Atherosclerosis leading to coronary artery disease (CAD) is a major health problem in humans and one of the leading causes of death today in the United States. Treatment with the use of percutaneous transluminal coronary angioplasty (PTCA), though effective, has been plagued by a high incidence of restenosis, or narrowing of the vessel lumen following balloon dilation. The vascular remodeling observed involves smooth muscle cell proliferation and migration. Therefore, therapeutic approaches aimed at limiting this proliferative response are being pursued. As such we have examined the effects of ribonucleotide reductase (RR) inhibition as a potential therapeutic approach to limit the incidence and degree of restenosis. RR catalyzes the reductive conversion of ribonucleotides to deoxynucleotides. This reductive reaction is a prime target for impeding cellular proliferation. To test this hypothesis, a rabbit model was used in which an initial carotid balloon injury was performed to produce a denuded endothelium and then the rabbits were placed on a high cholesterol diet which resulted in the development of an atherosclerotic plaque at the site of initial injury. Rabbits received either vehicle or 1 of 2 different ribonucleotide reductase inhibitors. At 8 wk post-injury, the animals were sacrificed and the degree of atheroma and vessel proliferation were evaluated using morphometric analysis. Both of the ribonucleotide reductase inhibitors used were able to reduce tunica media growth by an average of 61% from the injured rabbits and reduced the atheroma area by 42%. These results suggest that RR may serve as a therapeutic target for the development of pharmacological agents used to reduce or prevent the incidence of atheroproliferative disorders such as atherosclerosis and restenosis.