Summary

In the introduction of this thesis basic motives and assumptions are stated.

In chapter I data from literature on IGA-Nephropathy upto December 1983 are reviewed. A heuristic system of work-hypotheses concerning mesangial IgA-deposition is developed. Some of our own clinical observations and our results of therapies are described in order to complete the picture of IgA-Nephropathy.
The relation: circulating IgA ——> mesangial IgA-deposits ——> nephritic symptoms is discussed (and rejected).

In chapter II data on the 75 patients in our clinic with IgA-Nephropathy are used to construct overall survival curves and to test the "univariate" effect of single riskfactors on the prognosis of groups of patients. For individual prognosis it is necessary to determine the relative weight and interdependence of riskfactors. For non-mathematical readers it is explained how this can be done using multiple regression analysis, for instance by the proportional hazards model. Using standard methods, a numerical way to calculate point estimates of kidneys survival is developed. A new simple graphical method to determine individual prognosis by way of a nomogram is described. Confidence limits for these estimates are calculated by a statistical theory, which has been developed by one of the coauthors.
In our multiple regression analysis kidney survival is adversely influenced by signs of active glomerulonephritis if persisting more than 6 weeks after an attack of macroscopical haematuria (i.e. proteinuria, microscopical haematuria, low GFR). Moreover untreated hypertension turns out to be a bad omen. An unexpected finding is that patients without gross haematuria fare worse than patients with either "systemic exacerbations" or "semicontinuous gross haematuria".
Age, sex, and histological features do not provide additional information on kidney survival.

In chapter III for the Causasian subpopulation of our patients it is shown that patients with and without macroscopical haematuria differ in the following aspects: immunogenetics, morphology of the kidney biopsy, microscopical haematuria, proteinuria, GFR, age and univariate prognosis. The most simple explanation of these differences is that primary IgA-Nephropathy consists of at least two subentities.

In chapter IV infusion of a low dose of dopamine was used to assess the functional reserve capacity of patients with IgA-Nephropathy. Heart rate and bloodpressure remained constant. Only patients with a baseline GFR $>$ 73 ml/min turned out to be able to increase their GFR. We speculate that kidneys with a total GFR $<$ 73 ml/min cannot increase their baseline GFR because they are already maximally hyperfiltrating.

Chapter V shows that all patients with IgA-Nephropathy have mesangial deposits by electron microscopy (EM). Presence or absence of proteinuria turns out to be correlated with subendothelial deposits as visible by EM. Unexpected in these patients with sometimes impressive haematuria was the finding that proteinuria was "selective" in IgA-Nephropathy if GFR $\geq$ 22 ml/

min and proteinuria $\geq$ 0.5 g/24 hr.
We speculate, that mediators of inflammation may affect a charge barrier, which might cause selective proteinuria, subendothelial deposits, and perhaps also mesangial deposition or nephritic symptoms.

In chapter VI, lymphocytes of patients with IgA-Nephropathy were shown to produce an increased amount of the lymphokine V(aso)-P(ermability)-F(actor). This VPF is not correlated with the amount of proteinuria. We speculate that VPF plays some other role in IgA-Nephropathy, for instance in IgA-deposition.

Chapter VII shows the group of our patients with IgA-Nephropathy to have elevated IgA levels, although only in 20% of these patients IgA levels are higher than the 95% confidence levels of a normal population. The primary in vivo IgA-response on the subcutaneously injected test antigen Helix Pomatia Haemocyanin does not differ from normal controls and appears to be switched off rapidly.
IgA-anti-CMV-LA levels are also normal; however, IgA-anti-EBV-VCA and IgA-anti-diphtheria-antigen levels are elevated.
"Spontaneous" IgA synthesis in vitro by lymphocytes of IgA-Nephropathy patients tends to be increased, whereas PWM-stimulated IgA synthesis is normal.
These data do not allow one unifying hypothesis concerning regulation of the IgA-response in IgA-Nephropathy. Nevertheless there is neither a general overshoot of the IgA-response, nor a gross defect in clearance of serum IgA.
Possible causes might be dysregulation of the secondary immune response e.g. due to persistently active EBV infection or to a deficient mucosal barrier.

Chapter VIII summarizes the evidence for each of the three workhypotheses concerning the mechanism of mesangial IgA-deposition:
A: abnormal circulating IgA. B: primarily abnormal kidney; C: some indirect factor causing deposition of normal IgA in an originally normal kidney (for instance a mediator of inflammation).
In a longitudinal study we do not find evidence for hypothesis A. Also in a cross sectional survey, levels of soluble immunecomplexes (ICX) are only a small fraction of those in active SLE. No carrier bound immunecomplexes could be detected. No indirect proof of soluble ICX was provided by skin biopsies, transfer studies and measurement of Fc receptor function. In situ ICX formation could not be demonstrated. Hypothesis B can be eliminated in view of the experiences in human renal transplantation.
Hypothesis C is attractive because of: 1) "exclusion" of the alternatives A and B; 2) clinical observations (high prevalence of urticaria, selective proteinuria, rapidity of "systemic exacerbations", dissociation of IgA-deposits and nephritic symptoms); 3) the finding of abnormalities in the lymphokine VPF and in the plasmakine system.

In the general discussion, the concept of primary IgA-Nephropathy as one single disease entity is discussed.
The presence of abnormal amounts of IgA in IgA-Nephropathy and several other renal diseases and also in some normal controls cannot be denied. However, mesangial IgA-deposition is not specific for primary IgA-Nephropathy.

Even a more narrowly defined primary IgA-Nephropathy in Caucasians is probably not one single disease entity.
Therefore we tend to see mesangial IgA-deposits as a useful marker of renal disease, but not as a solid basis to define a disease entity, nor as the primum movens of such an entity. In our view an abnormality in a mediator system may be the ultimate cause of IgA-Nephropathy.