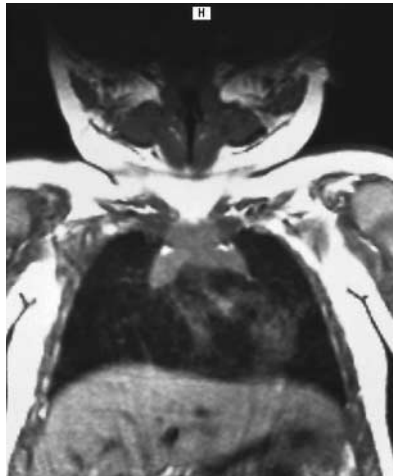




# This Week in the Journal

April 18, 2002

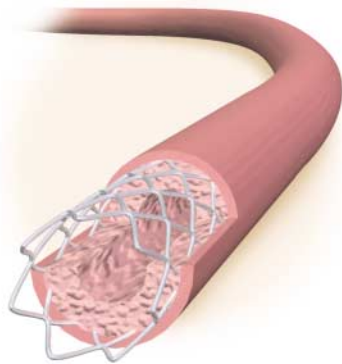


## Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy

Gene therapy was used in five boys with X-linked severe combined immunodeficiency disease. In this disorder, a mutation disables the common  $\gamma$  ( $\gamma$ C) chain, a component of five cytokine receptors that are essential for the development of T cells and natural killer cells. The disease is fatal within the first year of life unless treated with bone marrow transplantation. The immune system was restored in four patients, who remain well and have required no further treatment during follow-up of up to two years.

*This report describes a unique example of the successful treatment of a fatal congenital disease by the introduction of the missing normal  $\gamma$ C gene into autologous hematopoietic stem cells ex vivo with a retroviral vector. This form of gene therapy has potential applications in other congenital disorders involving the hematopoietic system.*

**see page 1185 (editorial, page 1241)**



## Intravascular Radiation for In-Stent Restenosis in Bypass Grafts

Obstructive lesions in saphenous-vein bypass grafts are a common long-term complication of coronary bypass surgery. Stenting is often performed, but its benefit is limited by restenosis. This placebo-controlled trial evaluated treatment with intravascular gamma radiation for the prevention of in-stent restenosis in coronary bypass grafts. Radiation therapy reduced the rate of restenosis and the rate of subsequent revascularization over a 12-month period.

*Although the results are promising, longer-term follow-up will be essential to ensure that the benefits are durable and that late complications, such as vascular damage or neoplasia, do not arise.*

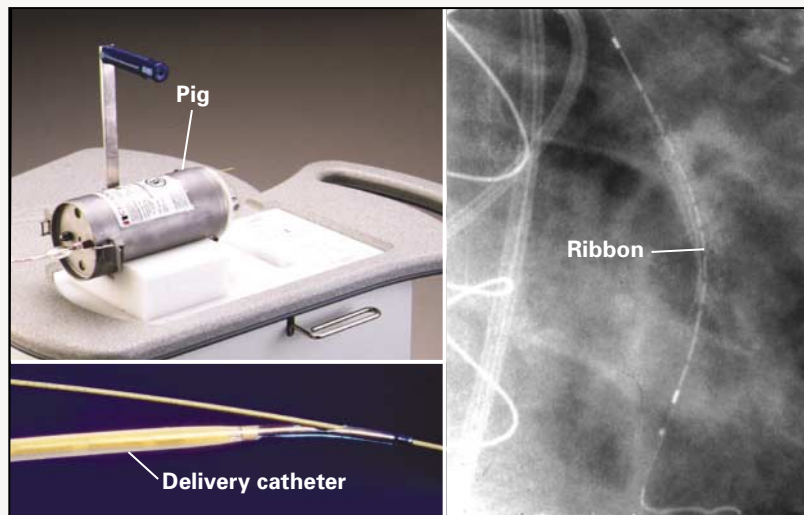
**see page 1194 (Perspective, page 1182)**

## PERSPECTIVE

## Restenosis after Angioplasty

Over the past two decades, percutaneous coronary intervention has revolutionized the treatment of symptomatic coronary artery disease, sparing countless patients the need for surgical revascularization. This year, up to a million procedures are likely to be performed in North America alone.

The success of percutaneous coronary intervention has been due largely to an explosion in technology development, with the introduction of a broad array of balloon catheters, atherectomy devices, lasers, and stents. The impetus for the development of such devices has been the occurrence — noted soon after the introduction of balloon angioplasty — of intimal tears, arterial recoil, and ingrowth of tissue in response to balloon expansion within the diseased arterial segment. The result is abrupt closure or restenosis after a period of weeks or months. The introduction of balloon-expandable stents has increased the success of percutaneous coronary intervention by allowing intimal flaps and dissections to be tacked to the arterial wall and by preventing recoil, but these stents did not eliminate the proliferation of fibrous and smooth-muscle tissue within and around the wire mesh of the stent. Because of the increased diameter of the lumen after the procedure, however, the subsequent ingrowth of tissue is less likely to limit blood flow to heart muscle, reducing the risk of recurrent angina and the need for retreatment. Nevertheless, with the use of devices that have been approved by the Food and Drug Ad-



Treatment of In-Stent Restenosis in a Saphenous-Vein Graft with the Use of Iridium-192.

The system consists of the “pig” (lead containment device), the ribbon containing radioactive seeds, and the catheter used to deliver the ribbon to the site of the lesion.

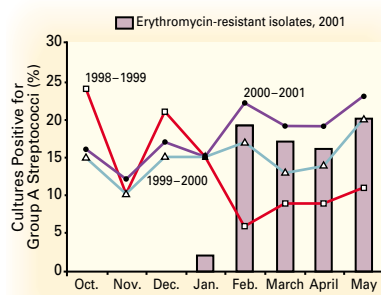
ministration (FDA), the rate of restenosis of the treated arterial segment ranges from 5 to 50 percent, depending on the length of the segment and the diameter of the artery.

Cognizant of the inhibitory effects of radiation on cellular proliferation, investigators have approached the problem of restenosis by using radiation within the restenosed arterial segment (brachytherapy), generally after repeated balloon angioplasty, atherectomy, or stenting. In 2000, on the basis of data from randomized clinical trials, the FDA approved two brachytherapy devices for the treatment of restenosis within stents implanted during a prior percutaneous coronary intervention. One device has a beta-particle-emitting source, and the other a gamma-ray-emitting source. In this issue of the *Journal*, Waksman and coworkers report on the use of the latter device to address a particularly difficult problem for interventionists: the treatment of in-stent restenosis within saphenous-vein

grafts in patients who have previously undergone coronary-artery bypass surgery (see pages 1194–1199). In the double-blind study by Waksman et al., 120 patients with in-stent restenosis in saphenous-vein grafts and angina pectoris were assigned at random to undergo treatment with iridium-192 contained in a ribbon that was positioned within the stent (see figure) or with non-radioactive seeds, after conventional treatment of the restenosis. At six months the incidence of in-stent restenosis was reduced by half in the radiation group as compared with the placebo group. At 12 months, significantly fewer radiation-treated patients required rehospitalization for angina, and the need for repeated treatment of restenosis in this group was reduced by 70 percent — important findings from a clinical perspective.

Will brachytherapy gain wide acceptance for the treatment of in-stent restenosis, whether in coronary arteries or in vein grafts? A

## Erythromycin-Resistant Group A Streptococci



In a longitudinal study at an elementary school in Pittsburgh, group A streptococci with resistance to erythromycin were unexpectedly identified in surveillance throat cultures in January 2001. Through May 2001, nearly half the isolates were resistant to erythromycin, and 22 of 46 children with resistant isolates had multiple cultures that were positive for this resistant streptococcus.

*This apparently clonal outbreak of infection with erythromycin-resistant group A streptococci signals a clinically significant change in the pattern of susceptibility of this organism in the United States. The change may be the result of the increasing use of macrolide antibiotics.*

see page 1200 (editorial, page 1243)

major problem with brachytherapy, especially with the use of gamma-emitting devices, is radiation exposure for both the patient and catheterization-laboratory personnel; special shielding and the participation of radiation oncologists and physicists are required to reduce the risk of exposure. Also, brachytherapy has been associated with increased risks of intralumenal thrombosis, possibly because of delayed endothelialization of the treated arterial segment, and ingrowth of tissue at the treatment margins (the so-called candy-wrapper effect). The rates of these complications were not significantly higher in the radiation group than in the placebo group in the trial reported by Waksman et al.

The methods and devices used for brachytherapy may become more user-friendly with time. Mean-

while, an innovative treatment strategy, which may eliminate restenosis as a clinical problem, has generated considerable interest in the interventionist community. Sousa and coworkers (*Circulation* 2001;104:2007-11) implanted stents coated with sirolimus (previously called rapamycin) in diseased coronary arteries in 45 patients in Brazil and the Netherlands. None of the patients had restenosis, as assessed by coronary angiography and intravascular ultrasonography, one year after treatment. Sirolimus is structurally similar to tacrolimus, a T-lymphocyte inhibitor used to prevent transplant rejection. In animal models of arterial injury, sirolimus inhibits intimal proliferation and hyperplasia. Several randomized, double-blind clinical trials are now in progress to determine whether the initial results with sirolimus-

eluting stents are confirmed in larger numbers of patients who require percutaneous coronary intervention. Other drug-eluting stents, the design of which may allow growth-inhibiting agents to be released for months or years, are being developed.

However, until this approach or others have been proved to be safe and effective in preventing restenosis after percutaneous coronary intervention in arteries and in vein grafts, restenosis will continue to require additional treatments, including brachytherapy, in selected patients.

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### Brief Report: **Development of Kaposi's Sarcoma in a Surgical Wound**

A patient infected with the human immunodeficiency virus (HIV) who had xerostomia and enlargement of the parotid glands underwent a diagnostic biopsy of a labial salivary gland. Within six days, a rapidly growing, fungating mass had appeared at the biopsy site. The lesion had the histologic features of Kaposi's sarcoma and contained antigens of human herpesvirus 8. After treatment with local radiotherapy, the lesion resolved.

*Kaposi's sarcoma in a surgical wound is unusual. The author speculates that proinflammatory cytokines and angiogenic factors may have had a role in triggering the development of the lesion in this HIV-infected patient.*

**see page 1207**

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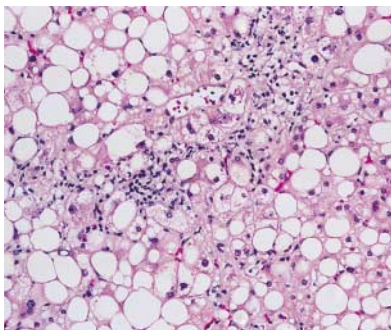


### Current Concepts: **Schistosomiasis**

Schistosomiasis is a parasitic-worm infection that affects about 200 million people in 74 countries. Despite major advances in treatment and control, this tropical disease continues to spread to new geographic areas. This review summarizes the manifestations of this disease, its diagnosis, medical treatment, and prophylaxis, and the prospects for a vaccine.

**see page 1212**

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### Medical Progress: **Nonalcoholic Fatty Liver Disease**

Alcohol abuse is the most common cause of fatty liver disease, but it is now apparent that fat deposition in the liver, and its consequences, may occur without alcohol abuse. The principal risk factors are obesity, non-insulin-dependent diabetes mellitus, and hyperlipidemia. The disorder has a wide clinical spectrum, ranging from asymptomatic steatosis to steatohepatitis, fibrosis, and cirrhosis. This article provides a broad overview of this increasingly recognized liver disease.

**see page 1221**

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