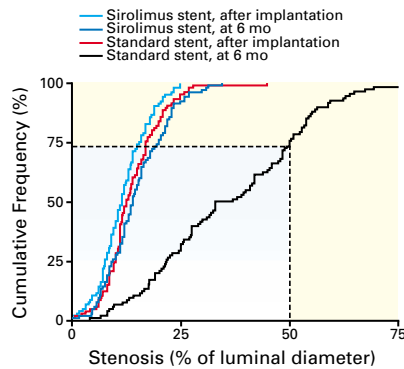




# This Week in the Journal

June 6, 2002



## Sirolimus-Eluting Stent for Coronary Revascularization

Despite advances in coronary angioplasty and stenting, restenosis remains an important problem that limits clinical success. This study compared a new coronary stent coated with sirolimus (rapamycin) with a standard (uncoated) stent in patients undergoing stenting for a single coronary lesion. At six months, the rate of restenosis was 26.6 percent in the standard-stent group and 0 percent in the sirolimus-stent group.

*The results after six months of follow-up are striking and suggest that the sirolimus-eluting stent has considerable promise. However, longer follow-up will be essential to examine the durability of the results, and it will be necessary to determine whether this new device is effective in patients with more complex coronary lesions.*

see page 1773 (Perspective, page 1770)

*“These results are compatible with the current strategy of starting to screen for colorectal cancer at the age of 50 among persons at average risk.”*

## Screening Colonoscopy among Persons 40 to 49 Years of Age

Because the prevalence of colonic neoplasms before the age of 50 is thought to be low, screening for colonic neoplasms by colonoscopy is currently recommended for people 50 years of age or older. In this retrospective study, investigators reviewed the records of 906 consecutive persons 40 to 49 years of age who participated in an employer-sponsored colonoscopic-screening program. No cancers were detected in this group, but hyperplastic polyps, tubular adenomas, or lesions scored as “advanced neoplasms” were found in 21 percent of those screened. Between 250 and 1000 people 40 to 49 years old would need to be screened to detect a single case of colon cancer.

*These data provide strong support for the recommendation that colonoscopic screening start at the age of 50. However, because the incidence of colon cancer among those less than 50 years of age is not zero, research is needed to develop a cost-effective method of finding these relatively rare cancers.*

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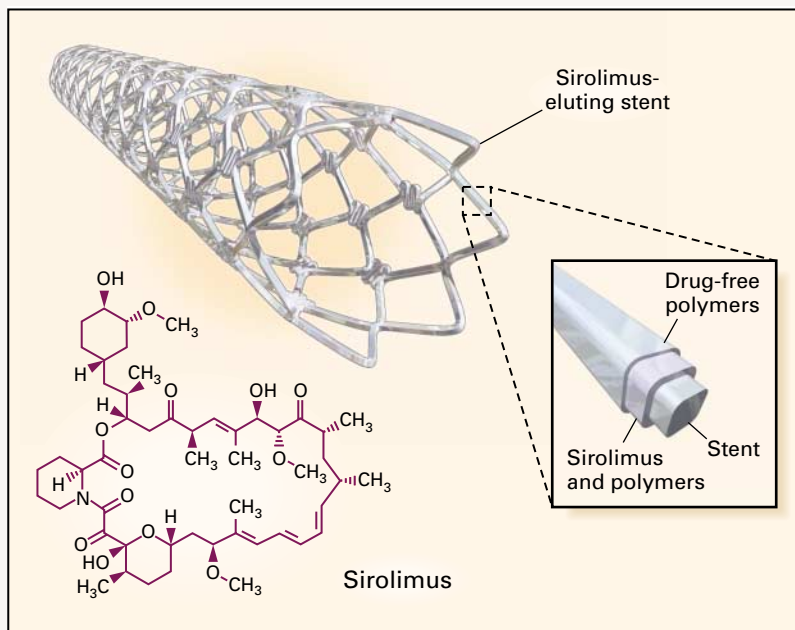
## PERSPECTIVE

## Sirolimus-Eluting Coronary Stents

The story of sirolimus began in 1975 on Easter Island, in the South Pacific, a remote, enigmatic place known for the prominent stone statues that punctuate its landscape. An actinomycete, *Streptomyces hygroscopicus*, cultured from a sample of the island's soil, was found to produce through natural fermentation a novel macrolide antibiotic with potent antifungal, immunosuppressive, and antimitotic activities. The generic name of the resulting drug is sirolimus (see Figure); it is also known as rapamycin, after Rapa Nui, the name given to Easter Island by its inhabitants.

Twenty-five years of intensive research led, in 1999, to the approval of sirolimus for use as an antirejection drug in organ-transplant recipients. Its immunosuppressive mechanism resides in its ability to block cytokine-stimulated proliferation of T lymphocytes by interfering with their progression through the cell cycle. The drug also has antiproliferative effects on a variety of other cell types. In just three years since it was approved for use, sirolimus has shown promise in the management of acute and chronic graft rejection, reducing the need for corticosteroids and cyclosporine, but its use is limited by the side effects of hyperlipidemia and thrombocytopenia.

In a seemingly unrelated development, while sirolimus was being investigated as an antirejection drug, coronary-artery stenting was beginning to be used as a means of preventing restenosis after coronary angioplasty. The American Heart Association reports that in 1999, the most recent year for which



The Sirolimus-Eluting Stent, Shown with the Chemical Structure of the Molecule.

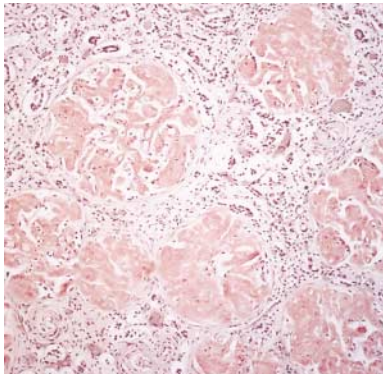
complete data are available, over 1 million coronary-angioplasty procedures were performed in the United States, nearly half of which (457,000) were stenting procedures. By comparison, in the same year, 571,000 coronary-artery bypass operations were performed. These figures affirm that coronary stenting has assumed a major role among coronary revascularization procedures.

Still, coronary stenting has limitations. Although the procedure was developed explicitly to prevent restenosis after angioplasty, it has been an imperfect solution, since 15 to 20 percent of stented arteries again become stenotic. Restenosis results from neointimal proliferation, in which smooth-muscle cells are stimulated to proliferate by inflammatory mediators released in response to vessel injury. Ingrowth of tissue through the struts of the stent eventually narrows the lumen of the vessel. Despite numerous attempts to block neointimal proliferation, no consistently successful interventions have been found —

until now. Reported in this issue of the *Journal* (see pages 1773–1780) is a possible solution to the problem of restenosis, stemming from the unanticipated intersection of research on sirolimus and on coronary stents.

On the supposition that the immunosuppressive and antimitotic properties of sirolimus might inhibit neointimal proliferation, a stent coated with sirolimus was devised. This was accomplished by coating the stent with a mixture of synthetic polymers blended with sirolimus, then applying a second coat of drug-free polymers to serve as a diffusion barrier (see Figure). The polymers act as a drug reservoir and allow for the gradual elution of sirolimus over a period of about 30 days, delivering the drug precisely to the site of interest. Only a small quantity of the drug is required, and systemic side effects are avoided.

The report in this issue of the *Journal* presents the results of the RAVEL study, a randomized clinical trial comparing a sirolimus-eluting stent with a standard (uncoated)

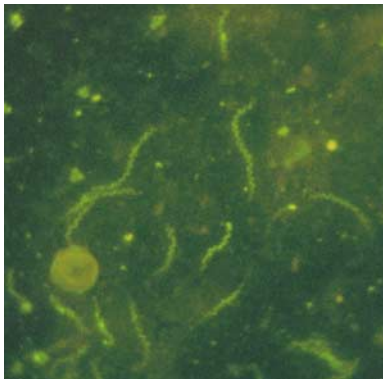


### Misdiagnosis of Hereditary Amyloidosis

Of 350 patients who were referred to the National Amyloidosis Centre in London with biopsy-proved amyloidosis and a presumed diagnosis of immunoglobulin light-chain amyloidosis, almost 10 percent actually had hereditary amyloidosis due to genetic variants of transthyretin, apolipoprotein A-I, lysozyme, or fibrinogen A  $\alpha$ -chain. Some of these patients had an incidental monoclonal gammopathy.

*The surprisingly high frequency of hereditary amyloidosis at this referral center has important clinical implications, because chemotherapy, a common treatment for immunoglobulin light-chain amyloidosis, is contraindicated in hereditary amyloidosis. Immunohistochemical analysis of the biopsy specimen or genetic tests may be required before combination chemotherapy is prescribed for a patient with amyloidosis.*

see page 1786 (editorial, page 1818)



### Improving Diagnostic Accuracy in Congenital Syphilis

Of 76 infants born to women with syphilis who had no in utero or postnatal exposure to antibiotics, 17 (22 percent) had spirochetes detected in the cerebrospinal fluid. Most of the infants with central nervous system infection could be identified by abnormalities on the physical examination, radiographic studies, or conventional tests, such as the cerebrospinal fluid white-cell count and the Venereal Disease Research Laboratory test. However, the results of IgM immunoblotting of serum and the polymerase-chain-reaction assay of serum or blood proved to be the best predictors of the detection of central nervous system infection by the rabbit-infectivity test.

*These results show that central nervous system involvement is common in infants infected with Treponema pallidum. Although identifying central nervous system infections has been difficult in infants with congenital syphilis, such testing is important because the result affects the treatment strategy.*

see page 1792

stent in patients with single coronary lesions amenable to stenting. Patients with complex coronary lesions, such as those containing substantial calcium or thrombus, were excluded from the study. Still, even though only relatively uncomplicated coronary lesions were studied, the results after six months of follow-up were striking. The sirolimus-eluting stent virtually eliminated angiographic evidence of neointimal hyperplasia and restenosis and greatly reduced the need for repeated revascularization procedures. Similar studies of stents coated with the an-

tineoplastic agent paclitaxel, which, like sirolimus, inhibits cell division, are in progress, and the preliminary results are encouraging.

The results of the RAVEL study have already piqued the interest of interventional cardiologists, but a great deal of work remains to be done. Many more patients must be studied to ensure the validity of the observations. To be broadly applicable, use of the stent will need to be extended to patients with complex coronary lesions. Longer follow-up will be necessary to ensure that the excellent initial results are

lasting and that late complications, such as stent thrombosis or restenosis at the edges of the stent, do not occur. Intravascular ultrasound studies will be essential. If these matters are successfully addressed and the initial promise of sirolimus-eluting stents is fulfilled, a new chapter will be opened in the story of this drug, which traces its origins to one of the most remote places on earth.

GREGORY D. CURFMAN, M.D.

*“Because clopidogrel is more costly, its incremental cost effectiveness is currently unattractive.”*

### Special Article: Cost Effectiveness of Aspirin and Clopidogrel in Coronary Disease

Aspirin and clopidogrel, alone or together, reduce the rate of cardiovascular events in patients with coronary disease, but their relative cost effectiveness is uncertain. In this study, the use of aspirin in all patients eligible to receive it was very cost effective. In contrast, clopidogrel as a substitute for or in addition to aspirin was not cost effective. At its current price, clopidogrel was cost effective only when used in the small number of patients who cannot take aspirin.

*One 75-mg tablet of clopidogrel (\$3.22) is 80 times as expensive as one 325-mg tablet of aspirin (\$0.04), which is why clopidogrel is not a cost-effective therapy. It becomes cost effective only when the price falls to \$0.60 per tablet or less. A different point of view is presented in an accompanying editorial.*

**see page 1800 (editorial, page 1819)**



### Clinical Practice: Carpal Tunnel Syndrome

A 64-year-old woman has a three-month history of intermittent numbness, tingling, and burning pain in the three radial digits of both hands. These symptoms awaken her several times each night. She has no atrophy of the thenar muscles. How should she be evaluated and treated?

*This article reviews the diagnosis and management of carpal tunnel syndrome.*

**see page 1807**



### Clinical Problem-Solving: Diagnosis Still in Question

A 59-year-old man who lives on a ranch in California has a three-week history of fevers and a rash. His aminotransferase levels are elevated, and his erythrocyte sedimentation rate is 125 mm per hour.

**see page 1813**