

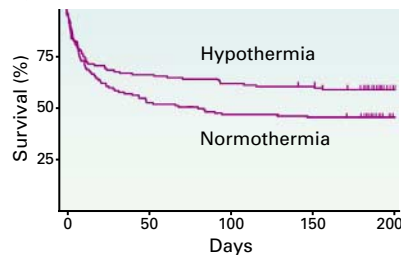


# This Week in the Journal

February 21, 2002

## Mild Therapeutic Hypothermia after Cardiac Arrest

Cerebral injury and associated cognitive dysfunction are common after sustained cardiac arrest. In this study, mild therapeutic hypothermia was compared with normothermia in patients who had been resuscitated after cardiac arrest due to ventricular fibrillation. A favorable neurologic outcome was significantly more frequent in the group treated with hypothermia.



*These results, in conjunction with those of another study in this issue, suggest that mild therapeutic hypothermia may have a substantial benefit in patients who have been resuscitated after cardiac arrest and that this approach should now be considered in the care of such patients.*

**see page 549 (editorial, page 612)**

*“Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation.”*

## Hypothermia in the Treatment of Comatose Survivors of Cardiac Arrest

Patients who remain unconscious after resuscitation from cardiac arrest outside the hospital have a poor prognosis. In this trial, 77 patients were assigned to treatment with moderate induced hypothermia or normothermia. Survival to hospital discharge with good neurologic recovery was more frequent in the hypothermia group than in the normothermia group.

*This study on its own would be regarded as preliminary, because it included only a small number of patients and had other important limitations. However, when considered in conjunction with the Hypothermia after Cardiac Arrest Study reported in this issue of the Journal, it indicates that moderate hypothermia may improve outcome in this otherwise ominous condition.*

**see page 557 (editorial, page 612)**

## PERSPECTIVE

## Hypothermia to Protect the Brain

For decades, cooling the body below the normal physiologic temperature has been used as a therapeutic tool. Hypothermia is used most often during cardiac surgery with cardiopulmonary bypass, as a means of protecting the brain from ischemic injury. Hypothermia is also used during some neurosurgical procedures and is being investigated as a treatment for ischemic stroke and traumatic brain injury. In this issue of the *Journal*, two groups of investigators report on the use of therapeutic hypothermia to prevent neurologic injury in comatose survivors of cardiac arrest.

Out-of-hospital cardiac arrest claims some 225,000 lives each year in the United States and a similar number in Europe, accounting for about half of all deaths due to cardiovascular disease. Even when resuscitation efforts are successful, recovery is too often limited by anoxic encephalopathy. The risk of this complication increases with the delay in resuscitation, and the prognosis for comatose survivors of cardiac arrest — albeit not hopeless — is poor. In an international study, less than a third of comatose survivors of out-of-hospital cardiac arrest awakened within seven days; the others either died or remained unconscious. Even if patients do regain consciousness, persistent neurologic or cognitive deficits are common. We urgently need better methods to protect the brain in victims of cardiac arrest.

The reports by the Hypothermia after Cardiac Arrest Study Group and by Bernard et al. (see pages 549–56 and 557–63) in this issue of the *Journal* represent an important first step toward reaching this goal. Working independently on two continents (Eu-



**Figure 1.** Cooling Device Used in the Hypothermia after Cardiac Arrest Study, Which Operates by Circulating Cool Air over the Patient.

rope and Australia), both research groups found that lowering the body temperature to 33°C for 12 or 24 hours in comatose survivors of cardiac arrest resulted in an impressive improvement in the neurologic outcome. The larger European study also showed significant improvement in overall survival. The methods used for cooling were remarkably simple — placement of ice packs on the patient's torso, or use of a device that circulates cool air over the patient (Fig. 1). It is surprising that the induction of brief, mild hypothermia led to such meaningful improvement in the clinical outcome.

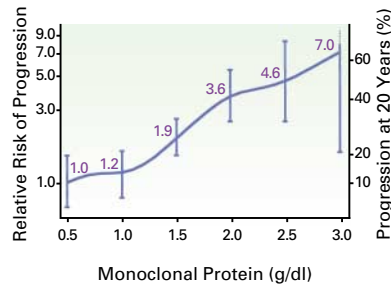
The simplest biologic explanation of how hypothermia may provide protection against anoxic brain injury is that it reduces the cerebral oxygen requirement. However, as Safar and Kochanek discuss in an accompanying editorial (page 612), the mechanisms involved are likely to be much more complex. An array of cellular pathways participate in the genesis of anoxic brain injury, and hypothermia may interrupt one or more of them, preventing free-radical injury, membrane damage, and injury due to the release of neurotrans-

mitters, as well as other types of damage.

The encouraging findings reported by these two groups of investigators should not necessarily be diminished by the contradictory results of studies of therapeutic hypothermia in patients with traumatic brain injury. Although one study (*N Engl J Med* 1997;336:540-6) reported a benefit in patients with nonpenetrating head trauma, a more recent study (*N Engl J Med* 2001;344:556-63) failed to confirm this observation. Traumatic and anoxic brain injuries differ in important ways, and it is possible that injury due to trauma is less easily reversed than anoxic injury after circulatory arrest.

The two studies of therapeutic hypothermia are mutually confirmatory. The findings, which may have profound clinical implications, are applicable to current resuscitation practice. Still, given the magnitude and complexity of the clinical problem, further studies of the efficacy and safety of therapeutic hypothermia in survivors of cardiac arrest should be given a high priority.

GREGORY D. CURFMAN, M.D.



## Prognosis in Monoclonal Gammopathy of Undetermined Significance

A monoclonal gammopathy of undetermined significance (MGUS) is diagnosed when there is serum monoclonal protein at a concentration of 3 g per deciliter or less in the absence of evidence of multiple myeloma or a related disorder. The condition is not rare in people over the age of 50 years and may progress to full-blown multiple myeloma over a period of years. This study of almost 1400 patients, who were followed for up to 35 years, defines the risk of progression to multiple myeloma and the important predictors of progression.

*It is impossible to tell whether MGUS is an innocent proliferation of a clone of B cells that produce a telltale monoclonal immunoglobulin, or the sinister precursor of multiple myeloma, amyloidosis, or a B-cell lymphoma. This comprehensive study of a large number of patients with MGUS provides clinically valuable information about the risk of progression to multiple myeloma and related disorders and about prognostic factors.*

see page 564

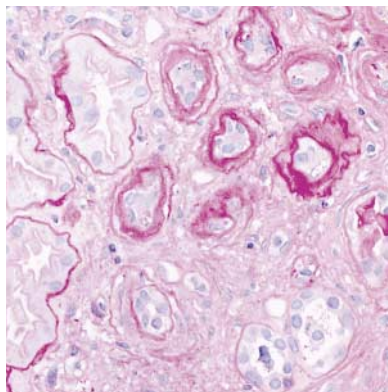


## Leptin Replacement in the Treatment of Lipodystrophy

Patients with severe lipodystrophy have a marked deficiency of the adipocyte hormone leptin. In this study nine female patients with marked lipodystrophy, hypertriglyceridemia, hepatic steatosis, and diabetes (in eight patients) received escalating doses of recombinant methionyl human leptin for four months. Leptin-replacement therapy improved glycemic control, lowered triglyceride levels, and decreased daily caloric intake and the resting metabolic rate.

*Leptin deficiency may be a major factor in the insulin resistance and other metabolic abnormalities that characterize severe lipodystrophy.*

see page 570



## Medical Progress: Improving Long-Term Outcomes after Renal Transplantation

This article provides a comprehensive, up-to-date review of methods to prevent early and late renal-allograft loss and to improve long-term outcomes in patients. The authors focus particular attention on the problem of late graft loss and discuss current antirejection therapy, including calcineurin blockers such as cyclosporine and tacrolimus, the interleukin-2 signal-transduction inhibitor sirolimus, and the purine-synthesis inhibitor mycophenolate mofetil, which inhibits the proliferation of T cells and B cells.

see page 580

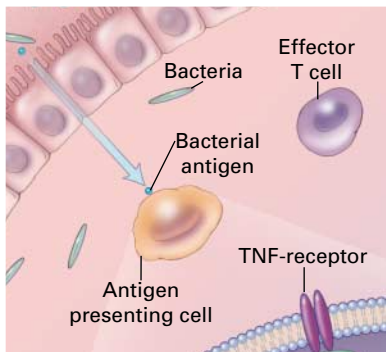
*“Obesity is a serious and prevalent disorder whose effective management requires ongoing care.”*

### Drug Therapy for Obesity

The most common nutritional disorders in the United States are overweight and obesity. This review discusses the treatment of overweight and obesity as chronic conditions that require a combined approach of behavioral therapy, exercise, dietary changes, and — in certain cases — medication. The authors consider the three classes of weight-loss drugs: those that suppress appetite, those that decrease nutrient absorption, and those that increase energy expenditure. Currently available and soon-to-be-released drugs are discussed.

*Weight-loss medications are best used as an adjunct in patients at substantial medical risk because of obesity in whom nonpharmacologic therapy has failed.*

see page 591



### Clinical Implications of Basic Research: New Therapeutic Targets in Crohn's Disease

*NOD2*, a gene conferring susceptibility to Crohn's disease, has been identified on chromosome 16. Homozygosity for a mutation that truncates the gene increases the risk of Crohn's disease by a factor of 20 to 40. No such mutations have been found in patients with ulcerative colitis. *NOD2* has a role in apoptosis and in the recognition of microbial endotoxins.

*The discovery of truncating mutations of NOD2 in Crohn's disease is an important advance. It opens new possibilities for screening for familial and sporadic cases and suggests avenues for treatment.*

see page 614

*“The events of September 11, 2001, show that a mass appeal is neither a safe nor an efficient way to collect blood.”*

### Sounding Board: Blood and Disaster

Almost immediately after the attacks that struck New York City and Washington, D.C., on September 11, 2001, the federal government and the American Red Cross issued an appeal for blood donors. Nationwide, more than 1 million prospective donors responded to the call and almost 500,000 units of blood were collected for the victims. Yet only 258 units were used. Many of the collected units were unusable.

*After a disaster, mass appeals for blood donors may be unnecessary. Blood banks in virtually all urban centers have enough blood on hand for at least the first three days of an emergency, and this supply can quickly be supplemented by stocks in neighboring cities. Disaster planning should include means of coordinating blood supplies.*

see page 617