STRUCTURAL AND PHYSIOLOGICAL ASPECTS OF MACROMOLECULAR HEPARIN. Alan A. Horner (Department of Physiology, University of Toronto, Toronto, Ontario Canada).

Evidence will be presented that the structural integrity of macromolecular heparin, the multi-chain form of heparin isolated from pronase-digested rat skin (Horner, J. Biol. Chem. 246, 231, 1971) depends on a unique polypeptide core containing only serine and glycine in equimolar proportions. The data supporting the proposed structure is derived from degradation studies using alkali in the presence of ^{3}H-borohydride, nitrous acid and an endoglycosidase present in mouse mastocytomal tissue (Robinson, Horner, Höök, Ögren and Lindahl, manuscript in preparation).

It follows from this model that the individual heparin chains linked to the polypeptide core are considerably longer than those of commercial heparin. Examples will be given, from work in progress in this laboratory (Young and Horner, manuscripts in preparation), of the sequential breakdown of macromolecular heparin by several depolymerases present in normal rat tissues, yielding chains in the same molecular size range as commercial heparins. These enzymes appear to act differently from the mastocytomal endoglycosidase in that products of different sizes are produced. The small intestine contains two depolymerase activities with pH optima of 6.0 and 7.4, whilst plasma contains activity with a pH optimum of 6.0 only. The plasma enzyme product formed at pH 6.0 is larger than the intestinal enzyme product formed at pH 6.0. These depolymerizing enzymes are not necessarily all endoglycosidases, one may cleave the proposed polypeptide core structure.

The possible physiological significance of the breakdown of macromolecular heparin *in vivo* will be discussed, with particular reference to the relationship between endogenous heparin and lipoprotein lipase. The pathological implications of impaired depolymerization of macromolecular heparin have been studied in an indirect manner by feeding an atherogenic diet to squirrel monkeys. The induction of atherosclerosis by dietary means was accompanied by the accumulation of macromolecular heparin in the small intestine, a tissue in which only low molecular weight heparin was found in healthy controls. Macromolecular heparin inhibits lipoprotein lipase activity *in vitro* (Horner, Proc. Nat. Acad. Sci. U.S.A. 69, 3469, 1972). Therefore the results of the squirrel monkey feeding experiment support the hypothesis of Zilversmit (Circulation Res. 33, 633, 1973) which contends that lipoprotein lipase and endogenous heparin are significant factors in the aetiology of atherosclerosis. The present work demonstrates that the enzymic depolymerization of macromolecular heparin is an additional factor which must be considered.