Focal and segmental glomerular hyalinosis and sclerosis (FSGHS) has been observed in renal biopsies of patients with a wide range of different kidney diseases and these glomerular lesions may therefore represent a type of secondary phenomenon. In various rat strains FSGHS-like lesions develop spontaneously during aging or can be induced more readily by experimental measures. The primary site of the histologic changes in the glomeruli appears to be the centrolobular mesangial area. Deposition of hyalin material leads to increased production of extracellular matrix with development of capillary collapse and adhesions to the Bowman capsule. In the course of time numerous etiologic and pathogenetic mechanisms have been proposed such as amino acid toxicity, immunologic factors, mechanical stress due to intraglomerular hypertension and hyperperfusion, coagulation processes, hormonal factors, and mesangial 'overload'. In this thesis the character and function of the glomerular mesangium in normal and experimental conditions (chapter I-IV) and the pathogenesis of glomerular sclerosis in various rat models (chapter V-VII) have been studied.

Chapter I describes the mesangial macromolecular uptake in normal and platelet and complement depleted rats. Colloidal carbon was injected intravenously as a tracer and the mesangial accumulation of these inert particles (200-300 Å in size) was measured semiquantitatively using an automatic scanning method. Carbon uptake of normal rats did not differ significantly from that of platelet or complement depleted rats. Vasoactive amines liberated from aggregating platelets or complement activation therefore do not seem to contribute to the mesangial accumulation of carbon particles. We therefore considered colloidal carbon useful as a tracer to study mesangial macromolecular kinetics. In normal circumstances, the mesangium appears to be a glomerular area in which circulating material freely permeate.

Chapter II describes the mesangial macromolecular processing in puromycin aminonucleoside (PAN) nephrosis, an animal model for the so-called minimal change disease in humans. We confirmed an increased accumulation of injected carbon colloidal carbon as previously demonstrated by other investigators. Using an immunoperoxidase technique at the ultrastructural level, increased amounts of endogenous im-

Summary
mumoglobulin G were detected in segmental mesangial areas, localised mainly in matrix substance of electron lucent appearance (so-called 'mesangial channels'). The main route of entrance of both injected carbon and endogenous plasma proteins is through the fenestrations in the covering endothelium. Increased mesangial cell uptake of tracers in this model may be caused by pooling in mesangial channels.

In chapter III the mesangial localization and distribution of sulfated glycosaminoglycans and sialoglycoproteins were studied. These anionic charged elements are thought to be important in the maintenance of capillary wall integrity and constitute a charge-selective filter. Analogous to their role in the peripheral glomerular capillary wall permeability sulfated glycosaminoglycans and sialoglycoproteins may also play a role in the permeability of the mesangial matrix to circulating substances. However, using the cationic dyes ruthenium red and colloidal iron we were unable to detect significant loss or altered configuration of anionic charged substances in the mesangial area of PAN-nephrotic rats. Other, as yet not defined mechanisms might be responsible for the increased mesangial accumulation of circulating substances in this model.

In chapter IV the mesangial accumulation of colloidal carbon in the remaining kidney after unilateral nephrectomy was studied. Compared to controls, 24 hours after carbon injection a significantly increased accumulation of carbon in the mesangium was detected in an uneven distribution over the glomerular population. This may reflect unequal glomerular reactions to hemodynamic changes after renal ablation. Conceivably, the glomeruli with large carbon depositions may represent the most vulnerable ones in which 'mesangial overloading' and sclerosis starts to develop.

The possibility of a relationship between development of FSGHS and locally increased mesangial deposition of circulating materials was studied in the unilateral nephrectomy model of focal sclerosis in chapter V. Rats underwent unilateral nephrectomy and received carbon after recovery. After 4 months, significantly more carbon was measured in the glomeruli of the remaining kidney of nephrectomized rats. Glomeruli with FSGHS lesions contained significantly more carbon than non-sclerotic glomeruli in the same kidney with a preferential localization of the carbon within the lesions. When carbon was injected before nephrectomy glomerular carbon content appeared to be equal in experimental and control groups except in the lesion itself where carbon content was significantly higher. It was concluded that FSGHS lesions in this model were caused by an increase in permeability of glomerular areas with increased accumulation of circulating substances. The lesions result from abnormal sulfated glycosaminoglycan and sialoglycoprotein patterns.

In chapter VI the mesangial localization and distribution of colloidal carbon after chronic PAN treatment was studied. Rats were nephrectomized rats at the age of 6 weeks and received carbon 4 weeks after onset of PAN treatment, the carbon was detected 24 hours after injection, as well as 1, 2, and 4 days after renal ablation. Significant increased accumulation of carbon in the mesangium was detected in an uneven distribution over the glomerular population. This may reflect unequal glomerular reactions to hemodynamic changes after renal ablation. Conceivably, the glomeruli with large carbon depositions may represent the most vulnerable ones in which 'mesangial overloadings' and sclerosis starts to develop.

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Body weight curves, protein, cholesterol, and plasma protein patterns were studied in rats made nephrotic by chronic PAN treatment, the other clearly different groups they share development of FSGHS as a common event in the development of the lesions in the underlying pathogenetic mechanisms.

In chapter VII the mesangial localization and distribution of colloidal carbon in rats made nephrotic by chronic PAN treatment was studied. Body weight curves, protein, cholesterol, and plasma protein patterns were studied in rats made nephrotic by chronic PAN treatment, the other clearly different groups they share development of FSGHS as a common event in the development of the lesions in the underlying pathogenetic mechanisms.
rimental and control rats and no preferential localization of carbon was found in the lesions. It could be excluded that deposition of carbon by itself was responsible for the development of FSGHS. From these data it was concluded that the preferential localization of carbon in the FSGHS lesions in rats nephrectomized before carbon injection was caused by an increased delivery of tracer shortly after injection to those glomerular areas where sclerosis will develop at a later time. The increased accumulation of tracer early in the experiment and the later development of FSGHS lesions in the same glomerular area suggest that the lesions result from a continuous local increased delivery of unknown harmful substances.

In chapter VI the same experimental approach was chosen in rats with chronic PAN nephropathy. Rats were treated with PAN and received colloidal carbon early after induction of proteinuria. Similarly to unilateral nephrectomized rats at sacrifice glomeruli with sclerosis contained significantly more carbon than non-sclerotic glomeruli in the same kidneys with a preferential localization of carbon in the lesions. Since the rate of egress of carbon from the mesangium did not change during chronic PAN treatment, this preferential carbon localization in the lesions is probably also due to an increased carbon uptake in apparent vulnerable areas where sclerosis will develop subsequently. Thus, although the unilateral nephrectomy model on the one hand and the PAN model on the other clearly differ with respect to many renal functional features, they share development of FSGHS possibly due to mesangial overloading as a common quality. The different intraglomerular distribution of the lesions in the two models, however, suggests a different underlying pathogenetic mechanism.

In chapter VII the relationship of mesangial accumulation of macromolecules, in particular lipids, to the development of FSGHS was studied in rats made nephrotic by administration of PAN or adriamycin. Body weight curves, degree of proteinuria, and serum levels of total protein, cholesterol, and triglycerides were similar in both groups. Lipoprotein patterns were not analysed. After 3 months the mesangial area in glomeruli of PAN treated rats showed significantly higher amounts of lipid as compared to glomeruli in adriamycin nephrotic rats and within FSGHS lesions in particular extensive accumulations of lipid was observed. In adriamycin nephrosis a very low incidence of FSGHS was observed and only scant amounts of lipid were detectable in the me-
sangial area. These differences are probably caused by differences in mesangial function between both models since PAN nephrosis the mesangial deposition of tracers is increased, whereas mesangial processing of carbon in adriamycin nephrosis was shown to be normal.

In the General Discussion the experimental data are integrated into a concept on the pathogenesis of FSGHS. Induction of mesangial overload or damage appears to be necessary to cause mesangial sclerosis and FSGHS in the rat. Since our results strongly support a relationship between lipid accumulation and development of mesangial sclerosis, hyperlipidemia may constitute an important second promoting factor. Glomerular sclerosis may therefore represent a local form of atherosclerosis. The exact mechanism by which mesangial sclerosis develops, however, needs further study. In vitro experiments in which cultured mesangial cells are exposed to different lipid classes and other plasma constituents may deepen our insight. Moreover, attention should be paid to the role of mesangially localized monocytes-macrophages and Ia-antigen bearing cells in the pathogenesis of glomerular sclerosis.