IMMUNOLOGICAL ARTERIAL INJURY IN ATHEROGENESIS, C.R. Minick, L.R. Williams, and D.R. Alonso, Department of Pathology, Cornell Medical College, New York, N.Y.

Our experiments indicate that the synergy of immunological arterial injury resulting from either immune complex disease or graft rejection and hypercholesterolemia will lead to atherosclerosis. Repeated or protracted immunological arterial injury in synergy with more modest hypercholesterolemia, like that in Western man, leads to arterial lesions which closely resemble chronic human atherosclerosis. Sites of immunological arterial injury retain their increased propensity to accumulate lipid for weeks and months following the injury.

Indirect evidence from experiments of others suggests that increased endothelial permeability may be the primary event in some immunologically induced arterial injury. Results of our experiments indicate that endothelial damage and/or loss and platelet interaction with the arterial wall may be an early event in the pathogenesis of immunologically induced atherosclerosis. Moreover, our results indicate that at least in the instance of graft rejection, endothelial injury and platelet interaction may not only be an early event, but that continued injury and platelet interaction may contribute to progression of atherosclerosis.

PLATELET SUPPRESSION THERAPY IN ARTERIAL DISEASE: PRESENT STATUS. J. A. Blakely. Dept. of Clinical Hematology, Sunnybrook Hospital, Toronto, Canada.

Arterial disease is a severe test of clinical trials methodology. Results to date have defined areas for further study, but clinical indications are not established. Dipyridamole reduces emboli from prosthetic heart valves but applicability to less thrombogenic valves is uncertain. Transient cerebral ischemic attacks are physiologically appropriate and there is preliminary evidence of reduced attacks with Sulfipyrazone, none with Dipyridamole, and favorable case reports with Aspirin. Effects on stroke and death in patients presenting with TIA or stroke are under study. Sulfipyrazone has failed to prolong patency time after peripheral vascular surgery. Administration of aspirin and of Sulfipyrazone to elderly populations has shown no detectable benefit from Aspirin, and has suggested that Sulfipyrazone should be further studied in patients recovered from thrombotic stroke. The greatest potential benefit may be secondary prevention of myocardial infarct, but to date efficacy has neither been demonstrated nor excluded. Studies in progress include: ASA and/or Sulfipyrazone and TIA, stroke and death in patients with TIA; ASA with and without Dipyridamole in patients with TIA; Sulfipyrazone and survival after recovery from thrombotic stroke; Secondary prevention of myocardial infarct with ASA, ASA or ASA + Dipyridamole, Sulfipyrazone, and Clofibrate; Sulfipyrazone, ASA, and ASA with anticoagulants and emboli from prosthetic valves. Platelet survival studies may permit selection of populations likely to benefit and assessment of adequacy of therapy.

Hypotheses tested by clinical trial must be distinguished from hypotheses formulated from retrospective analysis, and methods must permit effects of treatment to be distinguished from differences in risk.

THE ROLE OF ENDOTHELIAL CELL INJURY AND PLATELET RESPONSE IN ATHEROGENESIS. L.A. Harker, R. Ross, J. Glomset. University of Washington School of Medicine, Seattle, Washington, U.S.A.

Endothelium forms a resistant barrier between flowing blood and vessel wall structures. Endothelial thromboresistance is maintained in part by the synthesis of prostacyclin, a potent prostaglandin inhibitor of platelet function. Loss of endothelial cells, mediated by physical, chemical, infectious or immune mechanisms, exposes the subendothelium to flowing blood. Platelets react to the subendothelial connective tissue structures, undergoing adhesion and release of intracellular constituents, including a factor that is mitogenic to smooth muscle cells. This growth factor is a heat stable, basic protein (IP 7.4-9.4) of 20,000 Daltons and appears to be responsible for the intimal proliferation of smooth muscle cells that follows endothelial cell desquamation. After a single injury event the intimal lesion regresses over several months. Repeated or continuous endothelial cell loss results in progressive intimal proliferation of smooth muscle cells, their secretion of connective tissue matrix components (collagen, elastin and proteoglycans) and accumulation of lipid when animals are on a hypercholesterolemic diet to form early atherosclerotic intimal lesions. Discontinuance of endothelial injury and restoration of the endothelium appear to be followed by lesion regression except when lipid accumulation is extensive. Possible approaches to atherosclerosis prevention include: 1) protection of the endothelium by interruption or avoidance of endothelial injury factors, and perhaps by pharmacologic protection; 2) inhibition of platelet reactivity; 3) modification of SMC proliferation, secretion or lipid accumulation.