The End of the Beginning
Gene Transfer Into the Vessel Wall

Robert S. Meidell, MD; Robert D. Gerard, PhD; and R. Sanders Williams, MD

This is not the end; it is not even the beginning of the end; but perhaps it is the end of the beginning.

—Winston Churchill
6 June 1944

Gene transfer into tissues of living animals has now been accomplished in several laboratories with the use of a variety of methods.\textsuperscript{1–4} The initial wave of these reports has been exhilarating and has whetted the appetite for application of these methods to the treatment or prevention of cardiovascular diseases. As the novelty of delivering reporter genes into tissues wears off, it is time to take a hard look at practical issues that will determine the real potential of current gene transfer strategies to address clinical goals.

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The article by Flugelman and colleagues in this issue of Circulation makes some distinct contributions to this effort, even though the tale is cautionary and sobering rather than celebratory. Despite the application of sensitive analytical methods, the authors could detect no evidence of expression of foreign genes introduced into the vessel wall via inoculation with reasonable titer stocks of several different retroviral constructs through perforated balloon catheters. Although detection of virally encoded sequences by DNA amplification provided evidence for viral infection, the efficiency of gene transfer appeared to be vanishingly small: less than 100 of the estimated $4 \times 10^7$ cells present in the instrumented vessel segment. In view of the reported dependence of retrovirally\textsuperscript{4} mediated transduction on cell proliferation,\textsuperscript{5} it remains to be determined whether higher efficiency would be achieved in areas of vessel injury.

Despite the failure of in vivo infection by recombinant retroviral vectors to achieve efficient introduction and expression of foreign genes in the vessel wall, the experiments described in this study were well controlled and provide insights that should be useful to other investigators pursuing similar goals, including 1) further documentation of the unreliability of staining for $\beta$-galactosidase activity to detect expression of foreign genes in vascular tissue of some mammalian species; 2) demonstration of the absence of short-term toxicity to the host or inactivation of the retroviral vector when perforated balloon catheters are used to deliver these vectors into the vessel wall; 3) further illustration of the low efficiency of retroviral vectors for gene transfer into nonproliferating adult tissues; and 4) additional evidence of the potential for false-positive results of analytical tests based on the polymerase chain reaction despite extreme care to avoid contamination. (DNA extractions and amplifications were performed in another laboratory.)

These carefully analyzed experiments can represent, in our opinion, “the end of the beginning” of the gene transfer era in cardiovascular biology and medicine by emphasizing the long road that lies ahead. The transfer of foreign genes into somatic cells of living animals is no longer uncharted territory. Achieving both efficient gene transfer into target cell populations and stable expression of foreign gene products in biologically meaningful concentrations, however, remains a formidable goal that will require further innovations in viral vectors,\textsuperscript{1,2,6,7} physical methods for introduction of foreign DNA,\textsuperscript{3,4} cell-specific targeting strategies, and effective and minimally invasive delivery systems.

References

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From the Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Tex.

Address for correspondence: R. Sanders Williams, MD, UT Southwestern Medical Center, Department of Medicine, 5323 Harry Hines Blvd., Y9.206, Dallas, TX 75235-8573.
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R S Meidell, R D Gerard and R S Williams

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