served procedural mortality rates for both off-pump and on-pump CABG were excellent and well below those predicted according to standard risk models.

Third, neurocognitive testing was performed in only half the survivors and, in contrast with the results of a previous study, it did not show any longitudinal deficits in either surgical group. Finally, some will argue that newer off-pump techniques and improved medications for secondary prevention make the findings of the trial less applicable for contemporary care. However, several trials comparing off-pump with on-pump CABG are currently under way that can broaden our understanding.8,9

In summary, the ROOBY trial did not support off-pump procedures as an advance that should generally supplant traditional techniques. As such, it will probably remain a technique reserved for selected patients and skilled surgeon advocates. However, the trial should truly be seen as a very positive one. It clearly showed the feasibility and willingness of surgeons to subject new surgical innovations to large-scale rigorous evaluation. Investigators in future trials involving CABG will need to consider other proposed innovations, including the evolving use of endovascular vein-graft harvesting methods, hybrid PCI–CABG techniques, and even robotic procedures. Although the results of such studies will not always show that the new approach is an advance, much can be learned from this type of systematic study. Through this process of innovation and evaluation, cardiac surgery will continue to evolve and lead to improved outcomes for its recipients.

Human Papillomavirus Vaccine for Cancer Prevention

Olivera J. Finn, Ph.D., and Robert P. Edwards, M.D.

Cancer immunoprevention has become synonymous with the vaccines that have been approved for the prevention of infection with highly transmissible strains of human papillomavirus (HPV) that establish chronic infection and cause cervical and other cancers.1 Although many cancers may have a viral origin,2 only a small number of viruses have been implicated as causes of human cancer. Cancer having a viral origin provides an opportunity to develop virus-specific vaccines that lower infection rates and consequently lower the incidence of cancer; this is what the HPV vaccine is expected to do for cervical cancer and what the hepatitis B vaccine has already done for hepatocellular carcinoma.3

The question has been raised whether the same or similar HPV vaccines can be used in persons already infected with HPV to clear chronic infection or interrupt the process of oncogenesis that may have already started (in cervical or vulvar intraepithelial neoplasia) or progressed to cervical, vulvar, or other cancers. The past few decades of research in immunology have shown that cancer vaccines must elicit cellular as well as hu-
moral immune responses to be effective. Inasmuch as the current HPV vaccine is primarily designed to elicit neutralizing antiviral antibodies to prevent initial infection, different types of HPV vaccines are required to target HPV not as a virus but as a tumor antigen.

In this issue of the Journal, Kenter et al. report on the clinical and immunologic responses induced by an HPV vaccine composed of synthetic long peptides containing the HPV type 16 (HPV-16) epitopes E6 and E7 in patients with HPV-16–associated, grade 3 vulvar intraepithelial neoplasia. This article is the latest in a series of articles by the same authors who over the past several years have tested this vaccine in preclinical settings for its tumor-rejection potential and for its safety and immunogenicity in end-stage cervical cancer.

Twenty women with HPV-16–positive, grade 3 vulvar intraepithelial neoplasia were vaccinated with a mixture of peptides derived from HPV-16 oncoproteins E6 and E7 in incomplete Freund’s adjuvant (Montanide ISA-51). The peptides were 30 to 40 amino acids in length. Strong CD4+ and CD8+ T-cell responses were generated in all patients, and at 12 months of follow-up, 15 of 19 patients showed an objective clinical response as measured by symptom relief, the reduced size or disappearance of lesions, and the loss of HPV-16 DNA. Nine women had a complete response and remained disease-free at 24 months of follow-up.

This study is important for several reasons. In the context of the previous studies by this group of investigators, it suggests that more effective immune responses can be generated against precursor lesions than against late-stage disease. Many cancer vaccines based on nonviral tumor-associated antigens have been judged to be suboptimal because of their lack of efficacy in advanced disease, yet they might perform very differently if used in patients with premalignant disease.

Until recently, the treatment of vulvar intraepithelial neoplasia was limited to ablation with a carbon dioxide laser for low-grade lesions or wide local excision for high-grade vulvar intraepithelial neoplasia. Recurrence is the rule, and multiple treatments and excisions are required. Less invasive therapeutic approaches that provide durable protection from recurrence are needed. The study reported here provides support for immunotherapy as one such approach.

Many different formulations of cancer vaccines have been proposed and tested over the years, especially in the therapeutic setting, where the potential for greater efficacy has been matched by the greater complexity of design and delivery. This complexity requires sophisticated laboratories in major medical centers to complete the studies. If vaccines are to make a difference in the incidence of cancer worldwide, practicality must be one of the most important requirements. A synthetic peptide vaccine such as the one described in the article by Kenter et al. fulfills that requirement.

The benefit of a therapeutic approach to this disease based on an immune response has been foreshadowed by trials of imiquimod cream, an immune-response modulator that binds to toll-like receptor 7 and promotes type 1 T-cell–mediated immunity. A recent trial of imiquimod randomly assigned 52 women with multifocal grade 2 or 3 vulvar intraepithelial neoplasia to receive either imiquimod or a placebo cream. Complete lesion regression occurred at 20 weeks in nine patients treated with imiquimod and in no patients in the placebo group; this regression was associated with clearance of HPV DNA from the lesion as well as an increase in infiltrating dendritic cells, CD8+ T cells, and CD94+ natural killer cells.

Long-lasting clinical responses occurred in both the vaccine trial and the imiquimod trial, but both trials were limited to small numbers of patients and a short follow-up time. These promising approaches must be developed further to provide an alternative to standard surgical excision and ablation of vulvar intraepithelial neoplasia, especially since this disease is increasingly diagnosed in young women. The ultimate goal should be to further improve the efficacy of the HPV vaccine by combining it with immunotherapeutic agents with a proven ability to augment T-cell responses.

Kenter et al. focused here on HPV-16–positive, grade 3 vulvar intraepithelial neoplasia lesions and HPV-16–specific immunotherapy. However, at least 14 common types of HPV (e.g., types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are detected in grades 1 through 3 vulvar intraepithelial neoplasia, and eventually these types need to be considered for inclusion in the vaccine. HPV-negative vulvar intraepithelial neoplasia lesions also may give rise to epithelial cancers. These lesions might share with other epithelial premalignant lesions many nonviral tumor antigens first detected in epithelial tumors and later detected in their precursor lesions. Thus, tumor-associated antigens
common to several epithelial cancers such as pancreatic epithelial neoplasms, ductal carcinoma in situ of the breast, or adenomatous polyps (precursors to colon cancer) should be evaluated as potential target antigens in vulvar intraepithelial neoplasia.

A project carried out by the National Cancer Institute in collaboration with tumor immunologists prioritized cancer antigens to assist investigators in selecting the most promising antigens for further development. The list of the top 100 antigens includes HPV-16 oncoproteins E6 and E7 as well as others that are probably expressed in vulvar cancer and vulvar intraepithelial neoplasia and could be used in the development of vaccines for HPV-negative tumors. Long synthetic peptides derived from some of these antigens could be added to the peptides in the HPV vaccine reported on by Kenter et al. to cover most, if not all, vulvar intraepithelial neoplasia.

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End Run around Epo

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Recombinant human erythropoietin is arguably the most successful therapeutic application of recombinant DNA technology to date. Since the initial reports — which appeared 22 and 23 years ago — documented a cure of the anemia of chronic kidney disease with recombinant human erythropoietin, well over a million patients have been treated with it effectively and with minimal drug-related toxicity. Moreover, recombinant human erythropoietin has also been effective in the treatment of patients with cancer, particularly when anemia has been aggravated by chemotherapy.

Although recombinant human erythropoietin merits high marks for efficacy and safety, concerns have arisen about two distinct types of adverse effects. From 2000 through 2004, severe pure red-cell aplasia developed in several hundred patients with chronic kidney disease, primarily in Europe, after subcutaneous administration of recombinant human erythropoietin. Autoantibodies in the serum of these patients neutralized both recombinant human erythropoietin and endogenous erythropoietin. It is likely that in this cluster of cases, antibodies arose in part because of a defective formulation of the recombinant human erythropoietin that enabled the formation of neoantigens. Moreover, subcutaneous self-administration poses problems with storage and handling that could impair the stability of the molecule and enhance the formation of antibodies. With improved formulation and intravenous administration, the incidence of this complication has fallen to the extremely low, pre-