, SAS Insti-
tute), and StatXact (version 6.0). A P value of less 
than 0.05 was considered to indicate statistical 
significance, and all statistical tests for differ-
ences were two-sided.
RESULTS

Between January 1, 1994, and December 31, 2004, 1144 firefighter deaths were reported to the U.S. Fire Administration. We classified 449 deaths as due to coronary heart disease (39%). Of these deaths from coronary heart disease, 144 (32%) occurred during fire suppression, 138 (31%) occurred during alarm response or return, and the remaining 167 (37%) occurred during other duties (Table 1).

Table 2 shows the estimated proportion of time that firefighters spent each year in specific duties according to the three sources of fire-department activity data that we used. Among firefighters in Cambridge (our municipal data set), approximately 2% of duty time was spent in fire suppression. Among firefighters in our large metropolitan data set, approximately 5% of duty time was spent in fire suppression. Finally, among all firefighters in the United States (as represented in our national data set), approximately 1% of duty time was spent in fire suppression.

Table 3 shows the frequency of observed deaths from coronary heart disease according to duty as compared with the expected frequency. The observed distribution of deaths was significantly different from the expected distribution based on the estimates from each of the three data sources ($P < 0.001$ for the three comparisons). The ratios of observed to expected deaths associated with the various duties of firefighters were consistently higher than 1, with the exception of nonfire emergencies and nonemergency duties. Although 32% of deaths occurred during fire suppression, this activity was estimated to account for as little as 1 to 5% of the average firefighter’s professional time per year, so this duty was associated with the most significantly elevated ratios of observed to expected deaths.

Table 1. Deaths from Coronary Heart Disease among Firefighters, Classified According to Duty at the Time of Death.*

<table>
<thead>
<tr>
<th>Duty</th>
<th>Deaths (N = 449)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Fire suppression</td>
<td>144 (32.1)</td>
</tr>
<tr>
<td>Alarm response</td>
<td>60 (13.4)</td>
</tr>
<tr>
<td>Alarm return</td>
<td>78 (17.4)</td>
</tr>
<tr>
<td>Physical training</td>
<td>56 (12.5)</td>
</tr>
<tr>
<td>Emergency medical services and other nonfire emergencies</td>
<td>42 (9.4)</td>
</tr>
<tr>
<td>Fire-station and other nonemergency duties</td>
<td>69 (15.4)</td>
</tr>
</tbody>
</table>

* Data are based on narrative summaries from the records of the U.S. Fire Administration, Federal Emergency Management Agency, for the period from January 1, 1994, to December 31, 2004.19

Table 2. Fire Service Activity and the Estimated Proportion of Time Spent in Specific Firefighting Duties.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Municipal Fire Department</th>
<th>Large Metropolitan Fire Departments</th>
<th>National Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fire service activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population served (no.)</td>
<td>101,355</td>
<td>760,935±888,916</td>
<td>280,000,000</td>
</tr>
<tr>
<td>Uniformed firefighters (no.)</td>
<td>274</td>
<td>1063±785</td>
<td>1,082,855±14,446</td>
</tr>
<tr>
<td>Population served per firefighter (no.)</td>
<td>370</td>
<td>655±218</td>
<td>259±3</td>
</tr>
<tr>
<td>Emergency incidents (no./firefighter/yr)</td>
<td>44</td>
<td>92±24</td>
<td>18±2</td>
</tr>
<tr>
<td>Fire incidents (no./firefighter/yr)</td>
<td>2.0</td>
<td>7.0±6.3</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Duties (% of annual time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fire suppression</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Alarm response</td>
<td>6</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Alarm return</td>
<td>10</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Physical training</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Emergency medical services and other nonfire emergencies</td>
<td>23</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Fire-station and other nonemergency duties</td>
<td>51</td>
<td>29</td>
<td>65</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Municipal data are from the Cambridge Fire Department, Cambridge, Massachusetts (2002).18 Data for large metropolitan fire departments are from surveys of 17 large metropolitan fire departments conducted by the International Association of Fire Fighters (2005) (Moore-Merrell L: personal communication). National data are from annual national surveys conducted by the National Fire Protection Association (1994 through 2003).20
Table 4 includes the odds ratios and 95% CIs for the risk of death from coronary heart disease among firefighters engaged in each emergency duty and physical training as compared with the reference category of nonemergency tasks. On the basis of the three estimates of the time that firefighters spent on particular duties, death from coronary heart disease was 12 to 136 times as likely to occur during fire suppression as during nonemergency duties. An increased risk was also consistently observed for other emergency duties, as compared with nonemergency duties; the risk was increased by a factor of 2.8 to 14.1 during alarm response, 2.2 to 10.5 during alarm return, and 2.9 to 6.6 during physical training.

Figure 1A shows the risk of death from coronary heart disease per 1 million firefighters per year (deaths per 1 million person-years) for each duty according to age group, and Figure 1B shows the risk of death according to job status (volunteer or professional). As might be expected, the risk of coronary heart disease generally increased with age for each type of duty, whereas the results for job status were mixed.

**Discussion**

In this study, we used data from a nationwide registry of deaths among firefighters over an 11-year period and estimates from three different sources of time spent in various firefighting duties to estimate the duty-specific risks of death from coronary heart disease among firefighters. As compared with nonemergency duties, certain emergency duties and physical training were associated with an increased risk of death from coronary heart disease among firefighters. These findings are consistent with those of our previous, smaller study and with an analysis of cardiac events that led to retirement from firefighting.

Fire suppression, which represents only about 1 to 5% of firefighters’ professional time each year, accounted for 32% of deaths from coronary heart disease and was associated with a risk of death from coronary heart disease that was approximately 10 to 100 times as high as the risk associated with nonemergency duties. We think that the most likely explanation for these findings is the increased cardiovascular demand of fire suppression.

The risk of coronary heart disease events during fire suppression may be increased because...
many firefighters lack adequate physical fitness, have underlying cardiovascular risk factors, and have subclinical or clinical coronary heart disease. Even new firefighter recruits may be overweight and have low-to-normal aerobic capacities.23 Such problems are compounded during career tenure because more than 70% of fire departments lack programs to promote fitness and health.1 Most fire departments do not require firefighters to exercise regularly, undergo periodic medical examinations, or have mandatory return-to-work evaluations after a major illness. In addition, several studies have shown the high prevalence of risk factors for cardiovascular disease among firefighters24-29 as well as lower-than-expected exercise tolerance.30,31 Moreover, two studies have shown that among firefighters who had fatal events18 or nonfatal events22 related to coronary heart disease while on duty, 26% and 18%, respectively, had previously received a diagnosis of coronary heart disease, peripheral vascular disease, or cerebrovascular disease, and among the remainder, smoking, hypertension, and diabetes mellitus were significantly more prevalent than among active firefighters in the control group. Likewise, in our study, the risk of death from coronary heart disease increased with age for all types of duty. Unexpectedly, professional and volunteer firefighters had different risks of death from coronary heart disease, depending on the type of duty performed, although for both groups, the risk was highest during fire suppression.

In parallel with our finding of a significantly increased risk of death from coronary heart disease during fire suppression, as compared with nonemergency duties, the risk was significantly elevated during physical training. This finding is consistent with investigations implicating intense physical activity as a strong triggering factor, especially among physically inactive persons.32-35 Also consistent with the triggering hypothesis and with research documenting increased heart rates among firefighters responding to alarms8,9 was our finding that the risk of death from coronary heart disease associated with alarm response and alarm return was approximately five to seven times as high as that associated with nonemergency duties. Emergency medical services and other nonfire emergency responses were not associated with a significant increase in risk. These findings are consistent with the much lower proportion of deaths from coronary heart disease among emergency medical services workers who are not firefighters3 than among firefighters, and may reflect a lower level of exposure to physically demanding emergencies.

One limitation of our study is that the estimates of odds ratios for specific job duties are based on fairly wide approximations of time spent on different duties. The average work year of a professional firefighter in a major urban center is probably much different from that of a rural volunteer firefighter. In addition, there have been few if any comprehensive studies of how fire-

Table 4. Risk of Death from Coronary Heart Disease among Firefighters Engaged in Emergency Duties and Physical Training as Compared with Firefighters Engaged in Nonemergency Duties.*

<table>
<thead>
<tr>
<th>Duty</th>
<th>Municipal Fire Department</th>
<th>Large Metropolitan Fire Departments</th>
<th>National Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI) P Value</td>
<td>Odds Ratio (95% CI) P Value</td>
<td>Odds Ratio (95% CI) P Value</td>
</tr>
<tr>
<td>Fire suppression</td>
<td>53 (40–72) &lt;0.001</td>
<td>12.1 (9.0–16.4) &lt;0.001</td>
<td>136 (101–183) &lt;0.001</td>
</tr>
<tr>
<td>Alarm response</td>
<td>7.4 (5.1–11) &lt;0.001</td>
<td>2.8 (1.9–4.0) &lt;0.001</td>
<td>14.1 (9.8–20.3) &lt;0.001</td>
</tr>
<tr>
<td>Alarm return</td>
<td>5.8 (4.1–8.1) &lt;0.001</td>
<td>2.2 (1.6–3.1) &lt;0.001</td>
<td>10.5 (7.5–14.7) &lt;0.001</td>
</tr>
<tr>
<td>Emergency medical services and other nonfire emergencies</td>
<td>1.3 (0.9–2.0) 0.16</td>
<td>0.5 (0.3–0.8) &lt;0.001</td>
<td>2.6 (1.8–3.9) &lt;0.001</td>
</tr>
<tr>
<td>Physical training</td>
<td>5.2 (3.6–7.5) &lt;0.001</td>
<td>2.9 (2.0–4.2) &lt;0.001</td>
<td>6.6 (4.6–9.5) &lt;0.001</td>
</tr>
<tr>
<td>Nonemergency duties (fire station and other)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Municipal data are from the Cambridge Fire Department, Cambridge, Massachusetts (2002).18 Data for large metropolitan fire departments are from surveys of 17 large metropolitan fire departments conducted by the International Association of Fire Fighters (2005) (Moore-Merrell L.: personal communication). National data are from annual national surveys conducted by the National Fire Protection Association (1994 through 2003).20
Deaths from Heart Disease among Firefighters spend their time. Our estimate of the increase in risk is therefore subject to considerable uncertainty. However, even in the most conservative scenario (with the use of the time estimates from the large metropolitan fire departments), the risks associated with fire suppression remained remarkably high and were also significantly increased for alarm response, alarm return, and physical training.

Also, our three sets of risk estimates are not based on three completely distinct calculations. In each case, one set of national figures for “observed” deaths was used, and the resulting odds ratios represent risk relative to nonemergency duties, not absolute risks for one group of firefighters as compared with another. Our results should therefore not be used to suggest that the risk of death from coronary heart disease during fire suppression is higher in a small community fire department than in a large metropolitan fire department. Instead, the three calculations provide a range of estimates of the average risk for firefighters nationwide. Because only 14% of firefighters in the United States serve populations larger than 100,000 residents, we think that the average risk for most firefighters probably falls between the risk based on estimates of time spent in particular duties that were derived from a single municipal fire department and the risk based on the nationwide time estimates. Our estimate that fire suppression accounts for 1 to 2% of annual work time (for the nationwide and municipal scenarios, respectively) is consistent with a study of a large fire department in Montreal, where fire suppression accounted for 0.7 to 2.5% of annual work time.

A second limitation of our study was the need to base our evaluation on brief narratives, which lacked autopsy information for some of the deaths. However, the misclassification of deaths due to inadequate information would have contributed to a random error, most likely diluting the results of our study toward the null hypothesis. Although 26 deaths from cardiovascular but not coronary heart disease were excluded, this small number was unlikely to bias the overall results in a specific direction.

A third limitation of our analysis was the starting assumption that the number of deaths from coronary heart disease that occur during any given firefighting duty should be directly proportional to the amount of time spent performing that duty. It is well established, for example, that the risk of coronary heart disease events varies according to the time of day, as well as the season of the year. In this study, we could not examine the circadian pattern of deaths. However, in our previous, smaller study and in another, 10-year analysis, 67 to 77% of deaths from cardiac causes among on-duty firefighters occurred between noon and midnight, as did more than 60% of emergency responses. This pattern is in stark contrast to the peak period for cardiovascular events in the general population, which is 6 a.m. to noon. With respect to season, deaths from cardiac causes among firefighters are most frequent in the winter, as they are in the general population. When we analyzed duty-specific risks
separately for each of the four seasons, however, the resulting point estimates for each duty remained similar in magnitude and close to the range of our original confidence intervals. Finally, although we cannot completely account for the effects of the time of day and season, the highest estimates of these effects on event rates are at least an order of magnitude smaller than the relative risks we observed for specific duties.

In conclusion, we analyzed nationwide data on deaths among firefighters, as well as three separate estimates of time spent in various firefighting duties, to determine the duty-specific risks of death from coronary heart disease among firefighters. Our analysis showed that specific duties, especially fire suppression but also alarm response, alarm return, and physical training, are associated with significant increases in risk.

Supported in part by grants from the National Institute for Occupational Safety and Health (T42/CC122961-02, to Dr. Kales) and the Massachusetts Public Employees Retirement Administration Commission (to Dr. Kales). The funders had no involvement in the study design, data collection and analysis, writing of the paper, or decision to submit the paper for publication.

Dr. Kales and Dr. Christiani report serving as paid expert witnesses, independent medical examiners, or both in workers’ compensation and disability cases, including cases involving firefighters. No other potential conflict of interest relevant to this article was reported.

We thank Ken Pitts, John Gelinas, and Lori Moore-Merrell for providing fire-department incident, response, activity, and survey data.

REFERENCES


33. Mittleman MA, Machure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction
Deaths from Heart Disease among Firefighters


Copyright © 2007 Massachusetts Medical Society.
NALP1 in Vitiligo-Associated Multiple Autoimmune Disease

Ying Jin, M.D., Ph.D., Christina M. Mailloux, B.S., Katherine Gowan, B.S., Sheri L. Riccardi, B.S., Greggory LaBerge, M.S., Dorothy C. Bennett, Ph.D., Pamela R. Fain, Ph.D., and Richard A. Spritz, M.D.

BACKGROUND

Autoimmune and autoinflammatory diseases involve interactions between genetic risk factors and environmental triggers. We searched for a gene on chromosome 17p13 that contributes to a group of epidemiologically associated autoimmune and autoinflammatory diseases. The group includes various combinations of generalized vitiligo, autoimmune thyroid disease, latent autoimmune diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison’s disease.

METHODS

We tested 177 single-nucleotide polymorphisms (SNPs) spanning the 17p13 linkage peak for association with disease and identified a strong candidate gene. We then sequenced DNA in and around the gene to identify additional SNPs. We carried out a second round of tests of association using some of these additional SNPs, thus elucidating the association with disease in the gene and its extended promoter region in fine detail.

RESULTS

Association analyses resulted in our identifying as a candidate gene NALP1, which encodes NACHT leucine-rich-repeat protein 1, a regulator of the innate immune system. Fine-scale association mapping with the use of DNA from affected families and additional SNPs in and around NALP1 showed an association of specific variants with vitiligo alone, with an extended autoimmune and autoinflammatory disease phenotype, or with both. Conditional logistic-regression analysis of NALP1 SNPs indicated that at least two variants contribute independently to the risk of disease.

CONCLUSIONS

DNA sequence variants in the NALP1 region are associated with the risk of several epidemiologically associated autoimmune and autoinflammatory diseases, implicating the innate immune system in the pathogenesis of these disorders.
Autoimmune and autoinflammatory diseases are a group of about 80 disorders that can involve almost any tissue, organ, or system. A major source of illness and death, these diseases together affect 15 to 25 million people in the United States, particularly women, in whom they rank among the top 10 causes of death. The risk of autoimmune and autoinflammatory diseases is thought to depend on interactions between environmental factors and specific variants of specific genes, some of which may confer a risk that an individual disease will develop, and others a risk that several different diseases will develop.

Indeed, many patients eventually have more than one autoimmune or autoinflammatory disease. Various names have been applied to different combinations of so-called multiple autoimmune disease, such as Schmidt’s syndrome and autoimmune polyglandular syndromes. A few very rare multiple autoimmune disease syndromes result from mutations in single genes; however, most cases of multiple autoimmune disease do not follow mendelian patterns of inheritance, but rather have complex inheritance patterns. Susceptibility genes in these cases probably fall into two categories: some may specifically predispose patients to one or more of the component diseases, whereas others may affect the susceptibility of patients to autoimmune and autoinflammatory disease in general. The latter type of gene may represent a target in the treatment or even prevention of several different diseases.

We and others have observed that, among patients with generalized vitiligo, there is an increased frequency of several other autoimmune and autoinflammatory diseases, particularly autoimmune thyroid disease (Graves’ disease and autoimmune hypothyroidism), latent autoimmune diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison’s disease. There is also an increased frequency of these same disorders among first-degree relatives of patients with vitiligo, suggesting that some families have a genetic predisposition to this group of autoimmune and autoinflammatory diseases. By testing for genetic linkage between disease and polymorphic DNA markers spanning the whole genome in families with vitiligo and other autoimmune and autoinflammatory diseases, we have identified several chromosomal regions (or loci) that appear to contribute to this epidemiologic association, including one on chromosome 17p13. This genomic region also appears to contribute to systemic lupus erythematosus in members of families who inherit lupus together with either vitiligo or various other autoimmune and autoinflammatory diseases. This finding suggests that chromosome 17p13 is involved in the susceptibility to multiple autoimmune disease. To identify the autoimmunity susceptibility gene in the 17p13 region, we performed fine-scale genetic association and DNA sequence analyses in 114 families with vitiligo and associated autoimmune and autoinflammatory diseases.

METHODS

SUBJECTS

We obtained DNA samples from 656 persons from 114 extended families with multiple autoimmune disease associated with vitiligo from the United States and United Kingdom between 1996 and 2005. All families were white (as self-reported on multiple-answer questionnaires; see the Supplementary Appendix, available with the full text of this article at www.nejm.org) and were selected on the basis of having two or more family members with generalized vitiligo (multiplex families) and at least one having one or more of the other autoimmune and autoinflammatory diseases epidemiologically associated with vitiligo (autoimmune thyroid disease, rheumatoid arthritis, latent autoimmune diabetes in adults, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison’s disease). We studied two series of families. The first series comprised the 51 extended families (333 persons) we previously studied to map a vitiligo–multiple autoimmune disease locus to 17p13, and the second series comprised 63 similar, independent families (323 persons). Clinical information on all families from the first series and on about half the families from the second have been reported previously.

Available affected and unaffected family members completed a detailed questionnaire to provide the clinical history with regard to approximately 50 autoimmune and autoinflammatory diseases and immune-related diseases, including vitiligo, autoimmune thyroid disease (Graves’ disease and autoimmune hypothyroidism), rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, Addison’s disease, and...
The study investigators reviewed all data from the questionnaires and the lesion maps and the study staff examined most family members, both affected and unaffected. Inclusion criteria for family members with generalized vitiligo were the presence of depigmented patches of skin that were acquired; that had changed in extent and boundaries over time; that were nonfocal and bilateral; that typically involved the fingers, hands, feet, face, or crural areas; and that were not associated with concurrent underlying eczema or psoriasis or with exposure to depigmenting chemicals. Family members with diagnoses that were considered to be questionable on the basis of standard diagnostic criteria were excluded. Table 1 provides a summary of autoimmune diseases in the 114 study families (see Table 1 in the Supplementary Appendix for details of the clinical diagnoses).

Our study was approved by the Colorado Multiple Institutional Review Board and the South Thames Regional Multicentre Research Ethics Committee. Written informed consent was obtained from all participants.

**Genotyping**

DNA was prepared from peripheral-blood specimens with the use of a genomic DNA purification kit (Puregene, Gentra Systems) or from saliva specimens with the use of a DNA self-collection kit (Oragene, DNA Genotek). We initially used the Illumina genotyping service to genotype family members in the first series, assaying 177 known single-nucleotide polymorphisms (SNPs) selected from the Illumina SNP Knowledge Resource. Each SNP had a minor allele frequency exceeding 0.10 (i.e., the less common variant of the SNP occurred on at least 10% of chromosomes) in whites; altogether, these SNPs captured approximately 18% of the common genetic variation (r²≥0.5) across the genetic-linkage region of chromosome 17p (approximately 11.3 cM, or 6.19 Mb). We genotyped family members in the second series for the 23 SNPs that were significantly associated with disease in the first series according to both the pedigree disequilibrium test and the family-based association test. We then genotyped two insertion–deletion polymorphisms and 78 additional SNPs in all 114 families (both series combined). We identified most of these 78 SNPs by sequencing NALP1, the gene for NACHT leucine-rich-repeat protein 1, and its extended promoter region in 15 genetically informative family members. Additional details of genotyping are provided in the Supplementary Appendix.

**DNA Sequencing**

Having narrowed the 17p13 autoimmunity locus to NALP1 and its extended promoter region, we sought to identify DNA sequence variants within this region that we could use for further tests of association and for identification of the causal SNP or SNPs. We therefore sequenced 82.9 kb of the NALP1 gene and its extended promoter region in each of four parents (two from each series) who were heterozygous for a haplotype (a set of SNP alleles that occur on a single chromosome) of three adjacent Illumina SNPs (rs3926687, rs2733359, and rs878329) that initially appeared to confer a high risk (haplotype 1) and who had transmitted this haplotype to at least one affected offspring. We sequenced the same region in 11 unrelated patients who were homozygous for haplotype 1 (8 from the first series and 3 from the second series). Most of these patients had vitiligo and at least one other autoimmune disease. The sequenced regions included a contiguous segment of 69.1 kb that spanned the extended NALP1 promoter region and exons 1, 2, and 3, as well as 11 individual segments containing exons 4 through 18 with 90 to 500 bp of adjacent intronic sequences. We sequenced several small introns completely. The regions that we sequenced define the five known alternatively spliced isoforms of NALP1 messenger RNA (mRNA); approximately 77% of the sequence was

<table>
<thead>
<tr>
<th>Table 1. Autoimmune and Autoinflammatory Disease Phenotypes in 114 Multiplex Families.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Phenotype</strong></td>
</tr>
<tr>
<td>Vitiligo only</td>
</tr>
<tr>
<td>Vitiligo and autoimmune thyroid disease</td>
</tr>
<tr>
<td>Vitiligo, autoimmune thyroid disease, and other, nonthyroid autoimmune disease</td>
</tr>
<tr>
<td>Vitiligo and other autoimmune disease</td>
</tr>
<tr>
<td>Autoimmune thyroid disease only</td>
</tr>
<tr>
<td>Autoimmune thyroid disease and other autoimmune disease</td>
</tr>
<tr>
<td>Other autoimmune disease only</td>
</tr>
</tbody>
</table>

* A total of 567 family members reported at least one autoimmune and autoinflammatory disease; 175 reported more than one disease.
determined by analyzing both DNA strands. Nucleotide positions were obtained from the human genome sequence for chromosome 17 from the National Center for Biotechnology Information (NCBI) (Build 36).

The predicted effect of the substitution of histidine for leucine at position 155 (Leu155→His) on the secondary structure of the NALP1 protein was assessed with the use of the protein structure prediction server (PSIPRED). We investigated the potential effects of both alleles of all promoter-region variants on transcription-factor binding motifs predicted with the use of the Transcription Element Search System (TESS) and rVista 2.0 software.

STATISTICAL ANALYSIS
Details on preliminary analyses, genetic-linkage analyses, and conditional logistic-regression analysis are given in the Supplementary Appendix. We tested for Hardy–Weinberg equilibrium in founders (the earliest specified persons in lineages) and in persons not in the lineage, such as spouses, in all 114 families. Calculation of linkage disequilibrium between markers of the NALP1 region was carried out with Haploview software, version 3.32. We also calculated the association of each marker with vitiligo alone and with the entire group of autoimmune and autoinflammatory diseases associated with vitiligo, considering a family member with any of these diseases as “affected.” We used both the pedigree disequilibrium test and the family-based association test, which yielded generally similar results (Table 2 in the Supplementary Appendix). Both tests showed that 23 SNPs were associated with the vitiligo phenotype, with the expanded autoimmune and autoinflammatory disease phenotype, or with both, including a cluster of five adjacent SNPs — rs2301582, rs9889625, rs3926687, rs2733359, and rs878329 — spanning a 117-kb region (Fig. 1B).

To assess the reproducibility of these candidate association signals, we carried out an independent analysis in which we genotyped the 23 significant SNPs in a second series of 63 extended families with multiple autoimmune disease associated with vitiligo. The results of this analysis provided support for an association of three of the five adjacent SNPs — rs3926687, rs2733359, and rs878329 — with the vitiligo phenotype and with the expanded autoimmune and autoinflammatory disease phenotype, both in the second series and in all 114 families (Fig. 1B, and Table 2 in the Supplementary Appendix).
These three high-risk SNPs span a 61-kb segment that includes the proximal coding region and the extended promoter region of NALP1, which encodes a key regulator of the innate immune system (Fig. 1C). The genomic region around NALP1 is gene-sparse; SNPs located downstream of NALP1 were not associated with disease, and the closest upstream gene, KIAA0523, is more than 486 kb toward the centromere from NALP1. The results of the family-based association test showed that a preliminary haplotype defined by these three SNPs (haplotype 1) had the most significant association with both the vitiligo phenotype and the expanded autoimmune and autoinflammatory disease phenotype. The 18 exons of the NALP1 structural gene are indicated by the black bars (transcriptional orientation shown from right to left, blue arrow). Panel D shows pairwise r² values for linkage disequilibrium (with darker boxes indicating stronger disequilibrium) among the 19 of the 85 NALP1 region markers shown in Panel C that were most consistently associated with disease and thus were used in conditional logistic-regression analyses, graphed against the physical positions of the markers. Stars indicate markers for which potential independent effects could not be excluded through regression analysis.

With regard to correction for multiple testing, the 177 SNPs constituted approximately 100 independent tests (21 blocks of linkage disequilibrium and the 79 remaining SNPs), with a corrected P value of 0.04 for vitiligo-associated autoimmune and autoinflammatory diseases.

**SEQUENCE ANALYSIS AND HIGH-DENSITY ASSOCIATION ANALYSIS**

Sequence analysis of NALP1 and its extended promoter region was performed in 11 persons with vitiligo who were homozygous for haplotype 1 and in 4 unaffected heterozygotes who had transmitted haplotype 1 to at least one affected offspring. The analysis yielded a total of 261 sequence vari-
ants (Table 3 in the Supplementary Appendix), 54 of which were newly discovered. We also identified a segment of 524 bp that was missing from the NCBI human chromosome 17 sequence, immediately after nucleotide 5,466,866.

To define more precisely the NALP1 genomic region that confers susceptibility to autoimmune and autoimmune disease, we genotyped all 114 families for 78 additional SNPs (identified by means of sequence analysis) (Fig. 1C) and two small insertion–deletion polymorphisms (Table 4 in the Supplementary Appendix), selected on the basis of their physical positions, HapMap tag-SNP status, minor allele frequencies, and potential functional significance. The genotype frequencies of all variants tested were consistent with Hardy–Weinberg equilibrium and were similar in the two series (data not shown). As shown in Figure 1C, many NALP1 region variants were associated with vitiligo (with P values ranging from 0.048 to <0.001 and odds ratios ranging from 1.39 to 2.08) or with associated autoimmune and autoinflammatory disease (with P values ranging from 0.04 to <0.001 and odds ratios ranging from 1.25 to 1.93), in a pattern broadly distributed across the proximal portion of the NALP1 structural gene and its extended promoter region. In general, we observed a stronger association for the expanded autoimmune and autoinflammatory disease phenotype than for the smaller vitiligo subgroup (Table 4 in the Supplementary Appendix).

Apparent associations of disease with multiple markers in the NALP1 region may reflect multiple independent causal variants or may be a consequence of linkage disequilibrium between multiple markers and one true causal variant. The alignment of the genomic positions (Fig. 1C) and the linkage-disequilibrium pattern (Fig. 1D and Table 2) of the 19 NALP1 region markers (17 SNPs and 2 insertion–deletion polymorphisms) for which an association with disease was replicated in the two series (by means of the pedigree disequilibrium test and the family-based association test) suggested that at least two markers might be independently associated with disease. To distinguish markers that might reflect independent variants from those that merely reflect linkage disequilibrium, we carried out conditional logistic-regression analyses21 of these 19 markers (Table 2, and Table 5 in the Supplementary Appendix). On the basis of this analysis, three markers (rs6502867, rs8182352, and rs4790797) had the largest individual effects both for the expanded autoimmune and autoinflammatory disease phenotype (odds ratios, 1.93, 1.81, and 1.82, respectively; P<0.001 for all three markers) and for the vitiligo phenotype (odds ratios, 2.08, 2.01, and 2.01, respectively; P<0.001 for all three markers). The inclusion of rs6502867 significantly improved the fit of logistic-regression models that included any 1 of the 18 other markers; conversely, the fit of the model including rs6502867 was significantly improved by the inclusion of any 1 of 15 of the 18 other markers (Table 5 in the Supplementary Appendix). These results provide further support for the existence of at least two independent variants in the NALP1 region associated with the risk of disease: one variant tagged by rs6502867 and the other located further upstream, in the proximal coding region or in the transcriptional promoter.

The markers rs878329, rs7223628, rs8182352, and rs4790796 are in almost perfect linkage disequilibrium with rs4790797 (Table 6 in the Supplementary Appendix), indicating that these five SNPs, which span only 2107 bases, all represent the same signal. The colinearity among the five markers precludes logistic-regression analyses that include any two of them. Inclusion of rs4790797 significantly improved the fit of models that included any 1 of the 14 remaining markers, except for rs12150220 and rs2670660, whereas none of the 14 remaining markers, except for rs6502867, improved the fit of the model that included rs4790797. These results suggest that an association of 11 of the 14 markers (rs961826, rs11078575, rs1877658, rs295597, rs925598, rs3926687, the 12-bp deletion, rs2733359, rs35658367, rs2716914, and rs8182354) with disease may be secondary to linkage disequilibrium with the cluster of 5 SNPs represented by rs4790797. Overall, the marker most significantly associated with disease was rs4790797, but it could not be distinguished from rs12150220 and rs2670660 in the logistic-regression analysis (Table 5 in the Supplementary Appendix). The results for the vitiligo phenotype were similar to those for the expanded autoimmune and autoinflammatory disease phenotype, except that the association of rs12150220 with vitiligo also appeared to be secondary to linkage disequilibrium with rs4790797.

Thus, we detected at least two independent signals associated with autoimmune and autoinflammatory diseases: one located within the NALP1 structural gene, tagged by SNP rs6502867, and at
Table 2. Association of 19 NALP1 Variants with Vitiligo and Autoimmune and Autoinflammatory Disease in 114 Multiplex Families.*

<table>
<thead>
<tr>
<th>Variant/Allele</th>
<th>Pedigree Disequilibrium Test</th>
<th>P Value</th>
<th>Family-Based Association Test</th>
<th>Conditional Logistic-Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune and autoinflammatory disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6502867/A</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>1.93 (1.32–2.88)</td>
</tr>
<tr>
<td>rs961826/A</td>
<td>0.001</td>
<td>0.001</td>
<td>0.008</td>
<td>1.60 (1.14–2.24)</td>
</tr>
<tr>
<td>rs12150220/A</td>
<td>0.001</td>
<td>0.001</td>
<td>0.003</td>
<td>1.66 (1.19–2.31)</td>
</tr>
<tr>
<td>rs1107857/C</td>
<td>0.003</td>
<td>0.002</td>
<td>0.02</td>
<td>1.50 (1.08–2.08)</td>
</tr>
<tr>
<td>rs1877658/T</td>
<td>0.003</td>
<td>0.005</td>
<td>0.04</td>
<td>1.40 (1.01–1.93)</td>
</tr>
<tr>
<td>rs925597/A</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>1.62 (1.16–2.27)</td>
</tr>
<tr>
<td>rs925598/A</td>
<td>0.001</td>
<td>0.002</td>
<td>0.004</td>
<td>1.63 (1.17–2.26)</td>
</tr>
<tr>
<td>rs3926687/T</td>
<td>0.002</td>
<td>0.003</td>
<td>0.006</td>
<td>1.59 (1.15–2.21)</td>
</tr>
<tr>
<td>12-bp deletion‡</td>
<td>0.006</td>
<td>0.01</td>
<td>0.01</td>
<td>1.51 (1.10–2.09)</td>
</tr>
<tr>
<td>rs2670660/C</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>1.68 (1.20–2.35)</td>
</tr>
<tr>
<td>rs2733359/G</td>
<td>0.002</td>
<td>0.001</td>
<td>0.005</td>
<td>1.64 (1.17–2.30)</td>
</tr>
<tr>
<td>rs35658367/ATGA</td>
<td>0.001</td>
<td>0.001</td>
<td>0.004</td>
<td>1.64 (1.17–2.31)</td>
</tr>
<tr>
<td>rs2716914/C</td>
<td>0.003</td>
<td>0.004</td>
<td>0.02</td>
<td>1.49 (1.08–2.07)</td>
</tr>
<tr>
<td>rs878329/G</td>
<td>0.005</td>
<td>0.001</td>
<td>0.003</td>
<td>1.63 (1.17–2.26)</td>
</tr>
<tr>
<td>rs7223628/G</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>1.68 (1.21–2.35)</td>
</tr>
<tr>
<td>rs8182352/G</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.81 (1.28–2.56)</td>
</tr>
<tr>
<td>rs4790796/A</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>1.73 (1.24–2.42)</td>
</tr>
<tr>
<td>rs4790797/T</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.82 (1.29–2.56)</td>
</tr>
<tr>
<td>rs8182354/A</td>
<td>0.004</td>
<td>0.001</td>
<td>0.002</td>
<td>1.69 (1.22–2.36)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6502867/A</td>
<td>0.005</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>2.08 (1.37–3.15)</td>
</tr>
<tr>
<td>rs961826/A</td>
<td>0.002</td>
<td>0.003</td>
<td>0.007</td>
<td>1.67 (1.15–2.41)</td>
</tr>
<tr>
<td>rs12150220/A</td>
<td>0.002</td>
<td>0.002</td>
<td>0.004</td>
<td>1.69 (1.18–2.41)</td>
</tr>
<tr>
<td>rs1107857/C</td>
<td>0.005</td>
<td>0.005</td>
<td>0.02</td>
<td>1.55 (1.09–2.19)</td>
</tr>
<tr>
<td>rs1877658/T</td>
<td>0.004</td>
<td>0.007</td>
<td>0.03</td>
<td>1.49 (1.04–2.10)</td>
</tr>
<tr>
<td>rs925597/A</td>
<td>0.002</td>
<td>0.003</td>
<td>0.005</td>
<td>1.69 (1.18–2.44)</td>
</tr>
<tr>
<td>rs925598/A</td>
<td>0.003</td>
<td>0.003</td>
<td>0.005</td>
<td>1.66 (1.16–2.36)</td>
</tr>
<tr>
<td>rs3926687/T</td>
<td>0.004</td>
<td>0.004</td>
<td>0.008</td>
<td>1.61 (1.14–2.29)</td>
</tr>
<tr>
<td>12-bp deletion‡</td>
<td>0.001</td>
<td>0.009</td>
<td>0.007</td>
<td>1.66 (1.16–2.36)</td>
</tr>
<tr>
<td>rs2670660/C</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.002</td>
<td>1.80 (1.25–2.61)</td>
</tr>
<tr>
<td>rs2733359/G</td>
<td>0.001</td>
<td>0.004</td>
<td>0.004</td>
<td>1.75 (1.21–2.53)</td>
</tr>
<tr>
<td>rs35658367/ATGA</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.002</td>
<td>1.82 (1.24–2.67)</td>
</tr>
<tr>
<td>rs2716914/C</td>
<td>0.002</td>
<td>0.008</td>
<td>0.007</td>
<td>1.64 (1.15–2.35)</td>
</tr>
<tr>
<td>rs878329/G</td>
<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
<td>1.75 (1.22–2.51)</td>
</tr>
<tr>
<td>rs7223628/G</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.001</td>
<td>1.82 (1.26–2.63)</td>
</tr>
<tr>
<td>rs8182352/G</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>2.01 (1.36–2.95)</td>
</tr>
<tr>
<td>rs4790796/A</td>
<td>0.001</td>
<td>0.002</td>
<td>0.001</td>
<td>1.83 (1.26–2.63)</td>
</tr>
<tr>
<td>rs4790797/T</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>2.01 (1.39–2.91)</td>
</tr>
<tr>
<td>rs8182354/A</td>
<td>0.001</td>
<td>0.002</td>
<td>0.001</td>
<td>1.83 (1.27–2.64)</td>
</tr>
</tbody>
</table>

* The variants listed are those for which the association with disease was replicated by the pedigree disequilibrium test and the family-based association test in both series of families.

† Odds ratios were calculated from the coefficients of the regression equation.

‡ The 12-bp deletion includes nucleotides 5457169 through 5457180 (TATGACTATGTG).
least one other, located within a 64.7-kb linkage disequilibrium block tagged by the nonsynonymous coding SNP rs12150220 (Leu155→His) and six promoter-region SNPs (rs2670660, rs878329, rs7223628, rs8182352, rs4790796, and rs4790797). The significance (P=0.0001) of a model that includes two SNPs, rs6502867 and rs4790797, each of which represents one of the two independent association signals, was greater than that of either individual SNP (P<0.001 for each), and the haplotype carrying both high-risk alleles conferred the highest risk (odds ratio, 2.77; P<0.001) (Table 7 in the Supplementary Appendix).

We assessed the haplotype-specific effects of rs6502867 and rs4790797 (representing the cluster of five SNPs with perfect linkage disequilibrium) by comparing logistic-regression models that included the additive effects of both loci, with and without accounting for linkage phase. We did not detect haplotype-specific effects, which indicates that it makes no difference whether the two variants in the NALP1 region are cis or trans to one another. We also used logistic-regression models to evaluate the mode of inheritance of risks individually associated with rs6502867 and rs4790797. These analyses favored an additive model with no dominant or recessive effects.

**NALP1 PROMOTER-REGION VARIANTS**

We observed a total of 205 variants in the extended promoter region, all of which were assessed for predicted effects on transcription-factor binding motifs. Five of the six tightly linked SNPs in the promoter region that were associated with disease were found to affect high-probability mammalian transcription-factor binding sites (Table 3). Furthermore, rs2670660 occurs within a segment that is remarkably conserved in the human, chimpanzee, macaque, bush baby, cow, mouse, and rat, suggesting that this variant is functionally significant. It alters predicted binding motifs for the transcription factors HMG1 (HMG-I(Y)) and MYB. MYB regulates transcription during the differentiation, proliferation, and apoptosis of erythroid, myeloid, and lymphoid cell lineages. Whether any of these sequence variants

---

**Figure 2. Alignment of Predicted Primate NALP1 Amino Acid Sequences Surrounding the Leu155→His Substitution (Arrowhead).**

Residues in red are completely conserved among known primates; those in black are not. Dashes indicate gaps introduced to maximize sequence alignments. The NALP1 sequence of humans (Homo sapiens) is from ENSG00000091592 from the National Center for Biotechnology Information genome sequence (Build 36). The sequence of the chimpanzee (Pan troglodytes) is from ENSPTRG00000008637 from the PanTro, version 2.1, database. The sequence of the rhesus monkey (Macaca mulatta) was obtained through manual annotation of the entry for ENSMMUG00000030453 in the MMUL, version 1.0, database. The sequence of the bush baby (Otolemur garnettii) was obtained through manual assembly and annotation of data from scaffolds 14080 and 113389 from the bushtro, version 1.0, prerelease database. NALP1 in the cow, dog, mouse, rat, and ground squirrel lacks the entire NH1-terminal segment found in the primate protein, and sequences orthologous to NALP1 could not be identified in any other early-release genomic databases.
affects NALP1 transcription in humans requires further investigation.

**DISCUSSION**

Our study shows that variants of NALP1 confer susceptibility to autoimmune and autoinflammatory diseases that are associated with vitiligo. Confirmation of this finding will require additional studies in other patient groups, including analysis of the extent to which NALP1 is specifically involved in the component autoimmune disorders. Furthermore, the SNPs that we have implicated may not be the causal variants; identification of such variants will require the demonstration of specific effects on NALP1 transcription, mRNA, or protein function.

NALP1, also known as CARD7, DEFCAP, and NAC, is thought to mediate activation of the innate immune system in response to so-called pathogen-associated molecular patterns such as bacterial peptides.\(^{22-24}\) NALP1 is widely expressed at low levels but is expressed at a high level in immune cells, particularly T cells and Langerhans’ cells,\(^{25,26}\) patterns that are consistent with the particular involvement of NALP1 in skin autoimmunity. NALP1 recruits the adapter protein ASC, caspase 1, and caspase 5 to a complex termed the NALP1 inflammasome,\(^{23,24,26}\) which activates the proinflammatory cytokine interleukin-1β. Serum interleukin-1β levels are elevated in patients with generalized vitiligo,\(^{27}\) suggesting the involvement of this pathway in the pathogenesis of disease. NALP1 also appears to play a role in cellular apoptosis, its overexpression stimulating caspase-mediated apoptosis in a variety of cell types.\(^{22,26,29}\)

Mutations in at least two other NALP-related genes involved in the innate immune system are associated with autoinflammatory diseases. Variants in NOD2/CARD15 are associated with inflammatory bowel disease\(^{30,31}\) and the Blau syndrome.\(^{32}\) Mutations in NALP3/CIAS1, a homologue of NALP1 and a component of the NALP3 inflammasome,\(^{24,26}\) result in several autoinflammatory phenotypes, including the cold autoinflammatory syndrome, the Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease.\(^{33-35}\) Administration of an interleukin-1β inhibitor\(^{36,37}\) or a caspase-1 inhibitor\(^{38}\) ameliorates symptoms in patients with these disorders. If the association between NALP1 and autoimmune and autoinflammatory diseases is confirmed, and if NALP1 variants are found to result in the activation of interleukin-1β, then inhibitors of interleukin-1β and caspase might be effective in the treatment or prevention of NALP1-associated autoimmune and autoinflammatory diseases.

Supported by grants from the National Institutes of Health (AR45584, AI46374, and DK57538), the United Kingdom Vitiligo Society, and the U.S. National Vitiligo Foundation.

Dr. Spritz reports serving on the scientific advisory board of, and receiving stock options from, GammaCan International. No other potential conflict of interest relevant to this article was reported.

We thank the many families who participated in this study, the United Kingdom Vitiligo Society, the U.S. National Vitiligo Foundation, and Vitiligo Support International for their enthusiastic help in family ascertainment; Anita Amadi-Myers, Paulene Holland, Saunie Hutton, and Angela Wooden for their invaluable assistance; and Tasha Fingerlin for intellectual input.

---

**Table 3. Predicted Transcription-Factor Binding Motifs Affected by NALP1 Promoter-Region SNPs Associated with Disease.**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Nucleotide Position†</th>
<th>Transcription Factor</th>
<th>L_a</th>
<th>L_q</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2670660</td>
<td>5,459,730</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>HMGA1 [HMG-I(Y)]</td>
<td>22.00</td>
<td>0.917</td>
</tr>
<tr>
<td>C (high risk)</td>
<td></td>
<td>MYB</td>
<td>12.00</td>
<td>1.000</td>
</tr>
<tr>
<td>rs878329</td>
<td>5,493,974</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>PEBP2</td>
<td>18.00</td>
<td>0.900</td>
</tr>
<tr>
<td>G (high risk)</td>
<td></td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7223628</td>
<td>5,495,192</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>AP-1</td>
<td>18.00</td>
<td>0.900</td>
</tr>
<tr>
<td>G (high risk)</td>
<td></td>
<td>NFAT-1</td>
<td>14.00</td>
<td>1.000</td>
</tr>
<tr>
<td>rs8182352</td>
<td>5,495,711</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>PR</td>
<td>12.00</td>
<td>1.000</td>
</tr>
<tr>
<td>rs4790797</td>
<td>5,496,043</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>FOXF1</td>
<td>24.00</td>
<td>0.923</td>
</tr>
<tr>
<td>T (high risk)</td>
<td></td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The five SNPs are among the six promoter-region SNPs whose potential independent effects could not be ruled out by conditional logistic-regression analyses. L_a denotes the log-likelihood score. L_q, a measure of the goodness-of-fit of the DNA sequence to the consensus binding motif, was calculated by dividing L_a by the maximum L_a possible for the site model; the best possible L_q was 1.000.

† The NALP1 exon 1 (the site of the start of translation) begins at nucleotide 5,428,550.
ASSOCIATION OF NALP1 WITH MULTIPLE AUTOIMMUNE DISEASE

REFERENCES


Copyright © 2007 Massachusetts Medical Society.
Neurodevelopment and Cognition in Children after Enterovirus 71 Infection

Luan-Yin Chang, M.D., Ph.D., Li-Min Huang, M.D., Ph.D., Susan Shur-Fen Gau, M.D., Ph.D., Yu-Yu Wu, M.D., Shao-Hsuan Hsia, M.D., Tsui-Yen Fan, B.S., Kuang-Lin Lin, M.D., Yhu-Chering Huang, M.D., Ph.D., Chun-Yi Lu, M.D., and Tzou-Yien Lin, M.D.

From the Departments of Pediatrics (L.-Y.C., L.-M.H., T.-Y.F., C.-Y.L.) and Psychiatry (S.S.-F.G.), National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei; and the Departments of Child Psychiatry (Y.-Y.W.) and Pediatrics (S.-H.H., K.-L.L., Y.-C.H., T.-Y.L.), Chang Gung Children’s Hospital, Chang Gung University, Taoyuan — both in Taiwan. Address reprint requests to Dr. Chang at the Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 7, Chung-Shan South Rd., Taipei, Taiwan, or at ly7077@tpts6.seed.net.tw.

ABSTRACT

BACKGROUND
Enterovirus 71 is a common cause of hand, foot, and mouth disease and encephalitis in Asia and elsewhere. The long-term neurologic and psychiatric effects of this viral infection on the central nervous system (CNS) are not well understood.

METHODS
We conducted long-term follow-up of 142 children after enterovirus 71 infection with CNS involvement — 61 who had aseptic meningitis, 53 who had severe CNS involvement, and 28 who had cardiopulmonary failure after CNS involvement. At a median follow-up of 2.9 years (range, 1.0 to 7.4) after infection, the children received physical and neurologic examinations. We administered the Denver Developmental Screening Test (DDST II) to children 6 years of age or younger and the Wechsler intelligence test to children 4 years of age or older.

RESULTS
Nine of the 16 patients with a poliomyelitis-like syndrome (56%) and 1 of the 5 patients with encephalomyelitis (20%) had sequelae involving limb weakness and atrophy. Eighteen of the 28 patients with cardiopulmonary failure after CNS involvement (64%) had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Among patients who underwent DDST II assessment, delayed neurodevelopment was found in only 1 of 20 patients (5%) with severe CNS involvement and in 21 of 28 patients (75%) with cardiopulmonary failure (P<0.001 for the overall comparison). Children with cardiopulmonary failure after CNS involvement scored lower on intelligence tests than did children with CNS involvement alone (P=0.003).

CONCLUSIONS
Enterovirus 71 infection with CNS involvement and cardiopulmonary failure may be associated with neurologic sequelae, delayed neurodevelopment, and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well on neurodevelopment tests. (ClinicalTrials.gov number, NCT00172393.)
ENTEROVIRUS 71 (EV71) is a cause of hand, foot, and mouth disease and encephalitis. In Bulgaria in 1975, Hungary in 1978, and Malaysia in 1997, large outbreaks of EV71 infection resulted in dozens of deaths.\(^1\)\(^2\) In Taiwan, the most severe EV71 epidemic to date occurred in 1998.\(^4\) During that epidemic, almost all patients with cardiopulmonary failure died.\(^4\)\(^5\) In 2000, Taiwan developed a disease-management program to improve the survival rate of patients with the infection.\(^6\)\(^7\) Although that program led to a reduction of acute mortality,\(^7\) concern about long-term sequelae remains.

Neurodevelopment and cognitive function may be affected by viral encephalitis or by bacterial meningitis. In a meta-analysis involving 1602 children with bacterial meningitis, 16.4% of the survivors had major adverse outcomes, such as deafness, intellectual disability, epilepsy, and physical impairment.\(^8\) In another study of children with meningitis caused by \textit{Haemophilus influenzae} type b, poor school performance and more behavioral disturbances were found.\(^9\) Neurologic sequelae were found in one third to one half of patients in two studies of herpes encephalitis\(^\text{10}\)\(^\text{11}\) and in about one third of the survivors of Japanese encephalitis.\(^\text{12}\)\(^\text{13}\) It has been reported that the more severe the brain injury (as in cases of bacterial meningitis), the greater the effect on cognitive function and behavioral manifestations.\(^14\)\(^\text{15}\)

One of the most important causes of viral encephalitis is the enterovirus, and EV71 is especially important in Asia. Even though the survival rate from EV71 infection with central nervous system (CNS) involvement has improved in Taiwan, the effect of the virus on the subsequent neurodevelopment and cognitive function of the survivors is not known (unlike the effects of other forms of viral encephalitis). We conducted this study to assess the long-term neurologic sequelae, neurodevelopment, and cognitive function of children who had EV71 infection with CNS involvement.

The patients were clinically confirmed to have had laboratory-confirmed EV71 infection and one of the following: hand, foot, and mouth disease; herpangina; or febrile illness. The presence of EV71 infection was confirmed on the basis of positive viral isolation of EV71, positive EV71 IgM, or an increase by a factor of 4 in EV71 neutralizing antibody serotiters between a serum sample taken at the acute stage of infection and one taken at the convalescent stage.

In total, we found 621 patients who had EV71 infection (534 at the Chang Gung Children's Hospital and 87 at the National Taiwan University Hospital). Of these, 232 patients (37.4%) had CNS involvement. The clinical severity of the condition of patients with CNS involvement was classified according to the level of severity: group 1, mild CNS involvement (i.e., aseptic meningitis); group 2, severe CNS involvement (including encephalitis, a poliomyelitis-like syndrome, and encephalomyelitis); and group 3, cardiopulmonary failure after CNS involvement. Patients who were assigned to group 1 had headaches, irritability, and cerebrospinal fluid (CSF) pleocytosis (≥5×10^6 leukocytes per liter) but no altered level of consciousness or focal signs. Patients who were assigned to group 2 had encephalitis with an altered level of consciousness plus CSF pleocytosis, a poliomyelitis-like syndrome with acute limb weakness and decreased reflex and muscle strength, or encephalomyelitis with the occurrence of both encephalitis and a poliomyelitis-like syndrome. Patients who were assigned to group 3 had had cardiopulmonary failure 2 to 36 hours (median, 12 hours) after manifestations of EV71 infection with CNS involvement; these children all required the use of inotropic agents, endotracheal intubation, and ventilator support, and they had cardiopulmonary failure due to medullary damage without evidence of independent pneumonia, myocarditis, or bacterial sepsis.

Of the 232 children with CNS involvement, 25 (10.8%) died of cardiopulmonary failure and brainstem encephalitis during the acute phase, and 14 (6.0%) died from deep coma or aspiration pneumonia during the convalescent stage, which was defined as more than 1 month after the onset of disease. Of the remaining 193 patients with CNS involvement, 22 declined to be assessed and 29 could not be located. Therefore, a total of 142 patients (73.6%) were prospectively enrolled in our study and were assessed between January 2003 and

**METHODS**

**PATIENTS AND CLINICAL SEVERITY**

The institutional review board of the National Taiwan University Hospital approved the study. We prospectively identified all pediatric patients with EV71 infection who had been treated at Chang Gung Children's Hospital and at the National Taiwan University Hospital between 1998 and 2003.
December 2005 after written informed consent was obtained from their parents. There were no significant differences in clinical severity ($P = 0.22$), age at onset ($P = 0.33$), and sex ($P = 0.35$) among the 142 patients who were assessed and the 51 who were not.

**CLINICAL AND NEUROLOGIC ASSESSMENT**

All the children underwent physical and neurologic examination by a pediatrician or a pediatric neurologist during an outpatient visit or during their stay in chronic respiratory centers. Their physical handicap or neurologic sequelae, need for ventilator support, and need for tube feeding were recorded.

Patients with EV71 infection who were 6 years of age or younger during our evaluation were assessed with the Denver Developmental Screening Test (DDST II), which measured development in four categories: gross motor, fine motor, language, and personal–social. Each test item was scored as either pass or fail. For each category in the overall assessment, patients were considered to be developmentally delayed if they failed two or more test items that 75 to 90% of children of their age could pass or if they failed one or more test items that more than 90% of children younger than their age could pass. Otherwise, the development of the children was considered to be normal.

**ASSESSMENT OF COGNITIVE FUNCTION**

The profile on the Wechsler Intelligence Scale for Children, third edition (WISC-III), was individually assessed by a child psychologist for all children 4 years of age or older, except for three of

<table>
<thead>
<tr>
<th>Table 1. Clinical and Neurologic Outcomes of 142 Patients after EV71 Infection with CNS Involvement. *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
</tr>
<tr>
<td>Male sex — no.</td>
</tr>
<tr>
<td>Age at onset — yr</td>
</tr>
<tr>
<td>Age at assessment — yr</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Recovery — no. (%)</td>
</tr>
<tr>
<td>Focal limb weakness and atrophy — no. (%)</td>
</tr>
<tr>
<td>Dysphagia with tube feeding — no. (%)</td>
</tr>
<tr>
<td>Central hypoventilation with ventilator support — no. (%)</td>
</tr>
<tr>
<td>Facial nerve palsy — no. (%)</td>
</tr>
<tr>
<td>Seizure — no. (%)</td>
</tr>
<tr>
<td>Hypoxia-related psychomotor retardation — no. (%)</td>
</tr>
</tbody>
</table>

* Group 1 comprises patients with mild CNS involvement (aseptic meningitis); group 2 patients with severe CNS involvement: encephalitis (32 patients), a poliomyelitis-like syndrome (16 patients), or encephalomyelitis (5 patients); and group 3 patients with cardiopulmonary failure after CNS involvement.

† P values for the overall comparisons were calculated with the Kruskal–Wallis test for continuous variables or Fisher’s exact test for categorical variables.

‡ Sequelae of focal limb weakness and atrophy were found in 1 of 5 patients with encephalomyelitis (20%) and in 9 of 16 patients with a poliomyelitis-like syndrome (56%).

§ Facial nerve palsy was seen in 1 of 32 patients with encephalitis (3%).
the children who had tracheostomies and could not talk. The WISC-III is composed of 13 subtests to test children’s cognitive ability; the subtests are grouped into two scores: the performance IQ and the verbal IQ.17 Four factorially derived composite subscales have been created: information, similarities, vocabulary, and comprehension for verbal comprehension; picture completion, picture arrangement, block design, and object assembly for perceptual organization; arithmetic and digit span for freedom from distractibility; and coding and symbol search for process speed.17 Each of the IQ scores and four composite subscales yields a standard score with a mean of 100 and a standard deviation (SD) of 15. Borderline intelligence or below was defined as an IQ of less than 85.

**STATISTICAL ANALYSIS**

Fisher’s exact test was used for analysis of categorical data, and Student’s t-test and analysis of variance were used for continuous variables with normal distributions. Either the Mann–Whitney rank-sum test or the Kruskal–Wallis test was used for continuous variables without a normal distribution. If a significant difference was found by analysis of variance, pairwise comparison was performed with the use of the Scheffé method. Five separate multiple regression analyses were performed with the use of predictors identified in univariate analyses for the five separate cognitive outcomes (verbal IQ, performance IQ, full-scale IQ, verbal comprehension, and perceptual organization). All reported P values are two-sided; those under 0.05 are considered to be statistically significant. Statistical operations were performed with the use of the SAS Statistical Package, version 9.1 (SAS Institute).

**RESULTS**

**CLINICAL AND NEUROLOGIC OUTCOMES**

Of the 142 patients (85 boys and 57 girls) who had EV71 and CNS involvement, the median age at disease onset was 1.8 years (range, 0.1 to 13.5), the median age at the time of assessment was 5.0 years (range, 1.3 to 20.8), and the median interval from disease onset to assessment was 2.9 years (range, 1.0 to 7.4). There was no significant difference in the age distribution between boys and girls. The educational level of the parents was not found to be related to the clinical severity of the children’s disease (P=0.45 for education of the father, and P=0.68 for education of the mother). Demographic data and clinical and neurologic outcomes were analyzed according to the clinical severity of the CNS involvement (Table 1). Group 3 was found to have had a significantly lower age at onset and age at the time of assessment (P<0.001). Some difference between boys and girls was found among the three groups (P=0.04).

All the patients with mild CNS involvement (aseptic meningitis) recovered completely. Of the 53 patients with severe CNS involvement (encephalitis, a poliomyelitis-like syndrome, and encephalomyelitis), 1 of the 32 patients with encephalitis (3%) had mild left facial nerve palsy, and 9 of the 16 patients with a poliomyelitis-like syndrome (56%) and 1 of the 5 patients with encephalomyelitis (20%) had unilateral limb weakness and atrophy.

Of the 28 patients who had cardiopulmonary failure after CNS involvement, 21 (75%) had sequelae, including 18 with limb weakness and atrophy (64%), 7 with facial nerve palsy (25%), 17 with dysphagia necessitating tube feeding (61%), 16 with central hypoventilation necessitating ventilator support (57%), 4 with seizure (14%), and 5 with seizure and psychomotor retardation from hypoxia (18%). Nineteen patients with sequelae had abnormal findings on magnetic resonance imaging, including high-intensity lesions in the tegmentum of the brain stem or high-intensity lesions in the spinal cord on the T2-weighted image. Among patients who had cardiopulmonary failure after CNS involvement, the percentage with

<table>
<thead>
<tr>
<th>Type of Delay</th>
<th>Group 1 (N=43)</th>
<th>Group 2 (N=20)</th>
<th>Group 3 (N=28)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any delay</td>
<td>0 (0)</td>
<td>21 (75)</td>
<td>1 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gross motor delay</td>
<td>0 (0)</td>
<td>19 (68)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Fine motor delay</td>
<td>0 (0)</td>
<td>16 (57)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Language delay</td>
<td>0 (0)</td>
<td>18 (64)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Personal–social delay</td>
<td>0 (0)</td>
<td>15 (54)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement. The original denominators in group 1, group 2, and group 3 were 61, 53, and 28, respectively. Only 91 children who were 6 years of age or younger at the time of our study underwent assessment with the Denver Developmental Screening Test.

† The P value for the overall comparison was calculated with Fisher’s exact test.
sequelae was significantly higher than that among patients with CNS involvement alone (P<0.001).

NEURODEVELOPMENTAL OUTCOME

Of the 142 patients who had EV71 infection, 91 were 6 years of age or younger at the time of our study and were assessed with the use of DDST II. Neurodevelopment of all 43 patients with aseptic meningitis was normal; only 1 patient who had severe CNS involvement without cardiopulmonary failure had a delay in the gross motor and personal–social categories (Table 2). Of the 28 patients who had cardiopulmonary failure after CNS involvement, 21 (75%) were found to have delayed neurodevelopment: 4 patients had one of four categories of delay, 2 had delay in two categories, and the other 15 had delay in all four categories. The clinical severity of the CNS involvement was significantly associated with the children’s neurodevelopment (P<0.001).

COGNITIVE FUNCTION

The cognitive functions of 90 of the patients with EV71 infection who were 4 years of age or older were assessed with the use of the WISC-III (Table 3). In addition, three children in this age group could not be assessed because they had undergone tracheostomy and could not speak. Of the 90 patients who were assessed, 39 who were between the ages of 4 and 6 years were assessed with the use of both the DDST II and IQ tests. Of the 39 patients who underwent these tests, 1 in group 3 who had delayed development (according to the DDST II score) had a full-scale IQ of 47; the other 38 patients with normal scores on the DDST II had a mean (±SD) full-scale IQ of 98±13, with a median full-scale IQ of 97 (range, 67 to 118). Clinical severity, the age at disease onset, and the educational levels of the parents were significantly associated with IQ scores in the univariate analysis. For example, the mean full-scale IQ of

Table 3. Cognitive Function of 90 Patients after EV71 Infection with CNS Involvement.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Verbal IQ</th>
<th>Patients with Verbal IQ &lt;85 no. (%)</th>
<th>Performance IQ</th>
<th>Patients with Performance IQ &lt;85 no. (%)</th>
<th>Full-Scale IQ</th>
<th>Patients with Full-Scale IQ &lt;85 no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical severity‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>38</td>
<td>99±12</td>
<td>5 (13)</td>
<td>100±14</td>
<td>5 (13)</td>
<td>99±12</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Group 2</td>
<td>44</td>
<td>102±12</td>
<td>3 (7)</td>
<td>98±13</td>
<td>8 (18)</td>
<td>100±12</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Group 3</td>
<td>8</td>
<td>86±22</td>
<td>4 (50)</td>
<td>82±15</td>
<td>4 (50)</td>
<td>83±19</td>
<td>4 (50)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.01</td>
<td>0.01</td>
<td>0.004</td>
<td>0.06</td>
<td>0.003</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 yr</td>
<td>34</td>
<td>94±12</td>
<td>7 (21)</td>
<td>93±14</td>
<td>11 (32)</td>
<td>93±12</td>
<td>11 (32)</td>
</tr>
<tr>
<td>≥2 yr</td>
<td>56</td>
<td>102±13</td>
<td>5 (9)</td>
<td>100±14</td>
<td>6 (11)</td>
<td>101±13</td>
<td>3 (5)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.006</td>
<td>0.20</td>
<td>0.02</td>
<td>0.02</td>
<td>0.005</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Maternal educational level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>57</td>
<td>96±13</td>
<td>9 (16)</td>
<td>96±13</td>
<td>10 (18)</td>
<td>96±13</td>
<td>10 (18)</td>
</tr>
<tr>
<td>College or more</td>
<td>33</td>
<td>104±13</td>
<td>3 (9)</td>
<td>100±15</td>
<td>7 (21)</td>
<td>102±13</td>
<td>4 (12)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.01</td>
<td>0.52</td>
<td>0.29</td>
<td>0.78</td>
<td>0.04</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Paternal educational level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>54</td>
<td>96±13</td>
<td>8 (15)</td>
<td>96±15</td>
<td>11 (20)</td>
<td>96±13</td>
<td>10 (19)</td>
</tr>
<tr>
<td>College or more</td>
<td>36</td>
<td>104±13</td>
<td>4 (11)</td>
<td>99±13</td>
<td>6 (17)</td>
<td>102±13</td>
<td>4 (11)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.003</td>
<td>0.76</td>
<td>0.34</td>
<td>0.79</td>
<td>0.02</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The original denominators in group 1, group 2, and group 3 were 61, 53, and 28, respectively, but only 90 children who were 4 years of age or older underwent assessment of IQ with the Wechsler Intelligence Scale for Children, third edition. Each of the IQ scores and four composite subscales yields a standard score of 100±15. Borderline intelligence or below was defined as an IQ of less than 85. P values were calculated with analysis of variance, Student’s t-test, or Fisher’s exact test.

† Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement.
patients with cardiopulmonary failure after CNS involvement was significantly lower than that of the other patients (P<0.05 for the comparisons between group 1 and group 3 and between group 2 and group 3). Children who were less than 2 years of age at disease onset had lower full-scale IQs and were more likely to have a full-scale IQ of less than 85 than were children whose age at onset was 2 or more years. Moreover, patients whose parents had gone to college or had postgraduate training had higher full-scale IQs than did patients whose parents had lower educational levels. Sex was not associated with IQs (P=0.98 for verbal IQ, P=0.95 for performance IQ, and P=0.89 for full-scale IQ).

Table 4 shows the results of four composite subscales for the 48 children who were 6 years of age or older at the time of the assessment and who had CNS involvement alone, without cardiopulmonary failure. The subscales that assessed processing speed and freedom from distractibility were not associated with the clinical severity of disease, the age at onset, sex, or the educational level of the parents. Verbal comprehension was significantly associated with the age at onset (P<0.001), the educational level of the father (P=0.01), and the educational level of the mother (P=0.04), and perceptual organization was significantly associated with the age at onset (P=0.04).

Table 5 presents the regression coefficients for five predictors identified by univariate analysis in the five separate multivariate models with the use of multiple regression analyses. Clinical severity was associated with IQ. There was a signifi

<table>
<thead>
<tr>
<th>Table 4. Scores on Four Composite Subscales of the WISC-III in 48 Patients after EV71 Infection with Mild or Severe CNS Involvement but without Cardiopulmonary Failure.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Clinical severity†</td>
</tr>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>&lt;2 yr</td>
</tr>
<tr>
<td>≥2 yr</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>Maternal educational level</td>
</tr>
<tr>
<td>High school or less</td>
</tr>
<tr>
<td>College or more</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>Paternal educational level</td>
</tr>
<tr>
<td>High school or less</td>
</tr>
<tr>
<td>College or more</td>
</tr>
<tr>
<td>P value</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The original denominator of patients in group 1 was 61, and the original denominator in group 2 was 53, but only 48 patients in both groups who were 6 years of age or older underwent assessment for the four composite subscales. Because only one patient in group 3 underwent the complete subscale assessment, group 3 was not factored into the analysis. Each of the IQ scores and four composite subscales on the Wechsler Intelligence Scale for Children, third edition (WISC-III), yields a standard score of 100±15. P values for the overall comparison were calculated with Student’s t-test.

† Group 1 comprises patients with mild CNS involvement, and group 2 patients with severe CNS involvement.
cant association between the age at onset and the assessment of verbal comprehension ($P = 0.009$); the association between the age at onset and the assessment of perceptual organization did not reach statistical significance ($P = 0.07$).

At the time of our study, 47 of the 142 patients were attending school. Of those children, six (13%), including two in group 1 and four in group 2, had received the diagnosis of attention-deficit–hyperactivity disorder (ADHD) requiring medication; one of the six children with ADHD also had aggressive behavior, and another three (6%), all in group 3, required special education services at school.

**Discussion**

Our study assessed long-term neurologic sequelae, neurodevelopment, and cognitive function in patients who had EV71 infection with CNS involvement. We also found cognitive function to be associated with the clinical severity of the illness and the patient's age at the onset of infection. The cause of long-term neurologic sequelae is related to neuron damage. This complication could have been caused by a direct EV71 infection, by hypoxia, or in some cases, by hypoxia. The findings on imaging studies of our patients who had EV71 infection were compatible with the neuroanatomic lesions of their sequelae, similar to previous reports.

EV71 viral antigen has been seen in neurons with immunocytochemical staining. Therefore, direct EV71 invasion and subsequent neuron damage could be said to be the main cause of the sequelae. These clinical characteristics raise important questions about the biology of the virus and its mode of spread.

Further investigation into its virulence and its mode of transmission is mandatory to help control EV71 infection. There have been few studies to date on cognitive function after viral encephalitis. Therefore, our study may provide information that can be used to assess long-term prognosis of viral CNS infection. Patients with the most severe illness are those who had EV71 infection with CNS involvement. They also had aggressive behavior and another three (6%) required special education services at school.

#### Table 5. Multivariate Analysis of Factors Associated with IQ, Verbal Comprehension, and Perceptual Organization in Patients after EV71 Infection with CNS Involvement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Verbal IQ (N = 90)</th>
<th>Performance IQ (N = 90)</th>
<th>Full-Scale IQ (N = 90)</th>
<th>Verbal Comprehension (N = 48)</th>
<th>Perceptual Organization (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ P Value</td>
<td>$\beta$ P Value</td>
<td>$\beta$ P Value</td>
<td>$\beta$ P Value</td>
<td>$\beta$ P Value</td>
</tr>
<tr>
<td>Clinical severity (with group 1 as reference group)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>2.6 0.34</td>
<td>–1.6 0.60</td>
<td>0.5 0.86</td>
<td>3.8 0.28</td>
<td>–1.9 0.60</td>
</tr>
<tr>
<td>Group 3</td>
<td>–11.4 0.03</td>
<td>–17.0 0.003</td>
<td>–15.5 0.003</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Age at onset &lt;2 yr vs. ≥2 yr</td>
<td>–5.4 0.06</td>
<td>–4.3 0.16</td>
<td>–5.2 0.06</td>
<td>–11.8 0.009</td>
<td>–8.2 0.07</td>
</tr>
<tr>
<td>Male sex vs. female sex</td>
<td>–0.5 0.85</td>
<td>1.8 0.43</td>
<td>–1.8 0.51</td>
<td>1.0 0.80</td>
<td>–5.8 0.14</td>
</tr>
<tr>
<td>Maternal educational level of college or more vs. high school or less</td>
<td>2.4 0.50</td>
<td>0.5 0.86</td>
<td>4.7 0.18</td>
<td>3.6 0.45</td>
<td>–3.8 0.43</td>
</tr>
<tr>
<td>Paternal educational level of college or more vs. high school or less</td>
<td>6.5 0.07</td>
<td>1.6 0.65</td>
<td>6.3 0.18</td>
<td>6.3 0.43</td>
<td>0.3 0.86</td>
</tr>
</tbody>
</table>

*The original denominator of patients was 142, but only the 90 children who were 4 years of age or older underwent assessment of IQ with the Wechsler Intelligence Scale for Children, third edition, and only 48 patients in group 1 and group 2 who were 6 years of age or older underwent assessment with the composite subscales of verbal comprehension and perceptual organization. Adjusted P values were derived by multiple regression. $\beta$ denotes the regression coefficient in the multivariate model, and ND not done.

†Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement.
— those with severe CNS involvement plus cardiopulmonary failure — scored significantly lower on IQ evaluations than did patients with less severe illness, a difference that may have been due to both direct viral CNS effects and the indirect anoxic and ischemic effects on the CNS. However, we cannot exclude the possibility that the inability to attend school accounted for the patients’ poor testing results. Patients who had CNS involvement alone did well in the assessment of neurodevelopment, but children who were infected before the age of 2 years had lower scores on verbal comprehension than did children who were infected at older ages (Table 4 and Table 5). It is possible that neuron damage may be more profound when the CNS of younger children is infected by EV71. This possibility may be applied to CNS infection with other enteroviruses as well. The possibility that younger children who had CNS infection caused by other enteroviruses have reduced cognitive function also deserves further exploration.

Because psychiatric problems after EV71 infection may be noticed only when children start going to school, there may be higher rates of learning and behavioral problems at school age. For example, some of the patients we studied were found to have ADHD, resulting in behavioral problems and the need for medication or special educational services at school. Most children who had cardiopulmonary failure after CNS involvement were not yet old enough to attend school. Many severe learning and behavioral problems may be observed only after children start school. Careful follow-up is thus warranted. Our results suggest that children who have had EV71 infection with CNS involvement may benefit from early evaluation for psychiatric problems and early intervention.

In conclusion, EV71 infection with CNS involvement and cardiopulmonary failure may be associated with long-term neurologic sequelae, delayed neurodevelopment, and reduced cognitive function — conditions that may cause further learning and behavioral problems once children attend school. Patients who had EV71 infection with CNS involvement alone without cardiopulmonary failure did well on neurodevelopment testing but had reduced scores on verbal comprehension if they were under the age of 2 years at the onset of the infection. Early evaluation and intervention for psychiatric and cognitive problems may prove beneficial for children after EV71 infection with CNS involvement and cardiopulmonary failure and for children who are infected at a very young age.

Supported by grants (NSC 95-3112-B-002-025 and NSC 94-3112-B-002-028) from the National Research Program for Genomic Medicine, National Science Council, Taiwan.

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

REFERENCES


16. Frankenburgh WK, Dodds J, Archer P,
Neurodevelopment and cognition after enterovirus 71 infection


Copyright © 2007 Massachusetts Medical Society.
Redarkening of Port-Wine Stains 10 Years after Pulsed-Dye–Laser Treatment

Menno Huikeshoven, M.D., Ph.D., Petra H.L. Koster, M.D., Ph.D., Corianne A.J.M. de Borgie, M.D., Ph.D., Johan F. Beek, M.D., Ph.D., Martin J.C. van Gemert, Ph.D., and Chantal M.A.M. van der Horst, M.D., Ph.D.

BACKGROUND
Although pulsed-dye–laser therapy is currently the gold standard for the treatment of port-wine stains, few objective data are available on its long-term efficacy. Using objective color measurements, we performed a 10-year follow-up of a previously conducted prospective clinical study of the treatment of port-wine stains with a pulsed-dye laser.

METHODS
We invited the patients to undergo repeated color measurements performed by the same procedures as in the previous study. The results at long-term follow-up were compared with color measurements obtained before treatment and after completion of an average of five laser treatments of the complete port-wine stain. A questionnaire was used to investigate patients’ satisfaction with the treatment and their perception of long-term changes in the stain.

RESULTS
Of the 89 patients from whom color measurements were obtained in the previous study, 51 were included in this study. The patients had received a median of seven additional treatment sessions since the last color measurement, which had been made after an average of five treatments. The median length of follow-up was 9.5 years. On average, the stain when measured at follow-up was significantly darker than it was when measured after the last of the initial five laser treatments (P=0.001), but it was still significantly lighter than it was when measured before treatment (P<0.001). Fifty-nine percent of patients were satisfied with the overall treatment result. Six percent of patients reported that the stain had become lighter since their last treatment, 59% that it was unchanged, and 35% that it had become darker.

CONCLUSIONS
Using objective color measurements, we observed significant redarkening of port-wine stains at long-term follow-up after pulsed-dye–laser therapy. Patients should be informed about the possibility of redarkening before beginning treatment.
PORT-WINE STAINS ARE CAPILLARY MALFORMATIONS SEEN IN APPROXIMATELY 0.3% OF NEWBORNS. IN THIS BENIGN SKIN DISORDER, ECSTATIC DERMAL VENULES CAUSE THE CHARACTERISTIC RED SKIN COLOR. SINCE THE REPORT BY TAN AND COLLEAGUES IN 1989,1 TREATMENT WITH THE PULSED-DYE LASER HAS BEEN THE GOLD STANDARD. ALTHOUGH THERE HAS BEEN MUCH RESEARCH ON THE SHORT-TERM EFFICACY OF THE TREATMENT, LONG-TERM FOLLOW-UP INFORMATION IS SCARCELY AVAILABLE AND IS LIMITED TO CASE REPORTS2 AND QUESTIONNAIRES.3-8 WE PRESENT THE LONG-TERM FOLLOW-UP RESULTS OF A PREVIOUSLY PUBLISHED PROSPECTIVE STUDY THAT USED OBJECTIVE COLOR MEASUREMENTS TO INVESTIGATE THE EFFECT OF THE TIMING OF PULSED-DYE–LASER TREATMENT OF PORT-WINE STAINS.9

METHODS

The investigators in the previous study performed color measurements on 89 of 100 evaluated patients with previously untreated port-wine stains on the face or neck. The measurements were performed before treatment and after an average of five pulsed-dye–laser treatments of the complete stain. (One treatment of the complete stain may consist of more than one session.) In the present study, 51 of these patients underwent repeated color measurements and completed an evaluation questionnaire. Patients who had received additional treatment for their stains outside the study hospital after the first five treatments were excluded from the present study, as were patients who could not be located or who declined to participate.

The stains were treated with a Candela pulsed-dye laser (model SPTL-1) with a wavelength of 585 nm, a radiant exposure level of 6 to 8 J per square centimeter per pulse, a pulse duration of 45 msec, and a spot size of 5 to 7 mm. The area of the skin was cooled during treatment with gauze dressings drenched in ice water. Color measurements were performed as described in detail in the previous study.9 In short, the color of both the stain and the contralateral normal skin was measured with a Minolta chromometer (model CR-300) that used the L*a*b* color coordinate system, where L* denotes lightness, a* values from green to red, and b* values from blue to yellow. The difference in color between the stain and the normal skin was calculated using the L*a*b* coordinates and was denoted by ΔE. A small number for ΔE indicates a small color difference, and a large number for ΔE indicates a large difference. A review of the literature suggests that a ΔE value of 1 is the least noticeable difference by a human observer under optimal viewing conditions.10

In the previous study, the face and neck were mapped into 64 different areas, and the color of the skin at baseline was measured at the darkest spot in the darkest area of the port-wine stain.9 The location of the measurement was accurately documented on transparent overlays placed over photographs of the stain, and the overlays were used to ensure that the color was measured at the same location before treatment, after five treatments of the entire stain, and at long-term follow-up. The color both of the stain and of the normal skin was measured twice at the same location, and the average values were used. For each patient, the values for ΔE at long-term follow-up were compared with those determined in the previous study.

Each patient was asked two questions to evaluate the perception of the outcome of the treatment: Were you satisfied with the result at the end of treatment (which included any treatment sessions subsequent to the measurement taken after the first five treatments)? Since the last treatment session, has the stain become lighter, become darker, or remained the same color?

Since the previous study found no correlation between the age of the patient at treatment and the effect of treatment, we did not perform age-dependent analysis in the present study. All data sets were tested for normal distribution. Not all were normally distributed, and therefore the results are presented as medians with interquartile ranges, unless specified otherwise. Differences between groups in baseline characteristics and differences in ΔE values between follow-up and previous measurements were analyzed by nonparametric tests.

The study was approved by the hospital institutional review board. Written informed consent was obtained from each patient or the patient’s parent.

RESULTS

PATIENTS AND FOLLOW-UP

Table 1 shows the characteristics of the patients and the results of color measurements. Of the 89 patients included in the previous study, 13 could not be traced and 15 declined to participate or
did not reply. An additional 10 patients were excluded from the study because they had been treated outside the study hospital between the time of the last color measurement obtained after five treatments and the follow-up study (subgroup 2 in Table 1). Of these 10 patients, 6 had received laser treatments and 4 had received medical tattoos. Thus, 51 of the original 89 patients (57%) were included in the follow-up study. These 51 patients did not differ significantly from the original 89 patients with respect to age, baseline color measurements, color measurements obtained after an average of five treatments, or original effect of treatment (color measurements obtained after the first five treatments minus baseline color measurements) (P>0.50 by the Wilcoxon signed-rank test).

After completing five treatments and having their skin color measured in the previous study, 45 of the 51 patients included in the present study had additional treatment sessions in our hospital. In these sessions, either all or part of the stain was treated with the same laser and the same methods used in the previous treatments. The median duration of the original five-treatment regimen for the 51 patients was 1.9 years (interquartile range, 1.2 to 2.7 years).

### Table 1. Patient Characteristics and Results of Color Measurements.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 89)</th>
<th>Patients Included in Follow-up Study</th>
<th>Patients Excluded from Follow-up Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 51)</td>
<td>Subgroup 1 (N = 6)†</td>
<td>Subgroup 2 (N = 10)‡</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>65</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>Mean 24</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Range 12 to 42</td>
<td>12 to 42</td>
<td>23 to 41</td>
</tr>
<tr>
<td>Pretreatment ΔE</td>
<td>Median 15.3</td>
<td>15.2‡</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>Interquartile range 12.4 to 18.6</td>
<td>12.3 to 19.5</td>
<td>7.5 to 17.9</td>
</tr>
<tr>
<td>ΔE after five treatments</td>
<td>Median 8.5</td>
<td>8.9¶</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>Interquartile range 6.2 to 11.9</td>
<td>6.5 to 12.4</td>
<td>4.6 to 13.9</td>
</tr>
<tr>
<td>Original effect of treatment</td>
<td>Median −5.9</td>
<td>−5.7†</td>
<td>−3.8</td>
</tr>
<tr>
<td></td>
<td>Interquartile range −8.6 to −3.2</td>
<td>−8.1 to −3.0</td>
<td>−6.1 to −2.7</td>
</tr>
<tr>
<td>ΔE at 9.5-yr follow-up</td>
<td>Median —</td>
<td>12.4¶</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Interquartile range —</td>
<td>8.7 to 14.8</td>
<td>7.6 to 20.2</td>
</tr>
<tr>
<td>Change in ΔE at follow-up**</td>
<td>Median —</td>
<td>2.5‡</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Interquartile range —</td>
<td>−0.1 to 5.5</td>
<td>0.7 to 8.4</td>
</tr>
</tbody>
</table>

* ΔE denotes the difference in color between the port-wine stain and normal skin. The Wilcoxon signed-rank test was used to determine the statistical significance of changes in ΔE over time.
† Six patients received five treatments, had their skin color measured, and did not receive any additional treatments.
‡ Ten patients were excluded because they received treatment elsewhere after receiving five treatments in the study hospital. Six of these patients received additional laser treatments and four received medical tattoos.
§ P<0.001, indicating a significant persistent current effect (a decrease in ΔE) of pulsed-dye-laser treatment as compared with the pretreatment measurement.
¶ P=0.001, indicating significant redarkening of the stains (an increase in ΔE) between the measurement taken after the first five treatments and the follow-up measurement.
‖ The original effect of treatment is the color measurement obtained after the first five treatments minus the color measurement at baseline; negative values indicate a decrease in ΔE.
** The change in ΔE at follow-up is the 9.5-yr follow-up measurement minus the measurement taken after the first five treatments; positive values indicate an increase in ΔE.
The median number of additional sessions was 7 (interquartile range, 3 to 13; range, 1 to 39), and the median duration of the additional treatment regimen was 3.9 years (interquartile range, 1.1 to 5.4). The median time between the last treatment session and the follow-up measurement was 5.8 years (interquartile range, 4.1 to 8.9). The median time between the measurement obtained after the first five treatments and the follow-up measurement was 9.5 years (interquartile range, 9.2 to 10.1). Thus, the median duration of follow-up in this study was 9.5 years.

**Color Measurements**

The color measurements are summarized in Table 1. The median ΔE increased significantly from 8.9 (interquartile range, 6.5 to 12.4) after the first five treatments to 12.4 (interquartile range, 8.7 to 14.8) at a median of 9.5 years of follow-up ($P=0.001$). However, the median ΔE was still significantly lower at follow-up (12.4; interquartile range, 8.7 to 14.8) than before laser treatment (15.2; interquartile range, 12.3 to 19.5; $P<0.001$), indicating a persistent effect of pulsed-dye–laser treatment. Figure 1 illustrates the results by including recent photographs of the patients along with the illustrations used in the previous publication.

Of the 51 patients evaluated, only 6 (2 men and 4 women) did not receive treatment after the first five treatments; the results from these patients represent true follow-up results after treatment (subgroup 1 in Table 1). In all six of these patients, the value of ΔE was higher at follow-up than after the five treatments; the increases in ΔE were 0.2, 0.9, 1.3, 2.8, 6.8, and 13.1.

**Questionnaire**

Of the 51 patients evaluated, 30 (59%) were satisfied with the result of the pulsed-dye–laser treatment (including any treatment sessions subsequent to the measurement made after the first five treatments). The remaining 21 (41%) were not satisfied. Three patients (6%) reported that their stains had become lighter since their last treatment session, 18 (35%) reported that they had become darker, and the remaining 30 (59%) thought that they had not changed in color.

For the three patients who reported that their stains had become lighter, the changes in ΔE from the measurements made after the first five treatments to follow-up (i.e., the measured changes in the color of the stain over the previous 9.5 years) were −2.0, 1.1, and 1.7. The mean (±SD) change in ΔE was 1.6±4.7 (range, −10.7 to 7.5) for the 30 patients who considered their stains unchanged and 3.4±4.5 (range, −4.9 to 13.1) for the 18 patients who reported that their stains had darkened.

**Discussion**

This follow-up study used objective color measurements to assess the long-term efficacy of pulsed-dye–laser treatment of port-wine stains. The results show that the median ΔE (the difference in color between the stain and normal skin) increased from 8.9 to 12.4 at a median of 9.5 years after the last of five treatments of the complete stain, although the patients had received a median of seven additional laser treatment sessions after the initial five treatments. However, the follow-up ΔE was still lower than the pretreatment value (12.4 vs. 15.2). From these results, it can be concluded that the positive effect of five treatments is not completely durable and that significant re-darkening occurs at long-term follow-up.

The results of this study confirm previous anecdotal reports of the recurrence of port-wine stains after pulsed-dye–laser treatment. However, the previous reports were all based on questionnaires presented to the patients or treating physicians and show widely varying outcomes. Orten et al. reported a 50% recurrence rate of port-wine stains 5 years after treatment, and Mork et al. reported a recurrence rate of 11% “several” years after treatment. Michel et al., in a study investigating the effect of age at treatment on recurrence (at least 1 year after completion of treatment), found redarkening in 16% of patients. The authors found no correlation between the rate of recurrence and the duration of follow-up, indicating that recurrence may be mainly related to individual patient characteristics. Ho et al. investigated the effect of laser treatment in Chinese patients and surprisingly found no recurrence after a mean follow-up of 3.4 years. Finally, in a study by Hansen et al., 19% of patients reported recurrence of color at 7 years of follow-up.

In our study, even though 45 patients received additional treatment sessions, the ΔE of the whole group had increased at 9.5 years of follow-up. Only six patients did not receive more than five treatments. Among these patients (subgroup 1 in Table 1), the effect of five treatments of the com-
plete port-wine stain was smaller than the effect of treatment in the entire group; the change in ΔE was −3.8 in subgroup 1 and −5.7 in the entire group. The amount of redarkening at 9.5 years of follow-up was also somewhat smaller in subgroup 1 than in the entire group (change in ΔE, 2.0 vs. 2.5); however, the small number of patients precludes drawing conclusions.

There is no consensus on the mechanism of redarkening, although it has been widely discussed. Several mechanisms may contribute. First, it has frequently been hypothesized (but rarely objectively shown) that untreated port-wine stains darken with age.11 Natural darkening with age, possibly resulting from progressive ectasia of the remaining vessels, may have a role in the redarkening of incompletely eradicated port-wine stains. Support for this hypothesis includes our observation that redarkening occurred in all six patients who did not receive additional treatment after the first five treatments. Second, neovascularization resulting from post-treatment thrombus formation and angiogenesis from remaining parts of the stain — support the hypothesis that the cause of port-wine stains is the lack of surrounding neurons regulating blood flow through the ectatic postcapillary venules.13,14 Since pulsed-dye–laser treatment obviously does not increase neural control, both newly formed and persistent vessels would suffer from the same lack of neural control.

Two final points should be mentioned concerning the possible mechanism of redarkening. First, we assessed only color, whereas other characteristics of port-wine stains, such as size, surface structure, and hypertrophy,15 may also have a role in recurrence. Second, several changes in treatment (the use of longer wavelengths, greater pulse energies, larger spot size, and cryogen spray cooling) have been implemented in new generations of pulsed-dye lasers since the treatment of our patients with the Candela SPTL-1. Whether treatment of port-wine stains with these new lasers will reduce the incidence of redarkening at long-term follow-up remains to be investigated.

Fifty-nine percent of the 51 patients who un-
Redarkening of Laser-Treated Port-Wine Stains

underwent follow-up measurements were satisfied with the results of the treatment. On the other hand, 10 of the original 89 patients (11%) sought additional treatment (laser treatments or medical tattoos) outside our hospital. In these patients (subgroup 2 in Table 1), the original port-wine stain was not darker (i.e., the pretreatment ΔE was not higher) than in the rest of the patients, nor was the effect after five treatments lower. These results indicate that the patients did not seek additional treatment because their treatment results were worse than average.

In the three patients who reported that their stains had become lighter, the changes in color measurements were small but variable, whereas patients who considered their stains to be either unchanged or darker had an increase in ΔE. Thus, patients seem to underestimate the changes in color taking place in their stains, probably because the changes occur slowly over several years, making detection difficult. The discrepancies between the perceptions of the patients and color measurements emphasize the importance of using objective assessment instead of patient or physician questionnaires when assessing the long-term results of treatment of port-wine stains. Furthermore, although histopathological data are available from untreated port-wine stains, obtaining such data from treated port-wine stains is virtually impossible because very few patients will consent to repeated biopsies of their stains. Therefore, color measurement is currently the most objective method of assessing changes in port-wine stains after treatment.

In conclusion, although pulsed-dye–laser therapy remains the gold standard for the treatment of port-wine stains and has a persistent beneficial effect, the current study objectively shows that redarkening occurs at long-term follow-up. Therefore, we recommend that before commencing pulsed-dye–laser therapy, all patients should be informed of the possibility of redarkening of the stain after treatment.

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

We thank A.J. Leijen for her important contribution in tracing and contacting the patients and D. Ubbink for his assistance in data analysis.

REFERENCES


Copyright © 2007 Massachusetts Medical Society.
Intermittent Claudication

Christopher White, M.D.

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

A 58-year-old, previously healthy mail carrier reports cramping pain in his right calf when he walks. The discomfort has progressively worsened over the past 6 months and now forces him to rest after walking half a block on level ground at a normal pace. The pain is interfering with his ability to perform his job. He has a normal right femoral pulse and a diminished right popliteal pulse; the right ankle and foot pulses are absent. How should this patient be evaluated and treated? Should he undergo revascularization?

Peripheral arterial disease is a common manifestation of atherosclerosis, and its prevalence increases with age and the presence of cardiovascular risk factors. Cigarette smoking and diabetes mellitus are the strongest risk factors; more than 80% of patients with peripheral arterial disease are current or former smokers. Hypertension, dyslipidemia, and hyperhomocysteinemia also significantly increase the risk of peripheral arterial disease.

Most persons with this disease are asymptomatic, and the condition is detected during routine physical examination of abnormal pulses, vascular bruits, or an abnormal value for the ankle–brachial index. Less than 20% of patients with peripheral arterial disease report the typical symptom of intermittent claudication — leg-muscle discomfort on exertion that is relieved with rest. Many patients present with atypical symptoms, including leg fatigue, difficulty walking, and leg pain that is not typical of claudication.

Studies of the natural history of intermittent claudication indicate that the risk of limb loss for patients who do not have diabetes is low (2% or less). However, the risk of progression to limb-threatening ischemia is increased by a factor of three among patients with diabetes who require oral or insulin therapy as compared with patients without diabetes, and the risk increases by 20 to 25% for each 0.1-unit decrease in the ankle–brachial index.

Cardiovascular disease is the major cause of death in patients with intermittent claudication; the annual rate of cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) is 5 to 7%. Thus, the treatment of claudication is directed not only at improving walking distance but also, and more important, at reducing cardiovascular risk.

EVALUATION

A careful history taking and examination will generally distinguish intermittent claudication from nonvascular causes that may mimic claudication (pseudocludi-
The patient’s lower legs and feet should be examined with shoes and socks off, with attention to pulses, hair loss, skin color, and trophic skin changes. Calculation of the ankle–brachial index (Fig. 1) is recommended as the initial screening test. An abnormal result (0.9 or less) is sufficient to make the diagnosis of peripheral arterial disease in a clinically appropriate setting. When the disease is suspected on the basis of clinical observations but the resting ankle–brachial index is normal, the index should also be calculated after exercise — after the patient has performed toe raises (standing flat-footed and raising the heels off the ground repeatedly) or has walked on a treadmill. Patients with large-vessel “inflow” disease of the distal aorta or iliac arteries may have normal resting blood flow, but in the setting of exercise and associated vasodilatation, pressure gradients develop across the proximal stenoses, leading to symptoms and an abnormally low value for the ankle–brachial index.

If the diagnosis of peripheral arterial disease is uncertain, or if revascularization is being planned, further imaging with duplex ultrasound, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) may be useful. Segmental pressure recording and pulse-volume recording are used in some cases to assess the location and severity of the lesion. In patients with noncompressible vessels (usually patients with diabetes or renal failure), the diagnosis can be confirmed by measuring the toe–brachial index (determined according to the return of pulsatile flow on deflation of a small blood-pressure cuff on the great or second toe with a plethysmographic device).

Both CTA and MRA produce images of vascular structures in cross-sectional slices that can be reformatted into three-dimensional angiographic images (Fig. 2). In a randomized trial comparing MRA with CTA for initial imaging in peripheral arterial disease, the two techniques were similar in ease of use and clinical outcome, but total diagnostic costs were lower for CTA.11

The gold standard for diagnosis and evaluation of peripheral arterial disease is invasive digital-subtraction angiography, which is used if endovascular intervention is planned (Fig. 3). Serious complications of this procedure, which are infrequent, include reactions to the contrast material (in 4% of patients or less), bleeding (2% or less), nephropathy due to contrast material (0.2 to 1.4%), and cholesterol embolization (0.1% or less).12,13

Table 1. Differentiation of True Claudication from Pseudoclaudication (Nonvascular Causes).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intermittent Claudication</th>
<th>Spinal Stenosis</th>
<th>Arthritis</th>
<th>Venous Congestion</th>
<th>Compartment Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Character of discomfort</td>
<td>Cramping, tightness, or tiredness</td>
<td>Same symptoms as with claudication or tingling, weakness, or clumsiness</td>
<td>Aching</td>
<td>Tightness, bursting pain</td>
<td>Tightness, bursting pain</td>
</tr>
<tr>
<td>Location of discomfort</td>
<td>Buttock, hip, thigh, calf, foot</td>
<td>Buttock, hip, thigh</td>
<td>Hip, knee</td>
<td>Groin or thigh</td>
<td>Calf</td>
</tr>
<tr>
<td>Exercise-induced discomfort</td>
<td>Yes</td>
<td>Variable</td>
<td>Variable</td>
<td>After walking</td>
<td>After excessive exercise</td>
</tr>
<tr>
<td>Walking distance</td>
<td>Reproducible</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Discomfort with standing</td>
<td>No</td>
<td>Yes</td>
<td>Yes, changes with shift in position</td>
<td>Yes, changes with shift in position</td>
<td>Yes, changes with shift in position</td>
</tr>
<tr>
<td>Relief of discomfort</td>
<td>Rapid relief with rest</td>
<td>Relief with sitting or otherwise changing position</td>
<td>Slow relief with avoidance of bearing weight</td>
<td>Slow relief with leg elevation</td>
<td>Slow relief with leg elevation</td>
</tr>
<tr>
<td>Other</td>
<td>Associated with atherosclerosis and decreased pulses</td>
<td>History of lower-back problems</td>
<td>Discomfort at joint spaces</td>
<td>History of deep venous thrombosis, signs of venous congestion</td>
<td>May occur in athletes after strenuous exercise</td>
</tr>
</tbody>
</table>

Information is from the American Heart Association and the American College of Cardiology (Hirsch et al.9) and from Schmieder and Comerota.10
The advantages and disadvantages of digital-subtraction angiography, CTA, MRA, and duplex ultrasound are listed in Table 2.

**TREATMENT**

The mainstays of treatment for peripheral arterial disease include risk-factor modification, an exercise program, antiplatelet therapy, and, if warranted for symptomatic relief, additional pharmacologic therapy, and revascularization. Revascularization (endovascular or surgical) therapy is reserved for patients whose job performance or lifestyle is compromised by claudication, patients who do not have a response to exercise and pharmacotherapy, and patients for whom the risk–benefit ratio with revascularization is favorable.9

**Risk-Factor Modification**

Since cardiovascular events are the major cause of death in patients with peripheral arterial disease, modification of atherosclerotic risk factors is routinely warranted, with a particular emphasis on smoking cessation and regular exercise. Pharmacologic therapy and dietary modification should be tailored to meet current guidelines for risk factors: low-density lipoprotein cholesterol, less than 100 mg per deciliter (2.6 mmol per liter) or, for those at very high risk for ischemic events, less than 70 mg per deciliter (1.8 mmol per liter); blood pressure, less than 140 mm Hg systolic and 90 mm Hg diastolic or, for patients with diabetes or renal disease, less than 130 mm Hg systolic and 80 mm Hg diastolic; and glycated hemoglobin, less than 7% in patients with diabetes.14,15

Beta-blockers are effective as antihypertensive therapy and are not contraindicated in patients with peripheral arterial disease. In the Heart Outcomes Prevention Evaluation study, the risk of heart attack, stroke, and death from vascular causes was reduced by 22% for patients given an angiotensin-converting–enzyme inhibitor (ramipril).16

**Antiplatelet and Other Pharmacologic Therapy**

Antiplatelet therapy with aspirin (75 mg to 325 mg daily) reduces the risk of death from vascular causes, myocardial infarction, and stroke in patients with vascular diseases by 25% and is recommended for patients with peripheral arterial disease.17 A large, randomized, 3-year trial involv-
ing high-risk patients, including patients with peripheral vascular disease, showed that rates of death from vascular causes, myocardial infarction, and stroke were significantly, albeit modestly, lower with clopidogrel than with aspirin; the rates of bleeding complications were similar. Thus, the more expensive thienopyridines (ticlopidine and clopidogrel) may be considered as alternatives to aspirin, particularly in patients who cannot tolerate aspirin. Current data do not show an advantage of dual antiplatelet therapy (aspirin and clopidogrel) over single-agent therapy in patients with peripheral arterial disease.

Cilostazol is a phosphodiesterase type 3 inhibitor with vasodilator and mild antiplatelet properties. Several randomized trials have shown that walking distance is increased by about 50% with cilostazol (100 mg twice a day), as compared with placebo, after 3 to 6 months of therapy. The most common side effects include headache, diarrhea, palpitations, and dizziness. Cilostazol is contraindicated in patients with heart failure, because similar drugs, such as milrinone, are associated with increased mortality in this group. In a trial comparing cilostazol, pentoxifylline (a derivative of methylxanthine), and placebo, pentoxifylline was inferior to cilostazol and no better than placebo for relief from claudication. Oral vasodilator prostaglandins, vitamin E, and chelation therapy with EDTA have not proved to be effective in reducing symptoms or increasing walking distance. Table 3 summarizes the pharmacologic treatments for peripheral arterial disease and indicates the nature of the evidence supporting their use.

Exercise
A Cochrane review of three randomized trials showed that exercise increased maximal walking distance by 150% over a period of 3 to 12 months, as compared with usual care. A meta-analysis of eight randomized trials showed a greater symptomatic benefit with a supervised (as opposed to unsupervised) exercise program. Supervised exercise commonly involves walking on a treadmill, with the initial workload set to elicit symptoms within 3 to 5 minutes of walking. The patient is permitted to rest until the symptoms resolve and then resumes exercise. In a meta-analysis of 18 randomized and nonrandomized trials, the greatest benefit (assessed according to the distance walked before claudication developed) was associated with continued walking until pain was nearly maximal and with sessions that lasted longer than 30 minutes, took place three or more times per week, and continued for more than 6 months. Typically, it takes 1 to 2 months for the patient to begin to notice benefits, which gradually increase over a period of several months.

Revascularization
Superficial femoral-artery stenosis or occlusion is the most common lesion associated with claudication. Revascularization (surgery or percutane-

---

**Figure 2. Aortograms with Runoff Images in Three Patients.**
The digital-subtraction angiogram in Panel A shows occlusion of the right external iliac artery (arrow), bilateral narrowing of the superficial femoral arteries, and single-vessel runoff below the knees. The CTA in Panel B is a three-dimensional reconstruction showing very mild narrowing of the bilateral superficial femoral arteries (double-headed arrow). The MRA in Panel C, with enhancement from contrast material, shows bilateral occlusions of the superficial femoral arteries with a patent femoral–popliteal graft (arrow) on the right.
Ous transluminal angioplasty (PTA)) is indicated for relief in patients with claudication that limits their lifestyle or ability to perform their job and that has proved to be unresponsive to exercise and pharmacologic therapy.\textsuperscript{9,24,25} PTA is preferred when possible in patients who are 50 years of age or younger, because they have a higher risk of graft failure after surgical therapy than do older patients.\textsuperscript{9} Data from two randomized trials indicate that surgery and angioplasty result in similar mortality and amputation rates and in similar patency rates at 4 years among patients with ischemia of the legs or feet.\textsuperscript{26} However, because PTA is associated with lower estimated rates of both short-term mortality and major complications (0 to 2.9% and 2 to 10%, respectively) than is surgery (1.3 to 6.3% and 10 to 15%, respectively), PTA is preferred for lesions with favorable anatomical features, such as discrete stenoses or occlusions (those less than 15 cm long) (Table 4). Cost-effectiveness analyses suggest that PTA is preferable to surgery as long as the expected 5-year patency rate for the treated vessel is 30% or higher.\textsuperscript{28} Outcomes after femoral popliteal PTA have improved over time; patency rates of 87%, 69%, and 55% have been reported at 1, 3, and 5 years, respectively.\textsuperscript{26}

A single randomized trial comparing the effectiveness of surgery and exercise therapy showed no significant difference in outcomes — specifically, maximal walking distance and the need for further revascularization — at 8 to 9 months.\textsuperscript{28} A large prospective, matched cohort study of 526 patients with intermittent claudication showed that revascularization (surgery or PTA) was associated with improved walking distance and reduced pain as compared with medical therapy, but therapy was not optimized in the nonintervention group (e.g., only 40% of the patients in this group reported engaging in regular exercise, and cilostazol was not used).\textsuperscript{29} Outcomes of revascularization were better in patients with higher postprocedure ankle–brachial indexes, suggesting that the effectiveness of the limb revascularization procedure is directly related to the degree of symptomatic improvement.
Data from studies directly comparing exercise therapy and PTA are scarce. In one small trial, walking distance at 6 years was better for patients treated with exercise therapy than for those treated with PTA. A randomized trial comparing the effects of exercise and PTA (with both groups receiving pharmacologic therapy) demonstrated similar quality-of-life outcomes, similar maximal walking distances, and similar ankle–brachial indexes, but fewer patients in the PTA group had occluded arteries ($P = 0.004$). An analysis of combined data from seven studies that compared exercise with PTA in patients with claudication showed that PTA resulted in a greater increase in the ankle–brachial index but with no significant difference in quality of life. However, none of the studies included in the analysis compared the two interventions directly. A decision-analysis model comparing the costs and quality of life associated with PTA, bypass surgery, and exercise therapy showed that PTA, when feasible, was more effective than exercise therapy alone and was more cost-effective than bypass surgery ($38,000 vs. $311,000 per quality-adjusted year of life gained), but this conclusion, too, was not based on data from comparative clinical trials.

### AREAS OF UNCERTAINTY

#### STENTS

The role of primary stent placement in revascularization of the superficial femoral artery remains controversial. In contrast to the coronary arteries, for which stent placement has largely replaced angioplasty for revascularization, the superficial femoral artery is subject to longitudinal stretching, external compression, torsion, and flexion; these stresses may lead to stent fractures, which have been linked to restenosis. In early randomized trials comparing PTA with stent placement for the treatment of lesions in the superficial femoral artery, stent placement showed no advantage over angioplasty with bail-out stent placement. However, technology has improved, and a recent randomized trial involving 104 patients with severe claudication showed significantly higher patency rates at 1 year for lesions in the superficial femoral artery that were treated with stent placement than for lesions treated with PTA and bail-out stent placement (63% vs. 37%); the maximal walking distance and the ankle–brachial index were also significantly better in the stent group at 1 year. There were no major complications in either group.

A randomized trial of drug-coated (sirolimus) stents in the superficial femoral artery failed to show a reduction in the risk of restenosis as compared with the risk associated with bare-metal stents. Use of stents covered with polytetrafluoroethylene (PTFE), developed to seal arterial perforations or to exclude aneurysmal segments, was compared with the use of PTA alone in a randomized trial, and there was no significant difference in 1-year patency rates (50% and 45%, respectively); however, major adverse events were more frequent in the group that received PTFE-covered stents (8.2% vs. 4.0%).

---

**Table 2. Characteristics of Imaging Methods Used to Diagnose Peripheral Arterial Disease.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Duplex Ultrasound</th>
<th>Digital-Subtraction Angiography</th>
<th>Magnetic Resonance Angiography</th>
<th>Computed Tomographic Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Noninvasive, can be used to visualize and quantitate severity of lesion</td>
<td>Gold standard, high resolution, can be used to guide intervention</td>
<td>Noninvasive, no radiation or iodinated contrast material used, three-dimensional</td>
<td>Noninvasive, higher spatial resolution than with magnetic resonance angiography, three-dimensional</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Operator-dependent, imaging limited by dense calcification</td>
<td>Invasive, ionizing radiation and iodinated contrast material used, two-dimensional</td>
<td>Lower spatial resolution than with computed tomographic angiography, contraindicated if patient has claustrophobia, image artifact if stent present</td>
<td>Ionizing radiation (25% of dose with digital-subtraction angiography) and iodinated contrast material used, imaging limited by dense calcification</td>
</tr>
<tr>
<td>Charge (Medicare)*</td>
<td>$252.14</td>
<td>$474.07</td>
<td>$973.75</td>
<td>$530.45</td>
</tr>
</tbody>
</table>

* The charges shown represent the allowable total charge by Medicare in the New Orleans area.
Adjunctive Angioplasty

Adjunctive angioplasty techniques such as atherectomy, cryotherapy, and the use of a cutting balloon (a balloon with microtomes attached to its surface, which make shallow incisions in the surface of the lesion when the balloon is inflated) have not been tested in meaningful comparative trials in patients with femoral artery disease; the only available data that show the benefit of these approaches is from single-center studies and uncontrolled registries.

Laser angioplasty has not been shown to be superior to conventional PTA or stent placement.

Given the substantial additional expense of these approaches, more evidence of their efficacy is needed before widespread adoption can be justified.

Trials of brachytherapy (use of a catheter to deliver radiation to the lesion) for preventing restenosis in the superficial femoral artery after percutaneous PTA have had inconsistent results.

In one trial, the use of external-beam radiation (at a dose of 14 Gy) after PTA significantly reduced the rate of restenosis at 1 year after PTA, but these results require confirmation. The use of gene or cellular therapies in peripheral arterial disease has not resulted in a clear clinical benefit in small studies; larger, controlled clinical trials are needed to establish whether there is any role for these therapies in patients with claudication.

Follow-Up after Percutaneous Interventions

It is common to measure the ankle–brachial index within a week after a percutaneous intervention has been performed in order to establish a new baseline. Patients are often reevaluated at 3-month intervals for the first year (when the risk of restenosis is highest); these assessments include a detailed history taking, examination, and ankle–brachial index measurements; the value of a walking program and risk-factor modification should be reinforced during these visits. However, data on the optimal approach to follow-up are lacking.

Guidelines

Comprehensive guidelines for the management of peripheral arterial disease have recently been published by an expert multidisciplinary committee organized by the American College of Cardiology (ACC) and the American Heart Asso-
tion (AHA). The TransAtlantic Inter-Society Consensus, representing multiple international specialty societies, has also published guidelines for the management of peripheral arterial disease that are in general agreement with the ACC–AHA document (Table 4).

The ACC–AHA guidelines recommend endovascular therapy for patients whose condition interferes with their job performance or lifestyle and who have had an inadequate response to exercise or pharmacologic therapy, as long as the clinical features suggest a reasonable likelihood of symptomatic improvement and the risk–benefit ratio is very high.

The recommendations in this article are in agreement with the ACC–AHA guidelines.

**Summary and Recommendations**

The mail carrier described in the vignette has right-calf claudication that interferes with his ability to perform his job, and physical examination shows that his condition is consistent with stenosis or occlusion of the superficial femoral artery. The initial assessment should include measurement of his ankle–brachial index. Risk factors for atherosclerosis should be assessed, and appropriate modification instituted, including smoking cessation, dietary adjustment, and pharmacotherapy as warranted for dyslipidemia, hypertension, or hyperglycemia. He also should be treated with aspirin (75 mg to 325 mg per day).

Management in this case should include a supervised exercise program and a trial of cilostazol for claudication, an approach that is consistent with the AHA–ACC guidelines. Revascularization is warranted if the condition does not improve with conservative therapy and if the lesion has anatomical features that are associated with a good outcome of revascularization. PTA is preferred over surgery and may be considered up front if there is a high probability of success and a low procedural risk (Table 4). An imaging study (duplex ultrasonography, CTA, or MRA, with the choice guided by the physician’s preference and the availability of local expertise) is indicated in patients who are candidates for revascularization in order to determine the location and morphologic characteristics of the obstructive lesion (or lesions). If a percutaneous intervention is considered to be likely, one can proceed directly to digital-subtraction angiography, with a plan to perform the percutaneous intervention immediately if the angiographic anatomy is suitable. Regardless of the initial therapy for this patient’s claudication, follow-up care should involve ongoing attention to control of atherosclerotic risk factors, antiplatelet therapy with aspirin, and encouragement of the patient to engage in regular exercise.

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

---

**Table 4. TransAtlantic Inter-Society Consensus on Classification of Femoral Lesions and Recommended Approaches When Revascularization Is Planned.**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Characteristics</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Single stenosis ≤10 cm long</td>
<td>Percutaneous transluminal angioplasty strongly preferred</td>
</tr>
<tr>
<td></td>
<td>Single occlusion ≤5 cm long</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Multiple lesions, each ≤5 cm in length</td>
<td>Percutaneous transluminal angioplasty generally preferred</td>
</tr>
<tr>
<td></td>
<td>Single lesion ≤15 cm long, not involving the popliteal artery below the knee</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single or multiple lesions in the absence of continuous tibial vessels for distal bypass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavily calcified occlusion ≤5 cm long</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single popliteal stenosis</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Multiple lesions &gt;15 cm long</td>
<td>Percutaneous transluminal angioplasty or surgery, depending on risk–benefit ratio</td>
</tr>
<tr>
<td></td>
<td>Recurrent lesions after two endovascular interventions</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Occlusion &gt;20 cm long</td>
<td>Surgery generally preferred</td>
</tr>
<tr>
<td></td>
<td>Occlusion of the popliteal or tibial–peroneal vessels</td>
<td></td>
</tr>
</tbody>
</table>

* Information is from Norgren et al.27


Copyright © 2007 Massachusetts Medical Society.
A 84-YEAR-OLD MAN WITH A HISTORY OF GASTRIC CANCER AND HYPERTENSION was admitted to the emergency department in shock after loss of consciousness. Ten years earlier he had been given a diagnosis of a thoracic aortic aneurysm, 56 mm in diameter, and had declined surgical treatment. Although the aneurysm had increased in size over the decade — as documented at various years of age on computed tomographic (CT) studies — and had reached 98 mm in diameter, he had been asymptomatic until the current episode. CT scans revealed a rupturing aneurysm involving the ascending aorta, aortic arch, and descending aorta. He died shortly thereafter without having undergone emergency surgery. An autopsy confirmed that the aneurysm had ruptured into the left thoracic cavity, leaving a massive amount of blood in the subpleural space.

Copyright © 2007 Massachusetts Medical Society.
A 27-year-old woman was seen in the neurology clinic because of pain and swelling in her feet. She had been well until approximately 5 months earlier, when swelling of her ankles and lower legs developed that was worse on the left side, varied in severity from day to day, and was not affected by position. Approximately 6 weeks later, she was awakened from sleep by burning and stinging pain on the dorsal aspect of her left foot, which was aggravated by pressure and lasted for 3 to 4 hours. The next day, she noted tingling in the dorsum of her toes and feet, worse in the left foot than in the right. The soles of her feet felt normal. She saw her physician, who noted swelling of the legs and ankles and prescribed naproxen. The paresthesia was intense for 2 days and then improved but did not completely resolve. Two weeks later, the pain recurred and involved both feet, with increased swelling of her ankles and legs; a rash developed over her feet and toes. She came to the emergency department of this hospital.

On examination, a petechial rash was noted on the feet. An ultrasound study of both legs revealed no deep venous thrombosis. She was given a 10-day course of dicloxacillin for presumed cellulitis. Two weeks later, she saw her internist, who found that the serum electrolyte and thyroid-stimulating hormone levels and renal-function tests were normal; spironolactone was prescribed. The swelling of her legs and ankles improved. However, the pain persisted, even after the administration of nonsteroidal antiinflammatory agents, elevation, and icing, and it interfered with sleep. Three months later, she was referred to the neurology clinic of this hospital.

On examination, a petechial rash was noted on the feet. An ultrasound study of both legs revealed no deep venous thrombosis. She was given a 10-day course of dicloxacillin for presumed cellulitis. Two weeks later, she saw her internist, who found that the serum electrolyte and thyroid-stimulating hormone levels and renal-function tests were normal; spironolactone was prescribed. The swelling of her legs and ankles improved. However, the pain persisted, even after the administration of nonsteroidal antiinflammatory agents, elevation, and icing, and it interfered with sleep. Three months later, she was referred to the neurology clinic of this hospital.

On evaluation in the neurology clinic, the patient indicated that in addition to the pain, she believed that she had some sensory loss in the dorsum of her feet. She did not recall any injury and did not have back pain, weakness in her feet, or sensory loss in the soles of her feet. She did not have dry eyes or dry mouth. Her weight had not changed in the preceding 2 to 3 years. Depression had been diagnosed 5 years earlier and was controlled with fluoxetine. Hypothyroidism had been diagnosed 4 years earlier and was treated with levothyroxine. She had mild iron-deficiency anemia. Her medications included levothyroxine sodium, fluoxetine hydrochloride, iron supplement, ibuprofen, spironolactone, and tramadol. She did not abuse alcohol or drugs. There was no family history of neurologic disease.
On physical examination, her vital signs were normal, and she was obese. The weight was 159.1 kg, and the height 173 cm. There was tense edema of the ankles and legs. The circumferences of the legs, 15 cm below the lower border of the patella, were 48 cm on the right and 51 cm on the left. The skin over the lateral aspects of her feet was dry and scaling with a diffuse purpuric rash and a few petechiae on the anterior legs and dorsal aspects of the feet, more on the left limb than on the right (Fig. 1). There was pain on light touch over the lateral aspects of both feet. Motor strength was normal in both arms and legs. Deep-tendon reflexes and plantar responses were normal. There was reduced sensation to pinprick and vibration in the fourth and fifth toes bilaterally, worse on the left. A Romberg test was negative, and tandem gait was normal.

Laboratory studies performed during the next few weeks revealed normal levels of blood glucose after an overnight fast, thyroid-stimulating hormone, vitamin B₁₂, folate, and angiotensin-converting enzyme. Tests were negative for the presence of antineutrophil cytoplasmic antibody; rapid plasma reagin; cryoprotein; serum immunofixation; Lyme antibody; hepatitis B and C antibody; human immunodeficiency virus (HIV) antibody; anti–double-stranded DNA, anti-La, anti-Smith, anti-RNP, and anti–Scl-70 antibodies; and anticardiolipin antibodies. Results of other laboratory tests are shown in Table 1. Computed tomographic (CT) scanning of the abdomen and pelvis revealed no abnormality.

Electrophysiological studies revealed absent bilateral sural and superficial peroneal sensory potentials, normal nerve-conduction studies in the bilateral tibial and peroneal motor nerves, F-wave latencies, and fibrillation potentials in the flexor hallucis brevis bilaterally.

A diagnostic procedure was performed.

**Differential Diagnosis**

Dr. Jean-Michel Vallat: May we see the neurophysiological studies?

Dr. Didier P. Cros: The nerve-conduction studies examined both motor and sensory nerves. In the legs, the sural and the superficial peroneal sensory-nerve action potentials were unobtainable bilaterally. The median and ulnar sensory-nerve action potentials were normal in the left arms. The motor-conduction studies obtained in the arms and legs were normal. The needle electromyogram showed no abnormality in the gastrocnemius, tibialis anterior, or paraspinal muscles. However, there were fibrillations and positive sharp waves in the flexor hallucis brevis bilaterally, providing evidence for a length-dependent symmetric axonal polyneuropathy affecting both motor and sensory fibers. The examination of the flexor hallucis brevis muscle with needle electromyography is very important in the evaluation of the so-called length-related axonopathies, because it may establish motor involvement that is not otherwise apparent, as in this case.

Dr. Vallat: This patient had a peripheral neuropathy, which had an acute onset and is associated with swelling of ankles and legs and cutaneous lesions. These signs were asymmetrical at onset and located in the lower legs in the distribution of the sural and superficial peroneal nerves bilaterally. Sensation to pinprick and vibration were reduced in the fourth and fifth toes bilaterally. There was no ataxia, and deep-tendon reflexes

---

**Figure 1. Photograph of the Patient’s Lower Legs.**

There is a purpuric rash over the anterior surfaces of the ankles and the dorsal aspects of the feet, with a few petechiae; the changes are more marked on the left foot than on the right. (Photograph courtesy of Peter Siao, M.D.)
were present, so that a ganglionopathy (neuropathy) can be ruled out.

**SENSORIMOTOR NEUROPATHY**

The clinical data are consistent with a distal, acute, sensory multiple mononeuropathy affecting large and small myelinated fibers. Although nerve-conduction studies suggest a pure sensory axonopathy (with normal motor-conduction velocities and absent sensory-nerve action potentials in the lower limbs) fibrillation potentials in both flexor hallucis brevis muscles indicate subclinical involvement of motor fibers, so the patient may have a sensorimotor multiple mononeuropathy (mononeuropathy multiplex).

Predominantly sensory multiple mononeuropathy can be caused by sarcoidosis, malignant tumors, and infections such as retroviruses, leprosy, hepatitis, and Lyme disease; there is no evidence in this case for any of these causes or for an acquired demyelinating disease such as chronic inflammatory demyelinating polyneuropathy.

**VASULITIC NEUROPATHY**

The acute onset of symptoms one morning when the patient awoke suggests a vascular process, since primary neuropathic processes usually evolve more slowly. The skin of the patient’s feet was dry and scaly, and there were lesions described as petechiae, but these could represent palpable purpura, a manifestation of vasculitis. Laboratory studies revealed an inflammatory syndrome, with an elevated erythrocyte sedimentation rate, elevated levels of IgG, and the presence of rheumatoid factor, antinuclear antibody, and anti-Ro antibody. The combination of an acute multiple mononeuropathy, skin lesions, and evidence of a systemic inflammatory response is very suggestive of a connective-tissue disorder.

The findings in this case suggest vasculitic neuropathy. Vasculitic neuropathy is due to ischemic infarctions of the nerve fascicles. These infarctions induce multifocal acute axonal lesions as a result of multiple small-vessel occlusions in the affected nerves due to inflammation, and in some cases, fibrinoid necrosis within the walls.

---

**Table 1. Results of Laboratory Tests.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults</th>
<th>Result in This Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>White-cell count (per mm³)</td>
<td>4,500–11,000</td>
<td>8,600</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.0–16.0</td>
<td>11.6</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36.0–46.0</td>
<td>35.2</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–350,000</td>
<td>423,000</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>1–25</td>
<td>93</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>5.5–8.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5–5.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td>2.0–3.5</td>
<td>6.4</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>614–1295</td>
<td>4,300</td>
</tr>
<tr>
<td>IgA (mg/dl)</td>
<td>69–309</td>
<td>319</td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>53–334</td>
<td>53</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Normal pattern, marked diffuse increase in gamma globulin</td>
<td></td>
</tr>
<tr>
<td>Total complement (U/ml)</td>
<td>63–145</td>
<td>165</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative at 1:40 dilution</td>
<td>1:5120, speckled pattern</td>
</tr>
<tr>
<td>Rheumatoid factor (IU/ml)</td>
<td>&lt;30</td>
<td>205</td>
</tr>
<tr>
<td>Anti-Ro antibody</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
of the vasa nervorum. In this patient, edema and pain in the legs may also have been induced by vascilitic lesions of the small cutaneous nerves.

The Chapel Hill classification of vasculitides does not take into account neuropathic signs and is based only on the size of the vessels involved. Table 2 indicates the vasculitides that may cause peripheral neuropathies. A test for antineutrophil cytoplasmic antibodies was negative in this case; thus, disorders such as microscopic polyangiitis, Churg–Strauss disease, and Wegener’s granulomatosis can be ruled out. This patient did not report unexplained weight loss, her diastolic blood pressure was not elevated, and a test for hepatitis B antibodies was negative. According to the American College of Rheumatology guidelines, this patient did not have polyarteritis nodosa.

A test for rheumatoid factor was positive. Rheumatoid arthritis is the most common connective-tissue disease, but symptoms usually develop when the patient is between 35 and 50 years of age. A vascilitic neuropathy develops in 10% of all patients with rheumatoid arthritis; in half of these patients (5%), neuropathies are predominantly sensory, whereas others (5%) present with a slowly progressive, distal symmetrical sensory or sensory-motor polyneuropathy. However, these neuropathies appear in severe and long-standing rheumatoid arthritis and are unlikely to be the presenting manifestation. This patient is young and has no clinical arthritis. Thus, the presence of rheumatoid factor is probably nonspecific.

Systemic lupus erythematosus may induce vascilitic neuropathy. This patient’s symptoms and clinical signs do not fit with the recognized criteria for the classification of lupus; furthermore, a test for anti–double-stranded (native) DNA antibodies was negative.

**Sjögren’s Syndrome**

Sjögren’s syndrome is a common cause of mononeuropathy multiplex; 62% of the patients in one series had involvement of the peripheral nervous system. Various forms of such involvement have been described, including sensory neuropathy, multiple mononeuropathy, trigeminal and multiracial neuropathy, involvement of the autonomic system, chronic inflammatory demyelinating polyneuropathy, and radiculoneuropathy. The diagnosis of primary Sjögren’s syndrome relies on the presence of symptoms of xerophthalmia and xerostomia, objective evidence of keratoconjunctivitis, evidence of chronic lymphocytic sialadenitis, and the presence of anti-Ro (SS-A) or anti-La (SS-B) antibodies. Clinical symptoms of sicca complex are not mentioned in this case, but 44% of patients have sicca symptoms as the first manifestation of Sjögren’s syndrome. Pure sensory, asymmetric chronic neuropathy may be the first manifestation of Sjögren’s syndrome and may precede the development of clinical features of the syndrome by many years. Dyck has recently suggested that “it is the immune sensory and autonomic neuropathy, which should be seen as the primary manifestation, not the Sjögren’s phenomenon.”

Finally, this patient had been taking fluoxetine for depression for 4 years. In a few cases in the literature, this drug has been suspected to induce allergic reactions; nevertheless, I have been unable to find in the literature any case of vascilitic neuropathy induced by fluoxetine.

I assume that the diagnostic procedure was a biopsy of the left sural nerve to confirm the presence of axonal lesions induced by either a necrotizing or a nonnecrotizing vasculitis. I would also suggest that a Schirmer’s test and a salivary-gland biopsy should be performed in a case such as this to rule out Sjögren’s syndrome.

**Dr. Nancy Lee Harris** (Pathology): Dr. Siao, you saw this patient in the neurology clinic. Could

---

**Table 2. Disorders Associated with Vascilitic Neuropathy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarteritis nodosa</td>
<td>(59%)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td></td>
</tr>
<tr>
<td>Churg–Strauss syndrome</td>
<td></td>
</tr>
<tr>
<td>Nonsystemic vascilitic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis (1%)</td>
<td></td>
</tr>
<tr>
<td>Connective-tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis (16%)</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus (3%)</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome (3%)</td>
<td></td>
</tr>
<tr>
<td>Overlap syndromes (7%)</td>
<td></td>
</tr>
<tr>
<td>Infectious diseases</td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td></td>
</tr>
<tr>
<td>Human T-cell lymphotrophic virus type 1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus (cryoglobulinemia)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus (polyarteritis nodosa)</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic disorders</td>
<td></td>
</tr>
</tbody>
</table>

---
you tell us your thoughts and what the diagnostic procedure was?

Dr. Peter Siao (Neurology): The history of an asymmetric onset of neuropathy made me consider a possible vasculitic neuropathy. By the time this patient was examined, her sensory deficits and electromyographic findings were symmetric. I thought that she had an underlying systemic autoimmune disorder on the basis of the serologic findings and the skin abnormalities. Biopsy specimens of the sural nerve, gastrocnemius muscle, and skin were obtained as the diagnostic procedure.

**Clinical Diagnosis**

Vasculitic multiple mononeuropathy due to connective-tissue disease.

---

**Dr. Jean-Michel Vallat’s Diagnosis**

Vasculitic multiple mononeuropathy, possibly caused by Sjögren’s syndrome or unspecified connective-tissue disease.

**Pathologic Discussion**

Dr. E. Tessa Hedley-Whyte: Examination of the nerve-biopsy specimen revealed the presence of a chronic lymphoplasmacytic infiltrate around and in the walls of many small epineurial blood vessels, both arteries and veins (Fig. 2A). No definite fibrinoid necrosis was identified, although some of the small arteries were totally occluded (Fig. 2B). This small-vessel vasculitis was also present in the muscle- and skin-biopsy specimens. The nerve it-

---

**Figure 2. Biopsy Specimen of the Sural Nerve.**

A lymphoplasmacytic infiltrate surrounds a small vein in the epineurium of the nerve (Panel A, hematoxylin and eosin). Step sections through a small epineurial artery (Panel B, hematoxylin and eosin) reveal focal involvement by the inflammatory process and smooth-muscle hypertrophy. An Epon-embedded cross section of the sural nerve (Panel C) that was 1 μm thick (toluidine blue) shows a markedly smaller number of myelinated fibers than normal (arrows). A trichrome-stained, paraffin-embedded longitudinal section (Panel D) shows a reduced number of myelinated fibers (red), an increased amount of endoneurial collagen (green), and the presence of myelin ovoids (arrows), indicating Wallerian degeneration.
self showed focal geographic fiber loss typical of a vascular injury (Fig. 2C). On closer inspection, both macrophages and myelin ovoids were present, suggesting active axonal degeneration in addition to more chronic loss of nerve fibers (Fig. 2D). Electron-microscopical examination revealed a loss of small unmyelinated as well as myelinated axons.

The muscle had marked variation in fiber size, with occasional basophilic fibers suggestive of regenerative activity and some groups of small fibers (Fig. 3). The NADH histochemical stain revealed many targetoid fibers, which are typical of denervation. The ATPase stains further confirmed the neurogenic changes by demonstrating marked fiber-type grouping and grouped atrophic fibers. In addition, so-called nuclear bags that represent the remaining sarcolemmal nuclei of an atrophic, denervated myocyte were evident.

A lip biopsy was performed 4 weeks later. A minor salivary gland was present with a mild periductal lymphoplasmacytic infiltrate that did not meet the criteria for the diagnosis of Sjögren’s disease.

This type of vasculitis is not typical of the types associated with immune-complex disease and polyarteritis nodosa.1-14 This is a lymphoplasmacytic small-vessel vasculitis, which may be associated with collagen vascular diseases or a reaction to a drug. Another consideration that arose in the analysis of the skin-biopsy specimen was the possibility of spirochetal disease, but a Warthin–Starry stain and other clinical tests for spirochetal infection were negative.15 The size of the vessels that are involved and the lack of fibrinoid necrosis rules out the diagnosis of polyarteritis nodosa. The type of inflammatory reaction and the negative test for antineutrophil cytoplasmic antibodies rule against complement-related vasculitis.

**Dr. Siao:** The patient’s primary care physician began therapy with prednisone (30 mg a day), but her symptoms worsened. I increased the dose of prednisone to 60 mg a day, and within 3 weeks her pain resolved completely. She continued to take 60 mg of prednisone a day for about 6 weeks, and then it was gradually tapered and stopped over the period of 1 year. One or 2 weeks after the prednisone was discontinued, another bout of severe pain developed in both feet, with recurrence of the rash and edema in her legs and ankles. The recurrence lasted for about 3 days, and it resolved with no treatment.

**Dr. Harris:** The patient was referred to the Rheumatology, Immunology, and Allergy Department. Dr. Costenbader, would you tell us about your thinking at the time and about the subsequent workup and management?

**Dr. Karen H. Costenbader** (Rheumatology): I was asked to see the patient in rheumatologic consultation because of her serologic abnormalities. Therapy with prednisone had already been initiated when I saw her, and her symptoms had started to abate. We performed a Schirmer’s test, which was normal, with greater than 5 mm of wetting of the tear film in 5 minutes; we also obtained a labial salivary-gland–biopsy specimen to evaluate the possibility of Sjögren’s syndrome; a lymphocytic infiltrate was present, but it did not meet the criteria for Sjögren’s syndrome.7 Given the association of Sjögren’s syndrome with hematologic cancer, a bone-marrow biopsy was performed, which was also normal. My working diagnosis was Sjögren’s syndrome with a small-vessel vasculitis and a distal sensorimotor polyneuropathy, although this case definitely would not have been classified as such by the international criteria.

With prednisone, there was gradual resolution of the rash and the neurologic symptoms. She was very eager to discontinue corticosteroids...
because of her obesity, so the prednisone was gradually tapered and discontinued. I would have considered the addition of hydroxychloroquine had symptoms recurred, but they did not. Bariatric surgery was performed 16 months after this presentation, and she lost 63.5 kg in 15 months. The neurologic symptoms gradually resolved as the axons regenerated. After the surgery, vitamin B₁₂ deficiency developed; this can result from gastric bypass, but in this patient a test for anti-intrinsic factor was positive, confirming the diagnosis of autoimmune gastritis.

Dr. Harris: Do you think her hypothyroidism is related to her connective-tissue disease?

Dr. Costenbader: Autoimmune thyroid disease is commonly associated with Sjögren's syndrome, and cases of atrophic gastritis and pernicious anemia have also been reported in association with the syndrome. That is why I considered the possibility that the B₁₂ deficiency might be autoimmune as well.

Dr. Vallar: Can you comment on the specificity of the anti-Ro antibody?

Dr. Costenbader: Anti-Ro antibody is seen in at least 70% of those who have Sjögren's syndrome and is a diagnostic criterion for the syndrome, but it is also observed in systemic lupus erythematosus, subacute cutaneous lupus erythematosus, rheumatoid arthritis, scleroderma, primary biliary cirrhosis, and other autoimmune diseases. It may also develop in persons who do not have connective-tissue disease.

Dr. Cros: Vasculitic neuropathy is classically described as asymmetric because of random involvement of individual nerves. Such asymmetry is suggestive of vasculitis when documented by the comparison of bilateral nerve-conduction studies. In advanced cases of vasculitic neuropathy, the spatial summation of multiple bilateral lesions results in a rather symmetric fiber loss and symmetric clinical syndrome. The nerve-conduction studies are then similar to those seen in a generalized, symmetric axonal neuropathy.

Dr. Costenbader: Five and a half years after the diagnosis, the patient returned to see me because of increasing symptoms of dry eyes and dry mouth during a period of about a year and recurrent edema of the lower legs for a few months. Punctal plugs had been placed in both lacrimal ducts for the treatment of dry eyes. The skin over the lower legs showed chronic hyperpigmentation but no active petechiae. She did not wish to take prednisone, so I began treatment with hydroxychloroquine. At the most recent follow-up examination, almost 6 years after the diagnosis, she felt well, with no evidence of neuropathy. I believe she does have Sjögren's syndrome.

ANATOMICAL DIAGNOSIS

Axonal neuropathy due to lymphoplasmacytic small-vessel vasculitis, associated with connective-tissue disease with features of Sjögren's syndrome, associated with autoimmune thyroiditis and autoimmune gastritis.

Dr. Cros reports receiving consulting fees from FoldRx, XLTEK, and Biogen IDEC. No other potential conflict of interest relevant to this article was reported.

REFERENCES


Copyright © 2007 Massachusetts Medical Society.
Firefighting and Death from Cardiovascular Causes

Linda Rosenstock, M.D., M.P.H., and Jorn Olsen, M.D., Ph.D.

Among the approximately 1.1 million firefighters in the United States (of whom about 70% are volunteers and 30% are paid career personnel), about 100 die each year in the line of duty. With the exception of 2001, when 344 firefighters died as a result of the events of September 11 at the World Trade Center in New York City, the number of deaths per year has stayed relatively steady, even though the number of structural fires in the United States has been steadily decreasing. Nearly half of the deaths that occur while firefighters are on duty are related to cardiovascular events, and, in this issue of the Journal, Kales et al. describe an innovative approach to improving our understanding of this risk. Their findings shed light on sudden cardiac events and their prevention, not just for this vital and revered profession, but also for those who may encounter some of the same risks at work or elsewhere.

Firefighting is a high-hazard job, and the work is at times extremely physically demanding. It involves heavy lifting and maneuvering in sometimes awkward and unstable positions while wearing heavy clothing and protective gear in a hot environment. In addition, exposure to carbon monoxide and particulate matter in the air is routine, and there is a highly variable risk of exposure to a broad array of other toxic chemicals generated from the smoke of burning materials.

It is not surprising that firefighters face an increased risk of illness and death due to cardiovascular disease during periods of intense physical and even psychological stress at work. However, numerous mortality studies, some of which have shown evidence of an increased risk of some cancers (e.g., brain tumors and leukemia) and nonmalignant respiratory diseases, have not shown any consistent evidence of an increased risk of death from cardiovascular disease. Why not? First, firefighters as a group quintessentially show a “healthy worker effect.” That is, by the very nature of their generally high levels of fitness and health (mandated for all entry-level career firefighters and sometimes required for volunteers), they would be expected to have a lower risk of death (particularly due to cardiac events) than the general population. And they do — on average, a firefighter’s risk of dying from coronary heart disease is about 90% (standardized mortality ratio, 0.9) that of others in the general population. Thus, firefighters overall may not have an excess risk of dying from heart disease, or if they do, the excess risk is small. There is some suggestion of the latter, since many working industrial populations have an even lower risk of dying from coronary heart disease (standardized mortality ratio, 0.8) than firefighters as compared with the general population. One would expect firefighters to fare at least as well. Second, the overall mortality remains a definitive but crude measure of the relationship between exposure hazards and health, and most importantly, of the benefits of prevention. So, even if firefighters have little or no excess risk of death due to cardiovascular disease, there are reasons to both understand and try to prevent the cardiovascular events that do occur, including those that occur on the job.

Kales and colleagues build on the observation that cardiovascular events that occur while firefighters are on duty appear to cluster around specific activities (e.g., fire suppression and emergency response) and on their own earlier case-control study suggesting that specific duties are associated with deaths due to coronary heart disease. In this study, they reviewed data on all deaths that occurred while firefighters were on
duty over an 11-year period (1144 deaths). With the use of all available records, they independently classified these deaths according to cause and firefighting duty at the time of death. What is most compelling about this study is their effort to quantify the excess risk of dying during specific firefighting duties. They calculated odds ratios for death by comparing five specific emergency duties (e.g., fire suppression and alarm response) with nonemergency duties. These comparisons were based on three separate sources of data indicating how much time firefighters typically spend in each of these activities. Measures of the distribution of duty time are variable and imprecise, but the findings of Kales et al. are sufficiently large (e.g., the odds of death from coronary heart disease during fire suppression were 10 to 100 times as high as during nonemergency duties) to overcome concern that the direction of the results is wrong because of misclassification errors. They overcome at least part of the effect of the selection of healthy workers by making comparisons among groups of firefighters. In fact, the selection process according to health that may keep firefighters out of emergency duties without keeping them out of work may, if anything, lead to an underestimation of their odds of death from coronary heart disease.

The authors have not set out to show nor have they shown an overall increased risk of death from coronary heart disease among firefighters. However, they have convincingly shown that such an event is far more likely to occur during specific duties — dramatically so during fire suppression, but also during alarm response and return and physical training. When healthy workers die at work of “natural” causes, their deaths are predominantly from sudden cardiac events. The finding that these events might cluster around or be triggered by specific duties is also not new, so this pattern of increased deaths during emergency duties should not surprise us but should inform us.

Numerous studies over several decades have shown the role of heavy exertion — from snow shoveling to recreational exercise — in triggering sudden myocardial events and the protective role of regular exercise in mitigating them. This paradox — that regular exertion is good even though an episode may trigger an adverse event — is not a reason to dismiss these findings, but it should call for caution. Relative measures of association may be high because the incidence rate in the risk period (emergency situations) is high or because the incidence rate in the reference period (nonemergency situations) is low, or both. A physical fitness program may lower the incidence rate during the reference period (nonemergency duties) more than during the risk period, and thus it may increase the odds ratios for death during the risk period, even in a situation in which the overall mortality due to cardiovascular diseases is reduced. The evaluation of a preventive program — a step that naturally follows these findings — should take the overall mortality into consideration.

Firefighters have episodic exposure to extreme levels of physical exertion, and they face occupational hazards that may add to or amplify their risk of death due to cardiovascular causes. These hazards include chemicals (carbon monoxide, fine particulate matter, and other cardiac toxins) and thermal and emotional stress. Moreover, although there has been improvement over time in respiratory protection during active fire suppression, such protection may be abandoned during overhaul (the period immediately after fire suppression), when exposure to fine particulate matter (which has been shown to increase the risk of a sudden myocardial infarction) and other toxic chemicals may be particularly high. Firefighters enter the workforce particularly healthy, but they do not necessarily maintain that attribute over time. There is ample evidence that firefighters are not immune to the hazards of overeating and inadequate regular exercise. For a variety of reasons, including not only the nature of their work but also disability plans and presumptive legislation about work-related health conditions, career firefighters rarely serve as active firefighters after 50 years of age. Volunteer firefighters, in contrast, often serve with fewer entry and ongoing fitness requirements, but they serve until an older age, when most cardiac events occur. In 2005, of 115 deaths that occurred during on-duty activities, 81 (70%) occurred among volunteer firefighters.11

The implications of this study for firefighters are clear. Modifiable risk factors, whether or not they are related to occupation, should be aggressively addressed. We concur with the recommendations of the National Institute for Occupational Safety and Health arising from the Fire Fighter Fatality Investigation and Prevention Programs. First, fire departments should provide mandatory
The innate immune system is a phylogenetically ancient defense mechanism, which evolved to recognize and respond to non-self components, such as pathogens. It is composed of innate and adaptive components. The innate immune system provides immediate, non-specific protection against infections, whereas the adaptive immune system develops a specific response after initial exposure to an antigen, allowing for an immune memory to be established.

Recently, the role of the innate immune system in regulating the adaptive immune response has become increasingly recognized. A key component of this regulation is the involvement of regulatory T cells (Tregs), which play a crucial role in preventing autoimmunity by suppressing the activation and proliferation of autoreactive T cells.

Autoimmunity is the reflection of a basic problem confronting all living organisms — how to defend against foreign invasion while maintaining control of the defending forces. The B-cell and T-cell branches of the immune system can exhibit remarkable specificity for invading microorganisms, can adapt to changing threats, and can provide for long-term immunologic memory. At the same time, autoreactivity of B cells and T cells is present in all normal persons, and a complex set of regulatory mechanisms is required to prevent overt destruction of tissue through autoimmunity.

Our current understanding of autoimmunity rests on our knowledge of the immune system. Over the past 50 years, scientists have concentrated on the adaptive immune system, with a major focus on the diversity and specificity of autoantibodies and the ways in which T cells are regulated. Recently, however, high-throughput genetic and genomic studies have begun to focus attention on the innate immune mechanisms in autoimmunity. The report by Jin et al. in this issue of the Journal is one such study.

The innate immune system is a phylogenetical-
Catheter-Related Bloodstream Infections

TO THE EDITOR: The report by Pronovost et al. (Dec. 28 issue) on an intervention to decrease catheter-related bloodstream infections in the intensive care unit (ICU) would have been more convincing had the authors substantiated that the decline in the rate of these infections was matched by a decline in the number of positive blood cultures or in the use of antibiotics. A culture of safety in which the rates of catheter-related bloodstream infections were an explicit benchmark of quality could have biased clinicians against attributing positive blood cultures to such infections. The seemingly straightforward criteria for catheter-related bloodstream infections of the National Nosocomial Infections Surveillance (NNIS) system of the Centers for Disease Control and Prevention are deceptively ambiguous. For example, even though coagulase-negative staphylococcus is the most common cause of catheter-related bloodstream infections and the most common contaminant of blood cultures, the NNIS does not define a method to distinguish between the two possibilities. Clinical practice — whether positive blood cultures are repeated or automatically trigger treatment — affects the subsequent adjudication of the culture result as indicating contamination or a true bloodstream infection. Furthermore, attributing gram-negative bloodstream infections or candidemia to a catheter, when they occur in association with other potential sources of infection, is inherently subjective. The reduction in the rate of catheter-related bloodstream infections reported by Pronovost and colleagues may have been due to a collective bias against attributing bacteremia to catheters.

Elizabeth R. Jenny-Avital, M.D.
Jacobi Medical Center
Bronx, NY 10461
jennyavita@earthlink.net


TO THE EDITOR: In the study reported by Pronovost and colleagues, the handling of missing data is of concern. The scale of the missing data is difficult to determine. Complete data were obtained for only 53 of the 108 ICUs. A potential maximum of 324 ICU-months of data exist for each 3-month study period for these 108 ICUs. However, the ICU-months of data actually obtained for each 3-month period are not included in Table 3 of the article. Another report on this cohort by the same group documents 193 ICU-months of data obtained for the crucial postintervention period from 0 to 3 months. This value represents only 60% of the potential ICU-months of data. Calculations of low infection rates based on incomplete data are worrying. Subgroup analysis of the 49% of ICUs with complete data does not eliminate the prob-
lem. The paucity of information regarding the scale of the missing data affects the appraisal of the potential bias and internal validity of the study.

Mark R. Daley, B.Med.
Royal Prince Alfred Hospital
Sydney 2050, Australia
mark.daley@email.cs.nsw.gov.au


THE AUTHORS REPLY: Large-scale quality-improvement studies are challenging to conduct, and they receive substantially less funding than randomized trials of comparable size. In our study, staff in the 103 participating ICUs did not receive funding to support data collection. Thus, research intended to improve the quality of care must carefully balance the collection of data that are scientifically sound, feasible to collect, and focused on the specific aims of the study.¹

We chose to limit the quantity but not the quality of data collected. It was not feasible to collect data on the organisms cultured or the antibiotics used, as Jenny-Avital suggests. We used standardized though somewhat subjective surveillance rather than clinical definitions of catheter-related bloodstream infections.² However, we believe that potential bias was minimized, because infection-control practitioners who were independent of the ICU teams performed all measurements in their routine manner.

Daley’s comments highlight the importance of minimizing and reporting missing data in quality-improvement studies. We made great efforts to minimize information bias and missing data. To garner participation, the ICUs were permitted to choose when to implement the study intervention. The ICUs provided data at varying times, depending on when they joined the project and started data collection. Forty hospitals implemented the intervention immediately on initiation of the study, which precluded the collection of baseline data. Thus, data were not missing for these ICUs. The results of our sensitivity analysis, which excluded these hospitals, were similar to those of the primary analysis. During the period when each ICU reported data, 30 of 103 ICUs (29%) did not report completely, resulting in missing data for 113 of 2216 potential ICU-months (5%). This level of missing data represents an improvement over a preliminary report conducted before all ICUs had reported their data.³

The need to improve the quality of care is too great and the resources devoted to this effort are too limited to be uncertain about whether quality-improvement interventions actually work. Quality-improvement studies will require more rigor and resources. Since funding for such research has lagged behind funding for basic and clinical research by a factor of more than 100, additional funding will be needed to achieve the goal of improved care. Though our study has helped to advance the science of rigorous quality-improvement studies, more work is needed.

Peter J. Pronovost, M.D., Ph.D.
Dale M. Needham, M.D., Ph.D.
Sean Berenholtz, M.D.
Johns Hopkins University
Baltimore, MD 21205


1268

Adjuvant Therapy for Early Breast Cancer

TO THE EDITOR: Poole et al. (Nov. 2 issue)¹ conclude that patients with breast cancer benefit from the addition of four cycles of epirubicin to cyclophosphamide, methotrexate, and fluorouracil (CMF) in the adjuvant setting. In contrast to previously published data, the dose intensity of CMF did not seem to play a role.

Patients with breast cancer were included in the study irrespective of age, nodal status, or estrogen-receptor status. The degree of aggressiveness of the chemotherapy was not tailored to the risk of recurrence. The role of tamoxifen could not be evaluated because for many patients, neither hormone-receptor status nor tamoxifen scheduling
Peginterferon and Ribavirin for Hepatitis C

TO THE EDITOR: In their review of peginterferon and ribavirin for the treatment of hepatitis C, Hoofnagle and Seeff (Dec. 7 issue) do not include data on the association between the consumption of alcohol and both treatment response and disease progression. Level-one evidence of the deleterious effects of alcohol on hepatitis C virus (HCV) RNA levels, on the response to treatment, and on disease progression led the National Institutes of Health and the American Gastroenterological Association to issue position statements advising that “abstinence should be recommended before and during antiviral treatment...” [since] even moderate alcohol consumption can have a deleterious effect on the progression of liver disease in patients with chronic hepatitis C. Alcohol consumption may explain the marked dichotomy in progression rates that cannot be explained by the HCV genotype. Knowledge of alcohol’s effects on disease progression should provide reassurance to patients who want to alter the outcome of their disease, particularly since data for nondrinkers show a more benign course than the authors suggest. At a population level, targeting alcohol consumption may effectively reduce the excess deaths the authors anticipate.

Anne E. Duggan, M.D.
John Hunter Hospital
Newcastle 2310, Australia
anne.duggan@hnehealth.nsw.gov.au

John M. Duggan, M.D.
University of Newcastle
Newcastle 2308, Australia

3. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006;130:231-64.


TO THE EDITOR: The article by Hoofnagle and Seeff would have been more informative if it had indicated the relevance of insulin resistance in chronic hepatitis C. Insulin resistance induces interferon resistance by causing the progression of hepatic fibrosis. The mechanism by which insulin resistance promotes the progression of fibrosis includes steatosis, hyperleptinemia, increased production of tumor necrosis factor α, and impaired expression of peroxisome-proliferator–activated receptor γ. Insulin resistance has been found to be a common denominator in patients with difficult-to-treat hepatitis C (including those with the risk factors of cirrhosis, obesity, coinfection with the human immunodeficiency virus [HIV], and black race) and is independently associated with a decreased rate of response to peginterferon plus ribavirin. Whether the addition of insulin-sensitizing agents will improve the response rate remains to be determined.

Nimer Assy, M.D.
Oscaar Embon, M.D.
Sieff Hospital
13100 Safed, Israel
assy.n@ziv.health.gov.il


TO THE EDITOR: Hoofnagle and Seeff mention that autoimmune diseases are rare side effects of therapy with interferon alfa and ribavirin for hepatitis C, but they do not mention these conditions as possible contraindications. However, the risk
that potentially severe and even life-threatening diseases such as myasthenia gravis will develop or become worse should be considered. The development of myasthenia gravis in association with interferon alfa therapy has been reported.\(^1\)\(^2\)\(^3\) Moreover, worsening of myasthenia gravis can occur in patients under treatment, as we recently observed. A 32-year-old man with myasthenia gravis that was well controlled after thymectomy and with prednisone treatment received peginterferon alfa-2a (at a dose of 80 \(\mu\)g weekly) and ribavirin (800 mg daily) for chronic hepatitis C (genotype 2; serum HCV RNA level, \(>500,000\) IU per milliliter), with a good response (undetectable serum HCV RNA). After 6 months of treatment, severe worsening of myasthenia gravis occurred, with profound generalized weakness and life-threatening bulbar symptoms that required discontinuation of interferon alfa and ribavirin in addition to treatment with plasma exchange, high-dose prednisone, and azathioprine. We think that serious autoimmune diseases should be regarded as important contraindications to peginterferon and ribavirin therapy.

Amelia Evoli, M.D.
Serenella Servidei, M.D.
Catholic University
00168 Rome, Italy
a.evoli@rm.unicatt.it

TO THE EDITOR: In Table 2 of their article, Hoofnagle and Seeff list the major side effects of ribavirin and peginterferon. Pancreatitis is not included in the list. These agents can cause rare cases of drug-induced pancreatitis, with an incidence of 0.4% in treated patients.\(^1\) Biour et al. report on many such cases, with at least one of them recurring during rechallenge.\(^2\) The severity of the toxic effect of these drugs ranges from transiently elevated blood lipase and amylase levels to fatal pancreatitis. The interval between the initiation of therapy and the development of symptoms of pancreatitis ranges from 2 days to 8 months. The exact mechanism of the pancreatotoxicity of interferon has not been elucidated; ribavirin may induce pancreatitis through its effects on mitochondrial function.\(^3\)

Hoofnagle and Seeff note that patients should be fully informed about potential side effects of peginterferon and ribavirin. Pancreatitis should be considered for inclusion in the list of side effects, especially in patients who are coinfected with HIV, in whom antiviral drugs can also lead to acute pancreatitis.\(^4\)

Chaker Ben Salem, M.D.
Houssem Hmouda, M.D.
Kamel Bouraoui, M.D.
Faculty of Medicine of Sousse
4002 Sousse, Tunisia
chaker_doc@yahoo.fr

Hoofnagle and Seeff: there has been no randomized study that would confirm the clinical benefit of pharmacotherapy in patients with HCV infection. The history of medicine is full of examples of surrogate therapeutic end points that were not validated when appropriate clinical results were evaluated. Lowering the viral load is not a valuable goal in itself but rather a means to an end. When the pertinent results are available, using peginterferon and ribavirin in HCV infection may turn out to be similar to suppressing premature ventricular beats with class IC antiarrhythmic drugs after myocardial infarction or, in contrast, preventing cardiovascular events and reducing mortality by lowering blood pressure. It should be clearly stated that we still do not know the answer.

Michel Abramowicz, M.D.
Cavell Medical Institute
1180 Brussels, Belgium
mabra@skeynet.be


THE AUTHORS REPLY: All the correspondents raise important issues that might not have been adequately addressed in the space allocated for our review. More complete discussions of regimens, indications, side effects, implications, and outcomes of therapy are available from the published guidelines of two academic societies.

We fully agree with Duggan and Duggan that alcohol use may worsen the course of hepatitis C and decrease response rates to therapy. Patients with any liver disease should restrict their alcohol intake, and those receiving peginterferon should be advised to abstain during treatment. As pointed out by Assy and Embon, insulin resistance is associated with a decreased rate of response to antiviral therapy. In a recent study, sustained virologic responses to combination therapy in patients with genotype 1 occurred in 36% of patients without insulin resistance, as compared with 49% of those without insulin resistance. Nevertheless, sustained responses can be achieved in patients with diabetes, and they should not be denied treatment.

Evoli and Servidei and Salem et al. mention rare but important serious adverse events. Autoimmune disease is a relative contraindication to antiviral therapy for hepatitis C, and patients with potentially life-threatening autoimmune conditions should not receive peginterferon without carefully weighing the risks and benefits. Leiner recommends the use of erythropoietin to maintain hemoglobin levels during therapy. Erythropoietin can raise blood counts and alleviate symptoms of anemia during treatment. However, its use has not been shown to be effective in increasing response rates, and trials that documented response rates were done using dose reductions rather than growth factors. Erythropoietin also adds greatly to the cost of therapy and is not without side effects and thus should not be used routinely.

Finally, Abramowicz mentions that recommendations for hepatitis C therapy are based on the use of a surrogate end point (a sustained virologic response) rather than improvement in survival. Although this observation is correct, it is not appropriate to compare long-term eradication of a virus as an end point with mere suppression of a symptom or sign. A sustained virologic response, as marked by the absence of detectable serum HCV RNA 6 months after therapy, is associated with a durable absence of virus and absence of disease progression. Thus, it probably represents a cure rather than mere suppression of the viral infection — a surrogate but convincing end point.

Jay H. Hoofnagle, M.D.
Leonard B. Seeff, M.D.
National Institutes of Health
Bethesda, MD 20892
hoofnaglej@extra.niddk.nih.gov

2. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006;130:231-64.
Clinical Diagnostic Reasoning

To the Editor: Bowen’s review of educational strategies that can be used to promote clinical diagnostic reasoning (Nov. 23 issue) does not sufficiently emphasize the concept of premature closure. Acceptance of a diagnosis before sufficient verification has occurred and failure to consider plausible alternatives once a diagnosis has been reached are common causes of diagnostic error and can occur at any level of training. One possible effect of anchoring — the inability to assimilate subsequent or evolving data — is a particularly important contributing factor in premature closure and may lead to faulty synthesis of information. The risk of premature closure may be greatest when learners are pressed for time or expected to have a level of expertise they have not yet attained. Premature closure may be just as likely to result from an “unlucky” adherence to an illness script as from gaps in knowledge. Clinical educators should encourage learners to continuously integrate new information into the decision-making process.

Phillip D. Levy, M.D., M.P.H.
Robert L. Sherwin, M.D.
Gloria J. Kuhn, D.O., Ph.D.
Wayne State University
Detroit, MI 48201
phillevy_2000@yahoo.com


To the Editor: We agree with Bowen that clinical educators need to understand and analyze the varied diagnostic reasoning strategies applied by novices such as medical students to help them improve their performance. However, the diagnostic reasoning schema in Figure 1 of the article appears to oversimplify this process. Because of minimal clinical experience, the novice generally has poorly formed illness scripts and will often generate hypotheses using a pathophysiological, probabilistic, or rule-based representation of the problem (skills acquired during problem- or case-based learning). Such hypotheses are often more numerous, broader, and less accurate than those of experts and must be refined by the novice during the interview with the patient and during the physical examination, while the novice looks for the specific symptoms, risk factors, and signs that allow for iterative reweighting of the clinical diagnostic possibilities. We believe that acknowledgment of alternative bases for hypothesis generation and of the iterative nature of hypothesis refinement will further assist educators in improving students’ diagnostic reasoning strategies.

Geoffrey J. McColl, M.B., B.S., Ph.D.
Royal Melbourne Hospital
Parkville 3050, Australia
gjmccoll@unimelb.edu.au

Michele A. Groves, Ph.D.
Griffith University
Brisbane 9726, Australia


To the Editor: We use the technique outlined by Bowen in our own teaching. However, Bowen does not address the possibility of an incorrect diagnosis obtained through valid diagnostic reasoning. The clinical teacher should allow for this possibility as part of the case presentation. Correcting an incorrect diagnosis is a critical skill that requires the identification of alternative steps in the development of a representation of the problem and reevaluation of the differential diagnosis to include other conditions that may have features similar to those of the case under consideration.

Thus, Figure 1 of the article should have included a final step in which diagnostic reasoning leads to either a correct or an incorrect diagnosis. When a diagnosis is incorrect, the reasoning process expands to include the pertinent data for the missed diagnosis, leading the learner to improve the problem representation or illness script.

Melvin R. Echols, M.D.
Katherine S. Garman, M.D.
Kenneth W. Lyles, M.D.
Duke University Medical Center
Durham, NC 27710
melvin.echols@duke.edu
To the Editor: Bowen’s article excludes consideration of the fact that the diagnostic thought process depends on the situation. In some situations (e.g., a medical emergency or a one-time consultation), it is more parsimonious to use a reverse paradigm: identify and rule out (and treat) the most urgent or life- or health-threatening possibilities, and carry this approach through multiple iterations over time. In other words, instead of initially seeking the “right” diagnosis through an elaborate diagnostic process, one seeks to avoid the “wrong” one.

Ed Marsh, M.D.
14 Old England Rd.
Ipswich, MA 01938
ed.marsh@whsc.com

To the Editor: Bowen describes the analytic portion of diagnostic reasoning primarily as a discrete step occurring between the acquisition of data and the determination of the most probable diagnosis. In our experience, diagnostic reasoning is almost invariably a dynamic, iterative process. The probabilities of several competing diagnoses are assessed and then concurrently refined and amended on the basis of further inquiry.

Clinical diagnostic reasoning should be considered a tool to maximize the quality of care in a cost-effective manner. The most probable diagnosis is frequently not the most important diagnostic consideration in achieving this goal. Although gout was the most probable diagnosis in the case presented in Bowen’s article, the expert resident might have been well advised to address the less likely but more worrisome possibility of septic arthritis by further examining the history of episodes.

Bowen’s endorsement of cognitive tools such as illness scripts and anchoring prototypes warrants qualification. These are certainly essential assets in the diagnostician’s armamentarium. However, they can also easily lead to fallacious reasoning, occasionally with disastrous consequences.1,2

Paul D. Grossman, M.D.
Michael A. Rodriguez, M.D., M.P.H.
University of California, Los Angeles
Los Angeles, CA 90095


To the Editor: Bowen addresses the challenge of how educators can facilitate learning as their trainees acquire diagnostic reasoning skills. The primacy of information-gathering skills was recently illustrated when our diabetes consulting service was asked to see an elderly man with a long history of diabetes mellitus. The clinical information obtained was that despite twice-daily administration of premixed insulin, the capillary glucose readings performed at home were often in the range of 20 mmol per liter. At the bedside, I asked the patient how much insulin he took in the morning. His response was most instructive: “I give myself 40 units when my sugar reading is high.” My next question was what he did when his sugar reading was not high. He replied that he skipped his dose, thereby revealing the source of the problem. My trainee learned that determining that something does not occur is as important as determining that it does occur.

Alexander Sorisky, M.D.
University of Ottawa
Ottawa, ON K1Y 4E9, Canada
asorisky@ohri.ca

To the Author Replies: I agree with Grossman and Rodriguez that diagnostic reasoning is “a dynamic” process. However, illness scripts, anchoring prototypes, and pattern recognition are descriptions of mental processes, not diagnostic tools, as these authors suggest. McColl and Groves note that novices may tend to use a pathophysiological strategy for reasoning more often than they use pattern recognition. Neither strategy is likely to be used entirely in isolation. Both are conceptual models for the reasoning process. Similarly, Echols and colleagues note that coming to the wrong conclusion is the last stage of diagnosis, suggesting a change in Figure 1 of our article. The figure is not meant to represent an external view of a teacher observing a learner make a correct or incorrect diagnosis. Rather, it is one of many possible schematics for the steps clinicians are likely to take in their minds during the reasoning process.

Clinicians miss diagnoses for many reasons,1 premature closure among them, as Levy and colleagues point out. Clinical teachers must recognize that learners may come to premature closure and must probe learners’ thinking and interview and examine patients directly when there is sufficient doubt about the accuracy of a diagnosis. All cli-
Clinicians are at risk for premature closure, whether or not they are trainees, when experience with the clinical problem at hand is lacking or when the clinician is pressed for time. With increasing age and experience, physicians are more, not less, likely to go with their first hypothesis. This increasing reliance on early data does not necessarily result in poorer diagnosis. For complex, ill-defined clinical problems, new diagnostic considerations can be triggered at any point, and new questioning strategies emerge as a result. Once the clinician is satisfied, a diagnosis is rendered with more or less certainty about the conclusion. If the clinician is not satisfied, the reasoning process continues.

Diagnostic reasoning depends on the context. The context includes “the situation,” as Marsh describes. Clinical teachers also teach weighting of the diagnostic possibilities, “ruling out” must-not-miss diagnoses while continuing to search for the correct diagnosis. The situation can also influence which diagnoses learners consider. For example, learners who can readily recognize community-acquired pneumonia in hospitalized patients may not recognize the same presentation in the outpatient clinic until the teacher points it out.

Sorisky reminds us of the importance of role modeling. From experience, we build in memory repositories of questioning strategies that work particularly well and those that fail us. Sorisky’s learner might benefit from a deliberate discussion about interviewing strategies. One cannot assume that the clinical teacher’s “aha” is the same as the learner’s.

Judith L. Bowen, M.D.
Oregon Health and Science University
Portland, OR 97239
bowenj@ohsu.edu


Acromegaly

To the Editor: In Melmed’s otherwise excellent review of acromegaly (Dec. 14 issue), the clinical myth that headache is due to a local tumor effect is perpetuated in Table 1. It has been established in a prospective study that the size of a pituitary tumor does not determine the headache presentation. Moreover, the phenotype of headache presentations is wide, including migraine and the trigeminal autonomic cephalalgias, particularly cluster headache. An important clinical lesson in this context is the overrepresentation of cluster-headache–like presentations in patients with acromegaly and thus the higher yield in searching for pituitary-tumor–related disease when one sees atypical headache presentations.

Peter J. Goadsby, M.D., Ph.D.
University of California at San Francisco
San Francisco, CA 94143-0114
goadsbyp@neurology.ucsf.edu


To the Editor: Melmed does not emphasize the unique and highly characteristic visual abnormalities in patients with acromegaly. Nearly 20% of patients with this condition have some sort of visual-field abnormality. Most of these defects occur because of compression of the optic chiasm by the enlarged pituitary. Bilateral visual defects are more common than unilateral defects, with bitemporal hemianopsia and superior bitemporal quadrantanopsia being the most commonly detected defects. Other, less common defects include unilateral temporal hemianopsia, superotemporal quadrantanopsia, and inferotemporal quadrantanopsia. The earliest visual-field defect is usually in the superior temporal quadrant. In general, patients with visual-field defects tend to have higher levels of growth hormone and are usually younger than patients without such defects. Also, larger
in addition to those mentioned in the older study cited by Haddy. None of these mechanisms have been definitely proved, and treatment of hypertension in patients with acromegaly should follow standard guidelines.

Shlomo Melmed, M.D.
Cedars-Sinai Medical Center
Los Angeles, CA 90048
melmed@cshs.org

T o T h e E d i t o r : Hoffmann and colleagues (Dec. 21 issue) report on the use of statins and the outcome of immunotherapy with bacille Calmette–Guérin (BCG) vaccine in 84 patients with superficial bladder cancer. The authors report that over a median follow-up period of 46 months, 19 patients who were using statins had an increased risk of “more aggressive” disease.

We analyzed outcomes in a cohort of 156 patients (median follow-up, 56 months) who received BCG; 39 used statins during the treatment, and 117 did not. We found no significant differences between the two groups in the incidence of tumor recurrence (59% in both groups, P=0.80), the incidence of tumor progression (30% and 28%, respectively; P=0.57), or the number of deaths. Since the proposed immunomodulatory role of statins might be more relevant in patients receiving maintenance therapy, we performed a subgroup analysis of data from patients receiving only induction BCG therapy, as compared with those receiving BCG as both induction and maintenance therapy. We still found no effect of the use of statins. Our data do not support the authors’ conclusion that “discontinuation of statin therapy during BCG immunotherapy might improve the clinical outcome,” especially given the risk of adverse cardiac events associated with withdrawal of statins.

Ashish M. Kamat, M.D.
Xifeng Wu, Ph.D.
M.D. Anderson Cancer Center
Houston, TX 77030
akamat@mdanderson.org


T o T h e E d i t o r : Hoffmann et al. state that the groups they studied were “similar.” However, a multivariate logistic-regression analysis with adjustment for well-established risk factors in patients with bladder cancer would have better characterized the real contribution of statins in their patients.

Anna Orsola, M.D.
Lluís Cecchini, M.D.
Hospital Vall d’Hebron
08035 Barcelona, Spain
annaorsola@hotmail.com

Joaquim Bellmunt, M.D.
Hospital de Mar
08003 Barcelona, Spain

T h e A u t h o r s R e p l y : Although Kamat and Wu did not find significant differences between patients using statins and those not using statins in a study similar to ours, we believe that the statins can attenuate the immune response of type 1 helper cytokines that is involved in the action of BCG.
Orsola and colleagues question our statistical analyses. We were unable to present all our data in our letter to the editor. When patients were enrolled, we assessed age, date of diagnosis of cancer, tumor grade and pathological T-stage category after transurethral resectioning, presence or absence of concomitant carcinoma in situ, number of recurrences during the first year after diagnosis and total number of recurrences, pathological T-stage progression, time to cystectomy, and time to the appearance of distant metastases. We compared the outcomes for patients who were taking statins during BCG immunotherapy and those who were not by using univariate and multivariate logistic-regression analyses that included age and cholesterol level but that were not adjusted for the specific statin, given the small number of patients in the various statin groups. The adjusted odds ratio for older age and progression to more aggressive disease in the statin group was 5.02 (95% confidence interval [CI], 1.66 to 5.02; P = 0.004), and the adjusted odds ratio for older age and the need for cystectomy was 4.79 (95% CI, 1.48 to 4.79; P = 0.008).

Paul Hoffmann, M.D.
Jules Bordet Institute
1000 Brussels, Belgium
pahoffma@ulb.ac.be
Thierry Roumeguère, M.D.
Erasme Hospital
1070 Brussels, Belgium
Roland van Velthoven, M.D., Ph.D.
Jules Bordet Institute
1000 Brussels, Belgium


Medical Mystery — Paradoxical Embolism

TO THE EDITOR: With regard to Mathura and Jampol’s answer to the Medical Mystery about the visual-field defect (Dec. 7 issue),¹ we would like to raise a small point about the path taken by the paradoxical embolism to a left retinal artery branch in the patient with Eisenmenger’s syndrome associated with ventriculoseptal defect and a patent ductus arteriosus. Although the embolism is attributed to the clot passing through the patent ductus arteriosus, it is more likely that it passed through the septal defect. The ductus enters the aorta distal to the left common carotid artery and subclavian artery. A clot passing through the ductus would be more likely to travel downstream to the thoracic and abdominal aortas than upstream to the left common carotid artery, whereas a clot passing from right to left across the septum would flow downstream through the ascending and transverse portions of the aorta into the left common carotid artery.

Fred Mishkin, M.D.
Harbor–UCLA Medical Center
Torrance, CA 9009-2910
mishkin@schlossbros.com
Marvin Mishkin, M.D.
209 S. Second St.
Elkhart, IN 46516


Neurocysticercosis Uncovered by Single-Dose Albendazole

TO THE EDITOR: A 23-year-old woman noticed “worms” (small, flat, ribbonlike material) in her stool. She self-medicatted with a single 400-mg dose of albendazole. The next day, more parasitic material was eliminated in her feces. By noon she had malaise, mild headache, feverishness, episodic left-sided facial numbness, and weakness of the left arm. That night she was awakened by a headache with profuse sweating, which was partially responsive to analgesics. The following morning she had vomiting and an episode of disorientation, with abnormal tonic-clonic movements of her left hand and arm. On arrival at our center, she reported headache; she was disoriented and was having partial seizures, which secondarily generalized. She had no history of trauma or al-
Assessing Race, Ethnicity, and Gender in Health

A fair society promises equality in the pursuit of happiness. Yet society — often unwittingly — withholds that promise. Assessing Race, Ethnicity, and Gender in Health is a study of how different nations have categorized their populations by race, ethnicity, and gender. Sana Loue, a professor of bioethics, epidemiology, and law, makes the case that the categories nations use in their censuses, birth certificates, and many other records are not naturally occurring categories but are socially constructed, often shifting over time and reflecting current prejudices. In many countries, the census has focused on skin color, with constructs intended to distinguish those who are white from those who are not white. Until 1960 in the United States, it was the census taker — not the head of household, as is the case today — who determined a person’s race, using constructs such as “mulatto,” “quadroon,” or “octoroon,” or even “a single drop of black blood.” Inevitably, the ways in which societies label people influence the ways in which social policies are shaped.

With regard to human behavior, Loue develops the thesis that gender, like race and ethnicity, is a complex subject, one that cannot be understood only through the simple dichotomy of “It’s a boy” or “It’s a girl.” How little we understand gender diversity was the subject of a front-page article in the New York Times (December 2, 2006) about children who do not conform to gender norms. Accompanying the article was an idyllic image of two young girls skipping away, their long hair swinging in the wind. But the caption read that one of the children was a 5-year-old boy who had begun identifying as a girl after turning 3 years old. Parents who were interviewed for the article struggled to understand why their children insisted on cross-dressing and on other behaviors not typical for their sex and how these children could be protected from what they perceived as a hostile world. Pediatric experts have noted that such children are at risk for depression, suicidal feelings, and self-mutilation.

Loue summarizes a large body of literature on human sexuality and gender identity, including hermaphroditism, sexual orientation, and transsexual and transgender behaviors. A few decades ago, surgical correction was recommended for babies born with genitalia that appeared ambiguous. This recommendation was based on the theory that nurture shapes a child’s identification with the male or female sex and that children will take on the identity of the gender in which they are raised. The flaws in this theory become evident as the complexities of human biology, including the interplay of morphology, chromosomes, and hormones, are reviewed. Implicit throughout the book is the idea that sexual diversity and gender diversity are naturally occurring phenomena. There is no consensus on whether certain behaviors are deviant. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), transsexuality is included, whereas homosexuality is no longer included. Pediatricians, educators, mental health professionals, and parents who are concerned about these issues will find this book informative.

The author is to be especially commended for bringing together a number of resources for improving health and health care research. One chapter draws on published studies on topics such as diabetes and breast cancer to assess whether the variables of race, ethnicity, and sex used were sufficient to warrant the conclusions. Another chapter identifies several instruments designed by experts to capture the racial, ethnic, and gender diversity in a population under study. Throughout, hundreds of relevant references are provided.

Because this slim volume (only 158 pages) has so much to offer, I hesitate to find fault with the fact that it does not include a chapter on assessing socioeconomic status and health. Given that only a few biologic factors have been found to explain disparities in health, a question arises: Will improved race and ethnicity data be sufficient for studying health outcomes and health care, or is
it necessary to take variables such as income and education into account? Perhaps this question calls for an expanded edition of this fine book.

Marian E. Gornick
Centers for Medicare and Medicaid Services (Retired)
Baltimore, MD 21244
mgornick@aol.com

SKIN: A NATURAL HISTORY

This book is a rich mix of just about everything you would want to know about the necessary and complex covering of your body. Nina Jablonski writes not only as an anthropologist but also as an ethologist, comparative biologist, and psychologist. She weaves a vivid, compelling history, which at times is intertwined with social discourse (skin color and racism) and advice (skin and sun protection).

Jablonski argues that the skin of present-day humans is not vastly different from that of the earliest vertebrates in its function: it is protective, sensitive, and capable of interactions with the outside environment. The skin of primitive vertebrates, as well as that of modern humans, contains a multiplicity of cell types, which Jablonski describes in detail. Structural elements are also detailed. One example is keratin, the protein found in the external layer of the epidermis that functions as a mechanical reinforcement and is common to adult amphibians, reptiles, birds, and mammals. Keratin can also serve in the tough appendages of the skin, as feathers and claws in birds and as hair and nails in mammals.

From a psychological viewpoint, Jablonski discusses how our skin represents the wholeness of the self. This concept is highlighted by the ways in which we use our skin as a canvas for self-expression, identity, and individualism through body art (including tattoos, piercings, and scarification) and cosmetics. Being deprived of human touch can have devastating psychological and developmental effects on young children. Verbal expressions and figures of speech using the word “skin” have the power to convey intensely personal feelings and strong sentiments about identity (e.g., “I nearly jumped out of my skin” and “She has an incredibly thin skin”). Finally, sexuality and skin are enmeshed, as Jablonski writes: “The skin is the largest sexual organ of the human body. . . . Much of the pleasure of sexual intimacy comes from the exquisite expectation of touch and the delight and relief of skin-to-skin contact with another person, before, during, and after the sex act itself.”

The chapter on touch is particularly fascinating. It is defined as stimulation of the skin by mechanical, thermal, chemical, or electrical means, along with the resulting sensation of pressure, vibration, temperature, or pain. The role of skin and touch in the evolution of both primates and humans is largely unrecognized, according to Jablonski. Arboreal primates required touch for rapid and sure-footed locomotion through trees. Fingerprints, now used in forensics, initially functioned to enhance friction and help ensure that fingers and toes would not slip off when grasping slippery branches or other objects. In modern society, we use touch to check the ripeness of fruit in the supermarket; similarly, animals in the wild use touch (as well as smell) to assess the texture, softness, and quality of foods. Jablonski discusses the relationship between human communication and touch, including the importance of touch between mothers and infants and the increased levels of stress hormones — and the deleterious effects on the immune system — that result from touch deprivation. Also described is the impor-
tance of the word “touch” itself to express feelings, as in “Keep in touch” or “How touching” or “I am touched.”

Skin cannot be confused with a textbook on dermatology, although it is as carefully and thoroughly researched. Still, Jablonski does review several common skin disorders as well as the damage done to the skin by ultraviolet light and the need for protection from the sun. She critiques popular cosmetic procedures and points out how the ever-popular Botox injections can cause confusion in face-to-face communication when the emotions that would otherwise be expressed on the face are absent.

Jablonski helps us to understand that human skin, which comes in a wide range of colors and which we use as a canvas for decoration, “reflects our age, our ancestry, our state of health, our cultural identity, and much of what we want the world to know about us.”

Susan C. Taylor, M.D.
Columbia University
New York, NY 10032
drstaylor1@aol.com

BETWEEN THE DYING AND THE DEAD: DR. JACK KEVORKIAN’S LIFE AND THE BATTLE TO LEGALIZE EUTHANASIA


For decades, end-of-life decision making, and euthanasia in particular, has been a highly contested topic — not only in the fields of bioethics and medicine, but also in society in general. The debate involves various actors. It has its icons and symbols, like Nancy Cruzan and Terry Schiavo, who were maintained in a persistent vegetative state; Ramón Sampedro, who was paralyzed from the neck down in a diving accident and fought for almost 30 years for his right to die; and several well-known doctors. Perhaps the most disputed figure in this debate is Jack Kevorkian, the subject of Between the Dying and the Dead.

The authors of this book, longtime collaborators and friends of Kevorkian, try to show what kind of person he is and what has motivated him. The son of Armenian immigrants who sought refuge from genocide, he learned to mistrust governments and politicians. At school, he was a rebel and a joker — never a diplomat. In medical school, he was fascinated by science and death, astonishing his fellow residents with bizarre experiments. As a pathologist, he argued that prisoners on death row should be given the option of dying by surgical anesthesia rather than by other means of execution so their bodies could be used for organ donation and medical experimentation. He also made a case for the transfusion of blood from cadavers to patients. He had difficulty understanding why other people did not appreciate his ideas and research, and even found them macabre and eccentric. In 1987, during a trip to the Netherlands, he learned of euthanasia and started to make his so-called suicide machines. Through his involvement in assisted-suicide cases, he became an internationally known figure and went through several trials until he was finally convicted of second-degree murder in 1999.

After reading this book, I still find it unclear why Kevorkian did what he did. Was it the search for a cause that could make him famous, a compassion for the dying, or a predominantly technical and utilitarian view? The authors make exaggerated claims that the requirements for assisted suicide in the Oregon Act and similar bills in the United Kingdom are taken directly from Kevorkian’s publications, and that because of Kevorkian the medical community has begun to pay attention to palliative care. But the impression I have of Kevorkian is that of a tragic figure, often isolated, out of touch with reality, and without common sense. He is tragic because he charged himself with an impossible mission: questioning medical ethics, sometimes with the right arguments but often with the wrong solutions. Kevorkian was right in identifying such problems as physicians’ lack of attention to suffering and the shortage of organs for transplantation. But the authors also show that as long as medicine is considered a primarily technical profession, ethical arguments opposing assisted suicide and euthanasia are merely religious. The authors empathetically describe a man who has devoted his life to challenges and lost battles, but this is also a history of bioethics.

Henk A.M.J. ten Have, M.D., Ph.D.
University Medical Center
6500 HB Nijmegen, the Netherlands
h.tenhave@unesco.org
TREATMENT AND MANAGEMENT OF CANcer IN THE ELDERLY


The importance of this book to all of us who are involved in the care of older patients with cancer is evident from the first page of the preface. Currently in the United States, more than 50% of all cancers occur in the 12% of people who are 65 years of age or older. By the year 2030, this group will represent 20% of the U.S. population and will account for 70% of all cases of cancer. For this reason, it is vital that we understand the biologic and clinical aspects of cancer and aging. It is equally important to understand cancer treatments and the value of quality of life and supportive care, not only for elderly patients but also for their families. All these issues are well reviewed in Treatment and Management of Cancer in the Elderly, a state-of-the-art book on geriatric oncology written by an excellent group of contributors.

In the first section, the magnitude of the burden of cancer in the elderly is explored, along with new management approaches. Improved preoperative risk assessment and less invasive surgical approaches have increased the number of patients over the age of 70 years for whom surgery is now an option. Newer radiation techniques, such as intensity-modulated radiation treatment, provide more targeted approaches. Support for cytotoxic chemotherapy with hematopoietic growth factors and other, more targeted therapeutic strategies are also discussed. Another chapter reviews legal aspects of caring for the elderly. The practice of elder law is particularly relevant because it deals with advanced directives, guardianship, decision-making authority, and the increasingly complex Medicare health system. There is much useful information here for both patients and providers to consider.

The second section focuses on hematologic cancers, including summaries of current data on treatment outcomes for older patients with acute and chronic leukemia, myeloma, and lymphoma. Although there is universal agreement that the elderly have been underrepresented in clinical trials, specialists in hematologic cancers have long recognized how aging contributes to the biologic and clinical heterogeneity of these diseases. The authors discuss novel approaches to treatment, but they also consider the difficult choices confronting oncologists working with elderly patients with leukemia and their families — is aggressive, life-threatening chemotherapy an option, or is supportive care alone more appropriate?

A major portion of the book is devoted to a discussion of solid tumors. The chapter on breast cancer addresses the increased likelihood of favorable prognostic markers in older women with breast cancer. However, survival in older women with localized or regional-stage breast cancer is not better than survival in younger women, and in the case of metastatic breast cancer, the outcome for older women is worse. The authors summarize current results with chemotherapy and hormonal therapy in older patients with breast cancer and call for age-specific clinical trials in all settings but particularly in adjuvant treatment, where it is critical to understand the risks and benefits for elderly women.

In the case of lung cancer, the fit elderly can undergo treatments similar to those received by their younger counterparts. But coexisting conditions in older patients with lung cancer limit the options for treatment and make combined approaches difficult. The median age of diagnosis for lung cancer is now 71 — a mandate for clinical trials and outcomes research in older patients. The authors stress the importance of screening, diagnosis, and staging to identify localized prostate cancer and colorectal cancer. In colorectal cancer, improved surgical approaches have led to curative treatments in an increasing percentage of older patients. The book includes good summaries of ovarian cancer, other gynecologic cancers, genitourinary cancer, melanoma, nonmelanoma skin cancer, head and neck cancer, and soft-tissue sarcoma in the elderly.

The last section of the book deals with quality of life, supportive care, nursing, and the end of life. Chapters on health status and outcomes in older patients with cancer focus on the influence of age, coexisting conditions, multiple medications (polypharmacy), and social setting in geriatric assessment and case management. There is also an excellent review of the assessment of nutritional status and the implementation of nutritional interventions.

The editors of the book dedicated it to Dr. Byrl James ("B.J.") Kennedy, well recognized as one of the founders of geriatric oncology. They note that
he would have enjoyed reading this book, and I am certain that is the case. He also would have been impressed by the body of knowledge that has been accrued in this field. The editors and their contributors are to be congratulated for bringing us up to date and setting the agenda for future research.

Jeffrey Crawford, M.D.
Duke University Medical Center
Durham, NC 27710
crawf006@mc.duke.edu

PRINCIPLES AND PRACTICE OF GERIATRIC PSYCHIATRY

TRAINING IN GERIATRIC PSYCHIATRY IS often lacking, and the clinical results are often disastrous. Principles and Practice of Geriatric Psychiatry is an outstanding book on the topic for all clinicians involved in geriatrics. It serves two important purposes by providing both a thorough introduction to the specialty of geriatric psychiatry and an approachable, clinically focused treatise on the psychiatry of geriatrics.

In his foreword to the book, Robert Butler eloquently articulates its importance and relevance: “This unique textbook of geriatric psychiatry exemplifies the enormous strides made in aging over the past 30 years. It offers not only clinical science, but also a sense of advocacy and a broad social context; it does an excellent job spotlighting the importance of understanding the immediate relevance to our lives of the field of aging in general, and the relationship of mental health and illness in older persons in particular.” As one who has long drawn inspiration from Butler’s commentary, I could not have said it better.

This book steadfastly maintains its clinical focus and relevance, melding basic science, clinical research, and clinical experience. These themes are tied to vignettes of clinical cases that make it all work. The topics discussed include palliative and end-of-life care, ethics, spirituality, sexuality related to normal aging, mental health in the elderly, and the developmental stages associated with late life. The extensive range of subjects reflects the remarkable breadth of knowledge and experience of the editors and contributors.

Of particular note are the first three sections of the book, which include discussions of how to start a geriatric psychiatry practice and how to approach the geriatric patient. Several often-neglected issues are addressed, including developmental stage of life, the importance of the caregiver, cultural influences, and forensics. These broad themes lay the groundwork for an appreciation of mental health in geriatrics. The introductory sections by themselves make the book well worth having. They set the tone for subsequent chapters on the evaluation and management of psychiatric disorders in the elderly and the medical conditions associated with psychiatric problems. These clinically focused chapters feature discussions of the relevant basic science and clear, concise explanations of diagnosis and management, all illustrated by the clinical vignettes mentioned above.

Geriatric psychiatry is increasingly important for all physicians. Life expectancies are increasing, and patients over 85 years of age make up one of the most rapidly growing segments of psychiatry. This text is a wonderful exposition of the general issues associated with aging and the management of psychiatric disorders in geriatrics.

Larry E. Tune, M.D.
Emory University School of Medicine
Atlanta, GA 30329
ltune@emory.edu

Book Reviews Copyright © 2007 Massachusetts Medical Society.

CORRECTIONS

Diagnosis of Ventilator-Associated Pneumonia (December 21, 2006;355;2691-3). Dr. Kollef’s disclosure statement should have read “Dr. Kollef reports receiving consulting fees or honoraria from Pfizer, Merck, Kimberly Clark, and Elan, and grant support from Pfizer, Merck, Elan, and Bard Medical. No other potential conflict of interest relevant to this article was reported.” The text has been corrected on the Journal’s Web site at www.nejm.org.

Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children (February 15, 2007;356;685-96). The second to last sentence of the article (page 695) should have read “The high influenza attack rate among children in the inactivated-vaccine group who were less than 12 months of age and had a history of wheezing (14%) suggests that inactivated vaccine has low efficacy in this group.” rather than “who were less than 12 months of age (15%) suggests that inactivated vaccine has low efficacy among children in this age group.” The text has been corrected on the Journal’s Web site at www.nejm.org.
A 57-YEAR-OLD MAN WITH A HISTORY OF DIABETES MELLITUS AND ALCOHOL consumption was referred to the hand surgery unit owing to contractures of fingers of both hands. He reported that his brother and father had similar contractures. Physical examination revealed flexion contractures involving the bilateral third digits and the right fifth digit. The patient had a severe contracture of 100 degrees at the proximal interphalangeal joint of the right small finger and thickened palmar fascia with multiple cords ending in firm nodules. The condition was diagnosed as Dupuytren's contracture, a fibroproliferative disorder of the palmar fascia, and the patient subsequently underwent bilateral partial fasciectomy. Common risk factors for Dupuytren's contracture include a family history of the disorder, diabetes, alcohol consumption, and the use of vibratory machinery. In this case, healing was uneventful, and no recurrence of contracture was observed on follow-up.

Copyright © 2007 Massachusetts Medical Society.